Mathematical Models of Diffusion Through and Near Skin Appendages: Hair Follicle and Eccrine Sweat Gland Pathways

by

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A ma famille: mon père Jeffrey, ma mère Elaine, mon frère Kyrill (Zawardi) et ma soeur Jihane-Rachel (Loupatia)

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Abstract

Quantitative modeling of the transport of topically applied chemical substances into skin appendages and the surrounding skin tissue is important to topical and transdermal drug delivery, as well as risk assessment of chemical exposure, because skin appendages –in particular hair follicles and eccrine sweat glands– can contribute significantly to skin permeability by providing shunt pathways through the epidermal barrier. In addition, an understanding of follicular delivery per se may be of considerable importance in the treatment of diseases originating in the pilosebaceous unit and of interest to the cosmetics industry.

Part I of this Ph.D. thesis addresses the transport of chemicals into and near a hair follicle. A comprehensive 2-D axisymmetric finite difference model has been developed to solve the transient diffusion equation describing transport of an unionized chemical species through stratum corneum, viable epidermis, dermis and hypodermis in a large cylindrical volume surrounding a realistic geometrical representation of the hair shaft and encircling layers of the follicular sheath. The numerical technique introduces a novel non-orthogonal coordinate system fitted to the follicle's outer boundary. The barrier properties of the follicular infundibulum are modeled as a stratum corneum-like epithelium with a thickness diminishing with depth. Inputs to the calculation are the partition and diffusion coefficients of the applied drug in each skin layer, the permeability of the outer root sheath (ORS), taken as the hair follicle's outer boundary, and volumetric rate coefficients describing clearance into the systemic circulation via the dermal vasculature. Concentration profiles for a model permeant representing the lipophilic dye

Bodipy® FL C_5 (BFL) were obtained for upper and lower bound estimates on the permeability of the ORS and the concentration of BFL in the sebum. The results are compared to experimentally obtained published *in vitro* (no clearance via the vasculature) dye distributions around hair follicles, and show the infundibulum to be the structure via which the hair follicle increases permeation into dermal tissue. The contribution of the sebaceous duct to the permeability of the hair follicle is shown to further increase the delivery of BFL to the deeper dermis, in qualitative agreement with published experimental results. Simulations of the *in vivo* permeation of BFL show that typical levels of clearance by the vasculature yield maxima in the average concentration profiles calculated at the hair follicle/skin tissue boundary, and in the viable epidermis and the dermis near the follicle. Average dermal concentrations near the hair follicle are up to 90 % smaller than in the *in vitro* case. Furthermore we use the model to simulate the diffusion of BFL into the skin from a small patch-like device. Delivery to the skin is nearly non-existent for the region of the tissue does not lying directly below the patch.

Part II presents the mathematical structure for a 3-D model of the steady-state diffusion of an unionized chemical substance through and near the duct of an eccrine sweat gland. We develop the structure of the solution to the model equations with reference to physico-chemical parameter values for the diffusion of BFL.

1 Introduction

1.1 Topic of dissertation and motivation

The topic of this thesis is the investigation, from a mathematical modeling point of view, of the role that hair follicles and the duct of eccrine sweat glands play in the transport of chemical substances, therapeutic or toxic, into human skin. This subject is part of the broad field of study of percutaneous permeation, the term designating the movement of molecules by any means or mechanism across the skin.[1] We are specifically interested in studying mechanistically the potential pathway contributed by the hair follicles and the eccrine sweat glands to the diffusion of deliberately or unintentionally topically applied chemical substances through human skin. This means we assume that the molecules of the drug or toxic substance move from a region of greater concentration –an exterior donor compartment or a given volume in contact with the outer surface of the skin– to a region of less concentration, the interior of the skin, due to their spontaneous thermal agitation.[1]

The study of percutaneous permeation is a very active field of research, in particular experimental research, due to the applicability of the findings to the development of transdermal drug delivery systems. Around 40% of drug delivery candidates under clinical evaluation are related to delivery to or through the skin.[2] This mode of drug delivery offers the possibility of eliminating the pain and possible infection associated with injections, and, compared to oral delivery systems, enables the drug to bypass the first-pass effect of the liver, providing sustained release of the drug for up to 7

days.[3,4] In addition, understanding the mechanisms which enable chemicals to penetrate the skin is of prime importance for the assessment of risk to toxic substances.[5-8]

The focus on the skin appendages, and in particular on the pilosebaceous unit comprising the hair follicle and the associated sebaceous gland, is due to the fact that these structures provide punctures through the stratum corneum, the outermost cell layer of mammalian skin and the main barrier protecting the interior of the body from the outside environment. These shunt pathways are now widely thought to facilitate the transport of chemical compounds to the deeper layers of the skin and possibly into the systemic circulation.[9] An understanding of the transport of substances through the pilosebaceous unit is also necessary for the design of drugs which specifically target the hair follicle, such as for the treatment of skin diseases originating in the pilosebaceous unit[9,10] and for the development of cosmetic products.[10]

Scheuplein and coworkers in the late 1960s and early 1970s were the first to demonstrate theoretically the importance of the follicular pathway at early diffusion times.[11,12] Other early results (referenced in [50]) showed higher absorption of compounds in areas of greater follicular density beyond the initial diffusion process, but these were not considered conclusive, since corneocytes are smaller in areas of greater follicular density. In addition, many scientists assumed the follicular pathway to be of minor importance as it was understood that hair follicles account for only 0.1% of the total body surface area.[13] However, with the constant improvement of imaging techniques and the boom of nanotechnology (in the form of nano- or microparticles, which have been shown to be delivered to regions of the hair follicle[14-16]), experimental studies conducted over the past 15 years have provided strong evidence for the contribution of

hair follicles to the overall transport of chemicals through skin beyond the initial period of permeation. A small but representative sample of the body of work on hair follicles is reviewed in chapter 3, and work on eccrine sweat glands is reviewed in chapter 9. The recognition in a recent publication that the density of hair follicles and the size of the follicular orifice depend on the location on the body [13] adds credibility to the premise that hair follicles play an important role in the diffusion of chemical compounds through human skin and can be targeted to facilitate the delivery of drugs to the deeper skin tissue.

Despite the large number of studies on the subject of percutaneous permeation via the follicular pathway, no clear mechanistic understanding of how the hair follicles facilitate the transport of chemical compounds to the deeper skin layers has emerged and very little focus has been placed on the eccrine sweat gland pathway.

The major part of this thesis (Part I) deals with the development and application of a novel rigorous mathematical model which parametrizes the hair follicle and yields upper and lower bound predictions on the concentration of a chemical substance diffusing into it and into the surrounding skin tissue. The concentration profiles calculated from the model are based on estimates of the diffusion, partition and permeability coefficients of the substance in various regions of the hair follicle and the surrounding skin. The application of the model to the diffusion of a specific chemical substance demonstrates the possibility of conducting rigorous analyses of diffusion near the hair follicle, which take into account structural details of the appendages. At the same time, this work highlights the importance of having precise values of the physico-chemical parameters which govern the permeation of a substance into human skin near a hair follicle.

Part II of this thesis defines the mathematical structure for a corresponding model of steady-state diffusion through the duct of an eccrine sweat gland. The duct is modeled as a helical tube of infinite length embedded in skin tissue and may –depending on the geometry chosen– represent either the spiraled intraepidermal duct, the relatively straight duct embedded in the dermis or the coiled proximal duct. As in the hair follicle model, the input parameters are the partition, diffusion and permeability coefficients of the applied chemical in the duct the surrounding skin tissue. The concentrations inside the duct and in the surrounding skin are linear in depth into the skin with a perturbation term describing the effect of the presence of the duct. The perturbation to the permeant concentration inside the duct is linear in depth. Slender-body theory is used to approximate the perturbation to the dermal concentration as a distribution of dipole singularities along the centerline axis of the helix. The model is applied to the diffusion of a specific chemical substance and initial results for the strength of the perturbation to the concentration inside and outside the eccrine sweat duct are presented. Future work on this model would consist of obtaining results for the concentration of the applied chemical as a function of depth and radius away from the duct, and for the total flux through a horizontal plane of a block of dermal tissue containing one of the portions of the mentioned duct mentioned above.

1.2 Methodology and thesis outline

The mathematical models of transient diffusion through and near a hair follicle and an eccrine sweat duct are implemented in two separate FORTRAN programs. Both models are applied to the diffusion of the fluorescent dye 4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-

diaza-*s*-indacene-3-pentanoic acid (Bodipy® FL C_5). The model predictions on diffusion through and near a hair follicle are compared semi-quantitatively to experimental results for the transient *in vitro* diffusion of this dye through a piece of skin containing a hair follicle published by Bouwstra and coworkers.[17] The model is then used to simulate *in vivo* diffusion by predicting the effect of the presence of cutaneous microvasculature near the hair follicle, both for the case of a donor solution compartment partially covering the piece of skin (as in Bouwstra and coworkers' experiment and in the *in vitro* simulation) and for the case of a donor solution compartment fully covering the skin. This later *in vivo* case is considered in order to predict the concentration of drug delivered from a small patch-like device far from the hair follicle. The eccrine sweat duct model is used to predict the steady-state concentration profiles of Bodipy® FL C_5 diffusing into an eccrine sweat gland and in the surrounding skin tissue *in vitro*.

In chapter 2 we review of the structure and physico-chemistry of human skin and skin appendages and give an overview of the routes of penetration of chemical compounds into skin. Part I (comprising chapters 3 through 8) presents the mathematical model of transient diffusion through and near a hair follicle and the results obtained from it. Chapter 3 is an overview of the literature on the subject of the follicular pathway. In chapter 4 the model formulation is presented, and in chapter 5 the steps of the numerical calculation are detailed. Chapter 6 is devoted to the diagnostic tests that were conducted to ensure the proper functioning of the FORTRAN code. In chapter 7 we present the application of the model to the diffusion of the fluorescent dye Bodipy® FL C_5 near a hair follicle, compare the model predictions to Grams *et al.*'s published results and

present the predictions obtained from the simulations of diffusion *in vivo* in the cases of partially and fully covered skin.

Part II of this thesis defines the mathematical structure for a corresponding model of steady-state diffusion through the duct of an eccrine sweat gland. The duct is modeled as a helical tube of infinite length embedded in skin tissue and may –depending on the geometry chosen– represent either the spiraled intraepidermal duct, the relatively straight duct embedded in the dermis or the coiled proximal duct. As in the hair follicle model, the input parameters are the partition, diffusion and permeability coefficients of the applied chemical in the duct the surrounding skin tissue. The concentrations inside the duct and in the surrounding skin are linear in depth into the skin with a perturbation term describing the effect of the presence of the duct. The perturbation to the permeant concentration inside the duct is linear in depth. Slender-body theory is used to approximate the perturbation to the dermal concentration as a distribution of dipole singularities along the centerline axis of the helix. The model is applied to the diffusion of a specific chemical substance and initial results for the strength of the perturbation to the concentration inside and outside the eccrine sweat duct are presented. Future work on this model consists in obtaining results for the concentration of the applied chemical as a function of depth and radius away from the duct, and for the total flux through a horizontal plane of a block of dermal tissue containing one of the portions of the mentioned duct mentioned above.

2 The Structure and Physico-Chemistry of Skin and the Skin Appendages

2.1 The skin layers

2.1.1 The epidermis

The uppermost skin layer is the epidermis, consisting of the stratum corneum and the viable epidermis.

The stratum corneum is the outermost layer of the epidermis. It constitutes the main barrier to the penetration of foreign substances into the deeper skin layers and the body and to the loss of water from the body. The stratum corneum consists of a proteinaceous phase of closely packed interdigitated cells –corneocytes– and lipid intercellular space. The stratum corneum permeability has been approximated by many empirical correlations[18-23] and "brick-and-mortar" models,[24-35] in which the corneocytes are represented as bricks stacked in the continuous lipid phase (the mortar).

The proteinaceous phase of the stratum corneum consists of 10-20 layers of corneocytes[36-39] corresponding to a total stratum corneum thickness of 10-50 μm [40], depending on the location on the body. Corneocytes are flattened dead keratinized cells devoid of their nuclei and organelles[41] which are the end product of cell differentiation.[40] They are coated with a proteinous, cornified envelope[10,41] largely thought to be impermeable, although this concept has been recently challenged.[42,43] The interior of corneocytes is a mixture of keratin filaments surrounded by a lipid-protein matrix and water of hydration.[43] The barrier property of the stratum corneum is thought to be due to

the lipids in the intercellular space.[44,45] This phase consists mainly of triglycerides, free fatty acids, cholesterol and phospholipids,[40] arranged in layers forming lipid lamellae.[46].

The viable epidermis is 60-100 μm thick.[40] Overall, it can be viewed as a composite medium[43] containing about 40% protein, 40% water and 15-20% lipids.[40] Diffusion through it is akin to hindered diffusion through aqueous tissue, partly punctuated by crossings of cell membranes. It is actually subdivided into 3 layers, which –from the stratum corneum going deeper– are the stratum granulosum, stratum spinosum and, at the epidermis-dermis junction, the stratum basale.[41] Keratinocytes are the major cell type found in the viable epidermis and the precursor cells to corneocytes. Keratinocytes are produced in the stratum basale. They regenerate the entire viable epidermis and stratum corneum by migrating upwards from the stratum basale towards the skin surface. During the process of desquamation the cells produce keratin, flatten and die, forming the stratum corneum, before being shed at a rate equal to that of epidermal cell regeneration.[40] The undulating epidermal-dermal junction consists of dermal papilla which project from the dermis into the epidermis. This junction provides mechanical support for the epidermis and partially hinders the exchange of cells and large molecules.[41]

2.1.2 The dermis

The bulk of the skin is the dermis, a 300-4000 μm thick layer located below the epidermis. As for epidermis diffusion through the dermis is comparable to hindered diffusion through aqueous tissue, with the important difference that the dermis is predominantly acellular. The dermis is composed mainly of the protein collagen, which

gives the dermis great tensile strength,[41] and in smaller proportion elastin, for elasticity, surrounded by water. The top 100-200 μm [12] of the dermis located immediately below the dermis, called the papillary dermis, combines thin collagen fibers, elastic fibers, fibroblasts and ground substance. The reticular dermis forms the bulk of dermis and contains thick collagen fibers and coarse elastic fibers.[39] The dermis is the locus of blood vessels, nerves and lymphatics, and supports the skin appendages.[40] An approximate representation of clearance of drugs and chemicals (i.e., absorption by capillaries and delivery thence to the systemic circulation) figures significantly in the analysis of *in vivo* diffusion in chapter 7.

The papillary dermis contains a dense plexus of arterioles and venules running parallel to the surface of the skin.[47] Within each papilla of the epidermal-dermal junction a capillary loop arises from the horizontal network. Each capillary loop is comprised of ascending limb arising from a terminal arteriole of the horizontal plexus, an intrapapillary loop having a hairpin turn, and a descending limb which connects with a postcapillary venule of the horizontal plexus.[47] The purpose of these blood vessels is to provide nutrients to the unvascularized epidermis.[47] A second, much less dense plexus of arterioles and venules is found in the lower reticular dermis, near the dermal-hypodermal junction.[39,47] It is connected to the superior plexus by perpendicular ascending arterioles and descending venules.[39,48] These provide blood vessels to the heavily vascularized hair follicles and sweat glands.[47]

2.1.3 The hypodermis

The hypodermis, also called subcutaneous fat tissue, is located below the dermis and can be up to several mm thick.[40] It is composed mainly of fat cells interwoven by collagen fibers.[10] Its main purpose is to store energy and provide mechanical and thermal insulation for the interior of the body.[10,40]

2.2 The skin appendages

The term "skin appendages" includes the hair follicle, the sebaceous gland, the eccrine sweat gland, and the apocrine gland. In addition, each hair follicle (or possibly a group of hair follicles, as has been recently suggested[49]) has attached to it an arrector pili muscle, a bundle of smooth muscle[48] whose function is to keep the hair follicle erect.[49]

2.2.1 The hair follicle

Two kinds of hair follicles exist. Vellus hairs are fine (less than 0.3 mm thick), short (less than 2 cm) and extend approximately 1mm to the dermis, while terminal hair follicles are wider (more than 2 cm), thicker (more than 0.3 mm) and extend a least 3mm down to the hypodermis.[50] Although hair follicles of different sizes and shapes have the same basic structure,[51] the subject of this thesis pertains to the transport of substances near terminal a hair follicle, and thus the focus of the following description is on the terminal hair follicle.

Hair follicles are found in all parts of the body except the soles of the feet, the palms of the hands, the red portion of the lips are certain parts of the genital organs.[52] The

highest density of hair follicles (292 hair follicles per cm^2) has been measured on the forehead.[13]

The hair follicle is an elongated invagination of the epidermis, open to the surface of the skin at the level of the stratum corneum and extending into the hypodermis. At a depth of approximately 500 μm, [10,12] the hair follicle is pierced by a sebaceous duct, connecting it to the sebaceous gland. The upper part of the hair follicle, from the ostium at the surface of the skin to the sebaceous duct orifice is called the infundibulum. It is a roughly conical gap filled with sebum produced by the sebaceous glands and within which the hair shaft is unattached to the follicular wall and moves freely.[10] The stratum corneum at the surface of the skin extends into and is continuous with the epithelium lining the infundibulum but becomes thinner with depth.[10,53]

The cell wall of the infundibulum, the outer root sheath (ORS), is continuous with the epidermis[9,38,39] and extends down the entire length of the hair follicle. Cross-sections of the hair follicle show a number of tightly packed, roughly concentric cell layers below the sebaceous ducts. Proceeding from the exterior to the interior of the hair follicle, these are an outermost acellular membrane (the glassy membrane[50]) enveloping the ORS, the ORS, the inner root sheath (IRS) which includes the Henle's layer, the Huxley's layer and the cuticle of the IRS. The IRS is in direct contact with the hair shaft, which consists of a cuticle (its outermost cell layer), a hair cortex and the medulla (the central part of the hair shaft).[10]

Below the sebaceous duct, the area of the hair follicle where it is in contact with the arrector pili muscle is known as the bulge, due to its shape. The base of the hair follicle is bulbous in shape and referred to as the hair bulb.

The cells of the ORS above the sebaceous duct are keratinized and similar to the epidermal cells.[10] Below the sebaceous duct they lack keratinization, providing protection to the hair shaft and enabling it to mold.[10] The ORS also contains melanocytes, Langerhans' and Merkel cells which repopulate the epidermis after injury.[51] The cells of the IRS are keratinized deeper than the ORS cells. The bulge area of the hair follicle consists of highly proliferative cells[52] which play an important role in hair follicle growth regulation.[10] It has also been speculated that ORS cells in the bulge serve as a reservoir for epidermal cells and cells of the sebaceous gland.[51] The hair bulb is the site of the dermal papilla, papilla cells and hair matrix cells, all of which are critical for the development of the hair follicle, determining its shape and size.[51]

The hair follicle is heavily vascularized. The lower third of an active hair follicle is surrounded by parallel blood vessels running along the long axis of the hair follicle and interconnected by "cross-shunts".[54] The rest of the hair follicle is surrounded by parallel vessels, which form a continuous network with the capillaries enveloping the sebaceous glands.[54]

2.2.2 The follicular cycles

The life of the hair goes through three stages following its morphogenesis: the active growth stage, or anagen; the involuting stage, or catagen; and the resting stage, or telogen. During anagen, cells of the hair matrix in the bulb divide rapidly and form a new hair shaft which pushes upward toward the surface of the follicle and forces the previous hair, called club hair at this point, out.[39] The structure of the hair follicle described in section 2.2.1 is that of a mature anagen hair follicle. The calculations in this thesis are

restricted to diffusion around this particular kind of structure. Catagen is the stage at which the hair matrix cells stop proliferating.[39] The lower part of the hair follicle (below the bulge) regresses and undergoes involution, reflecting a "burst of programmed cell death (apoptosis) in the majority of follicular keratinocytes".[51] During telogen the club hair is at rest, before being shed by a newly developing hair shaft in the next anagen stage.

Although the length of time a given follicle spends in the anagen stage depends on the length of the hair it produces (hair follicles producing longer scalp hairs remain in the anagen stage for 2-8 years, whereas those giving rise to shorter eyebrow hairs stay in anagen for 2-3 months[51,55]), anagen is by far the longest of the three follicular cycles. Thus, there is strong motivation to study the transport properties of the follicular structure in this phase.

2.2.3 The sebaceous glands

Sebaceous glands are multiacinar, holocrine-secreting glands. They are either associated with a hair follicle, and connected to it via the sebaceous duct at a depth of about 500 μm,[10,12] or found independently, mainly in facial skin.[52] On the face and the scalp there are 400-900 sebaceous glands/cm^2, elsewhere on the body, excluding palms, soles and the lower lip, their density is less than 100 sebaceous glands/cm^2.[56] The diameter of sebaceous glands is 200-2000 μm.[57,58] The largest sebaceous glands are found either associated with small hair follicles or as "free" sebaceous glands. The sebaceous glands on the forehead and the face, for instance, are associated with vellus hair follicles.[56]

The acini of the sebaceous gland are wrapped in blood vessels. In bald scalp skin, the sebaceous glands are larger and more richly vascularized.[54]

Sebaceous glands produce sebum, a lipophilic substance formed by the disintegration of sebocytes (sebaceous gland cells) and consisting in decreasing order of importance of triglycerides, wax esters, squalene, cholesterol esters and cholesterol.[39,59,60] Free fatty acids are produced by the breakdown of the triglycerides by enzymes in the follicular infundibulum.[39] Some of the purposes of sebum are to protect the body against bacteria, of which the infundibulum contains a variety,[39] to transport antioxidants to the skin surface,[61] and to express pro- and anti-inflammatory properties.[59] In addition, sebum in known to provide a hydrophobic coat to protect the skin from overwetting, to provide heat insulation and to contribute via its lipid fraction to the integrity of the skin.[59] Sebum is produced in 3 weeks. The lag time between its liberation and appearance on the surface of the skin is 8 hours.[50]

2.2.4 The eccrine sweat glands

Eccrine sweat glands respond to thermal stress by producing sweat, which flows to the surface of the skin and cools the body by evaporation.[39] Sweat also improves the grip and sensitiviy of skin by keeping it damp.[40,48] Over 3 million sweat glands[48] are located all over the body, except in mucosal tissue.[10] The greatest densities are found on the palms, the sole, the axillae and the forehead.[48] The components of the eccrine sweat gland are: a hollow coiled secretory gland in its proximal portion, about 100 μm in diameter,[58,62] and located in the lower dermis or hypodermis,[57,58] a coiled duct leading upwards from the secretory gland to a straight duct rising through the dermis, leading in turn to a spiraled

intraepidermal duct opening to the surface of the skin.[39] Sodium is reabsorbed through the walls of this duct into the product of the secretory gland, called "precursor sweat", producing hypotonic sweat.[39,48] The reabsorption of water, salts and electrolytes through the walls of the sweat gland duct maintains the body's homeostasis during excessive perspiration.[48]

The eccrine sweat gland is well vascularized at the level of the secretory gland and the coiled, straight and spiraled portions of the duct.[54,62]

2.2.5 The apocrine glands

Similarly to the eccrine sweat glands, apocrine glands are coiled secretory glands located in the lower part of the dermis or the hypodermis.[39] But while the former occur all over the body and independently of the hair follicle, in adults apocrine glands are found only in the axillae and perineal areas and are connected to hair follicles by a straight duct that empties into the infundibulum, just above the entrance of the sebaceous duct.[39] The composition of the product of apocrine glands is not precisely known, as it mixes with the product of eccrine sweat glands and sebaceous glands in the infundibulum. Apocrine glands in humans do not contribute to the thermal regulation of the body and their precise function is unknown.[10,39]

As in the case of the pilosebaceous units and eccrine sweat glands, apocrine glands are surrounded by an intricate network of blood vessels.[54]

2.3 Overview of the routes of skin penetration

The routes of permeation through the skin for foreign chemical substances are the transcellular and intercellular route through the stratum corneum, the follicular route and the eccrine sweat gland route (Fig. 2-1).[63,64] Being a mainly lipophilic membrane in nature, the stratum corneum is considered to be an especially efficacious barrier to the passive diffusion of hydrophilic compounds.[65] Similarly, due to the lipophilic nature of sebum, the hair follicle has the potential of being an effective conduit for the diffusion of lipophilic compounds and a barrier to the diffusion of hydrophilic substances.[10]

In recent years the existence of "polar" or "aqueous" pathways has been proposed and incorporated in some mathematical models of skin permeability.[29,66] Mitragotri writes that these "imperfections" in the stratum corneum lipid bilayers may "manifest themselves as separation of grain boundaries, lattice vacancies, multi-molecular voids due to missing lipids, or defects created by steric constraints placed by the keratinocytes on intercellular lipid bilayers", but adds that the existence of such "pores" has not been proven.[66]

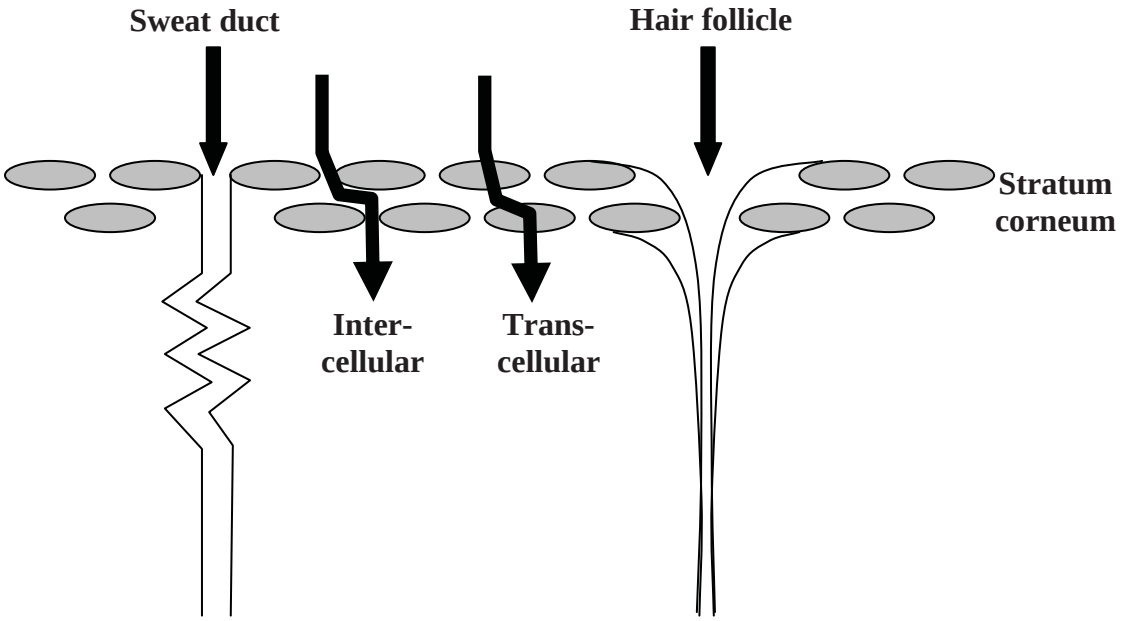


Figure 2-1: Schematic of the possible routes of penetration into human skin.

Part I

Diffusion In and Around a Hair Follicle

3 Literature Review

3.1 Theoretical studies

Scheuplein and coworkers were the first to propose a calculation of the relative importance of the follicular pathway to the transepidermal pathway across the stratum corneum and bulk skin.[11,12] They solved the boundary value problem describing transient diffusion through a membrane encompassing the epidermis and papillary dermis pierced by hair follicles and sweat glands in terms of the total amount of substance passing through the membrane. This analysis was based on a macroscopic description of tissue and appendageal pathways by effective diffusion coefficients (as opposed to a detailed geometrical micromodel as developed here). Penetration via the shunt pathway, characterized by higher nominal diffusion coefficients for the hair follicles and sweat glands then for bulk skin, was greater in the initial transient diffusion process, whereas at steady-state, penetration occurred predominantly across bulk skin. In addition, local concentration levels, expressed as the concentration in the tissue relative to that at the surface of the skin, can be significantly greater in the tissue surrounding the hair follicle than in the bulk tissue.[12]

Keister *et al*. fitted a 2-pathway transient diffusion model to experimental data for the diffusion of ibuprofen through human skin.[67] The skin was approximated as a homogeneous membrane. Two pathways through the skin, characterized by two different lag times (or diffusion coefficients) and two area fractions were postulated. The two-pathway model was fitted to data for the permeation of ionized ibuprofen through excised human skin and compared well to the experimental data, whereas a single-pathway did

not describe the data adequately. The authors' results showed that the shunt pathway accounts for 25% of the overall penetration through the skin at steady-state. A fast and a slow time scale were obtained from the fit, attributable to the shunt and skin pathways, respectively.

Edwards and Langer developed a 2-pathway model for transport across the stratum corneum by applying the theory of transport phenomena in porous media to the transport of charge, fluid-mass and solute across the stratum corneum and compared the theory predictions to existing experimental data.[29] In their model hair shafts are idealized as circular cylinders centered within cylindrical follicles. Five forms of transdermal transport were considered: forced mass convection, current flow, electroosmosis, iontophoresis and passive diffusion. The authors find that the shunt pathways play a dominant role in the case of forced convective mass, for which the hydraulic permeability of the shunt pathway is significantly larger than that of the transcorneocyte pathway. The intercellular/shunt is also important for large molecules in iontophoretic transport.

A mathematical model of skin permeability based on four permeation pathways in stratum corneum describing free-volume diffusion through lipid bilayers, lateral diffusion along lipid bilayers, diffusion through pores and diffusion through shunts (hair follicles and sweat ducts) has been proposed by Mitragotri.[66] Transport through shunts is modeled using a simple permeability model, in which the shunt contribution to the total skin permeability depends on the diffusion coefficient of the solute in the shunt estimated from the Wilke-Chang correlation or the Stokes-Einstein relationship, the length of the shunt and the area fraction of shunts available for diffusion. Mitragotri's results show that the dominant pathway for a permeating drug is a function of its molecular radius and

hydrophilicity. These results show that the shunt pathway plays an important role for large hydrophilic molecules.

More recently Ho proposed a probabilistic, 1-dimensional transient model of percutaneous absorption through three phases of the skin,[6] with the goal of assessing the relative importance of specific parameters and processes to the transport of chemicals through the skin. The model includes intercellular diffusion through the stratum corneum lipid phase, diffusion through sweat ducts and diffusion through hair follicles. Analytical solutions to Fick's law are used to describe the permeant concentration in each phase, the mass flux into the blood stream, and the cumulative amount of mass diffusing into the blood stream from each phase. The hair follicles and sweat ducts are represented as single-component oil and water phases, respectively. Both skin appendage phases are characterized by an effective diffusion coefficient, which depends on an oil phase (in the case of hair follicles) or aqueous-phase (in the case of sweat ducts) molecular diffusion coefficient, a tortuosity coefficient, the fractional area occupied by the appendages per unit area of the skin, and a retardation factor equal to the fractional area occupied by the appendages. The input parameters are stochastic variables. Distributions for each input parameter are calculated from values available in the literature. A Monte Carlo simulation is used to obtain a probabilistic distribution of results. The results show steady-state transport to be reached in the follicular phase in a median time of 24 min vs. 4 min in the sweat duct phase and 48 min in the stratum corneum phase. The mass flux into the bloodstream is greatest from stratum corneum and sweat duct phase at early times, and from the stratum corneum and hair follicles at steady-state. A sensitivity analysis shows the fixed aqueous concentration at the stratum corneum surface and the

thickness of the stratum corneum to be most important parameters in the transient and steady-state processes. At steady-state the next three most important parameters (the octanol-water partition coefficient, the oil molecular diffusion coefficient and the oil tortuosity coefficient) are associated with the follicular (oil) phase.

3.2 Experimental studies

In this section we review a small but representative subset of experimental studies published over the past 28 years which investigate the importance of the follicular pathway to percutaneous permeation. These papers are summarized in Table 3-1. They put forth evidence for the importance of the follicular pathway either by calculating permeability data or by visualizing the pathways of permeation, or in some cases, a combination of both.

Some of the experiments described below utilize excised animal skin, such as rat, hamster and mouse skin. Rodent skin differs from human in skin in important respects which must be kept in mind when considering these studies. Rodent skin possesses a hyperkeratinized stratum corneum, enlarged hair follicles and sebaceous glands, and frequently cysts are found in the epidermis, dermis and hair follicles.[9] Porcine skin is also used and is generally considered the best animal model for human skin.[68]

3.2.1 Calculation of permeability data

In 1988 Illel *et al*. compared the diffusion of labeled hydrocortisone through normal rat skin and appendage-free regrown rat skin.[69] The steady state flux and total diffusion at 24h through intact rat skin were 50 times greater than through appendage-free regrown

skin, indicating that the shunt pathway could be of significant importance during the first 24 h of diffusion at least.

Table 3-1. List of experimental studies (in order of publication date) pertaining to the role of hair follicles in percutaneous penetration reviewed in section 3.2.

AUTHORS	REF.	SKIN TYPE	DRUG	VEHICLES
Illel & Schaefer	69	Normal rat skin Appendage-free rat skin, *in vitro*	^{3}H-labeled hydrocortisone	Hydroalcoholic solution
Bamba & Wepierre	70	Normal rat skin Appendage-free rat skin, *in vitro*	^{14}C-labeled pirydostigmine	Ethanol DMSO 10% Nerol 8% Glycol 10% Azone 5%
Lauer *et al*.	71	Hairy rat skin Hairless rat skin, *in vivo*	Mannitol Progesterone	Aqueous, hydroalcoholic, non-ionic and phospholipid liposomal formulations
Wu *et al*.	15	Hairy mouse Hairless mouse Hairy rat skin, *in vitro*	Inulin	Water-in-oil nanoemulsions of various hydrophile-lipophile balances
Motwani *et al*.	72	Hamster skin, *in vitro*	Salicylic acid	Fatty and polar solutions, water-in-oil emulsions
Rolland *et al*.	14	Hairless rat skin, human skin, *in vitro* and *in vivo*	Adapalene in microspheres	Aqueous gels

Bernard *et al*.	73	Normal hairless rat skin, Induced scar hairless rat skin, *in vitro* and *in vivo*	Antiandrogen drug	Alcoholic solution, liposomes
Lieb *et al*.	74	Human scalp skin, *in vitro*	Oligonucleotides, rhodamine-labeled dextrans	Hydroalcoholic surfactant formulation, cationic lipid based formulation
Ogiso *et al*.	75	Human scalp skin, human abdominal skin, *in vitro*	Dyes: nile red, sodium fluorescin Drugs: melatonin, ketoprofen, fluorouracil, acyclovir	For drugs: alcoholic liquid formulations
Genina *et al*.	76	Human forearm and lower leg skin, *in vitro* and *in vivo*	Food dye indogo carmine, medical dye indocyanin green, phospholipid nanoemulsion	Various liquid formulations
Grams *et al*.	17	Human scalp skin, *in vitro*	Dye Bodipy® FL C_5	Citric acid buffer
Lademann *et al*.	16	Human volunteers, *in vivo*	Polymer nanoparticles labeled with 5-fluoresceinamine	Hydrogel formulation

Bamba and Wepierre confirmed these findings by comparing the diffusion of labeled pirydostigmine in various vehicles (ethanol, DMSO 10%, nerol 8%, propylene glycol 10% and azone 5%, all diluted in ethanol) through normal and appendage-free rat skin.[70] The relative importance of the transfollicular route to the transepidermal depended

on the vehicle. For all vehicles but nerol the follicular pathway was either the most important absorption route for the entire duration of the experiments (with ethanol, DMSO and PG in ethanol) or the most important pathway during the first hours of the experiments (with azone in ethanol). These results contradict Scheuplein's hypothesis that the transfollicular route is the major route only in the initial phases of diffusion. They indicate that with suitable formulation, the follicular pathway can play a much greater role.

Lauer *et al.* compared the permeation of mannitol (hydrophilic, non-ionic, very polar) to that of progesterone (very lipophilic) applied in aqueous, hydroalcoholic, non-ionic and phospholipid liposomal formulations in hairless and hairy rat skin.[71] The goal of this study was to compare both animal models, but the study also shed light on the possibility of hair follicles and sebaceous glands playing an important role in transdermal delivery. Hairy rat skin proved to be a more efficient barrier to the transport of mannitol to and through the skin than hairless rat skin provided no enhancers were used. The deposition of mannitol in hairy rat skin was only appreciable when the liposomal formulations were used. These results could be indicative of a follicular mechanism of delivery. Progesterone deposition was greater in hairless rat skin than in hairy rate skin, suggesting that non-follicular pathways may be the major route for lipophilic compounds, whereas the follicular pathway would be the preferred pathway for hydrophilic compounds. Hairy and hairless rat skins were pretreated with acetone to disrupt the sebaceous gland lipids while keeping the stratum corneum lipids intact. The deposition of progesterone in acetone pretreated skin was similar to that in untreated skin, whereas a large increase in mannitol deposition and systemic absorption was observed. Acetone

pretreatment may have facilitated the absorption of mannitol by providing a more hydrophilic compartment for transport, whereas the absorption of progesterone, which occurs mainly via partitioning into the stratum corneum lipids, is unaffected.

Wu *et al.* used hairy mouse skin to study the permeation of a model hydrophilic solute, inulin entrapped in water-in-oil nanoemulsions.[15] Water-in-oil nanoemulsions with lower hydrophile-lipophile balances (HLB), that is, with greater compatibility with the lipophilic environment of hair follicles yielded greater permeation values than nanoemulsions with greater HLB. The rates of transportation of two markers of vastly different molecular weights in the water-in-oil nanoemulsions were similar into and across the skin, leading the authors to believe that transport was dictated by the nanoemulsion itself and facilitated by the transfollicular pathway. An experiment comparing hairless mouse skin, hairy mouse and hairy rat skin yielded similar fluxes for the permeation of inulin in water-in-oil nanoemulsions across all three skin models, suggesting that the transfollicular pathway facilitated transport into the skin.

Motwani *et al*. studied the *in vitro* deposition of salicylic acid (SA) in fatty and polar vehicles into the sebaceous gland in hamster skin.[72] The intent of this work was to highlight the role of sebum, its compatibility with the permeant molecules and with the vehicle, in the transport of drugs to the hair follicles. Diffusion experiments conducted with various fatty and polar vehicles indicated that for fatty vehicles, the percent of applied dose of SA found in the sebaceous glands increases with the solubility of SA in the vehicle. The opposite trend was observed with the polar vehicles. The fatty vehicles appeared to be miscible with sebum, and thus an increase of solubility yielded greater delivery of the permeant to the sebaceous gland. In the case of polar vehicles, the

decrease in follicular delivery with increased solubility may be due to a partitioning effect. Motwani *et al*. also studied the delivery of SA into sebaceous glands using water-in-oil emulsions of SA in the same vehicles. When the oil phase was varied and the polar vehicle kept constant, the oil/water (o/w) emulsion delivered less SA to the follicle then the neat vehicle. It is argued that the water in the formulation, which makes up the continuous phase in contact with the skin, acts as a barrier to the follicular deposition of SA through the oil phase. Next, the oil phase was kept constant and the polar vehicle was varied. In most cases the o/w emulsions delivered more SA than the neat vehicles. This was attributed to the addition of the oil phase, which is miscible with sebum and assumed to increase SA delivery compared to the neat polar formulations from which the drug partitions into sebum. A third experiment was conducted to show that the oil phase affect follicular delivery to a higher degree than the polar or water phase of an emulsion. The delivery characteristics of a control emulsion consisting of an oil phase and water only was compared to emulsions consisting of additional polar vehicles. The addition of the polar vehicle increased the quantity of SA delivered in one case only. The authors assumed a synergistic effect between the oil phase and that polar vehicle. From this study Motwani *et al*. suggest that delivery to the sebaceous glands takes place via two main mechanisms, miscibility with sebum and partitioning from the vehicle into sebum, depending on the physico-chemistry of the drug and polarity of the vehicle.

3.2.2 Visualization of the follicular pathway

Rolland *et al*. were one of the early groups to investigate the use of microparticles in drug delivery. Adapalene, a drug used for the treatment of acne, was delivered to hairless rat

and human skin.[14] Aqueous gels containing adapalene-loaded microspheres were topically applied to hairless rat and human skin *in vitro*. The 5 μm microspheres were observed exclusively in the hair follicles. Penetration depth increased with time. 1 μm microspheres were distributed randomly in the stratum corneum and the hair follicles, and 20 μm microspheres did not penetrate the skin. An *in vitro* experiment in artificial sebum further indicated that the release of adapalene from the microspheres occurred in a much shorter time period than the release of sebum, which is 8 days in humans.[14] The *in vivo* application of an aqueous gel containing the 5 μm microspheres to the forearms of human volunteers yielded no irritation. The microspheres were visualized in the inner part of the hair shafts.

Bernard *et al*. studied the *in vitro* and *in vivo* permeation of an antiandrogen in normal hairless rat skin and scarred hairless rat skin lacking hair follicles and sebaceous glands. The vehicles used were an alcoholic solution and liposomes encapsulating the antiandrogen.[73] The *in vitro* experiment yielded a higher cumulative percentage of antiandrogen permeated through normal skin then through scarred with both vehicles. With the alcoholic solution the accumulation of the permeant in the stratum corneum and viable epidermis was significantly greater in normal skin, whereas the difference of permeant accumulated in the dermis was negligible. In the case of liposomes, the permeant accumulation in the stratum corneum and epidermis was similar in both skins, but the accumulation in the dermis was higher in normal skin. In the *in vivo* experiment, accumulation into the stratum corneum was greater with the alcoholic solution and the liposomes in the scarred skin, but accumulation was significantly higher in the viable epidermis and the dermis of the normal skin. The concentration distribution profiles

differed between both types of skin. Whereas in normal skin most of the permeant was found in the first 500 μm with a sharp decrease in concentration in the deep dermis, in scar skin the permeant concentration decreased at a depth of 40 μm in the epidermis and was negligible in the dermis. The ratio of normal skin concentration to scar skin concentration was greatest and for concentrations at a depth of 200-500 μm, corresponding approximately to the depth at which sebaceous glands are located. The ratio value obtained from the liposomal vehicles was 2 to 2.5 times greater than the ration obtained with the alcoholic solution. Bernard *et al*. used autoradiography to determine routes of penetration. 3 h after application in the alcoholic formulation, the antiandrogen was localized in the stratum corneum and viable epidermis, with diffused radioactivity measured in the sebaceous glands and the dermis. At greater times the radioactivity was more pronounced in the dermis and sebaceous glands. The radioactivity from liposome-delivered permeant was concentrated in the sebaceous glands 3 h after application with little in the viable epidermis and stratum corneum. The radioactivity measured in the sebaceous glands increased with time. These results show that the sebaceous route was the main pathway of permeation; it represented over 50% of the total absorption under all conditions. The antiandrogen favors localization in the stratum corneum when delivered in an alcoholic solution and in the sebaceous glands when encapsulated in liposomes.

In an often cited paper, Lieb *et al*. describe the visualization of *in vitro* deposition of oligonucleotides in formulations and low and high molecular weight rhodamine-labeled dextrans inside hair follicles of human scalp skin.[74] One oligonucleotide applied in a cationic lipid based formulation was visualized locally between the inner root sheath (IRS) and outer root sheath (ORS) of the hair follicle. A less negatively charged and more

hydrophilic oligonucleotide applied in an alcohol/surfactant formulation was observed at the IRS/ORS junction as well as at the level of the germinal components of the hair follicle. The lower molecular weight rhodamine permeated into the hair shaft, throughout the hair follicle and into the surrounding tissue. A similar pattern of permeation was observed for the higher molecular weight dextran. Overall, this study showed that the IRS/ORS junction could be a pathway for the permeation of larger molecules to the deeper parts of the hair follicle and into the surrounding tissue, and that pharmacologically active concentrations of high molecular weight compounds could be delivered to the deeper parts of the hair follicle.

Similar conclusions were reached by Ogiso and coworkers.[75] These researchers conducted studies on the diffusion of the lipophilic dye nile red and the hydrophilic dye sodium fluorescein in a liquid formulation through human scalp skin. After 3 h of application the lipophilic dye permeated into the IRS/ORS junction and into the dermis. After 6h the dye was visualized in the entire epidermis and at the IRS/ORS junction. For $t > 6$ h, a gradual decrease in the epidermis was observed, but the dye remained at the irs/ors junction. The authors concluded that diffusion into the dermis had occurred via the IRS/ORS junction. Similar observations for the permeation of the hydrophilic dye led to the conclusion that this compound had first permeated to the IRS/ORS junction, and then distributed into the dermis via the ORS. Ogiso *et al*. also compared the permeation of the lipophilic drugs melatonin (MT) and ketoprofen (KT) and of the hydrophilic drugs fluorouracil (5FU) and acyclovir (ACV) in scalp and abdominal skin. The fluxes of MT and 5FU were significantly higher (27 and 48 times, respectively) through scalp skin than through abdominal skin. The flux of KT was only 1.5 times higher through scalp skin, but

the lag time was about 3 times shorter, indicating that drugs, including hydrophilic ones, would penetrate the follicle-rich scalp skin more rapidly that abdominal skin. The drugs MT and ACV were also used to establish a good correlation between hair follicle density and flux through scalp skin.

Genina *et al*. are one of the few groups to have considered the hair follicle cycles in the study of permeation of chemicals to and through the hair follicle.[76] They studied the *in vivo* and *in vitro* diffusion of the food dye Indigo Carmine (IG) and of the medical dye Indocyanine Green (ICG) in forearm and lower leg skin at various stages of the follicular growth cycle. *In vivo* diffusion studies of ICG showed the dye present in the sebum of the hair canal (upper part of the infundibulum) of a telogen hair, as well as in the sebaceous gland and upper part of the club (hair shaft of a telogen hair). IC dyed the same areas of a telogen hair. ICG also stained the hair canal and sebaceous glands associated with anagen and catagen hairs. Overall the mean depth of dye penetration was larger in telogen and catagen hairs for ICG, IC and a third dye (Phospholipid Nanoemulsion with carbon nanoparticles) than in an anagen hair. This is explained by the absence of an IRS in a telogen hair follicle. As a hair club forms, the keratinized portion of the hair follicle increases and a gap between the hair shaft and the keratinized outer root sheath forms. The authors suggest that the region between the epidermal-dermal junction, opened to the skin surface, and the intraepidermal infundibulum is the path of dye penetration. Sebaceous glands serve as a reservoir for the dyes.

Grams *et al*. used an on-line diffusion cell setup combined with confocal laser scanning microscopy (CLMS) to follow the transient diffusion of the lipophilic dye Bodipy® FL C_5 (BFL) into a block of human scalp skin containing a hair follicle.[17] The

dye was shown to permeate to the deeper regions of the skin via the infundibulum. Initially the hair follicle cuticle and the upper infundibulum showed the fastest increase in fluorescence intensity. Below the epidermal-dermal junction the lower gap showed the fastest increase in fluorescence intensity. The sebum-filled infundibulum presented low resistance to the lipophilic dye. At early time points the dye diffused into the infundibulum and through the stratum corneum. From the infundibulum the dye penetrated into the deeper parts of the hair follicle, but the authors do not exclude the fact that the dye could have diffused from the infundibulum to the dermal tissue surrounding the hair follicle. Grams *et al*.'s experiment and results are discussed in greater detail in chapter 7, where we compare the model predictions for the diffusion of BFL near a hair follicle to these authors' results for the fluorescence intensity of the dye vs. time.

In an extension of this study, the authors showed that staining of the fat cells of the hypodermis began after 5 h of diffusion.[55] Beyond 5 h the autofluorescence-free areas of the sweat glands retained the dye.

Recently Lademann *et al*. showed that the hair follicles can act as a long-term reservoir for nanoparticles containing drugs.[16] Fluorescing particles in a hydrogel formulation were applied to human volunteers. The concentration of nanoparticles in the skin was determined by tape stripping. While 30 min after application the concentration of nanoparticles in the stratum corneum was about 8 times higher than in the hair follicles, they were stored for only 24 h in the stratum corneum but for up to 10 days in the hair follicles. The follicular reservoir is a long-term one, as depletion can only occur as a result of slow processes – penetration into the deeper dermis or outward flow with sebum.

4 Formulation of the Mathematical Model

4.1 Overview

The mathematical model describes the diffusion of a chemical substance applied topically from a donor compartment through whole skin and near a hair follicle. The viable epidermis, dermis and hypodermis are modeled as three distinct layers within which the concentration is determined as a function of the radial distance away from the hair follicle and depth into the skin. The dermis is subdivided into two layers, the dermis 1 and dermis 2, reflecting the presence of blood capillary loops in the upper part of the dermis (the papillary dermis), at the epidermal-dermal junction. The stratum corneum is modeled as an effective membrane, characterized by a steady-state permeability coefficient, separating the permeant donor solution and the viable epidermis.

Terminal hairs on the scalp of humans are in the anagen phase 80 to 90% of the time; vellus hairs on the forearm are in the anagen phase 30 to 50% of the time (Kasting GB. 2006. Personal communication). The mathematical model includes a geometrical representation of an anagen hair follicle, thus describing the predominant state in which hair follicle on the scalp are found and a significant state in which vellus hairs on other parts of the body are found. The outer root sheath cell layer is taken as the outer boundary of the hair follicle in contact with the skin layers. It is also modeled as an effective membrane. The model takes into account the presence of the sebaceous gland connected to the hair follicle by the sebaceous duct. Apocrine glands are not included in the model since these glands are less abundant in adult human skin than sebaceous glands.

4.2 The computational domain

Figure 4-1 shows the computational domain over which the permeant concentration is solved for. It is a 2-dimensional non-orthogonal curvilinear coordinate system fitted to the outer boundary of the hair follicle. The letter Ω denotes subregions of the computational domain, while boundaries are designated by the letter Γ .

The axial coordinate (*z*-axis) runs along the centerline of the hair follicle. The coordinate system is axis-symmetric with respect to the *z*-axis. In the *z*-direction the limits of the computational domain are at $z = 0$, denoting the stratum corneum/viable epidermis boundary $\Gamma_{sc/ve}$, and at a depth z_{min} located within a fictitious sublayer (subscript "sub") below the hypodermis. Proceeding from the stratum corneum/viable epidermis boundary in the direction of decreasing *z*, the subregions of the computational domain representing the skin layers are the viable epidermis (ve), the dermis 1 (de1), the dermis 2 (de2) and the hypodermis (hd). The horizontal boundaries separating the skin layers are denoted $\Gamma_{\alpha/\beta}$ with α = ve, β = de1; α = de1, β = de2 and α = de2, β = hd. For the purposes of the calculation a fictitious sublayer is included below the hypodermis; the horizontal boundary separating these two subregions is $\Gamma_{hd/sub}$.

The radial coordinate (*r*-axis) extends outwardly from the centerline of the hair follicle. The limits of the computational domain in the *r* direction are the boundary separating the hair follicle from the skin tissue, denoted $\Gamma_{ors/\alpha}$ in Figure 4-1, and a vertical boundary denoted Γ_{∞}, located at a radius r_{max} away from the centerline of the hair follicle. with α = ve, de1, de2 or hd. The boundary separating the hair follicle from the skin tissue within a given skin layer α is taken to be the outer wall of the hair follicle's outer

root sheath (ORS) whose shape is given by the function $r = f_{ors}(z)$. This function is obtained from a geometrical model of the hair follicle developed by Dr. Johannes M. Nitsche[77] and incorporated into our diffusion model. The geometrical model calculates the shape of the hair follicle cell layers based on input parameters for the diameter and length of the hair shaft. Figure 7-2 in section 7-2 shows the inner and outer walls of the outer root sheath and the outer wall of the cuticle of a hair shaft 4 mm in length and 50 μm in diameter.

The subregions representing the skin layers are divided into an "inner" region, close to the hair follicle, and an "outer" region, further away from it. The boundary separating the inner and outer regions, denoted $\Gamma_{inner/outer,\,\alpha}$ in Figure 4-1 and located at a radial distance $r_{inner/outer}(z)$ away from the centerline of the hair follicle, serves to separate the heavily vascularized region of the skin surrounding the hair follicle from the scarcely vascularized bulk tissue further away.

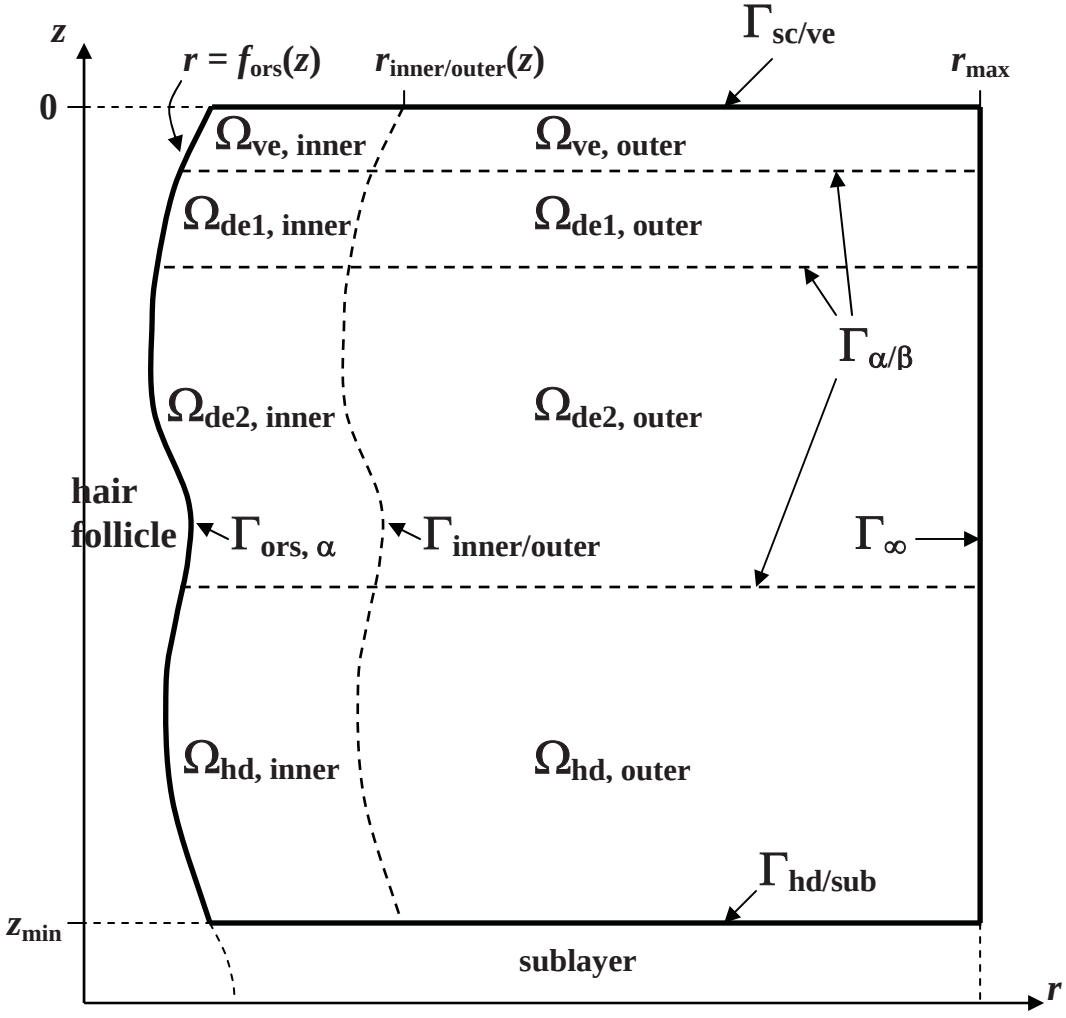


Figure 4-1: Schema of the computational domain over which the concentration of a topically applied dye diffusing into skin near a hair follicle is solved. The regions of the domain denoted by Ω are the inner and outer regions of the viable epidermis (ve), the dermis (de1 and de2) and the hypodermis (hd). The boundaries of the domain are denoted by Γ.

4.3 Physical processes modeled and relevant physico-chemical parameters

The physical processes modeled are:

- Diffusion of the permeant from the donor solution across the stratum corneum into the viable epidermis. The stratum corneum is modeled as an effective membrane characterized by a steady-state permeability coefficient $P_{sc/pH}$. The subscript refers to the fact that the permeability coefficient is defined for transport between compartments filled with reference solutions buffered at a specific pH [78] (see below).

- Molecular diffusion of the permeant across the skin layers. Each skin layer α is characterized by a permeant molecular diffusion coefficient D_α.

- Partitioning at the skin layer interfaces. Partitioning at the skin layer boundaries is described by an effective partition coefficient, also called distribution coefficient, $K_{\alpha/pH}$, which is the ratio of the permeant concentration in skin layer α and the permeant concentration in a reference solution buffered at a prescribed pH at equilibrium:

$$K_{\alpha/pH} = \frac{c_\alpha}{c_{pH}} \tag{1}$$

The concentrations in Eq. 1 refer to all forms of the permeant in the case of an ionizable compound. The corresponding diffusivity in phase α, D_α, is the average diffusivity of all forms of the permeant.

- Clearance due to the vasculature in the upper dermis (dermis 1) and surrounding the hair follicle in bulk dermis (dermis 2) and hypodermis. Clearance via the vasculature in the papillary dermis and in the dermis and hypodermis close to the hair follicle are characterized by a volumetric clearance coefficient k_α. Convective transport due to the blood vessels is not taken into account. Kretsos *et al*. have shown via the application of a distributed diffusion-clearance model to the *in vivo* penetration of salicylic acid into rat dermis that clearance due to vasculature does not "alter appreciably the effective diffusivity of the noncleared portion (…)".[78]

- Diffusion of the permeant from the infundibulum of the hair follicle across the outer root sheath, taken as the hair follicle outer boundary, into the surrounding tissue. Similarly to the stratum corneum, the outer root sheath of the hair follicle is modeled as a homogeneous membrane characterized by its steady-state permeability coefficient $P_{\text{ors/pH}}$.

4.4 Governing equations

The partial differential equation governing the transient transport of a given chemical substance through each subregion α, in the inner and outer regions of the skin is

$$\frac{\mathrm{d}c_\alpha(r,z)}{\mathrm{d}t} = D_\alpha(r,z)\nabla^2 c_\alpha(r,z) - k_\alpha(r,z)c_\alpha(r,z) \qquad (r,z)\in\Omega_{\text{inner},\alpha} \text{ and } (r,z)\in\Omega_{\text{outer},\alpha} \quad (2)$$

for α = ve, de1, de2 and hd. The right-hand-side of Eq. 2 expresses transport of the chemical substance through the skin via molecular diffusion (first term) and its clearance into the blood vessels making up the dermal vasculature (second term).

The boundary conditions in the axial direction describe transport of the chemical substance across the stratum corneum into the viable epidermis, and across the interfaces separating the skin layers. Eq. 3 describes transport from the topically applied donor solution ("ds") into the viable epidermis ("ve"):

$$\underline{\mathbf{n}}_{\mathbf{ve}} \cdot \left(- D_{\mathrm{ve}}(r,z) \underline{\nabla} c_{\mathrm{ve}}(r,z) \right) = P_{\mathrm{sc/pH}} \left(\frac{c_{\mathrm{ve}}(r,z)}{K_{\mathrm{ve/pH}}} - \frac{c_{\mathrm{ds}}(t)}{K_{\mathrm{ds/pH}}} \right) \qquad (r,z) \in \Gamma_{\mathrm{sc/ve}} \ \ (z=0) \qquad (3)$$

The flux into the viable epidermis (left-hand-side) is equal to the flux across the stratum corneum. The vector $\underline{\mathbf{n}}_{\mathbf{ve}}$ is the outward pointing normal to the domain representing the epidermis. The donor solution concentration c_{ds} (t) is a function of time in order to take into account the depletion of the donor solution. It is calculated in Appendix A from a mole balance on the system comprising the donor solution compartment, the infundibulum and the skin layers in contact with the infundibulum (viable epidermis, dermis 1 and dermis 2).

The boundary conditions for the transport of the permeant across the interfaces between two skin layers α and β on the interior of the domain express the equality of fluxes (Eq. 4) and partitioning equilibrium (Eq. 5) at the interface $\Gamma_{\alpha/\beta}$,

$$D_{\alpha}(r,z) \frac{\partial c_{\alpha}(r,z)}{\partial z} = D_{\beta}(r,z) \frac{\partial c_{\beta}(r,z)}{\partial z} \qquad (r,z) \in \Gamma_{\alpha/\beta} \qquad (4)$$

$$\frac{c_{\alpha}(r,z)}{K_{\alpha/\mathrm{pH}}} = \frac{c_{\beta}(r,z)}{K_{\beta/\mathrm{pH}}} \qquad (r,z) \in \Gamma_{\alpha/\beta} \qquad (5)$$

for α = ve, β = de1; α = de1, β = de2 and α = de2, β = hd.

The flux from the hypodermis into the fictitious sublayer below the hypodermis is calculated assuming the sublayer ("sub") to be a homogeneous membrane characterized by a permeability coefficient $P_{\mathrm{sub/pH}}$ and a drug partitioning coefficient $K_{\mathrm{sub/pH}}$:

$$\underline{\mathbf{n}}_{\mathbf{hd}} \cdot \left(-D_{\mathrm{hd}}(r,z)\underline{\nabla} c_{\mathrm{hd}}(r,z)\right) = P_{\mathrm{sub/pH}}\left(\frac{c_{\mathrm{hd}}(r,z)}{K_{\mathrm{hd/pH}}} - \frac{c_{\mathrm{sub}}}{K_{\mathrm{sub/pH}}}\right) \quad (r,z) \in \Gamma_{\mathrm{hd/sub}} \tag{6}$$

The vector $\underline{\mathbf{n}}_{\mathbf{hd}}$ is the outward pointing normal to the subregion representing the hypodermis. The concentration of the permeant in the sublayer is set to a constant value of zero. The permeability of the sublayer $P_{\mathrm{sub/pH}}$ is set equal to a very small value, 10^{-6}. The precise value of this permeability is not important since very little permeant reaches the bottom of the hypodermis.

In the radial direction the flux of permeant from the infundibulum of the hair follicle across the outer root sheath ("ors") into each skin region α is given by

$$\underline{\mathbf{n}}_{\mathbf{ors}} \cdot \left(-D_{\alpha}(r,z)\underline{\nabla} c_{\alpha}(r,z)\right) = P_{\mathrm{ors/pH}}\left(\frac{c_{\mathrm{sebum}}(z,t)}{K_{\mathrm{ors/pH}}} - \frac{c_{\alpha}(r,z)}{K_{\alpha\mathrm{/pH}}}\right) \quad (r,z) \in \Gamma_{\mathrm{ors}/\alpha} \tag{7}$$

for α = ve, de1, and de2. The permeant concentration in the sebum of the infundibulum is written as a function of depth z and time t. In the application of the mathematical model to the diffusion of the fluorescent dye Bodipy® FL C_5 (chapter 7), this concentration is indeed assumed to vary with depth inside the infundibulum and time. The estimation of the permeability of the outer root sheath $P_{\mathrm{ors/pH}}$ is discussed in section 7.3.

Across the boundary separating the inner region from the outer tissue region of skin layer α, equality of fluxes holds:

$$\underline{\mathbf{n}}_{\text{inner}} \cdot \left(-D_\alpha(r,z)\underline{\nabla} c_\alpha(r,z)\right)_{\text{inner}} = \underline{\mathbf{n}}_{\text{outer}} \cdot \left(-D_\alpha(r,z)\underline{\nabla} c_\alpha(r,z)\right)_{\text{outer}} \qquad \begin{matrix}(r,z)\in \Gamma_{\text{inner/outer}} \\ \left(r = r_{\text{inner/outer}}(z)\right)\end{matrix} \tag{8}$$

for α = ve, de1, de2 and hd.

Far from the hair follicle, at the radius $r_{\max}$, a no-flux boundary condition is used:

$$\frac{\partial c_\alpha(r,z)}{\partial r} = 0 \qquad (r,z)\in \Gamma_\infty \ \left(r = r_{\max}\right) \tag{9}$$

$\underline{\mathbf{n}}_{\mathbf{ors}}$, $\underline{\mathbf{n}}_{\mathbf{inner}}$ and $\underline{\mathbf{n}}_{\mathbf{outer}}$ are the outward pointing normal vectors to the hair follicle, the inner tissue region and the outer tissue region, respectively.

The inputs to the calculation are:

- The length and diameter of the hair shaft for the calculation of the function $r = f_{\text{ors}}(z)$. representing the shape of the outer wall of the hair follicle's outer root sheath.
- The diffusion coefficients D_α of the drug in each skin region α.
- The partition coefficient $K_{\alpha/\text{pH}}$ of the drug into each skin region α with respect to a reference solution buffered at a prescribed pH.
- The volumetric clearance rates k_α.
- The values of the permeability coefficients $P_{\text{sc/pH}}$, $P_{\text{ors/pH}}$ and $P_{\text{sub/pH}}$.

5 Numerical Calculation

5.1 Non-dimensionalization of the problem

The boundary-value problem (BVP) is inhomogeneous in the PDE and in the mixed boundary conditions and must be solved numerically. The first step in the numerical calculation is the non-dimensionalization of the dependent and independent variables. The characteristic variables are $L_0 = 100\,\mu\text{m}$ for length, $D_0 = 10^{-5}\,\text{cm}^2/\text{s}$ for the diffusion coefficient, and $c_0 = 0.1\,\text{mg}/\text{mL}$ for concentration. The characteristic volumetric clearance coefficient is $k_0 = D_0/L_0^2 = 0.1\,\text{s}^{-1}$ and the characteristic time is $t_0 = 10\,\text{s}$. The non-dimensional variables, denoted by a circumflex, are obtained from characteristic variables as follows:

$$\hat{r} = \frac{r}{L_0},\quad \hat{c} = \frac{c}{c_0},\quad \hat{D} = \frac{D}{D_0},\quad \hat{k} = \frac{k}{k_0} = \frac{k}{D_0/L_0^2},\quad \hat{t} = \frac{t}{t_0} = tk_0 \tag{10A-E}$$

5.2 Coordinate system transformation

The cylindrical coordinate system presented in section 4.2 is orthogonal, but the hair follicle's outer boundary does not correspond to any coordinate curve r = constant. We therefore introduce a non-orthogonal coordinate system using the transformation

$$\xi = \frac{\hat{r} - \hat{f}_{\text{ors}}(\hat{z})}{\hat{r}_{\max} - \hat{f}_{\text{ors}}(\hat{z})} \tag{11}$$

$$\zeta = \hat{z} \tag{12}$$

for the axial and radial coordinates respectively, for which the form of the hair follicle's outer boundary corresponds to the coordinate curve $\xi = 0$. While the axial coordinate transformation (Eq. 12) is a rescaling of the dimensional *z*-coordinate, the radial coordinate transformation (Eq. 11) involves a translation of the dimensional *r*-coordinate values followed by normalization by the difference between the maximum radius $r_{\max}$ and the radial coordinate value $\hat{r} = \hat{f}_{\text{ors}}(\hat{z})$ at the outer root sheath/skin tissue boundary for a given depth. Equations 2 to 9 in section 4.4 are non-dimensionalized and rewritten in terms of the dimensionless coordinates ξ and ζ using Eq. 11 and Eq. 12. Thus the governing PDE (Eq. 2) is

$$\begin{aligned}\frac{\partial \hat{c}_\alpha(\xi,\zeta)}{\partial \hat{t}} &= A_{10}\frac{\partial \hat{c}_\alpha(\xi,\zeta)}{\partial \xi} + A_{20}\frac{\partial^2 \hat{c}_\alpha(\xi,\zeta)}{\partial \xi^2} + A_{01}\frac{\partial \hat{c}_\alpha(\xi,\zeta)}{\partial \zeta} \\ &\quad + A_{02}\frac{\partial^2 \hat{c}_\alpha(\xi,\zeta)}{\partial \zeta^2} + A_{11}\frac{\partial^2 \hat{c}_\alpha(\xi,\zeta)}{\partial \xi \partial \zeta} + A_{00}\hat{c}_\alpha(\xi,\zeta)\end{aligned} \tag{13}$$

The values of the coefficients $A_{\text{kl}} = A_{\text{kl}}(\xi,\zeta)$ depend on the values of $\hat{r}_{\max}$, $\hat{f}_{\text{ors}}(\hat{z})$, $\hat{D}_\alpha = \hat{D}_\alpha(\xi,\zeta)$ and $\hat{k}_\alpha = \hat{k}_\alpha(\xi,\zeta)$. These coefficients are:

$$A_{10}(\xi,\zeta) = \frac{\hat{D}_\alpha}{\left\{\xi\left[\hat{r}_{\max} - \hat{f}_{\text{ors}}(\zeta)\right] + \hat{f}_{\text{ors}}(\zeta)\right\}\left[\hat{r}_{\max} - \hat{f}_{\text{ors}}(\zeta)\right]}$$

$$+ \frac{1}{\left[\hat{r}_{\max} - \hat{f}_{\text{ors}}(\zeta)\right]^2}\frac{\mathrm{d}\hat{D}_\alpha}{\mathrm{d}\xi} + \hat{D}_\alpha\left(\frac{\mathrm{d}^2\xi}{\mathrm{d}\zeta^2} + \frac{\mathrm{d}\xi}{\mathrm{d}\zeta}\frac{\mathrm{d}^2\xi}{\mathrm{d}\xi\mathrm{d}\zeta}\right) \tag{14}$$

$$A_{20}(\xi,\zeta) = \hat{D}_\alpha\left\{\frac{1}{\left[\hat{r}_{\max} - \hat{f}_{\text{ors}}(\zeta)\right]^2} + \left(\frac{\mathrm{d}\xi}{\mathrm{d}\zeta}\right)^2\right\} \tag{15}$$

$$A_{01}(\xi,\zeta)=\left(\frac{\mathrm{d}\hat{D}_{\alpha}}{\mathrm{d}\zeta}+\frac{\mathrm{d}\hat{D}_{\alpha}}{\mathrm{d}\xi}\frac{\mathrm{d}\xi}{\mathrm{d}\zeta}\right)\left(1+\frac{\mathrm{d}\xi}{\mathrm{d}\zeta}\right) \tag{16}$$

$$A_{02}(\xi,\zeta)=\hat{D}_{\alpha} \tag{17}$$

$$A_{11}(\xi,\zeta)=2\hat{D}_{\alpha}\frac{\mathrm{d}\xi}{\mathrm{d}\zeta} \tag{18}$$

$$A_{00}(\xi,\zeta)=\hat{k}_{\alpha} \tag{19}$$

Using Eqs. 10A-E, Eq. 11, and Eq. 12, the boundary conditions describing transport in the axial direction are re-written in terms of the ξ and ζ coordinates. At the stratum corneum/viable epidermis interface Eq. 3 becomes

$$\hat{D}_{\mathrm{ve}}\frac{\mathrm{d}\hat{c}_{\mathrm{ve}}(\hat{z})}{\mathrm{d}\hat{z}}=\hat{P}_{\mathrm{sc/pH}}\left(\frac{\hat{c}_{\mathrm{ve}}(\hat{z})}{K_{\mathrm{ve/pH}}}-\frac{\hat{c}_{\mathrm{ds}}(\hat{t})}{K_{\mathrm{ds/pH}}}\right)$$

$$\Rightarrow \hat{D}_{\mathrm{ve}}\left(\frac{\mathrm{d}\hat{c}_{\mathrm{ve}}(\zeta)}{\mathrm{d}\zeta}+\frac{\mathrm{d}\xi}{\mathrm{d}\zeta}\frac{\mathrm{d}\hat{c}_{\mathrm{ve}}(\zeta)}{\mathrm{d}\xi}\right)=\hat{P}_{\mathrm{sc/pH}}\left(\frac{\hat{c}_{\mathrm{ve}}(\zeta)}{K_{\mathrm{ve/pH}}}-\frac{\hat{c}_{\mathrm{ds}}(\hat{t})}{K_{\mathrm{ds/pH}}}\right) \tag{20}$$

At the interface between skin layers α and β, Eq. 4 yields

$$\hat{D}_{\alpha}\frac{\partial\hat{c}_{\alpha}(\hat{r},\hat{z})}{\partial\hat{z}}=\hat{D}_{\beta}\frac{\partial\hat{c}_{\beta}(\hat{r},\hat{z})}{\partial\hat{z}}$$

$$\Rightarrow \hat{D}_{\alpha}\left(\frac{\partial\hat{c}_{\alpha}(\xi,\zeta)}{\partial\zeta}+\frac{\mathrm{d}\xi}{\mathrm{d}\zeta}\frac{\partial\hat{c}_{\alpha}(\xi,\zeta)}{\partial\xi}\right)=\hat{D}_{\beta}\left(\frac{\partial\hat{c}_{\beta}(\xi,\zeta)}{\partial\zeta}+\frac{\mathrm{d}\xi}{\mathrm{d}\zeta}\frac{\partial\hat{c}_{\beta}(\xi,\zeta)}{\partial\xi}\right) \tag{21}$$

Eq. 5 becomes

$$\frac{\hat{c}_{\alpha}(\xi,\zeta)}{K_{\alpha/\mathrm{pH}}} = \frac{\hat{c}_{\beta}(\xi,\zeta)}{K_{\beta/\mathrm{pH}}} \tag{22}$$

At the hypodermis/sublayer interface Eq. 6 is re-written as

$$\hat{D}_{\mathrm{hd}} \frac{\mathrm{d}\hat{c}_{\mathrm{hd}}(\hat{z})}{\mathrm{d}\hat{z}} = -\hat{P}_{\mathrm{hd/sub}} \left(\frac{\hat{c}_{\mathrm{hd}}(\hat{z})}{K_{\mathrm{hd/pH}}} - \frac{\hat{c}_{\mathrm{sub}}}{K_{\mathrm{sub/pH}}} \right)$$

$$\Rightarrow \hat{D}_{\mathrm{hd}} \left(\frac{\mathrm{d}\hat{c}_{\mathrm{hd}}(\xi,\zeta)}{\mathrm{d}\zeta} + \frac{\mathrm{d}\xi}{\mathrm{d}\zeta} \frac{\mathrm{d}\hat{c}_{\mathrm{hd}}(\xi,\zeta)}{\mathrm{d}\xi} \right) = -\hat{P}_{\mathrm{hd/sub}} \left(\frac{\hat{c}_{\mathrm{hd}}(\xi,\zeta)}{K_{\mathrm{hd/pH}}} - \frac{\hat{c}_{\mathrm{sub}}}{K_{\mathrm{sub/pH}}} \right) \tag{23}$$

Similarly the boundary conditions describing transport in the radial direction are non-dimensionalized and re-written in terms of ξ and ζ using Eqs 11 and 12. At the outer root sheath/skin tissue boundary in any skin layer α, the boundary condition is now

$$-\hat{D}_{\alpha} \frac{1}{\sqrt{1+\left(\mathrm{d}\hat{f}_{\mathrm{ors}}(\hat{z})/\mathrm{d}\hat{z}\right)}} \left(\frac{\mathrm{d}\hat{c}_{\alpha}(\hat{r},\hat{z})}{\mathrm{d}\hat{r}} - \frac{\mathrm{d}\hat{f}_{\mathrm{ors}}(\hat{z})}{\mathrm{d}\hat{z}} \right) = \hat{P}_{\mathrm{ors/pH}}(\zeta) \left(\frac{\hat{c}_{\mathrm{ors}}(\hat{z})}{K_{\mathrm{ors/pH}}} - \frac{\hat{c}_{\alpha}(\hat{r},\hat{z})}{K_{\alpha/\mathrm{pH}}} \right)$$

$$\Rightarrow F_1(\zeta) \left(F_2(\zeta) \frac{\mathrm{d}\hat{c}_{\alpha}(\xi,\zeta)}{\mathrm{d}\xi} - \frac{\mathrm{d}\hat{f}(\zeta)}{\mathrm{d}\zeta} \frac{\mathrm{d}\hat{c}_{\alpha}(\xi,\zeta)}{\mathrm{d}\zeta} \right) = \hat{P}_{\mathrm{ors/pH}}(\zeta) \left(\frac{\hat{c}_{\mathrm{ors}}(\zeta)}{K_{\mathrm{ors/pH}}} - \frac{\hat{c}_{\alpha}(\xi,\zeta)}{K_{\alpha/\mathrm{pH}}} \right) \tag{24}$$

where the functions F_1 and F_2 are

$$F_1(\zeta) = \hat{D}_{\alpha} \frac{1}{\sqrt{1+\left(\mathrm{d}\hat{f}_{\mathrm{ors}}(\zeta)/\mathrm{d}\zeta\right)}} \tag{25}$$

$$F_2(\zeta) = \frac{1}{\hat{r}_{\max} - \hat{f}_{\mathrm{ors}}(\zeta)} - \frac{\mathrm{d}\hat{f}_{\mathrm{ors}}(\zeta)}{\mathrm{d}\zeta} \frac{\mathrm{d}\xi}{\mathrm{d}\zeta} \tag{26}$$

The boundary condition at the interface between the inner ("inner") and outer ("outer") tissue regions (Eq. 8) is

$$\frac{\hat{D}_{\alpha,\,\text{inner}}}{\sqrt{1+\left[\hat{f}_{\text{ors}}(\hat{z})\right]^2}}\left(\frac{\mathrm{d}\hat{c}_{\alpha,\,\text{inner}}(\hat{r},\hat{z})}{\mathrm{d}\hat{r}}-\hat{f}'_{\text{ors}}(\hat{z})\frac{\mathrm{d}\hat{c}_{\alpha,\,\text{inner}}(\hat{r},\hat{z})}{\mathrm{d}\hat{z}}\right)$$

$$=\frac{\hat{D}_{\alpha,\,\text{outer}}}{\sqrt{1+\left[\hat{f}_{\text{ors}}(\hat{z})\right]^2}}\left(\frac{\mathrm{d}\hat{c}_{\alpha,\,\text{outer}}(\hat{r},\hat{z})}{\mathrm{d}\hat{r}}-\hat{f}'_{\text{ors}}(\hat{z})\frac{\mathrm{d}\hat{c}_{\alpha,\,\text{outer}}(\hat{r},\hat{z})}{\mathrm{d}\hat{z}}\right)$$

$$\Rightarrow\ F_{3,\,\text{inner}}(\zeta)\left[F_{4,\,\text{inner}}(\xi,\zeta)\frac{\mathrm{d}\hat{c}_{\alpha,\,\text{inner}}(\xi,\zeta)}{\mathrm{d}\xi}-\frac{\mathrm{d}\hat{f}_{\text{ors}}(\zeta)}{\mathrm{d}\zeta}\frac{\mathrm{d}\hat{c}_{\alpha,\,\text{inner}}(\xi,\zeta)}{\mathrm{d}\zeta}\right]$$

$$=F_{3,\,\text{outer}}(\zeta)\left[F_{4,\,\text{outer}}(\xi,\zeta)\frac{\mathrm{d}\hat{c}_{\alpha,\,\text{outer}}(\xi,\zeta)}{\mathrm{d}\xi}-\frac{\mathrm{d}\hat{f}_{\text{ors}}(\zeta)}{\mathrm{d}\zeta}\frac{\mathrm{d}\hat{c}_{\alpha,\,\text{out}}(\xi,\zeta)}{\mathrm{d}\zeta}\right] \tag{27}$$

where

$$F_{3,\,\text{inner}}(\zeta)=\frac{\hat{D}_{\alpha,\,\text{inner}}}{\sqrt{1+\left[\hat{f}_{\text{ors}}(\zeta)\right]^2}} \tag{28}$$

$$F_{3,\,\text{outer}}(\zeta)=\frac{\hat{D}_{\alpha,\,\text{outer}}}{\sqrt{1+\left[\hat{f}_{\text{ors}}(\zeta)\right]^2}} \tag{29}$$

$$F_{4,\,\text{inner}}(\xi,\zeta)=\left[\frac{1}{\hat{r}_{\max}-\hat{f}_{\text{ors}}(\zeta)}-\frac{\mathrm{d}\hat{f}_{\text{ors}}(\zeta)}{\mathrm{d}\zeta}\frac{\mathrm{d}\xi}{\mathrm{d}\zeta}\right]_{\text{inner}} \tag{30}$$

$$F_{4,\,\text{outer}}(\xi,\zeta)=\left[\frac{1}{\hat{r}_{\max}-\hat{f}_{\text{ors}}(\zeta)}-\frac{\mathrm{d}\hat{f}_{\text{ors}}(\zeta)}{\mathrm{d}\zeta}\frac{\mathrm{d}\xi}{\mathrm{d}\zeta}\right]_{\text{outer}} \tag{31}$$

At the far right boundary at $\hat{r} = \hat{r}_{\max}$, the no-flux boundary (Eq. 9) in (ξ, ζ) coordinates is

$$\frac{\partial \hat{c}_{\alpha}(\xi, \zeta)}{\partial \xi} = 0 \tag{32}$$

From Eq. 11 the derivative $\mathrm{d}\xi/\mathrm{d}\zeta$ occurring in Eq. 26, Eq. 30, and 31 is

$$\frac{\mathrm{d}\xi}{\mathrm{d}\zeta} = \frac{\mathrm{d}\hat{f}_{\mathrm{ors}}(\zeta)}{\mathrm{d}\zeta}\left(\frac{\xi - 1}{\hat{r}_{\max} - \hat{f}_{\mathrm{ors}}(\zeta)}\right) \tag{33}$$

5.3 Computational mesh

The BVP is solved numerically at the nodes of a computational mesh representing the domain of solution described in section 4.2. The nodes are described by the coordinate pairs $(\xi_{\mathrm{i}}, \zeta_{\mathrm{j}})$. The input mesh parameters for the calculation of the $(\xi_{\mathrm{i}}, \zeta_{\mathrm{j}})$ coordinates in the inner and outer regions of each skin layer α are:

- The number of nodes in the inner and outer region of each skin layer, $\mathrm{i}_{\alpha,\mathrm{inner}}$, $\mathrm{i}_{\alpha,\mathrm{outer}}$, for α = ve, de1, de2, hd.

- The value of the radial coordinate $\xi_{\mathrm{i}=\mathrm{i}_{\mathrm{inner/outer}}}$ at the inner/outer region boundary at the stratum corneum/viable epidermis boundary.

- The number of nodes in each skin layer in the axial direction, j_{α}, for α = ve, de1, de2, hd.

- The dimensionless thickness in the axial direction of each skin layer α: $\hat{h}_{\alpha}^{\zeta}$, for α = ve, de1, de2, hd.

The dimensionless step sizes in the inner and outer regions of each skin layer, $\hat{s}^{\xi}_{\alpha,\,\text{inner}}$ and $\hat{s}^{\xi}_{\alpha,\,\text{outer}}$, are calculated from the $\xi_{i=i_{\text{inner/outer}}}$ coordinate and the number of nodes in the inner and outer regions:

$$\hat{s}^{\xi}_{\alpha,\,\text{inner}} = \frac{\xi_{i=i_{\text{inner/outer}}}}{i_{\alpha,\,\text{inner}}} \tag{34}$$

$$\hat{s}^{\xi}_{\alpha,\,\text{outer}} = \frac{1-\xi_{i=i_{\text{inner/outer}}}}{i_{\alpha,\,\text{outer}}} \tag{35}$$

The ξ_i coordinates in the inner and outer regions are calculated from

$$\xi_i = \hat{s}^{\xi}_{\alpha,\,\text{inner}} \cdot i \qquad \forall\, i \in \left[0,\, i_{\alpha,\,\text{inner}}\right] \tag{36}$$

and

$$\xi_i = \xi_{i=i_{in}} + \hat{s}^{\xi}_{\alpha,\,\text{outer}} \cdot \left(i - i_{\alpha,\,\text{inner}}\right) \qquad \forall\; i \in \left[i_{\alpha,\,\text{inner}}+1,\, i_{\alpha,\,\text{inner}}+i_{\alpha,\,\text{outer}}\right] \tag{37}$$

The dimensionless step size of each skin layer α in the axial direction is calculated from that skin layer's dimensionless thickness $\hat{h}^{\zeta}_{\alpha}$ and the number of nodes j_α:

$$\hat{s}^{\zeta}_{\alpha} = \frac{\hat{h}^{\zeta}_{\alpha}}{j_\alpha} \tag{38}$$

for α = "ve", "de1", "de2", "hd". The ζ_j coordinates in the skin layers α are calculated from

$$\zeta_j = \zeta_{j=j_{\alpha,\,\text{top}}} + \hat{h}^{\zeta}_{\alpha} \cdot \left(j_{\alpha,\,\text{top}} - j\right) \qquad \forall\, j \in \left[j_{\alpha,\,\text{top}},\, j_{\alpha,\,\text{bottom}}\right] \tag{39}$$

where $j_{\alpha,top}$ and $j_{\alpha,bottom}$ denote the indices for the top and bottom surfaces of skin layer α. The indices $j_{\alpha,top}$ and $j_{\alpha,bottom}$ are defined by the number of nodes j_α in the axial direction in skin layer α. They are

- in the viable epidermis: $j_{ve,top} = 0$; $j_{ve,bottom} = j_{ve}$
- in dermis 1: $j_{de1,top} = j_{ve}$; $j_{de1,bottom} = j_{ve} + j_{de1}$.
- in dermis 2: $j_{de2,top} = j_{ve} + j_{de1}$; $j_{de2,bottom} = j_{ve} + j_{de1} + j_{de2}$.
- in the hypodermis: $j_{hd,top} = j_{ve} + j_{de1} + j_{de2}$; $j_{hd,bottom} = j_{ve} + j_{de1} + j_{de2} + j_{hd}$.

Figure 5-1 shows the computational mesh generated for the values of the input mesh parameters given in Tables 5-1 and 5-2.

Table 5-1: Values of input mesh parameters for the calculation of the radial nodes of the computational mesh shown in Figure 5-1.

$i_{\alpha,\,inner}$	$i_{\alpha,\,outer}$	$\xi_{i=i_{inner/outer}}$	$\hat{r}_{max}$
10	20	0.0224	50

Table 5-2: Values of input mesh parameters for the calculation of the axial nodes of the computational mesh shown in Figure 5-1.

j_{ve}	j_{de1}	j_{de2}	j_{hd}	$\hat{h}^{\zeta}_{ve}$	$\hat{h}^{\zeta}_{de1}$	$\hat{h}^{\zeta}_{de2}$	$\hat{h}^{\zeta}_{de2}$	$\hat{h}^{\zeta}_{hd}$
10	10	40	40	30	1.0	2.0	17	30

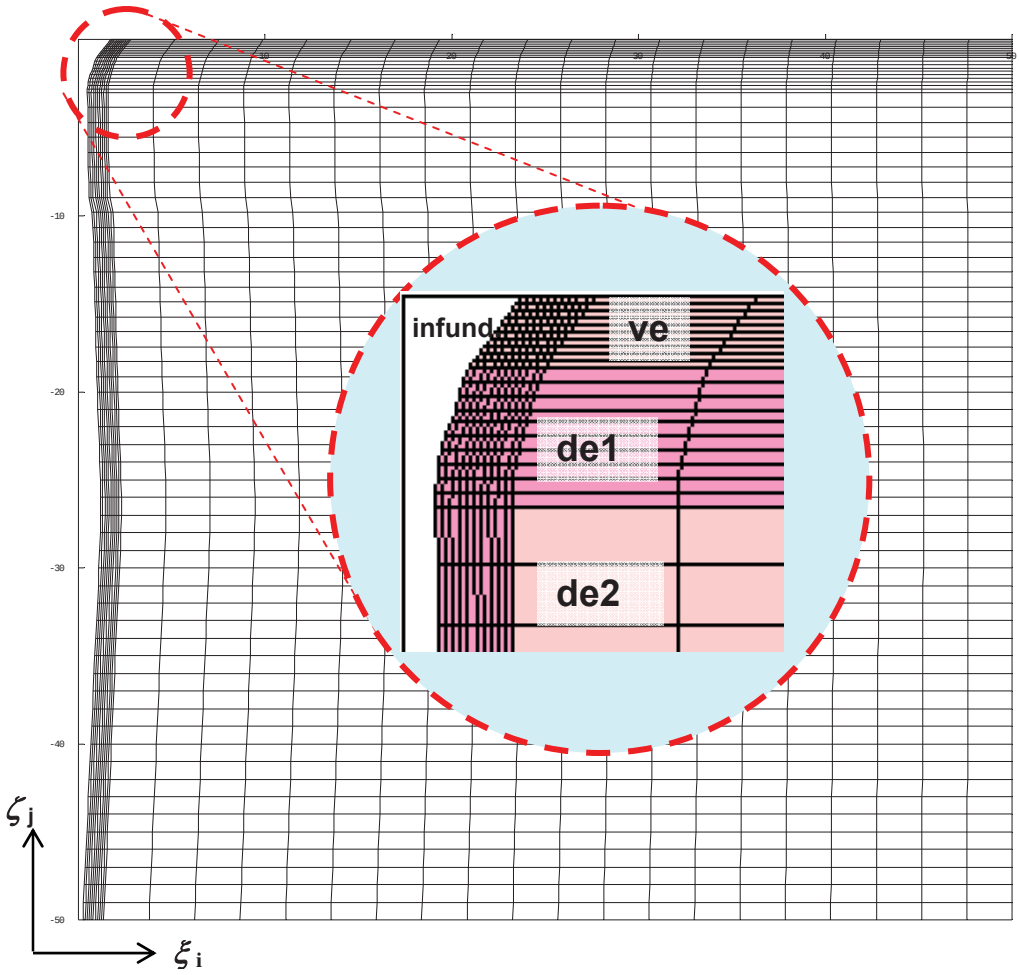


Figure 5-1: Mesh used for the discretization of the computational domain. Inset: viable epidermis (ve), dermis 1 (de1), dermis 2 (de2) and infundibulum (infund) of the hair follicle). The input mesh parameters are given in Tables 5-1 and 5-2.

The computational mesh shown in Figure 5-1 is used in the application of the mathematical model to the diffusion of the dye Bodipy FL® C_5 in the skin (Chapter 7). The input parameters are chosen such that the mesh is finer in the viable epidermis and dermis 1, as well as in the inner region of the computational domain, in order to obtain better resolution close to the surface of the skin (viable epidermis) and at the location of blood vessels (dermis 1 and inner region). The inset in Figure 5-1 clearly shows the shape

of the outer root sheath of the hair follicle taken as its outer boundary at the level of the infundibulum.

5.4 Discretization of the BVP

5.4.1 Discretization of the governing PDE

The dimensionless boundary-value problem is solved numerically by discretizing the derivatives of the PDE and boundary conditions using Finite Difference (FD) formulae. The FD formulae relevant to this calculation are derived in Appendix B.

The 1st and 2nd order spatial derivatives in Eq. 13 are approximated by $O\left(\left(\hat{s}_\alpha^\zeta\right)^2\right)$ and $O\left(\left(\hat{s}_\alpha^\xi\right)^2\right)$ central difference formulae (Eqs. B5, B6, B7). Time stepping is achieved using the explicit Euler method. The time derivative is replaced by an $O\left(\Delta\hat{t}\right)$ forward difference approximation (Eq. B3). Substituting the concentration value $\hat{c}_\alpha\left(\xi_\mathrm{i},\zeta_\mathrm{j}\right)$ at time $\hat{t}$ by $\hat{c}^{\hat{t}}_{\alpha;\mathrm{i,j}}$, the discretized version of Eq. 13 is

$$\begin{aligned}\frac{\hat{c}^{\hat{t}+\Delta\hat{t}}_{\alpha;\mathrm{i,j}}-\hat{c}^{\hat{t}}_{\alpha;\mathrm{i,j}}}{\Delta\hat{t}} &= A_{10}\,\frac{\hat{c}^{\hat{t}}_{\alpha;\mathrm{i+1,j}}-\hat{c}^{\hat{t}}_{\alpha;\mathrm{i-1,j}}}{2\hat{s}_\alpha^\xi}+A_{20}\,\frac{\hat{c}^{\hat{t}}_{\alpha;\mathrm{i+1,j}}-2\hat{c}^{\hat{t}}_{\alpha;\mathrm{i,j}}+\hat{c}^{\hat{t}}_{\alpha;\mathrm{i-1,j}}}{\left(\hat{s}_\alpha^\xi\right)^2}+A_{01}\,\frac{\hat{c}^{\hat{t}}_{\alpha;\mathrm{i,j-1}}-\hat{c}^{\hat{t}}_{\alpha;\mathrm{i,j+1}}}{2\hat{s}_\alpha^\zeta}\\ &+A_{02}\,\frac{\hat{c}^{\hat{t}}_{\alpha;\mathrm{i,j-1}}-2\hat{c}^{\hat{t}}_{\alpha;\mathrm{i,j}}+\hat{c}^{\hat{t}}_{\alpha;\mathrm{i,j+1}}}{\left(\hat{s}_\alpha^\zeta\right)^2}+A_{11}\,\frac{\hat{c}^{\hat{t}}_{\alpha;\mathrm{i-1,j+1}}-\hat{c}^{\hat{t}}_{\alpha;\mathrm{i-1,j-1}}-\hat{c}^{\hat{t}}_{\alpha;\mathrm{i+1,j+1}}+\hat{c}^{\hat{t}}_{\alpha;\mathrm{i+1,j-1}}}{4\hat{s}_\alpha^\xi\hat{s}_\alpha^\zeta}\\ &+A_{00}\,\hat{c}^{\hat{t}}_{\alpha;\mathrm{i,j}}\end{aligned} \tag{40}$$

Using the nabla operator Eq. 40 can be rewritten as:

$$\hat{c}^{\hat{t}+\Delta\hat{t}}_{\alpha;\mathrm{i,j}}=\hat{c}^{\hat{t}}_{\alpha;\mathrm{i,j}}+\Delta\hat{t}\left(\hat{\nabla}^2_{\mathrm{i,j}}\,\hat{c}^{\hat{t}}_{\alpha;\mathrm{i,j}}-A_{00}\hat{c}^{\alpha,\hat{t}}_{\mathrm{i,j}}\right) \tag{41}$$

yielding the concentration at time $\hat{t} + \Delta\hat{t}$ as a function of the concentration at the previous time step $\hat{t}$.

5.4.2 Discretization of the boundary conditions

The derivatives of the boundary conditions are discretized using various $O\left(\left(\hat{s}_\alpha^\zeta\right)^4\right)$ and $O\left(\left(\hat{s}_\alpha^\xi\right)^4\right)$ FD approximation formulae. The choice of the FD formulae depends on whether the boundary is a horizontal or a vertical boundary and on the location of the nodes on each boundary.

In the FORTRAN program implementing the solution of the BVP (Appendix E), the concentrations at the interior nodes of the computational domain are calculated first, at a given time $\hat{t}$, from Eq. 41 (section 5.5 provides details on the structure of the FORTRAN program). Following this the concentration values at the boundaries of each one of the 8 computational subregions (the inner and outer regions of the viable epidermis, the dermis 1, the dermis 2, and the hypodermis) are calculated using the concentration values obtained on the interior of each subdomain.

On each boundary the concentration values at the interior nodes of the boundary are calculated first, followed by the boundary nodes located between the interior boundary nodes and the corner nodes, followed by the corner nodes linking two boundaries.

5.4.3 Horizontal boundaries

On the boundaries parallel to the ξ-axis (at $j = 0$, $j = j_{ve}$, $j = j_{ve} + j_{de1}$, $j = j_{ve} + j_{de1} + j_{de2}$, $j = j_{ve} + j_{de1} + j_{de2} + j_{hd}$) describing transport in the ζ direction, the interior nodes, denoted by "A" in Figure 5-2, include the (ξ_i, ζ_j) nodes for which $2 \le i \le i_{in} - 2$ in the "inner" region and $i_{in} + 2 \le i \le i_{in} + i_{out} - 2$ in the "outer" region. The pair of nodes on either side of the interior boundary nodes of a horizontal boundary, for which

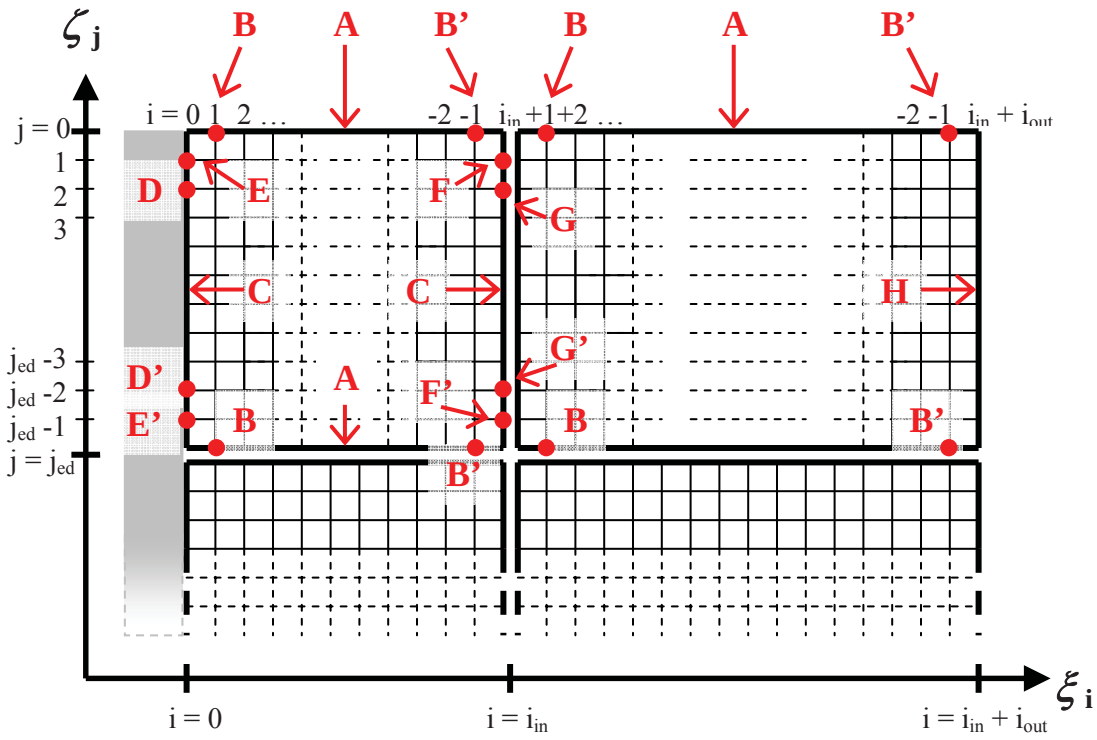


Figure 5-2: Schema of the orthogonal computational mesh in (ξ,ζ) coordinates over which the problem of diffusion through the skin near a hair follicle is solved. Letters assigned to representative interior and boundary nodes of the inner and outer regions of the viable epidermis skin layer indicate the type of finite difference formula used to solve for the permeant concentration at these nodes (see sections 5.4.3 and 5.4.4).

$i = 1$ or $i = i_{in} - 1$ in the "inner" region and $i = i_{in} + 1$ or $i_{in} + i_{out} - 1$ in the "outer" region are denoted by "B" and "B' ", respectively.

The $\partial \hat{c}_\alpha / \partial \zeta$ and $\partial \hat{c}_\beta / \partial \zeta$ derivatives of the horizontal boundary conditions (Eqs. 20, 21, and 23) at the interior boundary nodes are calculated using a one-sided $O\left(\left(\hat{s}_\alpha^\zeta\right)^4\right)$ forward FD formula (Eq. B13) if the α or β skin region is located below the boundary under consideration and using a one-sided $O\left(\left(\hat{s}_\alpha^\zeta\right)^4\right)$ backward FD formula (Eq. B14) if the α or β skin region is located above the boundary. The $\partial \hat{c}_\alpha / \partial \xi$ and $\partial \hat{c}_\beta / \partial \xi$ derivatives at the interior nodes of these boundary conditions are approximated by $O\left(h_\xi^4\right)$ central FD formulae (Eq. B10).

At the nodes located one position away from the corners of the ζ-direction boundaries (nodes "B", "B' ", Fig. 5-2), the $\partial \hat{c}_\alpha / \partial \zeta$ and $\partial \hat{c}_\beta / \partial \zeta$ derivatives are approximated by $O\left(\left(\hat{s}_\alpha^\zeta\right)^4\right)$ one-sided forward and backward difference formulae. The $\partial \hat{c}_\alpha / \partial \xi$ and $\partial \hat{c}_\beta / \partial \xi$ derivatives are approximated using $O\left(\left(\hat{s}_\alpha^\xi\right)^4\right)$ semi-1-sided forward or backward FD formulae (Eqs. B15, B16), depending on whether the node is to the left or to the right of the interior nodes on the boundary in question.

5.4.4 Vertical boundaries

On the boundaries parallel to the ζ-axis (at $i = 0$, $i = i_{in}$, $i = i_{in} + i_{out}$), the interior boundary nodes (nodes "C" in Fig. 5-2) include the (ξ_i, ζ_j) nodes for which $3 \le j \le j_{ve} - 3$ in the epidermis, $3 \le j \le j_{ve} + j_{de1} - 3$ in the dermis 1, $3 \le j \le j_{ve} + j_{de1} + j_{de2} - 3$ in the dermis 2 and $3 \le j \le j_{ve} + j_{de1} + j_{de2} + j_{hd} - 3$ in the hypodermis. The nodes denoted "E" and "E' "

are on the hair follicle boundary (i = 0) in each skin layer, one node below the above-lying horizontal boundary and one node above the lower-lying horizontal boundary. Nodes "F" and "F' " have the j indices as nodes "E" and "E' " but are located on the inner tissue / outer tissue boundary ($i = i_{in}$). Nodes "D" and "G" are just below nodes "E" and "F" and nodes "D' " and "G' " are just above nodes "E' " and "F' ". "H" denotes the interior nodes of the boundary at $\hat{r} = \hat{r}_{max}$ which consist of all nodes on that boundary except the corner nodes.

The derivatives of the vertical boundary conditions (Eqs. 24, 33, 32) are approximated in a similar way to the derivatives of the horizontal boundary conditions. The concentration values at the interior nodes "C" are calculated first from the concentration values at the nodes on the interior of the computational domain using $O\left(\left(\hat{s}_\alpha^\xi\right)^4\right)$ one-sided forward approximations (Eq. B13) for the $\partial\hat{c}_\alpha/\partial\xi$ (Eqs. 24, 32), $\partial\hat{c}_{\alpha,\,in}/\partial\xi$ (Eq. 24) and $\partial\hat{c}_{\alpha,\,out}/\partial\xi$ (Eq. 24) derivatives, if the boundary in question is to the left of the computational subdomain and $O\left(\left(\hat{s}_\alpha^\xi\right)^4\right)$ one-sided backward approximations (Eq. B14) if the boundary is to the right of the subdomain. The $\partial\hat{c}_\alpha/\partial\zeta$, $\partial\hat{c}_{\alpha,\,in}/\partial\zeta$ and $\partial\hat{c}_{\alpha,\,out}/\partial\zeta$ derivatives are evaluated using $O\left(h_\zeta^4\right)$ central difference formulae (Eq. B10). At the $\hat{r} = \hat{r}_{max}$ boundary, the derivative $\partial\hat{c}_\alpha/\partial\xi$ (Eq. 32) at all "H" nodes is calculated using a 1-sided $O\left(h_\xi^4\right)$ backward formula (Eq. B14).

The $\partial\hat{c}_\alpha/\partial\xi$, $\partial\hat{c}_{\alpha,\,in}/\partial\xi$ and $\partial\hat{c}_{\alpha,\,out}/\partial\xi$ derivatives at the "D", "D' ", "G" and "G"" nodes are approximated by $O\left(h_\xi^4\right)$ 1-sided forward or backward formulae, depending on whether the "inner" and "outer" computational domain is to the right or to

the left of the boundary in question. The $\partial \hat{c}_\alpha / \partial \zeta$, $\partial \hat{c}_{\alpha,\text{in}} / \partial \zeta$ and $\partial \hat{c}_{\alpha,\text{out}} / \partial \zeta$ derivatives at these nodes are replaced by $O\left(\left(\hat{s}_\alpha^\zeta\right)^4\right)$ semi-1-sided backward formulae (Eq. B16) if the node is near the top of the boundary and $O\left(\left(\hat{s}_\alpha^\zeta\right)^4\right)$ semi-1-sided forward formulae (Eq. B15) if the node is near the bottom of the boundary. The $\partial \hat{c}_\alpha / \partial \xi$, $\partial \hat{c}_{\alpha,\text{in}} / \partial \xi$ and $\partial \hat{c}_{\alpha,\text{out}} / \partial \zeta$ derivatives at the "E", "E' ", "F" and "F' " nodes are approximated by $O\left(\left(\hat{s}_\alpha^\xi\right)^4\right)$ 1-sided forward or backwards formulae, depending on whether the "inner" and "outer" computational domain is to the right or to the left of the boundary in question. The $\partial \hat{c}_\alpha / \partial \zeta$, $\partial \hat{c}_{\alpha,\text{in}} / \partial \zeta$ and $\partial \hat{c}_{\alpha,\text{out}} / \partial \zeta$ derivatives are evaluated using $O\left(\left(\hat{s}_\alpha^\xi\right)^4\right)$ backward formulae if the node is near the top of the boundary, and forward formulae if it is near the bottom of the boundary.

5.4.5 Corner nodes

The concentration values at the corner nodes are the last boundary nodes to be computed. The corner nodes are taken as being part of the horizontal boundaries on which they lie and the concentration values at these nodes are calculated using the horizontal boundary conditions. The $\partial \hat{c}_\alpha / \partial \zeta$, $\partial \hat{c}_\beta / \partial \zeta$, $\partial \hat{c}_\alpha / \partial \xi$, and $\partial \hat{c}_\beta / \partial \xi$ derivatives are approximated by either 1-sided forward or backward FD formulae.

5.5 Implementation of the non-dimensional problem in FORTRAN

The FORTRAN program (Appendix E) is highly modular in that each component of the calculation explained in chapter 5 is implemented in a separate subroutine. The first step is the calculation of the non-dimensional (ξ_i, ζ_j) coordinates (subroutine "xizetavalues", Appendix E, p. 236). The inputs to this calculation are the step sizes in the ξ and ζ direction, the number of nodes in the viable epidermis, dermis 1 and 2 and the hypodermis, and the value of $\hat{r}_{max}$. The values of the (ξ_i, ζ_j) coordinates and of the diffusion coefficients in each skin layer are used to calculate the derivative coefficients $A_{kl}(\xi_i, \zeta_j)$ (Eqs. 14-19). The initial donor solution concentration and the concentration values at each node of the computational mesh are set in a separate subroutine. Time stepping occurs within another subroutine called "step" (p. 276). Subroutine "step" updates the value of $\hat{t}$ to $\hat{t} + \Delta\hat{t}$, calls a subroutine named "laplacianapprox" (p. 251) which evaluates the Laplacian of concentration from FD approximation formulae for the concentration derivatives (Eq. 40) at time $\hat{t} + \Delta\hat{t}$. Subroutine "step" then calculates the concentration on the interior nodes of the each skin layer subdomain at time $\hat{t} + \Delta\hat{t}$ using the concentration values at time $\hat{t}$ (Eq. 41) and updates the boundary concentration values. A separate subroutine "donorsolconc" (p. 344) then updates the donor solution concentration, before a return to subroutine "step".

The concentration at the horizontal boundaries (Eqs. 20, 21. 23) at time $\hat{t} + \Delta\hat{t}$ is evaluated by making use of a temporary array of concentrations, $\left[\hat{c}_\alpha^{\hat{t}+\Delta\hat{t}}(\xi_i)\right]_{temp}$, which contains the concentration values at the closest node of the interior domain:

$\left[\hat{c}_\alpha^{\hat{t}+\Delta\hat{t}}\left(\xi_i\right)\right]_{temp} = \hat{c}_\alpha^{\hat{t}+\Delta\hat{t}}\left(\xi_i, \zeta_{j+1}\right)$. Updated values of temporary boundary concentrations $\left[\hat{c}_\alpha^{\hat{t}+\Delta\hat{t}}\left(\xi_i\right)\right]_{temp,\,new}$ are calculated from $\left[\hat{c}_\alpha^{\hat{t}+\Delta\hat{t}}\left(\xi_i\right)\right]_{temp}$ and the concentration values of the other surrounding nodes using the FD approximations detailed in section 5.4.3. The difference $temp = \left| \left[\hat{c}_\alpha^{\hat{t}+\Delta\hat{t}}\left(\xi_i\right)\right]_{temp,\,new} - \left[\hat{c}_\alpha^{\hat{t}+\Delta\hat{t}}\left(\xi_i\right)\right]_{temp} \right|$ is compared to a maximum difference variable *maxdiff* initially set to 0. The updated concentration at the boundary node in question is $\hat{c}_\alpha^{\hat{t}+\Delta\hat{t}}\left(\xi_i, \zeta_j\right) = \left[\hat{c}_\alpha^{\hat{t}+\Delta\hat{t}}\left(\xi_i\right)\right]_{temp,\,new}$ if *temp* < *maxdiff*. If *temp* > *maxdiff*, *maxdiff* is set equal to *temp* and compared to a tolerance value $\tau = 10^{-12}$. For *maxdiff* < τ, the concentration at the boundary node is $\hat{c}_\alpha^{\hat{t}+\Delta\hat{t}}\left(\xi_i, \zeta_j\right) = \left[\hat{c}_\alpha^{\hat{t}+\Delta\hat{t}}\left(\xi_i\right)\right]_{temp,\,new}$. For *maxdiff* > τ, $\left[\hat{c}_\alpha^{\hat{t}+\Delta\hat{t}}\left(\xi_i\right)\right]_{temp}$ is set equal to $\left[\hat{c}_\alpha^{\hat{t}+\Delta\hat{t}}\left(\xi_i\right)\right]_{temp,\,new}$ and a new $\left[\hat{c}_\alpha^{\hat{t}+\Delta\hat{t}}\left(\xi_i\right)\right]_{temp,\,new}$ is calculated recurrently until *temp* < *maxdiff* or *maxdiff* < τ. The algorithm is summarized below:

Step 1: on the horizontal boundaries, for all *i*: $\left[\hat{c}_\alpha^{\hat{t}+\Delta\hat{t}}\left(\xi_i\right)\right]_{temp} = \hat{c}_\alpha^{\hat{t}+\Delta\hat{t}}\left(\xi_i, \zeta_{j+1}\right)$

Step 2: for all *i*, calculate $\left[\hat{c}_\alpha^{\hat{t}+\Delta\hat{t}}\left(\xi_i\right)\right]_{temp,\,new}$ from $\left[\hat{c}_\alpha^{\hat{t}+\Delta\hat{t}}\left(\xi_i\right)\right]_{temp}$ and concentrations at neighboring nodes.

Step 3: set *maxdiff* = 0.

for all *i*, $temp = \left| \left[\hat{c}_\alpha^{\hat{t}+\Delta\hat{t}}\left(\xi_i\right)\right]_{temp,\,new} - \left[\hat{c}_\alpha^{\hat{t}+\Delta\hat{t}}\left(\xi_i\right)\right]_{temp} \right|$

if *temp* > *maxdiff*, then *maxdiff* = *temp*

else go to Step 4

for all *i*, if *maxdiff* > τ then $\left[\hat{c}_\alpha^{\hat{t}+\Delta\hat{t}}\left(\xi_i\right)\right]_{temp} = \left[\hat{c}_\alpha^{\hat{t}+\Delta\hat{t}}\left(\xi_i\right)\right]_{temp,\,new}$

go to Step 2

else go to Step 4

Step 4: for all i, $\hat{c}_{\alpha}^{\hat{t}+\Delta\hat{t}}\left(\xi_{\mathrm{i}},\zeta_{\mathrm{j}}\right)=\left[\hat{c}_{\alpha}^{\hat{t}+\Delta\hat{t}}\left(\xi_{\mathrm{i}}\right)\right]_{\mathrm{temp,new}}$.

The concentration values at all nodes of the vertical boundaries (Eqs. 24, 27, 32) except the corner nodes are calculated by organizing the FD approximations of a given boundary, detailed in section 5.4.4, into a linear system and using LU decomposition and back substitution to solve for the concentrations at each node. In the linear system

$$\mathbf{A}\mathbf{x}=\mathbf{b} \tag{42}$$

the vector **x** contains the unknown concentrations $\hat{c}_{\alpha}^{\hat{t}}\left(\xi_{\mathrm{i}},\zeta_{\mathrm{j}}\right)$ for a given i (depending on the vertical boundary) and $1 \le j \le j_{ve} - 1$ in the epidermis, $j_{ve} + 1 \le j \le j_{ve} + j_{de1} - 1$ in the dermis 1, $j_{ve} + j_{de1} + 1 \le j \le j_{ve} + j_{de1} + j_{de2} - 1$ in the dermis 2 and $j_{ve} + j_{de1} + j_{de2} + 1 \le j \le j_{ve} + j_{de1} + j_{de2} + j_{hd} - 1$ in the hypodermis. The matrix **A** contains the factors multiplying the unknowns and vector **b** the terms containing the known concentrations on the interior of skin layer α. The coefficients of **A** and **b** are obtained from the FD approximations of the vertical boundary conditions.

6 Diagnostic Tests

6.1 Overview

The program implementing the solution of the problem of 2-D diffusion of drugs through skin near a hair follicle was validated by running a series of diagnostic tests which separate the axial ($\hat{z}$) and radial ($\hat{r}$) dependency of the concentration and, in each direction, test independently of one another the numerical transient and steady-state solutions of the PDE on the interior of the computational domain and at the boundaries. Tests for the $\hat{z}$-dependent concentration were run in each one of the 8 subregions of the computational domain (tests "1z", "4z") separately as well as on the whole inner and outer skin tissue regions taken as two separate computational domains (tests "2z", "3z"). Tests for the $\hat{r}$-dependent concentration were also conducted independently in each subregion (tests "1r") as well as in the whole epidermis, dermis 1, dermis 2 and hypodermis, each taken as one independent computational domain (tests "2r", "3r", "4r"). The tests are conducted assuming the hair follicle to be a straight cylinder, thus $\hat{f}_{\text{ors}}(\hat{z})$ = constant. In each diagnostic test the numerical results can be compared to an analytical solution of the 1-D boundary-value problem resulting from the separation of the axial and radial directions. Table 6-1 gives an overview of the diagnostic tests performed. The $\hat{z}$-direction diagnostic tests were conducting using 30, 62, 18, 18 nodes in the $\hat{z}$ direction on the interior of the viable epidermis, dermis 1, dermis 2 and hypodermis, respectively, and 10 nodes in the $\hat{r}$ direction in the inner and outer skin regions. The $\hat{r}$-direction diagnostic test were conducted using 30, 30, 18 and 18 nodes in the $\hat{z}$ direction on the interior of the viable epidermis, dermis 1, dermis 2 and hypodermis and 18 and 28 nodes

on the interior or the inner and outer skin regions in the $\hat{r}$ direction. All diagnostic tests are performed with a time step $\Delta\hat{t} = 0.0001$.

Table 6-1. Overview of the diagnostic tests conducted to ascertain the proper functioning of the FORTRAN program implementing the numerical solution of the problem of 2-D diffusion of a chemical substance into skin near a hair follicle.

	TEST NAME	c_α **DEPENDENCY**	**TEST DOMAINS**	D_α	$K_{\alpha\,/\,pH}$
TRANSIENT	1z	z	8 subregions	constant	constant
	2z	z	inner region, outer region	constant	constant
	1r	r	8 subregions	constant	constant
	2r	r	full skin layers	constant	constant
STEADY-STATE	3z	z	inner region, outer region	constant	z-dependent
	4z	z	inner region, outer region	z-dependent	constant
	3r	r	full skin layers	constant	r-dependent
	4r	r	full skin layers	r-dependent	constant

6.2 The axial dependence of the concentration

Test "1z" is conducted on the interior of each skin layer in the inner and outer region, that is, in each one of the 8 subdomains shown in Figure 4-1, section 4.2. The dimensionless thickness of each skin layer is 1.0. The boundary conditions within each skin layer α are fixed as $\hat{c}_{\alpha,\,\text{top}} = 1$ and $\hat{c}_{\alpha,\,\text{bottom}} = 0$ at the top and bottom boundary of each subdomain. The initial condition on the interior nodes of each subdomain is $\hat{c}_{\alpha,\,0} = 0$. With the concentration depending only on the $\hat{z}$ coordinate, the transient problem is akin to diffusion of a solute into a semi-infinite medium from an infinite source of solute at a constant dimensionless concentration $\hat{c}_{\alpha,\,\text{top}}$. The analytical solution in each skin layer α for this problem is given by[79]

$$\hat{c}_{\alpha}\left(\hat{z},\hat{t}\right) = \left(\hat{c}_{\alpha,\,\text{top}} - \hat{c}_{\alpha,\,0}\right)\text{erfc}\left(\frac{\hat{z}_{\text{top}} - \hat{z}}{2\sqrt{\hat{D}_{\alpha}\hat{t}}}\right) + \hat{c}_{\alpha,\,0} \tag{43}$$

Figure 6-1 shows the numerically calculated concentration profiles and the analytical solution at $\hat{t} = 1.0$. The error calculated using

$$\text{error} = \frac{\text{analytical value} - \text{numerical value}}{\text{analytical value}} \cdot 100\% \tag{44}$$

ranges from percentages on the order of 10^{-4}% at the top of the viable epidermis, dermis 1, dermis 2 and hypodermis to 4-8% at the bottom of these skin layers. The error increases with depth due to the imposed boundary condition $\hat{c}_{\alpha,\,\text{bottom}} = 0$ at the bottom of each skin layer. The value of the concentration at the bottom of the viable epidermis,

dermis 1, dermis 2 and hypodermis calculated from Eq. 43 is approximately 0.0124. In each skin layer the mean square error varies from $O(10^{-10})$ at the top of each skin layer to $O(10^{-3})$ at the bottom.

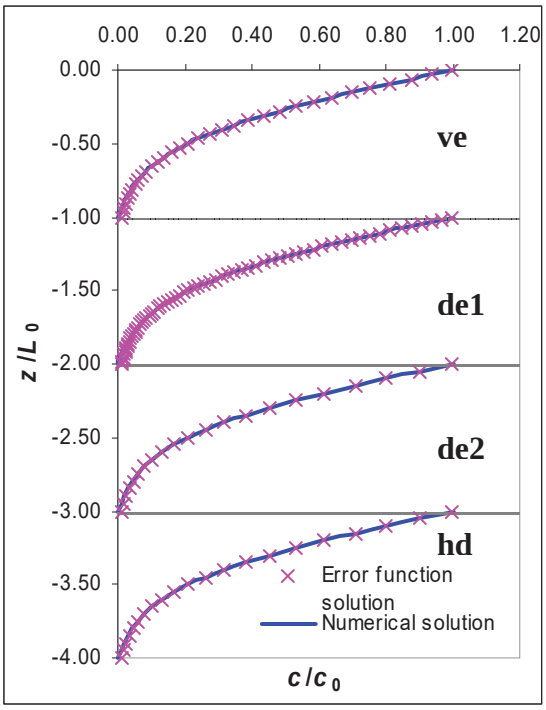


Figure 6-1: Result of test "1z"comparing the numerically obtained dimensionless concentration c/c_0 as a function of the dimensionless depth z/L_0 in the viable epidermis (ve), the dermis 1 (de1), the dermis 2 (de2) and the hypodermis (hd), to the concentration values obtained from the analytical solution to the semi-infinite medium problem (Eq. 43).

The imposed boundary conditions in test "2z" are $\hat{c}_{\text{sc/ve}} = 1$ at the stratum corneum/viable epidermis interface and $\hat{c}_{\text{hd/sub}} = 0$ at the hypodermis/sublayer interface. The initial concentration on the interior of the two computational domains, the whole inner tissue and the whole outer tissue is $\hat{c}_{\alpha,0} = 0$. The interfacial partitioning coefficients $K_{\text{ve/pH}}$, $K_{\text{de1/pH}}$, $K_{\text{de2/pH}}$, $K_{\text{ve/pH}}$ are set equal to each other. The numerically obtained

concentration values are compared to the exact solution of the semi-infinite medium problem, Eq.43, in which $\hat{c}_{sc/ve}$ replaces $\hat{c}_{\alpha,\,top}$. Figure 6.2 shows the numerical and the analytical concentration profiles in the inner tissue region at $\hat{t} = 3.0$. The profiles are the same in the outer tissue. The agreement is good, since the percent error calculated from

$$\text{error} = \frac{\text{numerical value} - \text{analytical value}}{\text{numerical value}} \cdot 100\% \qquad (45)$$

is $O(10^{-5})$ at the top of the epidermis in the inner outer skin regions, and increases to order $O(10^{-1})$ at the top of the hypodermis. The mean square error ranges from $O(10^{-15})$ to $O(10^{-10})$.

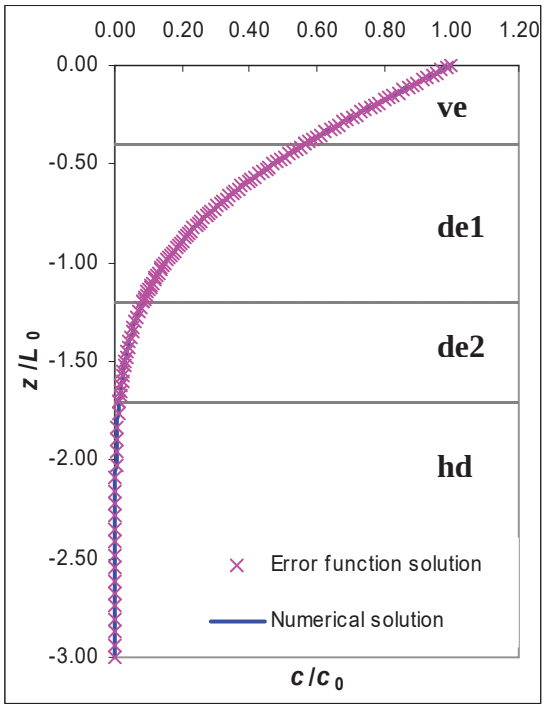


Figure 6-2: Result of test "2z"comparing the numerically obtained dimensionless concentration c/c_0 as a function of the dimensionless depth z/L_0 in the viable epidermis (ve), the dermis 1 (de1), the dermis 2 (de2) and the hypodermis (hd), to the concentration values obtained from the analytical solution to the semi-infinite medium problem (Eq. 43).

Figure 6-3 shows the results for test "3z" at $\hat{t}$ = 50, by which time the concentration has reached steady-state. The initial and boundary conditions are the same as in test 2z. The partitioning coefficients describing drug partitioning across the skin layer interfaces in the inner and outer skin regions are assigned different values: $K_{ve/pH}$ = 0.6, $K_{de1/pH}$ = 0.8, $K_{de2/pH}$ = 0.7, $K_{hd/pH}$ = 0.9. The ratios of the concentration values on either side of the boundaries match the ratios of the partition coefficients, indicating that the interfacial concentration values are computed correctly. In addition, the steady-state concentration profile in the each skin layer is linear with $\hat{z}$, as expected.

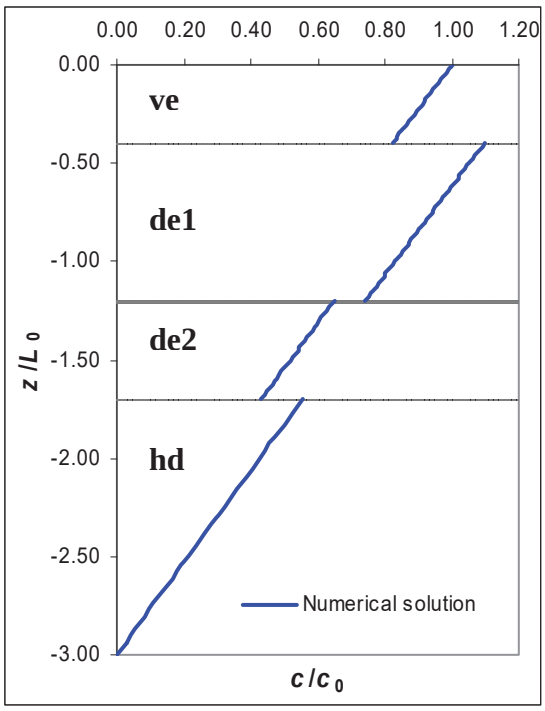


Figure 6-3: Result of test "3z"showing the steady-state dimensionless concentration c/c_0 in the viable epidermis (ve), dermis 1 (de1), dermis 2 (de2) and the hypodermis (hd) to decrease linearly with the dimensionless depth z/L_0, as expected. The ratios of the concentration values at the interfaces of the skin layers are equal to the values of partition coefficients stated in the text.

Diagnostic test "4z" shows that the program correctly computes concentration profiles for variable diffusion coefficients. In this case the steady-state concentration depends on the diffusion coefficient according the equation

$$\hat{c}(\hat{z}) = A_1 \int \frac{1}{\hat{D}(\hat{z})} d\hat{z} + A_2 \tag{46}$$

The values of the constants A_1 and A_2 depend on the boundary conditions. The diffusion coefficient $\hat{D}_\alpha(\hat{z})$ is made to vary linearly with respect to the axial coordinate $\hat{z}$. It is arbitrarily chosen to be

$$\hat{D}_\alpha(\hat{z}) = 0.08\,\hat{z} + 0.1 \tag{47}$$

in each skin layer α. As for test "1z" the boundary conditions are $\hat{c}_{\alpha,\,\text{top}} = 1$ at the top surface and $\hat{c}_{\alpha,\,\text{bottom}} = 0$ at the bottom interface of each skin layer, and the initial condition on the interior of each skin layer is $\hat{c}_{\alpha,\,0} = 0$. With the diffusivity given in Eq. 47 and these boundary conditions, the constants in Eq. 46 are A_1 = 0.207435 and A_2 = 6.970467 and the analytical solution is

$$\hat{c}_\alpha(\hat{z}) = 0.207435 \ln(0.08\,\hat{z} + 0.1) + 6.970467 \tag{48}$$

Figure 6-4 shows a good match between the numerical and analytical concentration profiles. The percent error calculated using Eq. 44 is $O(10^{-5})$ to $O(10^{-4})$ in the epidermis, $O(10^{-4})$ to $O(10^{-1})$ in the dermis 1, $O(10^{-8})$ to $O(10^{-6})$ in the dermis 2 and $O(10^{-6})$ to $O(10^{-5})$ in the hypodermis. The mean square error in each skin layer is essentially zero.

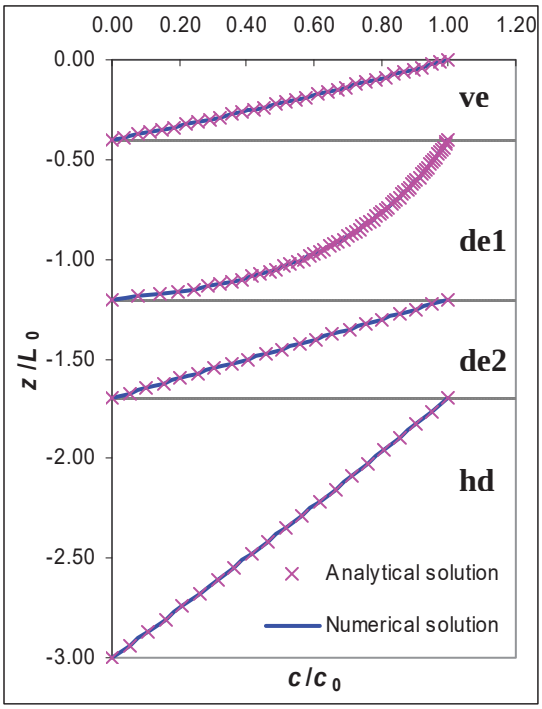


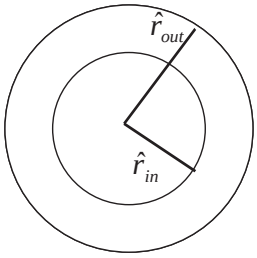
Figure 6-4: Result of test "4z"comparing the numerically obtained dimensionless concentration c/c_0 as a function of the dimensionless depth z/L_0 in the viable epidermis (ve), the dermis 1 (de1), the dermis 2 (de2) and the hypodermis (hd), to the concentration values obtained from the steady-state analytical solution (Eq. 46).

6.3 The radial dependence of the concentration

Test "1r" is a comparison of the numerical concentration values with the values of the analytical solution to the problem of diffusion through the wall of a hollow cylinder (Fig. 6-5).

For this diagnostic test, in which the comparison between the numerical and analytical values is conducted independently in each of the 8 subregions of the computational domain, the radii $\hat{r}_{\text{in}}$ and $\hat{r}_{\text{out}}$ correspond to the hair follicle boundary and the inner/outer region boundary for the subdomains of the inner tissue region, and the

inner/outer region boundary and the right boundary at $\hat{r} = \hat{r}_{\max}$ for the subdomains of the outer tissue region.



$$\hat{c}(\hat{r}_{in}) = \hat{c}_1$$
$$\hat{c}(\hat{r}_{in} \le \hat{r} \le \hat{r}_{out}) = \hat{c}_0$$
$$\hat{c}(\hat{r}_{out}) = \hat{c}_2$$

Figure 6-5: Geometry for the problem of diffusion of a substance through the wall of a hollow cylinder. Notation adapted from Crank[79].

The analytical solution to the problem of diffusion through the wall of a hollow cylinder problem is given by Crank[79]:

$$\hat{c} = \frac{\hat{c}_1 \log\left(\frac{\hat{r}_{\text{out}}}{\hat{r}}\right) + \hat{c}_2 \log\left(\frac{\hat{r}}{\hat{r}_{\text{in}}}\right)}{\log\left(\frac{\hat{r}_{\text{out}}}{\hat{r}_{\text{in}}}\right)} - \pi\, \hat{c}_0 \sum_{\text{n=1}}^{\infty} \frac{\text{J}_0(\hat{r}_{\text{in}}\alpha_n)\,\text{U}_0(\hat{r}\alpha_{\text{n}}) e^{-\hat{D}\alpha_{\text{n}}^2\hat{t}}}{\text{J}_0(\hat{r}_{\text{in}}\alpha_{\text{n}}) + \text{J}_0(\hat{r}_{\text{out}}\alpha_{\text{n}})}$$
$$- \pi \sum_{\text{n=1}}^{\infty} \frac{\{\hat{c}_2 \text{J}_0(\hat{r}_{\text{in}}\alpha_{\text{n}}) - \hat{c}_1 \text{J}_0(\hat{r}_{\text{out}}\alpha_{\text{n}})\}\,\text{J}_0(\hat{r}_{\text{in}}\alpha_{\text{n}})\text{U}_0(\hat{r}\alpha_{\text{n}})}{\text{J}_0^2(\hat{r}_{\text{in}}\alpha_{\text{n}}) - \text{J}_0^2(\hat{r}_{\text{out}}\alpha_{\text{n}})} e^{-\hat{D}\alpha_{\text{n}}^2\hat{t}} \tag{49}$$

J_0 is a Bessel function of the first kind and the function U_0 is given by[79]

$$\text{U}_0(r\alpha_{\text{n}}) = \text{J}_0(r\alpha_{\text{n}})\text{Y}_0(r_{\text{out}}\alpha_{\text{n}}) - \text{J}_0(r_{\text{out}}\alpha_{\text{n}})\text{Y}_0(r\alpha_{\text{n}}) \tag{50}$$

The α_{n} are the positive roots of

$$U_0(r_{in}\alpha_n) = 0 \tag{51}$$

The eigenvalues α_n depend on the ratio $\hat{r}_{out}/\hat{r}_{in}$. They were obtained by solving Eq. 50 numerically using Newton's method and compared to a table[79] of α_n values for given ratios $\hat{r}_{out}/\hat{r}_{in}$. The first 5 values for α_n were calculated. They agree with the tabulated values to 4 digits after the decimal point, the number of digits given in the table. Figure 6-6 shows the numerically obtained concentration values in each subdomain and the values obtained from Eq. 49 with $\hat{c}(\hat{r}_{in}) = \hat{c}_1 = 1$ and $\hat{c}(\hat{r}_{out}) = \hat{c}_2 = 0 \quad \forall \hat{t}$, and $\hat{c}(\hat{r}_{in} \le \hat{r} \le \hat{r}_{out}) = \hat{c}_0 = 0$ at $\hat{t} = 0$. The numerical values of the concentration obtained at $\hat{t} = 10$ match up well with the analytical values as the error calculated from Eq. 45 is on the order of 10^{-2} % in the inner tissue region of each skin layer and ranges from 10^{-3} % to about 6% near the far boundary ($\hat{r}_{out} = \hat{r}_{max}$) of the outer region. The mean square error ranges from $O(10^{-11})$ to $O(10^{-8})$.

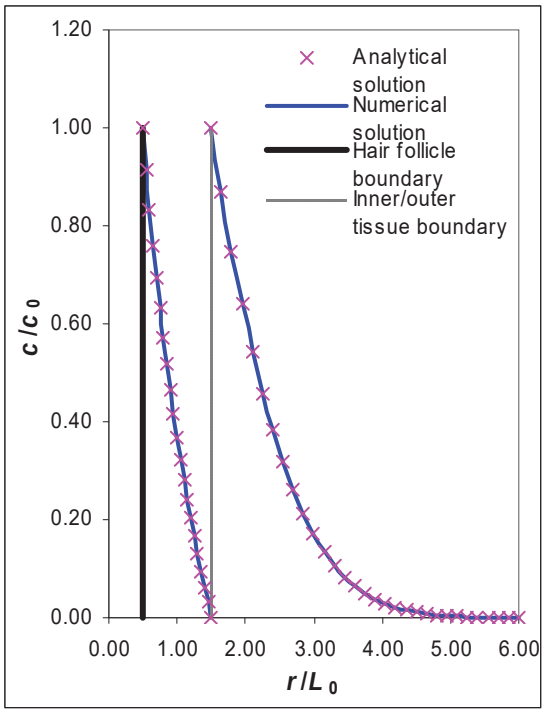


Figure 6-6: Result of test "1r"comparing the numerically obtained concentration values c/c_0 in the inner and outer regions of the computational domain as a function of the dimensionless radius r/L_0 to the concentration values obtained from the analytical solution to the problem of diffusion through the wall of a hollow cylinder (Eq. 49).

For test "2r", the imposed boundary conditions are $\hat{c}(\hat{r}_{in}) = 1$ at the hair follicle/skin tissue boundary and $\hat{c}(\hat{r}_{out} = \hat{r}_{max}) = 0$. The coefficients describing drug partitioning across the inner/outer tissue interface are taken to be equal. The numerical concentration values are compared to the exact values obtained from Eq. 49 in Figure 6-7. At $\hat{t} = 10$ the numerically calculated concentration values agree with the analytical values. The error calculated from Eq. 45 is on the order of 1 to 2% in the inner region of each skin layer and, in the "outer" region, ranges from 1% to 60% near the far boundary. The mean square error is $O(10^{-10})$ to $O(10^{-5})$.

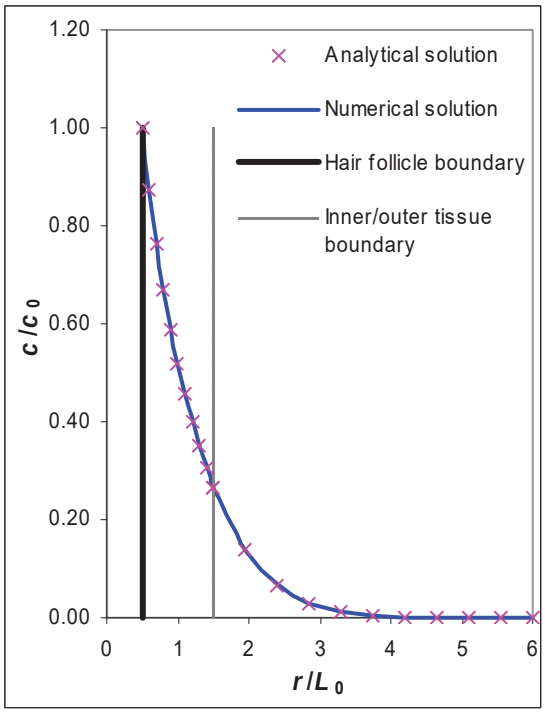


Figure 6-7: Result of test "2r"comparing the numerically obtained concentration values c/c_0 in the inner and outer regions of the computational domain as a function of the dimensionless radius r/L_0 to the concentration values obtained from the analytical solution to the problem of diffusion through the wall of a hollow cylinder (Eq. 49).

The diagnostics test "3r" tests the implementation of the boundary condition at the inner/outer region boundary of each skin layer. The test is performed over the same domains of solution as test "2r".

The partitioning coefficients describing drug partitioning across the inner/outer tissue boundary of each skin layer α are assigned different values: $K_{\alpha/\mathrm{pH,inner}} = 0.6$, $K_{\alpha/\mathrm{pH,outer}} = 0.8$. Figure 6-8 shows the results of this test with numerical concentration values calculated at $\hat{t} = 200$, which was the necessary time to obtain a steady-state profile showing a linear dependence of the concentration in the inner and outer regions of each skin layer on $\ln \hat{r}$.

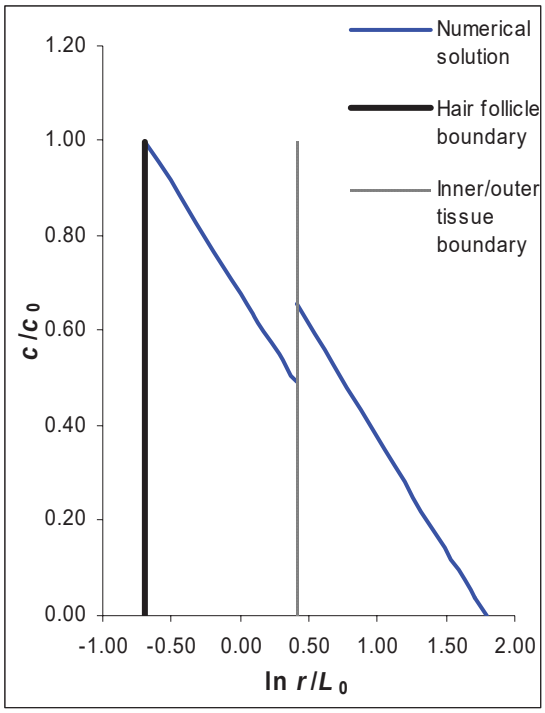


Figure 6-8: Result of test "3r" showing the steady-state dimensionless concentration c/c_0 in the inner and outer regions of the computational domain to decrease linearly with ln r/L_0, as expected. The ratio of the concentration values at the inner/outer tissue boundary is equal to the values of partition coefficients stated in the text.

Test "4r" was conducted to show that the program correctly computes concentration profiles for diffusion coefficients varying with the radius. Similarly to the $\hat{z}$ -dependent case "4z", at steady-state the concentration is given by

$$\hat{c}(\hat{r}) = B_1 \int \frac{1}{\hat{r}\hat{D}(\hat{r})} d\hat{r} + B_2 \qquad (52)$$

The values of the constants B_1, B_2 depend on the boundary conditions. With $\hat{c}(\hat{r}_{\text{in}}) = 1$, $\hat{c}(\hat{r}_{\text{out}} = \hat{r}_{\max}) = 0$ and the diffusivity arbitrarily chosen to be $\hat{D}_\alpha(\hat{z}) = 0.02\,\hat{z} + 0.1$ in each skin layer, the constants are B_1 = -0.055811 and B_2 = -0.338291. The analytical solution to his problem is thus

$$\hat{c}(\hat{r}) = -0.558111 \ln\left(\frac{\hat{r}}{\hat{r}+5}\right) - 0.338291 \tag{53}$$

Figure 6-9 shows good agreement at $\hat{t} = 100$ between the numerically obtained concentration values and the exact values. In the inner tissue region of each skin layer the error calculated from Eq. 45 is on the order of 10^{-2} to 10^{-1} % in the "inner" region and "outer" tissue regions. The mean square error ranges from $O(10^{-10})$ to $O(10^{-6})$.

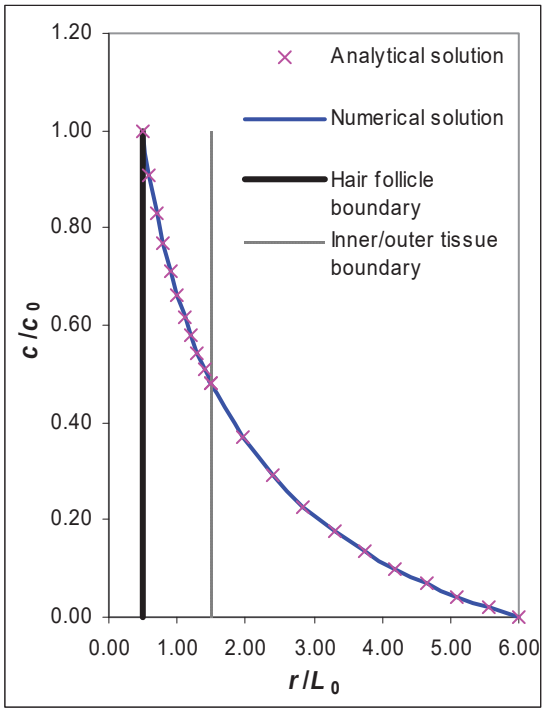


Figure 6-9: Result of test "4r"comparing the steady-state dimensionless concentration c/c_0 in the inner and outer regions of the computational domain as a function of ln r/L_0 to the concentration values obtained from the analytical solution (Eq. 52).

Taken together the results of the diagnostic tests show that the program accurately solves the PDE and the boundary values in the axial and radial direction of the computational domain.

7 Application of the Mathematical Model

7.1 Introduction

The mathematical model for diffusion near a hair follicle is applied to the diffusion of the fluorescent dye Bodipy® FL C_5 (molecular formula: $C_{16}H_{19}BF_2N_2O$, Fig. 7-1). Grams *et al.* have published a series of papers[17,55,80-82] dealing with the visualization of the pathway of diffusion of BFL and other dyes of varying lipophilicity through a block of skin containing hair follicles.

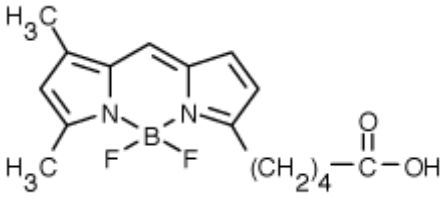


Figure 7-1: Chemical structure of 4,4-difluoro-5,7-dimethyl-4-bora-3a,4a-diaza-s-indacene-3-pentanoic acid or Bodipy® FL C_5.

In their 2004 paper[17] Grams and colleagues used an on-line diffusion cell setup combined with confocal laser scanning microscopy (CLMS) to visualize Bodipy® FL C_5 (BFL) diffusing into a piece of fresh human scalp skin over a period of 16 h. This experiment was conducted *in vitro* and thus neglects the possible effects of the vascularization of the skin on the transport of BFL. The authors write "Compared to *in vivo* studies where the vascularization of the hair follicle is intact, *in vitro* studies might underestimate the contribution of the hair follicle to the overall transport due to the lack of blood circulation and the decreases follicular opening."[17]

The mathematical model developed in chapter 5 is used to simulate the transport of BFL through the skin in the vicinity of a hair follicle. Various cases are considered in order to understand

1. The effect of the presence of the hair follicle on the BFL concentration profiles in the skin surrounding the hair follicle.
2. The effect of the vascularization of the skin on the BFL concentration profiles near the hair follicle.

The effect of the presence of the hair follicle is investigated by running the simulation for an impermeable and a permeable hair follicle. As the permeability of the hair follicle is given by the permeability of its outer boundary, i.e., the permeability of its outer root sheath $P_{ors/pH1.0}$ (section 4.4), the simulation is run assuming $P_{ors/pH1.0} = 0$ for an impermeable hair follicle and $P_{ors/pH1.0} \neq 0$ for a permeable hair follicle. As explained in section 4.4, the outer root sheath permeability has contribution from the intrinsic infundibulum permeability $P_{infund/pH1.0}$ and the additional permeability due to the duct of the sebaceous gland associated with the hair follicle, $P_{duct/pH1.0}$. We investigate the effect of the infundibulum and sebaceous duct permeability on the diffusion of BFL through the skin by looking at two cases for the non-zero outer root sheath permeability:

1. $P_{ors/pH1.0} = P_{infund/pH1.0}$, in which case the permeability of the outer root sheath is the intrinsic permeability of the infundibulum.
2. $P_{ors/pH1.0} = P_{infund/pH1.0} + P_{duct/pH1.0}$, in which case the permeability of the outer root sheath is the intrinsic permeability of the infundibulum plus the contribution due to the sebaceous duct.

In addition, we consider two different functional forms for the concentration of BFL in the infundibulum, c_{infund}. In one set of simulation runs we assume the dye diffuses downward into the sebum in the infundibulum according to a transient 1-D vertical concentration profile. In the second set of simulation runs we assume the dye concentration in the infundibulum to be well-mixed at the value set by the sebum/vehicle partition coefficient at the surface. The latter assumption constitutes an upper bound on the concentration level in the sebum.

7.2 Representation of the hair follicle

Figure 7-2 shows the representation of the outer root sheath obtained from the geometrical model of a hair follicle incorporated into the diffusion model, for hair shaft 4 mm in length and 50 μm in diameter. The outer wall of the outer root sheath, given by the function $f_{ors}(z)$, is taken as the outer boundary of the hair follicle.

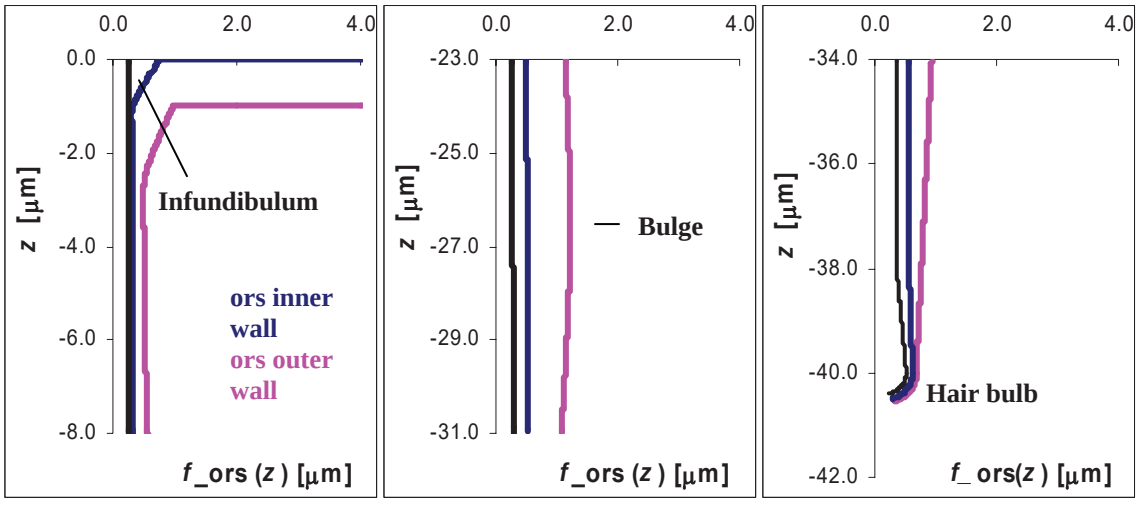


Figure 7-2: Geometric representation of the outer root sheath (ors) and the hair shaft of a hair follicle of length L = 4 mm and diameter d = 50 μm.

7.3 Overview of Grams *et al.*'s paper

7.3.1 The experimental setup

The piece of skin used by Grams and coworkers was 8 mm × 8 mm × 8 mm and included the stratum corneum, the epidermis, the dermis, the subcutaneous fat layer and hair follicles. It was in contact with a 100 μL donor compartment consisting of a 0.1 mg/mL saturated solution of BFL in a 50 mM citric acid buffer solution at pH 5.0, and an ≈ 100 μL receptor compartment consisting of phosphate buffer saline at pH 7.4 (Fig. 7-3). The donor phase was positioned in relation to the piece of skin such that only one hair follicle had access to the donor phase. The area of contact between the donor solution and the piece of skin was 10 mm^2 (Grams, YY. 2006. Personal communication).

The authors used the Image J software to obtain average the fluorescence intensity, the area of the analyzed section in μm^2 and the number of pixels for various sections within a 400 μm × 400 μm × 400 μm imaging volume which included the hair follicle of the skin block. These sections are the stratum corneum (a in Fig. 7.3), the viable epidermis (b), the dermis (c), the outer root sheath (d), the gap, i.e., the infundibulum (e), the cuticle of the hair shaft (f) and the hair shaft (g). Tables 7-1 and 7-2 compare important length and volumetric dimensions in Grams *et al.*'s skin block with the dimensions of the equivalent regions of the computational domain used in the mathematical model.

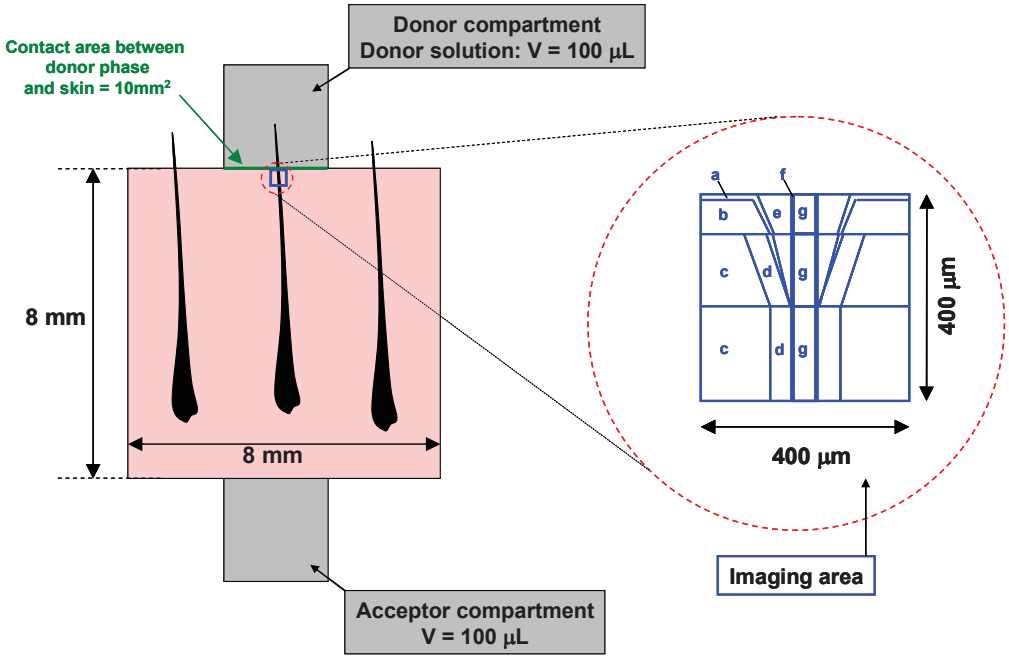


Figure 7-3: Schematic diagram of Grams *et al.*'s experimental system[17]. The insert labelled "Imaging area" is reproduced directly from Grams *et al.*'s publication.

Table 7-1. Comparison of physical characteristics in Grams *et al.*'s *in vitro* experiment[17] and in the 2-D mathematical model of diffusion near a hair follicle.

PHYSICAL CHARACTERISTIC [µm]	GRAMS *ET AL.*	MATHEMATICAL MODEL
Thickness of stratum corneum	9.6	No thickness [a]
Thickness of viable epidermis	76.8	100
Thickness of dermis [b]	313.6	285
Diameter of hair shaft	49.4	50
Depth of infundibulum	222.8	1000
Diameter of infundibulum opening	121.5	349.4
Width of upper ORS Width of lower ORS	49.0 33.1	No thickness [a]

[a] The stratum corneum and outer root sheath are characterized by a steady-state permeability coefficient (see section 4.4).
[b] Calculated from the stratum corneum and viable epidermis thicknesses given in [17].

Table 7-2. Comparison of volumes in Grams *et al.*'s *in vitro* experiment and in the 2-D mathematical model of diffusion near a hair follicle

PHYSICAL CHARACTERISTIC [μm^3]	GRAMS *ET AL.*	MATHEMATICAL MODEL
Volume of viable epidermis / 10^6	12.19	13.05
Volume of dermis / 10^6	48.99	23.26
Volume of infundibulum / 10^6	0.21	8.90

7.3.2 Grams *et al.*'s results and conclusions

Grams *et al.*'s paper[17] includes results for the fluorescence intensity, relative fluorescence distribution and relative dye accumulation as functions of time in each section of the imaging volume.

The fluorescence intensity was measured in each one of the subregions over the duration of the experiment (16 h) and plotted versus time (Fig. 7.4). Initially the hair follicle cuticle and the upper gap showed the fastest increase in fluorescence intensity.

The fluorescence intensity in the upper gap reached a maximum at t = 2 h, after which it decreased rapidly. Below the epidermal-dermal junction the lower gap showed the fastest increase in fluorescence intensity, reaching a maximum value around t = 6 h. The fluorescence intensity measured in the epidermis, the dermis and in the outer root sheath increased to a maximum value around t = 6 h before slowly decreasing. During the first 2 h the epidermal fluorescence intensity is 2 to 4 times greater than the fluorescence intensity measured in the outer root sheath. For $t > 2$ h the fluorescence intensity is about 1.7 to 1.76 times greater in the epidermis compared to the outer root sheath. For $0 \leq t \leq 2$

h, the fluorescence intensity measured in the epidermis is 2.5 to 3.3 times greater than that measured in the dermis, at later time this ratio is 2.0 to 2.2.

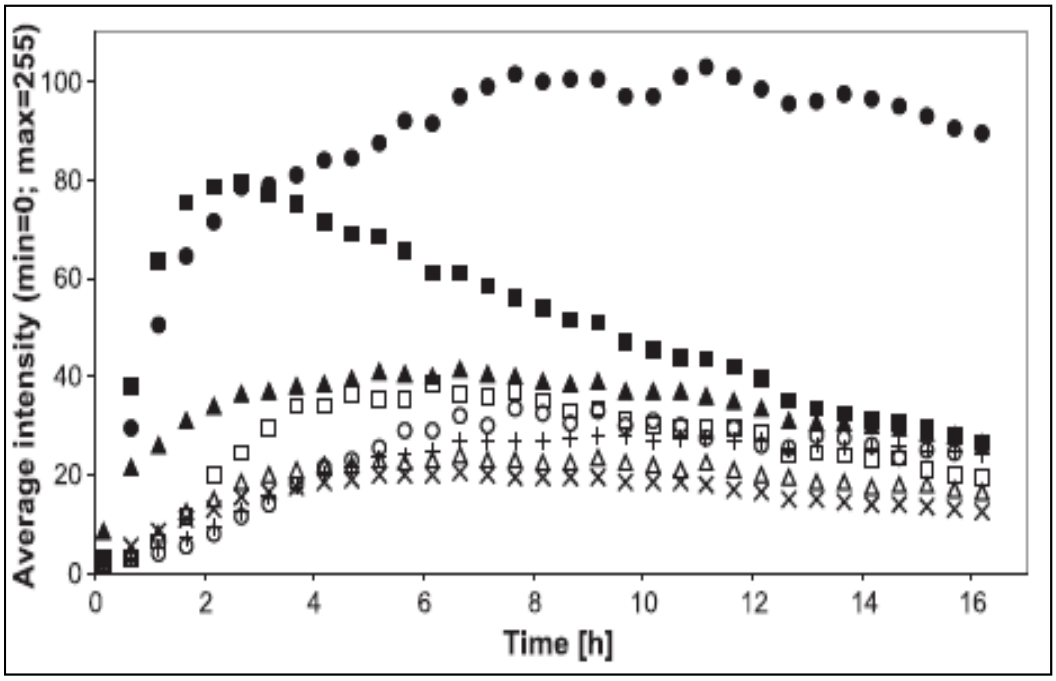


Figure 7-4: Experimental results for the average fluorescence intensity vs. time in various regions of the skin block reported by Grams *et al*. in Figure 2 of their publication.[17] The regions of the skin block are the upper gap (■), the lower gap (□), the lower cuticle (○), the outer root sheath (Δ), the hair shaft (+), the epidermis (▲), and the dermis (×) (from [17]).

For $0 \leq t \leq 2$ h, the fluorescence intensity measured in the outer root sheath is slightly lower than that measured in the dermis, but for $t > 2$ h, the outer root sheath fluorescence intensity is approximately 1.1 to 1.4 times that measured in the dermis.

The relative fluorescence distribution calculated by Grams *et al.* for each section of the skin block is a measure of the relative intensity of a given section divided by the sum of the total relative intensities of all sections. The sum of the relative fluorescence values of all sections of the skin block is equal to 1.[81] The relative fluorescence values

express the change in fluorescence distribution in a section of the skin block. The results presented in [17] show the relative fluorescence of the non-follicular sections of the skin block to be a minimum of 97.5% for $0 \leq t \leq 16$ h. The total contribution of the follicular parts is a maximum of 2.5%.

Relative fluorescence accumulation values $f_{acc,i}$ for each section i of the skin block were calculated in order to express the actual relative fluorescence of a given section to the relative fluorescence of the section in the case of homogeneous distribution. The relative fluorescence accumulation values yield information on the degree of accumulation of fluorescence in each section of the skin block. If the dye is distributed equally in all skin block sections, the accumulation factors are $f_{acc,i} = 1$; if fluorescence accumulation in a given section i relative to homogeneous distribution is present, the accumulation values are $f_{acc,i} > 1$.[17,81] Results presented in [17] show that initially, the highest fluorescence accumulation factors are observed in the upper part of the infundibulum and of the hair shaft cuticle. Early on diffusion dominated in these sections of the imaging volume. Over time the diffusion of BFL occurred through the stratum corneum as well as through the hair follicle. The accumulation values in the outer root sheath, the dermis and the lower section of the hair shaft increased slower than the accumulation values in the lower infundibulum and lower cuticle. This indicated that diffusion into the lower cuticle occurred from the hair canal and the upper cuticle, not from the outer root sheath, dermis, or hair shaft. Overall the results showed diffusion of the dye from the gap into the cuticle. The authors do not exclude the possibility of diffusion occurring along the hair shaft, from the outer root sheath of the infundibulum to the cuticle or from the infundibulum into the outer root sheath.

7.4 Simulation geometries

7.4.1 Simulation of Grams *et al.*'s experiment

The mathematical model is used to simulate Grams *et al.*'s *in vitro* diffusion experiment, as well as the same experiment under *in vivo* conditions, where the skin vasculature is taken into account. In both of these cases, the donor solution compartment partially covers the piece of skin (Fig. 7-5 A, B).

In the simulation the piece of skin through which BFL diffuses is taken is a cylinder of radius and height equal to 5 mm. The cylinder is pierced in its center by a hair follicle; the centerline of the cylinder is the centerline of the hair shaft.

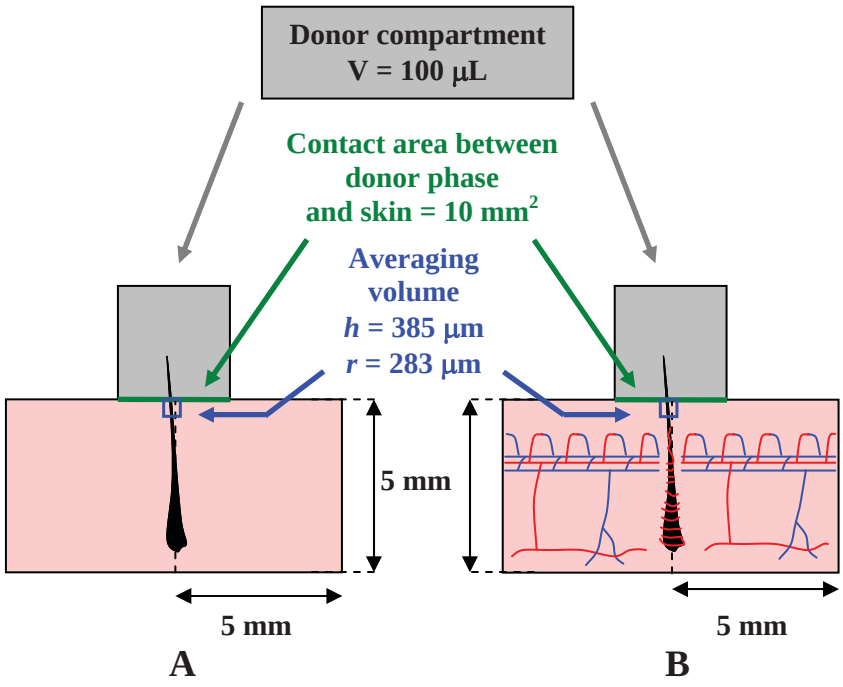


Figure 7-5: Diagram of simulated setup for *in vitro* (A) and *in vivo* (B) diffusion in the case of the piece of skin partially covered by the donor solution compartment.

The mathematical model includes a donor solution compartment which has the same dimensions as that in Grams *et al.*'s experiment. In the model the donor compartment is characterized by its height and area of contact between the donor solution and the skin. The area of contact between the donor compartment and the skin is taken to be A_{ds} = 10 mm^2, the same as in the actual experiment (Grams YY. 2006. Personal communication). From the volume of the donor solution (V_{ds} = 100 μL) and the contact area, the height of the donor compartment is calculated to be h_{ds} = 1 cm. The parameters A_{ds} and h_{ds} appear in the mathematical model in the calculation of the donor solution concentration $c_{ds}(t)$ (Appendix A).

The mathematical model does not include an acceptor compartment below the model piece of skin. In their study of diffusion of BFL through human scalp skin into deeper layers of the skin[55] Grams *et al.*'s results show that the amount of dye reaching a depth of 4000 μm is insufficient for CLSM detection. The fact that the fat cells of the hypodermis are not stained suggested to the authors that the majority of dye is retained at a depth of 2000 μm. Concentration profiles for the simulation of *in vitro* diffusion of BFL presented in section 7.4 show that in the case of maximum dye permeability into the skin surrounding the hair follicle, the concentration of BFL at the hair follicle/skin tissue boundary at t = 16 h is on the order of 10^{-10} mg/mL. At a distance of 5 mm away from the hair follicle, the concentration is on the order of 10^{-12} mg/mL at the same depth. It can thus be safely assumed that the concentration which would reach an acceptor compartment located below the piece of skin is negligible.

The dimensions of the skin layers and the hair follicles used in the mathematical model are given in Table 7-1 alongside the equivalent dimensions in Grams *et al.*'s

experimental setup. The important differences pertain to the size of the infundibulum and the thickness of the dermis. While the infundibulum reaches to a depth of 222.8 μm in Grams *et al*.'s skin block, the geometrical model of the hair follicle included in the 2-D mathematical model of diffusion yields a model of the hair follicle in which the cell layers of the inner root sheath (Henle's and Huxley's cell layers and the cuticle of the inner root sheath, see section 2.2.1) begin at a depth of 1000 μm for a hair follicle length of 4 mm and diameter of 50 μm. Since the cell layers of the inner root sheath are densely packed, we assumed that a substance will not diffuse within the hair follicle below a depth of 1000 μm. The diameter of the infundibulum opening in Grams *et al*.'s skin block is 121.5 μm. In our model we assumed that the outer root sheath constitutes the boundary between the hair follicle and the surrounding skin tissue (section 4.1). The geometrical model of the hair follicle indicates that at the skin surface, the outer root sheath is located at a distance of 174.7 μm away from the centerline of the hair shaft. In our model the diameter of the follicular opening at the skin surface is thus 349.4 μm.

The mathematical model yields results for the transient average concentration in a section of the viable epidermis and the dermis near the hair follicle. These average concentration profiles are compared qualitatively to Grams *et al*.'s average fluorescence intensities measured within the 400 μm × 400 μm × 400 μm imaging volume of the piece of skin. In the mathematical model the average concentrations in the epidermis, dermis and along the hair follicle/skin tissue boundary are calculated within an averaging volume which corresponds approximately to Grams *et al*.'s imaging volume. The details of the calculations are provided in Appendix C. The averaging volume is bounded by the hair follicle/skin tissue boundary and the inner/outer tissue boundary in the radial direction.

At the surface of the skin the inner/outer tissue boundary is located at a radial distance of $200\sqrt{2}$ μm = 282.8 μm away from the centerline of the hair follicle, which is the radius of a circle circumscribing the averaging volume in [17]. In the axial direction it reaches from the surface of the skin to a depth of 385 μm, corresponding approximately to the imaging volume depth of 400 μm in [17]. Table 7-2 shows the volume of the viable epidermis, the dermis within the averaging volume compared to the equivalent volumes in the imaging volume of [17]. Additionally, the volumes of the infundibulum experimental setup and in the mathematical model are compared.

The difference in the values of the epidermal volumes is about 6.6% of the volume of the viable epidermis in the experimental setup, which is small. The volume of the dermal layer within the averaging volume, calculated from the volume of the dermis 1 skin layer and a slab of dermis 2 (top 0.85 μm), is about half the value of the volume of dermis in Grams *et al*.'s experimental setup. This difference is due to the decrease in the radial distance of the inner/outer tissue boundary with depth. The *r* coordinates of the inner/outer boundary depend on the value of the function f_{ors} (z) which gives the shape of the hair follicle/skin tissue boundary (section 4.2). The volume of the part of the infundibulum included in the averaging volume is much larger than the part of the infundibulum included in the imaging volume in [17] since the dimensions of the infundibulum in the mathematical model is significantly larger than that of the skin block in [17]. Appendix C provides the details of the calculation of the volumes in the mathematical model.

7.4.2 Simulation of a "small patch"

In the *in vivo* simulation of a small patch covering the piece of skin, the donor solution compartment covers the entire piece of skin (Fig. 7-6). The volume of the donor solution compartment is identical to that in the cases of partially covered skin, thus the contact area between the donor phase and the skin is approximately 79 mm^2.

Since the case of the fully covered skin is presented only to investigate the effect of increasing the donor phase/skin contact area on the concentration profiles far from the hair follicle (r = 5 mm), the calculation of average concentrations within an averaging volume around the hair follicle is not needed in the case of fully covered skin.

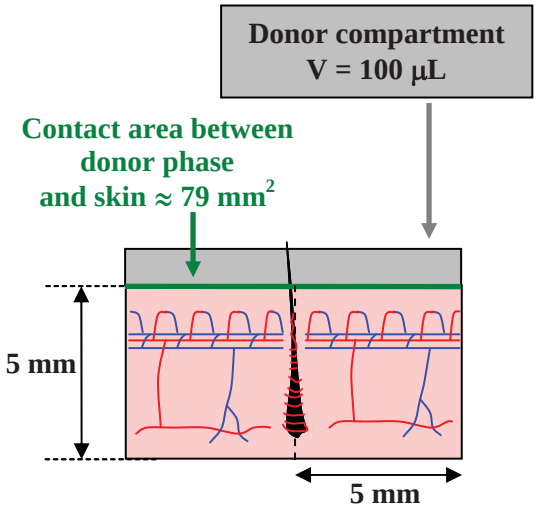


Figure 7-6: Diagram of simulated setup for *in vivo* diffusion in the case of the piece of skin fully covered by the donor solution compartment.

7.5 Calculation of the physico-chemical parameter values

7.5.1 Preliminary calculations

The steady-state permeability coefficients of Bodipy® FL C_5 (BFL) in the stratum corneum, the outer root sheath and the sublayer below the hypodermis, and the partition coefficients of BFL in the skin layers, the outer root sheath, the sebum and the sublayer, are calculated with respect to an aqueous solution at pH 1.0, in which the dye is effectively 100% unionized. The calculation of the steady-state permeability coefficients and partition coefficients of BFL in various regions of the computational domain necessitates the knowledge of the octanol/pH 1.0 partitioning coefficient of the unionized form of the dye and of its pK_a.

The physico-chemical parameters pertaining to BFL given in Grams *et al*.'s papers are the octanol/buffer partitioning coefficients of the dye in two buffer solutions of different pH representing the donor solution (citric acid buffer) and the acceptor solution (phosphate buffered saline) they used in their diffusion experiments.[80,82] These partition coefficients are

$$\log K_{\text{oct/pH 5.0}} = 2.5 \tag{54}$$

$$\log K_{\text{oct/pH 7.4}} = 1.2 \tag{55}$$

Their data is used to calculated the pKa and the octanol/pH 1.0 partition coefficient of the unionized form of the Bodipy® FL C_5 dye, $K^{\text{u}}_{\text{oct / pH 1.0}}$.

In general, for a weak acid solution buffered at a given pH, the ratio of the concentration of the ionized (superscript "i") form to the unionized (superscript "u") form of the chemical is given by the weak acid form of the Henderson-Hasselbalch equation,

$$\frac{c_{\mathrm{pH}}^{\mathrm{i}}}{c_{\mathrm{pH}}^{\mathrm{u}}} = 10^{\mathrm{pH}-\mathrm{p}K_{\mathrm{a}}} \tag{56}$$

The intrinsic octanol/aqueous solution ("oct/pH") partition coefficient of the unionized form of a chemical is

$$K_{\mathrm{oct/pH}}^{\mathrm{u}} = \frac{c_{\mathrm{oct}}^{\mathrm{u}}}{c_{\mathrm{pH}}^{\mathrm{u}}} \tag{57}$$

The distribution coefficient of dye in octanol/aqueous solution is

$$\overline{K}_{\mathrm{oct/pH}} = \frac{c_{\mathrm{oct}}^{\mathrm{u}} + c_{\mathrm{oct}}^{\mathrm{i}}}{c_{\mathrm{pH}}^{\mathrm{u}} + c_{\mathrm{pH}}^{\mathrm{i}}} \tag{58}$$

Substituting Eqs. 56 and 57 into Eq. 58 and taking into account the fact that the concentration of the ionized form of the dye in octanol, $c_{\mathrm{oct}}^{\mathrm{i}}$, is zero, the octanol/aqueous solution partition coefficient is found to be

$$\overline{K}_{\mathrm{oct/pH}} = \frac{c_{\mathrm{oct}}^{\mathrm{u}}}{c_{\mathrm{pH}}^{\mathrm{u}}\left(1 + \frac{c_{\mathrm{pH}}^{\mathrm{i}}}{c_{\mathrm{pH}}^{\mathrm{u}}}\right)} \tag{59}$$

or

$$\overline{K}_{\mathrm{oct/pH}} = \frac{K_{\mathrm{oct/pH}}^{\mathrm{u}}}{1 + 10^{\mathrm{pH}-\mathrm{p}Ka}} \tag{60}$$

Substituting the given data (Eqs. 54, 55) into Eq. 60 yields a system of two equations and two unknowns for pK_a and the octanol/aqueous solution partition coefficient of the unionized form of the permeant, $K^{u}_{oct/pH}$. The solution is

$$K^{u}_{oct/pH} = 342 \tag{61}$$

$$pK_a = 6.09 \tag{62}$$

7.5.2 Permeability coefficients

- **Permeability through the stratum corneum**

The *in vitro* (fully hydrated) and *in vivo* (partially hydrated) permeabilities of the dye through stratum corneum at steady-state, $P^{total}_{sc/pH1.0}$ and $\widetilde{P}^{total}_{sc/pH1.0}$, respectively, are functions of the radial distance r away from the hair follicle, since the contact area between the donor solution compartment and the skin is less than the surface area of the skin. The contact area between the donor solution and the skin is A_{ds} = 10 mm^2 (section 7.3.1), corresponding to a radius r = 1.78 mm. Thus, at the surface (z = 0) of the skin,

$$P^{total}_{sc/pH1.0}(r) \begin{cases} \neq 0 \text{ for } 174.7\,\mu m \le r \le 1.78\,mm \\ = 0 \text{ for } r > 1.78\,mm \end{cases} \tag{63}$$

$$\widetilde{P}^{total}_{sc/pH1.0}(r) \begin{cases} \neq 0 \text{ for } 174.7\,\mu m \le r \le 1.78\,mm \\ = 0 \text{ for } r > 1.78\,mm \end{cases} \tag{64}$$

where r = 174.7 μm is the radial distance of the hair follicle/skin tissue boundary away from the centerline of the hair shaft, at the surface of the skin (z = 0).

For $174.7\,\mu\text{m} \le r \le 1.78\,\text{mm}$, the total *in vitro* permeability of the dye through the stratum corneum at steady-state, $P_{\text{sc/pH1.0}}^{\text{total}}(r)$, is equal to the permeability of the unionized form of the dye through the stratum corneum at steady-state, given by the Potts and Guy correlation,[18]

$$P_{\text{sc/pH1.0}}^{\text{total}} = P_{\text{sc/pH1.0}}^{\text{u}} = -2.7 + 0.71 \log K_{\text{oct/pH1.0}}^{\text{u}} - 0.0061\,Mw \tag{65}$$

where $K_{\text{oct / pH1.0}}^{\text{u}}$ and *Mw* are the octanol/pH 1.0 solution partitioning coefficient and the molecular weight of the permeant, respectively.

Substituting Eq. 61 and the value of the molecular weight, *Mw* = 320.15 g/mol, into Eq. 65 yields

$$P_{\text{sc/pH1.0}}^{\text{total}}(r) \approx 0.0013\,\text{cm/h}, \quad 174.7\,\mu\text{m} \le r \le 1.78\,\text{mm} \tag{66}$$

The total dye permeability coefficient through the stratum corneum *in vivo*, or in partially hydrated skin, $\widetilde{P}_{\text{sc / pH1.0}}^{\text{total}}(r)$, is obtained following Miller *et al*. by dividing the *in vitro* permeability coefficient by a factor of three.[83] Thus,

$$\widetilde{P}_{\text{sc / pH1.0}}^{\text{total}}(r) \approx 4.3 \cdot 10^{-4}\ \text{cm/h},\ 174.7\,\mu\text{m} \le r \le 1.78\,\text{mm} \tag{67}$$

- **Permeability through the outer root sheath**

The permeability of the outer root sheath of the hair follicle/skin tissue boundary relative to an aqueous solution at pH 1.0 is assumed to be equal to the sum of the intrinsic permeability of the membrane lining the infundibulum ("infund/pH1.0") and the contribution of the duct of the sebaceous gland associated with the hair follicle

("duct/pH1.0"). Given the uncertainty in the estimation of the intrinsic permeability of the outer root sheath, we neglect the diffusional resistance of the viable cell layers of the outer root sheath relative to the membrane lining of the infundibulum.

The intrinsic permeability of the infundibulum is estimated by taking into account the presence of the thinning stratum corneum-like cell wall which lines the infundibulum (section 2.2.1). At the top surface of the infundibulum (z = 0), the resistance to penetration across the wall of the infundibulum, i.e., the inverse of the permeability, is assumed to be equivalent to the resistance provided by full-thickness stratum corneum. At the bottom surface of the infundibulum (depth z = -1000 μm), the resistance to permeability is assumed to be equivalent to that provided by a stratum corneum-like wall 1 cell layer in thickness, that is, one tenth of the resistance due to full-thickness stratum corneum. We assumed that the resistance to permeation across the wall of the infundibulum decreases linearly with depth z. In the *in vitro* case, the resistance as a function of depth is

$$\frac{1}{P_{\text{infund / pH1.0}}(z)} = az + b \tag{68}$$

At the top surface of the infundibulum,

$$\frac{1}{P_{\text{infund / pH1.0}}}(z = 0) = \frac{1}{P^{\text{total}}_{\text{sc / pH1.0}}} \tag{69}$$

At z = -1000 μm, the resistance to permeation is

$$\frac{1}{P_{\text{infund / pH1.0}}} = \frac{1}{10}\frac{1}{P_{\text{sc / pH1.0}}}(z = 0) \tag{70}$$

Substituting Eqs. 69 and 70 into Eq. 68 yields

$$\frac{1}{P_{\text{infund / pH 1.0}}(z)} = 0.324 \frac{\text{s}}{\mu\text{m}^2} z + 360 \frac{\text{s}}{\mu\text{m}} \tag{71}$$

In the *in vivo* case the intrinsic permeability of the infundibulum is equal to that in the *in vitro* case, because although the surface of the stratum corneum exposed to the environment is only partially hydrated the wall of the infundibulum remains occluded by the sebum. The conditions inside the infundibulum do not change when going from an *in vitro* experiment to an *in vivo* experiment (Bennes, JF. 2006. Personal communication). Thus,

$$\frac{1}{\widetilde{P}_{\text{infund/pH 1.0}}(z)} = \frac{1}{P_{\text{infund/pH 1.0}}(z)} \tag{72}$$

The contribution to the permeability of the outer root sheath due to the sebaceous duct is modeled as the permeability through a tube of radius r_{duct} in the outer root sheath whose centerline is located at a depth of -500 μm (section 2.2.1) below the surface of the skin (Fig. 7.7). The functional form of the contribution due to the sebaceous duct is assumed to be a Gaussian distribution in z centered at a mean depth z_{mean} = -500 μm:

$$P_{\text{duct / pH 1.0}}(z) = \frac{\gamma}{\sqrt{2\pi\sigma^2}} \text{e}^{-(z-z_{\text{mean}})^2/2\sigma^2} \tag{73}$$

where σ is the standard deviation.

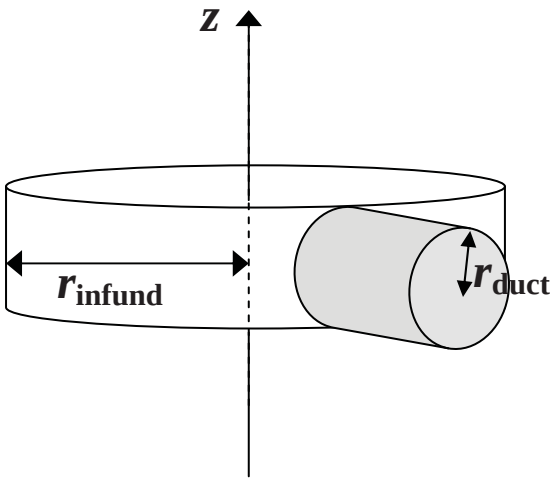


Figure 7-7: Diagram representing the sebaceous duct centered at a depth of -500 μm as a tube attached to the hair follicle.

The parameter γ is obtained by equating the total flow through the lateral area of a cylinder of radius r_{infund} representing the outer root sheath of the hair follicle (left-hand side of Eq. 74) to the total flow through the circular entrance of a tube representing the sebaceous duct connected to the hair follicle:

$$\int_{-\infty}^{\infty} P_{\text{duct / pH 1.0}}(z) \cdot 2\pi\, r_{\text{infund}}(z)\, \mathrm{d}z \cdot \Delta c = \frac{D_{\text{sebum}} K_{\text{sebum / pH 1.0}}}{l_{\text{diffusion}}} \cdot \pi\, r_{\text{duct}}^2 \cdot \Delta c \qquad (74)$$

where r_{infund} (z) is the radius of the infundibulum, given by the function f_{ors} (z) (section 4.2), D_{sebum} and $K_{\text{sebum/pH1.0}}$ are, respectively, the diffusion coefficient and the partition coefficient with respect to a pH 1.0 solution of the permeating dye, and $l_{\text{diffusion}}$ is the effective path length of diffusion from the entrance of the sebaceous duct to the surrounding tissue. The total flow through the lateral area of the cylinder representing the

outer root sheath is approximated as the flow through this boundary at the center of the sebaceous duct, thus $r_{\text{infund}}(z) \cong r_{\text{infund}}\big|_{z=\text{-}500\,\mu\text{m}}$. From Eq. 74 we have

$$2\pi\, r_{\text{infund}}\big|_{z=\text{-}500\,\mu\text{m}} \int_{-\infty}^{\infty} P_{\text{duct / pH 1.0}}(z)\,\mathrm{d}z \cdot \Delta c = \frac{D_{\text{sebum}} K_{\text{sebum / pH 1.0}}}{l_{\text{diffusion}}} \cdot \pi\, r_{\text{duct}}^2 \cdot \Delta c \qquad (75)$$

The value of the parameter γ in Eq. 74 is obtained by substituting γ for the integral in Eq. 75.

The calculation of D_{sebum} and $K_{\text{sebum/pH1.0}}$ is explained in detail in sections 7.4.3 and 7.4.4. The values are $D_{\text{sebum}} = 0.088 \cdot 10^{-5}$ cm^2/h and $K_{\text{sebum/pH1.0}} = 26$. The radius of the infundibulum is given by the value of the function $f_{\text{ors}}(z)$ which gives the shape of the outer wall of the outer root sheath (section 7.2). At a depth of -500 μm the radius of the outer root sheath is 52 μm. An extensive literature search was conducted in order to find values of r_{duct} and $l_{\text{diffusion}}$, but no data was found. Professor Dr. Christos C. Zouboulis of the Institute of Clinical Pharmacology and Toxicology at Charité-Universitätsmedizin Berlin confirmed that no reliable data for the radius of the sebaceous duct exists, in particular because of the variability in size from one pilosebaceous unit to the next and from one location in the body to the next (Zouboulis CC. 2006. Personal communication). We assumed the sebaceous duct radius to be of the same order of magnitude as the radius of the hair shaft and chose $r_{\text{duct}} = 25$ μm. The geometrical model of the outer root sheath yielded an outer root sheath thickness of 19 μm at a depth z = -500 μm. This value represents the lower limit for $l_{\text{diffusion}}$ (a, Fig. 7-8), but the actual value of $l_{\text{diffusion}}$ is almost certainly much larger. A chemical substance having diffused from the infundibulum into the sebaceous duct may either diffuse through the sebaceous duct wall

into the surrounding dermal tissue (b, Fig. 7-8), or into the sebaceous gland and from there through the sebaceous gland cells into the surrounding tissue (c, Fig. 7-8).

Given the fact that the radius of the sebaceous glands ranges from 100 μm to 1000 μm (section 2.2.3), we have chosen an effective path length of diffusion equal to 200 μm. A value closer to the lower limit of sebaceous gland radii was chosen because the inner region of the dermis 2 skin layer (near the hair follicle), in which the sebaceous duct lies, is assumed to be a composite medium incorporating the properties of a sebaceous gland and of dermal tissue (see section 7.4.3 and 7.4.4). With these parameter values Eq. 75 yields $\gamma = 0.069 \cdot 10^{-5}$ cm^2/s.

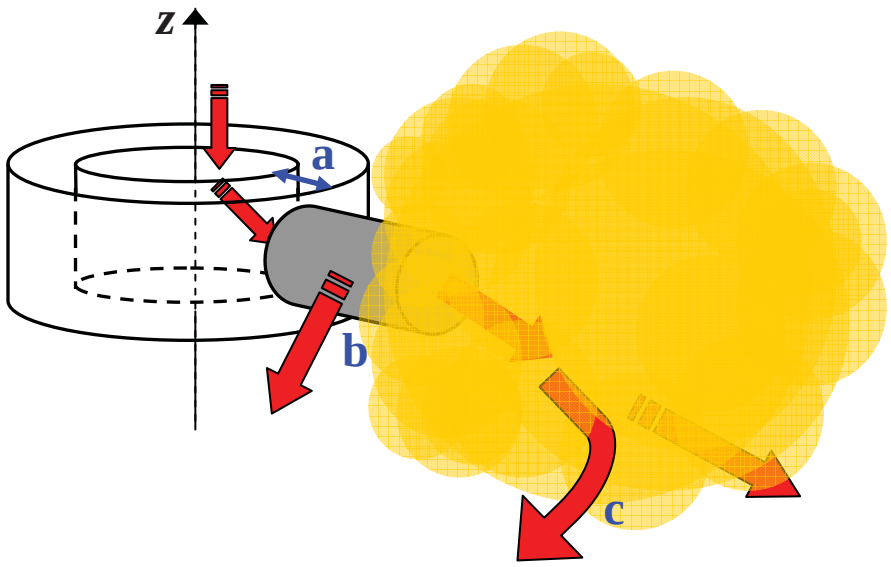


Figure 7-8: Schematic of the possible diffusion paths for a chemical substance diffusing from the hair follicle (cylinder) into the surrounding skin via the sebaceous duct (grey cylinder). The lower limit for the diffusion path is the thickness of the outer root sheath of the hair follicle (a). Upon entering the sebaceous duct a chemical can diffuse through the duct's wall (b), or through the sebaceous gland cells (c) into the surrounding dermal tissue.

Various diagrams[48,76,84,85] of the hair follicle and its associated sebaceous gland suggest that the entrance of the sebaceous duct at the point of attachment with the hair follicle is wider that the duct itself. We assume the contribution to the permeability due to the sebaceous duct to be spread over a distance of 100 μm above and below the centerline of the sebaceous duct at z = -500 μm. The standard deviation in Eq. 73 is thus chosen to be σ = 100 μm.

As described in section 7.1, three cases are considered for the permeability of the outer root sheath of the hair follicle. For the case in which we consider the infundibulum and the sebaceous duct as contributing together to the outer root sheath permeability, we assume their permeabilities to be connected in parallel. In this case the outer root sheath permeability *in vitro* and *in vivo* is the sum of these two permeabilities:

$$P_{\mathrm{ors/pH1.0}} = P_{\mathrm{infund/pH1.0}} + P_{\mathrm{duct/pH1.0}} \tag{76}$$

and

$$\widetilde{P}_{\mathrm{ors/pH1.0}} = \widetilde{P}_{\mathrm{infund/pH1.0}} + P_{\mathrm{duct/pH1.0}} \tag{77}$$

7.5.3 Partition coefficients

The epidermis and dermis 1 skin layers are modeled as homogeneous layers within each of which the partition coefficient of Bodipy® FL C_5 (BFL) is independent of location. The subscripts “ve” and “de1” in the calculation below thus refer to both the inner and outer regions of the viable epidermis and the dermis 1, respectively.

The subscripts “de2,i” refers to the inner region of the dermis 2, respectively. This region of the computational domain is approximated as a composite of sebaceous gland

and dermal tissue, in order to take into account the presence of the sebaceous gland close to the hair follicle. This is a coarse approximation of the biology of the pilosebaceous unit, since the sebaceous gland is not wrapped around the hair follicle, as the approximation suggests, but is embedded in dermal tissue near the hair follicle. The physico-chemical properties of the sebaceous gland tissue are assumed equal those of the sebum present in the infundibulum.

The outer region of the dermis 2 skin layer, denoted by the subscript "de2,o", is composed of dermal tissue. The partition and diffusion coefficient of the dye in this region of dermis 2 are thus equal to those calculated for the dermis 1 inner and outer region.

To take into account the nature of the fat cells of the hypodermis (section 2.1.3), the partition coefficient of the dye in the inner and outer regions of the hypodermis (collectively denoted by the subscript "hd") is calculated by assuming the hypodermis to be equivalent to a mixture of 80% olive oil and 20% water.

- **Partition coefficient in the donor solution**

The partition coefficient is calculated as the ratio of the total dye concentration in the donor solution (pH 5.0) relative to the total dye concentration in a solution at pH 1.0. The total dye concentration in a solution at a given pH is the sum of the concentrations of the ionized (superscript "i") and unionized (superscript "u") forms of the dye. Thus the partition coefficient in the donor solution is

$$\overline{K}_{\mathrm{pH\,5.0\,/\,pH\,1.0}} = \frac{c^{\mathrm{u}}_{\mathrm{pH\,5.0}} + c^{\mathrm{i}}_{\mathrm{pH\,5.0}}}{c^{\mathrm{u}}_{\mathrm{pH\,1.0}} + c^{\mathrm{i}}_{\mathrm{pH\,1.0}}} \tag{78}$$

Factoring out the concentration of the unionized form of the dye in the numerator and denominator and recognizing that the concentration of an unionized species is independent of pH yields

$$\overline{K}_{\mathrm{pH\,5.0\,/\,pH\,1.0}} = \frac{1 + \dfrac{c^{\mathrm{i}}_{\mathrm{pH\,5.0}}}{c^{\mathrm{u}}_{\mathrm{pH\,5.0}}}}{1 + \dfrac{c^{\mathrm{i}}_{\mathrm{pH\,1.0}}}{c^{\mathrm{u}}_{\mathrm{pH\,1.0}}}} \tag{79}$$

The ratios of concentrations of the ionized form of the dye to the unionized form at a given pH are given by the weak acid form of the Henderson-Hasselbalch equation (Eq. 56),

$$\frac{c^{\mathrm{i}}_{\mathrm{pH\,5.0}}}{c^{\mathrm{u}}_{\mathrm{pH\,5.0}}} = 10^{5.0-6.09} = 0.0813 \tag{80}$$

$$\frac{c^{\mathrm{i}}_{\mathrm{pH\,1.0}}}{c^{\mathrm{u}}_{\mathrm{pH\,1.0}}} = 10^{1.0-6.09} = 8.1283 \cdot 10^{-6} \tag{81}$$

Substituting Eqs. 80 and 81 into Eq. 79 yields

$$\overline{K}_{\mathrm{pH\,5.0\,/\,pH\,1.0}} = 1.0813 \approx 1.1 \tag{82}$$

- **Partition coefficient in epidermis and dermis 1 (inner and outer regions)**

The partition coefficients are calculated as the ratios of the total dye concentrations in a solution at the natural pH of the skin layers, taken to be pH 7.4 (Kasting GB. 2006. Personal communication), to the total dye concentration in an aqueous solution at pH 1.0, where the dye is effectively 100% unionized. The partition coefficients in the epidermis, dermis 1 and dermis 2, outer region, skin layers are

$$\overline{K}_{\mathrm{ve/pH\,1.0}} = \frac{c^{\mathrm{u}}_{\mathrm{pH\,7.4}} + c^{\mathrm{i}}_{\mathrm{pH\,7.4}}}{c^{\mathrm{u}}_{\mathrm{pH\,1.0}} + c^{\mathrm{i}}_{\mathrm{pH\,1.0}}} \cdot f_{\mathrm{excl,\,ve}} \tag{83}$$

$$\overline{K}_{\mathrm{de1\ /\,pH\,1.0}} = \frac{c^{\mathrm{u}}_{\mathrm{pH\,7.4}} + c^{\mathrm{i}}_{\mathrm{pH\,7.4}}}{c^{\mathrm{u}}_{\mathrm{pH\,1.0}} + c^{\mathrm{i}}_{\mathrm{pH\,1.0}}} \cdot f_{\mathrm{excl,\,de1}} \tag{84}$$

$f_{\mathrm{excl,\,ed}}$ and $f_{\mathrm{excl,\,de1}}$ are volume exclusion factors reflecting the volume fraction accessible to a solute in epidermis and dermis.[86] Factoring out the concentration of the unionized form of the dye in the numerator and denominator of Eqs. 83 and 84 and recognizing that the concentration of an unionized species is independent of pH yields

$$\overline{K}_{\mathrm{ve}} = \frac{1 + \dfrac{c^{\mathrm{i}}_{\mathrm{pH\,7.4}}}{c^{\mathrm{u}}_{\mathrm{pH\,7.4}}}}{1 + \dfrac{c^{\mathrm{i}}_{\mathrm{pH\,1.0}}}{c^{\mathrm{u}}_{\mathrm{pH\,1.0}}}} \cdot f_{\mathrm{excl,\,ve}} \tag{85}$$

and

$$\overline{K}_{\mathrm{de1}} = \frac{1 + \dfrac{c^{\mathrm{i}}_{\mathrm{pH\,7.4}}}{c^{\mathrm{u}}_{\mathrm{pH\,7.4}}}}{1 + \dfrac{c^{\mathrm{i}}_{\mathrm{pH\,1.0}}}{c^{\mathrm{u}}_{\mathrm{pH\,1.0}}}} \cdot f_{\mathrm{excl,\,de1}} \tag{86}$$

The ratio of concentrations of the ionized form of the dye to the unionized form at pH 1.0 is given in Eq. 81. Using the Henderson-Hasselbalch equation (Eq. 56) for the ratio at pH 7.4 yields

$$\frac{c^{\mathrm{i}}_{\mathrm{pH\,7.4}}}{c^{\mathrm{u}}_{\mathrm{pH\,7.4}}} = 10^{7.4-6.09} = 20.4174 \tag{87}$$

with the value of the dye pK_a calculated in section 7.5.1. Following the results of Khalil *et al*. for the diffusion of glucose into human cadaver skin,[87] the value of the epidermal and dermal volume exclusion factors are

$$f_{\mathrm{ecxl,\,ve}} = 0.8 \tag{88}$$

$$f_{\mathrm{ecxl,\,de1}} = 0.65 \tag{89}$$

Substituting Eqs. 81 and Eq. 88 into Eq. 85 and Eqs. 87 and 89 into Eq. 86 yields the partition coefficients in the inner and outer regions of the viable epidermis and dermis 1:

$$\overline{K}_{\mathrm{ve}} = 17.1335 \approx 17 \tag{90}$$

$$\overline{K}_{\mathrm{de1}} = 13.9209 \approx 14 \tag{91}$$

- **Partition coefficient in the dermis 2 inner and outer regions**

The partition coefficient of the dermis 2 inner region is calculated as a weighted average of the partition coefficients of dermis 1 and sebum assuming equal volume fractions of dermal and sebaceous gland tissue in the dermis 2. Thus

$$\overline{K}_{\mathrm{de2,\,i\,/\,pH\,1.0}} = 0.5 \cdot \overline{K}_{\mathrm{de1\,/\,pH\,1.0}} + 0.5 \cdot \overline{K}_{\mathrm{sebum\,/\,pH\,1.0}} \tag{92}$$

From Eq. 92 and the value of the dye partition coefficient in sebum, calculated below (Eqs. 99 to 101), the partition coefficient in the inner region of dermis 2 is

$$\overline{K}_{\mathrm{de2,\,i\,/\,pH\,1.0}} = 19.7764 \approx 20 \tag{93}$$

For the outer region of dermis 2,

$$\overline{K}_{\mathrm{de2,\,o\,/\,pH\,1.0}} = \overline{K}_{\mathrm{de1\,/\,pH\,1.0}} \approx 14 \tag{94}$$

- **Partition coefficient in the hypodermis inner and outer regions**

Approximating the hypodermal tissue as a mixture of 80% olive oil and 20% water, the partition coefficient of the dye in this skin layer is given by

$$\overline{K}_{\mathrm{hd}} = 0.8\,\overline{K}_{\mathrm{oil\,/\,pH\,1.0}} + 0.2\,\overline{K}_{\mathrm{pH\,7.4\,/\,pH\,1.0}} \tag{95}$$

where the subscript "oil" denote olive oil. The partition coefficient in olive oil referenced to an aqueous solution at pH 7.4 is obtained by applying a solvent regression equation for olive oil,[88]

$$\log K^{\mathrm{u}}_{\mathrm{oil\,/\,pH\,7.4}} = 1.099 \log K^{\mathrm{u}}_{\mathrm{oct\,/\,pH\,7.4}} - 1.310 \tag{96}$$

Substituting $K^{\mathrm{u}}_{\mathrm{oct\,/\,pH\,7.4}} = 342$ (Eq. 61) into Eq. 96 yields

$$K^{\mathrm{u}}_{\mathrm{oil\,/\,pH\,7.4}} = \frac{c^{\mathrm{u}}_{\mathrm{oil}}}{c^{\mathrm{u}}_{\mathrm{pH\,7.4}}} \approx \frac{c^{\mathrm{u}}_{\mathrm{oil}}}{c^{\mathrm{u}}_{\mathrm{pH\,1.0}}} = 29.8466 \tag{97}$$

where we have used the fact that the concentration of the unionized form of a chemical species is independent of pH. Using Eqs. 81, 87 and 96, Eq. 95 is rewritten as

$$\overline{K}_{\mathrm{hd/pH\,1.0}} = 0.8 \cdot \frac{c^{\mathrm{u}}_{\mathrm{oil}} + c^{\mathrm{i}}_{\mathrm{oil}}}{c^{\mathrm{u}}_{\mathrm{pH\,1.0}} + c^{\mathrm{i}}_{\mathrm{pH\,1.0}}} + 0.2 \cdot \frac{c^{\mathrm{u}}_{\mathrm{pH\,7.4}} + c^{\mathrm{i}}_{\mathrm{pH\,7.4}}}{c^{\mathrm{u}}_{\mathrm{pH\,1.0}} + c^{\mathrm{i}}_{\mathrm{pH\,1.0}}}$$

$$\Rightarrow \overline{K}_{\mathrm{hd/pH\,1.0}} = 0.8 \cdot \frac{29.8466\, c^{\mathrm{u}}_{\mathrm{pH\,1.0}}}{c^{\mathrm{u}}_{\mathrm{pH\,1.0}} + 8.1283 \cdot 10^{-6} c^{\mathrm{u}}_{\mathrm{pH\,1.0}}} + 0.2 \cdot \frac{c^{\mathrm{u}}_{\mathrm{pH\,7.4}} + 20.4174\, c^{\mathrm{u}}_{\mathrm{pH\,7.4}}}{c^{\mathrm{u}}_{\mathrm{pH\,1.0}} + 8.1283 \cdot 10^{-6} c^{\mathrm{u}}_{\mathrm{pH\,1.0}}}$$

from which we obtain

$$\overline{K}_{\mathrm{hd/pH\,1.0}} = 28.1632 \approx 28 \tag{98}$$

in the inner and outer regions of the hypodermis.

- **Partition coefficient in the sebum**

The partition coefficient of the dye in the sebum of the infundibulum is calculated by assuming the sebum to be equivalent to a mixture of 50% olive oil and 50% water (pH 7.4). Thus

$$\overline{K}_{\mathrm{sebum/pH\,1.0}} = 0.5 \cdot K_{\mathrm{oil/pH\,1.0}} + 0.5 \cdot K_{\mathrm{pH\,7.4/pH\,1.0}} \tag{99}$$

Replacing the partition coefficients by the ratios of concentrations in each phase yields

$$\overline{K}_{\mathrm{sebum/pH\,1.0}} = 0.5 \cdot \frac{c^{\mathrm{u}}_{\mathrm{oil}} + c^{\mathrm{i}}_{\mathrm{oil}}}{c^{\mathrm{u}}_{\mathrm{pH\,1.0}} + c^{\mathrm{i}}_{\mathrm{pH\,1.0}}} + 0.5 \cdot \frac{c^{\mathrm{u}}_{\mathrm{pH\,7.4}} + c^{\mathrm{i}}_{\mathrm{pH\,7.4}}}{c^{\mathrm{u}}_{\mathrm{pH\,1.0}} + c^{\mathrm{i}}_{\mathrm{pH\,1.0}}} \tag{100}$$

With $c^{\mathrm{i}}_{\mathrm{oil}} = 0$, and substituting Eq. 81, 87 and 97 into Eq. 101, the partition coefficient of the dye in sebum is

$$\overline{K}_{\mathrm{sebum/pH\,1.0}} = 25.6318 \approx 26 \tag{101}$$

- **Partition coefficient in outer root sheath**

Since the outer root sheath is continuous with the viable epidermis, we take the partition coefficient of BFL in the outer root sheath to be equal to that in viable epidermis. Thus

$$\overline{K}_{\text{ors / pH1.0}} = \overline{K}_{\text{ve / pH1.0}} \approx 17 \tag{102}$$

- **Partition coefficient in the sublayer**

The tissue properties of the sublayer used in the mathematical model below the hypodermis are assumed equivalent to the properties of the hypodermis. Thus

$$\overline{K}_{\text{sublayer / pH1.0}} = \overline{K}_{\text{hd / pH1.0}} \approx 28 \tag{103}$$

7.5.4 Diffusion coefficients

The diffusion coefficients of the dye in the inner and outer regions of the viable epidermis, dermis 1 and in the outer region of dermis 2 are calculated by estimating the diffusivity of the dye in water at very low concentration using the Wilke-Chang correlation. The cellular components of these skin layers are taken into account by multiplying the values obtained from the Wilke-Chang correlation by an appropriate hindrance factor.

As the hypodermis is modeled as a mixture of water and olive oil, the diffusivity of the dye in hypodermis is assumed to be the dye's diffusivity in the dominant component olive oil, also calculated using the Wilke-Chang correlation, modified by a hindrance factor.

Grams *et al.*'s diffusion experiment was performed at "ambient temperature" (Bouwstra JA. 2006. Personal communication). The temperature assumed in all calculations is 23 °C or 296 K.

As is the case for the partition coefficient, the diffusion coefficient of the dye in the inner region of dermis 2 is calculated by assuming this region of the computational domain to be a mixture of 50% dermal tissue and 50% sebum in order to take into account the presence of the sebaceous gland.

The diffusion coefficient of the dye in sebum is calculated by approximating sebum as an aqueous phase (sebaceous gland cells) dispersed in an oily matrix phase taken to be olive oil. The diffusivity of the dye is calculated from the Maxwell-Jeffrey formula[89,90] for the effective diffusivity of a substance in a 2-phase medium with unequal partitioning.

- **Diffusion coefficients in the viable epidermis and dermis 1 (inner and outer regions)**

The Wilke Chang correlation for the diffusivity of the dye in water is

$$D^{\circ}_{\text{dye, water}} = \frac{7.4 \cdot 10^{-8} \left(\phi_{\text{water}}\, Mw_{\text{water}}\right)^{0.5} T}{\mu_{\text{water}} V_{\text{dye}}^{0.6}} \tag{104}$$

where ϕ_{water} is the water association factor, Mw_{water} and μ_{water} are the molecular weight and viscosity of water, respectively, and V_{dye} is the molar volume of the diffusing dye. V_{dye} is calculated from an additive method known as Schroeder's method,[91] which yields an estimate of the molar volumes at the normal boiling point from the number of C, H, O,

N, S and halogen atoms, the number of double and triple bonds, and the presence of one ore more aromatic rings (counted the last term):

$$V_b = 7\left(N_C + N_H + N_O + N_N + N_{DB} + 2N_{TB}\right) + 31.5N_{Br} + 24.5N_{Cl} + 10.5N_F + 38.5N_I + 21N_S - 7* \quad (105)$$

In the case of Bodipy® FL C_5 the molar volume is 336 cm^3/mol. Table 7-3 gives the values of the water solvent parameters used to calculate the diffusivity of the dye in viable epidermis and dermis 1.

A hindrance factor of 1/3 is used to describe the diffusion of the dye in the dermis 1 skin layer (inner and outer regions) compared to diffusion in bulk water:

$$D_{de1} = \frac{1}{3} D^{\circ}_{dye,w} \quad (106)$$

This factor was obtained by Khalil *et al*. for the diffusion of glucose into human cadaver skin.[87] The cellular structure of the epidermis is expected to further hinder the diffusion of the dye. The diffusion coefficient of the dye in epidermis is assumed to be 1/10 of that in dermis 1:

$$D_{ve} = \frac{1}{10} D_{de1} = \frac{1}{30} D^{\circ}_{dye,w} \quad (107)$$

With these hindrance factors and the parameter values given in Table 7-3, the diffusion coefficients of the dye in the epidermis and dermis 1 inner and outer regions are

$$D_{ve} \approx 0.0152 \cdot 10^{-5} \text{ cm}^2/\text{s} \quad (108)$$

$$D_{de1} \approx 0.152 \cdot 10^{-5} \text{ cm}^2/\text{s} \quad (109)$$

- **Diffusion coefficients in the dermis 2 inner and outer regions**

The diffusion coefficient of the dye in the dermis 2 inner tissue (subscript "de2,i") is calculated as an average of the diffusion coefficients of the dye in dermis 1 and in sebum, weighted by the partition coefficients these media:

$$D_{\mathrm{de2,i}} = \frac{0.5 D_{\mathrm{de1}} K_{\mathrm{de1/pH1.0}} + 0.5 D_{\mathrm{sebum}} K_{\mathrm{sebum/pH1.0}}}{0.5 K_{\mathrm{de1/pH1.0}} + 0.5 K_{\mathrm{sebum/pH1.0}}} \tag{110}$$

From Eqs. 93, 101, 109 and $D_{\mathrm{sebum}} = 0.088 \cdot 10^{-5}$ cm^2/s (Eq. 117) this diffusivity is

$$D_{\mathrm{de2,i}} \approx 0.111 \cdot 10^{-5} \mathrm{cm}^2/\mathrm{s} \tag{111}$$

The outer region of dermis 2 is taken as pure dermal tissue without sebaceous gland tissue. The dye diffusion coefficient is set equal to that of the dermis 1 inner and outer regions:

$$D_{\mathrm{de2,o}} = D_{\mathrm{de1}} \approx 0.152 \cdot 10^{-5} \mathrm{cm}^2/\mathrm{s} \tag{112}$$

Table 7-3. Parameter values used for calculation of the dye diffusion coefficient in bulk water and olive oil from the Wilke-Chang correlation (Eq. 104)

	WATER	**OLIVE OIL**
ϕ	2.26 [a]	1.0 [a]
μ_w (*T*=23 °C) [cP]	0.94 [b]	74 [b]
Mw [g/mol]	18.05	885 [c]

[a] Source: ref. [92]
[b] Calculated from data obtained in the online version of the Smithsonian Physical Tables.[93]
[c] Average molecular weight of triolein, the main component of olive oil[94,95]

- **Diffusion coefficients in the hypodermis (inner and outer regions)**

The diffusion coefficient of BFL in bulk olive oil is calculated from the Wilke-Chang correlation using the parameter values for olive oil as a solvent (Table 7-3) and the molar volume V_{dye} = 336 cm^3/mol. The cellular structure of the hypodermis is assumed to hinder diffusion compared to bulk olive oil by a factor of 1/10. The diffusion coefficient of the dye in the inner and outer regions of the hypodermis is thus

$$D_{\text{hd}} = \frac{1}{10} D^{\circ}_{\text{dye,oil}} \approx 0.0027 \cdot 10^{-5}\,\text{cm}^2/\text{s} \tag{113}$$

- **Diffusion coefficient in sebum**

The Maxwell-Jeffrey formula for the effective diffusivity $\overline{D}$ in a 2-phase medium with equal partitioning, consisting of spherical inclusions with diffusivity D_2 a partition coefficient $K_{2/\text{ref}}$ and a volume fraction φ dispersed at a volume fraction $\varphi \ll 1$ in a matrix with diffusivity D_1 and a partition coefficient $K_{1/\text{ref}}$, is[90]

$$\overline{D} = \overline{D}\left[D_1, D_2, 1\right] = D_1\left[1 + 3\left(\frac{D_2 - D_1}{D_2 + 2D_1}\right)\varphi + c_2\varphi^2\right] \tag{114}$$

In the case of unequal partitioning between the phases, the 2-phase medium is taken as one with phase "2" having a diffusivity $D_2 K_{2/1}$; $K_{2/1}$ is the partition coefficient in phase "2" relative to phase "1". The effective diffusivity is then[96]

$$\overline{D} = \overline{D}\left[D_1, D_2 K_{2/1}, 1\right] = D_1\left[1 + 3\left(\frac{D_2 K_{2/1} - D_1}{D_2 K_{2/1} + 2D_1}\right)\varphi + c_2\varphi^2\right] \tag{115}$$

Eq. 115 is used to calculate the effective diffusivity of BFL in sebum, which is approximated as a composite medium consisting of spherical aqueous inclusions (the sebaceous gland cells) dispersed in an oily matrix assumed equivalent to olive oil. Since we are assuming sebum to be a 50% mixture of water and 50% olive oil, the volume fraction of the aqueous phase is $\varphi = 0.5$. Applying Eq. 115 to sebum thus yields

$$D_{\text{sebum}} = D^{\circ}_{\text{water}} \left[1 + 3 \left(\frac{D^{\circ}_{\text{oil}} K_{\text{oil/water}} - D^{\circ}_{\text{water}}}{D^{\circ}_{\text{oil}} K_{\text{oil/water}} + 2 D^{\circ}_{\text{water}}} \right) \varphi + c_2 \varphi^2 \right] \tag{116}$$

where D°_{water} and D°_{oil} are the dye diffusion coefficients in bulk water and olive oil calculated from the Wilke-Chang correlation, and $K_{\text{oil/water}} = K_{\text{oil/pH 1.0}} \big/ K_{\text{pH 7.4/pH 1.0}}$ is the partition coefficient of the dye in the oily phase (olive oil) with respect to the aqueous phase (pH 7.4), calculated from Eqs. 82, 87 and 97. The value of the constant c_2 depends on the ratio of the diffusivities and is obtained from [90]. The diffusivity of the dye Bodipy ® FL C_5 is calculated to be

$$D_{\text{sebum}} \approx 0.088 \cdot 10^{-5} \text{cm}^2/\text{s} \tag{117}$$

Table 7-4 summarizes the values of the diffusion and partition coefficients in the skin regions used to obtain the results presented in sections 7.4 and 7.5.

Table 7-4: Diffusion (D) and partition (K) coefficients in the skin regions used in the simulation of the diffusion of Bodipy® FL C_5 into the skin near a hair follicle.

		D / 10^{-5} [cm^2/s]	K / pH 1.0
	Sebum	0.088	26
	Outer root sheath	/	17
Inner region	**Viable epidermis**	0.0152	17
	Dermis 1	0.152	14
	Dermis 2	0.111	20
	Hypodermis	0.0027	28
Outer region	**Viable epidermis**	0.0152	17
	Dermis 1	0.152	14
	Dermis 2	0.152	14
	Hypodermis	0.0027	28

7.5.5 Rate coefficients for vascular clearance

To simulate the *in vitro* diffusion of BFL through the skin, the vascular clearance rate coefficients k_α in all skin regions α of the computational domain are set to zero.

In vivo diffusion is simulated by taking into account blood flow in the regions of dense vascularization. These are the entire papillary dermis, represented by the dermis 1 in the mathematical model, and the inner region of the computational domain, i.e. in the inner regions of dermis 2 and hypodermis near the hair follicle. In these regions the

vascular clearance rate coefficients k_α are set to non-zero values. In the other regions of the computational domain, where the network of blood vessels is much less dense, $k_\alpha = 0$.

From a distributed clearance model Kretsos *et al*. obtained values of the dermal clearance rate coefficient k_{de} ranging from $0.4 \cdot 10^{-4}$ to $10 \cdot 10^{-4}$ s^{-1} for a range of permeants (Kretsos *et al*., submitted). This value is an average over the volume of the entire dermis, whose thickness in Kretsos *et al*.'s model is taken to be 2 mm.[78]

In the present model we assume the value of the clearance coefficient in the outer region of the dermis 2, which has a thickness of 1.7 mm (section 4.2), to be the average of Kretsos *et al*.'s values, that is,

$$k_{\text{de 2, outer}} = 3.7 \cdot 10^{-4} \text{s}^{-1} \tag{118}$$

The dermis 1 skin layer is 200 μm thick. As an initial estimate, we assume the clearance rate coefficient in the inner and outer region of dermis 1, as well as in the inner region of the hypodermis, to be 10 times the values in the outer region of dermis 2:

$$k_{\text{de 1, inner}} = k_{\text{de 1, outer}} = k_{\text{de 2, inner}} = k_{\text{hd, inner}} = 3.7 \cdot 10^{-3} \text{s}^{-1} \tag{119}$$

Because of the lack of blood vessels in the epidermis and their scarcity in bulk hypodermis, we set the clearance rate coefficients in the inner and outer regions of the epidermis, and in the outer region of the hypodermis equal to zero:

$$k_{\text{ve, inner}} = k_{\text{ve, outer}} = k_{\text{hd, outer}} = 0 \tag{120}$$

The effect of capillary clearance in the papillary dermis (dermis 1) and close to the hair follicle on the BFL concentration levels is investigated by running the simulation of *in*

vivo diffusion for the value of the clearance rate coefficients $k_{\mathrm{de\,1,inner}}$, $k_{\mathrm{de\,1,outer}}$, $k_{\mathrm{de\,2,inner}}$, and $k_{\mathrm{hd,\,inner}}$ as given in Eq. 119 as well as equal to 5 times than value, or $1.85 \cdot 10^{-2}$ s^{-1} while keeping the clearance rates in the other regions constant at the values specified in Eq. 118 and 120.

7.5.6 Permeant concentration in sebum

Two cases are considered for the delivery of the permeant into the sebum of the infundibulum. In the first case the permeant is assumed to diffuse downward from the donor solution compartment into the sebum of the infundibulum according to a transient 1-D concentration profile in depth *z*,

$$c_{\mathrm{sebum}}(z,t) = \frac{K_{\mathrm{sebum\,/\,pH\,1.0}}}{K_{\mathrm{ds\,/\,pH\,1.0}}} c_{\mathrm{ds}}(t)\,\mathrm{erfc}\left(\frac{z_0 - z}{2\sqrt{D_{\mathrm{sebum}}t}}\right) \tag{121}$$

where $z_0 = 0$ denotes the infundibulum/donor compartment interface. The calculation of the donor solution concentration $c_{\mathrm{ds}}(t)$ is detailed in Appendix C.

The second case considers an upper bound value for the permeant concentration in the sebum. The permeant is assumed to be well-mixed in the sebum and its concentration is set by the sebum/donor solution partition coefficient at the infundibulum/donor compartment interface:

$$c_{\mathrm{sebum}}(t) = \frac{K_{\mathrm{sebum\,/\,pH\,1.0}}}{K_{\mathrm{ds\,/\,pH\,1.0}}} c_{\mathrm{ds}}(t) \tag{122}$$

The partition coefficients of the dye in the donor solution and in the sebum relative to a pH 1.0 solution are given by Eqs. 82 and 101.

7.5.7 Overview of cases

Tables 7.5 and 7.6 show the cases for which results for the concentration of BFL are presented in sections 7.4 and 7.5. The odd-numbered cases are for the transient concentration of BFL in the infundibulum of the hair follicle; the even-numbered cases are for the constant (well-mixed) dye concentration in the infundibulum. In cases 1 and 2, the hair follicle is impermeable, in cases 3 and 4, the permeability of the hair follicle is due only to the intrinsic permeability of the infundibulum, and in cases 5 and 6, it is a sum of the intrinsic infundibulum permeability and the contribution of the sebaceous duct. The letter "a" represents *in vitro* diffusion (k_α = 0for all skin layers α) and cases "b", "c", "d" and "e" represent *in vivo* diffusion with the various values of the clearance rate coefficients $k_{\text{de 1, inner}}$, $k_{\text{de 1, outer}}$, $k_{\text{de 2, inner}}$ and $k_{\text{hd, inner}}$ as explained in section 7.3.5.

Table 7-5: Overview of the simulation cases run for the diffusion of Bodipy® FL C_5 into the skin near a hair follicle.

	TRANSIENT c_{infund}	**CONSTANT** c_{infund}	
$P_{\text{ors / pH 1.0}} = 0$	Case 1a	Case 2a	***in vitro***
	Cases 1b, c, d, e	Cases 2b, c, d, e	***in vivo***
$P_{\text{ors / pH 1.0}} = P_{\text{infund / pH 1.0}}$	Case 3a	Case 4a	***in vitro***
	Cases 3b, c, d, e	Cases 4b, c, d, e	***in vivo***
$P_{\text{ors / pH 1.0}} = P_{\text{infund / pH 1.0}} + P_{\text{duct / pH 1.0}}$	Case 5a	Case 6a	***in vitro***
	Cases 5b, c, d, e	Cases 6b, c, d, e	***in vivo***

Table 7-6: Values of the clearance rate coefficients k_α [s^{-1}] used in the simulation of the diffusion of Bodipy® FL C_5 into the skin near a hair follicle.

CASE	$k_{ve,\,inner}$	$k_{ve,\,outer}$	$k_{de1,\,inner}$	$k_{de1,\,outer}$	$k_{de2,\,inner}$	$k_{de2,\,outer}$	$k_{hd,\,inner}$	$k_{hd,\,inner}$
a	0	0	0	0	0	0	0	0
b	0	0	0.0037	0.0037	0.0037	0.00037	0.0037	0
c	0	0	0.0185	0.0185	0.0185	0.00037	0.0185	0

7.6 Results for unvascularized tissue (comparison to Grams *et al.*'s *in vitro* results)

7.6.1 Presentation of results

In this section and in section 7.7 the concentration profiles of Bodipy® FL C_5 (BFL) obtained from the simulations for each case highlighted in Tables 7.5 and 7.6 are presented in three types of graphs:

1. The average BFL concentrations in the viable epidermis, $\bar{c}_{ve}(t)$, in the dermis, $\bar{c}_{de}(t)$, and at the hair follicle/skin tissue boundary $\bar{c}_{hf/skin}(t)$ as a function of the simulation time *t*. These average concentrations are calculated from Eqs. C4 to C6 (Appendix C) within the averaging volume defined in section 7.2.
2. The BFL concentration as a function of depth *z* into the skin at *t* = 16 h at the hair follicle/skin tissue boundary, $c_{hf/skin}(z)$, at the boundary of the inner and outer region

of the computational domain, $c_{\text{inner/outer}}(z)$, and at right horizontal boundary of the computational system $(r = 5\,\text{mm})$.

3. The BFL concentration as a function of radial distance *r* away from the hair follicle at *t* = 16 h at the top boundary of the viable epidermis, $c_{\text{sc/ve}}(r)$, at the viable epidermis/dermis 1 boundary $c_{\text{ve/de1}}(r)$, and at the dermis 1/dermis 2 boundary $c_{\text{de1/de2}}(r)$.

7.6.2 Case 1a: Impermeable hair follicle, transient dye penetration into sebum

- **Average concentrations (Figure 7-9A)**

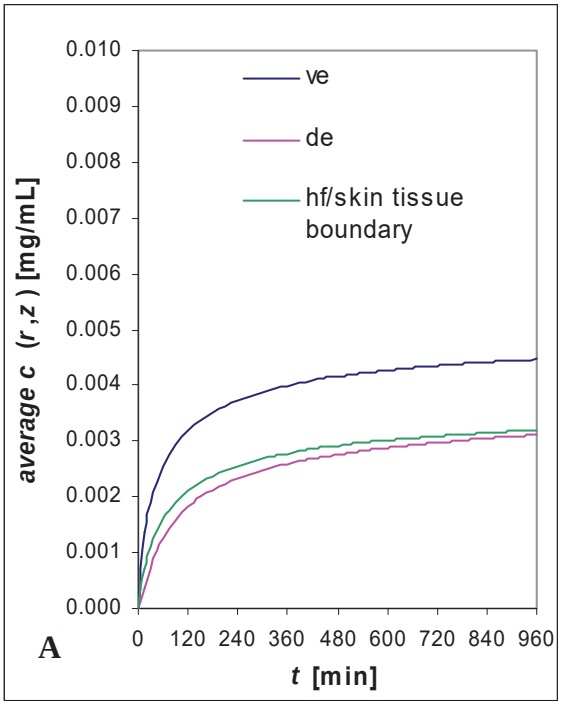
The average concentrations increase monotonously over the duration of the simulation, with $\bar{c}_{\text{ve}}(t) > \bar{c}_{\text{hf / skin}}(t) > \bar{c}_{\text{de}}(t)$ at all times *t*. The slope of the average concentrations is greater within the first 2 h of the simulation, increasing from 0 to $3.2 \cdot 10^{-3}$ mg/mL, $2.1 \cdot 10^{-3}$ mg/mL and $1.8 \cdot 10^{-3}$ mg/mL in the epidermis, at the hair follicle/skin tissue boundary and in the dermis, respectively. During this initial period of diffusion, the concentration ratios are $\bar{c}_{\text{ve}}(t)/\bar{c}_{\text{de}}(t)$ = 1.8 to 4.0, $\bar{c}_{\text{ve}}(t)/\bar{c}_{\text{hf / skin}}(t)$ = 1.5 to 2.0 and $\bar{c}_{\text{hf / skin}}(t)/\bar{c}_{\text{de}}(t)$ = 1.2 to 2.0. As time increases, the slopes of the average concentrations decrease significantly. At *t* = 16h, the average concentrations in the epidermis, at the hair follicle/skin tissue boundary and in the dermis are: $\bar{c}_{\text{ve}}(t = 16\,\text{h}) = 4.5 \cdot 10^{-3}$ mg/mL, $\bar{c}_{\text{hf / skin}}(t = 16\,\text{h}) = 3.2 \cdot 10^{-3}$ mg/mL, and $\bar{c}_{\text{de}}(t = 16\,\text{h}) = 3.1 \cdot 10^{-3}$ mg/mL. For 2 h < $t \leq$ 16 h, the concentration ratios are $\bar{c}_{\text{ve}}(t)/\bar{c}_{\text{de}}(t)$ = 1.4 to 1.7, $\bar{c}_{\text{ve}}(t)/\bar{c}_{\text{hf / skin}}(t)$ = 1.4 to 1.5 and $\bar{c}_{\text{hf / skin}}(t)/\bar{c}_{\text{de}}(t)$ = 1.0 to 1.1 and decrease with *t*.

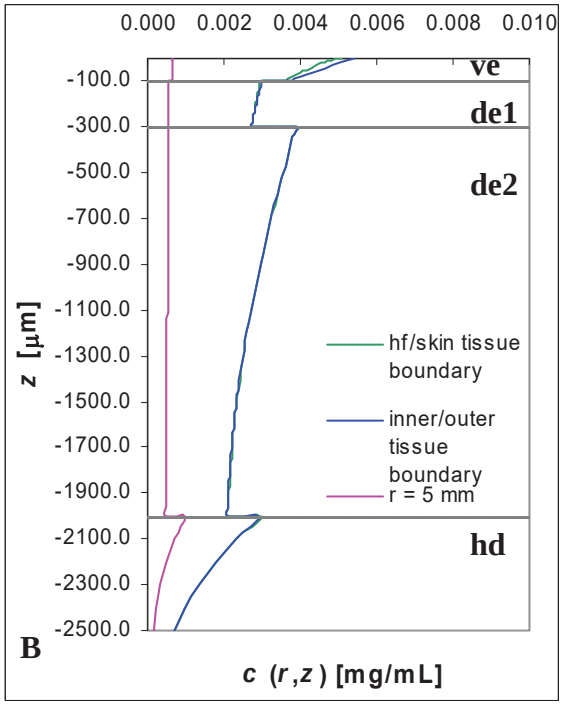
- **Concentration vs. depth *z* (Figure 7-9B)**

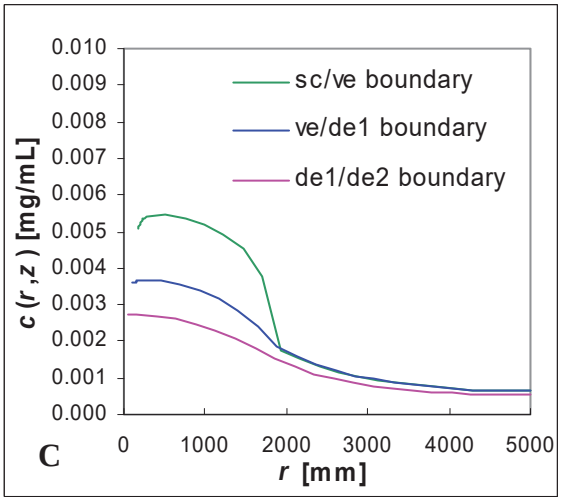
The concentration decreases monotonically with depth at the hair follicle/skin tissue boundary, at the inner/outer tissue boundary and at a distance r = 5 mm away from the hair follicle, where diffusion is essentially one dimensional in z. In the viable epidermis, the concentration at the inner/outer tissue boundary is 2 to 60% greater than the concentration at the hair follicle/skin tissue boundary, with the difference decreasing with increasing depth. In dermis 1 this difference decreases from 1.5% to essentially zero at the dermis 1/dermis 2 boundary. In bulk dermis 2 the model also yields $c_{\text{in / out}}(z) > c_{\text{hf / skin}}(z)$, but the differences is less than 1%.

- **Concentration vs. radial distance *r* (Figure 7-9C)**

These concentration profiles confirm the fact that for in the case of an impermeable hair follicle, the concentration increases up to 6% with r within the inner region of the computational domain. The magnitude of the increase decreases with increasing depth into the skin. The reason for the result is given in the discussion (section 7.7.1). Each profile of Figure 7.9B displays a notable decrease in the concentration is seen around r = 1.78 mm. This distance from the hair follicle marks the edge of the donor solution compartment and the permeability of the stratum corneum $P_{\text{sc / pH 1.0}}(r)$ is set to 0 for $r >$ 1.78 mm (Eq. 63). Outside this radius there is no supply of dye from above, the concentration levels are therefore lower. The magnitude of this decrease in concentration curve diminishes as depth into the skin increases.







Figures 7-9:
A: Average concentrations in viable epidermis (ve), dermis (de) and at hair follicle/skin tissue boundary, **B:** Concentration vs. depth profiles at t = 16 h at the hair follicle/skin tissue and the inner/outer region boundaries and at r = 5 mm from the hair follicle, **C:** Concentration vs. radial distance at t = 16 h at the stratum corneum (sc)/viable epidermis, the viable epidermis/dermis 1 (de1) and the dermis 1 /dermis 2 (de2) boundaries, for **Case 1a**: impermeable hair follicle and transient dye penetration in sebum.

7.6.3 Case 2a: Impermeable hair follicle, constant (well-stirred) dye concentration in sebum

The results obtained for an impermeable hair follicle, with a constant BFL concentration in the infundibulum of the hair follicle were identical as those obtained in Case 1a. The concentration profiles in the skin surrounding the hair follicle remained unchanged since the excess dye inside the infundibulum could not diffuse into the surrounding tissue. Although the donor solution depletion into the sebum is slightly greater in Case 2a than in Case 1a, the dye has nowhere to diffuse. The amount that penetrated into the skin tissue from the donor solution was identical in both cases even at t = 15 min, the first time point at which the concentrations are recorded.

7.6.4 Case 3a: Hair follicle permeability equal to intrinsic infundibulum permeability, transient dye penetration into sebum

- **Average concentrations (Figure 7-10A)**

Allowing BFL to diffuse from the infundibulum of the hair follicle into the surrounding skin tissue alters the amount of permeant inside the skin. While the average concentrations $\bar{c}_{ve}(t)$, $\bar{c}_{de}(t)$ and $\bar{c}_{hf/skin}(t)$ increase monotonically with time with $\bar{c}_{ve}(t) > \bar{c}_{hf/skin}(t) > \bar{c}_{de}(t)$ as in Case 1a, the average concentrations reached at t = 2 h are now $\bar{c}_{ve}(t = 2\,\text{h}) = 4.41 \cdot 10^{-3}$ mg/mL, $\bar{c}_{hf/skin}(t = 2\,\text{h}) = 3.40 \cdot 10^{-3}$ mg/mL, and $\bar{c}_{de}(t = 2\,\text{h}) = 2.59 \cdot 10^{-3}$ mg/mL. The maximum average concentrations reached in the epidermis, the dermis and at the hair follicle/skin tissue boundary are $\bar{c}_{ed}(t = 16\,\text{h}) = 6.15 \cdot 10^{-3}$ mg/mL, $\bar{c}_{hf/skin}(t = 16\,\text{h}) = 4.3610^{-3}$ mg/mL, and $\bar{c}_{de}(t = 16\,\text{h}) = 4.84 \cdot 10^{-3}$ mg/mL. These values are 40 to 50% higher than in the case of an impermeable hair follicle within

the viable epidermis and the dermis, and 50 to 60% higher at the hair follicle/skin tissue boundary. As in Case 1a the average concentration ratios decrease with time for $0 < t \leq 2$ h, but remain roughly constant for $t > 2$ h. For 2 h $< t \leq 16$ h, these ratios are essentially equal in Case 3a as in Case 1a: $\bar{c}_{ve}(t)/\bar{c}_{de}(t)$ = 1.4 to 1.7, $\bar{c}_{ve}(t)/\bar{c}_{hf\,/\,skin}(t) \approx 1.3$ and $\bar{c}_{hf\,/\,skin}(t)/\bar{c}_{de}(t)$ = 1.1 to 1.3.

- **Concentration vs. depth *z* (Figure 7-10B)**

A significant difference in the concentration profiles at t = 16 h is seen compared to Case 1a. The concentration decreases as the radial distance away from the hair follicle increases. The concentration at the top of the viable epidermis is $c_{hf/skin}(z = 0) = 7.47 \cdot 10^{-3}$ mg/mL at the hair follicle/skin tissue boundary and $c_{inner/outer}(z = 0) = 6.76 \cdot 10^{-3}$ mg/mL at the inner/outer tissue boundary. These values decrease to $c_{hf/skin}(z = -100\,\mu m) = 5.16 \cdot 10^{-3}$ mg/mL and $c_{inner/outer}(z = -100\,\mu m) = 4.91 \cdot 10^{-3}$ mg/mL at the viable epidermis/dermis 1 junction. Within the viable epidermis the concentrations at the hair follicle boundary are 5 to 12% greater than at the inner/outer tissue boundary.

At the viable epidermis/dermis 1 junction inside dermis 1, the concentrations at the vertical boundaries of the inner tissue region are $c_{hf/skin}(z = -100\,\mu m) = 4.27 \cdot 10^{-3}$ mg/mL and $c_{inner/outer}(z = -100\,\mu m) = 4.04 \cdot 10^{-3}$ mg/mL. At the bottom surface of dermis 1, they are $c_{hf/skin}(z = -300\,\mu m) = 3.97 \cdot 10^{-3}$ mg/mL and $c_{inner/outer}(z = -300\,\mu m) = 3.8 \cdot 10^{-3}$ mg/mL, respectively. Overall, within dermis 1, the concentration is 5 to 6% greater at the hair follicle boundary than at the inner/outer tissue boundary.

The effect of the permeability of the infundibulum, which increases linearly with depth for -1000 μm ≤ z ≤ 0 (Eq. 68), is preponderant in the deeper dermis. In dermis 2 the concentration at the hair follicle/skin tissue boundary decreases from $c_{\text{hf/skin}}(z = \text{-}300\,\mu\text{m})$ = $5.67 \cdot 10^{-3}$ mg/mL to a local minimum of $5.38 \cdot 10^{-3}$ mg/mL at z = -640 μm, before increasing to a local maximum of $5.67 \cdot 10^{-3}$ mg/mL at z = -895 μm. At the inner/outer boundary the concentration in dermis 2 decreases monotonically from $c_{\text{inner/outer}}(z = \text{-}300\,\mu\text{m}) = 5.39 \cdot 10^{-3}$ mg/mL. For -980 μm ≤ z ≤ -300 μm, the concentration in dermis 2 is at the hair follicle/skin tissue boundary is 6 to 23% greater than at the inner/outer tissue boundary. The concentrations decrease sharply at greater depths. For $\text{-}2000\,\mu\text{m} \le z \le \text{-}980\,\mu\text{m}$, the values range from $c_{\text{hf/skin}}(z = \text{-}980\,\mu\text{m}) = 5.59 \cdot 10^{-3}$ mg/mL to $c_{\text{hf/skin}}(z = \text{-}2000\,\mu\text{m}) = 2.75 \cdot 10^{-3}$ mg/mL at the hair follicle boundary. The concentrations at the inner/outer tissue boundary are 0.5 to 8% smaller, with the difference diminishing with increasing depth. The concentration values in the hypodermis shown in Figure 7.9B range from $c_{\text{hf/skin}}(z = \text{-}2000\,\mu\text{m}) = 3.85 \cdot 10^{-3}$ mg/mL to $c_{\text{hf/skin}}(z = \text{-}2500\,\mu\text{m}) = 6.91 \cdot 10^{-4}$ mg/mL. The concentrations at the inner/outer tissue boundary are 0.5 to 1.2% less.

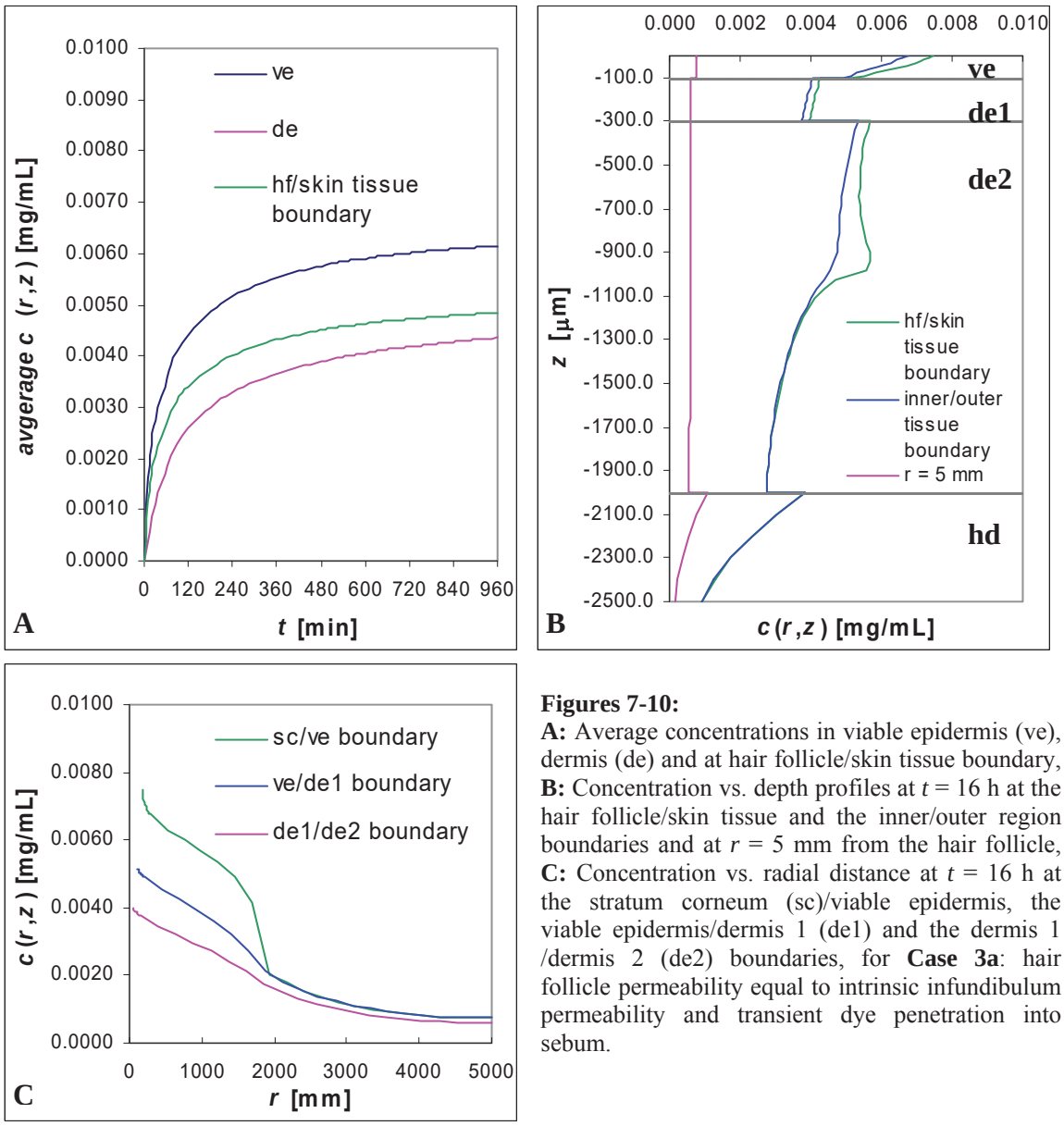
The concentration profile at a distance r = 5 mm away from the hair follicle is essentially 1-D diffusion as in Case 1a, with concentration values ranging from ~$7.4 \cdot 10^{-3}$ mg/mL in the viable epidermis to $1.5 \cdot 10^{-4}$ mg/mL at z = -2500 μm in the hypodermis. The important features in these concentration profiles are the maxima in the concentration near the hair follicle.

- **Concentration vs. radial distance *r* (Figure 7-10C)**

These concentration profiles confirm that the concentration decreases with increasing radial distance from the hair follicle. Within the inner region of the computational domain, the concentration decreases faster with *r* then at greater distances from the hair follicle, because of he supply from the infundibulum, but this effect diminishes with increasing depth into the skin. At the stratum corneum/viable epidermis boundary, the concentration drops about 9.5% from $c_{sc/ve}(r = 174.7\,\mu m) = 7.47{\cdot}10^{-3}$ mg/mL at the hair follicle/skin tissue boundary to $c_{sc/ve}(r = 282.8\,\mu m) = 6.76{\cdot}10^{-3}$ mg/mL the inner/outer tissue boundary. At the epidermis/dermis 1 boundary and the dermis 1/dermis 2 boundary, the concentration drops 5 to 6% within the inner region of the domain, from $c_{ve/de1}(r = 99.3\,\mu m) = 5.16{\cdot}10^{-3}$ mg/mL to $c_{ve/de1}(r = 209.0\,\mu m) = 4.91.0{\cdot}10^{-3}$ mg/mL at the first boundary and from $c_{de1/de2}(r = 48.8\,\mu m) = 3.97{\cdot}10^{-3}$ mg/mL to $c_{de1/de2}(r = 159.7\,\mu m) = 3.74{\cdot}10^{-3}$ mg/mL at the second boundary.

As in Case 1a a sharp concentration drop occurs around *r* = 1.78 mm, the edge of the donor solution compartment. At the top surface of the viable epidermis the concentrations at the preceding and following nodes are $c_{sc/ve}(r = 1698\,\mu m) = 4.13{\cdot}10^{-3}$ mg/mL and $c_{sc/ve}(r = 1933.8\,\mu m) = 2.01{\cdot}10^{-3}$ mg/mL, that is, the concentration drops about 50% around *r* = 1.78 mm. At the viable epidermis/dermis 1 and at the dermis 1/dermis 2 boundary this concentration drop is 22 and 16%, respectively. From the hair follicle boundary to the edge of the donor solution compartment, the concentration drop at the stratum corneum/viable epidermis is 39%, at the viable epidermis/dermis 1 and the dermis 1/dermis 2 boundaries it is around 44%.

The concentration far from the hair follicle, at r = 5 mm, is less than that at the hair follicle boundary by one order or magnitude or more.



Figures 7-10:
A: Average concentrations in viable epidermis (ve), dermis (de) and at hair follicle/skin tissue boundary, **B:** Concentration vs. depth profiles at t = 16 h at the hair follicle/skin tissue and the inner/outer region boundaries and at r = 5 mm from the hair follicle, **C:** Concentration vs. radial distance at t = 16 h at the stratum corneum (sc)/viable epidermis, the viable epidermis/dermis 1 (de1) and the dermis 1 /dermis 2 (de2) boundaries, for **Case 3a**: hair follicle permeability equal to intrinsic infundibulum permeability and transient dye penetration into sebum.

7.6.5 Case 4a: Hair follicle permeability equal to intrinsic infundibulum permeability, constant (well-stirred) dye concentration

- **Average concentrations (Figure 7-11A)**

The concentration profiles exhibit the same trends in Case 4a as in Case 3a, but since a greater amount of dye in available in the infundibulum to diffuse into the skin tissue over the 16 h period, the absolute concentration values are higher in Case 4a than in Case 3a.

At t = 2 h the average values are $\bar{c}_{ve}(t = 2\,\text{h}) = 4.84 \cdot 10^{-3}$ mg/mL, $\bar{c}_{de}(t = 2\,\text{h}) = 3.02 \cdot 10^{-3}$ mg/mL and $\bar{c}_{hf/skin}(t = 2\,\text{h}) = 3.79 \cdot 10^{-3}$ mg/mL, or 10 to 17 % higher than the equivalent values in Case 3a. The maximum average concentrations are $\bar{c}_{ve}(t = 16\,\text{h}) = 6.37 \cdot 10^{-3}$ mg/mL, $\bar{c}_{de}(t = 16\,\text{h}) = 4.58 \cdot 10^{-3}$ mg/mL and $\bar{c}_{hf/skin}(t = 16\,\text{h}) = 5.04 \cdot 10^{-3}$ mg/mL. These values are 4 to 5 % higher than the equivalent values in Case 3a. For 2 h $\leq t \leq$ 16 h the ratios of the average concentrations are the same as in Case 3: $\bar{c}_{ve}(t)/\bar{c}_{de}(t)$ = 1.4 to 1.6, $\bar{c}_{ve}(t)/\bar{c}_{hf/skin}(t) \approx 1.3$ and $\bar{c}_{hf/skin}(t)/\bar{c}_{de}(t)$ = 1.1 to 1.3.

- **Concentration vs. depth *z* (Figure 7-11B)**

At $t = 16\,\text{h}$ the concentration at the top of the viable epidermis boundary is $c_{hf/skin}(z = 0) = 7.71 \cdot 10^{-3}$ mg/mL at the hair follicle/skin tissue boundary and $c_{inner/outer}(z = 0) = 6.98 \cdot 10^{-3}$ mg/mL at the inner/outer tissue boundary. These values represent an increase of 3 to 5% compared to Case 3a. These concentrations decrease to $c_{hf\,/\,skin}(z = -100\,\mu\text{m}) = 5.40 \cdot 10^{-3}$ mg/mL and $c_{inner/outer}(z = -100\,\mu\text{m}) = 5.14 \cdot 10^{-3}$ mg/mL in the viable epidermis. Within the viable epidermis the concentrations at the hair follicle boundary are 5 to 12% greater than at the inner/outer tissue boundary, as in Case 3a.

Overall the concentration in the viable epidermis is 3 to 5% greater in Case 4a at the hair follicle boundary and at the inner/outer tissue boundary than in Case 3a.

At the top of dermis 1, the concentration values are $c_{\text{hf/skin}}(z = -100\,\mu\text{m}) = 4.47 \cdot 10^{-3}$ mg/mL and $c_{\text{inner/outer}}(z = -100\,\mu\text{m}) = 4.23 \cdot 10^{-3}$ mg/mL. At the bottom of dermis 1, these concentrations are $c_{\text{hf/skin}}(z = -300\,\mu\text{m}) = 4.19 \cdot 10^{-3}$ mg/mL and $c_{\text{inner/outer}}(z = -300\,\mu\text{m}) = 3.94 \cdot 10^{-3}$ mg/mL. Within dermis 1 the difference between the hair follicle/skin boundary and inner/outer boundary concentrations about 6%, as in Case 3a. The concentrations in dermis 1 in Case 4a are about 5% greater than the values in Case 3a.

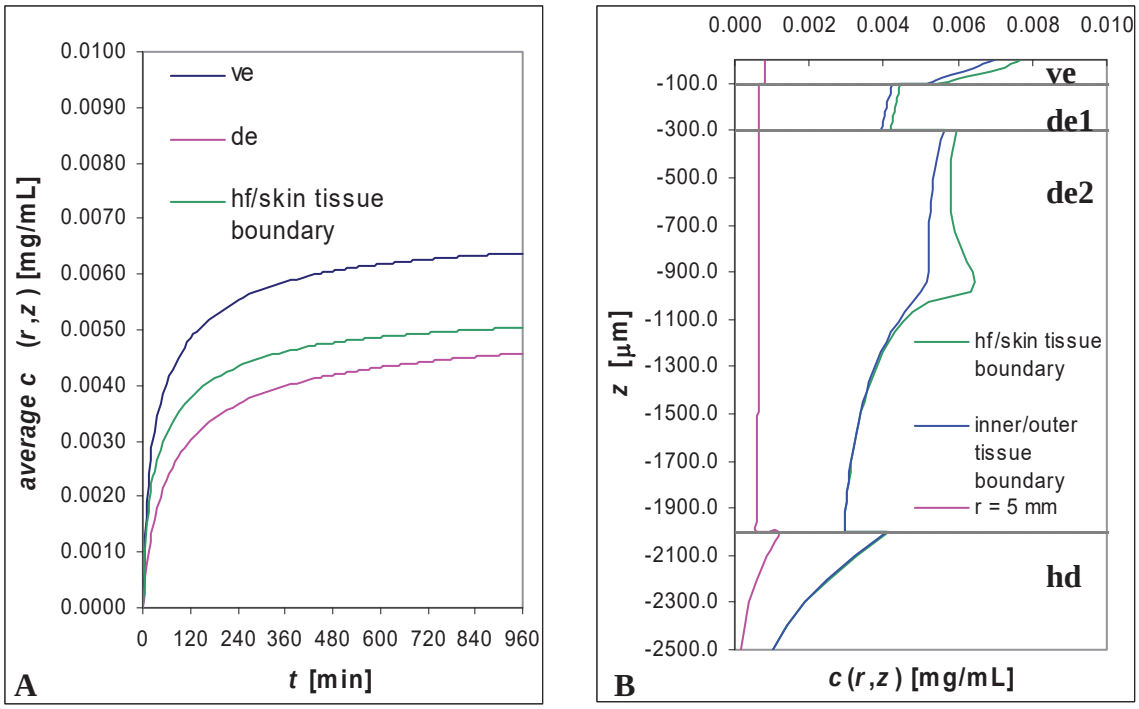
The local maximum in the concentration in dermis 2 at the hair follicle/skin tissue boundary, due to the maximum infundibulum permeability at z = -1000 μm, is $c_{\text{hf/skin}}(z = -937.5\,\mu\text{m}) = 6.43 \cdot 10^{-3}$ mg/mL. This value is 13 % greater than the maximum concentration obtained in Case 3a. In Case 4a sufficient dye permeates across the hair follicle outer boundary to yield a local concentration maximum of $5.22 \cdot 10^{-3}$ mg/mL at z = -895 μm at the inner/outer tissue boundary. This local maximum is not present in Case 3a.

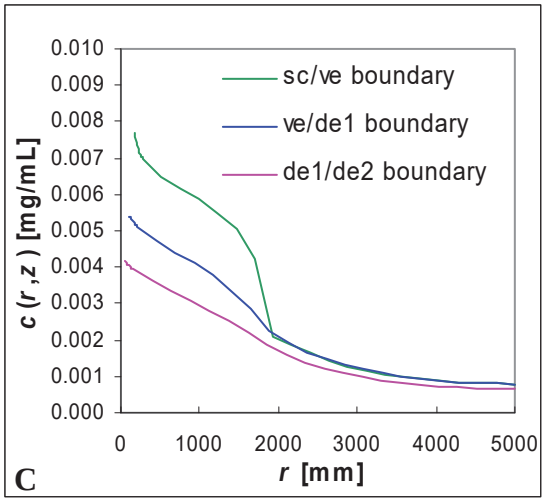
Below z = -1000 μm the concentrations in Case 4a in dermis 2 are up to 10% higher at the hair follicle/skin tissue and the inner/outer tissue boundaries. In hypodermis the difference to z = -2500 μm is about 1%.

As in Case 3a, the concentration profile at a distance r = 5 mm away from the hair follicle is 1-D diffusion in z.

- **Concentration vs. radial distance *r* (Figure 7-11C)**

As in Case 3a the concentration at the top of the viable epidermis, at the viable epidermis/dermis 1 and at the dermis 1/dermis 2 boundaries decreases within the inner region of the computational domain by 5 to 9%. The drop in concentration is greatest at the top horizontal boundary. Around r = 1.78 μm the concentration drop at the top of the viable epidermis is 50%; at the other two horizontal boundaries it is 22% and 16%, as in Case 3a.





Figures 7-11:
A: Average concentrations in viable epidermis (ve), dermis (de) and at hair follicle/skin tissue boundary, **B:** Concentration vs. depth profiles at t = 16 h at the hair follicle/skin tissue and the inner/outer region boundaries and at r = 5 mm from the hair follicle, **C:** Concentration vs. radial distance at t = 16 h at the stratum corneum (sc)/viable epidermis, the viable epidermis/dermis 1 (de1) and the dermis 1/dermis 2 (de2) boundaries, for **Case 4a**: hair follicle permeability equal to intrinsic infundibulum permeability and constant (well-stirred) dye penetration in sebum.

7.6.6 Case 5a: Hair follicle permeability equal to intrinsic infundibulum permeability plus contribution from the sebaceous duct, transient dye penetration into sebum

- **Average concentrations (Figure 7-12A)**

As in the previously discussed cases the average concentrations increase monotonically with time. Due to the increased permeability of the outer root sheath of the hair follicle, the average dermal concentration in Case 5a is either essentially equal or about 14 to 15% than the average concentration at the hair follicle/skin tissue boundary over the period 30 min $\leq t \leq$ 16 h, with the difference increasing with time. The average concentration in the dermis is nearly equal to the average concentration in the viable epidermis, with $\bar{c}_{ve}(t)/\bar{c}_{de}(t) \approx 1.0$ or $\bar{c}_{ve}(t)$ about 1% greater than $\bar{c}_{de}(t)$ for 2 h $\leq t \leq$ 16 h. At t = 2 h the values are $\bar{c}_{ve}(t = 2\,\text{h}) = 9.94 \cdot 10^{-3}$ mg/mL, $\bar{c}_{de}(t = 2\,\text{h}) = 9.84 \cdot 10^{-3}$ mg/mL and $\bar{c}_{hf\,/\,skin}(t = 2\,\text{h}) = 8.68 \cdot 10^{-3}$ mg/mL. The maximum average concentrations attained are $\bar{c}_{ve}(t = 16\,\text{h}) = 1.59 \cdot 10^{-2}$ mg/mL, $\bar{c}_{de}(t = 16\,\text{h}) = 1.57 \cdot 10^{-2}$ mg/mL and $\bar{c}_{hf\,/\,skin}(t = 16\,\text{h}) =$

$1.36 \cdot 10^{-2}$ mg/mL. The values at t = 2 h and t = 16 h are 2.3 to 2.6 times greater than the equivalent values in Case 3a. For 2 h $\leq t \leq$ 16 h the average concentrations in the viable epidermis, the dermis and at the hair follicle boundary are approximately 2.3 to 2.6, 3.6 to 3.8 and 2.8 times greater in Case 5a than in Case 3a.

- **Concentrations vs. depth *z* (Figure 7-12B)**

The concentrations at the horizontal boundaries of the viable epidermis are $c_{\text{hf / skin}}(z = 0)$ = $1.72 \cdot 10^{-2}$ mg/mL and $c_{\text{in / out}}(z = 0)$ = $1.58 \cdot 10^{-2}$ mg/mL at the inner / outer tissue boundary and $1.54 \cdot 10^{-3}$ mg/mL at a distance r = 5 mm away from the hair follicle. These values are 2.3 times greater than the equivalent concentration values in Case 3a. These values decrease to $c_{\text{hf / skin}}(z = \text{-}100\,\mu\text{m})$ = $1.59 \cdot 10^{-2}$ mg/mL and $c_{\text{in / out}}(z = \text{-}100\,\mu\text{m})$ = $1.49 \cdot 10^{-2}$ mg/mL, a 1.1-fold decrease, compared to 1.4-fold decrease that in Cases 3a and 4a. Within the viable epidermis the concentrations in Case 5a are 7 to 9% greater at the hair follicle/skin tissue boundary than at the inner/outer tissue boundary.

Contrary to Cases 3a and 4a, in dermis 1 the concentrations at the hair follicle/skin tissue boundary and at the inner/outer tissue boundary increase with depth z. These values range from $c_{\text{hf / skin}}(z = \text{-}100\,\mu\text{m})$ = $1.31 \cdot 10^{-2}$ mg/mL and $c_{\text{in / out}}(z = \text{-}100\,\mu\text{m})$ = $1.22 \cdot 10^{-2}$ mg/mL to $c_{\text{hf / skin}}(z = \text{-}300\,\mu\text{m})$ = $1.63 \cdot 10^{-3}$ mg/mL and $c_{\text{in / out}}(z = \text{-}300\,\mu\text{m})$ = $1.37 \cdot 10^{-3}$ mg/mL at z = -300 μm. This represents a difference of 7 to 16% within the dermis 1; this difference increases with depth. The dermis1 concentrations in Case 5a are 3 to 4 times greater than in Case 3a.

The increase in concentration with increasing depth seen in the dermis 1 is due to the large amount of permeant diffusing from the hair follicle into dermis 2 via the

sebaceous duct, centered at z = -500 μm. This additional permeability yields local concentration maxima in the dermis 2 near the hair follicle. At z = -512.5 μm, the z-coordinate of the computational mesh closest to z = -500 μm, the concentration at the hair follicle/skin tissue and inner/outer tissue boundaries are $3.51 \cdot 10^{-2}$ mg/mL and $2.24 \cdot 10^{-2}$ mg/mL, respectively. Because of these high local maxima the local minimum seen in Case 3a at the hair follicle/skin tissue boundary at z = -895 μm has disappeared. However, a change in the slope of the concentration at this boundary is visible below z = -1000 μm. Overall, for -300 μm $\leq z \leq$ -1022.5 μm, the concentration at the hair follicle/skin tissue boundary is 4 to 57% greater than that at the inner/outer tissue boundary with the largest difference occurring at z = -512.5 μm. The concentration at both boundaries decreases rapidly to ~$7.2 \cdot 10^{-3}$ mg/mL at z = -2000 μm. For -512.5 μm $\leq z \leq$ -300 μm the Case 5a concentrations are 4 to 7 times greater than the values in Case 3a (with the difference increasing with depth and larger at the hair follicle boundary). For z < -512.5 μm the difference is a factor of 2.6 to 6.

The concentration in the hypodermis varies from about $1.00 \cdot 10^{-2}$ mg/mL at the hair follicle/skin tissue at the inner/outer tissue boundary to about $1.6 \cdot 10^{-3}$ mg/mL at z = -2500 μm. These hypodermal values are 2.6 times greater than in Case 3a.

- **Concentration vs. radial distance *r* (Figure 7-12C)**

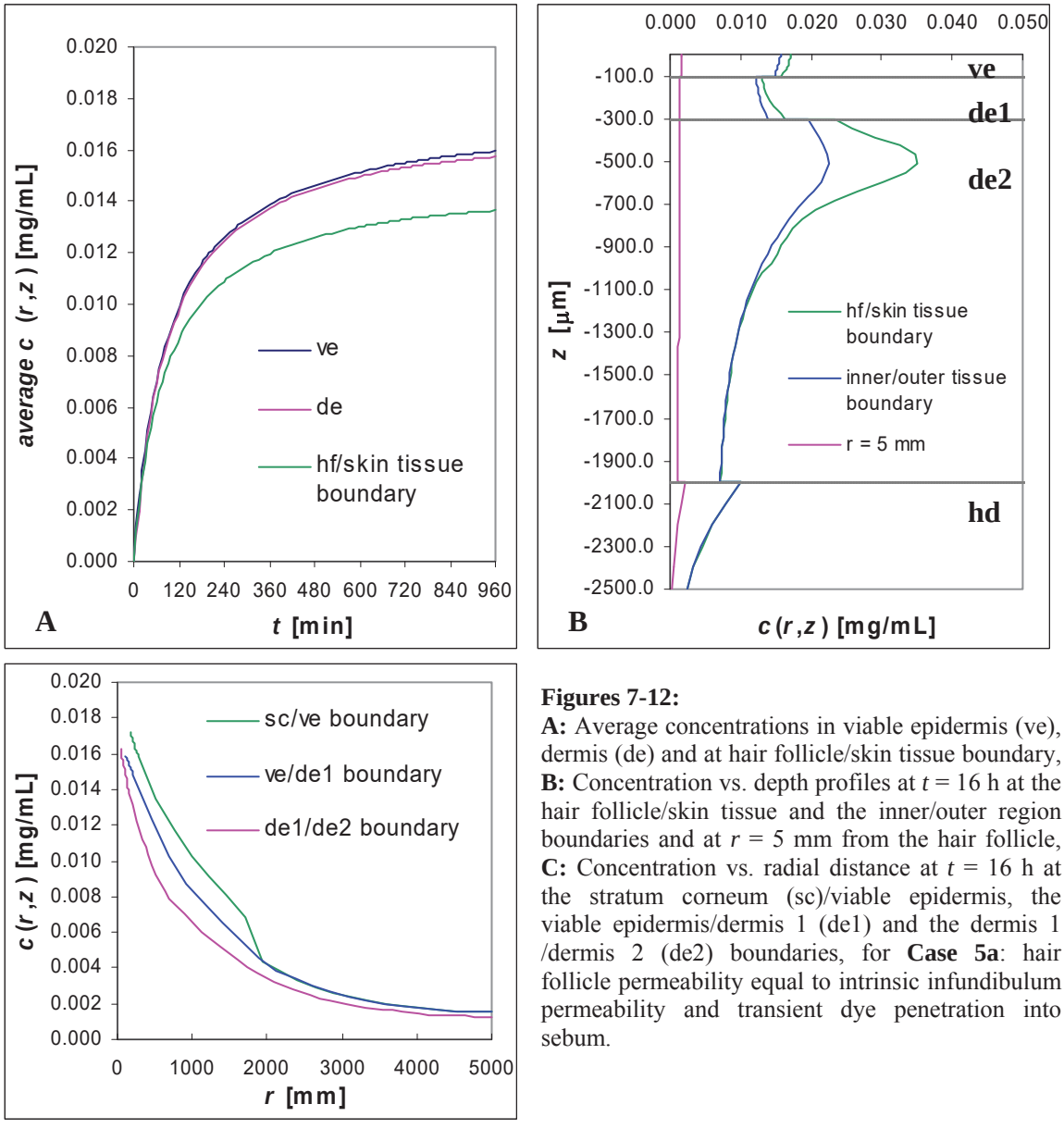
At the top of the viable epidermis within the inner region, the concentration decreases smoothly from $c_{sc/ve}(r = 174.7\,\mu m) = 1.72 \cdot 10^{-2}$ mg/mL at the hair follicle / skin tissue boundary to $c_{sc/ve}(r = 282.8\,\mu m) = 1.59 \cdot 10^{-2}$ mg/mL, a 9% drop in concentration, slightly below that seen in Cases 3a and 4a. At the viable epidermis/dermis 1 boundary the

concentrations in the inner region range from $c_{ve/de}(r = 99.3\,\mu m) = 1.59 \cdot 10^{-2}$ mg/mL to $c_{ve/de}(r = 209.0\,\mu m) = 1.49 \cdot 10^{-2}$ mg/mL (a 6.5% drop); at the dermis 1/dermis 2 boundary they range from $c_{de1/de2}(r = 48.8\,\mu m) = 1.63 \cdot 10^{-2}$ mg/mL to $c_{de1/de2}(r = 159.7\,\mu m) = 1.37 \cdot 10^{-2}$ mg/mL (a 16% drop). The concentration differences at each boundary are higher than in Cases 3a and 4a, with the difference increasing with depth. At the viable epidermis/dermis 1 and dermis 1/dermis 2 boundaries, the concentration decreases faster in Case 5a than in Cases 3a and 4a. Due to the greater amount of permeant in the infundibulum in Case 5a, the concentration at the hair follicle/skin tissue boundary on the dermis 1/dermis 2 interface (r = 48.8 μm) is slightly greater (2.6%) than at the dermis 1/viable epidermis boundary (r = 99.3 μm). This is not seen in Cases 3a and 4a.

The switch in the value of the stratum corneum permeability $P_{sc/pH1.0}(r)$ at r = 1.78 mm is noticeable in the concentration curve for the top of the viable epidermis, but, unlike in Cases 3a and 4a, it is longer evident in the profiles at the lower horizontal boundaries. From the hair follicle boundary to the edge of the donor solution compartment, the concentration drop at the stratum corneum/viable epidermis is 57%, at the viable epidermis/dermis 1 and the dermis 1/dermis 2 boundaries it is around 67%. At the top surface of the viable epidermis the concentrations on either side of r = 1.78 mm are $c_{sc/ve}(r = 1698\,\mu m) = 1.72 \cdot 10^{-2}$ mg/mL and $c_{sc/ve}(r = 1933.8\,\mu m) = 1.58 \cdot 10^{-3}$ mg/mL. This constitutes a 37% drop in the concentration which is significantly less than the 50% drop seen in Case 3a. At the viable epidermis/dermis 1 and the dermis 1/dermis 2 boundaries the concentration drop is 18% and 15%, respectively. These percentages are also less than in Cases 3a and 4a, but the difference is less important than for the top viable epidermis boundary. Overall the higher amount of permeant in the skin layers due

to the higher hair follicle permeability has smoothed out the effect of setting $P_{sc/pH1.0}(r)$ to 0.

The concentrations at r = 5 mm from the hair follicle are roughly one order of magnitude less than at the hair follicle/skin tissue boundary (r = 174.7 μm).



Figures 7-12:
A: Average concentrations in viable epidermis (ve), dermis (de) and at hair follicle/skin tissue boundary, **B:** Concentration vs. depth profiles at t = 16 h at the hair follicle/skin tissue and the inner/outer region boundaries and at r = 5 mm from the hair follicle, **C:** Concentration vs. radial distance at t = 16 h at the stratum corneum (sc)/viable epidermis, the viable epidermis/dermis 1 (de1) and the dermis 1 /dermis 2 (de2) boundaries, for **Case 5a**: hair follicle permeability equal to intrinsic infundibulum permeability and transient dye penetration into sebum.

7.6.7 Case 6a: Hair follicle permeability equal to intrinsic infundibulum permeability plus contribution from the sebaceous duct, constant (well-stirred) dye concentration in sebum

- **Average concentrations (Figure 7-13A)**

The combination of a constant BFL concentration in the infundibulum a higher permeability of the outer root sheath due to the contribution of the sebaceous duct yields an average concentration in the dermis which is larger than that in the viable epidermis for much of the simulation time. The results show $\bar{c}_{\mathrm{de}} > \bar{c}_{\mathrm{ve}} > \bar{c}_{\mathrm{hf\,/\,skin}}$ for $0 \le t \le 12.5$ h and $\bar{c}_{\mathrm{ve}} > \bar{c}_{\mathrm{de}} > \bar{c}_{\mathrm{hf/skin}}$ for $12.75 \le t \le 16$ h, but with $\bar{c}_{\mathrm{ve}}$ less than 0.5% greater than $\bar{c}_{\mathrm{de}}$ in the later period.

At t = 2 h the average concentrations in Case 6a are $\bar{c}_{\mathrm{ve}}(t = 2\,\mathrm{h}) = 1.40{\cdot}10^{-2}$ mg/mL, $\bar{c}_{\mathrm{de}}(t = 2\,\mathrm{h}) = 1.45{\cdot}10^{-2}$ mg/mL and $\bar{c}_{\mathrm{hf\,/\,skin}}(t = 2\,\mathrm{h}) = 1.25{\cdot}10^{-2}$ mg/mL. The maxima in the average concentrations attained are $\bar{c}_{\mathrm{ve}}(t = 16\,\mathrm{h}) = 1.96{\cdot}10^{-2}$ mg/mL, $\bar{c}_{\mathrm{de}}(t = 16\,\mathrm{h}) = 1.78{\cdot}10^{-2}$ mg/mL and $\bar{c}_{\mathrm{hf\,/\,skin}}(t = 16\,\mathrm{h}) = 1.52{\cdot}10^{-2}$ mg/mL. For $2\mathrm{h} \le t \le 16$ h the values in Case 6a are 11 to 37% greater than in Case 5a at the stratum corneum/viable epidermis boundary, 13 to 43% greater at the viable epidermis/dermis 1 boundary and 12 to 38% greater at the dermis 1/dermis 2 boundary. In each case the difference decreases as time increases.

- **Concentration vs. depth *z* (Figure 7-13B)**

The concentration vs. depth curve shows the concentrations at the top surface of the viable epidermis to be $c_{\mathrm{hf\,/\,skin}}(z = 0) = 1.91{\cdot}10^{-2}$ mg/mL and $c_{\mathrm{inner/outer}}(z = 0) = 1.75{\cdot}10^{-2}$ mg/mL. These values are 11 to 12% greater than the corresponding values in Case 5a. At

the viable epidermis/dermis 1 boundary they are $c_{\text{hf / skin}}(z = \text{-}100\,\mu\text{m})$ = $1.78{\cdot}10^{-2}$ mg/mL and $c_{\text{ve / de1}}(z = \text{-}100\,\mu\text{m})$ = $1.67{\cdot}10^{-2}$ mg/mL, about 12% greater than in Case 5a. As in that case, within the viable epidermis the concentration at the hair follicle/skin tissue boundary is 7 to 9% greater than at the inner/outer tissue boundary.

In dermis 1 the concentrations increase from $c_{\text{hf / skin}}(z = \text{-}100\,\mu\text{m})$ = $1.47{\cdot}10^{-2}$ mg/mL and $c_{\text{ve / de1}}(z = \text{-}100\,\mu\text{m})$ = $1.38{\cdot}10^{-2}$ mg/mL to $c_{\text{hf / skin}}(z = \text{-}300\,\mu\text{m})$ = $1.83{\cdot}10^{-2}$ mg/mL and $c_{\text{ve / de1}}(z = \text{-}300\,\mu\text{m})$ = $1.55{\cdot}10^{-2}$ mg/mL. These values are about 12% greater than the dermis 1 concentrations in Case 5a. The difference between the concentration values at both boundaries in dermis 1 is 7 to 18%, the same as in Case 5a.

The maximum concentrations in dermis 2 are $c_{\text{hf / skin}}(z = \text{-}512.5\,\mu\text{m})$ = $4.00{\cdot}10^{-2}$ mg/mL and $c_{\text{ve / de1}}(z = \text{-}512.5\,\mu\text{m})$ = $2.55{\cdot}10^{-2}$ mg/mL. These values are 14 % greater than the local concentration maxima in Case 5a. The concentration decreases to $8.34{\cdot}10^{-3}$ mg/mL and $8.29{\cdot}10^{-3}$ mg/mL at z = -2000 μm. For -2000 μm $\leq z <$ -512.5 μm the concentrations in Case 6a are 12 to 16% greater than in Case 5a, with the difference decreasing with depth.

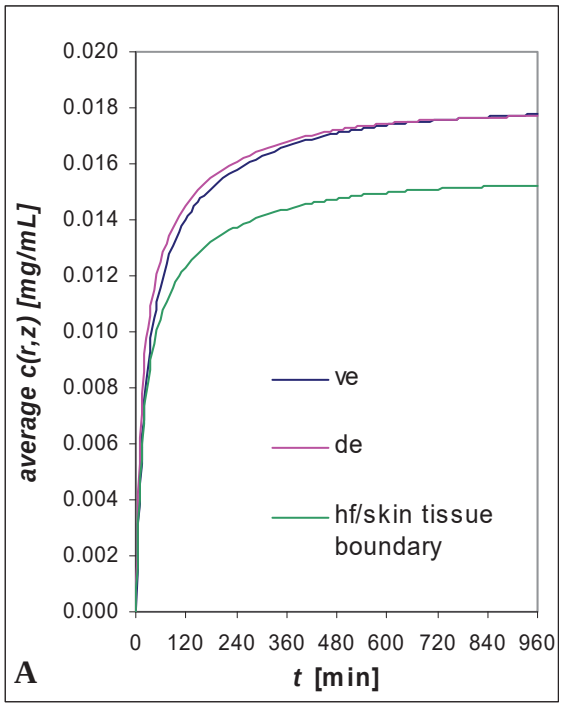
The hypodermis values shown in Figure 7-12B range from $c_{\text{hf/skin}}(z = \text{-}2000\,\mu\text{m})$ = $1.17{\cdot}10^{-2}$ mg/mL to $c_{\text{hf/skin}}(z = \text{-}2500\,\mu\text{m})$ = $2.06{\cdot}10^{-3}$ mg/mL and from $c_{\text{inner/outer}}(z = \text{-}2000\,\mu\text{m})$ = $1.16{\cdot}10^{-2}$ mg/mL to $c_{\text{inner/outer}}(z = \text{-}2500\,\mu\text{m}) = 2.04{\cdot}10^{-3}$ mg/mL. They are 16 to 17% greater than the corresponding values in Case 5a.

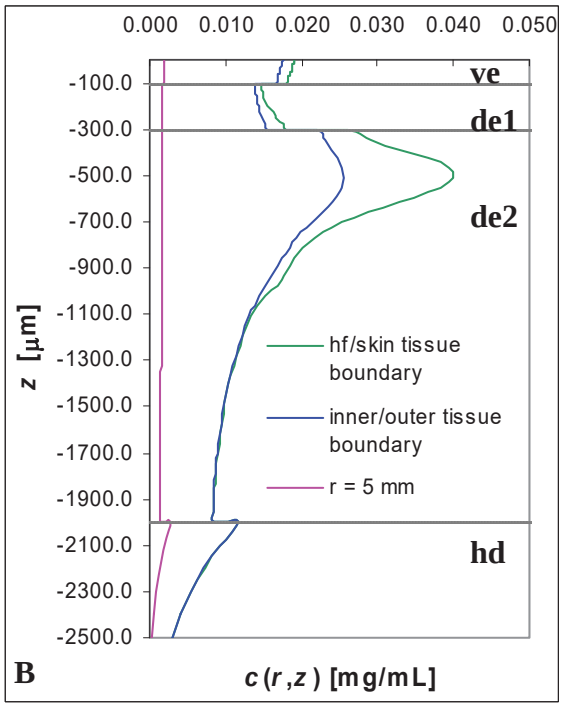
- **Concentration vs. radial distance *r* (Figure 7-13C)**

Within the inner region of the computational domain the concentration at the top of the viable epidermis decreases smoothly from a value of $c_{sc/ve}(r = 174.7\,\mu m) = 1.91 \cdot 10^{-2}$ mg/mL at the hair follicle boundary to $c_{sc/ve}(r = 282.8\,\mu m) = 1.75 \cdot 10^{-2}$ mg/mL, which represents a decrease of about 8%, almost twice as high as the corresponding drop in concentration in Case 5a. At the viable epidermis/dermis 1 and dermis 1/dermis 2 boundaries the concentration decrease within the inner region is 6% and 15%, comparable to the corresponding decreases in Case 5a.

The concentration on the dermis 1/dermis 2 interface is 2.7% than on the viable epidermis/dermis 1 boundary at the hair follicle/skin tissue boundary. In Cases 5a this percentage difference is 2.6%.

The concentrations at the top of the viable epidermis, on either side of r = 1.78 mm are $c_{sc/ed}(r = 1698\,mm) = 7.52 \cdot 10^{-3}$ mg/mL and $c_{sc/ed}(r = 1933.8\,mm) = 4.97 \cdot 10^{-3}$ mg/mL. The decrease due to setting the stratum corneum permeability equal to 0 is 34%, comparable to the value of 37% in Case 5a. At the viable epidermis/dermis 1 and dermis 1/dermis 2 boundaries, this concentration drop is 17% and 15%, also comparable to the corresponding percentages in Case 5a.





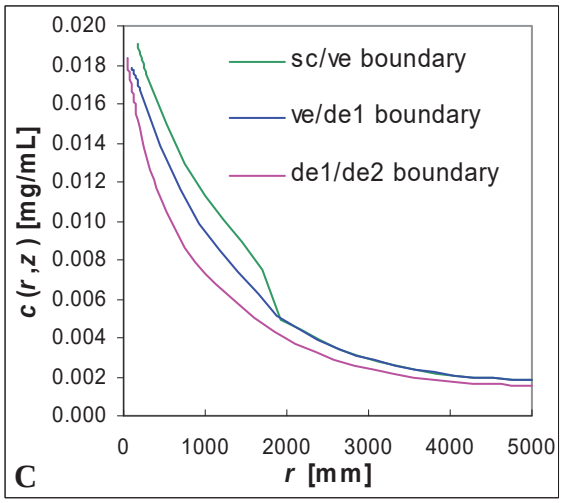


Figure 7-13:
A: Average concentrations in viable epidermis (ve), dermis (de) and at hair follicle/skin tissue boundary, **B:** Concentration vs. depth profiles at t = 16 h at the hair follicle/skin tissue and the inner/outer region boundaries and at r = 5 mm from the hair follicle, **C:** Concentration vs. radial distance at t = 16 h at the stratum corneum (sc)/viable epidermis, the viable epidermis/dermis 1 (de1) and the dermis 1 /dermis 2 (de2) boundaries, for **Case 6a**: hair follicle permeability equal to intrinsic infundibulum permeability and transient dye penetration into sebum.

7.7 Discussion of the *in vitro* simulation results

7.7.1 Impermeable vs. permeable hair follicle

Cases 1a and 2a address an unrealistic case, because there the infundibulum has some permeability. The results represent the lower-bound case where all penetration into the skin comes from above. They show the mathematical curiosity that the permeant concentration decreases with the distance from the hair follicle. The reason for this mathematical result is seen from the boundary condition expressing flux across the hair follicle/skin tissue boundary, that is, the outer root sheath boundary (Eq. 7). With $P_{\mathrm{ors/pH}} = 0$, the boundary condition in a given skin layer α becomes, upon division by $-D_\alpha(r,z)$, $\underline{\mathbf{n}}_{\mathbf{ors}} \cdot \underline{\nabla} c_\alpha(r,z) = 0$, or

$$\left(\mathrm{n}_{\mathrm{ors}}\right)_{\mathrm{r}} \frac{\partial c_\alpha}{\partial r} + \left(\mathrm{n}_{\mathrm{ors}}\right)_{\mathrm{z}} \frac{\partial c_\alpha}{\partial z} = 0 \tag{123}$$

The coordinate system described in section 4.2 is set up such that moving away from the hair follicle, the radial and axial components of the normal to the outer root sheath are $\left(\mathrm{n}_{\mathrm{ors}}\right)_{\mathrm{r}} > 0$ and $\left(\mathrm{n}_{\mathrm{ors}}\right)_{\mathrm{z}} < 0$. Since the concentration is decreasing with depth z (Fig. 7-9B) we have $\partial c_\alpha / \partial \mathrm{z} > 0$ in Eq. 123 and thus $\left(\mathrm{n}_{\mathrm{ors}}\right)_{\mathrm{z}} \partial c_\alpha / \partial \mathrm{z} < 0$. The first term must then be positive and $\left(\mathrm{n}_{\mathrm{ors}}\right)_{\mathrm{r}} > 0$, thus the partial derivative $\partial c_\alpha / \partial r$ must be positive.

Since the case of a totally impermeable hair follicle is considered unrealistic, the remainder of the discussion is restricted to Cases 3a-6a for a permeable hair follicle.

7.7.2 Effect of the non-zero infundibulum and sebaceous duct permeabilities

The intrinsic permeability of the infundibulum was modeled based on the knowledge that its stratum corneum-like cell wall decreases in thickness, from an equivalent of full-thickness skin at the surface of the skin to about 1/10 of that thickness at the bottom of the infundibulum. In our mathematical model the infundibulum reaches to a depth of -1 mm.

Figures 7-10B, 7-10C and 7-11B, 7-11C show that the intrinsic permeability of the infundibulum alone has a strong effect on the concentration of BFL in the deeper dermis, around -1 mm, near the hair follicle. The large supply of permeant yields a local maximum at this depth whose magnitude is a function of *z*. After 16 h of diffusion, the BFL concentration at a depth of about 1 mm at the hair follicle/skin tissue boundary is predicted to be roughly equal to the BFL concentration at a depth of about 90 μm inside the viable epidermis, and equal to the concentration at the dermis 1/dermis 2 boundary, at a depth of 300 μm, in Case 3a. (Fig. 7-10B). In Case 4a the maximum concentration attained in dermis 2 is roughly equal to the concentration at a depth of 60 μm in the viable epidermis. Figure 7-10C shows that at the top of the viable epidermis at the inner/outer region boundary, about 110 μm away from the edge of the hair follicle, the concentration is only about 10% less than at the hair follicle boundary. In the dermis at depths of -100 μm and -300 μm, at the same distance from the hair follicle, the concentration drop is about 5%. These data underline efficacy of the infundibulum in delivering BFL deep inside the dermis as well as to some distance away from the hair follicle.

The increase in the permeability of the hair follicle due to the contribution of the sebaceous duct is evident from Figures 7-12B, 7-12C and 7-13B, 7-13C. The added permeability (Case 5a) beyond the intrinsic infundibulum permeability (Case 3a) increases the concentration values within the viable epidermis 2 to 3-fold from the hair follicle boundary to a distance 110 μm away from it. Within the upper dermis (dermis 1) the difference is a factor of 3.0 to 4.0 greater, and in dermis 2, at z = -512.5 μm where the local maximum in concentration occurs, the concentration is 4.5 and 6.5 times greater at the inner/outer tissue boundary and at the hair follicle boundary (Figure 7-12B, 7-13B). These results agree qualitatively with those of Bernard *et al*. who studied the *in vitro* and *in vivo* permeation of the antiandrogen RU 58841 in normal hairless rat skin and scarred hair less rat skin lacking hair follicles and sebaceous glands.[73] These authors found the concentration of RU 58841 to be highest in the top 500 μm of normal skin. The ratio of the amount of RU 58841 in normal skin to that in scar skin was highest at a depth of 200 to 500 μm, where the sebaceous ducts are located. At the hair follicle/skin tissue boundary and within a distance of about 10 μm away from the hair follicle, the concentration on the dermis 1/dermis 2 interface (z = -300 μm) is 2.6% greater than at the viable epidermis/dermis 1 boundary, at z = -100 μm (Case 5a, Figure 7-12C)

Similarly to Bernard *et al.*'s results, the mathematical model shows the contribution provided by the sebaceous duct and the sebaceous gland to be of significant importance for the delivery of BFL to the deeper dermis.

7.7.3 Effect of constant (well-stirred) vs. transient permeant concentration in the infundibulum

The constant (well-stirred) permeant concentration in the infundibulum is an obvious upper bound on the delivery of the permeant to the skin surrounding the hair follicle.

In the case of the permeability of the hair follicle due only to the intrinsic permeability of the infundibulum, the functional form of the permeant concentration in the infundibulum increases the magnitude of the concentration in the viable epidermis and the upper dermis, but does not change the shape of the concentration profiles (Figure 7-11B). In the lower dermis a local maximum is reached at the inner/outer boundary, at a distance 110 μm from the hair follicle, which is not present in the case of a transient permeant concentration decreasing with increasing depth in the infundibulum.

The differences between a well-stirred and a decreasing infundibular permeant concentration are more pronounced in the case of increased follicular permeability due to contribution of the sebaceous duct (Figures 7-12B to 7-13C). Since the amount of BFL available in the bottom 500 μm of the infundibulum is significantly larger in the well-stirred case, the average dermal concentration near the hair follicle calculated in top 200 μm of the dermis is greater than the average concentration measured at the follicle/skin tissue boundary within the same volume for $0 < t \leq 16\,\mathrm{h}$. The average dermal concentration also exceeds the average concentration in the viable epidermis for $0 < t \leq 12.5\,\mathrm{h}$ (Case 6a, Figure 7-13A). At the hair follicle/skin tissue boundary the concentration at the dermis 1/dermis 2 boundary is 2.7% larger than the concentration at the viable epidermis/dermis 1 boundary (Figure 7-13C), equivalent to the 2.6% difference in Case 5a.

7.7.4 Comparison with Grams *et al.*'s results

The important difference between the average concentration values calculated in the epidermis, the dermis and at the hair follicle/skin tissue boundary and Grams *et al*.'s average fluorescence values (Figure 7-3) is the lack of maxima in the model predictions. In all cases of the *in vitro* simulation, the average concentrations increase monotonically with time. Personal communication with Mr. Edward Leber of Molecular Probes, the maker of the Bodipy® FL C_5 dye, as well as with Dr. Joke Bouwstra (corresponding author on Grams *et al*.'s article) have ascertained the fact that the dye probably did not degrade during the course of the 16 h experiment. It is also safe to assume that none of the dye traversed the entire 8 mm thick piece of skin during the course of the experiment.

The mathematical model predicts the concentration of permeating dye in the skin outside of the hair follicle. It does not take into account possible diffusion from the surrounding skin tissue into the hair follicle, and in particular does not include absorption of the dye from the infundibulum into the cuticle of the hair shaft. The existence of diffusion pathways into the hair shaft via the cuticle is a known fact.[97] Grams *et al*.'s results suggest that the cuticle absorbs the dye present in the interior of the infundibulum early on in the experiment and has a longer retention time than the infundibulum[17]. Earlier studies by the same group also show strong labeling of dyes of varying lipophilicity and applied in various formulations in the cuticular area of the hair shaft.[80,98] From personal communication Dr. Joke Bouwstra believes that the maximum average fluorescence intensities measured by Grams *et al*. (Figure 7-4) and the implied clearance of the dye from the skin layers and the outer root sheath of the hair follicle are due to the absorption of BFL into the cuticle of the hair shaft, a property not taken into account in

our mathematical model. If this is not the case, there must be another source of effective clearance from the skin block.

The difference in the relative volumes of the infundibulum and the dermis in Grams *et al*.'s skin block and our mathematical model (section 7.4.1) is another possible reason for the difference seen in their fluorescence intensity and our average concentration profiles.

Although the predicted average concentrations cannot be compared directly to the published average fluorescence intensities, a comparison of the ratios of the concentrations to the ratios of the fluorescence intensities at $t > 2$ h, shown in Tables 7-7 and 7-8, enables us to discriminate between the simulation cases. The average concentration ratios in Cases 3a and 4a agree best with the fluorescence intensity ratios. The comparison shows the average dermal concentration $\bar{c}_{\mathrm{de}}$ in Cases 5a and 6a to be too high, since $\bar{c}_{\mathrm{de}}/\bar{c}_{\mathrm{hf/skin}} > 1$. On the basis of this comparison one may conclude that the contribution of the sebaceous duct to the follicular permeability in the mathematical model is too high. Furthermore, from the fact that $\bar{c}_{\mathrm{de}}/\bar{c}_{\mathrm{ve}} > 1$ in Case 6a but not in Case 5a, it seems very likely that the assumption of 1-D transient diffusion of BFL downward in the infundibulum, described by Eq. 121, is a more appropriate assumption than that of a constant (well-mixed) BFL concentration in the infundibulum given by Eq. 122, which yields better agreement between the average concentrations predicted by the mathematical model and the average fluorescence intensities observed by Grams *et al*.

Returning to Cases 3a and 4a, the values in Tables 7-7 indicate that the values of the concentrations $\bar{c}_{\mathrm{hf/skin}}$ and $\bar{c}_{\mathrm{de}}$ need to be lower in order for the ratios $\bar{c}_{\mathrm{ve}}/\bar{c}_{\mathrm{hf/skin}}$ and $\bar{c}_{\mathrm{ve}}/\bar{c}_{\mathrm{de}}$ to agree with the corresponding fluorescence intensity ratios. The fact that the

ratio $\bar{c}_{\text{hf / skin}}/\bar{c}_{\text{de}}$ is in good agreement with the corresponding ratio $\bar{I}_{\text{ors}}/\bar{I}_{\text{de}}$ suggests that $\bar{c}_{\text{hf / skin}}$ and $\bar{c}_{\text{de}}$ need to decrease proportionately. Since these concentrations depend on the amount of BFL diffusing across the outer root sheath of the hair follicle (but not $\bar{c}_{\text{ve}}$, since the ratio $\bar{c}_{\text{ve}}/\bar{c}_{\text{hf / skin}}$ is the same in Cases 3a and 4a, we conclude that the hair follicle permeability as modeled in Cases 3a and 4a yields the correct orders of magnitude in the concentrations, but that the amount of dye diffusing across the follicular outer root sheath into the skin tissue is too large. This amount could decrease if the diffusion of the dye into the cuticle of the hair shaft were taken into account.

Table 7-7: Ratios of the average fluorescence intensities measured by Grams *et al*. in the viable epidermis (ve), the dermis (de) and the outer root sheath of the hair follicle (ors) of their model skin block.[17]

$\bar{I}_{\text{ve}}/\bar{I}_{\text{ors}}$	$\bar{I}_{\text{ve}}/\bar{I}_{\text{de}}$	$\bar{I}_{\text{ors}}/\bar{I}_{\text{de}}$
1.7 – 2.3	2 – 2.5	1.1 – 1.3

Table 7-8: Ratios of the predicted average concentrations in the viable epidermis (ve), the dermis (de) and at the hair follicle/skin tissue boundary (hf/skin) for 2 h < $t \leq 16$ h, calculated from Eqs. C4 to C6 in Appendix C.

	CASE 3a	**CASE 4a**	**CASE 5a**	**CASE 6a**
$\bar{c}_{ve}/\bar{c}_{hf/skin}$	~ 1.3	~ 1.3	~1.16	~1.16
$\bar{c}_{ve}/\bar{c}_{de}$	1.4 – 1.7	1.4 – 1.6	~1.0 [a]	~1.0 [b]
$\bar{c}_{hf/skin}/\bar{c}_{de}$	1.1 – 1.3	1.1 – 1.2	~0.87	~0.86

[a] $\bar{c}_{ve} > \bar{c}_{de}$ for $0 < t \leq 12.5$ h, [b] $\bar{c}_{de} > \bar{c}_{ve}$ for $0 < t \leq 16$ h

7.8 Results for vascularized tissue (*in vivo*), case of partially covered skin

Results on the effect of capillary clearance via the network of blood vessels in the papillary dermis and around the hair follicle are presented for the cases of a permeable hair follicle with a decreasing and a constant BFL concentration in the infundibulum. The values of the clearance rate coefficients corresponding to the cases discussed below are given in Table 7-6. As in the *in vitro* case, the donor solution compartment covers only part of the piece of skin.

7.8.1 Cases 3b, c: Hair follicle permeability due to infundibulum, transient dye concentration in the infundibulum

- **Average concentrations vs. time (Figures 7-14A & B, p. 167)**

The non-zero clearance rate coefficients cause a maximum in the average concentration profiles in the epidermis, dermis and at the hair follicle/skin tissue boundary. In Case 3b these maximum values are $\bar{c}_{\mathrm{ve,\,max}} = 1.31 \cdot 10^{-3}$ mg/mL at t = 6.0 h, $\bar{c}_{\mathrm{de,\,max}} = 4.52 \cdot 10^{-4}$ mg/mL at t = 12.5 h and $\bar{c}_{\mathrm{hf\,/\,skin,\,max}} = 1.78 \cdot 10^{-3}$ mg/mL at t = 7.0 h. The final concentration values are $\bar{c}_{\mathrm{ve}}(t = 16\,\mathrm{h}) = 1.29 \cdot 10^{-3}$ mg/mL, $\bar{c}_{\mathrm{de}}(t = 16\,\mathrm{h}) = 4.51 \cdot 10^{-4}$ mg/mL and $\bar{c}_{\mathrm{hf\,/\,skin}}(t = 16\,\mathrm{h}) = 1.16 \cdot 10^{-3}$ mg/mL. During the first 105 min of the simulation, the ratios of the average concentrations are $\bar{c}_{\mathrm{ve}}/\bar{c}_{\mathrm{de}}$ = 3 to 4.5, $\bar{c}_{\mathrm{ve}}/\bar{c}_{\mathrm{hf\,/\,skin}} \approx 1.1$ and $\bar{c}_{\mathrm{de}}/\bar{c}_{\mathrm{hf\,/\,skin}}$ = 2.8 to 4.0. For 2 h $\leq t \leq$ 16 h, these ratios are $\bar{c}_{\mathrm{ve}}/\bar{c}_{\mathrm{de}}$ = 2.9 to 3.1, $\bar{c}_{\mathrm{ve}}/\bar{c}_{\mathrm{hf\,/\,skin}}$ = 1.1 and $\bar{c}_{\mathrm{de}}/\bar{c}_{\mathrm{hf\,/\,skin}}$ = 2.6 to 2.8 for 2 h $\leq t \leq$ 16 h.

Within the initial 105 min of diffusion, the average concentration values in Case 3b are 50 to 70% less than in Case 3a in the viable epidermis, 64 to 85% less in the dermis, and 30 to 60% less at the hair follicle/skin tissue boundary. For 2 h $\leq t \leq$ 16 h the corresponding percentage decreases are 72 to 80%, 85 to 90% and 60 to 74%. In each case the percentage difference increases with time.

The maximum concentration values in Case 3c are $\bar{c}_{\mathrm{ve,\,max}} = 1.01 \cdot 10^{-3}$ mg/mL at t = 4 h, $\bar{c}_{\mathrm{de,\,max}} = 1.55 \cdot 10^{-3}$ mg/mL at t = 11 h and $\bar{c}_{\mathrm{hf\,/\,skin,\,max}} = 9.06 \cdot 10^{-4}$ mg/mL at t = 5.25 h. The values at t = 16 h are $\bar{c}_{\mathrm{ve}}(t = 16\,\mathrm{h}) = 9.88 \cdot 10^{-4}$ mg/mL, $\bar{c}_{\mathrm{de}}(t = 16\,\mathrm{h}) = 1.55 \cdot 10^{-4}$ mg/mL and $\bar{c}_{\mathrm{hf\,/\,skin}}(t = 16\,\mathrm{h}) = 8.87 \cdot 10^{-4}$ mg/mL. Within the first 105 min the ratios of the

average concentration values are $\bar{c}_{ve}/\bar{c}_{de}$ = 7 to 9, $\bar{c}_{ve}/\bar{c}_{hf\,/\,skin} \approx 1.1$ and $\bar{c}_{hf/skin}/\bar{c}_{de}$ = 6 to 8. For 2 h $\leq t \leq$ 16 h these ratios are 6.4 to 7, 1.1 and 5.7 to 6.1, with the values decreasing as t increases. Compared to Case 3b the average concentrations obtained in the first 105 min of simulation are 12 to 22% smaller in the viable epidermis, 57 to 65% smaller in the dermis and 14 to 22% smaller at the hair follicle/skin tissue boundary. For 2 h $\leq t \leq$ 16 h the corresponding percentages are 22 to 23%, 65 to 66 % and 22 to 24%.

- **Concentration vs. depth *z* at *t* = 16 h (Figures 7-14C & D, p. 167)**

In Case 3b the concentrations at the hair follicle/skin tissue boundary and at the inner/outer region boundary range from $c_{hf\,/\,skin}(z=0) = 2.30\cdot10^{-3}$ mg/mL and $c_{in\,/\,out}(z=0) = 1.35\cdot10^{-3}$ mg/mL to $c_{hf\,/\,skin}(z=-100\,\mu m) = 7.68\cdot10^{-4}$ mg/mL and $c_{in\,/\,out}(z=-100\,\mu m) = 5.01\cdot10^{-4}$ mg/mL, a 67 and 63 % decrease at these boundaries. A maximum concentration value is obtained in Case 3b (as in Case 3c) within the viable epidermis, just below the stratum corneum/viable epidermis boundary $(z=-10\,\mu m)$. In each one of these cases this maximum is 2 % greater than the value at z = 0. Within dermis 1 the values range from $c_{hf\,/\,skin}(z=-100\,\mu m) = 6.53\cdot10^{-4}$ mg/mL and $c_{in\,/\,out}(z=-100\,\mu m) = 4.12\cdot10^{-4}$ mg/mL to $c_{hf\,/\,skin}(z=-300\,\mu m) = 5.16\cdot10^{-4}$ mg/mL and $c_{in\,/\,out}(z=-300\,\mu m) = 3.11\cdot10^{-4}$ mg/mL, a 21 % decrease at the hair follicle boundary and at 24 % decrease at the inner/outer region boundary. In dermis 2 the hair follicle and inner/outer tissue boundary concentrations decrease from $c_{hf/skin}(z=-300\,\mu m) = 7.37\cdot10^{-4}$ mg/mL and $c_{inner/outer}(z=-300\,\mu m) = 4.46\cdot10^{-4}$ mg/mL to the local minima $c_{hf/skin}(z=-385\,\mu m) = 7.17\cdot10^{-4}$ mg/mL and $c_{inner/outer}(z=-385\,\mu m) = 4.26\cdot10^{-4}$ mg/mL,

then increase to the maximum concentrations $c_{\text{hf/skin}}(z = \text{-}980\,\mu\text{m}) = 1.67\cdot10^{-3}$ mg/mL and $c_{\text{inner/outer}}(z = \text{-}895\,\mu\text{m}) = 7.05\cdot10^{-4}$ mg/mL. At the hair follicle boundary and at the inner/outer tissue boundary these maximum concentrations are 1.6 to 2.3 times greater and about 60% greater than the values at z = -300 μm. The concentrations then decrease to $c_{\text{hf/skin}}(z = \text{-}2000\,\mu\text{m}) = 2.74\cdot10^{-5}$ mg/mL and $c_{\text{inner/outer}}(z = \text{-}2000\,\mu\text{m}) = 3.12\cdot10^{-5}$ mg/mL. In the lower dermis 2 the values at the inner/outer tissue boundary are up to 14% greater than at the hair follicle boundary. In the hypodermis the concentrations shown in Figures 7.14C and D range from $c_{\text{hf/skin}}(z = \text{-}2000\,\mu\text{m}) = 3.84\cdot10^{-5}$ mg/mL and $c_{\text{inner/outer}}(z = \text{-}2000\,\mu\text{m}) = 4.37\cdot10^{-5}$ mg/mL to values on the order of 10^{-8} mg/mL and 10^{-6} mg/mL at z = -2500 μm.

The concentration values obtained in Case 3b in the viable epidermis are 3 to 7 times smaller at the hair follicle/skin tissue boundary and 5 to 10 times smaller at the inner/outer boundary than the corresponding concentrations in Case 3a. In dermis 1 the concentrations in Case 3b are 7 to 8 times smaller and 10 to 12 smaller than in Case 3a at these boundaries. These fractions increase with depth into the skin. The corresponding factors in dermis 2 are 3 to 8 and 7 to 12 from the dermis 1/dermis 2 boundary to the local maxima, with the difference decreasing with increasing depth as the concentration approaches its maximum values. Below the depths at which the local maxima occur and within the hypodermis, the difference between the Case 3a and Case 3b values increases and is unbounded.

In Case 3c the concentration in the viable epidermis drops 80%, from $c_{\text{hf/skin}}(z = 0) = 2.00\cdot10^{-3}$ mg/mL to $c_{\text{hf / skin}}(z = \text{-}100\,\mu\text{m}) = 4.06\cdot10^{-4}$ mg/mL at the hair

follicle/skin tissue boundary and 82%, from $c_{\text{in / out}}(z = 0)$ = $1.08 \cdot 10^{-4}$ mg/mL to $c_{\text{in / out}}(z = -100\,\mu\text{m})$ = $1.97 \cdot 10^{-4}$ mg/mL at the inner/outer tissue boundary. In dermis 1 the concentrations drop from $c_{\text{hf / skin}}(z = -100\,\mu\text{m})$ = $3.55 \cdot 10^{-4}$ mg/mL to $c_{\text{hf / skin}}(z = -300\,\mu\text{m})$ = $2.35 \cdot 10^{-4}$ mg/mL (34 %) and from $c_{\text{in / out}}(z = -100\,\mu\text{m})$ = $1.62 \cdot 10^{-4}$ mg/mL to $c_{\text{in / out}}(z = -300\,\mu\text{m})$ = $7.40 \cdot 10^{-5}$ mg/mL (54%). In dermis 2 the concentrations first decrease from $c_{\text{hf / skin}}(z = -300\,\mu\text{m})$ = $3.36 \cdot 10^{-4}$ mg/mL and $c_{\text{inner/outer}}(z = -300\,\mu\text{m})$ = $1.06 \cdot 10^{-4}$ mg/mL to the local minima $c_{\text{hf/skin}}(z = -342.5\,\mu\text{m})$ = $3.21 \cdot 10^{-4}$ mg/mL and $c_{\text{inner/outer}}(z = -385\,\mu\text{m})$ = $9.52 \cdot 10^{-5}$ mg/mL, then increase to the local maxima $c_{\text{hf/skin}}(z = -980\,\mu\text{m})$ = $1.08 \cdot 10^{-3}$ mg/mL and $c_{\text{in / out}}(z = -937.5\,\mu\text{m})$ = $2.28 \cdot 10^{-4}$ mg/mL. These maxima are 69% and over 2-fold greater than the concentration values at the dermis 1/dermis 2 boundary (z = -300 μm). In the lower dermis 2 the concentration at the inner/outer boundary is up to 90 % greater than at the hair follicle/skin tissue boundary. The values at the dermis 2/hypodermis boundary, at a depth of z = -2000 μm, are on the order of 10^{-6} mg/mL on either side of the boundary, at the hair follicle/skin tissue and the inner/outer tissue boundaries. The concentration values at a depth of z = -2500 μm in the hypodermis are on the order of 10^{-9} mg/mL and 10^{-7} mg/mL.

Going from Case 3b to Case 3c the concentration decreases by 13 to 47% in the viable at the hair follicle boundary and 19 to 61% at the inner/outer boundary within the viable epidermis, by 46 to 54% and 61 to 78% at these boundaries in the dermis 1, with these percentage difference decreasing with increasing depth. In dermis 2, for -980 μm ≤ z ≤ -300 μm, the difference in concentration in Case 3c is 35 to 54% less at the hair follicle/skin tissue boundary and 68 to 76% less at the inner/outer tissue boundary.

Within dermis 2 the differences first increase with depth until the local concentration minima are reached, but then decrease to the depths at which the local concentration maxima occur. Below these depths the difference in concentration increases with depth and reaches 90 to 100% at z = -2500 μm.

- **Concentration vs. radial distance *r* at *t* = 16 h (Figures 7-14E & F, p. 167)**

The Case 3b concentration values at the top of the viable epidermis, and at the viable epidermis/dermis 1 and dermis 1/dermis 2 boundaries are $c_{sc/ve}(r = 174.7\,\mu m) = 2.30 \cdot 10^{-3}$ mg/mL at the hair follicle/skin tissue boundary and $c_{sc/ve}(r = 282.8\,\mu m) = 1.35 \cdot 10^{-3}$ mg/mL at the inner/outer tissue boundary, $c_{ve/de1}(r = 99.3\,\mu m) = 7.68 \cdot 10^{-4}$ mg/mL and $c_{ve/de1}(r = 209.0\,\mu m) = 5.01 \cdot 10^{-4}$ mg/mL and $c_{de1/de2}(r = 48.8\,\mu m) = 5.16 \cdot 10^{-4}$ mg/mL and $c_{de1/de2}(r = 159.7\,\mu m) = 3.12 \cdot 10^{-4}$ mg/mL. Thus the concentration drop at each one of these horizontal boundaries within the inner region of the computational domain is 42%, 35% and 40%. At the nodes of the computational domain preceding the edge of the donor solution compartment $(r = 1.78\,mm)$, the concentrations are $c_{sc/ve}(r = 1.70\,\mu m) = 6.57 \cdot 10^{-4}$ mg/mL, $c_{ve/de1}(r = 1.65\,mm) = 1.18 \cdot 10^{-4}$ mg/mL and $c_{de1/de2}(r = 1.61\,mm) = 4.90 \cdot 10^{-5}$ mg/mL, yielding concentration drops from the hair follicle boundary of 72%, 85%, and 91%. Far from the hair follicle, at r = 5 mm, the concentrations are on the order of 10^{-6} mg/mL at the top of the viable epidermis and the viable epidermis/dermis 1 boundary and 10^{-7} mg/mL at the dermis 1/dermis 2 boundary.

Within the inner region the concentrations in Case 3b are 3 to 5 times, 7 to 10 times and 8 to 12 times smaller than the concentrations in Case 3a at the top of the viable

epidermis, the viable epidermis/dermis 1 boundary the dermis 1/dermis 2 boundary, respectively. These percentage differences increase with distance r away from the hair follicle. At the edge of the donor solution compartment $(r = 1.78\,\text{mm})$, the concentrations in Case b are about 6 times, 24 times and over 40 times smaller than in Case 3a.

In Case 3c the concentrations at the horizontal boundaries are $c_{\text{sc/ve}}(r = 174.7\,\mu\text{m})$ = $2.00 \cdot 10^{-3}$ mg/mL and $c_{\text{sc/ve}}(r = 282.8\,\mu\text{m})$ = $1.08 \cdot 10^{-3}$ mg/mL, $c_{\text{ve/de1}}(r = 99.3\,\mu\text{m})$ = $4.06 \cdot 10^{-4}$ mg/mL and $c_{\text{ve/de1}}(r = 209.0\,\mu\text{m})$ = $1.97 \cdot 10^{-4}$ mg/mL and $c_{\text{de1/de2}}(r = 48.8\,\mu\text{m})$ = $2.35 \cdot 10^{-4}$ mg/mL and $c_{\text{de1/de2}}(r = 159.7\,\mu\text{m})$ = $7.40 \cdot 10^{-5}$ mg/mL. The concentration drop at each one of these horizontal boundaries within the inner region of the computational domain is 46%, 52% and 69%. At the nodes of the computational domain occurring just before the edge of the donor solution compartment $(r = 1.78\,\text{mm})$, the concentrations are $c_{\text{sc/ve}}(r = 1.70\,\mu\text{m})$ = $6.01 \cdot 10^{-4}$ mg/mL, $c_{\text{ve/de1}}(r = 1.65\,\text{mm})$ = $5.35 \cdot 10^{-5}$ mg/mL and $c_{\text{de1/de2}}(r = 1.61\,\text{mm})$ = $7.77 \cdot 10^{-6}$ mg/mL; the decrease from the edge of the hair follicle is 70%, 87%, and 97%. At the viable epidermis/dermis 1 boundary, the values of the concentration one node beyond the distance r = 1.78 mm, at r = 1.93 mm, is negative. Thereafter the concentrations are positive. This is attributed to numerical error. Far from the hair follicle, at r = 5 mm, the concentrations are also on the order of 10^{-6} mg/mL at the top of the viable epidermis and the viable epidermis/dermis 1 boundary and 10^{-7} mg/mL at the dermis 1/dermis 2 boundary.

Going from Case 3b to Case 3c the concentration values decrease by 9 to 19% at the stratum corneum/viable epidermis boundary for 174.7 μm ≤ r ≤ 1.70 mm. Within this segment the difference increases with r from 13 to 19% in the inner region of the

computational domain $(\text{to } r = 282.8\,\mu\text{m})$, then decreases in the outer region. The difference tends to ~14% as $r \rightarrow 5$ mm. At the viable epidermis/dermis 1 boundary the percentage difference is 47% to 69% for 209.0 μm ≤ r ≤ 1.65 mm. Within this segment the difference increases with r from 47% to 61% in the inner region; in the outer region it increases to 81%, then decreases to 61%. For r > 1.65 mm the difference increases to 54% but stabilizes at ~42% as $r \rightarrow 5$ mm. At the dermis1/dermis 2 boundary the concentration values in Case 3c are 54% to 84% less than in Case 3b for 159.7 μm ≤ r ≤ 1.61 mm. Within this segment the difference increases with r from 54% to 76% in the inner region; in the outer region it increases to 86%, then decreases to 84%. For r > 1.61 mm, the difference increases to 93% but approaches 86% as $r \rightarrow 5$ mm.

7.8.2 Cases 4b, c: Hair follicle permeability due to infundibulum, constant dye concentration in the infundibulum

- **Average concentration vs. time (Figures 7-15A & B, p. 168)**

In Case 4b the maximum average concentration values are $\bar{c}_{\text{ve, max}} = 1.38 \cdot 10^{-3}$ mg/mL at t = 1.25 h, $\bar{c}_{\text{de, max}} = 5.05 \cdot 10^{-4}$ mg/mL at t = 1.5 h and $\bar{c}_{\text{hf / skin, max}} = 1.25 \cdot 10^{-3}$ mg/mL at t = 1.25 h. The final concentration values are $\bar{c}_{\text{ve}}(t = 16\,\text{h}) = 1.32 \cdot 10^{-3}$ mg/mL, $\bar{c}_{\text{de}}(t = 16\,\text{h}) = 4.83 \cdot 10^{-4}$ mg/mL and $\bar{c}_{\text{hf / skin}}(t = 16\,\text{h}) = 1.19 \cdot 10^{-3}$ mg/mL. During the entire simulation run the ratios of the average concentrations are $\bar{c}_{\text{ve}}/\bar{c}_{\text{de}} \approx 3$, $\bar{c}_{\text{ve}}/\bar{c}_{\text{hf / skin}} \approx 1.1$ and $\bar{c}_{\text{de}}/\bar{c}_{\text{hf / skin}} = 2.5$.

Within the initial 105 min of diffusion, the average concentration values in Case 4b are 48 to 72% less than in Case 4a in the viable epidermis, 56 to 83% less in the dermis, and 38 to 67% less at the hair follicle/skin tissue boundary. For 2 h ≤ t ≤ 16 h the

corresponding percentage decreases are 72 to 79%, 84 to 89% and 68 to 76%. In each case the percentage difference increases with time.

Switching to Case 4c, the maximum average concentration values are $\bar{c}_{\text{ve, max}}$ = $1.05 \cdot 10^{-3}$ mg/mL, $\bar{c}_{\text{de, max}}$ = $1.72 \cdot 10^{-4}$ mg/mL and $\bar{c}_{\text{hf / skin, max}}$ = $9.48 \cdot 10^{-4}$ mg/mL, all occurring at t = 0.75 h. The final values are $\bar{c}_{\text{ve}}(t = 16\,\text{h})$ = $1.0 \cdot 10^{-3}$ mg/mL, $\bar{c}_{\text{de}}(t = 16\,\text{h})$ = $1.64 \cdot 10^{-4}$ mg/mL and $\bar{c}_{\text{hf / skin}}(t = 16\,\text{h})$ = $9.04 \cdot 10^{-4}$ mg/mL. The ratios of the average concentration values for $0 \le t \le 16$ h are constant at $\bar{c}_{\text{ve}} / \bar{c}_{\text{de}}$ = 6.1, $\bar{c}_{\text{ve}} / \bar{c}_{\text{hf / skin}}$ = 1.1 and $\bar{c}_{\text{de}} / \bar{c}_{\text{hf / skin}}$ = 5.5. Within the first 105 min of diffusion, the average concentration values in Case 4c are 18 to 24% less than in Case 4b in the viable epidermis, 62 to 66% less in the dermis, and 20 to 24% less at the hair follicle/skin tissue boundary. These percentages remain constant at 24%, 66% and 24% for the remainder of the simulation.

- **Concentration vs. depth *z* at *t* = 16 h (Figures 7-15C & D, p. 168)**

In Case 4b the concentrations at the hair follicle/skin tissue boundary and at the inner/outer region boundary range from $c_{\text{hf / skin}}(z = 0)$ = $2.34 \cdot 10^{-3}$ mg/mL and $c_{\text{in / out}}(z = 0)$ = $1.37 \cdot 10^{-3}$ mg/mL to $c_{\text{hf / skin}}(z = -100\,\mu\text{m})$ = $8.02 \cdot 10^{-4}$ mg/mL and $c_{\text{in / out}}(z = -100\,\mu\text{m})$ = $5.23 \cdot 10^{-4}$ mg/mL, a 66 and 62% decrease at these boundaries. As in Cases 3b, c, d, in these cases the highest concentration in the viable epidermis is just below the stratum corneum/viable epidermis boundary, at z = -10 μm, and is about 2% larger than the value at the surface. Within dermis 1 the values range from $c_{\text{hf / skin}}(z = -100\,\mu\text{m})$ = $6.82 \cdot 10^{-4}$ mg/mL and $c_{\text{in / out}}(z = -100\,\mu\text{m})$ = $4.31 \cdot 10^{-4}$ mg/mL to $c_{\text{hf / skin}}(z = -300\,\mu\text{m})$ = $3.38 \cdot 10^{-4}$ mg/mL and $c_{\text{in / out}}(z = -300\,\mu\text{m})$ = $5.58 \cdot 10^{-4}$ mg/mL, an

18% decrease at the hair follicle boundary and a 22% decrease at the inner/outer region boundary. In dermis 2 the hair follicle and inner/outer tissue boundary concentrations initially decrease to $c_{\text{hf / skin}}(z = \text{-}342.5\,\mu\text{m})$ = $7.85 \cdot 10^{-4}$ mg/mL and $c_{\text{inner/outer}}(z = \text{-}385\,\mu\text{m})$ = $4.71 \cdot 10^{-4}$ mg/mL, then increase to the local maxima $c_{\text{hf / skin}}(z = \text{-}980\,\mu\text{m})$ = $2.15 \cdot 10^{-3}$ mg/mL and $c_{\text{in / out}}(z = \text{-}895\,\mu\text{m})$ = $8.84 \cdot 10^{-4}$ mg/mL. These maximum concentrations are 2.7-fold and 83% greater than the dermis 2 values at z = -300 μm. The concentrations then decrease to values on the order of $3.0 \cdot 10^{-5}$ mg/mL to $4.0 \cdot 10^{-5}$ mg/mL at z = -2000 μm. In the hypodermis the concentrations shown in Figure 7-15C range from about $5.0 \cdot 10^{-5}$ mg/mL at z = -2000 μm to values on the order of 10^{-8} mg/mL and 10^{-7} mg/mL at z = -2500 μm.

The concentration values obtained in Case 4b in the viable epidermis are 3 to 7 times and 5 to 10 times smaller than the corresponding concentrations in Case 4a at the hair follicle and the inner/outer boundaries. In dermis 1 the concentrations in Case 4b are 7 to 7.5 times smaller and 10 to 12 smaller than in Case 4a at these boundaries. These fractions increase with depth into the skin. The corresponding fraction ranges in dermis 2 are 3 to 7.5 and 6 to 12 from the dermis 1/dermis 2 boundary to the local maxima, with the difference first increasing then decreasing with increasing depth. Below the depths at which the local maxima occur and within the hypodermis, the difference between the Case 4a and Case 4b values increases and is unbounded.

Within the viable epidermis of Case 4c the concentration drops 79%, from $c_{\text{hf / skin}}(z = 0)$ = $2.02 \cdot 10^{-3}$ mg/mL to $c_{\text{hf / skin}}(z = \text{-}100\,\mu\text{m})$ = $4.19 \cdot 10^{-4}$ mg/mL at the hair follicle/skin tissue boundary and 82%, from $c_{\text{in / out}}(z = 0)$ = $1.09 \cdot 10^{-3}$ mg/mL to $c_{\text{in / out}}(z = \text{-}100\,\mu\text{m})$ = $2.02 \cdot 10^{-4}$ mg/mL at the inner/outer tissue boundary. In dermis 1 the

concentrations drop from $c_{\mathrm{hf/skin}}(z = -100\,\mu\mathrm{m}) = 3.66\cdot10^{-4}$ mg/mL to $c_{\mathrm{hf/skin}}(z = -300\,\mu\mathrm{m})$ = $2.54\cdot10^{-4}$ mg/mL (31%) and from $c_{\mathrm{in/out}}(z = -100\,\mu\mathrm{m})$ = $1.66\cdot10^{-4}$ mg/mL to $c_{\mathrm{in/out}}(z = -300\,\mu\mathrm{m})$ = $7.97\cdot10^{-5}$ mg/mL (52%). In dermis 2 the concentrations first drops from $c_{\mathrm{hf/skin}}(z = -300\,\mu\mathrm{m}) = 3.63\cdot10^{-4}$ mg/mL and $c_{\mathrm{in/out}}(z = -300\,\mu\mathrm{m}) = 1.14\cdot10^{-4}$ mg/mL to the local minima $c_{\mathrm{hf/skin}}(z = -342.5\,\mu\mathrm{m}) = 3.51\cdot10^{-4}$ mg/mL and $c_{\mathrm{in/out}}(z = -385\,\mu\mathrm{m})$ = $1.05\cdot10^{-4}$ mg/mL, then increase to the local maxima $c_{\mathrm{hf/skin}}(z = -980\,\mu\mathrm{m})$ = $1.41\cdot10^{-3}$ mg/mL and $c_{\mathrm{in/out}}(z = -895\,\mu\mathrm{m})$ = $2.93\cdot10^{-4}$ mg/mL. At the hair follicle boundary the maximum is greater by a factor of 3.9 than the concentration values at the dermis 1/dermis 2 boundary; at the inner/outer boundary it is 2.6 times greater. The values at the dermis 2/hypodermis boundary, at a depth of z = -2000 μm, range from $1.5\cdot10^{-6}$ mg/mL to $4.0\cdot10^{-5}$ mg/mL. The concentration values at a depth of z = -2500 μm in the hypodermis are on the order of 10^{-11} mg/mL and 10^{-7} mg/mL.

Going from Case 4b to 4c, the concentration decreases by 14 to 48% at the hair follicle boundary and 20 to 61% at the inner/outer boundary within the viable epidermis, and by 46 to 55% and 61 to 76% at these boundaries in the dermis 1, with these percentage difference decrease with increasing depth. From the top surface of dermis 2 (z = -300 μm) to the local maxima, the concentration decreases by 36 to 55% at the hair follicle/skin tissue boundary and 67 to 77% at the inner/outer tissue boundary. Within dermis 2 the difference decreases to the depths at which the local concentration maxima occur. Below these depths the difference increases with increasing depth. At z = -2000 μm the values in Case 4c are an average of 94% less than the values in Case 4b.

- **Concentration vs. radial distance *r* at *t* = 16 h (Figures 7-15E & F, p. 168)**

The Case 4b concentration values at the top of the viable epidermis, and at the viable epidermis/dermis 1 and dermis 1/dermis 2 boundaries are $c_{sc/ve}(r = 174.7\,\mu m) = 2.31 \cdot 10^{-3}$ mg/mL and $c_{sc/ve}(r = 282.8\,\mu m) = 1.37 \cdot 10^{-3}$ mg/mL, $c_{ve/de1}(r = 99.3\,\mu m) = 8.02 \cdot 10^{-4}$ mg/mL and $c_{ve/de1}(r = 209.0\,\mu m) = 5.23 \cdot 10^{-4}$ mg/mL and $c_{de1/de2}(r = 48.8\,\mu m) = 5.89 \cdot 10^{-4}$ mg/mL and $c_{de1/de2}(r = 159.7\,\mu m) = 3.38 \cdot 10^{-4}$ mg/mL at the hair follicle/skin tissue and inner/outer tissue boundaries. Thus the concentration drop at each one of these horizontal boundaries within the inner region of the computational domain is 42%, 35% and 40%. At the nodes of the computational domain occurring just before the edge of the donor solution compartment $(r = 1.78\,mm)$, the concentrations are $c_{sc/ve}(r = 1.70\,\mu m) = 6.57 \cdot 10^{-4}$ mg/mL, $c_{ve/de1}(r = 1.65\,mm) = 1.19 \cdot 10^{-4}$ mg/mL and $c_{de1/de2}(r = 1.61\,mm) = 4.97 \cdot 10^{-5}$ mg/mL. These values are 72%, 85% and 91% less than the concentrations at the hair follicle boundary. Far from the hair follicle, at r = 5 mm, the concentrations are on the order of 10^{-6} mg/mL at the top of the viable epidermis and the viable epidermis/dermis 1 boundary and 10^{-7} mg/mL at the dermis 1/dermis 2 boundary.

Within the inner region the concentrations in Case 4b are 3 to 5 times, 7 to 10 times and 8 to 12 times smaller than the concentrations in Case 3a at the top of the viable epidermis, the viable epidermis/dermis 1 boundary the dermis 1/dermis 2 boundary, respectively. These percentage differences increase with distance r away from the hair follicle. At the edge of the donor solution compartment $(r = 1.78\,mm)$, the concentrations in Case b are about 6 times, 24 times and over 40 times smaller than in Case 4a. These factors are identical to the corresponding ones in Case 3b compared to Case 3a.

The Case 4c concentrations at the horizontal boundaries are $c_{sc/ve}(r = 174.7\,\mu m)$ = $2.02 \cdot 10^{-3}$ mg/mL and $c_{sc/ve}(r = 282.8\,\mu m)$ = $1.09 \cdot 10^{-3}$ mg/mL, $c_{ve/de1}(r = 99.3\,\mu m)$ = $4.19 \cdot 10^{-4}$ mg/mL and $c_{ve/de1}(r = 209.0\,\mu m)$ = $2.02 \cdot 10^{-4}$ mg/mL and $c_{de1/de2}(r = 48.8\,\mu m)$ = $2.54 \cdot 10^{-4}$ mg/mL and $c_{de1/de2}(r = 159.7\,\mu m)$ = $7.97 \cdot 10^{-5}$ mg/mL. Thus the concentration drop at each one of these horizontal boundaries within the inner region of the computational domain is 46%, 52% and 69%. At the nodes of the computational domain occurring just before the edge of the donor solution compartment $(r = 1.78\,mm)$, the concentrations are $c_{sc/ve}(r = 1.70\,\mu m)$ = $6.01 \cdot 10^{-4}$ mg/mL, $c_{ve/de1}(r = 1.65\,mm)$ = $5.35 \cdot 10^{-5}$ mg/mL and $c_{de1/de2}(r = 1.61\,mm)$ = $7.83 \cdot 10^{-6}$ mg/mL. These values are 70%, 87%, and 97% less than at the hair follicle/skin tissue boundary. The values of the concentration on node beyond the distance r = 1.78 mm, at r = 1.93 mm, is negative. This is attributed to numerical error. Far from the hair follicle, at r = 5 mm, the concentrations are also on the order of 10^{-6} mg/mL at the top of the viable epidermis and the viable epidermis/dermis 1 boundary and 10^{-7} mg/mL at the dermis 1/dermis 2 boundary.

The concentrations in Case 4c are 9 to 20% less than in Case 4b at the stratum corneum/viable epidermis boundary for 174.7 μm ≤ r ≤ 1.70 mm. Within this segment the difference is 14 to 20% in the inner region of the computational domain $(\text{to } r = 282.8\,\mu m)$, and decreases to 9% in the outer region. The difference is greater at r = 1.93 mm due to the negative concentration value obtained in Case 4b, but decreases to 14% as $r \rightarrow 5$ mm. At the viable epidermis/dermis 1 boundary the percentage difference is 48% to 70% for 209.0 μm ≤ r ≤ 1.65 mm. Within this segment the difference increases with r from 48% to 61% in the inner region; in the outer region it increases to 70%, then

drops to 55%. For $r > 1.65$ mm the difference increases to 88% but tends to 61% as $r \rightarrow 5$ mm. At the dermis1/dermis 2 boundary the concentration values in Case 4c are 55% to 86% less than in Case 4b for 159.7 μm $\leq r \leq$ 1.61 mm. Within this segment the difference increases with r from 55% to 76% in the inner region; in the outer region it increases to 86%, then decreases to 84%. For $r > 1.61$ mm, the difference increases to 93% but approaches 86% as $r \rightarrow 5$ mm.

7.8.3 Cases 5b, c: Hair follicle permeability due to infundibulum and the sebaceous duct, transient dye concentration in the infundibulum

- **Average concentrations vs. time (Figures 7-16A & B, p. 169)**

In Case 5b the maximum average concentration values are $\bar{c}_{ve,\,max} = 2.95 \cdot 10^{-3}$ mg/mL at t = 13.5 h, and $\bar{c}_{hf\,/\,skin,\,max} = 3.06 \cdot 10^{-3}$ mg/mL at t = 14 h. $\bar{c}_{de,\,max}$ does not reach a maximum value. The average concentrations remain essentially constant after reaching their maxima. During the first 105 min of the simulation, the ratios of the average concentrations are $\bar{c}_{ve}/\bar{c}_{de}$ = 0.8 to 1.2, $\bar{c}_{ve}/\bar{c}_{hf\,/\,skin} \approx 1.0$ and $\bar{c}_{de}/\bar{c}_{hf\,/\,skin}$ = 0.8 to 1.14. The ratios of the average concentrations are $\bar{c}_{de}/\bar{c}_{ve}$ = 1.2 to 1.3, $\bar{c}_{hf\,/\,skin}/\bar{c}_{ve} \approx 1.0$ (with $\bar{c}_{hf\,/\,skin} > \bar{c}_{ve}$ by 3 to 4%) and $\bar{c}_{de}/\bar{c}_{hf\,/\,skin} \approx 1.2$ for 2 h $\leq t \leq$ 16 h. Within the initial 105 min of diffusion, the average concentration values in Case 5b are 48 to 74% less than in Case 5a in the viable epidermis, 42 to 69% less in the dermis, and 38 to 69% less at the hair follicle/skin tissue boundary. For 2 h $\leq t \leq$ 16 h the corresponding percentage decreases are 74 to 82%, 69 to 76% and 70 to 78%. In each case the percentage difference increases with time.

The maximum concentration values in Case 5c are $\bar{c}_{\text{ve, max}} = 1.23 \cdot 10^{-3}$ mg/mL at t = 7 h and $\bar{c}_{\text{hf / skin, max}} = 1.31 \cdot 10^{-3}$ mg/mL at t = 9 h. There is no maximum in the average dermal concentration. The values at t = 16 h are $\bar{c}_{\text{ve}}(t = 16\,\text{h}) = 1.21 \cdot 10^{-3}$ mg/mL, $\bar{c}_{\text{de}}(t = 16\,\text{h}) = 1.12 \cdot 10^{-3}$ mg/mL and $\bar{c}_{\text{hf / skin}}(t = 16\,\text{h}) = 1.30 \cdot 10^{-3}$ mg/mL. Within the first 105 min the ratios of the average concentration values the ratio $\bar{c}_{\text{ve}} / \bar{c}_{\text{de}}$ decreases from 2.2 to 1.3, $\bar{c}_{\text{hf/skin}} / \bar{c}_{\text{ve}} \approx 1.0$ and $\bar{c}_{\text{hf/skin}} / \bar{c}_{\text{de}}$ decreases from 2.1 to 1.3. For 2 h $\leq t \leq$ 16 h these ratios are 1.1 to 1.2, 1.1 and 1.2 to 1.3, with the values decreasing as t increases. Compared to Case 5b the average concentrations obtained in the first 105 min of simulation are 26 to 54% smaller in the viable epidermis, 59 to 69% smaller in the dermis and 30 to 53% smaller at the hair follicle/skin tissue boundary. For 2 h $\leq t \leq$ 16 h the corresponding percentages are 54 to 59%, 69 to 70% and 54 to 57%.

- **Concentration vs. depth *z* (Figures 7-16C & D, p. 169)**

In Case 5b the concentrations at the hair follicle/skin tissue boundary and at the inner/outer region boundary range from $c_{\text{hf / skin}}(z = 0) = 3.95 \cdot 10^{-3}$ mg/mL and $c_{\text{in / out}}(z = 0) = 2.68 \cdot 10^{-3}$ mg/mL to $c_{\text{hf / skin}}(z = -100\,\mu\text{m}) = 2.87 \cdot 10^{-3}$ mg/mL and $c_{\text{in / out}}(z = -100\,\mu\text{m}) = 2.18 \cdot 10^{-3}$ mg/mL, a 27% and 19% decrease. The highest concentration in the viable epidermis is just below the stratum corneum/viable epidermis boundary, at z = -10 μm, and is 1.7% larger than the value at the surface. In Case 5c this percentage increases to 2.1%. Within dermis 1 the values increase from $c_{\text{hf / skin}}(z = -100\,\mu\text{m}) = 2.38 \cdot 10^{-3}$ mg/mL and $c_{\text{in / out}}(z = -100\,\mu\text{m}) = 1.80 \cdot 10^{-3}$ mg/mL to $c_{\text{hf / skin}}(z = -300\,\mu\text{m}) = 5.35 \cdot 10^{-3}$ mg/mL and $c_{\text{in / out}}(z = -300\,\mu\text{m}) = 3.11 \cdot 10^{-3}$ mg/mL, a

2.2-fold increase at the hair follicle boundary and 1.7-fold increase at the inner/outer region boundary. In dermis 2 the hair follicle and inner/outer tissue boundary concentrations increase from $c_{\text{hf / skin}}(z = -300\,\mu\text{m})$ = $7.64 \cdot 10^{-3}$ mg/mL and $c_{\text{in / out}}(z = -300\,\mu\text{m})$ = $4.44 \cdot 10^{-3}$ mg/mL to the local maxima $c_{\text{hf / skin}}(z = -512.5\,\mu\text{m})$ = $2.01 \cdot 10^{-2}$ mg/mL and $c_{\text{in / out}}(z = -512.5\,\mu\text{m})$ = $7.48 \cdot 10^{-3}$ mg/mL. These maximum concentrations are respectively 2.6 and 1.7 greater than the values at z = -300 μm. The concentrations then decrease to $c_{\text{hf / skin}}(z = -2000\,\mu\text{m})$ = $1.12 \cdot 10^{-4}$ mg/mL and $c_{\text{in / out}}(z = -2000\,\mu\text{m})$ = $1.29 \cdot 10^{-4}$ mg/mL. In the hypodermis the concentrations shown in Figure 7.16 C and D range from $c_{\text{hf / skin}}(z = -2000\,\mu\text{m})$ = $1.58 \cdot 10^{-4}$ mg/mL and $c_{\text{in / out}}(z = -2000\,\mu\text{m})$ = $1.80 \cdot 10^{-4}$ mg/mL to values on the order of 10^{-7} mg/mL and 10^{-6} mg/mL at z = -2500 μm.

From Case 5a to Case 5b the concentrations in the viable epidermis decrease by a factor of 4.5 to 5.5 at the hair follicle boundary and 6.0 to 6.8 at the inner/outer boundary, with the difference increasing with depth. In dermis 1 the concentrations decrease by factors of 3.0 to 5.5 and 4.4 to 6.8 at these boundaries, with the difference decreasing with increasing depth into the skin. For -512.5 μm ≤ z ≤ -300 μm in dermis 2 the concentrations decrease by factors of 1.8 to 3.0 and 3.0 to 4.4 at these boundaries, with the differences decreasing with z. Below the depths at which the local maxima occur and within the hypodermis, the difference between the Case 5a and Case 5b values increases and is unbounded.

Within the viable epidermis of Case 5c the concentration drops 67%, from $c_{\text{hf / skin}}(z = 0)$ = $2.23 \cdot 10^{-3}$ mg/mL to $c_{\text{hf / skin}}(z = -100\,\mu\text{m})$ = $7.41 \cdot 10^{-4}$ mg/mL at the hair

follicle/skin tissue boundary from $c_{\text{in / out}}(z = 0)$ = 1.24·10^{-3} mg/mL to $c_{\text{in / out}}(z = \text{-}100\ \mu\text{m})$ = 4.10·10^{-4} mg/mL at the inner/outer tissue boundary. In dermis 1 the concentrations increases by a factor of 3.8 at the hair follicle/skin tissue boundary from $c_{\text{hf / skin}}(z = \text{-}100\ \mu\text{m})$ = 6.29·10^{-4} mg/mL to $c_{\text{hf / skin}}(z = \text{-}300\ \mu\text{m})$ = 2.39·10^{-3} mg/mL and by a factor of 2.3 at the inner/outer tissue boundary, from $c_{\text{in / out}}(z = \text{-}100\ \mu\text{m})$ = 3.37·10^{-4} mg/mL to $c_{\text{in / out}}(z = \text{-}300\ \mu\text{m})$ = 7.92·10^{-4} mg/mL. Unlike Case 5b, the minimum dermis 1 concentration values in Cases 5c occur at a depth of z = -120 μm instead of at the viable epidermis/dermis 1 boundary (z = -100 μm). These minima are $c_{\text{hf/skin}}(z = \text{-}120\ \mu\text{m})$ = 6.15·10^{-4} mg/mL and $c_{\text{inner/outer}}(z = \text{-}120\ \mu\text{m})$ = 3.31·10^{-4} mg/mL. In dermis 2 the concentrations increase from $c_{\text{hf / skin}}(z = \text{-}300\ \mu\text{m})$ = 3.42·10^{-3} mg/mL and $c_{\text{in / out}}(z = \text{-}300\ \mu\text{m})$ = 1.13·10^{-3} mg/mL to the local maxima $c_{\text{hf/skin}}(z = \text{-}512.5\ \mu\text{m})$ = 1.30·10^{-2} mg/mL and $c_{\text{in / out}}(z = \text{-}512.5\ \mu\text{m})$ = 2.58·10^{-3} mg/mL. At the hair follicle boundary the maximum is greater by a factor of 3.8 than the concentration values at the dermis 1/dermis 2 boundary; at the inner/outer boundary it is 2.3 times greater. The values at the dermis 2/hypodermis boundary, at a depth of z = -2000 μm, are on the order of 10^{-6} at the hair follicle/skin tissue boundary and 10^{-5} mg/mL at the inner/outer tissue boundary. These concentration values at a depth of z = -2500 μm in the hypodermis are on the order of 10^{-10} mg/mL and 10^{-7} mg/mL, respectively.

Going from Case 5b to 5c, the concentration decreases by 44 to 74% at the hair follicle boundary and 54 to 81% at the inner/outer boundary within the viable epidermis, with these percentage differences increasing with depth. Within dermis 1 the concentration decreases by 55 to 71% and 75 to 81% at these boundaries, with these

percentage differences decreasing with increasing depth. From the top surface of dermis 2 (z = -300 μm) to the local maximum at z = -512.5 μm, the concentration decreases by 35 to 55% at the hair follicle/skin tissue boundary and 66 to 76% at the inner/outer tissue boundary. Within dermis 2 the difference decreases to the depths at which the local concentration maxima occur. Below these depths the difference increases with increasing depth. At z = -2000 μm the values in Case 5c are 93 to 96% less than the values in Case 5b.

- **Concentration vs. radial distance *r* (Figures 7-16E & F, p. 169)**

The Case 5b concentration values at the top of the viable epidermis, and at the viable epidermis/dermis 1 and dermis 1/dermis 2 boundaries are $c_{sc/ve}(r = 174.7\,\mu m) = 3.95 \cdot 10^{-3}$ mg/mL and $c_{sc/ve}(r = 282.8\,\mu m) = 2.68 \cdot 10^{-3}$ mg/mL, $c_{ve/de1}(r = 99.3\,\mu m) = 2.87 \cdot 10^{-3}$ mg/mL and $c_{ve/de1}(r = 209.0\,\mu m) = 2.18 \cdot 10^{-3}$ mg/mL and $c_{de1/de2}(r = 48.8\,\mu m) = 5.35 \cdot 10^{-3}$ mg/mL and $c_{de1/de2}(r = 159.7\,\mu m) = 3.11 \cdot 10^{-3}$ mg/mL at the hair follicle/skin tissue and inner/outer tissue boundaries. The concentration drop at each one of these horizontal boundaries within the inner region of the computational domain is 32%, 24% and 42%. At the nodes of the computational domain occurring just before the edge of the donor solution compartment $(r = 1.78\,mm)$, the concentrations are $c_{sc/ve}(r = 1.70\,\mu m) = 6.75 \cdot 10^{-4}$ mg/mL, $c_{ve/de1}(r = 1.65\,mm) = 1.39 \cdot 10^{-4}$ mg/mL and $c_{de1/de2}(r = 1.61\,mm) = 7.31 \cdot 10^{-5}$ mg/mL. These values are 83%, 95% and 97% less than the concentrations at the hair follicle boundary. Far from the hair follicle, at r = 5 mm, the concentrations are on the order of 10^{-6} mg/mL at the top of the viable epidermis and the viable epidermis/dermis 1 boundary and 10^{-7} mg/mL at the dermis 1/dermis 2 boundary.

Within the inner region the concentrations in Case 5b are 4 to 6 times, 6 to 7 times and 3 to 4 times smaller than the concentrations in Case 5a at the top of the viable epidermis, the viable epidermis/dermis 1 boundary the dermis 1/dermis 2 boundary, respectively. These factors increase with distance r away from the hair follicle. At the edge of the donor solution compartment $(r = 1.78\,\text{mm})$, the concentrations in Case 5b at these boundaries are about 10, 40 and 60 times smaller than in Case 5a.

In Case 5c the concentrations at the horizontal boundaries are $c_{\text{sc/ve}}(r = 174.7\,\mu\text{m})$ = $2.23 \cdot 10^{-3}$ mg/mL and $c_{\text{sc/ve}}(r = 282.8\,\mu\text{m})$ = $1.24 \cdot 10^{-3}$ mg/mL, $c_{\text{ve/de1}}(r = 99.3\,\mu\text{m})$ = $7.41 \cdot 10^{-4}$ mg/mL and $c_{\text{ve/de1}}(r = 209.0\,\mu\text{m}) = 4.10 \cdot 10^{-4}$ mg/mL and $c_{\text{de1/de2}}(r = 48.8\,\mu\text{m})$ = $2.39 \cdot 10^{-3}$ mg/mL and $c_{\text{de1/de2}}(r = 159.7\,\mu\text{m}) = 7.92 \cdot 10^{-4}$ mg/mL. The concentration drop at each one of these horizontal boundaries within the inner region of the computational domain is 44%, 45% and 67%. At the nodes of the computational domain occurring just before the edge of the donor solution compartment $(r = 1.78\,\text{mm})$, the concentrations are $c_{\text{sc/ve}}(r = 1.70\,\mu\text{m})$ = $6.02 \cdot 10^{-4}$ mg/mL, $c_{\text{ve/de1}}(r = 1.65\,\text{mm})$ = $5.39 \cdot 10^{-5}$ mg/mL and $c_{\text{de1/de2}}(r = 1.61\,\text{mm}) = 9.32 \cdot 10^{-6}$ mg/mL; the decrease from the edge of the hair follicle is 73%, 93%, and 100%. At the viable epidermis/dermis 1 boundary, the values of the concentration one node beyond the distance r = 1.78 mm, at r = 1.93 mm, is negative. Thereafter the concentrations are positive. This is attributed to numerical error. Far from the hair follicle, at r = 5 mm, the concentrations are also on the order of 10^{-6} mg/mL at the top of the viable epidermis and the viable epidermis/dermis 1 boundary and 10^{-7} mg/mL at the dermis 1/dermis 2 boundary.

Going from Case 5b to Case 5c the concentration values decrease by 11 to 54 % at the stratum corneum/viable epidermis boundary for 174.7 μm ≤ r ≤ 1.70 mm. Within this segment the difference increases with r from 44 to 54 % in the inner region of the computational domain $(\text{to } r = 282.8\,\mu\text{m})$, then decreases in the outer region. The difference tends to ~14% as $r \rightarrow 5$ mm. At the viable epidermis/dermis 1 boundary the percentage difference is 61% to 87% for 209.0 μm ≤ r ≤ 1.65 mm. Within this segment the difference increases with r from 74% to 81% in the inner region; in the outer region it increases to 87%, then decreases to 61%. For r > 1.65 mm the difference increases to 91% but stabilizes at 62% as $r \rightarrow 5$ mm. At the dermis1/dermis 2 boundary the concentration values in Case 5c are 55% to 89% less than in Case 5b for 159.7 μm ≤ r ≤ 1.61 mm. Within this segment the difference increases with r from 55% to 75% in the inner region; in the outer region it increases to 89%, then decreases to 87%. For r > 1.61 mm, the difference increases to 94% but approaches 86% as $r \rightarrow 5$ mm.

7.8.4 Cases 6b, c: Hair follicle permeability due to infundibulum and the sebaceous duct, constant dye concentration in the infundibulum

- **Average concentrations vs. time (Figures 7-17A & B, p. 170)**

In Case 6b the maximum average concentration values are $\bar{c}_{\text{ve, max}} = 3.31 \cdot 10^{-3}$ mg/mL at t = 1.5 h, $\bar{c}_{\text{de, max}} = 4.33 \cdot 10^{-3}$ mg/mL at t = 1.25 h and $\bar{c}_{\text{hf / skin, max}} = 3.46 \cdot 10^{-3}$ mg/mL at t = 1.25 h. The average concentrations remain essentially constant after reaching their maxima. The ratios of the average concentrations are constant during the 16h-simulation at $\bar{c}_{\text{de}}/\bar{c}_{\text{ve}} = 1.3$, $\bar{c}_{\text{hf/skin}}/\bar{c}_{\text{ve}} \approx 1.0$ and $\bar{c}_{\text{de}}/\bar{c}_{\text{hf / skin}} = 1.3$. Within the initial 105 min of diffusion, the average concentration values in Case 6b are 53 to 76% less than in Case 6a

in the viable epidermis, 48 to 70% less in the dermis, and 48 to 72% less at the hair follicle/skin tissue boundary. For 2 h ≤ t ≤ 16 h the corresponding percentage decreases are 77 to 82%, 70 to 77% and 73 to 78%. In each case the percentage difference increases with time.

The maximum concentration values in Case 6c are $\bar{c}_{\text{ve, max}} = 1.31 \cdot 10^{-3}$ mg/mL at t = 45 min, $\bar{c}_{\text{de, max}} = 1.30 \cdot 10^{-3}$ mg/mL at t = 30 min and $\bar{c}_{\text{hf/skin, max}} = 1.43 \cdot 10^{-3}$ mg/mL at t = 45 min. The values at t = 16 h are $\bar{c}_{\text{ve}}(t = 16\,\text{h}) = 1.24 \cdot 10^{-3}$ mg/mL, $\bar{c}_{\text{de}}(t = 16\,\text{h}) = 1.23 \cdot 10^{-3}$ mg/mL and $\bar{c}_{\text{hf / skin}}(t = 16\,\text{h}) = 1.36 \cdot 10^{-3}$ mg/mL. The ratios of the average concentrations are $\bar{c}_{\text{ve}} / \bar{c}_{\text{de}} = 1.0$, $\bar{c}_{\text{hf/skin}} / \bar{c}_{\text{ve}} = 1.0$ and $\bar{c}_{\text{hf/skin}} / \bar{c}_{\text{de}} = 1.1$. Compared to Case 6b the average concentrations are 54 to 61% smaller in the viable epidermis, 68 to 70% smaller in the dermis and 55 to 59% smaller at the hair follicle/skin tissue boundary.

- **Concentration vs. depth *z* (Figures 7-17C & D, p. 170)**

In Case 6b the concentrations at the hair follicle/skin tissue boundary and at the inner/outer region boundary range from $c_{\text{hf/skin}}(z = 0) = 4.18 \cdot 10^{-3}$ mg/mL and $c_{\text{inner/outer}}(z = 0) = 2.87 \cdot 10^{-3}$ mg/mL to $c_{\text{hf / skin}}(z = -100\,\mu\text{m}) = 3.15 \cdot 10^{-3}$ mg/mL and $c_{\text{in / out}}(z = -100\,\mu\text{m}) = 2.41 \cdot 10^{-3}$ mg/mL, a 25% and 16% decrease. The highest concentration in the viable epidermis is just below the stratum corneum/viable epidermis boundary, at z = -10 μm, and is 1.7% larger than the value at the surface. In Cases 6c and 6d this percentage is slightly higher at 2.0 and 2.2%, respectively. Within dermis 1 the values increase from $c_{\text{hf / skin}}(z = -100\,\mu\text{m}) = 2.61 \cdot 10^{-3}$ mg/mL and $c_{\text{in / out}}(z = -100\,\mu\text{m}) = 1.98 \cdot 10^{-3}$ mg/mL to $c_{\text{hf / skin}}(z = -300\,\mu\text{m}) = 5.94 \cdot 10^{-3}$ mg/mL and $c_{\text{in / out}}(z = -300\,\mu\text{m}) =$

$3.48 \cdot 10^{-3}$ mg/mL, a 2.3-fold increase at the hair follicle boundary and 1.8-fold increase at the inner/outer region boundary. In dermis 2 the hair follicle and inner/outer tissue boundary concentrations increase from $c_{\text{hf / skin}}(z = -300\,\mu\text{m}) = 8.47 \cdot 10^{-3}$ mg/mL and $c_{\text{in / out}}(z = -300\,\mu\text{m}) = 4.97 \cdot 10^{-3}$ mg/mL to the local maxima $c_{\text{hf / skin}}(z = -512.5\,\mu\text{m}) = 2.30 \cdot 10^{-2}$ mg/mL and $c_{\text{in / out}}(z = -512.5\,\mu\text{m}) = 8.54 \cdot 10^{-3}$ mg/mL. These maximum concentrations are 2.7 and 1.7 greater than the values at z = -300 μm, respectively. The concentrations then decrease to $c_{\text{hf / skin}}(z = -2000\,\mu\text{m}) = 1.32 \cdot 10^{-4}$ mg/mL and $c_{\text{in / out}}(z = -2000\,\mu\text{m}) = 1.50 \cdot 10^{-4}$ mg/mL. In the hypodermis the concentrations shown in Figure 7.17 C and D range from $c_{\text{hf / skin}}(z = -2000\,\mu\text{m}) = 1.85 \cdot 10^{-4}$ mg/mL and $c_{\text{in / out}}(z = -2000\,\mu\text{m}) = 2.11 \cdot 10^{-4}$ mg/mL to values on the order of 10^{-7} mg/mL and 10^{-6} mg/mL at z = -2500 μm.

From Case 6a to Case 6b the concentrations in the viable epidermis decrease by a factor of 4.6 to 5.7 at the hair follicle boundary and 6.1 to 6.9 at the inner/outer boundary, with the difference increasing with depth. In dermis 1 the concentrations decrease by factors of 3.1 to 5.6 and 4.5 to 6.9 at these boundaries, with the difference decreasing with increasing depth into the skin. For -512.5 μm $\leq z \leq$ -300 μm in dermis 2 the concentrations decrease by factors of 1.7 to 3.1 and 3.0 to 4.5 at these boundaries, with the differences decreasing with z. Below the depths at which the local maxima occur and within the hypodermis, the difference between the Case 6a and Case 6b values increases and is unbounded.

Within the viable epidermis of Case 6c the concentration drops 65%, from $c_{\text{hf / skin}}(z = 0) = 2.67 \cdot 10^{-3}$ mg/mL to $c_{\text{hf / skin}}(z = -100\,\mu\text{m}) = 7.85 \cdot 10^{-4}$ mg/mL at the hair

follicle/skin tissue boundary from $c_{\text{in / out}}(z = 0)$ = 1.26·10^{-3} mg/mL to $c_{\text{in / out}}(z = \text{-}100\,\mu\text{m})$ = 4.36·10^{-4} mg/mL at the inner/outer tissue boundary. In dermis 1 the concentrations increases by a factor of 3.9 at the hair follicle/skin tissue boundary from $c_{\text{hf / skin}}(z = \text{-}100\,\mu\text{m})$ = 6.66·10^{-4} mg/mL to $c_{\text{hf / skin}}(z = \text{-}300\,\mu\text{m})$ = 2.63·10^{-3} mg/mL and by a factor of 2.4 at the inner/outer tissue boundary, from $c_{\text{in / out}}(z = \text{-}100\,\mu\text{m})$ = 3.59·10^{-4} mg/mL to $c_{\text{in / out}}(z = \text{-}300\,\mu\text{m})$ = 8.78·10^{-4} mg/mL. Unlike Case 6b, the minimum dermis 1 concentration values in Cases 6c occur at a depth of z = -120 μm instead of at the viable epidermis/dermis 1 boundary (z = -100 μm). These minima are $c_{\text{hf/skin}}(z = \text{-}120\,\mu\text{m})$ = 6.54·10^{-4} mg/mL and $c_{\text{inner/outer}}(z = \text{-}120\,\mu\text{m})$ = 3.54·10^{-4} mg/mL. In dermis 2 the concentrations increase from $c_{\text{hf / skin}}(z = \text{-}300\,\mu\text{m})$ = 3.75·10^{-3} mg/mL and $c_{\text{in / out}}(z = \text{-}300\,\mu\text{m})$ = 1.25·10^{-3} mg/mL to the local maxima $c_{\text{hf/skin}}(z = \text{-}512.5\,\mu\text{m})$ = 1.49·10^{-2} mg/mL and $c_{\text{in / out}}(z = \text{-}512.5\,\mu\text{m})$ = 2.95·10^{-3} mg/mL. At the hair follicle boundary the maximum is greater by a factor of 4.0 than the concentration values at the dermis 1/dermis 2 boundary; at the inner/outer boundary it is 2.4 times greater. The values at the dermis 2/hypodermis boundary, at a depth of z = -2000 μm, are on the order of 10^{-6} at the hair follicle/skin tissue boundary and 10^{-5} mg/mL at the inner/outer tissue boundary. These concentration values at a depth of z = -2500 μm in the hypodermis are on the order of 10^{-10} mg/mL and 10^{-7} mg/mL, respectively.

Going from Case 6b to 6c, the concentration decreases by 46 to 75% at the hair follicle boundary and 56 to 82% at the inner/outer boundary within the viable epidermis, with these percentage differences increasing with depth. Within dermis 1 the concentration decreases by 55 to 75% and 75 to 82% at these boundaries, with these

percentage differences decreasing with increasing depth. From the top surface of dermis 2 (z = -300 μm) to the local maximum at z = -512.5 μm, the concentration decreases by 35 to 56% at the hair follicle/skin tissue boundary and 65 to 75% at the inner/outer tissue boundary. Within dermis 2 the difference decreases to the depths at which the local concentration maxima occur. Below these depths the difference increases with increasing depth. At z = -2000 μm the values in Case 6c are 93 to 96% less than the values in Case 6b.

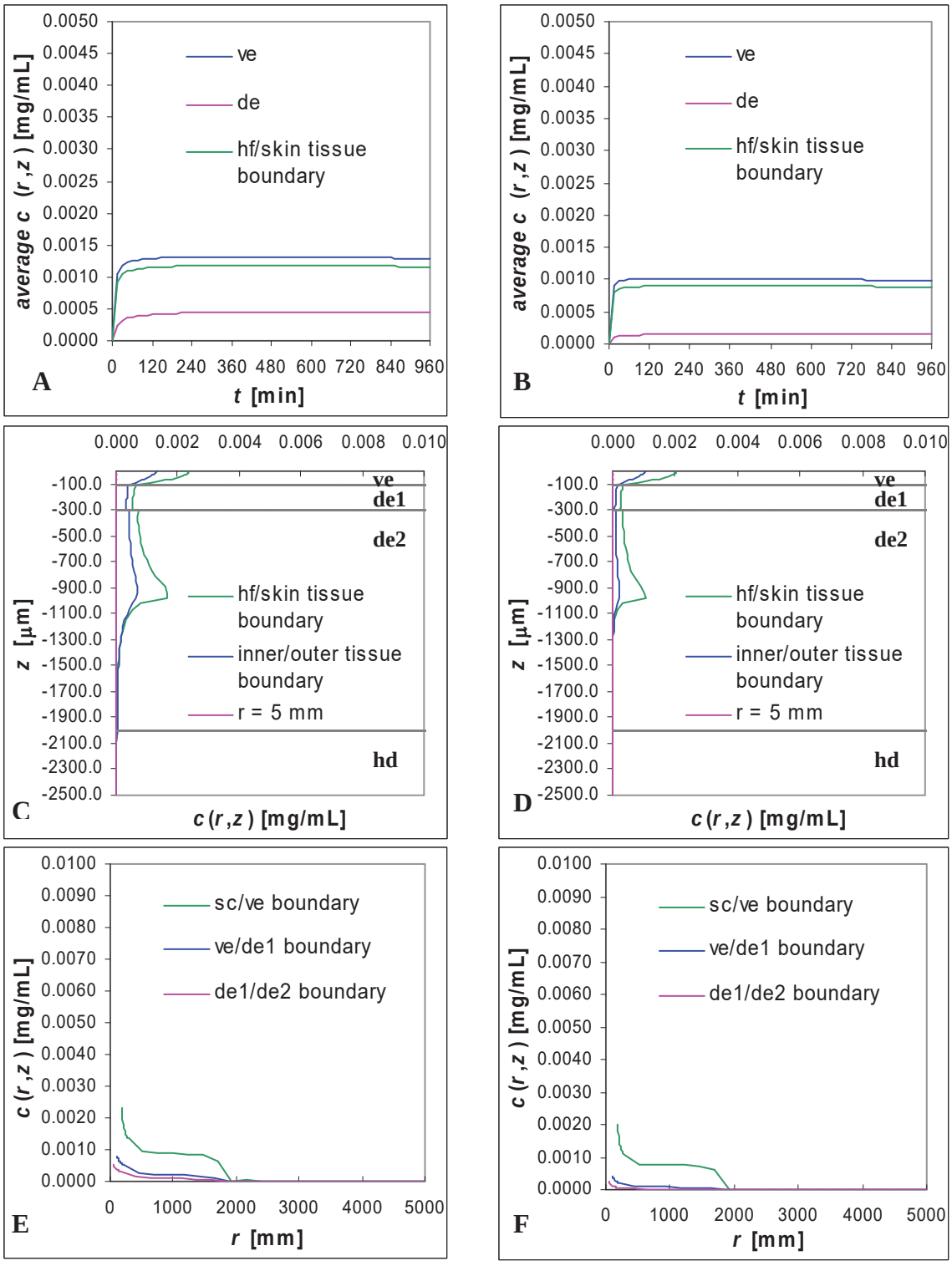
- **Concentration vs. radial distance *r* (Figures 7-17E & F, p. 170)**

The Case 6b concentration values at the top of the viable epidermis, and at the viable epidermis/dermis 1 and dermis 1/dermis 2 boundaries are $c_{sc/ve}(r = 174.7\,\mu m) = 4.18 \cdot 10^{-3}$ mg/mL and $c_{sc/ve}(r = 282.8\,\mu m) = 2.87 \cdot 10^{-3}$ mg/mL, $c_{ve/de1}(r = 99.3\,\mu m) = 3.15 \cdot 10^{-3}$ mg/mL and $c_{ve/de1}(r = 209.0\,\mu m) = 2.41 \cdot 10^{-3}$ mg/mL and $c_{de1/de2}(r = 48.8\,\mu m) = 5.94 \cdot 10^{-3}$ mg/mL and $c_{de1/de2}(r = 159.7\,\mu m) = 3.48 \cdot 10^{-3}$ mg/mL at the hair follicle/skin tissue and inner/outer tissue boundaries. The concentration drop at each one of these horizontal boundaries within the inner region of the computational domain is 32%, 24% and 42%. At the nodes of the computational domain occurring just before the edge of the donor solution compartment $(r = 1.78\,mm)$, the concentrations are $c_{sc/ve}(r = 1.70\,\mu m) = 6.79 \cdot 10^{-4}$ mg/mL, $c_{ve/de1}(r = 1.65\,mm) = 1.42 \cdot 10^{-4}$ mg/mL and $c_{de1/de2}(r = 1.61\,mm) = 7.73 \cdot 10^{-5}$ mg/mL. These values are 84%, 95% and 99% less than the concentrations at the hair follicle boundary. Far from the hair follicle, at r = 5 mm, the concentrations are on the order of 10^{-6} mg/mL at the top of the viable epidermis and the viable epidermis/dermis 1 boundary and 10^{-7} mg/mL at the dermis 1/dermis 2 boundary.

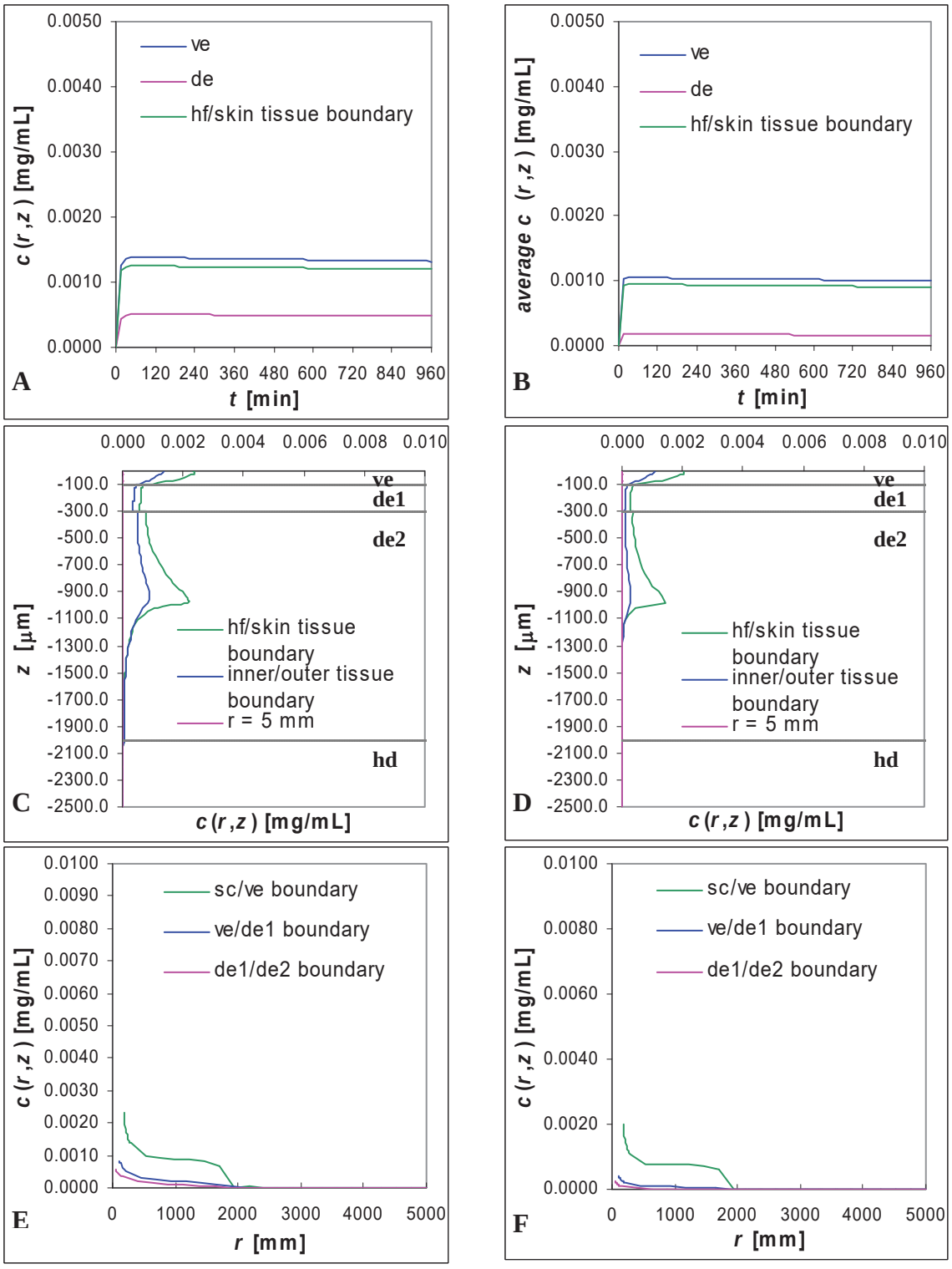
Within the inner region the concentrations in Case 6b are 5 to 6 times, 6 to 7 times and 3 to 4 times smaller than the concentrations in Case 6a at the top of the viable epidermis, the viable epidermis/dermis 1 boundary the dermis 1/dermis 2 boundary, respectively. These factors increase with distance r away from the hair follicle. At the edge of the donor solution compartment $(r = 1.78\,\text{mm})$, the concentrations in Case 6b at these boundaries are about 11, 44 and 65 times smaller than in Case 6a.

In Case 6c the concentrations at the horizontal boundaries are $c_{\text{sc/ve}}(r = 174.7\,\mu\text{m})$ = $2.27 \cdot 10^{-3}$ mg/mL and $c_{\text{sc/ve}}(r = 282.8\,\mu\text{m})$ = $1.26 \cdot 10^{-3}$ mg/mL, $c_{\text{ve/de1}}(r = 99.3\,\mu\text{m})$ = $7.85 \cdot 10^{-4}$ mg/mL and $c_{\text{ve/de1}}(r = 209.0\,\mu\text{m}) = 4.36 \cdot 10^{-4}$ mg/mL and $c_{\text{de1/de2}}(r = 48.8\,\mu\text{m})$ = $2.63 \cdot 10^{-3}$ mg/mL and $c_{\text{de1/de2}}(r = 159.7\,\mu\text{m}) = 8.78 \cdot 10^{-4}$ mg/mL. The concentration drop at each one of these horizontal boundaries within the inner region of the computational domain is 44%, 44% and 67%. At the nodes of the computational domain occurring just before the edge of the donor solution compartment $(r = 1.78\,\text{mm})$, the concentrations are $c_{\text{sc/ve}}(r = 1.70\,\mu\text{m})$ = $6.02 \cdot 10^{-4}$ mg/mL, $c_{\text{ve/de1}}(r = 1.65\,\text{mm})$ = $5.40 \cdot 10^{-5}$ mg/mL and $c_{\text{de1/de2}}(r = 1.61\,\text{mm}) = 9.62 \cdot 10^{-6}$ mg/mL; the decrease from the edge of the hair follicle is 73%, 93%, and 100%. At the viable epidermis/dermis 1 boundary, the values of the concentration one node beyond the distance r = 1.78 mm, at r = 1.93 mm, is negative. Thereafter the concentrations are positive. This is attributed to numerical error. Far from the hair follicle, at r = 5 mm, the concentrations are also on the order of 10^{-6} mg/mL at the top of the viable epidermis and the viable epidermis/dermis 1 boundary and 10^{-7} mg/mL at the dermis 1/dermis 2 boundary.

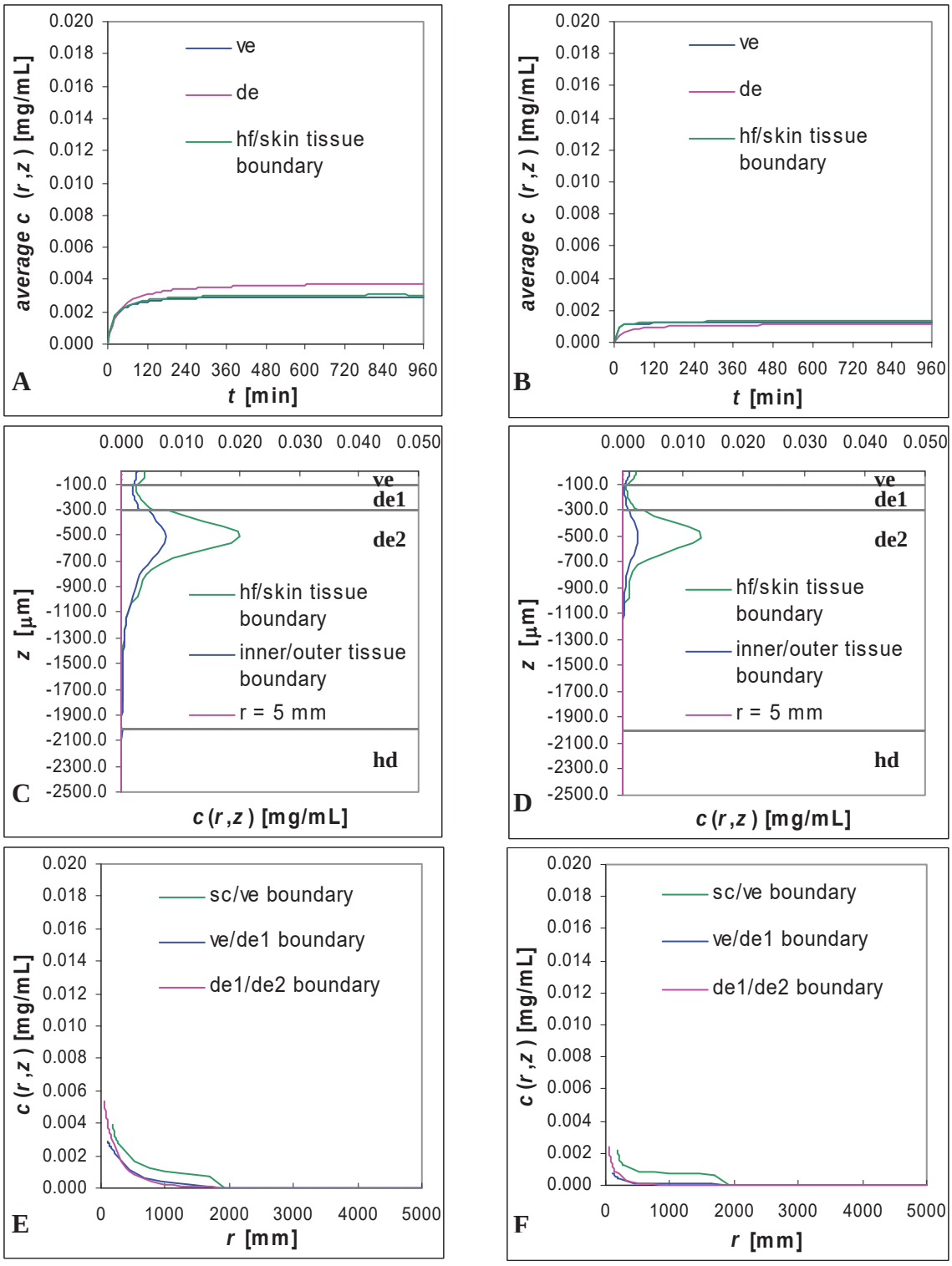
Going from Case 6b to Case 6c the concentration values decrease by 11 to 56% at the stratum corneum/viable epidermis boundary for 174.7 μm ≤ r ≤ 1.70 mm. Within this segment the difference increases with r from 46 to 56% in the inner region of the computational domain $(\text{to } r = 282.8\,\mu\text{m})$, then decreases in the outer region. The difference tends to ~14% as $r \rightarrow 5$ mm. At the viable epidermis/dermis 1 boundary the percentage difference is 62% to 87% for 209.0 μm ≤ r ≤ 1.65 mm. Within this segment the difference increases with r from 75% to 82% in the inner region; in the outer region it increases to 87%, then decreases to 82%. For r > 1.65 mm the difference increases to 92% but stabilizes at 62% as $r \rightarrow 5$ mm. At the dermis1/dermis 2 boundary the concentration values in Case 6d are 56% to 89% less than in Case 6b for 159.7 μm ≤ r ≤ 1.61 mm. Within this segment the difference increases with r from 56% to 75% in the inner region; in the outer region it increases to 89%, then decreases to 88%. For r > 1.61 mm, the difference increases to 94% but approaches 86% as $r \rightarrow 5$ mm.



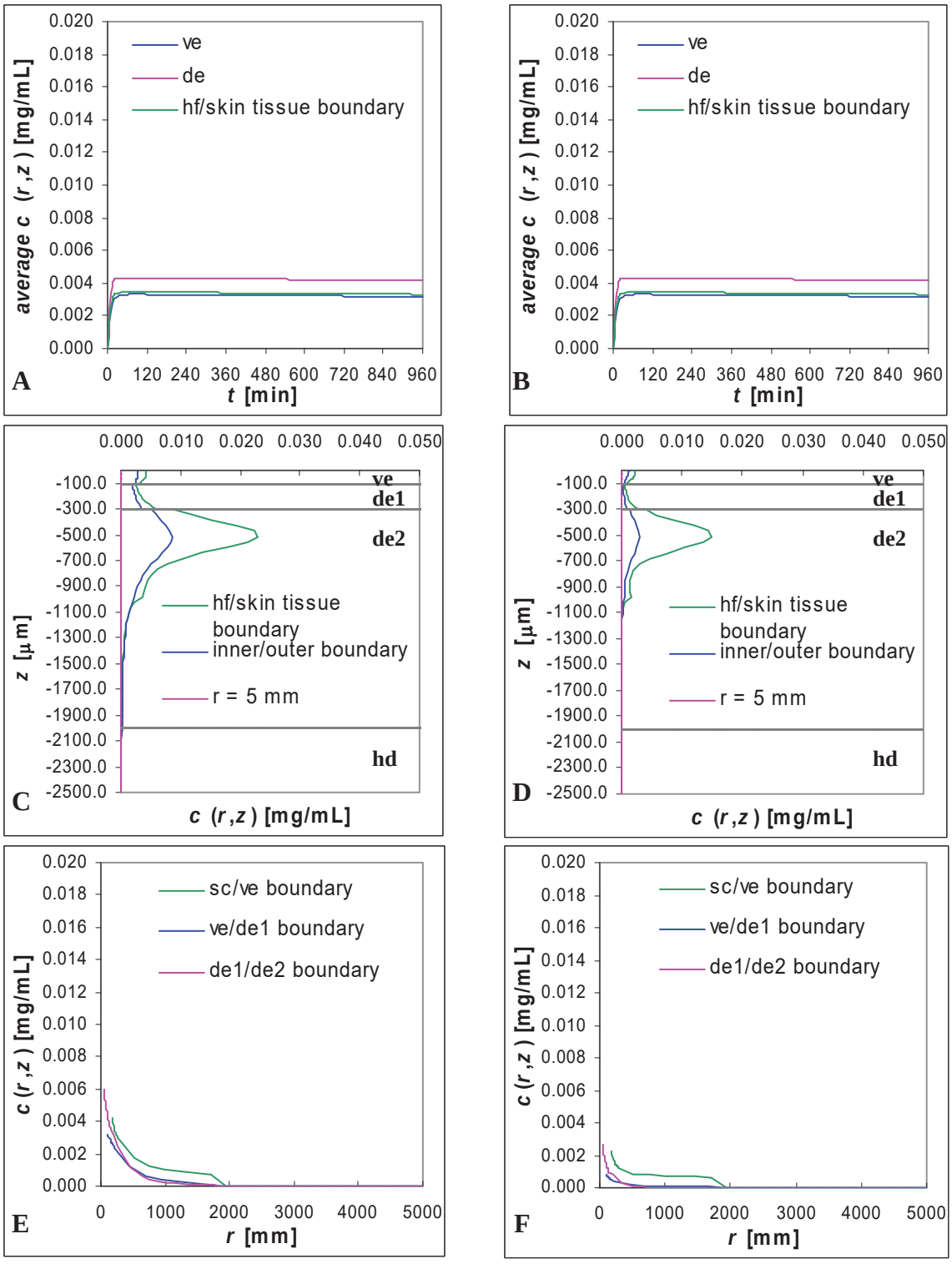
Figures 7-14: A, B: Average concentrations in viable epidermis (ve), dermis (de) and at hair follicle/skin tissue boundary, **C, D:** Concentration vs. depth profiles at t = 16 h at the hair follicle/skin tissue and the inner/outer region boundaries and at r = 5 mm from the hair follicle, **E, F:** Concentration vs. radial distance at t = 16 h at the stratum corneum/viable epidermis, the viable epidermis/dermis 1 and the dermis 1/dermis 2 boundaries, for **Cases 3b, 3c**: Hair follicle permeability equal to intrinsic infundibulum permeability and transient dye penetration into sebum, clearance rate coefficients as given in Table 7-6.



Figures 7-15 A, B: Average concentrations in viable epidermis (ve), dermis (de) and at hair follicle/skin tissue boundary, **C, D:** Concentration vs. depth profiles at t = 16 h at the hair follicle/skin tissue and the inner/outer region boundaries and at r = 5 mm from the hair follicle, **E, F:** Concentration vs. radial distance at t = 16 h at the stratum corneum/viable epidermis, the viable epidermis/dermis 1 and the dermis 1/dermis 2 boundaries, for **Cases 4b, 4c**: Hair follicle permeability equal to intrinsic infundibulum permeability and constant (well-stirred) dye concentration in sebum, clearance rate coefficients as given in Table 7-6.



Figures 7-16 A, B: Average concentrations in viable epidermis (ve), dermis (de) and at hair follicle/skin tissue boundary, **C, D:** Concentration vs. depth profiles at t = 16 h at the hair follicle/skin tissue and the inner/outer region boundaries and at r = 5 mm from the hair follicle, **E, F:** Concentration vs. radial distance at t = 16 h at the stratum corneum/viable epidermis, the viable epidermis/dermis 1 and the dermis 1/dermis 2 boundaries, for **Cases 5b, 5c**: Hair follicle permeability equal to intrinsic infundibulum permeability plus contribution from sebaceous duct and transient dye penetration into sebum, clearance rate coefficients as given in Table 7-6.



Figures 7-17: A ,B: Average concentrations in viable epidermis (ve), dermis (de) and at hair follicle/skin tissue boundary; **C, D:** Concentration vs. depth profiles at t = 16 h at the hair follicle/skin tissue and the inner/outer region boundaries and at r = 5 mm from the hair follicle; **E, F:** Concentration vs. radial distance at t = 16 h at the stratum corneum/viable epidermis, the viable epidermis/dermis 1 and the dermis 1/dermis 2 boundaries, for **Cases 6b, 6c:** Hair follicle permeability equal to intrinsic infundibulum permeability plus contribution from sebaceous duct and constant (well-stirred) dye concentration in sebum, clearance rate coefficients as given in Table 7-6.

7.9 Results for vascularized tissue (*in vivo*), case of fully covered skin

Results for the case of fully covered skin are presented for the cases of a permeable hair follicle with a transient dye concentration in the sebum of the infundibulum with volumetric clearance rate coefficients corresponding to the "b" case in Table 7-6 (Cases 3b and 5b).

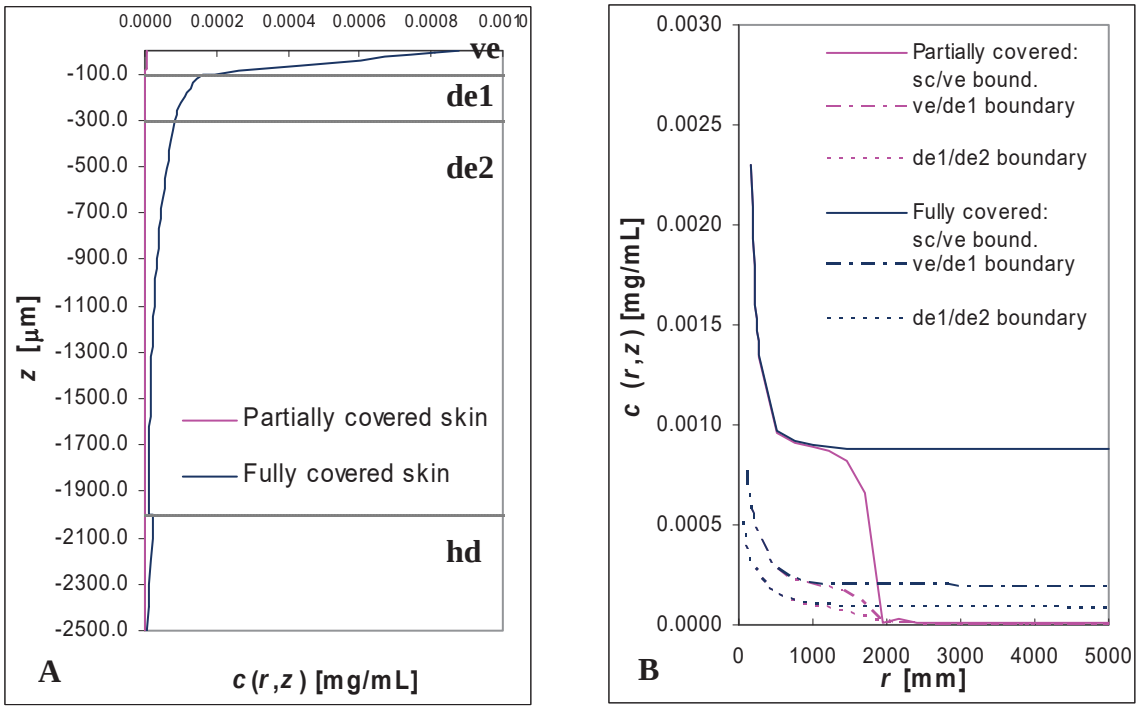
7.9.1 Case 3b: Hair follicle permeability due to infundibulum, transient dye concentration in the infundibulum

The results show that a change in concentration profiles due to an increase in the contact area between the donor solution compartment and the skin affects concentrations as distance from the hair follicle increases. The difference is less than 0.5% at the hair follicle/skin tissue boundary in the viable epidermis, the dermis 1 and in dermis 2 to a depth of z = -1022.5 μm. At the dermis 2/hypodermis boundary (z = -2000 μm), the difference is about 8%. At the inner/outer region boundary, the difference is 0.3% at the viable epidermis/dermis 1 boundary (z = -100 μm), 0.5% at the dermis 1/dermis 2 boundary (z = -300 μm) and increases to 8% at the dermis 2/hypodermis boundary.

Figure 7-18A shows the concentration vs. depth profile at a distance r = 5 mm from the hair follicle for Case 3b in the case of fully and partially covered skin. In the case of fully covered skin, the concentration in the viable epidermis drops 78%, from $c_\infty(z=0)$ = $8.78\cdot10^{-4}$ mg/mL to $c_\infty(z=\text{-}100\,\mu\text{m})$ = $1.95\cdot10^{-4}$ mg/mL. In dermis 1 the concentration drop is 47 %, from $c_\infty(z=\text{-}100\,\mu\text{m})$ = $1.60\cdot10^{-4}$ mg/mL to $c_\infty(z=\text{-}300\,\mu\text{m})$ = $8.50\cdot10^{-5}$ mg/mL. In dermis 2 the concentration decreases monotonically with increasing depth, from $c_\infty(z=\text{-}300\,\mu\text{m})$ = $8.50\cdot10^{-5}$ mg/mL to $c_\infty(z=\text{-}2000\,\mu\text{m})$ =

$1.16 \cdot 10^{-5}$ mg/mL. Within the viable epidermis and dermis 1, the concentrations in the case of fully covered skin are two orders of magnitude larger than in the case of partially covered skin. Within dermis 2, the values are 65 to 110 times larger, with this fraction decreasing with increasing depth.

Figure 7-18B shows the concentration vs. radius profiles at the stratum corneum/viable epidermis, the viable epidermis/dermis 1 and the dermis 1/dermis 2 boundaries in the cases of fully and partially covered skin. In the inner region of the computational domain, the concentration profiles at the stratum corneum/viable epidermis, viable epidermis/dermis 1 and dermis 1/dermis 2 boundaries are unaffected by the increase in the donor solution/skin contact area, since this region of the skin lies below the donor solution compartment in both cases. Within the inner region the largest difference is seen at the interface of the dermis 1 and dermis 2 skin layers (z = -300 μm) at the inner/outer boundary, where it is 0.5%. As expected the difference in concentrations increases with r beyond the inner/outer region boundary. At the distance closest to the edge of the smaller of the two donor solution compartments, the concentration in the case of fully covered skin is 25, 40 and 44% greater than in the case of partially covered skin at the stratum corneum/viable epidermis, viable epidermis/dermis 1 and dermis 1/dermis 2 boundaries, respectively. The difference increases with increasing distance from the hair follicle, such that at r = 5 mm, the concentration in the case of fully covered skin is about 100% larger than in the case of partially covered skin.



Figures 7-18: A: Concentration vs. depth profiles at t = 16 h at the hair follicle/skin tissue and the inner/outer region boundaries and at r = 5 mm from the hair follicle; **B:** Concentration vs. radial distance at t = 16 h at the stratum corneum/viable epidermis, the viable epidermis/dermis 1 and the dermis 1/dermis 2 boundaries, for **Cases 3b:** Hair follicle permeability equal to intrinsic infundibulum permeability plus contribution from sebaceous duct and constant (well-stirred) dye concentration in sebum, clearance rate coefficients as given in Table 7-6.

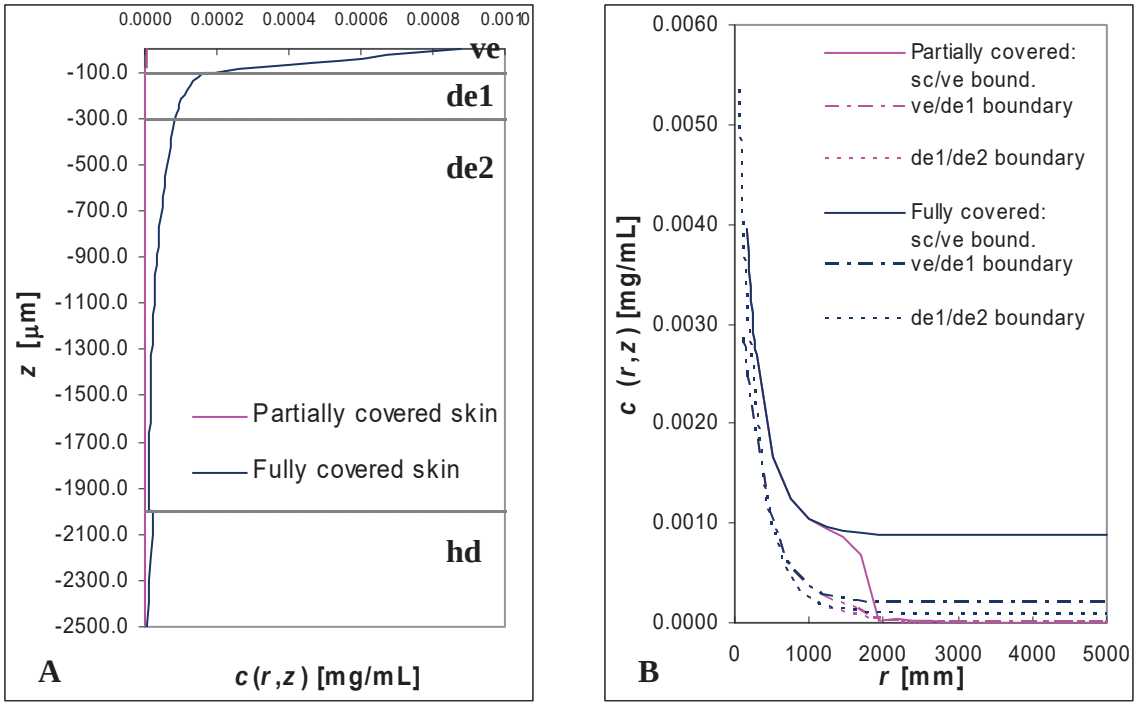
7.9.2 Cases 5b: Hair follicle permeability due to infundibulum and the sebaceous duct, transient dye concentration in the infundibulum

As in Case 3, the concentration profiles at the hair follicle boundary and at the inner/outer region boundary are identical in the case of fully and partially covered skin. The difference reaches 0.5% at a depth of z = -1235 μm only. At the dermis 2/hypodermis boundary (z = -2000 μm), the difference is 2%.

Figure 7-19A shows the concentration vs. depth profile in the case of fully and partially covered skin at r = 5 mm from the hair follicle. The concentration values are equal to those obtained in Case 3 (Fig. 7-18A) in the viable epidermis, dermis 1 and the

top half of dermis 2. At a depth of z = 1107.5 μm is the difference approximately 0.5 %, and at the dermis 2/hypodermis boundary is it about 1.2 %.

Figure 7-19B shows the concentration vs. radius profiles at the stratum corneum/viable epidermis, the viable epidermis/dermis 1 and the dermis 1/dermis 2 boundaries in the cases of fully and partially covered skin. Within the inner region of the computational domain the concentrations are equal in the case of fully and partially covered skin. At the distance closest to the edge of the smaller of the two donor solution compartments, the concentration in the case of fully covered skin is 25, 36 and 35 % greater than in the case of partially covered skin at the stratum corneum/viable epidermis, viable epidermis/dermis 1 and dermis 1/dermis 2 boundaries, respectively. As in Case 3b, the difference increases further with distance r. At r = 5 mm, the concentration in the case of fully hydrated skin are 100 % greater than in the case of partially hydrated skin.



Figures 7-19A: Concentration vs. depth profiles at t = 16 h at the hair follicle/skin tissue and the inner/outer region boundaries and at r = 5 mm from the hair follicle; **B:** Concentration vs. radial distance at t = 16 h at the stratum corneum/viable epidermis, the viable epidermis/dermis 1 and the dermis 1/dermis 2 boundaries, for **Cases 5b:** Hair follicle permeability equal to intrinsic infundibulum permeability plus contribution from sebaceous duct and constant (well-stirred) dye concentration in sebum, clearance rate coefficients as given in Table 7-6.

7.10 Discussion of the *in vivo* simulation results

7.10.1 Cases of partially covered skin

- **Average concentrations**

The results for the preceding section show that non-zero volumetric clearance rate coefficients in the dermis the hypodermis near the hair follicle yield maxima in the average concentration profiles. In Cases 3, 4 and 6, maximum values are obtained in the average concentrations calculated in the viable epidermis, the dermis and at the hair follicle/skin tissue boundary. In Case 5 maximum values are obtained in the average

concentrations calculated in the viable epidermis and at the hair follicle/skin boundary tissue only. The occurrence of maximum average concentrations indicates that from a specific time onwards, enough dye is present in the tissue for clearance from the tissue to overcome and remain more important than diffusion into the tissue from the infundibulum of the hair follicle. In Cases 4 and 6, where the dye concentration in sebum is high at any given time, the high flux of dye into the tissue yields maximum concentration values which occur early in the diffusion process, from t_{max} = 30 min to t_{max} = 1.5 h. In Case 3, in which the dye concentration in sebum increases with time and the permeability of the outer root sheath depends only on the intrinsic infundibulum permeability, the maxima occur from t_{max} = 4 h to t_{max} = 12.5 h. More time is needed for enough dye to be present in the skin tissue in order for clearance from the tissue to overcome diffusion into it. Contrary to Case 3, in Case 5, in which the flux of dye into the skin is significantly augmented by the contribution of the sebaceous duct, a maximum in the average dermal concentration is lacking. In this case the increase in supply of dye to the dermal tissue over time is such that the maximum is suppressed.

The times at which the maxima occur in Cases 4b and 4c are equal or greater than those in Cases 6b and 6c by 15 min. In contrast the times at which the maxima occur in Cases 3b and 3c differ from those of Cases 5b and 5c by 3 h or more. In the latter two cases, in which the concentration of Bodipy® FL C_5 (BFL) in the sebum is transient and decreases with depth, the contribution of the sebaceous duct to the permeability of the hair follicle's outer root sheath is significant enough to appreciably increase the values of t_{max}. In Cases 4 and 6 the BFL concentration in the sebum is constant (well-mixed) and the contribution of the sebaceous duct has little effect only on the values of t_{max}.

The values of ratios of the average concentrations for $t \geq 2$ h show that the concentration levels in dermis are the most affected by clearance, which is expected. As the clearance rate coefficients increase, the ratios $\bar{c}_{ve}/\bar{c}_{de}$ increase from about 3.0 (Case 3b) to 6.7 (Case 3c) and from 2.7 (Case 4b) to about 6.1 (Case 4c). The ratio $\bar{c}_{hf\,/\,skin}/\bar{c}_{de}$ increases from about 2.7 (Case 3b) to about 6.0 (Case 3c) and from 2.5 (Case 4b) to about 5.5 (Case 4c). In contrast, the ratio $\bar{c}_{ve}/\bar{c}_{hf/skin}$ is equal to 1.1 in Cases 3b and 4b and remains at this value when the clearance rate coefficients are increased. In Cases 5b and 6b the average dermal concentration is greater than the average epidermal concentration, with $\bar{c}_{de}/\bar{c}_{ve}$ = 1.2 to 1.3. The ratio $\bar{c}_{hf/skin}/\bar{c}_{ve}$ is about 1.0, with $\bar{c}_{hf/skin} > \bar{c}_{ve}$. The average dermal concentration is greater than that at the hair follicle/skin tissue boundary, with $\bar{c}_{de}/\bar{c}_{hf/skin}$ = 1.1 to 1.3 in Cases 5b and 6b. Going from Case 5b to Case 5c, the increase in the clearance rate coefficients in dermis 1 and near the hair follicle by a factor of 5 yields average dermal values which are larger than the average concentration at the hair follicle/skin tissue boundary, and $\bar{c}_{hf/skin}/\bar{c}_{de}$ = 1.2 to 1.3 for $t \geq 2$ h. The ratio $\bar{c}_{de}/\bar{c}_{ve}$ is roughly equal with values of 1.1 to 1.3, and the ratio $\bar{c}_{hf/skin}/\bar{c}_{ve}$ is about 1.1. Going from Cases 6b to 6c the ratios $\bar{c}_{de}/\bar{c}_{ve}$ and $\bar{c}_{de}/\bar{c}_{hf/skin}$ decrease to 1.0 and 1.1. In these cases the average dermal concentration remains larger than that at the hair follicle/skin tissue boundary, showing the effect of the high flux into the skin tissue. The ratio $\bar{c}_{hf/skin}/\bar{c}_{ve}$ with a value of 1.1 is similar in Case 6c to Case 6b.

- **Concentration vs. depth profiles**

With the outer root sheath permeability equal to the intrinsic permeability of the infundibulum, the switch from unvascularized tissue to vascularized tissue with k_α = 0.0037 s^{-1} in the top 200 μm of the dermis (dermis 1) and 0.00037 s^{-1} in bulk dermis (dermis 2) and hypodermis (Cases 3a, 4a to 3b, 4b) yields concentrations near the hair follicle which decrease by up to a factor of 10. This decrease increases with depth in dermis 1. In the cases in which the contribution of the sebaceous duct is taken into account (Cases 5a, b; 6a, b), the largest decrease in concentration in the viable epidermis is by a factor of 7. In dermis 1 the decrease in concentration diminishes with increasing depth due to the large amount of dye permeating from the infundibulum into the skin tissue. Both in Cases 3, 4 and 5, 6 the decrease in concentration due to clearance is smallest at the maximum concentration values. But the maxima in Cases 3 and 4 occur at depths near -1000 μm, whereas in Cases 5 and 6 they occur at a depth near -500 μm. Overall the greater the flux from the infundibulum into the skin tissue, the smaller the decrease in concentration due to clearance near the maximum concentration as well as in the above-lying skin layers.

The increase in the clearance rate coefficients in dermis 1 and in the inner regions of dermis 2 and the hypodermis, from k_α = 0.0037 s^{-1} to k_α = 0.0185 s^{-1}, has a stronger effect in the viable epidermis and dermis 1 in the cases of increased permeability of the outer root sheath (Cases 5b, 5c and 6b, 6c) than in the cases in which this permeability is due only to the intrinsic permeability of the infundibulum (Cases 3b, 3c and 4b, 4c). In Cases 5c and 6c, the concentration at the hair follicle/skin tissue boundary is 44 to 74% lower in the viable epidermis and 55 to 74% lower in dermis 1 than in Cases 5b and 6b.

Going from Cases 3b and 4b to Cases 3c and 4c, the concentration drops less, 46 to 54% in the viable epidermis and 13 to 47 % in dermis 1. The amount of BFL available for clearance in the viable epidermis and in dermis 1 is greater in Cases 5c and 6c due to the greater permeability of the outer root sheath of the hair follicle. The value of the clearance rate coefficient, $k_\alpha = 0.0185\ s^{-1}$, is large enough to clear a greater fraction of BFL from the viable epidermis and dermis 1 compared to the value $k_\alpha = 0.0037\ s^{-1}$. In Cases 3c and 4c, less BFL is available for clearance in the viable epidermis and the dermis. The results is a greater concentration drop in these skin regions in Cases 5c and 6c than in Cases 3c and 4c.

- **Concentration vs. radial distance profiles**

The effect of clearance is also evident at greater distances away from the hair follicle. From the inner/outer tissue boundary to a radial distance of $r \approx 1.7$ mm, the radial distance in the computational mesh nearest to the edge of the donor compartment (r = 1.78 mm, Eq. 63) on the side of the hair follicle, the concentration decreases 5 to 6.4-fold at the top of the viable epidermis, going from Cases 3a and 4a to 3b and 4b. Going from Cases 5a and 6a to Cases 5b and 6b, the decrease is 6 to 10-fold. These factors increase to 10 to 24-fold and 7 to 40-fold at the viable epidermis/dermis 1 boundary and decrease and 12 to 44-fold and 4.4 to 60-fold at the dermis 1/dermis 2 boundary.

The effect of increasing the clearance rate coefficients from $k_\alpha = 0.0037\ s^{-1}$ ("b" cases) to $k_\alpha = 0.0185\ s^{-1}$ ("c" cases) yields concentrations at the top of the viable epidermis, at the viable epidermis/dermis and at the dermis 1/dermis 2 boundaries which

are up to 20, 70 and 84 % smaller due to the increase in clearance in Cases 3c and 4c and up to 54, 87 and 89 % smaller in Cases 5c and 6c.

7.10.2 Fully covered skin vs. partially covered skin

The results of the preceding section show that it is possible to utilize the model in order to predict drug concentration levels several mm from the hair follicle due to diffusion from a topically applied patch-like device. The results presented above were for a "patch" with a contact surface area of approximately 79 mm^2. The radius of the cylindrical piece of skin into which the drug diffuses can be increased to any value, thus diffusion from a patch-like device of any contact area can be simulated.

In the case of partially covered skin, the supply of concentration to the skin tissue far from the hair follicle is very low, as no permeant is diffusing into the tissue from the top of the piece of skin and very little is delivered laterally. The comparison of these results with those obtained for a fully covered piece of skin show that delivery to the tissue is nearly non-existent if the tissue does not lie directly below the donor solution compartment.

7.10.3 Remarks

- **Comparison of Bodipy® FL C_5 mass depletion with a without a hair follicle**

The amount of solution depleted from the donor solution compartment *in vitro* in the case of an impermeable hair follicle (Case 1a) is calculated from the amount present in the donor solution, $m_{ds}(t)$, and in the sebum of the infundibulum, $m_{sebum}(t)$, from

$$m_{ds,\,depleted}(t) = m_{ds}(t=0) - \left[m_{ds}(t) + m_{sebum}(t)\right] \tag{124}$$

The mass of permeant in the sebum is included in the second term on the right hand side of Eq. 124 because it is mass which would remain in the donor solution concentration if no hair follicle was present. The mass of permeant depleted from the donor solution concentration at time *t* is the mass present in the skin layers.

The amount of solution depleted from the donor solution compartment in the case of a permeable hair follicle *in vitro* (Case 3a or 5a) is calculated from

$$m_{\text{ds, depleted}}(t) = m_{\text{ds}}(t=0) - m_{\text{ds}}(t) \tag{125}$$

In this case the mass depleted from the donor solution compartment at time *t* is taken as the mass of permeant in the sebum of the infundibulum and in the skin tissue. The amount of dye in the donor solution is calculated from the donor solution concentration at a given time *t* (Eq. A8). The mass of dye in the sebum at a given time *t* is calculation from the numerator of Eq. C1 applied to the concentration of BFL in the sebum, given by Eq. 121.

Table 7-9 shows the percentage of the initial amount of BFL in the donor solution compartment (0.01 mg) of BFL in the skin, for 2 h $\leq t \leq$ 16 h, in both cases. Figure 7-20 shows the amount of BFL in the skin layers as a function of time for Case 1a, and in the infundibulum and the skin layers for Case 3a or 5a. The mass of BFL in the skin in Case 3a is about 12% greater than in Case 1a at t = 2 h. The difference decreases with time and reaches about 2% at t = 16 h.

Table 7-9: Effect of the hair follicle on the mass of Bodipy® FL C_5 (BFL) in the skin: % of initial mass of BFL in the donor solution compartment (0.01 mg) present in the skin at time *t* for the case of no hair follicle (Case 1a) and the case of an impermeable hair follicle (Case 3a).

***t* [h]**	**% of initial BFL mass in donor solution (0.01 mg) present in the skin – impermeable hair follicle**	**% of initial BFL mass in donor solution (0.01 mg) present in the skin – permeable hair follicle**
2	1.7	1.9
4	3.5	3.7
6	5.2	5.5
8	7.0	7.2
10	8.7	8.9
12	10.3	10.6
14	12.0	12.3
16	13.6	13.9

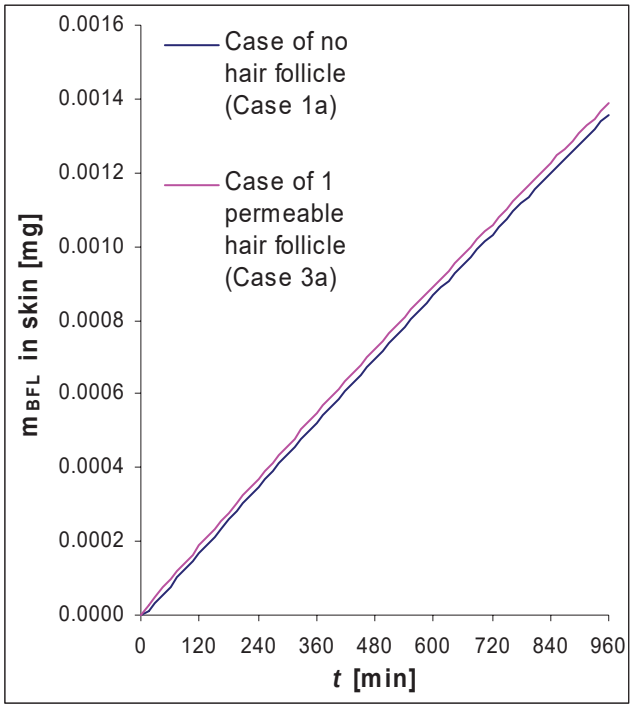


Figure 7-20: Mass of BFL in the skin layers in the case of no hair follicle (Case 1a) and in the case of one permeable hair follicle, as a function of time *t*.

These results are obtained in the case of a hair follicle density of N_0 = 1 hair follicle/0.79 cm^2. In the case of N = 230 hair follicles/0.79 cm^2, which corresponds to the average scalp skin follicular density of 292 follicles/cm^2, the fraction of mass depletion in the case of permeable hair follicles over mass depletion in the case of impermeable hair follicles is given by

$$f_{N=230} = f_{N_0} \frac{N}{N_0} \tag{126}$$

and equal to $f_{N=230} = 1.02 \cdot 230 \approx 235$. Thus in a block of skin of surface area A = 0.79 cm^2 and depth 5 mm the donor solution depletion into the skin would be 235 times greater with the presence of 230 hair follicles than in the case of unperturbed skin, assuming the effect of each hair follicle on the permeation of BFL to be independent of the presence of the other follicles. However, it is likely that at high follicular density, interaction between the hair follicles would have to be accounted for.

- **Precision of the mathematical model**

Although the shape of the outer boundary of the hair follicle is modeled in a precise way, the results for drug concentration in the skin surrounding the hair follicle are most sensitive to the diameter of the infundibulum at the surface of the skin as well as to its conical shape. The grossest parameters are the volume of sebum and the lateral surface area of the infundibulum.

- **Stratum corneum lag time**

In the current model the stratum corneum is modeled as a membrane with a given instantaneous steady-state permeability $P_{sc/pH\ 1.0}$ (r). We have not taken into account the time lag for diffusion through the stratum corneum, which, for small molecules, is on the order of 30 min.[35,42] On the time scale of a 16 h simulation, the incorporation of the stratum corneum time lag would have little effect on the dye concentration levels in the skin tissue. Nevertheless the stratum corneum could be regarded as a skin layer included in the computational domain with tissue-specific diffusion and partition coefficients by reassigning the layers of the computational domain. As shown in Table 7-10, the uppermost skin layer, which for this thesis we have taken to be the viable epidermis, could be taken as the stratum corneum. The skin layer below would then be taken as the viable epidermis. The layer below the viable epidermis would then be taken either a dermis 1 or an average dermis layer, depending on whether the dermal vasculature were to be restricted to the upper dermis or averaged over the entire dermis, and on whether or not the hypodermis needed to be taken into account.

Table 7-10: Possible uses of the mathematical model incorporating the stratum corneum as a skin layer within which the transient diffusion of a permeant is calculated.

CURRENT USE OF MODEL	POSSIBLE USES OF MODEL	
viable epidermis (ve)	stratum corneum	stratum corneum
dermis 1 (de1)	viable epidermis	viable epidermis
dermis 2 (de2)	dermis 1	full-thickness dermis
hypodermis (hd)	dermis 2	hypodermis

- **Estimation of the outer root sheath permeability**

The estimation of the permeability of the outer root sheath (Eqs. 68 to 73) is based on the epithelium lining of the infundibulum only. We did not take into account the barrier properties of the outer root sheath cells, which from diagrams and micrographs[48] appears to have a thickness of 3 to 4 cell layers. This approximation was made based on the fact that at the top surface of the skin, the stratum corneum rather than the viable epidermis is the main barrier to permeation into the skin. We have not, however, taken into account the difference in the level of keratinization of the ORS cells. These are keratinized above the sebaceous duct and only partially or not keratinized below the sebaceous duct.[10]

7.11 Conclusion and future work

Whereas the there is quite a good understanding of the mechanisms of

interfollicular diffusion across the stratum corneum, with the basic intrinsic properties of unbroken stratum corneum well understood,[29,35,48,99] the mechanisms of

intrafollicular diffusion are not well understood. This mathematical model is a first attempt at elucidating the mechanisms by which the hair follicle increases permeation through the skin.

The application of the mathematical model to the diffusion of the fluorescent dye Bodipy FL C_5 (BFL) shows very clearly that the hair follicle increases the permeability of BFL into the surrounding skin, and in particular into the dermis, via the sebum-filled infundibulum. This result may be considered reliable, since the diffusion model utilizes a reasonable geometric model of the shape of the follicular structure. We use this geometrical model to calculate the shape of the outer root sheath taken as the outer boundary of the hair follicle and are confident that the shape of the infundibulum is modeled in a sensible way. In addition the diffusion model incorporates key structural and biological properties of the infundibulum which are well documented in the literature. These are the nature of sebum, an oily substance containing sebaceous gland cells, approximated in the model as an olive oil matrix containing spherical aqueous inclusions, and the stratum corneum-like wall of the infundibulum, whose thinning with increasing depth into the infundibulum we take into account in the equation for the intrinsic permeability of the infundibulum. In addition we discriminated between an upper-bound on the BFL concentration in the infundibulum, assuming BFL to be well-stirred and its concentration constant in the sebum, and a transient 1-D diffusion of BFL in depth z. The comparison of *in vitro* simulation results with Gram's *et al.*'s average fluorescence intensity results[17] showed that the later assumption is likely to be closer to reality.

An important difference between our model results and Gram's *et al*.'s experimental results is the lack of a maximum in time in the former. In the *in vitro* case the model does not have a mechanism allowing the average BFL concentration to go through a maximum during the simulation time of 16 h. Maximum average concentrations are obtained only when a mechanism for clearance is included in the model. The model shows that large drops in the concentration within the viable epidermis and, as expected, within the dermis, are obtained due to clearance from the vasculature. The magnitude of the drop in concentration in these skin layers is a function of the amount of dye that has permeated into the tissue and of the magnitude of volumetric clearance rate coefficients.

Future work should focus on modeling the absorbing properties of the hair follicle, and in particular of the cuticle of the hair shaft. As explained in section 7.7.4, Grams *et al*.'s results provide compelling evidence for the importance of this phenomenon. It is quite possible that the inclusion of the absorbing properties of the cuticle would lead to maxima in the predicted *in vitro* concentration profiles.

A further useful application of the model parametrized for a terminal anagen hair follicle would be the study of the absorption of zinc pyrithione (ZPT) through the hair follicle and into the surrounding tissue and the blood circulatory system (Kasting GB. 2006. Personal communication). ZPT is a component of shampoos used to treat dandruff.[100-103] Early studies focused on the penetration of ZPT through the skin of various animals. Extrapolation of this data led to the conclusion that ZPT could be used in small doses in shampoos, with no harm to humans.[100,104] The mechanism of action of ZPT on dandruff remains an important topic of research,[102,105] but to our knowledge there

aren't any studies focusing on the penetration of ZPT into human scalp skin from a microscopic viewpoint. Our model is very well suited to study the absorption of ZPT into and around a hair follicle.

In this study we have focused in the permeation of one chemical substance into and near an anagen hair follicle of typical size in scalp skin. The geometry of the hair follicle and pattern of vasculature apply to this particular case. It is premature, at this point, to draw any general conclusions regarding the contribution of hair follicles to permeation into the skin at various sites of the body, based on these results. This mathematical model can, however, be reparametrized to study the contribution to permeation of hair follicles of varying sizes at different sites on the body. Otberg *et al*. have shown that the vellus hair follicle density (per cm^2) is greatest on the lateral forehead, followed by the upper arm, the back, the thorax the forearm, the thigh and the calf.[13] These authors have also calculated the diameter of the hair shaft in these regions. Seago *et al*. have calculated the hair shaft length in the upper arm and the thigh,[106] and Blume *et al*. have calculated the maximum length of vellus hairs on the forehead and the back.[107] The data on the length and diameter of the hairs in given regions of the body can be used as input parameters to the model to obtain the shape of the outer root sheath, taken as the outer boundary of the hair follicle, and the model can be used to assess the contribution of hair follicles to percutaneous penetration in various parts of the body.

For a given region of the body, consideration of the follicular cycles would yield a more complete picture of the contribution of hair follicles to the absorption of a chemical into the skin, since the morphology of the hair follicle and the pattern of vasculature around it depends on the follicular cycles (section 2.2.2). The hair follicle spends about 9

% of its lifetime as a catagen, 21% of its lifetime as a telogen and 70% of its lifetime as an anagen hair follicle.[51,108] With information on the size of a hair follicle in a given cycle in a given skin region, the time fractions $f_{cat} = 0.09$, $f_{tel} = 0.21$ and $f_{ana} = 0.70$ can be used to take into account the variation in morphology and blood perfusion due to the catagen, telogen and anagen cycles, respectively. The concentration levels calculated in the absence of a hair follicle would be multiplied by the fractions $1- f_{cat}$, $1- f_{tel}$ and $1- f_{ana}$.

References 51 and 108 do not indicate which skin regions the percentages of time spent by a hair follicle in the three cycles refer to. Seago *et al*. show, however, that the duration of the anagen and telogen cycles depends on location on the body.[106] Other factors which may be taken into account in conjunction with the location of the hair follicles on the body and the follicular cycles are gender[106] and seasonal variations in hair growth.[109,110]

Further extensions of this work consist in using this model to study the permeation of compounds of varying molecular weight and lipophilicity in order to explore how these characteristics play out in terms of calculated dermal concentration levels, as well as a starting point for a mathematical model of an array of hair follicles within an piece of skin of area 1 cm × 1 cm and a thickness of 5 mm, for example.

Part II

Diffusion In and Around an Eccrine Sweat Duct

8 Introduction

8.1 Overview of the mathematical model

The goal of this part of the thesis is to set up a mathematical model describing how an eccrine sweat gland duct might perturb the steady-state concentration of a permeant diffusing through a block of skin containing eccrine sweat gland duct, and to present initial results obtained from the model. Although the eccrine sweat gland pathway is recognized as one of the possible shunt pathways through the skin,[63,64,111] to our knowledge no detailed model seeking to understand the sweat duct's effect on the concentration of a diffusing chemical substance has been published.

The sweat duct is modeled as a 3-D helical tube of infinite length. The duct in any skin stratum would constitute a finite segment of this infinite duct. The model is applicable to the various parts of the eccrine sweat duct in the various skin layers, i.e., the helical tube can be chosen to approximate the spiraled intraepidermal duct, the relatively straight duct embedded in bulk dermis, or the coiled duct linking the secretory gland to the straight duct.

The concentration profile of the chemical substance diffusing into a given skin tissue layer α of the skin slab is written as an "α" component, $c_{\alpha}(\underline{\boldsymbol{x}})$, for the concentration outside the sweat duct, and a "duct" component, $c_{\text{duct}}(\underline{\boldsymbol{x}})$, for the concentration inside the duct. The vector $\underline{\boldsymbol{x}}$ denotes 3-D position within the skin. Each component of the concentration has a linear term in depth z for the concentration far from the duct/skin tissue boundary, and a term describing the perturbation in the linear concentration caused by the presence of the helical duct. In the case of the concentration

inside the duct, $c_{\text{duct}}(\underline{\boldsymbol{x}})$, the perturbation term linear in *z*. Slender-body theory is used to describe the perturbation to the concentration in the surrounding skin tissue, $c_{\alpha}(\underline{\boldsymbol{x}})$. In slender-body theory, the concentration near a long slender body can be approximated as an axial distribution of singularities along the centerline of the slender body.[112]

8.2 Slender-body theory

Slender-body theory was developed in the 1960s and 1970s to solve the problem of Stokes flow around long slender bodies, that is, bodies with a ratio of the transverse cross-sectional radius to the length of the body much less than unity. The method relies on the possibility of constructing a solution from a "distribution of flow singularities (such as sources and sinks)" along the center-line of the body such that the "irrotational flow associated with the these singularities in combination with a uniform stream satisfies approximately the condition of zero normal component of velocity at the surface of a body of given shape".[113]

Cox used slender-body theory to solve the creeping motion equations around a slender body of cross-sectional radius *b* and length *l* using an outer expansion of the velocity field in terms of the parameter $\kappa = b/l$, in which the body is taken as a line distribution of singularities ($\kappa \to 0$ as $b \to 0$), and an inner expansion in κ defined at each point of the body's center-line, at which the body is taken as an infinite cylinder ($\kappa \to 0$ as $l \to \infty$).[114] A solution to the problem is obtained by asymptotically matching the inner and outer expansions at a general point P on the center-line. Batchelor has applied slender-body theory for Stokes flow to bodies of non-circular cross-section.[115]

Johnson described the velocity field in a Stokes flow problem past a slender body of circular cross-section and arbitrary center-line configuration as a superposition of distributions of singularities along the center-line of the body.[116] A solution for the velocity field is obtained by matching an inner and outer expansion of the integrand of the velocity field valid close to the body's surface.

In a diffusion problem closer to the present application, Balgi *et al*. applied slender-body theory to calculate the concentration of avidin molecules near an absorbing fiber optic sensor of cylindrical shape.[117] The avidin concentration field is equal to the avidin concentration in bulk liquid, to which the perturbation in the avidin concentration near the cylindrical surface is added. This second concentration term is given by a line distribution of point-sinks on the center-line of the cylinder[117]:

$$C(r,z) = C_{\text{bulk}} + \int_{-L}^{L} \frac{F(s)\mathrm{d}s}{4\pi\sqrt{r^2 - (z-s)^2}} \tag{127}$$

$2L$ is the length of the absorbing cylinder and F is the sink density as a function of the distance s along the center-line of the cylinder.

9 Literature review

The vast majority of the literature pertaining to the transport of chemical substances in relation to the human eccrine sweat gland deals with the transport of water and electrolytes across the sweat duct and their concentration in sweat. Bijman and Sato have written good introductions to sweat gland secretory pathways.[118,119]

In the early 1970s Johnson and Maibach studied the excretion in human eccrine sweat of four drugs of varying pK_a and partition coefficients with the goal of confirming results obtained by other groups on the functional nature of the human sweat gland epithelium.[120] The authors found that the drugs antipyrine and aminopyrine, with oil/water partition coefficients $K_{\text{oil/water}} \geq 0.05$, yielded 10 to 20-fold higher sweat to plasma concentration ratios than the drugs sulfaguanidine and sulfadiazine with $K_{\text{oil/water}} \approx 0.001$. The sweat to plasma concentration ratio was found to be characteristic for the drug in question, and independent of the drug concentration in plasma. The authors concluded that the permeability of the sweat gland epithelium is similar to that of other body membranes, such as the blood-brain barrier and the renal tubular system in that "lipid solubility is a factor of prime importance in determining the rates of drug passage into sweat." [120]

Jackson and Davis developed a mathematical model of transient 1-D ion diffusion down the sweat duct taken as a uniform tube with a given cross-sectional area and diameter.[121] The model is based on Fick's law of diffusion and gives the concentration of material in an element m of the duct based on the concentration in elements m – 1 and m + 1. Concentration profiles vs. time and depth are given for various cases in which the

effect of sweat flow and solvent evaporation from the surface of the skin are investigated. The results for a 20 % w/w aluminum chlorhydrate solution applied to the skin surface show that in the absence of sweat production, the concentration at various depths inside the sweat duct increases more rapidly in the case of an increase in solution concentration due to solvent evaporation than in the case of a constant solvent concentration maintained through occlusion of the surface (1% of the applied solution is attained at a depth of 2 mm in 50 min instead of 1 h). The sweat duct is predicted to act as a reservoir in the case of 20 min occlusion of the skin surface under non-sweating conditions followed by removal of the excess solution from the surface. The concentration at a depth of 0.2 mm is over half the applied concentration after 20 min. The ionic solution continues to diffuse into the duct following removal from the surface. However, the concentration level beyond 20 min is much lower than in the case of solvent evaporation (non-occluded drying). In the case of sweating, the concentration at a depth of 0.2 mm does not exceed 1 % of the applied concentration.

10 Formulation of the Mathematical Model

10.1 Geometry

10.1.1 Position along the centerline of the helical tube

The geometrical parameters describing the helical tube are its radius R and pitch p, and the small parameter ε yielding the tube radius $a = \varepsilon R$ (Fig. 10-1). The origin of the coordinate system in Figure 10-1 is assumed to be a point inside dermal tissue. The helical duct is of infinite length in the positive and in the negative z directions. The centerline of the helix is defined by the vector (Fig. 10-1)

$$\underline{\boldsymbol{x}}_0 = \underline{\mathbf{i}}\, R\cos t + \underline{\mathbf{j}}\, R\sin t + \underline{\mathbf{k}}\,\frac{p}{2\pi}t \tag{128}$$

where t is the familiar cylindrical-coordinate angle θ in the x-y plane. An increase in the pitch p stretches the helix, while a decrease compresses it.

The position along the centerline of the helix is parametrized in the arclength. The arclength is defined as a function of t as[122]

$$s(t) = \int_{t_0}^{t} \sqrt{\underline{\boldsymbol{x}}'_{\mathbf{0}}(\tau)\cdot\underline{\boldsymbol{x}}'_{\mathbf{0}}(\tau)}\,\mathrm{d}\tau \tag{129}$$

Taking the initial angle $t_0 = 0$ the arclength is computed using Eq. 129 to be

$$s(t) = \sqrt{R^2 + \left(\frac{p}{2\pi}\right)^2}\,t = \nu t \tag{130}$$

Thus the distance along the centerline of the helix as a function of the arclength s is

$$\underline{\boldsymbol{x}}_0(s) = \underline{\mathbf{i}}\, R\cos\left(\frac{s}{\nu}\right) + \underline{\mathbf{j}}\, R\sin\left(\frac{s}{\nu}\right) + \underline{\mathbf{k}}\,\frac{p}{2\pi}\frac{s}{\nu} \tag{131}$$

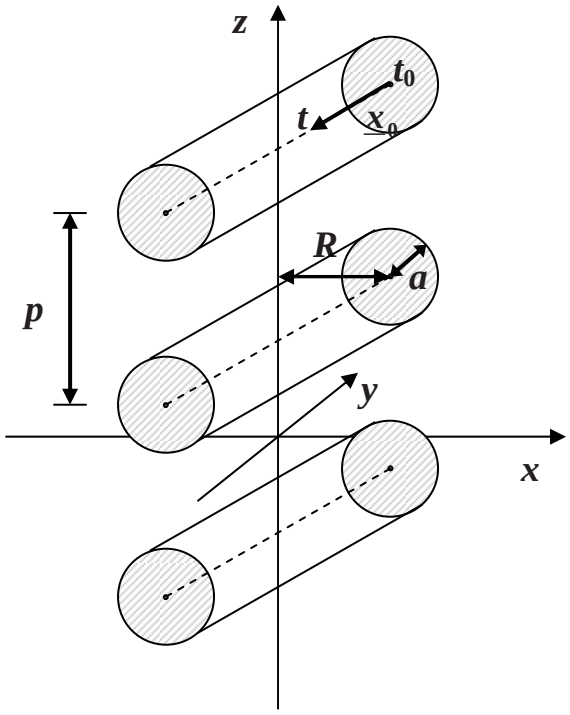


Figure 10-1: Diagram of A-A cross section of the helical tube representing an eccrine sweat gland. Dotted line: centerline of the helix. Shaded areas: meridional planes of the helix (see Fig. 10-2).

10.1.2 Position on the surface of the helical tube

Figure 10-2 shows a circular meridional plane of the helical tube, with the tangent vector $\underline{\mathbf{T}} = \mathrm{d}\underline{\boldsymbol{x}}_0/\mathrm{d}s$, the principal normal $\underline{\mathbf{N}}$ and the binormal $\underline{\mathbf{B}} = \underline{\mathbf{T}} \times \underline{\mathbf{N}}$.

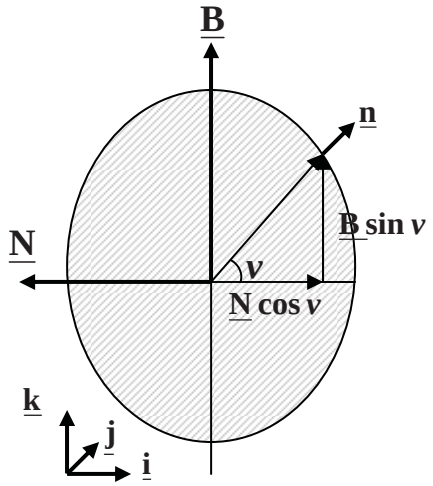


Figure 10-2: *x-z* meridian plane of helical tube showing the principal normal vector $\underline{\mathbf{N}}$, and projections of the binormal vector $\underline{\mathbf{B}}$ and the normal to the surface of the helical duct $\underline{\mathbf{n}}$ onto this meridian plane.

The tangent vector is given by

$$\underline{\mathbf{T}} = -\underline{\mathbf{i}}\frac{R}{\nu}\sin\left(\frac{s}{\nu}\right) + \underline{\mathbf{j}}\frac{R}{\nu}\cos\left(\frac{s}{\nu}\right) + \underline{\mathbf{k}}\frac{p'}{\nu} \tag{132}$$

where $p' = p/2\pi$. The principal normal is obtained from the tangent vector from[123]

$$\frac{\mathrm{d}\mathbf{T}}{\mathrm{d}s} = \kappa\underline{\mathbf{N}} \tag{133}$$

in which κ is the curvature of the helix. Eq. 133 yields

$$\underline{\mathbf{N}} = -\underline{\mathbf{i}}\cos\left(\frac{s}{\nu}\right) - \underline{\mathbf{j}}\sin\left(\frac{s}{\nu}\right) \tag{134}$$

and $\kappa = r/\nu^2$. The binormal vector is given by

$$\underline{\mathbf{B}} = \underline{\mathbf{i}}\left[\frac{p'}{\nu}\sin\left(\frac{s}{\nu}\right)\right] - \underline{\mathbf{j}}\left[\frac{p'}{\nu}\cos\left(\frac{s}{\nu}\right)\right] + \underline{\mathbf{k}}\frac{R}{\nu} \tag{135}$$

The position on the surface of the helical tube is calculated from the position on the centerline of the helix (Eq. 131) and the normal and binormal vectors according to the equation

$$\underline{\boldsymbol{x}}(u) = \underline{\boldsymbol{x}}_{\mathbf{0}}(u) + \underline{\mathbf{N}}(u)\cos(v) + \underline{\mathbf{B}}(u)\sin(v) \tag{136}$$

where v denotes the angle in the meridian plane of the helical tube (Fig. 10-2) and the arclength s has been replaced by the parametrization variable u. Upon substitution of Eqs. 131, 134 and 135 into Eq. 136, the components of the vector describing the position on the surface of helical duct are obtained as

$$\begin{cases} x(u,v) = (R - a\cos v)\cos\left(\dfrac{u}{\nu}\right) + \dfrac{ap'}{\nu}\sin(v)\sin\left(\dfrac{u}{\nu}\right) \\ y(u,v) = (R - a\cos v)\sin\left(\dfrac{u}{\nu}\right) - \dfrac{ap'}{\nu}\sin(v)\cos\left(\dfrac{u}{\nu}\right) \\ z(u,v) = \dfrac{p'}{\nu}u + a\cos\left(\dfrac{R}{\nu}\right) \end{cases} \tag{137}$$

Figure 10.3 shows a picture of a helix obtained in *Maple* from Eq. 136 with R = 100 μm, a = 50 μm and $p = 2\pi p' = 400$ μm, for $-2\pi\nu \le u \le 2\pi\nu$ and $0 \le v \le 2\pi$.

The vector normal to the surface of the helical tube, $\underline{\mathbf{n}}$, has the same direction as the vector resulting from the sum of the vectors $\underline{\mathbf{N}}\cos v$ and $\underline{\mathbf{T}}\sin v$ which originate at the centerpoint of the meridian plane (Fig. 10-2). Thus $\underline{\mathbf{n}}$ is calculated as

$$\underline{\mathbf{n}} = \underline{\mathbf{N}}\cos(v) + \underline{\mathbf{T}}\sin(v) \tag{138}$$

and is equal to

$$\begin{aligned}\underline{\mathbf{n}} = \underline{\mathbf{i}}\left[-\cos(v)\cos\left(\frac{u}{v}\right)+\frac{p'}{v}\sin(v)\sin\left(\frac{u}{v}\right)\right] \\ +\underline{\mathbf{j}}\left[-\cos(v)\sin\left(\frac{u}{v}\right)-\frac{p'}{v}\cos(v)\sin\left(\frac{u}{v}\right)\right]+\underline{\mathbf{k}}\frac{R}{v}\sin(v)\end{aligned} \tag{139}$$

10.2 Governing equations

The steady-state concentration of a permeant diffusing into the skin is given by the Laplace equation. The boundary conditions express transport into the duct from the surrounding skin tissue and equality of fluxes at the sweat duct/skin tissue interface. Thus the boundary value problem is

$$\nabla^2 c(\underline{\boldsymbol{x}}) = 0 \tag{140}$$

$$P_{\text{epithelium/ref}}\left(\frac{c_{\text{duct}}(\underline{\boldsymbol{x}})}{K_{\text{duct/ref}}}-\frac{c_{\alpha}(\underline{\boldsymbol{x}})}{K_{\alpha/\text{ref}}}\right) = -D_{\text{duct}}\,\underline{\mathbf{n}}\cdot\underline{\nabla}c_{\text{duct}}(\underline{\boldsymbol{x}}) \tag{141}$$

$$-D_{\text{duct}}\,\underline{\mathbf{n}}\cdot\underline{\nabla}c_{\text{duct}}(\underline{\boldsymbol{x}}) = -D_{\alpha}\,\underline{\mathbf{n}}\cdot\underline{\nabla}c_{\alpha}(\underline{\boldsymbol{x}}) \tag{142}$$

Where $P_{\text{epithelium/ref}}$ is the steady-state permeability coefficient of the epithelium lining the sweat duct.

The solution is given in terms of a permeant concentration $c_{\text{duct}}(\underline{\boldsymbol{x}})$ as a function of position $\underline{\boldsymbol{x}}$ inside the sweat duct and a concentration $c_{\alpha}(\underline{\boldsymbol{x}})$ in the surrounding skin tissue layer α:

$$c_{\text{duct}}(\underline{\boldsymbol{x}}) = A_{\text{duct}}z_0(s)+B_{\text{duct}}+\left[z(u,v)-z_0(s)\right]K \tag{143}$$

$$c_{\alpha}(\underline{\boldsymbol{x}}) = A_{\alpha} z + B_{\alpha} + \int_{-\infty}^{\infty} F\, G(\underline{\boldsymbol{x}}(u,v) - \underline{\boldsymbol{x}}_{\mathbf{0}}(s))\mathrm{d}s \tag{144}$$

In Eq. 142, s represents the value of the arclength at which the helix crosses the meridional plane established by the value of x and y. In Eq. 143, s is a dummy variable of integration.

The perturbation to the concentration inside the duct (Eq. 143) is linear in z and of constant strength K. In the case of the dermal concentration (Eq. 144), the perturbation is modeled as a superposition of dipole singularities

$$G(\underline{\boldsymbol{x}}(u,v) - \underline{\boldsymbol{x}}_0(s)) = \frac{z(u,v) - z_0(s)}{4\pi \left|\underline{\boldsymbol{x}}(u,v) - \underline{\boldsymbol{x}}_0(s)\right|^3} \tag{145}$$

distributed over the length of the centerline of the helical sweat duct. An approximate expression for the distance term $\left|\underline{\boldsymbol{x}}(u,v) - \underline{\boldsymbol{x}}_0(s)\right|$ is used in the calculation of the constants K and F, as described below (section 10.3.3).

The constant A_{in} and B_{in} are related to the constants A_{out} and B_{out} by the ratio of the partition coefficients. Substituting the z-component of the position on the surface of the helical tube (Eq. 137), into Eq. 144 yields

$$c_{\text{duct}}(\underline{\boldsymbol{x}}_{\mathbf{0}}) = A_{\text{duct}} z_0(s) + B_{\text{duct}} + \text{linear perturbation term} \tag{146}$$

$$c_{\alpha}(\underline{\boldsymbol{x}}) = A_{\alpha} z_0(s) + B_{\alpha} + \text{integrated dipolar perturbation term} \tag{147}$$

Applying boundary condition 1 (Eq. 141) with $P_{\text{epithelium/ref}} \to \infty$ (yielding a boundary condition expressing equilibrium partitioning) to the linear parts of the concentration expressions yields

$$A_{\text{duct}} = \frac{K_{\text{duct/ref}}}{K_{\alpha/\text{ref}}} A_{\alpha} \tag{148}$$

and

$$B_{\text{duct}} = \frac{K_{\text{duct/ref}}}{K_{\alpha/\text{ref}}} B_{\alpha} \tag{149}$$

10.3 Solution to the problem

10.3.1 Non-dimensionalization of the problem

The boundary-values problem is rewritten using non-dimensional variables. The characteristic variables are the same as the ones used in the model of diffusion into a near a hair follicle: for length, L_0 = 100 μm, for diffusivity, D_0 = $1 \cdot 10^{-5}$ cm^2/s and for concentration, c_0 = 0.1 mg/mL. From Eqs. 143 and 144 we obtained the characteristic variables for the constants A_{out}, B_{out}, and the perturbation strengths K, F, as

$$A_0 = \frac{c_0}{L_0} = 10 \text{ mg}/(\text{mL cm}) \tag{150}$$

$$B_0 = c_0 = 0.1 \text{ mg}/\text{mL} \tag{151}$$

$$K_0 = \frac{c_0}{L_0} = 10 \text{ mg}/(\text{mL cm}) \tag{152}$$

$$F_0 = c_0 L_0 = 10^{-3} \ \left(\text{mg cm}\right)/\text{mL} \tag{153}$$

The dimensionless variables are obtained from the characteristic variables as described by Eqs. 10A-E. The following calculations are in dimensionless variables denoted by a circumflex.

10.3.2 Concentration and flux inside the sweat duct

For an arbitraty point $(\hat{x}, \hat{y}, \hat{z})$ inside the sweat duct, the cross-section in the $\hat{x}$ - $\hat{y}$ plane at which the point is located is given by $\hat{y}/\hat{x} = \tan(\hat{s}/\hat{\nu})$, from which we have

$$\frac{\hat{s}}{\hat{\nu}} = \arctan\left(\frac{\hat{y}}{\hat{x}}\right) \tag{154}$$

Thus the $\hat{z}$ -component of the position on the centerline of the helical duct (Eq. 128) can be rewritten as

$$\hat{z}_0(\hat{u}, v) = \hat{p}' \arctan\left(\frac{\hat{y}(\hat{u}, v)}{\hat{x}(\hat{u}, v)}\right) \tag{155}$$

Using Eqs. 148, 149 and 151, the concentration inside the sweat duct (Eq. 143) is written in dimensionless form as

$$\hat{c}_{\text{duct}}\left(\underline{\hat{x}}(\hat{u}, v)\right) = \frac{\hat{B}_\alpha K_{\text{duct/ref}}}{K_{\alpha/\text{ref}}} + \left(\hat{A}_{\text{duct}} \frac{K_{\text{duct/ref}}}{K_{\alpha/\text{ref}}} - \hat{K}\right) \hat{p}' \arctan\left(\frac{\hat{y}(\hat{u}, v)}{\hat{x}(\hat{u}, v)}\right) + \hat{K}\, \hat{z}(\hat{u}, v) \tag{156}$$

Since the helical duct is assumed infinite in length, the effect of the presence of the duct felt at a point located a distance $\hat{u}$ along the centerline of the helix is equal at all points of the helix. Thus without loss of generality the value of $\hat{u}$ may be chosen as

$\hat{u}=0$. Substituting the components $\hat{x}(\hat{u}=0,v)$, $\hat{y}(\hat{u}=0,v)$ and $\hat{z}(\hat{u}=0,v)$ into Eq. 156 yields

$$\hat{c}_{\text{duct}}\left(\underline{\hat{\boldsymbol{x}}}(0,v)\right)=\frac{\hat{B}_{\alpha}K_{\text{duct/ref}}}{K_{\alpha/\text{ref}}}+\left(\hat{K}\hat{\nu}-\hat{A}_{\text{duct}}\frac{K_{\text{duct/ref}}}{K_{\alpha/\text{ref}}}\frac{(\hat{p}')^2}{\hat{\nu}}\right)\varepsilon\sin(v)+O(\varepsilon^2) \tag{157}$$

where we have used the equation $a = \varepsilon R$ relating the radius a of the tube to the helix radius R.

Using the dimensionless form of Eq. 139 for the normal to the surface of the helical duct, the dimensionless flux inside the sweat duct is obtained from Eq. 157 as

$$-\underline{\mathbf{n}}\cdot\underline{\nabla}\hat{c}_{\text{duct}}\left(\underline{\hat{\boldsymbol{x}}}(0,v)\right)=-\left[\frac{1}{\hat{R}}+\left(\hat{K}\hat{\nu}-\hat{A}_{\text{duct}}\frac{K_{\text{duct/ref}}}{K_{\alpha/\text{ref}}}\frac{(\hat{p}')^2}{\hat{\nu}}\right)\sin(v)+\frac{O(\varepsilon)}{\hat{R}}\right] \tag{158}$$

10.3.3 Concentration and flux outside the sweat duct

In order to calculate the value of the perturbation strengths K and F, the dimensionless form of the distance $\left|\underline{\boldsymbol{x}}(u,v)-\underline{\boldsymbol{x}}_0(s)\right|$ (Eq. 145) is replaced by an approximation to the distance in which the position on the surface of the helical tube depends only on the dimensionless arclength $\hat{u}$:

$$\left|\underline{\hat{\boldsymbol{x}}}(\hat{u},v)-\underline{\hat{\boldsymbol{x}}}_0(\hat{s})\right|\cong\left|\underline{\hat{\boldsymbol{x}}}(\hat{u},v)-\underline{\hat{\boldsymbol{x}}}_0(\hat{s})\right|_{\text{approx}}=\sqrt{\left|\underline{\hat{\boldsymbol{x}}}(\hat{u})-\underline{\hat{\boldsymbol{x}}}_0(\hat{s})\right|^2+\hat{a}^2} \tag{159}$$

As in the previous section we set $\hat{u}=0$ without loss of generality. Using Eq. 136 the approximation to the distance term is thus

$$\left|\underline{\hat{\boldsymbol{x}}}(\hat{u},v)-\underline{\hat{\boldsymbol{x}}}_0(\hat{s})\right|_{\text{approx}}=\sqrt{2\hat{R}^2-2\hat{R}^2\cos\left(\frac{\hat{s}}{\hat{\nu}}\right)+\left(\frac{\hat{p}'\hat{s}}{\hat{\nu}}\right)^2+\hat{a}^2} \tag{160}$$

The expression for the distance is asymptotic to the exact distance (see Appendix F). In addition, this approximation yields a perfectly dipolar perturbation term (sinusoidal dependence on *v*) in both the concentration in and the flux into the skin tissue (Eqs. 161, 163).

The dimensionless concentration in the tissue surrounding the sweat duct is

$$\hat{c}_\alpha(\underline{\hat{\boldsymbol{x}}})=\hat{A}_\alpha\hat{z}+\hat{B}_\alpha+\hat{F}\int_{-\infty}^{\infty}\frac{\hat{z}(\hat{u},v)-\hat{z}_0(\hat{s})}{4\pi\left|\underline{\hat{\boldsymbol{x}}}(\hat{u},v)-\underline{\hat{\boldsymbol{x}}}_{\boldsymbol{0}}(\hat{s})\right|^3}\,\mathrm{d}\hat{s} \tag{161}$$

Using Eqs. 131 and 137 for the $\hat{z}$-component of the position on the centerline and on the surface of the helical tube, and substituting the components $\hat{x}(\hat{u}=0,\mathrm{v})$, $\hat{y}(\hat{u}=0,\mathrm{v})$ and $\hat{z}(\hat{u}=0,\mathrm{v})$ into Eq. 161 yields

$$\hat{c}_\alpha(\underline{\hat{\boldsymbol{x}}}(0,v))=\hat{B}_\alpha+\frac{\hat{r}^2}{\hat{\nu}}\left[\hat{A}_\alpha+\hat{F}I_1(\hat{s})\right]\varepsilon\sin(v)+O(\varepsilon) \tag{162}$$

where $I_1(\hat{s})$ is the integral

$$I_1(\hat{s})=\int_{-\infty}^{\infty}\frac{1}{4\pi\left|\underline{\hat{\boldsymbol{x}}}(\hat{u},v)-\underline{\hat{\boldsymbol{x}}}(\hat{s})\right|_{\text{approx}}^3}\,\mathrm{d}\hat{s} \tag{163}$$

The dimensionless form of Eq. 139 for the normal to the surface of the helical duct is used to calculate the dimensionless flux outside the sweat duct. It is

$$-\underline{\mathbf{n}}\cdot\underline{\nabla}\hat{c}_{\alpha}\left(\underline{\hat{\mathbf{x}}}(0,v)\right)=-\left\{\frac{\hat{R}}{\hat{\nu}}\hat{A}_{\alpha}+\hat{F}\left[I_1(\hat{s})-3\left(p'\right)^2 I_1(\hat{s})\right]\sin(v)\right\} \tag{164}$$

where the integral $I_1(\hat{s})$ is given by Eq. 163 and the integral $I_2(\hat{s})$ is

$$I_2(\hat{s})=\int_{-\infty}^{\infty}\frac{\frac{\hat{s}}{\hat{\nu}}\left(\frac{\hat{s}}{\hat{\nu}}-\sin\frac{\hat{s}}{\hat{\nu}}\right)}{4\pi\left|\underline{\hat{\mathbf{x}}}(\hat{u},v)-\underline{\hat{\mathbf{x}}}(\hat{s})\right|_{\text{approx}}^{3}}\,\mathrm{d}\hat{s} \tag{165}$$

From Eq. 157, 158 and 162, 164, we see that the concentration perturbation (due to the solute diffusivities in the duct and the surrounding tissue) is dipolar in nature both inside and outside the sweat duct.

10.3.4 Calculation of the constant perturbation strengths *K, F*

A FORTRAN program (Appendix G) was written to calculate the values of the constant perturbation strengths *K* and *F* from the system of two equations given by the boundary conditions (Eqs. 141, 142). The concentration and fluxes inside and outside the sweat gland in Eqs. 141 and 142 are given in section 10.3.3. The integrals I_1 and I_2 (Eqs. 163 and 165) are evaluated numerically in the FORTRAN program using Simpson's rule.

10.3.5 Calculation of the constants $\hat{A}_{\alpha}$ and $\hat{B}_{\alpha}$

The constants $\hat{A}_{\alpha}$ and $\hat{B}_{\alpha}$ are calculated from the background dermal concentration, given by

$$\hat{c}_{\alpha}(\hat{z})=\hat{A}_{\alpha}\hat{z}+\hat{B}_{\alpha} \tag{166}$$

In Chapter 11 we assume a value of the background concentration at two depths $\hat{z}$.

11 Application of the Mathematical Model

11.1 Introduction

In this chapter we apply the model to the diffusion of two different compounds through and near a helical duct embedded in skin tissue taken as the dermis (in the following sections the subscript "de" denotes the dermis). For both cases we present results for the strengths in-duct vertical concentration gradient (K) and the linear dipole strength appearing in the slender-body approximation for the dermal concentration (F) (Eqs. 143, 144).

The first compound (section 11.3) is assumed to partition equally into the duct and into the dermal tissue. We further assume that its structure and molecular weight are equal to that of the fluorescent dye Bodipy® FL C_5. Sweat is a dilute solution containing primarily Na^+, Cl^-, K^+ and HCO_3^- electrolytes.[118,119] The diffusion coefficient of the compound inside the duct is taken as the diffusion coefficient of a dilute solution of Bodipy® FL C_5 in water, given by the Wilke-Chang correlation (Eq. 104). The diffusion coefficient in dermis is taken as the diffusion coefficient of Bodipy® FL C_5 in bulk dermis omitting the presence of a sebaceous gland (Eq. 109).

In the second case (section 11.4), we present results for the diffusion of Bodipy® FL C_5 through and near a sweat gland. In this case the partition coefficients the partition coefficients are those of Bodipy® FL C_5 in water and in bulk dermis without the sebaceous gland, with respect to an aqueous solution at pH 1.0. As in the first case, the diffusion coefficients are given by Eqs. 104 and 109.

The values of the dimensionless parameters A_α and B_α are obtained from the background dermal concentration (Eq. 166) by assuming $c_{de}(z = 0)$ = 0.1 mg/mL and $c_{de}(z = \text{-}0.5\ \text{cm})$ = 0. The values of the parameters are

$$A_\alpha = 0.2\ \text{mg}/(\text{mL cm}) \tag{167}$$

and

$$B_\alpha = 0.1\ \text{mg/mL} \tag{168}$$

11.2 Sweat gland geometry

Relatively little data on the geometry of the human eccrine sweat duct is available. In 1983 Sato *et al*. published a study which includes micrographs of eccrine sweat gland secretory coils of men, 22 to 43 years of age.[124] The micrographs also include a small segment of the proximal sweat duct. From these micrographs we have estimated the radius *a* of the sweat duct near the secretory coil to be approximately 15 μm. A micrograph in an older study on human eccrine sweat glands[125] shows the radius *a* to be approximately 10 μm.

The value of the parameter ε is chosen as ε = 0.1, yielding a helix radius of $R = a/\varepsilon$ = 150 μm. Sato *et al*. state that the human sweat gland can vary as much as fivefold.[119] Photomicrographs provided in references 124 and 125, show the lengths of the major axis of the secretory coils of healthy volunteers to range from about 500 μm (Ref. 124) to about 1500 μm (Ref. 125). The length of the minor axis of an average-sized sweat gland shown in Reference 124 is about 317 μm. Given that the proximal segment

of the sweat duct connects the secretory coil to the straight segment of the duct, we believe our value of the radius R of the proximal portion of the duct to be reasonable. We have not found any reliable data enabling us to estimate the value of the pitch of the proximal segment of the duct. We assume a value of $p = 200$ μm.

Table 11-1 shows the values of the duct geometrical parameters used in the applications of the model. These values substituted into the equations for the components of the position on the surface of the helical duct (Eq. 137), with $0 \leq v \leq 2\pi$, yield the helical duct shown in Figure 11-1.

Table 11-1: Geometrical parameters of the helical tube simulating an eccrine sweat duct. R: helix radius; p: helix pitch; ε: dimensionless parameter yielding the tube radius a.

R [μm]	p [μm]	ε	$a = \varepsilon R$ [μm]
150	200	0.1	15

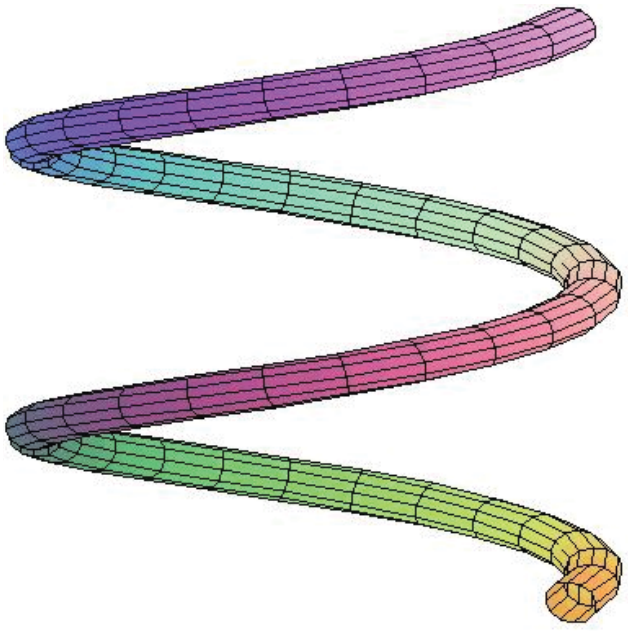


Figure 11-1: Helix obtained in *Maple* from the coordinates describing position on the surface of the helix (Eq. 137). Input parameters are $R = 150$ μm, $a = 15$ μm and $p = 200$ μm (Table 11-1); the angle v is $0 \leq v \leq 2\pi$.

11.3 Equal partitioning at the sweat duct/skin tissue interface

The partition coefficients of the diffusing compound inside the sweat duct and in the surrounding dermal tissue with respect to an aqueous solution at pH 1.0 are

$$K_{\text{duct/pH1.0}} = K_{\text{de/pH1.0}} = 1.0 \tag{169}$$

The diffusion coefficients are

$$D_{\text{duct}} = 0.455 \cdot 10^{-5}\,\text{cm}^2/\text{s} \tag{170}$$

$$D_{\text{de}} = 0.152 \cdot 10^{-5}\,\text{cm}^2/\text{s} \tag{171}$$

The permeability of the epithelial lining of the sweat duct is assumed to be large,

$$P_{\text{epithelium/pH1.0}} = 1000\,\text{cm/s} \tag{172}$$

With a large value of the permeability boundary condition 1 (Eq. 141) expresses equilibrium partitioning across the epithelial lining of the sweat duct.

The values of the strengths of the perturbations to the concentration (Eqs. 143, 144) in the case of equal partitioning are

$$K = 8.7017 \cdot 10^{-5}\ \text{mg}/(\text{mL cm}) \tag{173}$$

$$F = -2.8167 \cdot 10^{-6}\ (\text{mg cm})/\text{mL} \tag{174}$$

11.4 Unequal partitioning at the skin tissue/sweat duct interface

In this case we model the diffusion of the fluorescent dye Bodipy® FL C_5 into and near the eccrine sweat duct. The values of the diffusion coefficients inside the sweat duct and in the surrounding tissue are as given by Eqs. 170 to 171. The partition coefficient of Bodipy® FL C_5 inside the duct is assumed equal to the partition coefficient of Bodipy® FL C_5 in water at pH 7.4 with respect to an aqueous solution at pH 1.0, $\overline{K}_{\text{pH 7.4/pH 1.0}}$. As for the calculation of the partition coefficients of Bodipy® FL C_5 in the viable epidermis and dermis 1 (Eqs. 85 and 86), this partition coefficient is calculated as the ratio of the total dye concentration in a solution at pH 7.4 to the total dye concentration in a solution at pH 1.0. Thus we have

$$\overline{K}_{\text{duct/pH 1.0}} = \overline{K}_{\text{pH 7.4/pH 1.0}} = \frac{c^{\text{u}}_{\text{pH 7.4}} + c^{\text{i}}_{\text{pH 7.4}}}{c^{\text{u}}_{\text{pH 1.0}} + c^{\text{i}}_{\text{pH 1.0}}} \tag{175}$$

Factoring out the concentration of the unionized form of the dye and recognizing that the concentration of an unionized species is independent of pH yields

$$\overline{K}_{\text{duct/pH 1.0}} = \frac{1 + \dfrac{c^{\text{i}}_{\text{pH 7.4}}}{c^{\text{u}}_{\text{pH 7.4}}}}{1 + \dfrac{c^{\text{i}}_{\text{pH 1.0}}}{c^{\text{u}}_{\text{pH 1.0}}}} \tag{176}$$

Substituting Eqs. 81 and 84 into Eq. 176 yields

$$\overline{K}_{\text{duct/pH 1.0}} = 21.4172 \approx 21 \tag{177}$$

The partition coefficient of Bodipy® FL C_5 in the dermal tissue surrounding the sweat duct, $\overline{K}_{\text{de/pH1.0}}$, is taken as partition coefficient of Bodipy® FL C_5 in the dermis 1 and the outer region of dermis 2 in the mathematical model of diffusion through and near a hair follicle (Eqs. 91 and 94). Thus we have

$$\overline{K}_{\text{de/pH1.0}} \approx 14 \tag{178}$$

The values of the perturbation strenghts to the concentration in the case of unequal partitioning are

$$K = 1.5170 \cdot 10^{-3} \text{ mg/(mL cm)} \tag{179}$$

$$F = -2.7512 \cdot 10^{-6} \text{ (mg cm)/mL} \tag{180}$$

11.5 Discussion

The results for the strengths of the perturbation to the concentration inside and outside the sweat duct were obtained for a large value of the permeability of the ductal epithelium, $P_{\text{epithelium/pH1.0}}$ = 1000 cm/s. Although the epithelial lining of the sweat duct consists of only two cell layers,[119,126] this value of the permeability is an overstatement. In absence of the information on the permeability of the epithelium, we choose simply to consider the case it presents negligible mass transfer resistance. A large value of the permeability coefficients reduces boundary condition 1 (Eq. 141) to an equation expressing partitioning equilibrium across the epithelium.

The perturbation strength K is positive as it represents the vertical permeant concentration gradient inside the duct. The perturbation strength F is negative due to the

fact that the dipolar singularity being integrated to produce the dermal concentration (Eq. 144) is positive above and negative below the $z = 0$ plane. In the presence of the duct, the dermal concentration has to be less than the background dermal concentration above the duct, and greater below it, when $D_{duct} > D_{de}$. Thus the dipolar singularity has to be multiplied by a negative F.

The increase in the ratio of the partition coefficients $\overline{K}_{duct/pH\,1.0} \big/ \overline{K}_{de/pH\,1.0}$ from a value of 1.0 to 1.5 increases the strength of the perturbation to the concentration inside the sweat duct by a factor of 200. The strength of the perturbation to the concentration outside the sweat duct increases by about 3.5%.

11.6 Conclusion and future work

The mathematical model presented in Part II is, to our knowledge, the first rigorous 3-D model of steady-state diffusion through and near the duct of an eccrine sweat gland. Previously published mathematical models lump eccrine sweat glands and ducts with hair follicles as cylindrically-shaped shunt pathways.[6,29] The only theoretical paper[121] devoted solely to the eccrine sweat duct we have found assumes a 1-D straight shape. In this study the shape of the duct is modeled as a 3-D helical tube. The concentrations inside and outside the sweat duct contain a linear term in depth z and a perturbation term which quantifies the effect of the presence of the sebaceous duct on the concentrations. In the case of the concentration inside the duct, the perturbation is linear in depth z. The perturbation in the concentration outside the duct is described using slender-body theory, which assumes that the concentration near a long slender body can be approximated as an axial distribution of singularities along the

centerline of the slender body.[112] In this model the singularities along the axis of the helix are dipole singularities.

In order to complete this model, the final step would be to compute the concentration of the applied chemical as a function of depth and radius away from the duct, and the total flux through a horizontal plane of a block of dermal tissue containing the proximal sweat duct.

This model represents a first step towards a realistic model of the diffusion through and near an eccrine sweat duct. To gain a quantitative understanding of the effect of the eccrine sweat duct comparable to the level of understanding we have gained of the role of the hair follicle, we would need to investigate transient diffusion through and near a sweat duct of finite length. The coiled and straight segments of the sweat duct are as richly vascularized as the secretory coil,[54] and, as in the case of the hair follicle, is it is likely that inclusion of the vascularization would significantly alter concentration profiles. Once a working model of the same precision as our model of diffusion through and near a hair follicle is available, further extensions, as in the case of the hair follicle model, would consists in investigating the permeation of compounds of various lipophilicity and molecular size. To gain a true understanding of the way skin appendages collectively affect the diffusion of chemical compounds through human skin, we would include eccrine sweat ducts into a model of a $1cm^2$ piece of skin containing hair follicles.

A Calculation of donor solution concentration

The donor solution concentration at time t, $c_{ds}(t)$, is calculated from the mole balance on the system comprising the donor solution compartment, the infundibulum and the skin layers in contact with the infundibulum (epidermis, dermis 1 and dermis 2). The terms of the mole balance describe depletion from the donor solution compartment, depletion from the infundibulum, diffusion across the stratum corneum / epidermis boundary and diffusion across the infundibulum / skin tissue boundary at the level of the epidermis, dermis 1 and dermis 2:

$$\underbrace{-h_{ds}A_{ds}\frac{dc_{ds}}{dt}}_{\text{depletion from donor solution}}\underbrace{-\frac{d}{dt}\int c_{infund}(z)\left[\pi\, f_{ors}^{2}(z)\right]dz}_{\text{depletion from infundibulum}}$$

$$=\underbrace{\iint P_{sc/ds}\left(\frac{c_{ds}}{K_{ds/ds}}-\frac{c_{ed}\big|_{z=0}}{K_{ed/ds}}\right)dA}_{\text{diffusion across sc / ed barrier}}+\underbrace{\iint P_{infund/ds}(z)\left(\frac{c_{sebum}(t)}{K_{sebum/ds}}-\frac{c_{ed}}{K_{ed/ds}}\right)dA}_{\text{diffusion across infundibulum / ed barrier}}$$

$$+\underbrace{\iint P_{infund/ds}(z)\left(\frac{c_{sebum}(z,t)}{K_{sebum/ds}}-\frac{c_{de1}}{K_{de1/ds}}\right)dA}_{\text{diffusion across infundibulum / de1 barrier}}+\underbrace{\iint P_{infund/ds}(z)\left(\frac{c_{sebum}(z,t)}{K_{sebum/ds}}-\frac{c_{de2}}{K_{de2/ds}}\right)dA}_{\text{diffusion across infundibulum / de2 barrier}} \qquad \text{(A1)}$$

Substituting Eq. D9 from Appendix D for the differential area element dA yields

$$-h_{ds}A_{ds}\frac{dc_{ds}(t)}{dt}-\pi\frac{K_{sebum/pH}}{K_{ds/pH}}c_{ds}(t)\int_{z_{min}}^{z_{max}}\operatorname{erfc}\left(\frac{z_0-z}{2\sqrt{D_{sebum}t}}\right)f^{2}(z)\,dz$$

$$= \int_0^{2\pi} \int_{f(z)}^{r_{\max}} P_{\mathrm{sc/pH}}(r) \left(\frac{c_{\mathrm{ds}}(t)}{K_{\mathrm{ds/pH}}} - \frac{c_{\mathrm{ve}}\big|_{z=0}}{K_{\mathrm{ve/pH}}} \right) r \, \mathrm{d}r \, \mathrm{d}\theta$$

$$+ \int_0^{2\pi} \int_{z_{\mathrm{ve,min}}}^{z_{\mathrm{ve,max}}} P_{\mathrm{infund/pH}}(z) \left(\frac{c_{\mathrm{sebum}}(z,t)}{K_{\mathrm{sebum/pH}}} - \frac{c_{\mathrm{ve}}(r,z)}{K_{\mathrm{ve/pH}}} \right) f_{\mathrm{ors}}(z) \sqrt{1 + \left[f'_{\mathrm{ors}}(z) \right]^2} \, \mathrm{d}z \, \mathrm{d}\theta$$

$$+ \int_0^{2\pi} \int_{z_{\mathrm{de1,min}}}^{z_{\mathrm{de1,max}}} P_{\mathrm{infund/pH}}(z) \left(\frac{c_{\mathrm{sebum}}(z,t)}{K_{\mathrm{sebum/pH}}} - \frac{c_{\mathrm{de1}}(r,z)}{K_{\mathrm{de1/pH}}} \right) f_{\mathrm{ors}}(z) \sqrt{1 + \left[f'_{\mathrm{ors}}(z) \right]^2} \, \mathrm{d}z \, \mathrm{d}\theta$$

$$+ \int_0^{2\pi} \int_{z_{\mathrm{de2,min}}}^{z_{\mathrm{de2,max}}} P_{\mathrm{infund/pH}}(z) \left(\frac{c_{\mathrm{sebum}}(z,t)}{K_{\mathrm{sebum/pH}}} - \frac{c_{\mathrm{de2}}(r,z)}{K_{\mathrm{de2/pH}}} \right) f_{\mathrm{ors}}(z) \sqrt{1 + \left[f'_{\mathrm{ors}}(z) \right]^2} \, \mathrm{d}z \, \mathrm{d}\theta \qquad \text{(A2)}$$

Regrouping the terms containing $c_{\mathrm{ds}}(t)$ on the left-hand side of the equation:

$$- h_{\mathrm{ds}} A_{\mathrm{ds}} \frac{\mathrm{d}c_{\mathrm{ds}}(t)}{\mathrm{d}t} - \pi \frac{K_{\mathrm{sebum/pH}}}{K_{\mathrm{ds/pH}}} c_{\mathrm{ds}}(t) \int_{z_{\min}}^{z_{\max}} \mathrm{erfc} \left(\frac{z_0 - z}{2\sqrt{D_{\mathrm{sebum}} t}} \right) f_{\mathrm{ors}}^2(z) \, \mathrm{d}z$$

$$- \left[\pi \frac{K_{\mathrm{sebum/pH}}}{K_{\mathrm{ds/pH}}} \int_{z_{\min}}^{z_{\max}} \mathrm{erfc} \left(\frac{z_0 - z}{2\sqrt{D_{\mathrm{sebum}} t}} \right) f^2(z) \, \mathrm{d}z \right] \frac{\mathrm{d}c_{\mathrm{ds}}(t)}{\mathrm{d}t}$$

$$= 2\pi \frac{P_{\mathrm{sc/pH}}(r) c_{\mathrm{ds}}(t)}{K_{\mathrm{ds/pH}}} \int_{f(z)}^{r_{\max}} r \, \mathrm{d}r - 2\pi \frac{P_{\mathrm{sc/pH}}(r)}{K_{\mathrm{ve/pH}}} \int_{f(z)}^{r_{\max}} c_{\mathrm{ve}}(r,z)\big|_{z=0} r \, \mathrm{d}r$$

$$+ \frac{2\pi}{K_{\mathrm{sebum/pH}}} \int_{z_{\min}}^{z_{\max}} P_{\mathrm{infund/pH}}(z) \frac{K_{\mathrm{sebum/pH}}}{K_{\mathrm{ds/pH}}} c_{\mathrm{ds}}(t) \, \mathrm{erfc} \left(\frac{z_0 - z}{2\sqrt{D_{\mathrm{sebum}} t}} \right) f_{\mathrm{ors}}(z) \sqrt{1 + \left[f'_{\mathrm{ors}}(z) \right]^2} \, \mathrm{d}z \, \mathrm{d}\theta$$

$$- \frac{2\pi}{K_{\mathrm{ve/pH}}} \int_{z_{\mathrm{ve,min}}}^{z_{\mathrm{ve,max}}} P_{\mathrm{infund/pH}}(z) c_{\mathrm{ve}}(r,z) \, f_{\mathrm{ors}}(z) \sqrt{1 + \left[f'_{\mathrm{ors}}(z) \right]^2} \, \mathrm{d}z$$

$$-\frac{2\pi}{K_{\mathrm{de1/pH}}}\int_{z_{\mathrm{de1,min}}}^{z_{\mathrm{de1,max}}} P_{\mathrm{infund/pH}}(z)\,c_{\mathrm{de1}}(r,z)\,f_{\mathrm{ors}}(z)\sqrt{1+\left[f'_{\mathrm{ors}}(z)\right]^2}\;\mathrm{d}z$$

$$-\frac{2\pi}{K_{\mathrm{de2/pH}}}\int_{z_{\mathrm{de2,min}}}^{z_{\mathrm{de2,max}}} P_{\mathrm{infund/pH}}(z)\,c_{\mathrm{de2}}(r,z)\,f_{\mathrm{ors}}(z)\sqrt{1+\left[f'_{\mathrm{ors}}(z)\right]^2}\;\mathrm{d}z \tag{A3}$$

Further rearrangement yields a 1st order ODE for the donor solution concentration $c_{\mathrm{ds}}(t)$:

$$\underbrace{-\left[h_{\mathrm{ds}}A_{\mathrm{ds}}+\pi\frac{K_{\mathrm{sebum/pH}}}{K_{\mathrm{ds/pH}}}\int_{z_{\min}}^{z_{\max}}\mathrm{erfc}\left(\frac{z_0-z}{2\sqrt{D_{\mathrm{sebum}}t}}\right)f_{\mathrm{ors}}^2(z)\,\mathrm{d}z\right]}_{\mathrm{V}}\frac{\mathrm{d}c_{\mathrm{ds}}(t)}{\mathrm{d}t}$$

$$=c_{\mathrm{ds}}(t)\Bigg\{\underbrace{2\pi\frac{P_{\mathrm{sc/pH}}(r)}{K_{\mathrm{ds/pH}}}\int_{f(z)}^{r_{\max}} r\,\mathrm{d}r}_{\mathrm{T_1}}+\underbrace{\pi\frac{K_{\mathrm{sebum/pH}}}{K_{\mathrm{ds/pH}}}\frac{\mathrm{d}}{\mathrm{d}t}\int_{z_{\min}}^{z_{\max}}\mathrm{erfc}\left(\frac{z_0-z}{2\sqrt{D_{\mathrm{sebum}}t}}\right)f_{\mathrm{ors}}^2(z)\,\mathrm{d}z}_{\mathrm{T_2}}$$

$$+\underbrace{\frac{2\pi}{K_{\mathrm{ds/pH}}}\int_{z_{\min}}^{z_{\max}}P_{\mathrm{infund/pH}}(z)\frac{K_{\mathrm{sebum/pH}}}{K_{\mathrm{ds/pH}}}c_{\mathrm{ds}}(t)\,\mathrm{erfc}\left(\frac{z_0-z}{2\sqrt{D_{\mathrm{sebum}}t}}\right)f(z)\sqrt{1+\left[f'(z)\right]^2}\;\mathrm{d}z\,\mathrm{d}\theta}_{\mathrm{T_3}}\Bigg\}$$

$$-2\pi\Bigg\{\underbrace{\frac{P_{\mathrm{sc/pH}}(r)}{K_{\mathrm{ve/pH}}}\int_{f_{\mathrm{ors}}(z)}^{r_{\max}}c_{\mathrm{ve}}(r,z)\big|_{z=0}\,r\,\mathrm{d}r}_{\mathrm{T_4}}+\underbrace{\frac{1}{K_{\mathrm{ve/pH}}}\int_{z_{\mathrm{ve,min}}}^{z_{\mathrm{ve,max}}}P_{\mathrm{infund/pH}}(z)\;c_{\mathrm{ve}}(r,z)\,f_{\mathrm{ors}}(z)\sqrt{1+\left[f'_{\mathrm{ors}}(z)\right]^2}\;\mathrm{d}z}_{\mathrm{T_5}}$$

$$+\underbrace{\frac{1}{K_{\mathrm{de1/pH}}}\int_{z_{\mathrm{de1,min}}}^{z_{\mathrm{de1,max}}}P_{\mathrm{infund/pH}}(z)\;c_{\mathrm{de1}}(r,z)\,f_{\mathrm{ors}}(z)\sqrt{1+\left[f'_{\mathrm{ors}}(z)\right]^2}\;\mathrm{d}z}_{\mathrm{T_6}}$$

$$+\underbrace{\frac{1}{K_{\mathrm{de2/pH}}}\int_{z_{\mathrm{de2,min}}}^{z_{\mathrm{de2,max}}} P_{\mathrm{infund/pH}}(z)\; c_{\mathrm{de2}}(r,z)\; f_{\mathrm{ors}}(z)\sqrt{1+\left[f'_{\mathrm{ors}}(z)\right]^2}\;\mathrm{d}z}_{\mathrm{T}_7}\Bigg\} \tag{A4}$$

Eq. A4 is rewritten in terms of ξ, ζ coordinates using the coordinate transformation equation (Eq. 11). This equation well as the derivative $\mathrm{d}r/\mathrm{d}\xi = r_{\max} - f(z)$ obtained from it are substituted into terms T_1 and T_4 of Eq. A4, yielding, in dimensionless coordinates,

$$\mathrm{T}_1:\; 2\pi\frac{\hat{P}_{\mathrm{sc/pH}}(\hat{r})}{K_{\mathrm{ds/pH}}}\int_{\hat{f}_{\mathrm{ors}}(\zeta)}^{\hat{r}_{\max}}\hat{r}\,\mathrm{d}\hat{r}$$

$$=2\pi\frac{\hat{P}_{\mathrm{sc/pH}}(\hat{r})}{K_{\mathrm{ds/pH}}}\int_{\xi=0}^{\xi=1}\left\{\xi\left[\hat{r}_{\max}-\hat{f}_{\mathrm{ors}}(\zeta)\right]+\hat{f}_{\mathrm{ors}}(\zeta)\right\}\left[\hat{r}_{\max}-\hat{f}_{\mathrm{ors}}(\zeta)\right]\mathrm{d}\xi \tag{A5}$$

and

$$\mathrm{T}_4:\;\frac{\hat{P}_{\mathrm{sc/pH}}(\hat{r})}{K_{\mathrm{ds/pH}}}\int_{\hat{f}(\hat{z})}^{\hat{r}_{\max}}\hat{\mathrm{c}}_{\mathrm{ed}}(\hat{r},\hat{z})\big|_{\hat{z}=0}\,\hat{r}\,\mathrm{d}\hat{r}$$

$$=\frac{\hat{P}_{\mathrm{sc/pH}}(\xi)}{K_{\mathrm{ds/pH}}}\int_{\xi=0}^{\xi=1}\hat{\mathrm{c}}_{\mathrm{ed}}(\xi,\zeta)\big|_{\zeta=0}\left\{\xi\left[\xi_{\max}-\hat{f}(\zeta)\right]+\hat{f}(\zeta)\right\}\left[\xi_{\max}-\hat{f}(\zeta)\right]\mathrm{d}\xi \tag{A6}$$

Terms T_2 and T_3 are non-dimensionalized using the coordinate system transformation $z/L_0 = \hat{z} = \zeta$ (Eq. 12). The ODE for the dimensionless donor solution concentration $\hat{c}_{\mathrm{ds}}(\hat{t})$ is rewritten as

$$-\mathrm{V}\frac{\mathrm{d}\hat{c}_{\mathrm{ds}}\left(\hat{t}\right)}{\mathrm{d}\hat{t}}=\mathrm{A}_1\hat{c}_{\mathrm{ds}}\left(\hat{t}\right)-\mathrm{A}_2 \tag{A7}$$

where $\mathrm{A}_1=\mathrm{T}_1+\mathrm{T}_2+\mathrm{T}_3$ and $\mathrm{A}_2=2\pi\left(\mathrm{T}_4+\mathrm{T}_5+\mathrm{T}_6+\mathrm{T}_7\right)$. The solution to Eq. A7 is

$$\hat{c}_{\mathrm{ds}}\left(\hat{t}\right)=\frac{\mathrm{A}_1}{\mathrm{A}_2}+\left(1-\frac{\mathrm{A}_1}{\mathrm{A}_2}\right)\mathrm{e}^{-(\mathrm{A}_1/\mathrm{V})\hat{t}} \tag{A8}$$

A test for the calculation of the dimensionless donor solution concentration is incorporated into the code implementing the mathematical model. The volume balance

$$\left\{\begin{matrix}\text{drug in ds}\\ \text{at time t}\end{matrix}\right\}+\left\{\begin{matrix}\text{drug in infundibulum}\\ \text{at time t}\end{matrix}\right\}+\left\{\begin{matrix}\text{drug in skin tissue}\\ \text{at time t}\end{matrix}\right\}=\left\{\begin{matrix}\text{drug in ds}\\ \text{at time t = 0}\end{matrix}\right\} \tag{A9}$$

must hold if $\hat{c}_{\mathrm{ds}}\left(\hat{t}\right)$ is calculated correctly. Eq. A9 yields

$$\hat{h}_{\mathrm{ds}}\hat{A}_{\mathrm{ds}}\hat{c}_{\mathrm{ds}}\left(\hat{t}\right)+\frac{K_{\mathrm{sebum/pH1.0}}}{K_{\mathrm{pH5.0/pH1.0}}}\hat{c}_{\mathrm{ds}}\left(\hat{t}\right)\int_{\hat{z}_{\min}}^{\hat{z}_{\max}}\operatorname{erfc}\left(\frac{\hat{z}_0-\hat{z}}{2\sqrt{\hat{D}_{\mathrm{sebum}}\,\hat{t}}}\right)\left[\pi\,\hat{f}_{\mathrm{ors}}^{2}\left(\hat{z}\right)\right]\mathrm{d}\hat{z}+\int_{\hat{f}_{\mathrm{ors}}(\hat{z})}^{\hat{r}_{\max}}\int_{0}^{2\pi}\int_{\hat{z}_{\min}}^{\hat{z}_{\max}}\hat{c}\left(\hat{r},\hat{z}\right)\hat{r}\;\mathrm{d}\hat{z}\;\mathrm{d}\theta\;\mathrm{d}\hat{r}$$

$$=\hat{c}_{\mathrm{ds}}\left(\hat{t}=0\right)\hat{h}_{\mathrm{ds}}\hat{A}_{\mathrm{ds}} \tag{A10}$$

or, in ξ, ζ coordinates,

$$\begin{aligned}&\hat{h}_{\mathrm{ds}}\hat{A}_{\mathrm{ds}}\hat{c}_{\mathrm{ds}}\left(\hat{t}\right)+\hat{c}_{\mathrm{ds}}\left(\hat{t}\right)\pi\frac{K_{\mathrm{sebum/pH1.0}}}{K_{\mathrm{pH5.0/pH1.0}}}\int_{\zeta_{\min}}^{\zeta_{\max}}\operatorname{erfc}\left(\frac{\zeta_0-\zeta}{2\sqrt{\hat{D}_{\mathrm{sebum}}\,\hat{t}}}\right)\hat{f}_{\mathrm{ors}}^{2}\left(\zeta\right)\mathrm{d}\zeta\\&+2\pi\int_{\zeta_{\min}}^{\zeta_{\max}}\int_{\xi_{\min}}^{\xi_{\max}}\hat{c}\left(\xi,\zeta\right)\left[\hat{r}_{\max}-\hat{f}\left(\zeta\right)\right]\left\{\xi\left[\hat{r}_{\max}-\hat{f}\left(\zeta\right)\right]+\hat{f}\left(\zeta\right)\right\}\mathrm{d}\xi\;\mathrm{d}\zeta\\&=\hat{h}_{\mathrm{ds}}\hat{A}_{\mathrm{ds}}\hat{c}_{\mathrm{ds}}\left(\hat{t}=0\right)\end{aligned} \tag{A11}$$

B Finite Difference approximation formulae

The method of Finite Differences replaces derivatives by algebraic formulae whose terms are the value of the concentration at nodes adjacent to the node at which the derivative is computed. Finite Difference formulae for the partial derivatives of a function $f(x,y)$ can be derived from the Taylor Series (TS) expansions of $f(x,y)$. The TS expansions of $f(x,y)$ about *x* are:

$$f(x+h_x,y)=f(x,y)+h_x\frac{\partial f}{\partial x}(x,y)+\frac{1}{2}h_x^2\frac{\partial^2 f}{\partial x^2}(x,y)+\frac{1}{6}h_x^3\frac{\partial^3 f}{\partial x^3}(x,y)+O(h_x^4) \tag{B1}$$

$$f(x-h_x,y)=f(x,y)-h_x\frac{\partial f}{\partial x}(x,y)+\frac{1}{2}h_x^2\frac{\partial^2 f}{\partial x^2}(x,y)-\frac{1}{6}h_x^3\frac{\partial^3 f}{\partial x^3}(x,y)+O(h_x^4) \tag{B2}$$

where h_x is the step size separating adjacent coordinate points in the *x* direction. From these equations the forward and backward difference formulae for the first derivative of *f* with respect to *x* are obtained:

$$\frac{\partial f}{\partial x}(x,y)=\frac{f(x+h_x,y)-f(x,y)}{h_x}+O(h_x) \tag{B3}$$

$$\frac{\partial f}{\partial x}(x,y)=\frac{f(x,y)-f(x-h_x,y)}{h_x}+O(h_x) \tag{B4}$$

Subtraction of Eq. B2 from Eq. B1 yields the $O(h_x^2)$ central difference formula for $\partial f/\partial x$:

$$\frac{\partial f}{\partial x}(x,y)=\frac{f(x+h_x,y)-f(x-h_x,y)}{2h_x}+O(h_x^2) \tag{B5}$$

The $O(h_y)$ and $O(h_y^2)$ finite difference formulae for the derivative $\partial f/\partial y$ is derived in the same way using a step size h_y in the y direction.

Adding Eq. B1 to B2 yields the central difference formula for the second derivative of f with respect to x:

$$\frac{\partial^2 f}{\partial x^2}(x,y)=\frac{f(x+h_x,y)-2f(x,y)+f(x-h_x,y)}{h_x^2}+O(h_x^2) \tag{B6}$$

The FD approximation for the mixed second derivative $\partial^2 f/\partial x\partial y$ is obtained by adding the TS expansions formulae for $f(x+h_x, y+h_y)$, $f(x+h_x, y-h_y)$, $f(x-h_x, y+h_y)$, $f(x-h_x, y-h_y)$. This FD approximation is

$$\frac{\partial^2 f}{\partial x\partial y}(x,y)=\frac{f(x+h_x,y+h_y)+f(x+h_x,y-h_y)+f(x-h_x,y+h_y)f(x-h_x,y-h_y)}{4h_xh_y} + O(h_x^2,h_y^2) \tag{B7}$$

By using more TS expansions and more terms in the TS, one obtains higher order FD approximation formulae. Combining

$$f(x+2h_x,y)=f(x,y)+2h_x\frac{\partial f}{\partial x}(x,y)+2h_x^2\frac{\partial^2 f}{\partial x^2}(x,y)+\frac{8}{6}h_x^3\frac{\partial^3 f}{\partial x^3}(x,y)+O(h_x^4) \tag{B8}$$

and

$$f(x-2h_x,y)=f(x,y)-2h_x\frac{\partial f}{\partial x}(x,y)+2h_x^2\frac{\partial^2 f}{\partial x^2}(x,y)-\frac{8}{6}h_x^3\frac{\partial^3 f}{\partial x^3}(x,y)+O(h_x^4) \tag{B9}$$

with Eqs. B1 and B2 yields the $O(h_x^4)$ central difference formula for $\partial f/\partial x$:

$$\frac{\partial f}{\partial x}(x,y)=\frac{-f(x+2h_x,y)+8f(x+h_x,y)-8f(x-h_x,y)+f(x-2h_x,y)}{12h_x}+O(h_x^4) \tag{B10}$$

Combining Eqs. B1 and B8 yields the $O(h_x^2)$ forward FD formula for $\partial f/\partial x$ (Eq. B11) while combining Eqs. B2 and B9 yields the $O(h_x^2)$ backward FD formula for $\partial f/\partial x$ (Eq. B12):

$$\frac{\partial f}{\partial x}(x,y)=\frac{-f(x+2h_x,y)+4f(x+h_x,y)-3f(x,y)}{2h_x}+O(h_x^2) \tag{B11}$$

$$\frac{\partial f}{\partial x}(x,y)=\frac{3f(x,y)-4f(x-h_x,y)+f(x-2h_x,y)}{2h_x}+O(h_x^2) \tag{B12}$$

$O(h_x^4)$ forward, backward and semi-one-sided formulae for $\partial f/\partial x$ (Eqs. B13-B16) can be derived similarly. These are:

Forward formula

$$\frac{\partial f}{\partial x}(x,y)=\frac{-f(x+4h_x,y)+16f(x+3h_x,y)-36f(x+2h_x,y)+48f(x+h_x,y)-25f(x,y)}{12h_x}+O(h_x^4) \tag{B13}$$

Backward formula

$$\frac{\partial f}{\partial x}(x,y)=\frac{25f(x,y)-48f(x-h_x,y)+36f(x-2h_x,y)-16f(x-3h_x,y)+3f(x-4h_x,y)}{12h_x} + O(h_x^4) \tag{B14}$$

Semi-one-sided forward formula

$$\frac{\partial f}{\partial x}(x,y)=\frac{f(x+3h_x,y)-6f(x+2h_x,y)+18f(x+h_x,y)-10f(x,y)-3f(x-h_x,y)}{12h_x} + O(h_x^4) \tag{B15}$$

Semi-one-sided backward formula

$$\frac{\partial f}{\partial x}(x,y)=\frac{3f(x+h_x,y)+10f(x,y)-18f(x-h_x,y)+6f(x-2h_x,y)+f(x-3h_x,y)}{12h_x} + O(h_x^4) \tag{B16}$$

C Calculation of average concentrations

- **General formula for the dimensionless average concentrations in the viable epidermis and dermis**

The dimensionless average concentration of a permeant in a skin layer α is

$$\hat{\bar{c}}_\alpha = \frac{\int_{\hat{V}_\alpha} \hat{c}_\alpha d\hat{V}_\alpha}{\int_{\hat{V}_\alpha} d\hat{V}_\alpha} \tag{C1}$$

Where $\hat{V}_\alpha$ is the dimensionless volume of skin layer α. Eq. C2 is re-written in cylindrical coordinates, with the limits in the radial direction given by the function $\hat{r} = \hat{f}_{\text{ors}}(\hat{z})$ defining the shape of the outer root sheath and the maximum radius $\hat{r}_{\max}$ and the limits in the axial direction given by the top and bottom axial coordinate of the skin layer α, $\hat{z}_{\max}$ and $\hat{z}_{\min}$:

$$\hat{\bar{c}}_\alpha = \frac{\int_{\hat{z}_{\min}}^{\hat{z}_{\max}} \int_0^{2\pi} \int_{\hat{f}_{\text{ors}}(\hat{z})}^{\hat{r}_{\max}} \hat{c}_\alpha(\hat{r},\hat{z})\,\hat{r}\,\mathrm{d}\hat{r}\,\mathrm{d}\theta\,\mathrm{d}\hat{z}}{\int_{\hat{z}_{\min}}^{\hat{z}_{\max}} \int_0^{2\pi} \int_{\hat{f}_{\text{ors}}(\hat{z})}^{\hat{r}_{\max}} \hat{r}\,\mathrm{d}\hat{r}\,\mathrm{d}\theta\,\mathrm{d}\hat{z}} \tag{C2}$$

Eq. C2 is written in terms of ξ,ζ coordinates using the coordinate transformation equations (Eqs. 11, 12). The change of variable in the integrals of Eq. C2 is obtained using the absolute value of the Jacobian $J(\xi,\zeta)$ as follows:

$$\hat{\bar{c}}_\alpha = \frac{\int_{\hat{z}_{\min}}^{\hat{z}_{\max}} \int_{\hat{f}_{\mathrm{ors}}(\hat{z})}^{\hat{r}_{\max}} \hat{c}_\alpha(\hat{r},\hat{z})\,\hat{r}\,\mathrm{d}\hat{r}\,\mathrm{d}\hat{z}}{\int_{\hat{z}_{\min}}^{\hat{z}_{\max}} \int_{\hat{f}_{\mathrm{ors}}(\hat{z})}^{\hat{r}_{\max}} \hat{r}\,\mathrm{d}\hat{r}\,\mathrm{d}\hat{z}} = \frac{\int_{\zeta_{\min}}^{\zeta_{\max}} \int_{\xi_{\min}}^{\xi_{\max}} \hat{c}_\alpha(\hat{r},\hat{z})\,\hat{r}\,|J(\xi,\zeta)|\,\mathrm{d}\xi\,\mathrm{d}\zeta}{\int_{\zeta_{\min}}^{\zeta_{\max}} \int_{\xi_{\min}}^{\xi_{\max}} \hat{r}\,|J(\xi,\zeta)|\,\mathrm{d}\xi\,\mathrm{d}\zeta}$$

$$= \frac{\int_{\zeta_{\min}}^{\zeta_{\max}} \int_{\xi_{\min}}^{\xi_{\max}} \hat{c}_\alpha(\xi,\zeta)\left\{\xi\left[\hat{r}_{\max} - \hat{f}_{\mathrm{ors}}(\hat{z})\right] + \hat{f}_{\mathrm{ors}}(\hat{z})\right\}\left\|\begin{matrix}\hat{r}_\xi & \hat{r}_\zeta \\ \hat{z}_\xi & \hat{z}_\zeta\end{matrix}\right\|\mathrm{d}\xi\,\mathrm{d}\zeta}{\int_{\zeta_{\min}}^{\zeta_{\max}} \int_{\xi_{\min}}^{\xi_{\max}} \left\{\xi\left[\hat{r}_{\max} - \hat{f}_{\mathrm{ors}}(\hat{z})\right] + \hat{f}_{\mathrm{ors}}(\hat{z})\right\}\left\|\begin{matrix}\hat{r}_\xi & \hat{r}_\zeta \\ \hat{z}_\xi & \hat{z}_\zeta\end{matrix}\right\|\mathrm{d}\xi\,\mathrm{d}\zeta}$$

where we have used Eq. 11 to write $\hat{r}$ in terms of ξ and ζ. Upon evaluation of the determinant of the Jacobian, the average concentration in skin layer α in dimensionless ξ,ζ coordinates is obtained as

$$\hat{\bar{c}}_\alpha(\xi,\zeta) = \frac{\int_{\zeta_{\min}}^{\zeta_{\max}} \int_{\xi_{\min}}^{\xi_{\max}} \hat{c}_\alpha(\xi,\zeta)\left\{\xi\left[\hat{r}_{\max} - \hat{f}_{\mathrm{ors}}(\hat{z})\right] + \hat{f}_{\mathrm{ors}}(\hat{z})\right\}\left[\hat{r}_{\max} - \hat{f}_{\mathrm{ors}}(\hat{z})\right]\mathrm{d}\xi\,\mathrm{d}\zeta}{\int_{\zeta_{\min}}^{\zeta_{\max}} \int_{\xi_{\min}}^{\xi_{\max}} \left\{\xi\left[\hat{r}_{\max} - \hat{f}_{\mathrm{ors}}(\hat{z})\right] + \hat{f}_{\mathrm{ors}}(\hat{z})\right\}\left[\hat{r}_{\max} - \hat{f}_{\mathrm{ors}}(\hat{z})\right]\mathrm{d}\xi\,\mathrm{d}\zeta} \qquad \text{(C3)}$$

- **Application of Eq. C3**

Eq. C3 is applied to the evaluation of the average concentration in the viable epidermis ("ve"), the dermis ("de") and at the hair follicle/skin boundary tissue within the averaging volume defined in section 7.3. As described in that section the averaging volume is bounded by the hair follicle/skin tissue boundary and the inner/outer tissue boundary in

the radial direction and descends from the stratum corneum/viable epidermis boundary to a depth of z = -385 μm within the dermis 2 skin layer of the computational domain.

With the indices i, j describing nodes in the radial and axial direction in the ξ, ζ coordinate system, as explained in section 5.3, the average concentration in the viable epidermis is calculated using Eq. C3 as

$$\hat{\bar{c}}_{ve} = \frac{\int_{\zeta_{j=0}}^{\zeta_{j=j_{ve}}} \int_{\xi_{i=0}}^{\xi_{i=i_{inner/outer}}} \hat{c}_{ve}(\xi_i,\zeta_j)\left\{\xi_i\left[\hat{r}_{max}-\hat{f}_{ors}(\zeta_j)\right]+\hat{f}_{ors}(\zeta_j)\right\}\left[\hat{r}_{max}-\hat{f}_{ors}(\zeta_j)\right]d\xi_i\, d\zeta_j}{\int_{\zeta_{j=j_{ve}}}^{\zeta_{j=0}} \int_{\xi_{i=0}}^{\xi_{i=i_{inner/outer}}} \left\{\xi_i\left[\hat{r}_{max}-\hat{f}_{ors}(\zeta_j)\right]+\hat{f}_{ors}(\zeta_j)\right\}\left[\hat{r}_{max}-\hat{f}_{ors}(\zeta_j)\right]d\xi_i\, d\zeta_j} \tag{C4}$$

where $\xi_{i=i_{in}}$ in the radial node at the inner/outer tissue boundary and $\zeta_{j=j_{ve}}$ in the axial node at the bottom of the epidermis (z = -100 μm).

The averaging volume includes the dermis 1 skin layer of the computational domain as well as the top 85 μm of the dermis 2 skin layer. Eq. C3 is applied to the calculation of an average dermis concentration by separating the dividing the integral in the ζ-direction into two integrals for dermis 1 and dermis 2. Thus Eq. C3 yields

$$\hat{\bar{c}}_{de} = \frac{\int_{\zeta_{j=j_{ve}+j_{de1}}}^{\zeta_{j=j_{ve}}} \int_{\xi_{i=0}}^{\xi_{i=i_{inner/outer}}} \hat{c}_{de1,\,inner}(\xi_i,\zeta_j)\, g(\xi_i,\zeta_j)\, d\xi_i\, d\zeta_j}{\int_{\zeta_{j=j_{ve}+j_{de1}}}^{\zeta_{j=j_{ve}}} \int_{\xi_{i=0}}^{\xi_{i=i_{inner/outer}}} g(\xi_i,\zeta_j)\, d\xi_i\, d\zeta_j + \int_{\zeta_{j=j_{min}}}^{\zeta_{j=j_{ve}+j_{de1}}} \int_{\xi_{i=0}}^{\xi_{i=i_{inner/outer}}} g(\xi_i,\zeta_j)\, d\xi_i\, d\zeta_j}$$

$$+ \frac{\int_{\zeta_{j=j_{min}}}^{\zeta_{j=j_{ve}+j_{de1}}} \int_{\xi_{i=0}}^{\xi_{i=i_{inner/outer}}} \hat{c}_{de2,\,inner}(\xi_i,\zeta_j)\, g(\xi_i,\zeta_j)\, d\xi_i\, d\zeta_j}{\int_{\zeta_{j=j_{ve}+j_{de1}}}^{\zeta_{j=j_{ve}}} \int_{\xi_{i=0}}^{\xi_{i=i_{inner/outer}}} g(\xi_i,\zeta_j)\, d\xi_i\, d\zeta_j + \int_{\zeta_{j=j_{min}}}^{\zeta_{j=j_{ve}+j_{de1}}} \int_{\xi_{i=0}}^{\xi_{i=i_{inner/outer}}} g(\xi_i,\zeta_j)\, d\xi_i\, d\zeta_j} \tag{C5}$$

where we have used $g(\xi_i,\zeta_j)=\{\xi_i\left[\hat{r}_{max}-\hat{f}_{ors}(\zeta_j)\right]+\hat{f}_{ors}(\zeta_j)\}\left[\hat{r}_{max}-\hat{f}_{ors}(\zeta_j)\right]$ for convenience. The subscript $j = j_{min}$ in Eq. C5 denotes the bottom of the averaging region (z = -385 μm). The double integrals in Eqs. C4 and C5 are evaluated numerically using Simpson's composite rule.[127]

- **Dimensionless average concentration at the hair follicle/skin tissue boundary**

The general formula for the average dimensionless concentration at the boundary of the hair follicle and a skin layer α is

$$\hat{\bar{c}}_{hf\,/\,skin,\alpha}=\frac{\int_0^{2\pi}\int_{\hat{z}_{min,\alpha}}^{\hat{z}_{max,\alpha}}\hat{c}_\alpha\left(\hat{r}_{hf/skin,\alpha},\hat{z}\right)d\hat{A}_\alpha}{\int_0^{2\pi}\int_{\hat{z}_{min,\alpha}}^{\hat{z}_{max,\alpha}}d\hat{A}_\alpha} \tag{C6}$$

where dA_α is the differential lateral area element of the infundibulum of the hair follicle in contact with skin layer α. Substituting the non-dimensional form of Eq. D9 (Appendix D) into Eq. C6 yields

$$\hat{\bar{c}}_{hf/skin,\alpha}=\frac{\int_{\hat{z}_{min,\alpha}}^{\hat{z}_{max,\alpha}}\hat{c}_\alpha\left(\hat{r}_{hf/skin,\alpha},\hat{z}\right)\hat{f}_{ors}(\hat{z})\sqrt{1+\left[\hat{f}'_{ors}(\hat{z})\right]^2}\,d\hat{z}}{\int_{\hat{z}_{min,\alpha}}^{\hat{z}_{max,\alpha}}\hat{f}_{ors}(\hat{z})\sqrt{1+\left[\hat{f}'_{ors}(\hat{z})\right]^2}\,d\hat{z}} \tag{C7}$$

Eq. C6 is used to calculate the average concentration at the hair follicle/skin tissue boundary in the viable epidermis and the dermis within the averaging volume defined in section 7.3. Written in ξ, ζ coordinates using the coordinate transformation equations

(Eqs. 11 and 12), the discretized forms of Eq. C6 applied to the viable epidermis and dermis within the averaging volume are

$$\hat{\bar{c}}_{\mathrm{hf/skin,\,ve}} = \frac{\int_{\zeta_{j=j_{ve}}}^{\zeta_{j=0}} \hat{c}_{ve}\left(\xi_{i=0},\zeta_j\right)\hat{f}_{ors}\left(\zeta_j\right)\sqrt{1+\left[\hat{f}'_{ors}\left(\zeta_j\right)\right]^2}\,d\zeta_j}{\int_{\zeta_{j=j_{ve}}}^{\zeta_{j=0}} \hat{f}_{ors}\left(\zeta_j\right)\sqrt{1+\left[\hat{f}'_{ors}\left(\zeta_j\right)\right]^2}\,d\zeta_j} \tag{C8}$$

and

$$\hat{\bar{c}}_{\mathrm{hf/skin,\,de}} = \frac{\int_{\zeta_{j=j_{ve}+j_{de1}}}^{\zeta_{j=j_{ve}}} \hat{c}_{de1}\left(\xi_{i=0},\zeta_j\right)\hat{f}_{ors}\left(\zeta_j\right)\sqrt{1+\left[\hat{f}'_{ors}\left(\zeta_j\right)\right]^2}\,d\zeta_j + \int_{\zeta_{j=j_{min}}}^{\zeta_{j=j_{ve}+j_{de1}}} \hat{c}_{de2}\left(\xi_{i=0},\zeta_j\right)\hat{f}_{ors}\left(\zeta_j\right)\sqrt{1+\left[\hat{f}'_{ors}\left(\zeta_j\right)\right]^2}\,d\zeta_j}{\int_{\zeta_{j=j_{ve}+j_{de1}}}^{\zeta_{j=j_{ve}}} \hat{f}_{ors}\left(\zeta_j\right)\sqrt{1+\left[\hat{f}'_{ors}\left(\zeta_j\right)\right]^2}\,d\zeta_j + \int_{\zeta_{j=j_{min}}}^{\zeta_{j=j_{ve}+j_{de1}}} \hat{f}_{ors}\left(\zeta_j\right)\sqrt{1+\left[\hat{f}'_{ors}\left(\zeta_j\right)\right]^2}\,d\zeta_j} \tag{C9}$$

The integrals in Eqs. C8 and C9 are evaluated numerically using Simpson's composite rule.[127]

- **Tests for the evaluation of the average concentrations**

The calculation of the average concentrations is verified by running tests for the evaluation of the volume integrals which occur in the denominators of Eqs. C4 and C5 and for the area integrals in Eqs. C8 and C9. Since the integrals in the numerators of these equations are calculated in the same way as those in the denominators using

Simpson's composite rule, positive test results for the tests of the volume integrals indicate that the average concentrations are evaluated correctly.

The volumes of the viable epidermis, of dermis 1 and of the section of dermis 2 included in the calculations obtained from Eqs. C4 and C5 are compared to values obtained by assuming the outer root sheath of the hair follicle and the inner/outer boundary within each skin layer α to be linear in z:

$$\hat{f}_{\mathrm{ors},\alpha}(\hat{z}) = \mathrm{a}_\alpha \hat{z} + \mathrm{b}_\alpha \tag{C10}$$

$$\hat{r}_{\mathrm{inner/outer},\alpha}(\hat{z}) = \mathrm{c}_\alpha \hat{z} + \mathrm{d}_\alpha \tag{C11}$$

The constants a_α, b_α, are calculated from the values of $\hat{f}_{\mathrm{ors},\alpha}(\hat{z})$ at the top and bottom surfaces of each skin layer given by the geometrical model of the hair follicle. The constants c_α and d_α are obtained from the values of the radius $\hat{r}_{\mathrm{inner/outer},\alpha}$ at the top and bottom surfaces of each skin layer α, calculated from Eq. 11 for the appropriate values of z. An approximate value of the volume of each averaging region is calculated from subtracting the volume of the infundibular region defined by Eq. C10 from the volume of the region defined by Eq. C11, which includes the infundibular region and the inner region within a given skin layer α. Thus the approximate volumes are given by

$$\hat{V}_{\mathrm{approx},\alpha} = \pi \int_{\hat{z}_{\mathrm{min},\alpha}}^{\hat{z}_{\mathrm{max},\alpha}} \hat{r}^2_{\mathrm{inner/outer}}(\hat{z})\,\mathrm{d}\hat{z} - \pi \int_{\hat{z}_{\mathrm{min},\alpha}}^{\hat{z}_{\mathrm{max},\alpha}} \hat{f}^2_{\mathrm{ors},\alpha}(\hat{z})\,\mathrm{d}\hat{z} \tag{C12}$$

The approximate volume values agree very well with the numerical values of the denominators of Eqs. C4 and C5 multiplied by 2π.

Similarly, the implementation of Eqs. C8 and C9 is tested by setting the function $f_{\text{ors}}(z)$ constant and fitting a curve to the values of the viable epidermis and dermis concentrations at the hair follicle/skin tissue boundary at an arbitrarily chosen time, in order to obtain an expression for the concentration as a function of depth. This test showed that the integrals in Eqs. C8 and C9 are evaluated correctly.

D Differential area element for the hair follicle/skin tissue boundary

The shape of the infundibulum is given by the parametric equation

$$\underline{\boldsymbol{R}} = (x, y, z) = (r\cos\theta, r\sin\theta, z) \tag{D1}$$

where the radius r is given by the shape of the outer boundary of the hair follicle, $f_{\text{ors}}(z)$. Let $u = r$ and $v = \theta$ be the curvilinear coordinates representing the surface of the infundibulum. The general formula for a differential element dA of a surface S defined parametrically by $\underline{\boldsymbol{R}}(u,v) = x(u,v)\underline{\mathbf{i}} + y(u,v)\underline{\mathbf{j}} + z(u,v)\underline{\mathbf{k}}$ is (Figure D-1) is[122]

$$\mathrm{d}A = \left\| \underline{\boldsymbol{R}}_{\mathrm{u}} \times \underline{\boldsymbol{R}}_{\mathrm{v}} \right\| \mathrm{d}u\, \mathrm{d}v \tag{D2}$$

or

$$\mathrm{d}A = \left\| \frac{\mathrm{d}\underline{\boldsymbol{x}}}{\mathrm{d}u} \times \frac{\mathrm{d}\underline{\boldsymbol{x}}}{\mathrm{d}v} \right\| \mathrm{d}u\, \mathrm{d}v \tag{D3}$$

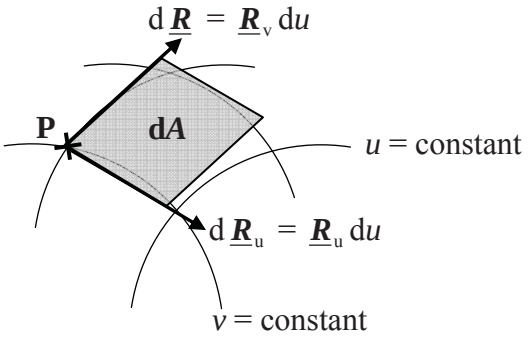


Figure D-1: Area element dA. Diagram adapted from [122].

The individual terms in Eq. D3 are

$$\underline{\boldsymbol{x}} = \underline{\mathbf{i}}\, f_{\text{ors}}(u)\cos v + \underline{\mathbf{j}}\, f_{\text{ors}}(u)\sin v + \underline{\mathbf{k}}\, u \tag{D4}$$

$$\frac{\mathrm{d}\underline{\boldsymbol{x}}}{\mathrm{d}u} = \underline{\mathbf{i}}\, f'_{\text{ors}}(u)\cos v + \underline{\mathbf{j}}\, f'_{\text{ors}}(u)\sin v + \underline{\mathbf{k}} \tag{D5}$$

$$\frac{\mathrm{d}\underline{\boldsymbol{x}}}{\mathrm{d}v} = -\underline{\mathbf{i}}\, f_{\text{ors}}(u)\sin v + \underline{\mathbf{j}}\, f_{\text{ors}}(u)\cos v \tag{D6}$$

The cross product in Eq. D3 is

$$\frac{\mathrm{d}\underline{\boldsymbol{x}}}{\mathrm{d}u} \times \frac{\mathrm{d}\underline{\boldsymbol{x}}}{\mathrm{d}v} = \underline{\mathbf{i}}\left[- f_{\text{ors}}(u)\cos v\right] + \underline{\mathbf{j}}\left[- f_{\text{ors}}(u)\sin v\right] + \underline{\mathbf{k}}\left[f'_{\text{ors}}(u)\mathrm{f}(u)\cos^2 v + f'_{\text{ors}}(u)\, f_{\text{ors}}(u)\sin^2 v\right]$$

$$= \underline{\mathbf{k}}\, f'_{\text{ors}}(u)\, f_{\text{ors}}(u) - \left(\underline{\mathbf{i}}\cos v + \underline{\mathbf{j}}\sin v\right) f_{\text{ors}}(u)$$

$$= f_{\text{ors}}(u)\left(-\underline{\mathbf{i}}_{\mathbf{r}} + \underline{\mathbf{k}}\, f'_{\text{ors}}(u)\right) \tag{D7}$$

where we have used the fact that the orthonormal basis vector $\underline{\mathbf{i}}_{\mathbf{r}}$ in cylindrical coordinates can be written in terms of the Cartesian basis vectors $\underline{\mathbf{i}}$, $\underline{\mathbf{j}}$, $\underline{\mathbf{k}}$, as follows[122]:

$$\underline{\mathbf{i}}_{\mathbf{r}} = \left(\underline{\mathbf{i}}_{\mathbf{r}} \cdot \underline{\mathbf{i}}\right)\underline{\mathbf{i}} + \left(\underline{\mathbf{i}}_{\mathbf{r}} \cdot \underline{\mathbf{j}}\right)\underline{\mathbf{j}} + \left(\underline{\mathbf{i}}_{\mathbf{r}} \cdot \underline{\mathbf{k}}\right)\underline{\mathbf{k}}$$

$$= \left\|\underline{\mathbf{i}}_{\mathbf{r}}\right\| \left\|\underline{\mathbf{i}}_{\mathbf{r}}\right\| (\cos v)\underline{\mathbf{i}} + \left\|\underline{\mathbf{i}}_{\mathbf{r}}\right\| \left\|\underline{\mathbf{j}}\right\| \left[\cos\left(\frac{\pi}{2} - v\right)\right]\underline{\mathbf{j}} + \left\|\underline{\mathbf{i}}_{\mathbf{r}}\right\| \left\|\underline{\mathbf{k}}\right\| \left(\cos\frac{\pi}{2}\right)\underline{\mathbf{k}}$$

$$= \underline{\mathbf{i}}\cos v + \underline{\mathbf{j}}\sin v \tag{D8}$$

Substituting Eq. D7 into Eq. D3 and replacing the parameters u, v by the cylindrical coordinates yields

$$\mathrm{d}A = \sqrt{f_{\mathrm{ors}}^2(u) + f_{\mathrm{ors}}^2(u)\left[f'_{\mathrm{ors}}(u)\right]^2}\ \mathrm{d}u\ \mathrm{d}v$$

$$= f_{\mathrm{ors}}(z)\sqrt{1+\left[f'_{\mathrm{ors}}(z)\right]^2}\ \mathrm{d}z\ \mathrm{d}\theta \qquad \text{(D9)}$$

E Fortran code implementing the model of diffusion through and near a hair follicle

E.1 Main program

```
      program main
      implicit double precision (a - z)
C
      call readinput
      call xizetavalues
      call setup_geom
      call try
      call plotmesh
      call derivcoeffs
      call boundaryfunctions
      call evolve
C
      stop
      end
C
C
      subroutine readinput
      implicit double precision (a - z)
      integer ioption1, ioption2, iin, iout
      integer jed, jde1, jde2, jhd
C
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
      common /thicknesses/ hd_ed, hd_de1, hd_de2, hd_hd
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
      common /param/ deltat, deltah, ratek_edi, ratek_edo,
     1       ratek_de1i, ratek_de1o, ratek_de2i, ratek_de2o,
     1       ratek_hdi, ratek_hdo
C
      open (unit = 22, file = 'tparam.txt', status = 'old')
      read(22,*) deltat, deltah, ratek_edi, ratek_edo, ratek_de1i,
     1           ratek_de1o, ratek_de2i, ratek_de2o, ratek_hdi,
     1           ratek_hdo
      close(22)
C
      print*, 'Which value for datamesh.txt values 1 or 2?'
      read*, ioption1
      print*, 'ok'
C
      if (ioption1 .eq. 1) then
```

```
         open (unit = 10, file = 'datamesh1.txt', status = 'old')
         read (10,*) iin, iout, xi_in, rd_max
         read (10,*) jed, jde1, jde2, jhd, hd_ed, hd_de1,
     1               hd_de2, hd_hd
         close (10)
       else if (ioption1 .eq. 2) then
         open (unit = 9, file = 'datamesh2.txt', status = 'old')
         read (9,*) iin, iout, xi_in, rd_max
         read (9,*) jed, jde1, jde2, jhd, hd_ed, hd_de1,
     1               hd_de2, hd_hd
         close (9)
       end if
C
       print*, 'Which value of option2 for boundary data, 1, 2, or 3?'
       read*, ioption2
       print*, 'ok'
C
       if (ioption2 .eq. 1) then
         open (unit = 69, file = 'pcparam1.txt')
         read(69,*) L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
         close(69)
       else if (ioption2 .eq. 2) then
         open (unit = 70, file = 'pcparam2.txt')
         read(70,*) L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Dsebum
         close(70)
       end if
C
       return
       end
C
C
       subroutine xizetavalues
       implicit double precision (a - z)
       integer iin, iout, jed, jde1, jde2, jhd
       integer i, idim, j, jdim
       parameter (idim = 500, jdim = 500)
C
       dimension xia(0:idim), zda(0:jdim)
C
       common /xizetaval/ xia, zda
       common /mesh_i/ xi_in, rd_max, iin, iout
       common /mesh_j/ jed, jde1, jde2, jhd
       common /steps_radial/ hxi_in, hxi_out
       common /steps_axial/  hzd, hzd1, hzd2, hzd3
       common /thicknesses/ hd_ed, hd_de1, hd_de2, hd_hd
       common /param/ deltat, deltah, ratek_edi, ratek_edo,
     1       ratek_de1i, ratek_de1o, ratek_de2i, ratek_de2o,
     1       ratek_hdi, ratek_hdo
C
C ****************
C Radial direction
C ****************
C
```

```
C Inner tissue
C
      hxi_in = xi_in / dble(iin)
       do 100, i = 0, iin
            xia(i) = hxi_in * dble(i)
100    continue
C
C Outer tissue
C
      hxi_out = (1.0d0 - xi_in) / dble(iout)
       do 150, i = iin + 1, iin + iout
            xia(i) = xi_in + hxi_out * dble(i-iin)
150    continue
C
C *************************
C Epidermis, axial direction
C *************************
C
      hzd = hd_ed / dble(jed)
       do 200, j = 0, jed
            zda(j) = -hzd * dble(j)
200    continue
C
C *************************
C Dermis 1, axial direction
C *************************
C
      j = jed
      zed = zda(j)
      hzd1 = hd_de1 / dble(jde1)
        do 250, j = jed + 1, jed + jde1
           zda(j) = zed + hzd1 * (jed - j)
250     continue
        print*, hzd1*(jed+1)+ zed - hzd1
C
C *************************
C Dermis 2, axial direction
C *************************
C
      j = jed + jde1
      zde1 = zda(j)
      hzd2 = hd_de2 / dble(jde2)
      do 350, j = jed + jde1 + 1, jed + jde1 + jde2
         zda(j) = zde1 + hzd2 * (jed + jde1 - j)
350   continue
      print*, hzd2*(jed+jde1+1) + zde1 - hzd2
C
C *************************
C Hypodermis, axial direction
C *************************
C
      j = jed + jde1 + jde2
      zde2 = zda(j)
      hzd3 = hd_hd / dble(jhd)
      do 400, j = jed + jde1 + jde2 + 1, jed + jde1 + jde2 + jhd
         zda(j) = zde2 + hzd3 * (jed + jde1 + jde2- j)
400   continue
```

```
      print*, hzd3*(jed+jde1+jde2+1) + zde2 - hzd3
C
      open (unit = 96, file = 'xizeta.txt')
C
      do 500, i = 0, iin + iout
         do 450, j = 0, jed + jde1 + jde2 + jhd
            write (96, 9100) i, j, xia(i), zda(j)
450      continue
500   continue
C
C Formats
C
9000  format (i3, t5, i3, t10, d23.16)
9100  format (i3, t5, i3, t10, d23.16, t40, d23.16)
C
      return
      end
C
C
      subroutine plotmesh
      implicit double precision (a - z)
      integer i, j, iin, iout, jed, jde1, jde2, jhd
      integer idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      dimension fval(0:idim), dfval(0:idim)
C
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /f_values/ fval, dfval
C
      open (unit = 53, file = 'outmesh.txt')
      write (53, 9000)
C
C plot mesh, vertical curves
C
       write (53, 9100)
       do 110, i = 0, iin + iout
            do 100, j = 0, jed + jde1 + jde2 + jhd
               zd = zda(j)
               rd = fval(j) + xia(i) * (rd_max - fval(j))
               write (53, 9200) rd, zd
100         continue
            write (53, 9300)
            write (53, 9100)
110    continue
       write (53, 9300)
C
C plot mesh, horizontal curves
C
       write (53, 9100)
       do 130, j = 0, jed + jde1 + jde2 + jhd
            zd = zda(j)
            do 120, i = 0, iin + iout
               rd = fval(j) + xia(i) * (rd_max - fval(j))
```

```
               write (53, 9200) rd, zd
120         continue
            write (53, 9300)
            write (53, 9100)
130    continue
       write (53, 9300)
C
C FORMATS
C
9000   format ('0.0d0 50.0d0 10.0d0' / '-50.0d0 0.0d0 10.0d0')
9100   format ('solid')
9200   format (d23.16, 3x, d23.16)
9300   format ('1.0d32 0.0d0')
C
C
       return
       end
C
C
      subroutine derivcoeffs
      implicit double precision (a - z)
      integer i, j, iin, iout, jed, jde1, jde2, jhd
      integer idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      dimension a_20edi(0:idim,0:jdim), a_10edi(0:idim,0:jdim)
      dimension a_11edi(0:idim,0:jdim), a_02edi(0:idim,0:jdim)
      dimension a_01edi(0:idim,0:jdim)
      dimension a_20de1i(0:idim,0:jdim), a_10de1i(0:idim,0:jdim)
      dimension a_11de1i(0:idim,0:jdim), a_02de1i(0:idim,0:jdim)
      dimension a_01de1i(0:idim,0:jdim)
      dimension a_20de2i(0:idim,0:jdim), a_10de2i(0:idim,0:jdim)
      dimension a_11de2i(0:idim,0:jdim), a_02de2i(0:idim,0:jdim)
      dimension a_01de2i(0:idim,0:jdim)
      dimension a_20hdi(0:idim,0:jdim), a_10hdi(0:idim,0:jdim)
      dimension a_11hdi(0:idim,0:jdim), a_02hdi(0:idim,0:jdim)
      dimension a_01hdi(0:idim,0:jdim)
C
      dimension a_20edo(0:idim,0:jdim), a_10edo(0:idim,0:jdim)
      dimension a_11edo(0:idim,0:jdim), a_02edo(0:idim,0:jdim)
      dimension a_01edo(0:idim,0:jdim)
      dimension a_20de1o(0:idim,0:jdim), a_10de1o(0:idim,0:jdim)
      dimension a_11de1o(0:idim,0:jdim), a_02de1o(0:idim,0:jdim)
      dimension a_01de1o(0:idim,0:jdim)
      dimension a_20de2o(0:idim,0:jdim), a_10de2o(0:idim,0:jdim)
      dimension a_11de2o(0:idim,0:jdim), a_02de2o(0:idim,0:jdim)
      dimension a_01de2o(0:idim,0:jdim)
      dimension a_20hdo(0:idim,0:jdim), a_10hdo(0:idim,0:jdim)
      dimension a_11hdo(0:idim,0:jdim), a_02hdo(0:idim,0:jdim)
      dimension a_01hdo(0:idim,0:jdim)
C
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
```

```
      common /coeffs/ a_20edi, a_10edi, a_02edi, a_01edi, a_11edi,
     1       a_20de1i, a_10de1i, a_02de1i, a_01de1i, a_11de1i,
     1       a_20de2i, a_10de2i, a_02de2i, a_01de2i, a_11de2i,
     1       a_20hdi, a_10hdi, a_02hdi, a_01hdi, a_11hdi,
     1       a_20edo, a_10edo, a_02edo, a_01edo, a_11edo,
     1       a_20de1o, a_10de1o, a_02de1o, a_01de1o, a_11de1o,
     1       a_20de2o, a_10de2o, a_02de2o, a_01de2o, a_11de2o,
     1       a_20hdo, a_10hdo, a_02hdo, a_01hdo, a_11hdo
        common /param/ deltat, deltah, ratek_edi, ratek_edo,
     1       ratek_de1i, ratek_de1o, ratek_de2i, ratek_de2o,
     1       ratek_hdi, ratek_hdo
C
C Derivative coefficients
C ```````````````````````
C
      do 560, i = 0, iin
         do 550, j = 0, jed
            a_20edi(i,j) = a20edi(xia(i),zda(j))
            a_10edi(i,j) = a10edi(xia(i),zda(j))
            a_02edi(i,j) = a02edi(xia(i),zda(j))
            a_01edi(i,j) = a01edi(xia(i),zda(j))
            a_11edi(i,j) = a11edi(xia(i),zda(j))
550      continue
560   continue
C
      do 565, i = iin, iin + iout
         do 555, j = 0, jed
            a_20edo(i,j) = a20edo(xia(i),zda(j))
            a_10edo(i,j) = a10edo(xia(i),zda(j))
            a_02edo(i,j) = a02edo(xia(i),zda(j))
            a_01edo(i,j) = a01edo(xia(i),zda(j))
            a_11edo(i,j) = a11edo(xia(i),zda(j))
555      continue
565   continue
C
      do 580, i = 0, iin
         do 570, j = jed, jed + jde1
            a_20de1i(i,j) = a20de1i(xia(i),zda(j))
            a_10de1i(i,j) = a10de1i(xia(i),zda(j))
            a_02de1i(i,j) = a02de1i(xia(i),zda(j))
            a_01de1i(i,j) = a01de1i(xia(i),zda(j))
            a_11de1i(i,j) = a11de1i(xia(i),zda(j))
570      continue
580   continue
C
      do 585, i = iin, iin + iout
         do 575, j = jed, jed + jde1
            a_20de1o(i,j) = a20de1o(xia(i),zda(j))
            a_10de1o(i,j) = a10de1o(xia(i),zda(j))
            a_02de1o(i,j) = a02de1o(xia(i),zda(j))
            a_01de1o(i,j) = a01de1o(xia(i),zda(j))
            a_11de1o(i,j) = a11de1o(xia(i),zda(j))
575      continue
585   continue
C
      do 600, i = 0, iin
         do 590, j = jed + jde1, jed + jde1 + jde2
```

```
            a_20de2i(i,j) = a20de2i(xia(i),zda(j))
            a_10de2i(i,j) = a10de2i(xia(i),zda(j))
            a_02de2i(i,j) = a02de2i(xia(i),zda(j))
            a_01de2i(i,j) = a01de2i(xia(i),zda(j))
            a_11de2i(i,j) = a11de2i(xia(i),zda(j))
590      continue
600   continue
C
      do 605, i = iin, iin + iout
         do 595, j = jed + jde1, jed + jde1 + jde2
            a_20de2o(i,j) = a20de2o(xia(i),zda(j))
            a_10de2o(i,j) = a10de2o(xia(i),zda(j))
            a_02de2o(i,j) = a02de2o(xia(i),zda(j))
            a_01de2o(i,j) = a01de2o(xia(i),zda(j))
            a_11de2o(i,j) = a11de2o(xia(i),zda(j))
595      continue
605   continue
C
      do 620, i = 0, iin
         do 610, j = jed + jde1 + jde2, jed + jde1 + jde2 + jhd
            a_20hdi(i,j) = a20hdi(xia(i),zda(j))
            a_10hdi(i,j) = a10hdi(xia(i),zda(j))
            a_02hdi(i,j) = a02hdi(xia(i),zda(j))
            a_01hdi(i,j) = a01hdi(xia(i),zda(j))
            a_11hdi(i,j) = a11hdi(xia(i),zda(j))
610      continue
620   continue
C
      do 625, i = iin, iin + iout
         do 615, j = jed + jde1 + jde2, jed + jde1 + jde2 + jhd
            a_20hdo(i,j) = a20hdo(xia(i),zda(j))
            a_10hdo(i,j) = a10hdo(xia(i),zda(j))
            a_02hdo(i,j) = a02hdo(xia(i),zda(j))
            a_01hdo(i,j) = a01hdo(xia(i),zda(j))
            a_11hdo(i,j) = a11hdo(xia(i),zda(j))
615      continue
625   continue
C
C Formats
C
9000  format (i3, t5, i3, t10, d23.16)
C
      return
      end
C
C
      subroutine boundaryfunctions
      implicit double precision (a - z)
      integer i, j, idim, jdim, iin, iout,
     1        jed, jde1, jde2, jhd
      parameter (idim = 500, jdim = 500)
C
      dimension Bedl1(1:jdim)
      dimension Bedl2(1:jdim)
      dimension Bedl3(1:jdim)
      dimension Bedl4(1:jdim)
      dimension Bde1l1(1:jdim)
```

```
      dimension Bde1l2(1:jdim)
      dimension Bde1l3(1:jdim)
      dimension Bde1l4(1:jdim)
      dimension Bde2l1(1:jdim)
      dimension Bde2l2(1:jdim)
      dimension Bde2l3(1:jdim)
      dimension Bde2l4(1:jdim)
      dimension Bhdl1(1:jdim)
      dimension Bhdl2(1:jdim)
      dimension Bhdl3(1:jdim)
      dimension Bhdl4(1:jdim)
C
      dimension Bedio1i(0:jdim)
      dimension Bedio1o(0:jdim)
      dimension Bedio2i(0:jdim)
      dimension Bedio2o(0:jdim)
      dimension Bde1io1i(0:jdim)
      dimension Bde1io1o(0:jdim)
      dimension Bde1io2i(0:jdim)
      dimension Bde1io2o(0:jdim)
      dimension Bde2io1i(0:jdim)
      dimension Bde2io1o(0:jdim)
      dimension Bde2io2i(0:jdim)
      dimension Bde2io2o(0:jdim)
      dimension Bhdio1i(0:jdim)
      dimension Bhdio1o(0:jdim)
      dimension Bhdio2i(0:jdim)
      dimension Bhdio2o(0:jdim)
C
      dimension Bsced1i(0:idim)
      dimension Bsced1o(0:idim)
      dimension Bsced2i(0:idim)
      dimension Bsced2o(0:idim)
      dimension Bsced3i(0:idim)
      dimension Bsced3o(0:idim)
      dimension Bsced4(0:idim)
C
      dimension Bedde11i(0:idim)
      dimension Bedde11o(0:idim)
      dimension Bedde12i(0:idim)
      dimension Bedde12o(0:idim)
      dimension Bedde13i(0:idim)
      dimension Bedde13o(0:idim)
      dimension Bedde14i(0:idim)
      dimension Bedde14o(0:idim)
C
      dimension Bde1de21i(0:idim)
      dimension Bde1de21o(0:idim)
      dimension Bde1de22i(0:idim)
      dimension Bde1de22o(0:idim)
      dimension Bde1de23i(0:idim)
      dimension Bde1de23o(0:idim)
      dimension Bde1de24i(0:idim)
      dimension Bde1de24o(0:idim)
C
      dimension Bde2hd1i(0:idim)
      dimension Bde2hd1o(0:idim)
```

```
      dimension Bde2hd2i(0:idim)
      dimension Bde2hd2o(0:idim)
      dimension Bde2hd3i(0:idim)
      dimension Bde2hd3o(0:idim)
      dimension Bde2hd4i(0:idim)
      dimension Bde2hd4o(0:idim)
C
      dimension Bhdsub1i(0:idim)
      dimension Bhdsub1o(0:idim)
      dimension Bhdsub2i(0:idim)
      dimension Bhdsub2o(0:idim)
      dimension Bhdsub3i(0:idim)
      dimension Bhdsub3o(0:idim)
      dimension Bhdsub4(0:idim)
C
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /leftboundary/ Bedl1, Bedl2, Bedl3, Bedl4,
     1  Bde1l1, Bde1l2, Bde1l3, Bde1l4,
     1  Bde2l1, Bde2l2, Bde2l3, Bde2l4,
     1  Bhdl1, Bhdl2, Bhdl3, Bhdl4
      common /topboundary/ Bsced1i, Bsced1o,
     1  Bsced2i, Bsced2o, Bsced3i, Bsced3o, Bsced4
      common /inoutboundary/ Bedio1i, Bedio1o, Bedio2i, Bedio2o,
     1  Bde1io1i, Bde1io1o, Bde1io2i, Bde1io2o,
     1  Bde2io1i, Bde2io1o, Bde2io2i, Bde2io2o,
     1  Bhdio1i, Bhdio1o, Bhdio2i, Bhdio2o
      common /edde1boundary/ Bedde11i, Bedde11o,
     1  Bedde12i, Bedde12o, Bedde13i, Bedde13o, Bedde14i, Bedde14o
      common /de1de2boundary/ Bde1de21i, Bde1de21o,
     1  Bde1de22i, Bde1de22o, Bde1de23i, Bde1de23o, Bde1de24i, Bde1de24
      common /de2hdboundary/ Bde2hd1i, Bde2hd1o,
     1  Bde2hd2i, Bde2hd2o, Bde2hd3i, Bde2hd3o, Bde2hd4i, Bde2hd4o
      common /bottom/ Bhdsub1i, Bhdsub1o, Bhdsub2i, Bhdsub2o,
     1  Bhdsub3i, Bhdsub3o, Bhdsub4
C
C Left boundary
C
      i = 0
      do 1000, j = 1, jed - 1
         Bedl1(j) = f_Bedl1(i,j)
         Bedl2(j) = f_Bedl2(i,j)
         Bedl3(j) = f_Bedl3(i,j)
         Bedl4(j) = f_Bedl4(i,j)
1000  continue
C
      do 1010, j = jed, jed + jde1
         Bde1l1(j) = f_Bde1l1(i,j)
         Bde1l2(j) = f_Bde1l2(i,j)
         Bde1l3(j) = f_Bde1l3(i,j)
         Bde1l4(j) = f_Bde1l4(i,j)
1010  continue
C
      do 1020, j = jed + jde1, jed + jde1 + jde2
         Bde2l1(j) = f_Bde2l1(i,j)
         Bde2l2(j) = f_Bde2l2(i,j)
         Bde2l3(j) = f_Bde2l3(i,j)
```

```
         Bde2l4(j) = f_Bde2l4(i,j)
1020  continue
C
      do 1030, j = jed + jde1 + jde2, jed + jde1 + jde2 + jhd
         Bhdl1(j) = f_Bhdl1(i,j)
         Bhdl2(j) = f_Bhdl2(i,j)
         Bhdl3(j) = f_Bhdl3(i,j)
         Bhdl4(j) = f_Bhdl4(i,j)
1030  continue
C
C Inner/outer region boundary
C
      i = iin
      do 1040, j = 0, jed
         Bedio1i(j) = f_Bedio1i(i,j)
         Bedio1o(j) = f_Bedio1o(i,j)
         Bedio2i(j) = f_Bedio2i(i,j)
         Bedio2o(j) = f_Bedio2o(i,j)
1040  continue
C
      do 1050, j = jed, jed + jde1
         Bde1io1i(j) = f_Bde1io1i(i,j)
         Bde1io1o(j) = f_Bde1io1o(i,j)
         Bde1io2i(j) = f_Bde1io2i(i,j)
         Bde1io2o(j) = f_Bde1io2o(i,j)
1050  continue
C
      do 1060, j = jed + jde1, jed + jde1 + jde2
         Bde2io1i(j) = f_Bde2io1i(i,j)
         Bde2io1o(j) = f_Bde2io1o(i,j)
       Bde2io2i(j) = f_Bde2io2i(i,j)
         Bde2io2o(j) = f_Bde2io2o(i,j)
1060  continue
C
      do 1070, j = jed + jde1 + jde2, jed + jde1 + jde2 + jhd
         Bhdio1i(j) = f_Bhdio1i(i,j)
         Bhdio1o(j) = f_Bhdio1o(i,j)
       Bhdio2i(j) = f_Bhdio2i(i,j)
         Bhdio2o(j) = f_Bhdio2o(i,j)
1070  continue
C
C Ed top boundary
C
      j = 0
      do 1080, i = 0, iin
         Bsced1i(i) = f_Bsced1i(i,j)
         Bsced2i(i) = f_Bsced2i(i,j)
         Bsced3i(i) = f_Bsced3i(i,j)
         Bsced4(i) = f_Bsced4(i,j)
1080  continue
C
      do 1090, i = iin, iin + iout
         Bsced1o(i) = f_Bsced1o(i,j)
         Bsced2o(i) = f_Bsced2o(i,j)
         Bsced3o(i) = f_Bsced3o(i,j)
         Bsced4(i) = f_Bsced4(i,j)
1090  continue
```

```
C
C Ed/De1 boundary
C
      j = jed
      do 1100, i = 0, iin
         Bedde11i(i) = f_Bedde11i(i,j)
         Bedde12i(i) = f_Bedde12i(i,j)
         Bedde13i(i) = f_Bedde13i(i,j)
         Bedde14i(i) = f_Bedde14i(i,j)
1100  continue
C
      do 1110, i = iin , iin + iout
         Bedde11o(i) = f_Bedde11o(i,j)
         Bedde12o(i) = f_Bedde12o(i,j)
         Bedde13o(i) = f_Bedde13o(i,j)
         Bedde14o(i) = f_Bedde14o(i,j)
1110  continue
C
C De1/De2 boundary
C
      j = jed + jde1
      do 1120, i = 0, iin
         Bde1de21i(i) = f_Bde1de21i(i,j)
         Bde1de22i(i) = f_Bde1de22i(i,j)
         Bde1de23i(i) = f_Bde1de23i(i,j)
         Bde1de24i(i) = f_Bde1de24i(i,j)
1120  continue
C
      do 1130, i = iin , iin + iout
         Bde1de21o(i) = f_Bde1de21o(i,j)
         Bde1de22o(i) = f_Bde1de22o(i,j)
         Bde1de23o(i) = f_Bde1de23o(i,j)
         Bde1de24o(i) = f_Bde1de24o(i,j)
1130  continue
C
C De2/Hd boundary
C
      j = jed + jde1 + jde2
      do 1140, i = 0, iin
         Bde2hd1i(i) = f_Bde2hd1i(i,j)
         Bde2hd2i(i) = f_Bde2hd2i(i,j)
         Bde2hd3i(i) = f_Bde2hd3i(i,j)
         Bde2hd4i(i) = f_Bde2hd4i(i,j)
1140  continue
C
      do 1150, i = iin , iin + iout
         Bde2hd1o(i) = f_Bde2hd1o(i,j)
         Bde2hd2o(i) = f_Bde2hd2o(i,j)
         Bde2hd3o(i) = f_Bde2hd3o(i,j)
         Bde2hd4o(i) = f_Bde2hd4o(i,j)
1150  continue
C
C Hd bottom boundary
C
      j = jed + jde1 + jde2 + jhd
      do 1160, i = 0, iin
         Bhdsub1i(i) = f_Bhdsub1i(i,j)
```

```
         Bhdsub2i(i) = f_Bhdsub2i(i,j)
         Bhdsub3i(i) = f_Bhdsub3i(i,j)
         Bhdsub4(i) = f_Bhdsub4(i,j)
1160  continue
C
      do 1170, i = iin, iin + iout
         Bhdsub1o(i) = f_Bhdsub1o(i,j)
         Bhdsub2o(i) = f_Bhdsub2o(i,j)
         Bhdsub3o(i) = f_Bhdsub3o(i,j)
         Bhdsub4(i) = f_Bhdsub4(i,j)
1170  continue
C
      return
      end
C
      subroutine try
      implicit double precision (a - z)
      integer idim, jdim, j, jed, jde1, jde2, jhd
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      dimension fval(0:idim), dfval(0:idim)
      dimension fcut(0:jdim)
C
      common /xizetaval/ xia, zda
      common /mesh_j/ jed, jde1, jde2, jhd
      common /f_values/ fval, dfval
      common /cuticle/ fcut
C
      open (unit = 97, file = 'fvalues.txt')
C
      write (97,9000)
      do 100, j = 0, jed + jde1 + jde2 + jhd
         zeta = zda(j)
         fval(j) = fd_outer(zeta)
         dfval(j) = dfd_outer(zeta)
         fcut(j) = fd_cu(zeta)
C
         write (97, 9100) zeta, fval(j), dfval(j), fcut(j)
C
100   continue
C
9000  format ('zeta',3x,'fd_outer',3x,'dfd_outer',3x,
     1        'fd_cut')
9100  format (d23.16, 2x, d23.16, 2x, d23.16, 2x, d23.16)
C
      return
      end
C
C
C**********************************************************************
C
      subroutine concentrationarrays
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd
      integer i, idim, j, jdim
      parameter (idim = 500, jdim = 500)
```

```
C
      dimension xia(0:idim), zda(0:jdim)
      dimension c_edi(0:idim,0:jdim)
      dimension c_edo(0:idim,0:jdim)
      dimension c_de1i(0:idim,0:jdim)
      dimension c_de1o(0:idim,0:jdim)
      dimension c_de2i(0:idim,0:jdim)
      dimension c_de2o(0:idim,0:jdim)
      dimension c_hdi(0:idim,0:jdim)
      dimension c_hdo(0:idim,0:jdim)
C
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /iconcarrays/ c_edi, c_de1i, c_de2i, c_hdi
      common /oconcarrays/ c_edo, c_de1o, c_de2o, c_hdo
C
      open (unit = 14, file = 'diagnconc.txt')
      write(14,7000)
C
C Ed inner tissue
C ```````````````
      do 1050, i = 0, iin
         do 1000, j = 0, jed
            c_edi(i,j) = c(xia(i),zda(j))
            write(14, 8500) i, j, xia(i), zda(j), c_edi(i,j)
1000     continue
1050  continue
C
      write(14, 7050)
C
C Ed outer tissue
C ```````````````
      do 1150, i = iin, iin + iout
         do 1100, j = 0, jed
            c_edo(i,j) = c(xia(i),zda(j))
            write(14, 8500) i, j, xia(i), zda(j), c_edo(i,j)
1100     continue
1150  continue
C
      write(14,7100)
C
C De1 inner tissue
C ```````````````
      do 1250, i = 0, iin
         do 1200, j = jed, jed + jde1
            c_de1i(i,j) = c(xia(i),zda(j))
            write(14, 8500) i, j, xia(i), zda(j), c_de1i(i,j)
1200     continue
1250  continue
C
      write(14,7150)
C
C De1 outer tissue
C ```````````````
      do 1350, i = iin, iin + iout
         do 1300, j = jed, jed + jde1
```

```
            c_de1o(i,j) = c(xia(i),zda(j))
            write(14, 8500) i, j, xia(i), zda(j), c_de1o(i,j)
1300     continue
1350  continue
C
      write(14,7200)
C
C De2 inner tissue
C ````````````````
      do 1450, i = 0, iin
         do 1400, j = jed + jde1, jed + jde1 + jde2
            c_de2i(i,j) = c(xia(i),zda(j))
            write(14, 8500) i, j, xia(i), zda(j), c_de2i(i,j)
1400     continue
1450  continue
C
      write(14,7250)
C
C De2 outer tissue
C ````````````````
      do 1550, i = iin, iin + iout
         do 1500, j = jed + jde1, jed + jde1 + jde2
            c_de2o(i,j) = c(xia(i),zda(j))
            write(14, 8500) i, j, xia(i), zda(j), c_de2o(i,j)
1500     continue
1550  continue
C
      write(14,7300)
C
C Hd inner tissue
C ````````````````
      do 1650, i = 0, iin
         do 1600, j = jed + jde1 + jde2, jed + jde1 + jde2 + jhd
            c_hdi(i,j) = c(xia(i),zda(j))
            write(14, 8500) i, j, xia(i), zda(j), c_hdi(i,j)
1600     continue
1650  continue
C
      write(14,7350)
C
C Hd outer tissue
C ````````````````
      do 1750, i = iin, iin + iout
         do 1700, j = jed + jde1 + jde2, jed + jde1 + jde2 + jhd
            c_hdo(i,j) = c(xia(i),zda(j))
            write(14, 8500) i, j, xia(i), zda(j), c_hdo(i,j)
1700     continue
1750  continue
C
C Formats
C
7000  format ('Epidermis - inner tissue', 2(/), t3, 'i', t8, 'j',
     1       t29, 'xia(i)', t56, 'zda(j)', t65, 'c_edi')
7050  format (/, 'Epidermis - outer tissue', 2(/), t3, 'i', t8, 'j',
     1       t29, 'xia(i)', t56, 'zda(j)', t65, 'c_edo')
7100  format ('Dermis 1 - inner tissue', 2(/), t3, 'i', t8, 'j',
     1       t29, 'xia(i)', t56, 'zda(j)', t65,
```

```
     1       'c_de1i', t113, 'd20', t141, 'd10',
     1       t168, 'd02', t195, 'd01', t222, 'd11')
7150  format (/, 'Dermis 1 - outer tissue', 2(/), t3, 'i', t8, 'j',
     1       t29, 'xia(i)', t56, 'zda(j)', t65,
     1       'c_de1o', t113, 'd20', t141, 'd10',
     1       t168, 'd02', t195, 'd01', t222, 'd11')
7200  format (/, 'Dermis 2 - inner tissue', 2(/), t3, 'i', t8, 'j',
     1       t29, 'xia(i)', t56, 'zda(j)', t65,
     1       'c_de2i', t113, 'd20', t141, 'd10',
     1       t168, 'd02', t195, 'd01', t222, 'd11')
7250  format (/, 'Dermis 2 - outer tissue', 2(/), t3, 'i', t8, 'j',
     1       t29, 'xia(i)', t56, 'zda(j)', t65,
     1       'c_de2o', t113, 'd20', t141, 'd10',
     1       t168, 'd02', t195, 'd01', t222, 'd11')
7300  format (/, 'Hypodermis - inner tissue', 2(/), t3, 'i', t8, 'j',
     1       t29, 'xia(i)', t56, 'zda(j)', t65,
     1       'c_hdi', t113, 'd20', t141, 'd10',
     1       t168, 'd02', t195, 'd01', t222, 'd11')
7350  format (/, 'Hypodermis - outer tissue', 2(/), t3, 'i', t8, 'j',
     1       t29, 'xia(i)', t56, 'zda(j)', t65,
     1       'c_hdo', t113, 'd20', t141, 'd10',
     1       t168, 'd02', t195, 'd01', t222, 'd11')
8500  format (i3, t6, i3, t12, d23.16, t39, d23.16, t66, d23.16)
8550  format (i3, t6, i3, t12, d23.16, t39, d23.16, t66, d23.16,
     1       t93, d23.16)
C
      return
      end
C*********************************************************************
C
      subroutine orspermeability
      implicit double precision (a - z)
      integer i, j, iin, iout, idim, jdim, jed, jde1, jde2, jhd
      integer idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:idim)
      dimension c_edi(0:idim,0:jdim)
      dimension c_de1i(0:idim,0:jdim)
      dimension c_de2i(0:idim,0:jdim)
      dimension c_hdi(0:idim,0:jdim)
      dimension P_ors_ed(1:jdim)
      dimension P_ors_de1(1:jdim)
      dimension P_ors_de2(1:jdim)
      dimension P_ors_hd(1:jdim)
      dimension A_ors(1:jdim), B_ors(1:jdim)
      dimension dcdxi(1:jdim), dcdzeta(1:jdim)
C
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
      common /iconcarrays/ c_edi, c_de1i, c_de2i, c_hdi
      common /ors_perm_ed/ P_ors_ed
      common /ors_perm_de1/ P_ors_de1
```

```
      common /ors_perm_de2/ P_ors_de2
      common /ors_perm_hd/ P_ors_hd
C
      open (unit = 15, file = 'Pors.txt')
      write (15, 9000)
C
      corsed = 1.0d0
      corsde1 = 1.0d0
      corsde2 = 1.0d0
      corshd = 1.0d0
C
      i = 0
C
C Ed
C ``
      do 1000, j = 1, jed - 1
         A_ors(j) = -Dedi(xia(i),zda(j))
     1          / (sqrt(1.0d0+(dfd_outer(zda(j)))**2))
         B_ors(j) = (1.0d0/(rd_max-fd_outer(zda(j))))
     1          - dfd_outer(zda(j))*dxidzeta(xia(i),zda(j))
         dcdxi(j) = 0.5d0
         dcdzeta(j) = -1.0d0
         P_ors_ed(j) = (A_ors(j)*B_ors(j)*dcdxi(j)
     1                 - A_ors(j)*dfd_outer(zda(j))*dcdzeta(j))
     1                 / ((corsed/Korsed) - (c_edi(i,j)/Kedi))
         write (15, 9100)j,A_ors(j),B_ors(j),dxidzeta(xia(i),zda(j)),
     1                    P_ors_ed(j), fd_outer(zda(j))
1000  continue
C
C De1
C ```
      do 1100, j = jed + 1, jed + jde1 - 1
         A_ors(j) = -Dde1i(xia(i),zda(j))
     1          / (sqrt(1.0d0+(dfd_outer(zda(j)))**2))
         B_ors(j) = (1.0d0/(rd_max-fd_outer(zda(j))))
     1          - dfd_outer(zda(j))*dxidzeta(xia(i),zda(j))
         dcdxi(j) = 0.5d0
         dcdzeta(j) = -1.0d0
         P_ors_de1(j) = (A_ors(j)*B_ors(j)*dcdxi(j)
     1                 - A_ors(j)*dfd_outer(zda(j))*dcdzeta(j))
     1                 / ((corsde1/Korsde1) - (c_de1i(i,j)/Kde1i))
         write (15, 9100)j,A_ors(j),B_ors(j),dxidzeta(xia(i),zda(j)),
     1                    P_ors_de1(j), fd_outer(zda(j))
1100  continue
C
C De2
C ```
      do 1200, j = jed + jde1 + 1, jed + jde1 + jde2 - 1
         A_ors(j) = -Dde2i(xia(i),zda(j))
     1          / (sqrt(1.0d0+(dfd_outer(zda(j)))**2))
         B_ors(j) = (1.0d0/(rd_max-fd_outer(zda(j))))
     1          - dfd_outer(zda(j))*dxidzeta(xia(i),zda(j))
         dcdxi(j) = 0.5d0
         dcdzeta(j) = -1.0d0
         P_ors_de2(j) = (A_ors(j)*B_ors(j)*dcdxi(j)
     1                 - A_ors(j)*dfd_outer(zda(j))*dcdzeta(j))
     1                 / ((corsde2/Korsde2) - (c_de2i(i,j)/Kde2i))
```

```
         write (15, 9100)j,A_ors(j),B_ors(j),dxidzeta(xia(i),zda(j)),
     1                    P_ors_de2(j), fd_outer(zda(j))
1200  continue
C
C Hd
C ``
      do 1300, j = jed + jde1 + jde2 + 1, jed + jde1 + jde2 + jhd - 1
         A_ors(j) = -Dhdi(xia(i),zda(j))
     1          / (sqrt(1.0d0+(dfd_outer(zda(j)))**2))
         B_ors(j) = (1.0d0/(rd_max-fd_outer(zda(j))))
     1          - dfd_outer(zda(j))*dxidzeta(xia(i),zda(j))
         dcdxi(j) = 0.5d0
         dcdzeta(j) = -1.0d0
         P_ors_hd(j) = (A_ors(j)*B_ors(j)*dcdxi(j)
     1                - A_ors(j)*dfd_outer(zda(j))*dcdzeta(j))
     1                / ((corshd/Korshd) - (c_hdi(i,j)/Khdi))
         write (15, 9100)j,A_ors(j),B_ors(j),dxidzeta(xia(i),zda(j)),
     1                    P_ors_hd(j), fd_outer(zda(j))
1300  continue
C
C Formats
9000  format ('j', 2x, 'Pors')
9100  format (i3, 2x, d23.16, 2x, d23.16, 2x, d23.16, 2x, d23.16,
     1        2x, d23.16)
C
      return
      end
C*********************************************************************
C
C
C
C
      subroutine laplacianapprox
      implicit double precision (a-z)
      integer iin, iout, jed, jde1, jde2, jhd
      integer i, idim, j, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
C
      dimension a_20edi(0:idim,0:jdim), a_10edi(0:idim,0:jdim)
      dimension a_11edi(0:idim,0:jdim), a_02edi(0:idim,0:jdim)
      dimension a_01edi(0:idim,0:jdim)
      dimension a_20de1i(0:idim,0:jdim), a_10de1i(0:idim,0:jdim)
      dimension a_11de1i(0:idim,0:jdim), a_02de1i(0:idim,0:jdim)
      dimension a_01de1i(0:idim,0:jdim)
      dimension a_20de2i(0:idim,0:jdim), a_10de2i(0:idim,0:jdim)
      dimension a_11de2i(0:idim,0:jdim), a_02de2i(0:idim,0:jdim)
      dimension a_01de2i(0:idim,0:jdim)
      dimension a_20hdi(0:idim,0:jdim), a_10hdi(0:idim,0:jdim)
      dimension a_11hdi(0:idim,0:jdim), a_02hdi(0:idim,0:jdim)
      dimension a_01hdi(0:idim,0:jdim)
C
      dimension a_20edo(0:idim,0:jdim), a_10edo(0:idim,0:jdim)
      dimension a_11edo(0:idim,0:jdim), a_02edo(0:idim,0:jdim)
      dimension a_01edo(0:idim,0:jdim)
      dimension a_20de1o(0:idim,0:jdim), a_10de1o(0:idim,0:jdim)
```

```
      dimension a_11de1o(0:idim,0:jdim), a_02de1o(0:idim,0:jdim)
      dimension a_01de1o(0:idim,0:jdim)
      dimension a_20de2o(0:idim,0:jdim), a_10de2o(0:idim,0:jdim)
      dimension a_11de2o(0:idim,0:jdim), a_02de2o(0:idim,0:jdim)
      dimension a_01de2o(0:idim,0:jdim)
      dimension a_20hdo(0:idim,0:jdim), a_10hdo(0:idim,0:jdim)
      dimension a_11hdo(0:idim,0:jdim), a_02hdo(0:idim,0:jdim)
      dimension a_01hdo(0:idim,0:jdim)
C
      dimension cedia(0:idim,0:jdim)
      dimension cedoa(0:idim,0:jdim)
      dimension cde1ia(0:idim,0:jdim)
      dimension cde1oa(0:idim,0:jdim)
      dimension cde2ia(0:idim,0:jdim)
      dimension cde2oa(0:idim,0:jdim)
      dimension chdia(0:idim,0:jdim)
      dimension chdoa(0:idim,0:jdim)
C
      dimension d20edia(0:idim,0:jdim)
      dimension d10edia(0:idim,0:jdim)
      dimension d02edia(0:idim,0:jdim)
      dimension d01edia(0:idim,0:jdim)
      dimension d11edia(0:idim,0:jdim)
      dimension d20eda(0:idim,0:jdim)
      dimension d10eda(0:idim,0:jdim)
      dimension d02eda(0:idim,0:jdim)
      dimension d01eda(0:idim,0:jdim)
      dimension d11eda(0:idim,0:jdim)
C
      dimension d20de1a(0:idim,0:jdim)
      dimension d10de1a(0:idim,0:jdim)
      dimension d02de1a(0:idim,0:jdim)
      dimension d01de1a(0:idim,0:jdim)
      dimension d11de1a(0:idim,0:jdim)
      dimension d20de2a(0:idim,0:jdim)
      dimension d10de2a(0:idim,0:jdim)
      dimension d02de2a(0:idim,0:jdim)
      dimension d01de2a(0:idim,0:jdim)
      dimension d11de2a(0:idim,0:jdim)
      dimension d20hda(0:idim,0:jdim)
      dimension d10hda(0:idim,0:jdim)
      dimension d02hda(0:idim,0:jdim)
      dimension d01hda(0:idim,0:jdim)
      dimension d11hda(0:idim,0:jdim)
C
      dimension lapedia(0:idim,0:jdim)
      dimension lapedoa(0:idim,0:jdim)
      dimension lapde1ia(0:idim,0:jdim)
      dimension lapde1oa(0:idim,0:jdim)
      dimension lapde2ia(0:idim,0:jdim)
      dimension lapde2oa(0:idim,0:jdim)
      dimension laphdia(0:idim,0:jdim)
      dimension laphdoa(0:idim,0:jdim)
C
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
```

```
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
      common /concarrays/ cedia, cedoa, cde1ia, cde1oa, cde2ia,
     1                    cde2oa, chdia, chdoa
      common /secondderived/ d20eda, d10eda, d02eda, d01eda, d11eda,
     1       d20edia, d10edia, d02edia, d01edia, d11edia
      common /secondderivde1/ d20de1a, d10de1a, d02de1a, d01de1a,
     1                        d11de1a
      common /secondderivde2/ d20de2a, d10de2a, d02de2a, d01de2a,
     1                        d11de2a
      common /secondderivhd/ d20hda, d10hda, d02hda, d01hda,
     1                       d11hda
      common /coeffs/ a_20edi, a_10edi, a_02edi, a_01edi, a_11edi,
     1       a_20de1i, a_10de1i, a_02de1i, a_01de1i, a_11de1i,
     1       a_20de2i, a_10de2i, a_02de2i, a_01de2i, a_11de2i,
     1       a_20hdi, a_10hdi, a_02hdi, a_01hdi, a_11hdi,
     1       a_20edo, a_10edo, a_02edo, a_01edo, a_11edo,
     1       a_20de1o, a_10de1o, a_02de1o, a_01de1o, a_11de1o,
     1       a_20de2o, a_10de2o, a_02de2o, a_01de2o, a_11de2o,
     1       a_20hdo, a_10hdo, a_02hdo, a_01hdo, a_11hdo
      common /lapapprox/ lapedia, lapedoa, lapde1ia, lapde1oa,
     1                   lapde2ia, lapde2oa, laphdia, laphdoa
      common /time/ t
C
C ************************
C Inner tissue / epidermis
C ************************
C
C Calculation of Laplacian in (xi,zeta) coordinates
C
C Ed inner tissue
C ````````````````
C
      do 1050, i = 1, iin - 1
      do 1000, j = 1, jed - 1
C
      d20edia(i,j) = (cedia(i+1,j) - 2.0d0*cedia(i,j)
     1            + cedia(i-1,j)) / (hxi_in**2)
C
      d10edia(i,j) = (cedia(i+1,j)-cedia(i-1,j))
     1            / (2.0d0*hxi_in)
C
      d02edia(i,j) = (cedia(i,j-1)-2.0d0*cedia(i,j)
     1            + cedia(i,j+1)) / (hzd**2)
C
C
      d01edia(i,j) = (-cedia(i,j+1)+cedia(i,j-1))
     1            / (2.0d0 * hzd)
C
      d11edia(i,j) = (-cedia(i+1,j+1)+cedia(i+1,j-1)
     1            + cedia(i-1,j+1)-cedia(i-1,j-1))
     1            / (4.0d0*hxi_in*hzd)
C
      lapedia(i,j) = a_20edi(i,j) * d20edia(i,j)
     1             + a_10edi(i,j) * d10edia(i,j)
     1             + a_02edi(i,j) * d02edia(i,j)
     1             + a_01edi(i,j) * d01edia(i,j)
```

```
     1             + a_11edi(i,j) * d11edia(i,j)
C
1000  continue
1050  continue
C
C ************************
C Outer tissue / epidermis
C ************************
C
C
      do 1150, i = iin + 1, iin + iout - 1
      do 1100, j = 1, jed - 1
      d20eda(i,j) = (cedoa(i+1,j) - 2.0d0 * cedoa(i,j)
     1            + cedoa(i-1,j)) / (hxi_out**2)
C
      d10eda(i,j) = (cedoa(i+1,j)-cedoa(i-1,j))
     1            / (2.0d0*hxi_out)
C
      d02eda(i,j) = (cedoa(i,j-1)-2.0d0*cedoa(i,j)
     1            + cedoa(i,j+1)) / (hzd**2)
C
      d01eda(i,j) = (-cedoa(i,j+1)+cedoa(i,j-1))
     1            / (2.0d0 * hzd)
C
      d11eda(i,j) = (-cedoa(i+1,j+1)+cedoa(i+1,j-1)
     1            + cedoa(i-1,j+1)-cedoa(i-1,j-1))
     1            / (4.0d0*hxi_out*hzd)
C
      lapedoa(i,j) = a_20edo(i,j) * d20eda(i,j)
     1             + a_10edo(i,j) * d10eda(i,j)
     1             + a_02edo(i,j) * d02eda(i,j)
     1             + a_01edo(i,j) * d01eda(i,j)
     1             + a_11edo(i,j) * d11eda(i,j)
C
1100  continue
1150  continue
C
C ***********************
C Inner tissue / dermis 1
C ***********************
C
      do 1250, i = 1, iin - 1
      do 1200, j = jed + 1, jed + jde1 - 1
C
      d20de1a(i,j) = (cde1ia(i+1,j) - 2.0d0 * cde1ia(i,j)
     1             + cde1ia(i-1,j)) / (hxi_in**2)
C
      d10de1a(i,j) = (cde1ia(i+1,j)-cde1ia(i-1,j))
     1             / (2.0d0*hxi_in)
C
      d02de1a(i,j) = (cde1ia(i,j-1)-2.0d0*cde1ia(i,j)
     1             + cde1ia(i,j+1)) / (hzd1**2)
C
      d01de1a(i,j) = (-cde1ia(i,j+1)+cde1ia(i,j-1))
     1             / (2.0d0 * hzd1)
C
      d11de1a(i,j) = (-cde1ia(i+1,j+1)+cde1ia(i+1,j-1)
```

```
     1             + cde1ia(i-1,j+1)-cde1ia(i-1,j-1))
     1             / (4.0d0*hxi_in*hzd1)
C
      lapde1ia(i,j) = a_20de1i(i,j) * d20de1a(i,j)
     1              + a_10de1i(i,j) * d10de1a(i,j)
     1              + a_02de1i(i,j) * d02de1a(i,j)
     1              + a_01de1i(i,j) * d01de1a(i,j)
     1              + a_11de1i(i,j) * d11de1a(i,j)
C
1200  continue
1250  continue
C
C ***********************
C Outer tissue / dermis 1
C ***********************
C
      do 1350, i = iin + 1, iin + iout - 1
      do 1300, j = jed + 1, jed + jde1 - 1
C
      d20de1a(i,j) = (cde1oa(i+1,j) - 2.0d0 * cde1oa(i,j)
     1             + cde1oa(i-1,j)) / (hxi_out**2)
C
      d10de1a(i,j) = (cde1oa(i+1,j)-cde1oa(i-1,j))
     1             / (2.0d0*hxi_out)
C
      d02de1a(i,j) = (cde1oa(i,j-1)-2.0d0*cde1oa(i,j)
     1             + cde1oa(i,j+1)) / (hzd1**2)
C
      d01de1a(i,j) = (-cde1oa(i,j+1)+cde1oa(i,j-1))
     1             / (2.0d0 * hzd1)
C
      d11de1a(i,j) = (-cde1oa(i+1,j+1)+cde1oa(i+1,j-1)
     1             + cde1oa(i-1,j+1)-cde1oa(i-1,j-1))
     1             / (4.0d0*hxi_out*hzd1)
C
      lapde1oa(i,j) = a_20de1o(i,j) * d20de1a(i,j)
     1              + a_10de1o(i,j) * d10de1a(i,j)
     1              + a_02de1o(i,j) * d02de1a(i,j)
     1              + a_01de1o(i,j) * d01de1a(i,j)
     1              + a_11de1o(i,j) * d11de1a(i,j)
C
1300  continue
1350  continue
C
C ***********************
C Inner tissue / dermis 2
C ***********************
C
      do 1450, i = 1, iin - 1
      do 1400, j = jed + jde1 + 1, jed + jde1 + jde2 - 1
C
      d20de2a(i,j) = (cde2ia(i+1,j) - 2.0d0 * cde2ia(i,j)
     1             + cde2ia(i-1,j)) / (hxi_in**2)
C
      d10de2a(i,j) = (cde2ia(i+1,j)-cde2ia(i-1,j))
     1             / (2.0d0*hxi_in)
C
```

```
      d02de2a(i,j) = (cde2ia(i,j-1)-2.0d0*cde2ia(i,j)
     1             + cde2ia(i,j+1)) / (hzd2**2)
C
      d01de2a(i,j) = (-cde2ia(i,j+1)+cde2ia(i,j-1))
     1             / (2.0d0 * hzd2)
C
      d11de2a(i,j) = (-cde2ia(i+1,j+1)+cde2ia(i+1,j-1)
     1             + cde2ia(i-1,j+1)-cde2ia(i-1,j-1))
     1             / (4.0d0*hxi_in*hzd2)
C
      lapde2ia(i,j) = a_20de2i(i,j) * d20de2a(i,j)
     1              + a_10de2i(i,j) * d10de2a(i,j)
     1              + a_02de2i(i,j) * d02de2a(i,j)
     1              + a_01de2i(i,j) * d01de2a(i,j)
     1              + a_11de2i(i,j) * d11de2a(i,j)
C
1400  continue
1450  continue
C
C      write (16, 7250)
C
C
C ***********************
C Outer tissue / dermis 2
C ***********************
C
      do 1550, i = iin + 1, iin + iout - 1
      do 1500, j = jed + jde1 + 1, jed + jde1 + jde2 - 1
C
      d20de2a(i,j) = (cde2oa(i+1,j) - 2.0d0 * cde2oa(i,j)
     1             + cde2oa(i-1,j)) / (hxi_out**2)
C
      d10de2a(i,j) = (cde2oa(i+1,j)-cde2oa(i-1,j))
     1             / (2.0d0*hxi_out)
C
      d02de2a(i,j) = (cde2oa(i,j-1)-2.0d0*cde2oa(i,j)
     1             + cde2oa(i,j+1)) / (hzd2**2)
C
      d01de2a(i,j) = (-cde2oa(i,j+1)+cde2oa(i,j-1))
     1             / (2.0d0 * hzd2)
C
      d11de2a(i,j) = (-cde2oa(i+1,j+1)+cde2oa(i+1,j-1)
     1             + cde2oa(i-1,j+1)-cde2oa(i-1,j-1))
     1             / (4.0d0*hxi_out*hzd2)
C
      lapde2oa(i,j) = a_20de2o(i,j) * d20de2a(i,j)
     1              + a_10de2o(i,j) * d10de2a(i,j)
     1              + a_02de2o(i,j) * d02de2a(i,j)
     1              + a_01de2o(i,j) * d01de2a(i,j)
     1              + a_11de2o(i,j) * d11de2a(i,j)
C
1500  continue
1550  continue
C
C      write (16, 7300)
C
C
```

```
C ************************
C Inner tissue / hypodermis
C ************************
C
      do 1650, i = 1, iin - 1
      do 1600, j = jed + jde1 + jde2 + 1, jed + jde1 + jde2 + jhd - 1
C
      d20hda(i,j) = (chdia(i+1,j) - 2.0d0 * chdia(i,j)
     1            + chdia(i-1,j)) / (hxi_in**2)
C
      d10hda(i,j) = (chdia(i+1,j)-chdia(i-1,j))
     1            / (2.0d0*hxi_in)
C
      d02hda(i,j) = (chdia(i,j-1)-2.0d0*chdia(i,j)
     1            + chdia(i,j+1)) / (hzd3**2)
C
      d01hda(i,j) = (-chdia(i,j+1)+chdia(i,j-1))
     1            / (2.0d0 * hzd3)
C
      d11hda(i,j) = (-chdia(i+1,j+1)+chdia(i+1,j-1)
     1            + chdia(i-1,j+1)-chdia(i-1,j-1))
     1            / (4.0d0*hxi_in*hzd3)
C
      laphdia(i,j) = a_20hdi(i,j) * d20hda(i,j)
     1             + a_10hdi(i,j) * d10hda(i,j)
     1             + a_02hdi(i,j) * d02hda(i,j)
     1             + a_01hdi(i,j) * d01hda(i,j)
     1             + a_11hdi(i,j) * d11hda(i,j)
C
1600   continue
1650   continue
C
C ************************
C Outer tissue / hypodermis
C ************************
C
      do 1750, i = iin + 1, iin + iout - 1
      do 1700, j = jed + jde1 + jde2 + 1, jed + jde1 + jde2 + jhd - 1
C
      d20hda(i,j) = (chdoa(i+1,j) - 2.0d0 * chdoa(i,j)
     1            + chdoa(i-1,j)) / (hxi_out**2.0d0)
C
      d10hda(i,j) = (chdoa(i+1,j)-chdoa(i-1,j))
     1            / (2.0d0*hxi_out)
C
      d02hda(i,j) = (chdoa(i,j-1)-2.0d0*chdoa(i,j)
     1            + chdoa(i,j+1)) / (hzd3**2.0d0)
C
      d01hda(i,j) = (-chdoa(i,j+1)+chdoa(i,j-1))
     1            / (2.0d0 * hzd3)
C
      d11hda(i,j) = (-chdoa(i+1,j+1)+chdoa(i+1,j-1)
     1            + chdoa(i-1,j+1)-chdoa(i-1,j-1))
     1            / (4.0d0*hxi_out*hzd3)
C
      laphdoa(i,j) = a_20hdo(i,j) * d20hda(i,j)
     1             + a_10hdo(i,j) * d10hda(i,j)
```

```
     1             + a_02hdo(i,j) * d02hda(i,j)
     1             + a_01hdo(i,j) * d01hda(i,j)
     1             + a_11hdo(i,j) * d11hda(i,j)
C
1700   continue
1750   continue
C
C
C Formats
C
6500  format (/, 'Time = ', d23.16)
7000  format (/, 'Epidermis - inner tissue', 2(/), t3, 'i', t8, 'j',
     1       t29, 'xia(i)', t56, 'zda(j)', t65,
     1       'lapedia', t113, 'd20', t141, 'd10',
     1       t168, 'd02', t195, 'd01', t222, 'd11')
7050  format (/, 'Epidermis - outer tissue', 2(/), t3, 'i', t8, 'j',
     1       t29, 'xia(i)', t56, 'zda(j)', t65,
     1       'lapedoa', t113, 'd20', t141, 'd10',
     1       t168, 'd02', t195, 'd01', t222, 'd11')
7100  format (/, 'Dermis 1 - inner tissue', 2(/), t3, 'i', t8, 'j',
     1       t29, 'xia(i)', t56, 'zda(j)', t65,
     1       'lapde1ia', t113, 'd20', t141, 'd10',
     1       t168, 'd02', t195, 'd01', t222, 'd11')
7150  format (/, 'Dermis 1 - outer tissue', 2(/), t3, 'i', t8, 'j',
     1       t29, 'xia(i)', t56, 'zda(j)', t65,
     1       'lapde1oa', t113, 'd20', t141, 'd10',
     1       t168, 'd02', t195, 'd01', t222, 'd11')
7200  format (/, 'Dermis 2 - inner tissue', 2(/), t3, 'i', t8, 'j',
     1       t29, 'xia(i)', t56, 'zda(j)', t65,
     1       'lapde2ia', t113, 'd20', t141, 'd10',
     1       t168, 'd02', t195, 'd01', t222, 'd11')
7250  format (/, 'Dermis 2 - outer tissue', 2(/), t3, 'i', t8, 'j',
     1       t29, 'xia(i)', t56, 'zda(j)', t65,
     1       'lapde2oa', t113, 'd20', t141, 'd10',
     1       t168, 'd02', t195, 'd01', t222, 'd11')
7300  format (/, 'Hypodermis - inner tissue', 2(/), t3, 'i', t8, 'j',
     1       t29, 'xia(i)', t56, 'zda(j)', t65,
     1       'laphdia', t113, 'd20', t141, 'd10',
     1       t168, 'd02', t195, 'd01', t222, 'd11')
7350  format (/, 'Hypodermis - outer tissue', 2(/), t3, 'i', t8, 'j',
     1       t29, 'xia(i)', t56, 'zda(j)', t65,
     1       'laphdoa', t113, 'd20', t141, 'd10',
     1       t168, 'd02', t195, 'd01', t222, 'd11')
8500  format (i3, t6, i3, t12, d23.16, t39, d23.16, t66, d23.16,
     1       t93, d23.16, t121, d23.16, t148, d23.16, t175, d23.16,
     1       t202, d23.16)
8550  format (i3, t6, i3, t12, d23.16, t39, d23.16, t66, d23.16,
     1       t93, d23.16)
C 9100  format (d23.16)
C
C
      return
      end
C
C
      subroutine laplacianexact
      implicit double precision (a - z)
```

```
      integer iin, iout, jed, jde1, jde2, jhd
      integer i, idim, j, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
C
      dimension r_d(0:idim,0:jdim)
      dimension z_d(0:idim,0:jdim)
      dimension d20edex(0:idim,0:jdim)
      dimension d10edex(0:idim,0:jdim)
      dimension d02edex(0:idim,0:jdim)
      dimension d01edex(0:idim,0:jdim)
      dimension d11edex(0:idim,0:jdim)
      dimension d20de1ex(0:idim,0:jdim)
      dimension d10de1ex(0:idim,0:jdim)
      dimension d02de1ex(0:idim,0:jdim)
      dimension d01de1ex(0:idim,0:jdim)
      dimension d11de1ex(0:idim,0:jdim)
      dimension d20de2ex(0:idim,0:jdim)
      dimension d10de2ex(0:idim,0:jdim)
      dimension d02de2ex(0:idim,0:jdim)
      dimension d01de2ex(0:idim,0:jdim)
      dimension d11de2ex(0:idim,0:jdim)
      dimension d20hdex(0:idim,0:jdim)
      dimension d10hdex(0:idim,0:jdim)
      dimension d02hdex(0:idim,0:jdim)
      dimension d01hdex(0:idim,0:jdim)
      dimension d11hdex(0:idim,0:jdim)
      dimension lapex(0:idim,0:jdim)
C
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /rzcoord/ r_d, z_d
C
      open (unit = 18, file = 'diagnlapex.txt')
      write (18, 6000)
C
      do 1850, i = 0, iin + iout
         do 1800, j = 0, jed + jde1 + jde2 + jhd
            r_d(i,j) = rdf(xia(i),zda(j))
            z_d(i,j) = zdf(xia(i),zda(j))
1800     continue
1850  continue
C
      h = 0.001d0
C
C ************************
C Epidermis / inner tissue
C ************************
C
      do 1950, i = 1, iin - 1
       do 1900, j = 1, jed - 1
C
       d20edex(i,j) = (c(r_d(i,j)+h,z_d(i,j))
     1              - 2.0d0*c(r_d(i,j),z_d(i,j))
     1              + c(r_d(i,j)-h,z_d(i,j))) / (h**2)
```

```
C
       d10edex(i,j) = (c(r_d(i,j)+h,z_d(i,j))
     1              - c(r_d(i,j)-h,z_d(i,j))) / (2.0d0*h)
C
       d02edex(i,j) = (c(r_d(i,j),z_d(i,j)+h)
     1              - 2*c(r_d(i,j),z_d(i,j))
     1              + c(r_d(i,j),z_d(i,j)-h)) / (h**2)
C
       lapex(i,j) = d20edex(i,j)+(1/r_d(i,j))*d10edex(i,j)+d02edex(i,j)
C
       write (18, 6500) i, j, r_d(i,j), z_d(i,j), lapex(i,j),
     1                  d20edex(i,j), d10edex(i,j), d02edex(i,j)
C
1900   continue
1950  continue
C
      write (18, 6050)
C
C ************************
C Epidermis / outer tissue
C ************************
C
      do 2050, i = 1, iin - 1
       do 2000, j = 1, jed - 1
C
       d20edex(i,j) = (c(r_d(i,j)+h,z_d(i,j))
     1              - 2.0d0*c(r_d(i,j),z_d(i,j))
     1              + c(r_d(i,j)-h,z_d(i,j))) / (h**2)
C
       d10edex(i,j) = (c(r_d(i,j)+h,z_d(i,j))
     1              - c(r_d(i,j)-h,z_d(i,j))) / (2.0d0*h)
C
       d02edex(i,j) = (c(r_d(i,j),z_d(i,j)+h)
     1              - 2*c(r_d(i,j),z_d(i,j))
     1              + c(r_d(i,j),z_d(i,j)-h)) / (h**2)
C
       lapex(i,j) = d20edex(i,j)+(1/r_d(i,j))*d10edex(i,j)+d02edex(i,j)
C
       write (18, 6500) i, j, r_d(i,j), z_d(i,j), lapex(i,j),
     1                  d20edex(i,j), d10edex(i,j), d02edex(i,j)
C
2000   continue
2050  continue
C
      write (18, 6100)
C
C ************************
C Dermis 1 / inner tissue
C ************************
C
      do 2150, i = 1, iin - 1
       do 2100, j = jed + 1, jed + jde1 - 1
C
       d20de1ex(i,j) = (c(r_d(i,j)+h,z_d(i,j))
     1               - 2.0d0*c(r_d(i,j),z_d(i,j))
     1               + c(r_d(i,j)-h,z_d(i,j))) / (h**2)
C
```

```
       d10de1ex(i,j) = (c(r_d(i,j)+h,z_d(i,j))
     1               - c(r_d(i,j)-h,z_d(i,j))) / (2.0d0*h)
C
       d02de1ex(i,j) = (c(r_d(i,j),z_d(i,j)+h)
     1               - 2*c(r_d(i,j),z_d(i,j))
     1               + c(r_d(i,j),z_d(i,j)-h)) / (h**2)
C
       lapex(i,j) = d20de1ex(i,j)+(1/r_d(i,j))*d10de1ex(i,j)
     1            + d02de1ex(i,j)
C
       write (18, 6500) i, j, r_d(i,j), z_d(i,j), lapex(i,j),
     1                  d20de1ex(i,j), d10de1ex(i,j), d02de1ex(i,j)
C
2100   continue
2150  continue
C
      write (18, 6150)
C
C ************************
C Dermis 1 / outer tissue
C ************************
C
      do 2250, i = iin + 1, iin + iout - 1
       do 2200, j = jed + 1, jed + jde1 - 1
C
       d20de1ex(i,j) = (c(r_d(i,j)+h,z_d(i,j))
     1               - 2.0d0*c(r_d(i,j),z_d(i,j))
     1               + c(r_d(i,j)-h,z_d(i,j))) / (h**2)
C
       d10de1ex(i,j) = (c(r_d(i,j)+h,z_d(i,j))
     1               - c(r_d(i,j)-h,z_d(i,j))) / (2.0d0*h)
C
       d02de1ex(i,j) = (c(r_d(i,j),z_d(i,j)+h)
     1               - 2*c(r_d(i,j),z_d(i,j))
     1               + c(r_d(i,j),z_d(i,j)-h)) / (h**2)
C
       lapex(i,j) = d20de1ex(i,j)+(1/r_d(i,j))*d10de1ex(i,j)
     1            + d02de1ex(i,j)
C
       write (18, 6500) i, j, r_d(i,j), z_d(i,j), lapex(i,j),
     1                  d20de1ex(i,j), d10de1ex(i,j), d02de1ex(i,j)
C
2200   continue
2250  continue
C
      write (18, 6200)
C
C ************************
C Dermis 2 / inner tissue
C ************************
C
      do 2350, i = 1, iin - 1
       do 2300, j = jed + jde1 + 1, jed + jde1 + jde2 - 1
C
       d20de2ex(i,j) = (c(r_d(i,j)+h,z_d(i,j))
     1               - 2.0d0*c(r_d(i,j),z_d(i,j))
     1               + c(r_d(i,j)-h,z_d(i,j))) / (h**2)
```

```
C
       d10de2ex(i,j) = (c(r_d(i,j)+h,z_d(i,j))
     1               - c(r_d(i,j)-h,z_d(i,j))) / (2.0d0*h)
C
       d02de2ex(i,j) = (c(r_d(i,j),z_d(i,j)+h)
     1               - 2*c(r_d(i,j),z_d(i,j))
     1               + c(r_d(i,j),z_d(i,j)-h)) / (h**2)
C
       lapex(i,j) = d20de2ex(i,j)+(1/r_d(i,j))*d10de2ex(i,j)
     1            + d02de2ex(i,j)
C
       write (18, 6500) i, j, r_d(i,j), z_d(i,j), lapex(i,j),
     1                  d20de2ex(i,j), d10de2ex(i,j), d02de2ex(i,j)
C
2300   continue
2350  continue
C
      write (18, 6250)
C
C ************************
C Dermis 2 / outer tissue
C ************************
C
      do 2450, i = iin + 1, iin + iout - 1
       do 2400, j = jed + jde1 + 1, jed + jde1 + jde2 - 1
C
       d20de2ex(i,j) = (c(r_d(i,j)+h,z_d(i,j))
     1               - 2.0d0*c(r_d(i,j),z_d(i,j))
     1               + c(r_d(i,j)-h,z_d(i,j))) / (h**2)
C
       d10de2ex(i,j) = (c(r_d(i,j)+h,z_d(i,j))
     1               - c(r_d(i,j)-h,z_d(i,j))) / (2.0d0*h)
C
       d02de2ex(i,j) = (c(r_d(i,j),z_d(i,j)+h)
     1               - 2*c(r_d(i,j),z_d(i,j))
     1               + c(r_d(i,j),z_d(i,j)-h)) / (h**2)
C
       lapex(i,j) = d20de2ex(i,j)+(1/r_d(i,j))*d10de2ex(i,j)
     1            + d02de2ex(i,j)
C
       write (18, 6500) i, j, r_d(i,j), z_d(i,j), lapex(i,j),
     1                  d20de2ex(i,j), d10de2ex(i,j), d02de2ex(i,j)
C
2400   continue
2450  continue
C
      write (18, 6300)
C
C ************************
C Hypodermis / inner tissue
C ************************
C
      do 2550, i = 1, iin - 1
       do 2500, j = jed + jde1 + jde2 + 1, jed + jde1 + jde2 + jhd - 1
C
       d20hdex(i,j) = (c(r_d(i,j)+h,z_d(i,j))
     1               - 2.0d0*c(r_d(i,j),z_d(i,j))
```

```
     1               + c(r_d(i,j)-h,z_d(i,j))) / (h**2)
C
       d10hdex(i,j) = (c(r_d(i,j)+h,z_d(i,j))
     1               - c(r_d(i,j)-h,z_d(i,j))) / (2.0d0*h)
C
       d02hdex(i,j) = (c(r_d(i,j),z_d(i,j)+h)
     1               - 2*c(r_d(i,j),z_d(i,j))
     1               + c(r_d(i,j),z_d(i,j)-h)) / (h**2)
C
       lapex(i,j) = d20hdex(i,j)+(1/r_d(i,j))*d10hdex(i,j)
     1            + d02hdex(i,j)
C
       write (18, 6500) i, j, r_d(i,j), z_d(i,j), lapex(i,j),
     1                  d20hdex(i,j), d10hdex(i,j), d02hdex(i,j)
C
2500   continue
2550  continue
C
      write (18, 6350)
C
C ************************
C Hypodermis / outer tissue
C ************************
C
      do 2650, i = iin + 1, iin + iout - 1
       do 2600, j = jed + jde1 + jde2 + 1, jed + jde1 + jde2 + jhd - 1
C
       d20hdex(i,j) = (c(r_d(i,j)+h,z_d(i,j))
     1               - 2.0d0*c(r_d(i,j),z_d(i,j))
     1               + c(r_d(i,j)-h,z_d(i,j))) / (h**2)
C
       d10hdex(i,j) = (c(r_d(i,j)+h,z_d(i,j))
     1               - c(r_d(i,j)-h,z_d(i,j))) / (2.0d0*h)
C
       d02hdex(i,j) = (c(r_d(i,j),z_d(i,j)+h)
     1               - 2*c(r_d(i,j),z_d(i,j))
     1               + c(r_d(i,j),z_d(i,j)-h)) / (h**2)
C
       lapex(i,j) = d20hdex(i,j)+(1/r_d(i,j))*d10hdex(i,j)
     1            + d02hdex(i,j)
C
       write (18, 6500) i, j, r_d(i,j), z_d(i,j), lapex(i,j),
     1                  d20hdex(i,j), d10hdex(i,j), d02hdex(i,j)
C
2600   continue
2650  continue
C
C Formats
C
6000  format ('Epidermis - inner tissue', 2(/), t3, 'i', t8, 'j',
     1       t33, 'rd', t61, 'zd', t80, 'del2c(rd,zd)', t114,
     1       'd20ep', t144, 'd10ep', t174, 'd02ep')
6050  format (/, 'Epidermis - outer tissue', 2(/), t3, 'i', t8, 'j',
     1       t33, 'rd', t61, 'zd', t80, 'del2c(rd,zd)',  t114,
     1       'd20ep', t144, 'd10ep', t174, 'd02ep')
6100  format (/, 'Dermis 1 - inner tissue', 2(/), t3, 'i', t8, 'j',
     1       t33, 'rd', t61, 'zd', t80, 'del2c(rd,zd)', t114,
```

```
     1       'd20ep', t144, 'd10ep', t174, 'd02ep')
6150  format (/, 'Dermis 1 - outer tissue', 2(/), t3, 'i', t8, 'j',
     1       t33, 'rd', t61, 'zd', t80, 'del2c(rd,zd)', t114,
     1       'd20ep', t144, 'd10ep', t174, 'd02ep')
6200  format (/, 'Dermis 2 - inner tissue', 2(/), t3, 'i', t8, 'j',
     1       t33, 'rd', t61, 'zd', t80, 'del2c(rd,zd)', t114,
     1       'd20ep', t144, 'd10ep', t174, 'd02ep')
6250  format (/, 'Dermis 2 - outer tissue', 2(/), t3, 'i', t8, 'j',
     1       t33, 'rd', t61, 'zd', t80, 'del2c(rd,zd)', t114,
     1       'd20ep', t144, 'd10ep', t174, 'd02ep')
6300  format (/, 'Hypodermis - inner tissue', 2(/), t3, 'i', t8, 'j',
     1       t33, 'rd', t61, 'zd', t80, 'del2c(rd,zd)', t114,
     1       'd20ep', t144, 'd10ep', t174, 'd02ep')
6350  format (/, 'Hypodermis - outer tissue', 2(/), t3, 'i', t8, 'j',
     1       t33, 'rd', t61, 'zd', t80, 'del2c(rd,zd)', t114,
     1       'd20ep', t144, 'd10ep', t174, 'd02ep')
6500  format (i3, t6, i3, t12, d23.16, t40, d23.16, t69, d23.16,
     1       t96, d23.16, t126, d23.16, t156, d23.16)
C
      return
      end
C
C
C ***********************************************
C Transient calculation of concentration
C ***********************************************
C
      subroutine evolve
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd
      integer idim, jdim, l, k, lreport, kwrite, type, j
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      dimension cedia(0:idim,0:jdim)
      dimension cedoa(0:idim,0:jdim)
      dimension cde1ia(0:idim,0:jdim)
      dimension cde1oa(0:idim,0:jdim)
      dimension cde2ia(0:idim,0:jdim)
      dimension cde2oa(0:idim,0:jdim)
      dimension chdia(0:idim,0:jdim)
      dimension chdoa(0:idim,0:jdim)
C
      dimension lapedia(0:idim,0:jdim)
      dimension lapedoa(0:idim,0:jdim)
      dimension lapde1ia(0:idim,0:jdim)
      dimension lapde1oa(0:idim,0:jdim)
      dimension lapde2ia(0:idim,0:jdim)
      dimension lapde2oa(0:idim,0:jdim)
      dimension laphdia(0:idim,0:jdim)
      dimension laphdoa(0:idim,0:jdim)
C
      dimension cedia_new(0:idim,0:jdim)
      dimension cedoa_new(0:idim,0:jdim)
      dimension cde1ia_new(0:idim,0:jdim)
      dimension cde1oa_new(0:idim,0:jdim)
      dimension cde2ia_new(0:idim,0:jdim)
```

```
      dimension cde2oa_new(0:idim,0:jdim)
      dimension chdia_new(0:idim,0:jdim)
      dimension chdoa_new(0:idim,0:jdim)
C
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
      common /xizetaval/ xia, zda
      common /lapapprox/ lapedia, lapedoa, lapde1ia, lapde1oa,
     1                   lapde2ia, lapde2oa, laphdia, laphdoa
      common /concarrays/ cedia, cedoa, cde1ia, cde1oa, cde2ia,
     1                    cde2oa, chdia, chdoa
      common /newvalues/ cedia_new, cedoa_new, cde1ia_new, cde1oa_new,
     1                   cde2ia_new, cde2oa_new, chdia_new, chdoa_new
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
      common /time/ t
      common /lreport_value/ l
       common /param/ deltat, deltah, ratek_edi, ratek_edo,
     1       ratek_de1i, ratek_de1o, ratek_de2i, ratek_de2o,
     1       ratek_hdi, ratek_hdo
C
      open (unit = 17, file = 'f16h_c_ed.txt')
      write (17, 9000)
      open (unit = 19, file = 'f16h_c_de1.txt')
      write (19, 9000)
      open (unit = 98, file = 'f16h_c_de2.txt')
      write (98, 9000)
      open (unit = 21, file = 'f16h_c_hd.txt')
      write (21, 9000)
C
C**********************************************************************
C
C
C Values of average concentration at each t step
C
      open (unit = 48, file = 'f16h_average_c.txt')
      write (48, 9200)
C
C Donor solution concentration data
C
      open (unit = 49, file = 'f16h_donorsolconc.txt')
      write (49, 9300)
C      open (unit = 50, file = '16h_donorsoldata.txt')
C      write (50, 9400)
C      open (unit = 51, file = '16h_donorsoldata_2.txt')
C      write (51, 9500)
      open (unit = 52, file = 'f16h_donorsoltest.txt')
      write (52, 9600)
      open (unit = 54, file = 'f16h_infundconc.txt')
      open (unit = 55, file = 'f16h_avg_conc_inf.txt')
      open (unit = 56, file = 'f16h_avg_conc_inf_2.txt')
      open (unit = 57, file = 'f16h_avg_left_b.txt')
C      open (unit = 55, file = 'testIderde1.txt')
C
```

```
C*********************************************************************
C
C
C Initialization
C
      print*, 'for r-dir. type 1, for z-dir. type 2'
      read*, type
      print*, 'ok'
C
      if (type .eq. 1) then
         call init_r
      else if (type .eq. 2) then
         call init_z
      end if
C
      call report
C
C Time iterations
C
C       lreport = 2
      lreport = 64
      kwrite = 9000
C      kwrite = 1000
C       kwrite = 1
C
      do 3450, l = 1, lreport
         do 3400, k = 1, kwrite
            call step
            print*, t
            call donorsolconc
            call testcds
            call avgconc
3400     continue
C        call avgconc
         call report
C         if (t .ge. 7.9999d0) then
C            call report
C            call errorfunction
C         end if
3450  continue
C
C Test for function erfcomp(z,t)
C Need to change arg in function erfcomp(z,t)
C      x = 0.0d0
C      s = 1.0d0
C      do j = 0, 59
C        x = x + 0.05d0
C         test = erfcomp(x,s)
C         print*, x, test
C      end do
C
C
9000  format('Transient values of c, Dt = 0.01')
9100  format(i3, 1x, d23.16, 1x, d23.16, 1x, d23.16, 1x, d23.16)
9200  format ('Time',3x,'ac_ed',3x,'ac_de')
9300  format ('Time',3x,'i',3x,'cds(i)',3x,'cdso(i)')
9400  format ('I_der',3x,'t1',3x,'t2',3x,'t3',3x,'t4')
```

```
9500  format ('t5',3x,'t6',3x,'t7')
9600  format ('lhs', 3x, 'rhs', 3x, 'lhsterm1', 3x, 'lhsterm2',
     1       3x, 'lhsterm3')
C
      return
      end
C
C
C **************
C Initialization
C **************
C
      subroutine init_r
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd
      integer i, idim, j, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension cedia(0:idim,0:jdim)
      dimension cedoa(0:idim,0:jdim)
      dimension cde1ia(0:idim,0:jdim)
      dimension cde1oa(0:idim,0:jdim)
      dimension cde2ia(0:idim,0:jdim)
      dimension cde2oa(0:idim,0:jdim)
      dimension chdia(0:idim,0:jdim)
      dimension chdoa(0:idim,0:jdim)
      dimension cds(0:idim)
C
      common /time/ t
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /concarrays/ cedia, cedoa, cde1ia, cde1oa,
     1                    cde2ia, cde2oa, chdia, chdoa
      common /dsconctemp/ cds
C
      t = 0.0d0
C
C Donor solution concentration
C
      do 3400, i = 0, iin + iout
         cds(i) = 1.0d0
3400  continue
C
C For r-dependence diagnostics
C Ed inner tissue
C
      i = 0
      do 3549, j = 0, jed
         cedia(i,j) = 1.0d0
3549   continue
C
      do 3550, i = 1, iin
         do 3500, j = 0, jed
            cedia(i,j) = 0.0d0
3500     continue
3550  continue
C
```

```
C Ed outer tissue
C
      i = iin
      do 3649, j = 0, jed
         cedoa(i,j) = 0.0d0
3649  continue
C
      do 3650, i = iin + 1, iin + iout
         do 3600, j = 0, jed
            cedoa(i,j) = 0.0d0
3600     continue
3650  continue
C
C
C De1 inner tissue
C
      i = 0
      do 3749, j = jed, jed + jde1
         cde1ia(i,j) = 1.0d0
3749  continue
C
      do 3750, i = 1, iin
         do 3700, j = jed, jed + jde1
            cde1ia(i,j) = 0.0d0
3700     continue
3750  continue
C
C De1 outer tissue
C
      i = iin
      do 3849, j = jed, jed + jde1
         cde1oa(i,j) = 0.0d0
3849  continue
C
      do 3850, i = iin + 1, iin + iout
         do 3800, j = jed, jed + jde1
            cde1oa(i,j) = 0.0d0
3800     continue
3850  continue
C
C
C De2 inner tissue
C
      i = 0
      do 3949, j = jed + jde1, jed + jde1 + jde2
         cde2ia(i,j) = 1.0d0
3949  continue
C
      do 3950, i = 1, iin
         do 3900, j = jed + jde1, jed + jde1 + jde2
            cde2ia(i,j) = 0.0d0
3900     continue
3950  continue
C
C De2 outer tissue
C
      i = iin
```

```
      do 4049, j = jed + jde1, jed + jde1 + jde2
         cde2oa(i,j) = 0.0d0
4049  continue
C
      do 4050, i = iin + 1, iin + iout
         do 4000, j = jed + jde1, jed + jde1 + jde2
            cde2oa(i,j) = 0.0d0
4000     continue
4050  continue
C
C
C hd inner tissue
C
      i = 0
      do 4149, j = jed + jde1 + jde2, jed + jde1 + jde2 + jhd
         chdia(i,j) = 1.0d0
4149  continue
C
      do 4150, i = 1, iin
         do 4100, j = jed + jde1 + jde2, jed + jde1 + jde2 + jhd
            chdia(i,j) = 0.0d0
4100    continue
4150  continue
C
C hd outer tissue
C
      i = iin
      do 4249, j = jed + jde1 + jde2, jed + jde1 + jde2 + jhd
         chdoa(i,j) = 0.0d0
4249  continue
C
      do 4250, i = iin + 1, iin + iout
         do 4200, j = jed + jde1 + jde2, jed + jde1 + jde2 + jhd
            chdoa(i,j) = 0.0d0
4200    continue
4250  continue
C
      return
      end
C
C
      subroutine init_z
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd
      integer i, idim, j, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      dimension cedia(0:idim,0:jdim)
      dimension cedoa(0:idim,0:jdim)
      dimension cde1ia(0:idim,0:jdim)
      dimension cde1oa(0:idim,0:jdim)
      dimension cde2ia(0:idim,0:jdim)
      dimension cde2oa(0:idim,0:jdim)
      dimension chdia(0:idim,0:jdim)
      dimension chdoa(0:idim,0:jdim)
      dimension cds(0:idim)
```

```
C
      common /xizetaval/ xia, zda
      common /time/ t
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /concarrays/ cedia, cedoa, cde1ia, cde1oa,
     1                    cde2ia, cde2oa, chdia, chdoa
      common /dsconctemp/ cds
C
      t = 0.0d0
C
C Donor solution concentration
C
      do 4000, i = 0, iin + iout
         cds(i) = 1.0d0
4000  continue
C
C
C For z-dependence diagnostics
C Ed inner tissue
C
      j = 0
      do 4251, i = 0, iin
         cedia(i,j) = 0.0d0
4251  continue
C
      do 4253, i = 0, iin
         do 4252, j = 1, jed
            cedia(i,j) = 0.0d0
4252     continue
4253  continue
C
C Ed outer tissue
C
      j = 0
      do 4254, i = iin, iin + iout
         cedoa(i,j) = 0.0d0
4254  continue
C
      do 4256, i = iin , iin + iout
         do 4255, j = 1, jed
            cedoa(i,j) = 0.0d0
4255     continue
4256  continue
C
C De1 inner tissue
C
      j = jed
      do 4257, i = 0, iin
         cde1ia(i,j) = 0.0d0
4257  continue
C
      do 4259, i = 0, iin
         do 4258, j = jed + 1, jed + jde1
            cde1ia(i,j) = 0.0d0
4258     continue
4259  continue
```

```
C
C De1 outer tissue
C
      j = jed
      do 4260, i = iin, iin + iout
         cde1oa(i,j) = 0.0d0
4260  continue
C
      do 4262, i = iin, iin + iout
         do 4261, j = jed + 1, jed + jde1
            cde1oa(i,j) = 0.0d0
4261  continue
4262  continue
C
C De2 inner tissue
C
      j = jed + jde1
      do 4263, i = 0, iin
         cde2ia(i,j) = 0.0d0
4263  continue
C
      do 4265, i = 0, iin
         do 4264, j = jed + jde1 + 1, jed + jde1 + jde2
            cde2ia(i,j) = 0.0d0
4264     continue
4265  continue
C
C De2 outer tissue
C
      j = jed + jde1
      do 4266, i = iin, iin + iout
         cde2oa(i,j) = 0.0d0
4266  continue
C
      do 4268, i = iin, iin + iout
         do 4267, j = jed + jde1 + 1, jed + jde1 + jde2
            cde2oa(i,j) = 0.0d0
4267     continue
4268  continue
C
C hd inner tissue
C
      j = jed + jde1 + jde2
      do 4269, i = 0, iin
         chdia(i,j) = 0.0d0
4269  continue
C
      do 4271, i = 0, iin
         do 4270, j = jed + jde1 + jde2 + 1, jed + jde1 + jde2 + jhd
            chdia(i,j) = 0.0d0
4270     continue
4271  continue
C
C hd outer tissue
C
      j = jed + jde1 + jde2
      do 4272, i = iin, iin + iout
```

```
         chdoa(i,j) = 0.0d0
4272  continue
C
      do 4274, i = iin, iin + iout
         do 4273, j = jed + jde1 + jde2 + 1, jed + jde1 + jde2 + jhd
            chdoa(i,j) = 0.0d0
4273     continue
4274  continue
C
      return
      end
C
C
C ***************************************
C Writing concentration values to textfile
C ***************************************
C
      subroutine report
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd
      integer i, idim, j, jdim, l
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
C
      dimension cedia(0:idim,0:jdim)
      dimension cedoa(0:idim,0:jdim)
      dimension cde1ia(0:idim,0:jdim)
      dimension cde1oa(0:idim,0:jdim)
      dimension cde2ia(0:idim,0:jdim)
      dimension cde2oa(0:idim,0:jdim)
      dimension chdia(0:idim,0:jdim)
      dimension chdoa(0:idim,0:jdim)
      dimension cds(0:idim), lhs(0:idim)
      dimension t1(0:idim), t3(0:idim)
      dimension testterm1(0:idim),testterm2(0:idim),
     1          testterm3(0:idim)
C
      dimension d20edia(0:idim,0:jdim)
      dimension d10edia(0:idim,0:jdim)
      dimension d02edia(0:idim,0:jdim)
      dimension d01edia(0:idim,0:jdim)
      dimension d11edia(0:idim,0:jdim)
      dimension d20eda(0:idim,0:jdim)
      dimension d10eda(0:idim,0:jdim)
      dimension d02eda(0:idim,0:jdim)
      dimension d01eda(0:idim,0:jdim)
      dimension d11eda(0:idim,0:jdim)
C
      dimension lapedia(0:idim,0:jdim)
      dimension lapedoa(0:idim,0:jdim)
      dimension lapde1ia(0:idim,0:jdim)
      dimension lapde1oa(0:idim,0:jdim)
      dimension lapde2ia(0:idim,0:jdim)
      dimension lapde2oa(0:idim,0:jdim)
      dimension laphdia(0:idim,0:jdim)
      dimension laphdoa(0:idim,0:jdim)
```

```
C
      dimension cors(0:jdim)
C
      common /xizetaval/ xia, zda
C
      common /secondderived/ d20eda, d10eda, d02eda, d01eda, d11eda,
     1       d20edia, d10edia, d02edia, d01edia, d11edia
C
      common /lapapprox/ lapedia, lapedoa, lapde1ia, lapde1oa,
     1                   lapde2ia, lapde2oa, laphdia, laphdoa
      common /concarrays/ cedia, cedoa, cde1ia, cde1oa, cde2ia,
     1                            cde2oa, chdia, chdoa
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
       common /param/ deltat, deltah, ratek_edi, ratek_edo,
     1       ratek_de1i, ratek_de1o, ratek_de2i, ratek_de2o,
     1       ratek_hdi, ratek_hdo
      common /time/ t
      common /lreport_value/ l
C
      common /avgconc_values/ ac_ed, ac_de
      common /avgconcdata/ num_edi, num_edo, num_de1i, num_de1o,
     1        num_de2i, num_de2o, num_hdi, num_hdo
      common /donorsoldata/ I_der, t1, t2, t3, t4, t5, t6, t7
      common /dsconctemp/ cds
      common /testcdsdata/ lhs, rhs, testterm1, testterm2,
     1                     testterm3
      common /inf_conc/ cors
      common /avginfconc/ ac_inf,num_inf_ed,den_inf_ed,
     1     num_inf_de1,den_inf_de1, num_inf_de2, den_inf_de2
      common /avg_left/ ac_ors
      common /test/ Idered1,Idered2,Idered3,Idered4
      common /test/ Iderde1, test1Iderde1, test2Iderde1
C
C Reporting concentration values
C ``````````````````````````````
C
      write (17, 8500) t
      write (17, 9000)
      write (19, 8500) t
      write (19, 9200)
      write (98, 8500) t
      write (98, 9400)
      write (21, 8500) t
      write (21, 9600)
      write (49, 8500) t
      write (50, 8500) t
      write (51, 8500) t
      write (52, 8500) t
      write (54, 8500) t
C
C Time in min
C
      s = dble(l)*15.0d0/60.0d0
C
C Ed inner tissue
C ```````````````
```

```
      do 3650, i = 0, iin
         do 3600, j = 0, jed
           write(17, 8000) i, j, cedia(i,j)
3600     continue
3650  continue
      write (17, 9100)
C
C Ed outer tissue
C ```````````````
      do 3750, i = iin, iin + iout
         do 3700, j = 0, jed
           write(17, 8000) i, j, cedoa(i,j)
3700     continue
3750  continue
C      write (17, 9200)
C
C De1 inner tissue
C ```````````````
      do 3850, i = 0, iin
         do 3800, j = jed, jed + jde1
           write(19, 8000) i, j, cde1ia(i,j)
3800     continue
3850  continue
      write (19, 9300)
C
C De1 outer tissue
C ```````````````
      do 3950, i = iin, iin + iout
         do 3900, j = jed, jed + jde1
           write(19, 8000) i, j, cde1oa(i,j)
3900     continue
3950  continue
C      write (19, 9400)
C
C De2 inner tissue
C ```````````````
      do 4050, i = 0, iin
         do 4000, j = jed + jde1, jed + jde1 + jde2
           write(98, 8000) i, j, cde2ia(i,j)
4000     continue
4050  continue
      write (98, 9500)
C
C De2 outer tissue
C ```````````````
      do 4150, i = iin, iin + iout
         do 4100, j = jed + jde1, jed + jde1 + jde2
           write(98, 8000) i, j, cde2oa(i,j)
4100     continue
4150  continue
C      write (98, 9600)
C
C hd inner tissue
C ```````````````
      do 4250, i = 0, iin
         do 4200, j = jed + jde1 + jde2, jed + jde1 + jde2 + jhd
           write(21, 8000) i, j, chdia(i,j)
```

```
4200     continue
4250  continue
      write (21, 9700)
C
C Hd outer tissue
C ```````````````
      do 4350, i = iin, iin + iout
         do 4300, j = jed + jde1 + jde2, jed + jde1 + jde2 + jhd
           write(21, 8000) i, j, chdoa(i,j)
4300     continue
4350  continue
C
C
C Reporting average concentration at time s [min]
C *********************************************
C
      write (48, 9800) s, ac_ed, ac_de
C
C Reporting donor solution data at time t
C ***************************************
C
      do 4375, i = 0, iin + iout
         write (50, 9850) I_der, t1(i), t2, t3(i), t4
         write (51, 9800) t5, t6, t7
4375  continue
C
C Reporting donor solution data at time s [min]
C *********************************************
C
      write (49,9800) s, cds(0)

C      do 4400, i = 0, iin + iout
         write (49, 9825) i, cds(i)
         write (52, 9850) lhs(i), rhs, testterm1(i),
     1               testterm2(i), testterm3(i)
4400  continue
C
C Reporting conc of dye in infundibulum
C *************************************
      do 4500, j = 0, jed + jde1 + jde2
         write (54, 9825) j, cors(j)
4500  continue
C
C Rerporting average conc. of dye in infundibulum
C ***********************************************
      write (55, 9800) s, ac_inf, num_inf_ed, den_inf_ed
C
      write (56, 9850)  num_inf_de1, den_inf_de1, num_inf_de2,
den_inf_de2
C
C Reporting average concentration at ORS/skin boundary
C ****************************************************
      write (57, 9800) s, ac_ors
C
C
C Formats
C `````````
```

```
8000  format (i3, t6, i3, t18, d23.16)
8500  format (/, 'Time = ', d12.5)
9000  format (/, 'Epidermis - inner tissue', 2(/), 'i', t8, 'j',
     1        t29, 'cedia(i,j)')
9100  format (/, 'Epidermis - outer tissue', 2(/), 'i', t8, 'j',
     1        t29, 'cedoa(i,j)')
9200  format (/, 'Dermis 1 - inner tissue', 2(/), 'i', t8, 'j',
     1        t29, 'cde1ia(i,j)')
9300  format (/, 'Dermis 1 - outer tissue', 2(/), 'i', t8, 'j',
     1        t29, 'cde1oa(i,j)')
9400  format (/, 'Dermis 2 - inner tissue', 2(/), 'i', t8, 'j',
     1        t29, 'cde2ia(i,j)')
9500  format (/, 'Dermis 2 - outer tissue', 2(/), 'i', t8, 'j',
     1        t29, 'cde2oa(i,j)')
9600  format (/, 'Hypodermis - inner tissue', 2(/), 'i', t8, 'j',
     1        t29, 'chdia(i,j)')
9700  format (/, 'Hypodermis - outer tissue', 2(/), 'i', t8, 'j',
     1        t29, 'chdoa(i,j)')
9800  format (d10.4, 1x, d23.16, 1x, d23.16, 1x, d23.16)
9825  format (i3, 2x, d23.16)
9850  format (d23.16,2x,d23.16,2x,d23.16,2x,d23.16,2x,d23.16)
C
      return
      end
C
C
C *********
C Time step
C *********
C
      subroutine step
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd, n
      integer i, idim, j, jdim
      integer iscrat, idsgn, k, l
      parameter (idim = 500, jdim = 500)
C*****************************************************************
C
C For test of left boundary
      dimension x(0:jdim)
      dimension xia(0:idim), zda(0:jdim)
      dimension P_ors_ed(1:jdim)
      dimension P_ors_de1(1:jdim)
      dimension P_ors_de2(1:jdim)
      dimension P_ors_hd(1:jdim)
      dimension c_edi(0:idim,0:jdim)
      dimension c_de1i(0:idim,0:jdim)
      dimension c_de2i(0:idim,0:jdim)
      dimension c_hdi(0:idim,0:jdim)
      dimension c_edo(0:idim,0:jdim)
      dimension c_de1o(0:idim,0:jdim)
      dimension c_de2o(0:idim,0:jdim)
      dimension c_hdo(0:idim,0:jdim)
      dimension b_test(1:jdim)
C*****************************************************************
C
C
```

```
      dimension cedia(0:idim,0:jdim)
      dimension cedoa(0:idim,0:jdim)
      dimension cde1ia(0:idim,0:jdim)
      dimension cde1oa(0:idim,0:jdim)
      dimension cde2ia(0:idim,0:jdim)
      dimension cde2oa(0:idim,0:jdim)
      dimension chdia(0:idim,0:jdim)
      dimension chdoa(0:idim,0:jdim)
      dimension cds(0:idim)
C
      dimension cedia_new(0:idim,0:jdim)
      dimension cedoa_new(0:idim,0:jdim)
      dimension cde1ia_new(0:idim,0:jdim)
      dimension cde1oa_new(0:idim,0:jdim)
      dimension cde2ia_new(0:idim,0:jdim)
      dimension cde2oa_new(0:idim,0:jdim)
      dimension chdia_new(0:idim,0:jdim)
      dimension chdoa_new(0:idim,0:jdim)
C
      dimension lapedia(0:idim,0:jdim)
      dimension lapedoa(0:idim,0:jdim)
      dimension lapde1ia(0:idim,0:jdim)
      dimension lapde1oa(0:idim,0:jdim)
      dimension lapde2ia(0:idim,0:jdim)
      dimension lapde2oa(0:idim,0:jdim)
      dimension laphdia(0:idim,0:jdim)
      dimension laphdoa(0:idim,0:jdim)
C
      dimension cedib(0:idim)
      dimension cedib_new(0:idim)
      dimension cedic(0:idim)
      dimension cedic_new(0:idim)
      dimension cedob(0:idim)
      dimension cedob_new(0:idim)
      dimension cedoc(0:idim)
      dimension cedoc_new(0:idim)
      dimension cedie(0:jdim)
      dimension cedie_new(0:jdim)
      dimension cde1ib(0:idim)
      dimension cde1ib_new(0:idim)
      dimension cde1ie(0:jdim)
      dimension cde1ie_new(0:jdim)
      dimension cde1ic(0:idim)
      dimension cde1ic_new(0:idim)
      dimension cde1ob(0:idim)
      dimension cde1ob_new(0:idim)
      dimension cde1oc(0:idim)
      dimension cde1oc_new(0:idim)
      dimension cde2ib(0:idim)
      dimension cde2ib_new(0:idim)
      dimension cde2ie(0:jdim)
      dimension cde2ie_new(0:jdim)
      dimension cde2ic(0:idim)
      dimension cde2ic_new(0:idim)
      dimension chdic(0:idim)
      dimension chdic_new(0:idim)
      dimension cde2ob(0:idim)
```

```
      dimension cde2ob_new(0:idim)
      dimension cde2oc(0:idim)
      dimension cde2oc_new(0:idim)
      dimension chdib(0:idim)
      dimension chdib_new(0:idim)
      dimension chdie(0:jdim)
      dimension chdie_new(0:jdim)
      dimension chdob(0:idim)
      dimension chdob_new(0:idim)
      dimension chdoc(0:idim)
      dimension chdoc_new(0:idim)
C
      dimension Bedl1(1:jdim)
      dimension Bedl2(1:jdim)
      dimension Bedl3(1:jdim)
      dimension Bedl4(1:jdim)
      dimension Bde1l1(1:jdim)
      dimension Bde1l2(1:jdim)
      dimension Bde1l3(1:jdim)
      dimension Bde1l4(1:jdim)
      dimension Bde2l1(1:jdim)
      dimension Bde2l2(1:jdim)
      dimension Bde2l3(1:jdim)
      dimension Bde2l4(1:jdim)
      dimension Bhdl1(1:jdim)
      dimension Bhdl2(1:jdim)
      dimension Bhdl3(1:jdim)
      dimension Bhdl4(1:jdim)
C
      dimension Bedio1i(0:jdim)
      dimension Bedio1o(0:jdim)
      dimension Bedio2i(0:jdim)
      dimension Bedio2o(0:jdim)
      dimension Bde1io1i(0:jdim)
      dimension Bde1io1o(0:jdim)
      dimension Bde1io2i(0:jdim)
      dimension Bde1io2o(0:jdim)
      dimension Bde2io1i(0:jdim)
      dimension Bde2io1o(0:jdim)
      dimension Bde2io2i(0:jdim)
      dimension Bde2io2o(0:jdim)
      dimension Bhdio1i(0:jdim)
      dimension Bhdio1o(0:jdim)
      dimension Bhdio2i(0:jdim)
      dimension Bhdio2o(0:jdim)
C
      dimension Bsced1i(0:idim)
      dimension Bsced1o(0:idim)
      dimension Bsced2i(0:idim)
      dimension Bsced2o(0:idim)
      dimension Bsced3i(0:idim)
      dimension Bsced3o(0:idim)
      dimension Bsced4(0:idim)
C
      dimension Bedde11i(0:idim)
      dimension Bedde11o(0:idim)
      dimension Bedde12i(0:idim)
```

```
      dimension Bedde12o(0:idim)
      dimension Bedde13i(0:idim)
      dimension Bedde13o(0:idim)
      dimension Bedde14i(0:idim)
      dimension Bedde14o(0:idim)
C
      dimension Bde1de21i(0:idim)
      dimension Bde1de21o(0:idim)
      dimension Bde1de22i(0:idim)
      dimension Bde1de22o(0:idim)
      dimension Bde1de23i(0:idim)
      dimension Bde1de23o(0:idim)
      dimension Bde1de24i(0:idim)
      dimension Bde1de24o(0:idim)
C
      dimension Bde2hd1i(0:idim)
      dimension Bde2hd1o(0:idim)
      dimension Bde2hd2i(0:idim)
      dimension Bde2hd2o(0:idim)
      dimension Bde2hd3i(0:idim)
      dimension Bde2hd3o(0:idim)
      dimension Bde2hd4i(0:idim)
      dimension Bde2hd4o(0:idim)
C
      dimension Bhdsub1i(0:idim)
      dimension Bhdsub1o(0:idim)
      dimension Bhdsub2i(0:idim)
      dimension Bhdsub2o(0:idim)
      dimension Bhdsub3i(0:idim)
      dimension Bhdsub3o(0:idim)
      dimension Bhdsub4(0:idim)
C
      dimension a(1:jdim,1:jdim), b(1:jdim), iscrat(1:jdim)
C
      dimension cors(0:idim)
C
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
      common /concarrays/ cedia, cedoa, cde1ia, cde1oa,
     1                    cde2ia, cde2oa, chdia, chdoa
      common /newvalues/ cedia_new, cedoa_new, cde1ia_new, cde1oa_new,
     1                   cde2ia_new, cde2oa_new, chdia_new, chdoa_new
      common /lapapprox/ lapedia, lapedoa, lapde1ia, lapde1oa,
     1                   lapde2ia, lapde2oa, laphdia, laphdoa
       common /param/ deltat, deltah, ratek_edi, ratek_edo,
     1       ratek_de1i, ratek_de1o, ratek_de2i, ratek_de2o,
     1       ratek_hdi, ratek_hdo
C
      common /leftboundary/ Bedl1, Bedl2, Bedl3, Bedl4,
     1  Bde1l1, Bde1l2, Bde1l3, Bde1l4,
     1  Bde2l1, Bde2l2, Bde2l3, Bde2l4,
     1  Bhdl1, Bhdl2, Bhdl3, Bhdl4
```

```
      common /topboundary/ Bsced1i, Bsced1o,
     1  Bsced2i, Bsced2o, Bsced3i, Bsced3o, Bsced4
      common /inoutboundary/ Bedio1i, Bedio1o, Bedio2i, Bedio2o,
     1  Bde1io1i, Bde1io1o, Bde1io2i, Bde1io2o,
     1  Bde2io1i, Bde2io1o, Bde2io2i, Bde2io2o,
     1  Bhdio1i, Bhdio1o, Bhdio2i, Bhdio2o
      common /edde1boundary/ Bedde11i, Bedde11o,
     1  Bedde12i, Bedde12o, Bedde13i, Bedde13o, Bedde14i, Bedde14o
      common /de1de2boundary/ Bde1de21i, Bde1de21o,
     1  Bde1de22i, Bde1de22o, Bde1de23i, Bde1de23o, Bde1de24i, Bde1de24
      common /de2hdboundary/ Bde2hd1i, Bde2hd1o,
     1  Bde2hd2i, Bde2hd2o, Bde2hd3i, Bde2hd3o, Bde2hd4i, Bde2hd4o
      common /bottom/ Bhdsub1i, Bhdsub1o, Bhdsub2i, Bhdsub2o,
     1  Bhdsub3i, Bhdsub3o, Bhdsub4
C
      common /inf_conc/ cors
      common /ors_perm_ed/ P_ors_ed
      common /ors_perm_de1/ P_ors_de1
      common /ors_perm_de2/ P_ors_de2
      common /ors_perm_hd/ P_ors_hd
      common /time/ t
      common /dsconctemp/ cds
C
C**********************************************************************
C
C For test of left boundary
      common /xizetaval/ xia, zda
      common /iconcarrays/ c_edi, c_de1i, c_de2i, c_hdi
      common /oconcarrays/ c_edo, c_de1o, c_de2o, c_hdo
C**********************************************************************
C
C
      tol = 1.0d-12
C
      t = t + deltat
C
C
C Calculation of dye concentration in infundibulum
C ````````````````````````````````````````````````
      i = 0
      do 900, j = 0, jed + jde1 + jde2 + jhd
         cors(j) = (Ksebref/Ksolref)*cds(i)*erfcomp(zda(j),t)
C
C**********************************************************************
C
C           cors(j) = Ksebref/Ksolref
C**********************************************************************
C
C
900   continue
C
C
C Calculation of Laplacian
C ````````````````````````
      call laplacianapprox
C
C
```

```
C Transient calculation
C ``````````````````````
C Ed inner tissue / interior nodes
C ````````````````````````````````
      do 1010, i = 1, iin - 1
       do 1000, j = 1, jed - 1
        cedia_new(i,j) = cedia(i,j) + deltat*(lapedia(i,j)
     1                  - ratek_edi*cedia(i,j))
        cedia(i,j) = cedia_new(i,j)
C*********************************************************************
C
C        cedia(i,j) = c(xia(i),zda(j))
C*********************************************************************
C
1000   continue
1010  continue
C
C
C Ed outer tissue / interior nodes
C ````````````````````````````````
      do 1030, i = iin + 1, iin + iout - 1
       do 1020, j = 1, jed - 1
        cedoa_new(i,j) = cedoa(i,j) + deltat*(lapedoa(i,j)
     1                  - ratek_edo*cedoa(i,j))
        cedoa(i,j) = cedoa_new(i,j)
C*********************************************************************
C
C        cedoa(i,j) = c(xia(i),zda(j))
C*********************************************************************
C
1020   continue
1030  continue
C
C
C De1 inner tissue / interior nodes
C ````````````````````````````````
      do 1050, i = 1, iin - 1
       do 1040, j = jed + 1 , jed + jde1 - 1
        cde1ia_new(i,j) = cde1ia(i,j)+deltat*(lapde1ia(i,j)
     1                  - ratek_de1i*cde1ia(i,j))
        cde1ia(i,j) = cde1ia_new(i,j)
C*********************************************************************
C
C        cde1ia(i,j) = c(xia(i),zda(j))
C*********************************************************************
C
1040   continue
1050  continue
C
C
C De1 outer tissue / interior nodes
C ````````````````````````````````
      do 1070, i = iin + 1, iin + iout - 1
       do 1060, j = jed + 1 , jed + jde1 - 1
        cde1oa_new(i,j) = cde1oa(i,j)+deltat*(lapde1oa(i,j)
     1                  - ratek_de1o*cde1oa(i,j))
        cde1oa(i,j) = cde1oa_new(i,j)
```

```
C*********************************************************************
C
C        cde1oa(i,j) = c(xia(i),zda(j))
C*********************************************************************
C
1060   continue
1070  continue
C
C
C De2 inner tissue / interior nodes
C ````````````````````````````````
      do 1090, i = 1, iin - 1
       do 1080, j = jed + jde1 + 1 , jed + jde1 + jde2 - 1
        cde2ia_new(i,j) = cde2ia(i,j)+deltat*(lapde2ia(i,j)
     1                  - ratek_de2i*cde2ia(i,j))
        cde2ia(i,j) = cde2ia_new(i,j)
C*********************************************************************
C
C        cde2ia(i,j) = c(xia(i),zda(j))
C*********************************************************************
C
1080   continue
1090  continue
C
C
C De2 outer tissue / interior nodes
C ````````````````````````````````
      do 1110, i = iin + 1, iin + iout - 1
       do 1100, j = jed + jde1 + 1, jed + jde1 + jde2 - 1
        cde2oa_new(i,j) = cde2oa(i,j)+deltat*(lapde2oa(i,j)
     1                  - ratek_de2o*cde2oa(i,j))
        cde2oa(i,j) = cde2oa_new(i,j)
C*********************************************************************
C
C        cde2oa(i,j) = c(xia(i),zda(j))
C*********************************************************************
C
1100   continue
1110  continue
C
C
C hd inner tissue / interior nodes
C ````````````````````````````````
      do 1114, i = 1, iin - 1
       do 1112, j = jed + jde1 + jde2 + 1 , jed + jde1 + jde2 + jhd - 1
        chdia_new(i,j) = chdia(i,j)+deltat*(laphdia(i,j)
     1                 - ratek_hdi*chdia(i,j))
        chdia(i,j) = chdia_new(i,j)
C*********************************************************************
C
C        chdia(i,j) = c(xia(i),zda(j))
C*********************************************************************
C
1112   continue
1114  continue
C
C
```

```
C hd outer tissue / interior nodes
C ````````````````````````````````
      do 1118, i = iin + 1, iin + iout - 1
       do 1116, j = jed + jde1 + jde2 + 1, jed + jde1 + jde2 + jhd - 1
        chdoa_new(i,j) = chdoa(i,j)+deltat*(laphdoa(i,j)
     1                 - ratek_hdo*chdoa(i,j))
        chdoa(i,j) = chdoa_new(i,j)
C**********************************************************************
C
C        chdoa(i,j) = c(xia(i),zda(j))
C**********************************************************************
C
1116   continue
1118  continue
C
C
C r-direction boundaries in Ed
C ````````````````````````````
C
C Ed left inner boundary
C ``````````````````````
C Solution for concentration by LU decomposition
C and back substitution
C
C Initialize coefficients of A:
C
      do 1122, k = 1, jdim
         do 1120, l = 1, jdim
            a(k,l) = 0.0d0
1120     continue
1122  continue
C
C Fill in coeff. values corresponding to unknowns:
C
      i = 0
C
      j = 1
      a(1,1) = (25.0d0/12.0d0)*(Bedl1(j)+Bedl2(j))-Bedl3(j)
      a(1,2) = -4.0d0*Bedl2(j)
      a(1,3) = 3.0d0*Bedl2(j)
      a(1,4) = (-4.0d0/3.0d0)*Bedl2(j)
      a(1,5) = 0.25d0*Bedl2(j)
C
      b(1) = Bedl1(j)*(4.0d0*cedia(i+1,j)-3.0d0*cedia(i+2,j)
     1     + (4.0d0/3.0d0)*cedia(i+3,j)-0.25d0*cedia(i+4,j))
     1     - Bedl4(j)*cors(j)
C
C**********************************************************************
C
C      open (unit = 35, file = 'test_b.txt')
      b_test(j) = a(1,1)*c_edi(0,1)+a(1,2)*c_edi(0,2)
     1          + a(1,3)*c_edi(0,3)+a(1,4)*c_edi(0,4)
     1          + a(1,5)*c_edi(0,5)
C      write (35, 7940)
C      write (35,9400) i, j, b_test(j), b(j)
C**********************************************************************
C
```

```
C
      j = 2
C      print*, j, Bedl1(j), Bedl2(j), Bedl3(j)
      a(2,1) = 0.25d0*Bedl2(j)
      a(2,2) = (25.0d0/12.0d0)*Bedl1(j)+(10.0d0/12.0d0)
     1         * Bedl2(j)-Bedl3(j)
      a(2,3) = -1.5d0*Bedl2(j)
      a(2,4) = 0.5d0*Bedl2(j)
      a(2,5) = (-1.0d0/12.0d0)*Bedl2(j)
C
      b(2) = Bedl1(j)*(4.0d0*cedia(i+1,j)-3.0d0*cedia(i+2,j)
     1     + (4.0d0/3.0d0)*cedia(i+3,j)-0.25d0*cedia(i+4,j))
     1     - Bedl4(j)*cors(j)
C
C**********************************************************************
C
      b_test(j) = a(2,1)*c_edi(0,1)+a(2,2)*c_edi(0,2)
     1          + a(2,3)*c_edi(0,3)+a(2,4)*c_edi(0,4)
     1          + a(2,5)*c_edi(0,5)
C      write (35,9400) i, j, b_test(j), b(j)
C**********************************************************************
C
C
      do 1124, j = 3, jed - 3
C         print*, j, Bedl1(j), Bedl2(j), Bedl3(j)
         a(j,j-2) = (1.0d0/12.0d0)*(-1.0d0)*Bedl2(j)
         a(j,j-1) = (1.0d0/12.0d0)*8.0d0*Bedl2(j)
         a(j,j)   = (25.0d0/12.0d0)*Bedl1(j)-Bedl3(j)
         a(j,j+1) = (1.0d0/12.0d0)*(-8.0d0)*Bedl2(j)
         a(j,j+2) = (1.0d0/12.0d0)*1.0d0*Bedl2(j)
C
         b(j) = Bedl1(j)*(4.0d0*cedia(i+1,j)-3.0d0*cedia(i+2,j)
     1     + (4.0d0/3.0d0)*cedia(i+3,j)-0.25d0*cedia(i+4,j))
     1     - Bedl4(j)*cors(j)
1124  continue
C
C**********************************************************************
C
      do 1126, j = 3, jed - 3
         b_test(j) = a(j,j-2)*c_edi(0,j-2)+a(j,j-1)*c_edi(0,j-1)
     1             + a(j,j)*c_edi(0,j)+a(j,j+1)*c_edi(0,j+1)
     1             + a(j,j+2)*c_edi(0,j+2)
C         write (35,9400) i, j, b_test(j), b(j)
1126  continue
C**********************************************************************
C
C
      j = jed - 2
C      print*, j, Bedl1(j), Bedl2(j), Bedl3(j)
      a(jed-2,jed-5) = (1.0d0/12.0d0)*Bedl2(j)
      a(jed-2,jed-4) = -0.5d0*Bedl2(j)
      a(jed-2,jed-3) = 1.50d0*Bedl2(j)
      a(jed-2,jed-2) = (25.0d0/12.0d0)*Bedl1(j)-(10.0d0/12.0d0)
     1                 * Bedl2(j)-Bedl3(j)
      a(jed-2,jed-1) = -0.25d0*Bedl2(j)
C
      b(jed-2) = Bedl1(j)*(4.0d0*cedia(i+1,j)-3.0d0*cedia(i+2,j)
```

```
     1     + (4.0d0/3.0d0)*cedia(i+3,j)-0.25d0*cedia(i+4,j))
     1     - Bedl4(j)*cors(j)
C
C*********************************************************************
C
      b_test(j) = a(jed-2,jed-5)*c_edi(0,jed-5)
     1          + a(jed-2,jed-4)*c_edi(0,jed-4)
     1          + a(jed-2,jed-3)*c_edi(0,jed-3)
     1          + a(jed-2,jed-2)*c_edi(0,jed-2)
     1          + a(jed-2,jed-1)*c_edi(0,jed-1)
C      write (35,9400) i, j, b_test(j), b(j)
C*********************************************************************
C
C
      j = jed - 1
C      print*, j, Bedl1(j), Bedl2(j), Bedl3(j)
      a(jed-1,jed-5) = -0.25d0*Bedl2(j)
      a(jed-1,jed-4) = (4.0d0/3.0d0)*Bedl2(j)
      a(jed-1,jed-3) = -3.0d0*Bedl2(j)
      a(jed-1,jed-2) = 4.0d0*Bedl2(j)
      a(jed-1,jed-1) = (25.0d0/12.0d0)*(Bedl1(j)-Bedl2(j))
     1                 - Bedl3(j)
C
      b(jed-1) = Bedl1(j)*(4.0d0*cedia(i+1,j)-3.0d0*cedia(i+2,j)
     1     + (4.0d0/3.0d0)*cedia(i+3,j)-0.25d0*cedia(i+4,j))
     1     - Bedl4(j)*cors(j)
C
C*********************************************************************
C
      b_test(j) = a(jed-1,jed-5)*c_edi(0,jed-5)
     1          + a(jed-1,jed-4)*c_edi(0,jed-4)
     1          + a(jed-1,jed-3)*c_edi(0,jed-3)
     1          + a(jed-1,jed-2)*c_edi(0,jed-2)
     1          + a(jed-1,jed-1)*c_edi(0,jed-1)
C      write (35,9400) i, j, b_test(j), b(j)
C*********************************************************************
C
C      open (unit = 39, file = 'testmatrix.txt')
C      write (39, 7940)
C
      do 5000, k = 1, jed - 1
         x(k) = c_edi(0,k)
5000  continue
C
      do 1129, k = 1, jed - 1
         sum = 0.0d0
         do 1131, l = 1, jed - 1
            sum = sum + a(k,l)*x(l)
1131     continue
C         write (39, 8000) i, sum, b(k)
1129  continue
C*********************************************************************
C
C
      call lu(jdim,jed-1,iscrat,a,detlog,idsgn)
      call back(jdim,jed-1,iscrat,a,b)
C
```

```
      do 1128, j = 1, jed - 1
         cedia(i,j) = b(j)
C         cedia(i,j) = 1.0d0
1128  continue
C
C
C Ed inner/outer tissue boundary
C ````````````````````````````
C
C Solution for concentration by LU decomposition
C and back substitution
C
C Initialize coefficients of A:
C
      do 1132, k = 1, jdim
         do 1130, l = 1, jdim
            a(k,l) = 0.0d0
1130     continue
1132  continue
C
C Fill in coeff. values corresponding to unknowns:
C
      i = iin
C
C Inner region
      j = 1
C
      a(1,1) = (-25.0d0/12.0d0)*(Bedio1i(j)+Bedio1o(j)*(Kedo/Kedi))
     1       + (25.0d0/12.0d0)*dfd_outer(zda(j))*Bedio2i(j)
      a(1,2) = -4.0d0*dfd_outer(zda(j))*Bedio2i(j)
      a(1,3) = 3.0d0*dfd_outer(zda(j))*Bedio2i(j)
      a(1,4) = (-4.0d0/3.0d0)*dfd_outer(zda(j))*Bedio2i(j)
      a(1,5) = 0.25d0*dfd_outer(zda(j))*Bedio2i(j)
C
      b(1) = Bedio1i(j)*(0.25d0*cedia(i-4,j)-(4.0d0/3.0d0)*cedia(i-3,j)
     1     + 3.0d0*cedia(i-2,j)-4.0d0*cedia(i-1,j))
     1     - Bedio1o(j)*(4.0d0*cedoa(i+1,j)-3.0d0*cedoa(i+2,j)
     1     + (4.0d0/3.0d0)*cedoa(i+3,j)-0.25d0*cedoa(i+4,j))
C
C*********************************************************************
C
C      open (unit = 35, file = 'test_b.txt')
      b_test(j) = a(1,1)*c_edi(iin,1)+a(1,2)*c_edi(iin,2)
     1          + a(1,3)*c_edi(iin,3)+a(1,4)*c_edi(iin,4)
     1          + a(1,5)*c_edi(iin,5)
C      write (35,9400) i, j, b_test(j), b(j)
C*********************************************************************
C
C
      j = 2
C
      a(2,1) = 0.25d0*dfd_outer(zda(j))*Bedio2i(j)
      a(2,2) = (-25.0d0/12.0d0)*(Bedio1i(j)+Bedio1o(j)
     1       * (Kedo/Kedi))+(10.0d0/12.0d0)*dfd_outer(zda(j))
     1       * Bedio2i(j)
      a(2,3) = -1.5d0*dfd_outer(zda(j))*Bedio2i(j)
      a(2,4) = 0.5d0*dfd_outer(zda(j))*Bedio2i(j)
```

```
      a(2,5) = -(1.0d0/12.0d0)*dfd_outer(zda(j))*Bedio2i(j)
C
      b(2) = Bedio1i(j)*(0.25d0*cedia(i-4,j)-(4.0d0/3.0d0)*cedia(i-3,j)
     1     + 3.0d0*cedia(i-2,j)-4.0d0*cedia(i-1,j))
     1     - Bedio1o(j)*(4.0d0*cedoa(i+1,j)-3.0d0*cedoa(i+2,j)
     1     + (4.0d0/3.0d0)*cedoa(i+3,j)-0.25d0*cedoa(i+4,j))
C
C*********************************************************************
C
      b_test(j) = a(2,1)*c_edi(iin,1)+a(2,2)*c_edi(iin,2)
     1          + a(2,3)*c_edi(iin,3)+a(2,4)*c_edi(iin,4)
     1          + a(2,5)*c_edi(iin,5)
C      write (35,9400) i, j, b_test(j), b(j)
C*********************************************************************
C
C
      do 1134, j = 3, jed - 3
C
         a(j,j-2) = (1.0d0/12.0d0)*(-1.0d0)*Bedio2i(j)
         a(j,j-1) = (1.0d0/12.0d0)*8.0d0*Bedio2i(j)
         a(j,j)   = (-25.0d0/12.0d0)*(Bedio1i(j)+Bedio1o(j)
     1            * (Kedo/Kedi))
         a(j,j+1) = (1.0d0/12.0d0)*(-8.0d0)*Bedio2i(j)
         a(j,j+2) = (1.0d0/12.0d0)*(1.0d0)*Bedio2i(j)
C
         b(j) = Bedio1i(j)*(0.25d0*cedia(i-4,j)-(4.0d0/3.0d0)
     1      * cedia(i-3,j)+3.0d0*cedia(i-2,j)-4.0d0*cedia(i-1,j))
     1      - Bedio1o(j)*(4.0d0*cedoa(i+1,j)-3.0d0*cedoa(i+2,j)
     1      + (4.0d0/3.0d0)*cedoa(i+3,j)-0.25d0*cedoa(i+4,j))
1134  continue
C
C*********************************************************************
C
      do 1135, j = 3, jed - 3
         b_test(j) = a(j,j-2)*c_edi(iin,j-2)+a(j,j-1)*c_edi(iin,j-1)
     1             + a(j,j)*c_edi(iin,j)+a(j,j+1)*c_edi(iin,j+1)
     1             + a(j,j+2)*c_edi(iin,j+2)
C         write (35,9400) i, j, b_test(j), b(j)
1135  continue
C*********************************************************************
C
C
      j = jed - 2
C
      a(jed-2,jed-5) = (1.0d0/12.0d0)*dfd_outer(zda(j))*Bedio2i(j)
      a(jed-2,jed-4) = -0.5d0*dfd_outer(zda(j))*Bedio2i(j)
      a(jed-2,jed-3) = 1.5d0*dfd_outer(zda(j))*Bedio2i(j)
      a(jed-2,jed-2) = (-25.0d0/12.0d0)*(Bedio1i(j)+Bedio1o(j)
     1             * (Kedo/Kedi))-(10.0d0/12.0d0)*dfd_outer(zda(j))
     1             * Bedio2i(j)
      a(jed-2,jed-1) = -0.25d0*dfd_outer(zda(j))*Bedio2i(j)
C
      b(jed-2) = Bedio1i(j)*(0.25d0*cedia(i-4,j)-(4.0d0/3.0d0)
     1     * cedia(i-3,j)+3.0d0*cedia(i-2,j)-4.0d0*cedia(i-1,j))
     1     - Bedio1o(j)*(4.0d0*cedoa(i+1,j)-3.0d0*cedoa(i+2,j)
     1     + (4.0d0/3.0d0)*cedoa(i+3,j)-0.25d0*cedoa(i+4,j))
C
```

```
C*********************************************************************
C
      b_test(j) = a(jed-2,jed-5)*c_edi(iin,jed-5)
     1          + a(jed-2,jed-4)*c_edi(iin,jed-4)
     1          + a(jed-2,jed-3)*c_edi(iin,jed-3)
     1          + a(jed-2,jed-2)*c_edi(iin,jed-2)
     1          + a(jed-2,jed-1)*c_edi(iin,jed-1)
C      write (35,9400) i, j, b_test(j), b(j)
C*********************************************************************
C
C
      j = jed - 1
C
      a(jed-1,jed-5) = -0.25d0*dfd_outer(zda(j))*Bedio2i(j)
      a(jed-1,jed-4) = (4.0d0/3.0d0)*dfd_outer(zda(j))*Bedio2i(j)
      a(jed-1,jed-3) = -3.0d0*dfd_outer(zda(j))*Bedio2i(j)
      a(jed-1,jed-2) = 4.0d0*dfd_outer(zda(j))*Bedio2i(j)
      a(jed-1,jed-1) = (-25.0d0/12.0d0)*(Bedio1i(j)+Bedio1o(j)
     1               * (Kedo/Kedi))-(25.0d0/12.0d0)*dfd_outer(zda(j))
     1               * Bedio2i(j)
C
      b(jed-1) = Bedio1i(j)*(0.25d0*cedia(i-4,j)-(4.0d0/3.0d0)
     1     * cedia(i-3,j)+3.0d0*cedia(i-2,j)-4.0d0*cedia(i-1,j))
     1     - Bedio1o(j)*(4.0d0*cedoa(i+1,j)-3.0d0*cedoa(i+2,j)
     1     + (4.0d0/3.0d0)*cedoa(i+3,j)-0.25d0*cedoa(i+4,j))

C
C*********************************************************************
C
      b_test(j) = a(jed-1,jed-5)*c_edi(iin,jed-5)
     1          + a(jed-1,jed-4)*c_edi(iin,jed-4)
     1          + a(jed-1,jed-3)*c_edi(iin,jed-3)
     1          + a(jed-1,jed-2)*c_edi(iin,jed-2)
     1          + a(jed-1,jed-1)*c_edi(iin,jed-1)
C      write (35,9400) i, j, b_test(j), b(j)
C*********************************************************************
C
      do 5100, k = 1, jed - 1
         x(k) = c_edi(iin,k)
5100  continue
C
      do 5200, k = 1, jed - 1
         sum = 0.0d0
         do 5300, l = 1, jed - 1
            sum = sum + a(k,l)*x(l)
5300     continue
C         write (39, 8000) i, sum, b(k)
5200  continue
C*********************************************************************
C
C
      call lu(jdim,jed-1,iscrat,a,detlog,idsgn)
      call back(jdim,jed-1,iscrat,a,b)
C
      do 1136, j = 1, jed - 1
         cedia(i,j) = b(j)
1136  continue
```

```
C
C
C Outer region
      j = 1
C
      a(1,1) = (-25.0d0/12.0d0)*(Bedio1i(j)*(Kedi/Kedo)+Bedio1o(j))
     1       + (25.0d0/12.0d0)*dfd_outer(zda(j))*Bedio2o(j)
      a(1,2) = -4.0d0*dfd_outer(zda(j))*Bedio2o(j)
      a(1,3) = 3.0d0*dfd_outer(zda(j))*Bedio2o(j)
      a(1,4) = (-4.0d0/3.0d0)*dfd_outer(zda(j))*Bedio2o(j)
      a(1,5) = 0.25d0*dfd_outer(zda(j))*Bedio2o(j)
C
      b(1) = Bedio1i(j)*(0.25d0*cedia(i-4,j)-(4.0d0/3.0d0)*cedia(i-3,j)
     1     + 3.0d0*cedia(i-2,j)-4.0d0*cedia(i-1,j))
     1     - Bedio1o(j)*(4.0d0*cedoa(i+1,j)-3.0d0*cedoa(i+2,j)
     1     + (4.0d0/3.0d0)*cedoa(i+3,j)-0.25d0*cedoa(i+4,j))
C
C**********************************************************************
C
C      open (unit = 35, file = 'test_b.txt')
      b_test(j) = a(1,1)*c_edo(iin,1)+a(1,2)*c_edo(iin,2)
     1          + a(1,3)*c_edo(iin,3)+a(1,4)*c_edo(iin,4)
     1          + a(1,5)*c_edo(iin,5)
C      write (35,9400) i, j, b_test(j), b(j)
C**********************************************************************
C
C
      j = 2
C
      a(2,1) = 0.25d0*dfd_outer(zda(j))*Bedio2o(j)
      a(2,2) = (-25.0d0/12.0d0)*(Bedio1i(j)*(Kedi/Kedo)
     1       + Bedio1o(j))+(10.0d0/12.0d0)*dfd_outer(zda(j))
     1       * Bedio2o(j)
      a(2,3) = -1.5d0*dfd_outer(zda(j))*Bedio2o(j)
      a(2,4) = 0.5d0*dfd_outer(zda(j))*Bedio2o(j)
      a(2,5) = -(1.0d0/12.0d0)*dfd_outer(zda(j))*Bedio2o(j)
C
      b(2) = Bedio1i(j)*(0.25d0*cedia(i-4,j)-(4.0d0/3.0d0)*cedia(i-3,j)
     1     + 3.0d0*cedia(i-2,j)-4.0d0*cedia(i-1,j))
     1     - Bedio1o(j)*(4.0d0*cedoa(i+1,j)-3.0d0*cedoa(i+2,j)
     1     + (4.0d0/3.0d0)*cedoa(i+3,j)-0.25d0*cedoa(i+4,j))
C
C**********************************************************************
C
      b_test(j) = a(2,1)*c_edo(iin,1)+a(2,2)*c_edo(iin,2)
     1          + a(2,3)*c_edo(iin,3)+a(2,4)*c_edo(iin,4)
     1          + a(2,5)*c_edo(iin,5)
C      write (35,9400) i, j, b_test(j), b(j)
C**********************************************************************
C
C
      do 1138, j = 3, jed - 3
C
         a(j,j-2) = (1.0d0/12.0d0)*(-1.0d0)*Bedio2o(j)
         a(j,j-1) = (1.0d0/12.0d0)*8.0d0*Bedio2o(j)
         a(j,j)   = (-25.0d0/12.0d0)*(Bedio1i(j)*(Kedi/Kedo)
     1            + Bedio1o(j))
```

```
         a(j,j+1) = (1.0d0/12.0d0)*(-8.0d0)*Bedio2o(j)
         a(j,j+2) = (1.0d0/12.0d0)*(1.0d0)*Bedio2o(j)
C
         b(j) = Bedio1i(j)*(0.25d0*cedia(i-4,j)-(4.0d0/3.0d0)
     1     * cedia(i-3,j)+3.0d0*cedia(i-2,j)-4.0d0*cedia(i-1,j))
     1     - Bedio1o(j)*(4.0d0*cedoa(i+1,j)-3.0d0*cedoa(i+2,j)
     1     + (4.0d0/3.0d0)*cedoa(i+3,j)-0.25d0*cedoa(i+4,j))
1138  continue
C
C*********************************************************************
C
      do 1139, j = 3, jed - 3
         b_test(j) = a(j,j-2)*c_edo(iin,j-2)+a(j,j-1)*c_edo(iin,j-1)
     1               + a(j,j)*c_edo(iin,j)+a(j,j+1)*c_edo(iin,j+1)
     1               + a(j,j+2)*c_edo(iin,j+2)
C         write (35,9400) i, j, b_test(j), b(j)
1139  continue
C*********************************************************************
C
C
      j = jed - 2
C
      a(jed-2,jed-5) = (1.0d0/12.0d0)*dfd_outer(zda(j))*Bedio2o(j)
      a(jed-2,jed-4) = -0.5d0*dfd_outer(zda(j))*Bedio2o(j)
      a(jed-2,jed-3) = 1.5d0*dfd_outer(zda(j))*Bedio2o(j)
      a(jed-2,jed-2) = (-25.0d0/12.0d0)*(Bedio1i(j)*(Kedi/Kedo)
     1               + Bedio1o(j))-(10.0d0/12.0d0)*dfd_outer(zda(j))
     1               * Bedio2o(j)
      a(jed-2,jed-1) = -0.25d0*dfd_outer(zda(j))*Bedio2o(j)
C
      b(jed-2) = Bedio1i(j)*(0.25d0*cedia(i-4,j)-(4.0d0/3.0d0)
     1     * cedia(i-3,j)+3.0d0*cedia(i-2,j)-4.0d0*cedia(i-1,j))
     1     - Bedio1o(j)*(4.0d0*cedoa(i+1,j)-3.0d0*cedoa(i+2,j)
     1     + (4.0d0/3.0d0)*cedoa(i+3,j)-0.25d0*cedoa(i+4,j))
C
C*********************************************************************
C
      b_test(j) = a(jed-2,jed-5)*c_edo(iin,jed-5)
     1          + a(jed-2,jed-4)*c_edo(iin,jed-4)
     1          + a(jed-2,jed-3)*c_edo(iin,jed-3)
     1          + a(jed-2,jed-2)*c_edo(iin,jed-2)
     1          + a(jed-2,jed-1)*c_edo(iin,jed-1)
C      write (35,9400) i, j, b_test(j), b(j)
C*********************************************************************
C
C
      j = jed - 1
C
      a(jed-1,jed-5) = -0.25d0*dfd_outer(zda(j))*Bedio2o(j)
      a(jed-1,jed-4) = (4.0d0/3.0d0)*dfd_outer(zda(j))*Bedio2o(j)
      a(jed-1,jed-3) = -3.0d0*dfd_outer(zda(j))*Bedio2o(j)
      a(jed-1,jed-2) = 4.0d0*dfd_outer(zda(j))*Bedio2o(j)
      a(jed-1,jed-1) = (-25.0d0/12.0d0)*(Bedio1i(j)*(Kedi/Kedo)
     1               + Bedio1o(j))-(25.0d0/12.0d0)*dfd_outer(zda(j))
     1               * Bedio2o(j)
C
      b(jed-1) = Bedio1i(j)*(0.25d0*cedia(i-4,j)-(4.0d0/3.0d0)
```

```
     1     * cedia(i-3,j)+3.0d0*cedia(i-2,j)-4.0d0*cedia(i-1,j))
     1     - Bedio1o(j)*(4.0d0*cedoa(i+1,j)-3.0d0*cedoa(i+2,j)
     1     + (4.0d0/3.0d0)*cedoa(i+3,j)-0.25d0*cedoa(i+4,j))

C
C*********************************************************************
C
      b_test(j) = a(jed-1,jed-5)*c_edo(iin,jed-5)
     1          + a(jed-1,jed-4)*c_edo(iin,jed-4)
     1          + a(jed-1,jed-3)*c_edo(iin,jed-3)
     1          + a(jed-1,jed-2)*c_edo(iin,jed-2)
     1          + a(jed-1,jed-1)*c_edo(iin,jed-1)
C      write (35,9400) i, j, b_test(j), b(j)
C*********************************************************************
C
      do 5400, k = 1, jed - 1
         x(k) = c_edo(iin,k)
5400  continue
C
      do 5500, k = 1, jed - 1
         sum = 0.0d0
         do 5600, l = 1, jed - 1
            sum = sum + a(k,l)*x(l)
5600     continue
C         write (39, 8000) i, sum, b(k)
5500  continue
C*********************************************************************
C
C
      call lu(jdim,jed-1,iscrat,a,detlog,idsgn)
      call back(jdim,jed-1,iscrat,a,b)
C
      do 1140, j = 1, jed - 1
         cedoa(i,j) = b(j)
1140  continue
C
C
C Ed right outer boundary
C ```````````````````````
      i = iin + iout
C
      do 1142, j = 1, jed - 1
C
      cedoa(i,j) = (48.0d0*cedoa(i-1,j)-36.0d0*cedoa(i-2,j)
     1   + 16.0d0*cedoa(i-3,j)-3.0d0*cedoa(i-4,j))
     1   / 25.0d0
C      cedoa(i,j) = 0.0d0
1142  continue
C
C
C r-direction boundaries in De1
C ```````````````````````````````
C
C Solution for concentration by LU decomposition
C and back substitution
C
C Initialize coefficients of A:
```

```
C
      do 1446, k = 1, jdim
         do 1444, l = 1, jdim
            a(k,l) = 0.0d0
1444     continue
         b(k) = 0.0d0
         iscrat(k) = 0.0d0
1446  continue
C
C Fill in coeff. values corresponding to unknowns:
C
      i = 0
C
      j = jed + 1
      a(1,1) = (25.0d0/12.0d0)*(Bde1l1(j)+Bde1l2(j))-Bde1l3(j)
      a(1,2) = -4.0d0*Bde1l2(j)
      a(1,3) = 3.0d0*Bde1l2(j)
      a(1,4) = (-4.0d0/3.0d0)*Bde1l2(j)
      a(1,5) = 0.25d0*Bde1l2(j)
C
      b(1) = Bde1l1(j)*(4.0d0*cde1ia(i+1,j)-3.0d0*cde1ia(i+2,j)
     1     + (4.0d0/3.0d0)*cde1ia(i+3,j)-0.25d0*cde1ia(i+4,j))
     1     - Bde1l4(j)*cors(j)
C
C**********************************************************************
C
C
      b_test(1) = a(1,1)*c_de1i(0,jed+1)+a(1,2)*c_de1i(0,jed+2)
     1          + a(1,3)*c_de1i(0,jed+3)+a(1,4)*c_de1i(0,jed+4)
     1          + a(1,5)*c_de1i(0,jed+5)
C      write (35, 7950)
C      write (35,9400) i, 1, b_test(1), b(1)
C**********************************************************************
C
C
      j = jed + 2
      a(2,1) = 0.25d0*Bde1l2(j)
      a(2,2) = (25.0d0/12.0d0)*Bde1l1(j)+(10.0d0/12.0d0)
     1         * Bde1l2(j)-Bde1l3(j)
      a(2,3) = -1.5d0*Bde1l2(j)
      a(2,4) = 0.5d0*Bde1l2(j)
      a(2,5) = (-1.0d0/12.0d0)*Bde1l2(j)
C
      b(2) = Bde1l1(j)*(4.0d0*cde1ia(i+1,j)-3.0d0*cde1ia(i+2,j)
     1     + (4.0d0/3.0d0)*cde1ia(i+3,j)-0.25d0*cde1ia(i+4,j))
     1     - Bde1l4(j)*cors(j)
C
C**********************************************************************
C
C
      b_test(2) = a(2,1)*c_de1i(0,jed+1)+a(2,2)*c_de1i(0,jed+2)
     1          + a(2,3)*c_de1i(0,jed+3)+a(2,4)*c_de1i(0,jed+4)
     1          + a(2,5)*c_de1i(0,jed+5)
C      write (35,9400) i, 2, b_test(2), b(2)
C**********************************************************************
C
C
```

```
      do 1448, j = jed + 3, jed + jde1 - 3
         a(j-jed,j-jed-2) = (1.0d0/12.0d0)*(-1.0d0)*Bde1l2(j)
         a(j-jed,j-jed-1) = (1.0d0/12.0d0)*8.0d0*Bde1l2(j)
         a(j-jed,j-jed)   = (25.0d0/12.0d0)*Bde1l1(j)-Bde1l3(j)
         a(j-jed,j-jed+1) = (1.0d0/12.0d0)*(-8.0d0)*Bde1l2(j)
         a(j-jed,j-jed+2) = (1.0d0/12.0d0)*1.0d0*Bde1l2(j)
C
         b(j-jed) = Bde1l1(j)*(4.0d0*cde1ia(i+1,j)-3.0d0*cde1ia(i+2,j)
     1     + (4.0d0/3.0d0)*cde1ia(i+3,j)-0.25d0*cde1ia(i+4,j))
     1     - Bde1l4(j)*cors(j)
C
C*********************************************************************
C
1448  continue
C
      do 1450, j = jed + 3, jed + jde1 - 3
C
         b_test(j-jed) = a(j-jed,j-jed-2)*c_de1i(0,j-2)
     1             + a(j-jed,j-jed-1)*c_de1i(0,j-1)
     1             + a(j-jed,j-jed)*c_de1i(0,j)
     1             + a(j-jed,j-jed+1)*c_de1i(0,j+1)
     1             + a(j-jed,j-jed+2)*c_de1i(0,j+2)
C         write (35,9400) i, j-jed, b_test(j-jed), b(j-jed)
1450  continue
C*********************************************************************
C
C
      j = jed + jde1 - 2
      a(jde1-2,jde1-5) = (1.0d0/12.0d0)*Bde1l2(j)
      a(jde1-2,jde1-4) = -0.5d0*Bde1l2(j)
      a(jde1-2,jde1-3) = 1.50d0*Bde1l2(j)
      a(jde1-2,jde1-2) = (25.0d0/12.0d0)*Bde1l1(j)
     1            -(10.0d0/12.0d0) * Bde1l2(j)-Bde1l3(j)
      a(jde1-2,jde1-1) = -0.25d0*Bde1l2(j)
C
      b(jde1-2) = Bde1l1(j)*(4.0d0*cde1ia(i+1,j)-3.0d0
     1              * cde1ia(i+2,j)+(4.0d0/3.0d0)*cde1ia(i+3,j)
     1              - 0.25d0*cde1ia(i+4,j))-Bde1l4(j)*cors(j)
C
C*********************************************************************
C
C
      b_test(jde1-2) = a(jde1-2,jde1-5)*c_de1i(0,jed + jde1-5)
     1               + a(jde1-2,jde1-4)*c_de1i(0,jed + jde1-4)
     1               + a(jde1-2,jde1-3)*c_de1i(0,jed + jde1-3)
     1               + a(jde1-2,jde1-2)*c_de1i(0,jed + jde1-2)
     1               + a(jde1-2,jde1-1)*c_de1i(0,jed + jde1-1)
C      print*, c_de1i(0,jde1-5), c_de1i(0,jde1-4),
C     1 c_de1i(0,jde1-3), c_de1i(0,jde1-2), c_de1i(0,jde1-1)
C      write (35,9400) i, jde1-2, b_test(jde1-2), b(jde1-2)
C*********************************************************************
C
C
      j = jed + jde1 - 1
      a(jde1-1,jde1-5) = -0.25d0*Bde1l2(j)
      a(jde1-1,jde1-4) = (4.0d0/3.0d0)*Bde1l2(j)
      a(jde1-1,jde1-3) = -3.0d0*Bde1l2(j)
```

```
      a(jde1-1,jde1-2) = 4.0d0*Bde1l2(j)
      a(jde1-1,jde1-1) = (25.0d0/12.0d0)*(Bde1l1(j)
     1                         - Bde1l2(j))-Bde1l3(j)
C
      b(jde1-1) = Bde1l1(j)*(4.0d0*cde1ia(i+1,j)-3.0d0
     1              * cde1ia(i+2,j)+(4.0d0/3.0d0)*cde1ia(i+3,j)
     1              - 0.25d0*cde1ia(i+4,j))-Bde1l4(j)*cors(j)
C
C**********************************************************************
C
C
      b_test(jde1-1) = a(jde1-1,jde1-5)*c_de1i(0,jed + jde1-5)
     1               + a(jde1-1,jde1-4)*c_de1i(0,jed + jde1-4)
     1               + a(jde1-1,jde1-3)*c_de1i(0,jed + jde1-3)
     1               + a(jde1-1,jde1-2)*c_de1i(0,jed + jde1-2)
     1               + a(jde1-1,jde1-1)*c_de1i(0,jed + jde1-1)
C      write (35,9400) i, jde1-1, b_test(jde1-1), b(jde1-1)
C**********************************************************************
C
C      write (39, 7950)
      do 5700, k = jed + 1, jed + jde1 - 1
         x(k-jed) = c_de1i(0,k)
5700  continue
C
      do 5800, k = 1, jde1 - 1
         sum = 0.0d0
         do 5900, l = 1, jde1 - 1
            sum = sum + a(k,l)*x(l)
5900     continue
C         write (39, 8000) i, sum, b(k)
5800  continue
C**********************************************************************
C
C
      call lu(jdim,jde1-1,iscrat,a,detlog,idsgn)
      call back(jdim,jde1-1,iscrat,a,b)
C
C      open (unit = 36, file = 'test_c_val.txt')
C
      do 1452, j = jed + 1, jed + jde1 - 1
         cde1ia(i,j) = b(j-jed)
C         cde1ia(i,j) = 1.0d0
C
C**********************************************************************
C
C         write (36,9350), i, j, cde1ia(i,j), b(j-jed)
C**********************************************************************
C
1452  continue
C
C
C De1 inner/outer tissue boundary
C ````````````````````````````````
C
C Solution for concentration by LU decomposition
C and back substitution
C
```

```
C Initialize coefficients of A:
C
      do 1156, k = 1, jdim
         do 1154, l = 1, jdim
            a(k,l) = 0.0d0
1154     continue
1156  continue
C
C Fill in coeff. values corresponding to unknowns:
C
      i = iin
C
C Inner region
      j = jed + 1
C
      a(1,1) = (-25.0d0/12.0d0)*(Bde1io1i(j)+Bde1io1o(j)*(Kde1o/Kde1i))
     1       + (25.0d0/12.0d0)*dfd_outer(zda(j))*Bde1io2i(j)
      a(1,2) = -4.0d0*dfd_outer(zda(j))*Bde1io2i(j)
      a(1,3) = 3.0d0*dfd_outer(zda(j))*Bde1io2i(j)
      a(1,4) = (-4.0d0/3.0d0)*dfd_outer(zda(j))*Bde1io2i(j)
      a(1,5) = 0.25d0*dfd_outer(zda(j))*Bde1io2i(j)
C
      b(1) = Bde1io1i(j)*(0.25d0*cde1ia(i-4,j)-(4.0d0/3.0d0)
     1     * cde1ia(i-3,j)+3.0d0*cde1ia(i-2,j)-4.0d0*cde1ia(i-1,j))
     1     - Bde1io1o(j)*(4.0d0*cde1oa(i+1,j)-3.0d0*cde1oa(i+2,j)
     1     + (4.0d0/3.0d0)*cde1oa(i+3,j)-0.25d0*cde1oa(i+4,j))
C
C*****************************************************************
C
C      open (unit = 35, file = 'test_b.txt')
      b_test(1) = a(1,1)*c_de1i(iin,jed+1)+a(1,2)*c_de1i(iin,jed+2)
     1          + a(1,3)*c_de1i(iin,jed+3)+a(1,4)*c_de1i(iin,jed+4)
     1          + a(1,5)*c_de1i(iin,jed+5)
C      write (35,9400) i, 1, b_test(1), b(1)
C*****************************************************************
C
C
      j = jed + 2
C
      a(2,1) = 0.25d0*dfd_outer(zda(j))*Bde1io2i(j)
      a(2,2) = (-25.0d0/12.0d0)*(Bde1io1i(j)+Bde1io1o(j)
     1       * (Kde1o/Kde1i))+(10.0d0/12.0d0)*dfd_outer(zda(j))
     1       * Bde1io2i(j)
      a(2,3) = -1.5d0*dfd_outer(zda(j))*Bde1io2i(j)
      a(2,4) = 0.5d0*dfd_outer(zda(j))*Bde1io2i(j)
      a(2,5) = -(1.0d0/12.0d0)*dfd_outer(zda(j))*Bde1io2i(j)
C
      b(2) = Bde1io1i(j)*(0.25d0*cde1ia(i-4,j)-(4.0d0/3.0d0)
     1     * cde1ia(i-3,j)+3.0d0*cde1ia(i-2,j)-4.0d0*cde1ia(i-1,j))
     1     - Bde1io1o(j)*(4.0d0*cde1oa(i+1,j)-3.0d0*cde1oa(i+2,j)
     1     + (4.0d0/3.0d0)*cde1oa(i+3,j)-0.25d0*cde1oa(i+4,j))
C
C*****************************************************************
C
      b_test(2) = a(2,1)*c_de1i(iin,jed+1)+a(2,2)*c_de1i(iin,jed+2)
     1          + a(2,3)*c_de1i(iin,jed+3)+a(2,4)*c_de1i(iin,jed+4)
     1          + a(2,5)*c_de1i(iin,jed+5)
```

```
C      write (35,9400) i, 2, b_test(2), b(2)
C*********************************************************************
C
C
      do 1158, j = jed + 3, jed + jde1 - 3
C
         a(j-jed,j-jed-2) = (1.0d0/12.0d0)*(-1.0d0)*Bde1io2i(j)
         a(j-jed,j-jed-1) = (1.0d0/12.0d0)*8.0d0*Bde1io2i(j)
         a(j-jed,j-jed)   = (-25.0d0/12.0d0)*(Bde1io1i(j)+Bde1io1o(j)
     1            * (Kde1o/Kde1i))
         a(j-jed,j-jed+1) = (1.0d0/12.0d0)*(-8.0d0)*Bde1io2i(j)
         a(j-jed,j-jed+2) = (1.0d0/12.0d0)*(1.0d0)*Bde1io2i(j)
C
         b(j-jed) = Bde1io1i(j)*(0.25d0*cde1ia(i-4,j)-(4.0d0/3.0d0)
     1     * cde1ia(i-3,j)+3.0d0*cde1ia(i-2,j)-4.0d0*cde1ia(i-1,j))
     1     - Bde1io1o(j)*(4.0d0*cde1oa(i+1,j)-3.0d0*cde1oa(i+2,j)
     1     + (4.0d0/3.0d0)*cde1oa(i+3,j)-0.25d0*cde1oa(i+4,j))
1158  continue
C
C*********************************************************************
C
      do 1159, j = jed + 3, jed + jde1 - 3
         b_test(j-jed) = a(j-jed,j-jed-2)*c_de1i(iin,j-2)
     1                 + a(j-jed,j-jed-1)*c_de1i(iin,j-1)
     1                 + a(j-jed,j-jed)*c_de1i(iin,j)
     1                 + a(j-jed,j-jed+1)*c_de1i(iin,j+1)
     1                 + a(j-jed,j-jed+2)*c_de1i(iin,j+2)
C         write (35,9400) i, j-jed, b_test(j-jed), b(j-jed)
1159  continue
C*********************************************************************
C
C
      j = jed + jde1 - 2
C
      a(jde1-2,jde1-5) = (1.0d0/12.0d0)*dfd_outer(zda(j))*Bde1io2i(j)
      a(jde1-2,jde1-4) = -0.5d0*dfd_outer(zda(j))*Bde1io2i(j)
      a(jde1-2,jde1-3) = 1.5d0*dfd_outer(zda(j))*Bde1io2i(j)
      a(jde1-2,jde1-2) = (-25.0d0/12.0d0)*(Bde1io1i(j)+Bde1io1o(j)
     1               * (Kde1o/Kde1i))-(10.0d0/12.0d0)*dfd_outer(zda(j))
     1               * Bde1io2i(j)
      a(jde1-2,jde1-1) = -0.25d0*dfd_outer(zda(j))*Bde1io2i(j)
C
      b(jde1-2) = Bde1io1i(j)*(0.25d0*cde1ia(i-4,j)-(4.0d0/3.0d0)
     1     * cde1ia(i-3,j)+3.0d0*cde1ia(i-2,j)-4.0d0*cde1ia(i-1,j))
     1     - Bde1io1o(j)*(4.0d0*cde1oa(i+1,j)-3.0d0*cde1oa(i+2,j)
     1     + (4.0d0/3.0d0)*cde1oa(i+3,j)-0.25d0*cde1oa(i+4,j))
C
C*********************************************************************
C
      b_test(jde1-2) = a(jde1-2,jde1-5)*c_de1i(iin,jed+jde1-5)
     1          + a(jde1-2,jde1-4)*c_de1i(iin,jed+jde1-4)
     1          + a(jde1-2,jde1-3)*c_de1i(iin,jed+jde1-3)
     1          + a(jde1-2,jde1-2)*c_de1i(iin,+jed+jde1-2)
     1          + a(jde1-2,jde1-1)*c_de1i(iin,+jed+jde1-1)
C      write (35,9400) i, jde1-2, b_test(jde1-2), b(jde1-2)
C*********************************************************************
C
```

```
C
      j =  jed + jde1 - 1
C
      a(jde1-1,jde1-5) = -0.25d0*dfd_outer(zda(j))*Bde1io2i(j)
      a(jde1-1,jde1-4) = (4.0d0/3.0d0)*dfd_outer(zda(j))*Bde1io2i(j)
      a(jde1-1,jde1-3) = -3.0d0*dfd_outer(zda(j))*Bde1io2i(j)
      a(jde1-1,jde1-2) = 4.0d0*dfd_outer(zda(j))*Bde1io2i(j)
      a(jde1-1,jde1-1) = (-25.0d0/12.0d0)*(Bde1io1i(j)+Bde1io1o(j)
     1               * (Kde1o/Kde1i))-(25.0d0/12.0d0)*dfd_outer(zda(j))
     1               * Bde1io2i(j)
C
      b(jde1-1) = Bde1io1i(j)*(0.25d0*cde1ia(i-4,j)-(4.0d0/3.0d0)
     1     * cde1ia(i-3,j)+3.0d0*cde1ia(i-2,j)-4.0d0*cde1ia(i-1,j))
     1     - Bde1io1o(j)*(4.0d0*cde1oa(i+1,j)-3.0d0*cde1oa(i+2,j)
     1     + (4.0d0/3.0d0)*cde1oa(i+3,j)-0.25d0*cde1oa(i+4,j))

C
C*********************************************************************
C
      b_test(jde1-1) = a(jde1-1,jde1-5)*c_de1i(iin,jed + jde1-5)
     1          + a(jde1-1,jde1-4)*c_de1i(iin,jed + jde1-4)
     1          + a(jde1-1,jde1-3)*c_de1i(iin,jed + jde1-3)
     1          + a(jde1-1,jde1-2)*c_de1i(iin,jed + jde1-2)
     1          + a(jde1-1,jde1-1)*c_de1i(iin,jed + jde1-1)
C      write (35,9400) i, jde1-1, b_test(jde1-1), b(jde1-1)
C*********************************************************************
C
      do 5910, k = jed + 1, jed + jde1 - 1
         x(k-jed) = c_de1i(iin,k)
5910  continue
C
      do 6000, k = 1, jde1 - 1
         sum = 0.0d0
         do 6100, l = 1, jde1 - 1
            sum = sum + a(k,l)*x(l)
6100           continue
C         write (39, 8000) i, sum, b(k)
6000      continue
C*********************************************************************
C
C
      call lu(jdim,jde1-1,iscrat,a,detlog,idsgn)
      call back(jdim,jde1-1,iscrat,a,b)
C
      do 1160, j = jed + 1, jed + jde1 - 1
         cde1ia(i,j) = b(j-jed)
1160  continue
C
C Outer region
      j = jed + 1
C
      a(1,1) = (-25.0d0/12.0d0)*(Bde1io1i(j)*(Kde1i/Kde1o)+Bde1io1o(j))
     1       + (25.0d0/12.0d0)*dfd_outer(zda(j))*Bde1io2o(j)
      a(1,2) = -4.0d0*dfd_outer(zda(j))*Bde1io2o(j)
      a(1,3) = 3.0d0*dfd_outer(zda(j))*Bde1io2o(j)
      a(1,4) = (-4.0d0/3.0d0)*dfd_outer(zda(j))*Bde1io2o(j)
      a(1,5) = 0.25d0*dfd_outer(zda(j))*Bde1io2o(j)
```

```
C
      b(1) = Bde1io1i(j)*(0.25d0*cde1ia(i-4,j)-(4.0d0/3.0d0)
     1     * cde1ia(i-3,j)
     1     + 3.0d0*cde1ia(i-2,j)-4.0d0*cde1ia(i-1,j))
     1     - Bde1io1o(j)*(4.0d0*cde1oa(i+1,j)-3.0d0*cde1oa(i+2,j)
     1     + (4.0d0/3.0d0)*cde1oa(i+3,j)-0.25d0*cde1oa(i+4,j))
C
C*****************************************************************
C
C      open (unit = 35, file = 'test_b.txt')
      b_test(1) = a(1,1)*c_de1o(iin,jed+1)+a(1,2)*c_de1o(iin,jed+2)
     1          + a(1,3)*c_de1o(iin,jed+3)+a(1,4)*c_de1o(iin,jed+4)
     1          + a(1,5)*c_de1o(iin,jed+5)
C      write (35,9400) i, 1, b_test(1), b(1)
C*****************************************************************
C
C
      j = jed + 2
C
      a(2,1) = 0.25d0*dfd_outer(zda(j))*Bde1io2o(j)
      a(2,2) = (-25.0d0/12.0d0)*(Bde1io1i(j)*(Kde1i/Kde1o)
     1       + Bde1io1o(j))+(10.0d0/12.0d0)*dfd_outer(zda(j))
     1       * Bde1io2o(j)
      a(2,3) = -1.5d0*dfd_outer(zda(j))*Bde1io2o(j)
      a(2,4) = 0.5d0*dfd_outer(zda(j))*Bde1io2o(j)
      a(2,5) = -(1.0d0/12.0d0)*dfd_outer(zda(j))*Bde1io2o(j)
C
      b(2) = Bde1io1i(j)*(0.25d0*cde1ia(i-4,j)-(4.0d0/3.0d0)
     1     * cde1ia(i-3,j)
     1     + 3.0d0*cde1ia(i-2,j)-4.0d0*cde1ia(i-1,j))
     1     - Bde1io1o(j)*(4.0d0*cde1oa(i+1,j)-3.0d0*cde1oa(i+2,j)
     1     + (4.0d0/3.0d0)*cde1oa(i+3,j)-0.25d0*cde1oa(i+4,j))
C
C*****************************************************************
C
      b_test(2) = a(2,1)*c_de1o(iin,jed+1)+a(2,2)*c_de1o(iin,jed+2)
     1          + a(2,3)*c_de1o(iin,jed+3)+a(2,4)*c_de1o(iin,jed+4)
     1          + a(2,5)*c_de1o(iin,jed+5)
C      write (35,9400) i, 2, b_test(2), b(2)
C*****************************************************************
C
C
      do 1162, j = jed + 3, jed + jde1 - 3
C
         a(j-jed,j-jed-2) = (1.0d0/12.0d0)*(-1.0d0)*Bde1io2o(j)
         a(j-jed,j-jed-1) = (1.0d0/12.0d0)*8.0d0*Bde1io2o(j)
         a(j-jed,j-jed)   = (-25.0d0/12.0d0)*(Bde1io1i(j)*(Kde1i/Kde1o)
     1             + Bde1io1o(j))
         a(j-jed,j-jed+1) = (1.0d0/12.0d0)*(-8.0d0)*Bde1io2o(j)
         a(j-jed,j-jed+2) = (1.0d0/12.0d0)*(1.0d0)*Bde1io2o(j)
C
         b(j-jed) = Bde1io1i(j)*(0.25d0*cde1ia(i-4,j)-(4.0d0/3.0d0)
     1     * cde1ia(i-3,j)+3.0d0*cde1ia(i-2,j)-4.0d0*cde1ia(i-1,j))
     1     - Bde1io1o(j)*(4.0d0*cde1oa(i+1,j)-3.0d0*cde1oa(i+2,j)
     1     + (4.0d0/3.0d0)*cde1oa(i+3,j)-0.25d0*cde1oa(i+4,j))
1162  continue
C
```

```
C*********************************************************************
C
      do 1163, j = jed + 3, jed + jde1 - 3
         b_test(j-jed) = a(j-jed,j-jed-2)*c_de1o(iin,j-2)
     1                 + a(j-jed,j-jed-1)*c_de1o(iin,j-1)
     1                 + a(j-jed,j-jed)*c_de1o(iin,j)
     1                 + a(j-jed,j-jed+1)*c_de1o(iin,j+1)
     1                 + a(j-jed,j-jed+2)*c_de1o(iin,j+2)
C         write (35,9400) i, j-jed, b_test(j-jed), b(j-jed)
1163  continue
C*********************************************************************
C
C
      j = jed + jde1 - 2
C
      a(jde1-2,jde1-5) = (1.0d0/12.0d0)*dfd_outer(zda(j))*Bde1io2o(j)
      a(jde1-2,jde1-4) = -0.5d0*dfd_outer(zda(j))*Bde1io2o(j)
      a(jde1-2,jde1-3) = 1.5d0*dfd_outer(zda(j))*Bde1io2o(j)
      a(jde1-2,jde1-2) = (-25.0d0/12.0d0)*(Bde1io1i(j)*(Kde1i/Kde1o)
     1               + Bde1io1o(j))-(10.0d0/12.0d0)*dfd_outer(zda(j))
     1               * Bde1io2o(j)
      a(jde1-2,jde1-1) = -0.25d0*dfd_outer(zda(j))*Bde1io2o(j)
C
      b(jde1-2) = Bde1io1i(j)*(0.25d0*cde1ia(i-4,j)-(4.0d0/3.0d0)
     1     * cde1ia(i-3,j)+3.0d0*cde1ia(i-2,j)-4.0d0*cde1ia(i-1,j))
     1     - Bde1io1o(j)*(4.0d0*cde1oa(i+1,j)-3.0d0*cde1oa(i+2,j)
     1     + (4.0d0/3.0d0)*cde1oa(i+3,j)-0.25d0*cde1oa(i+4,j))
C
C*********************************************************************
C
      b_test(jde1-2) = a(jde1-2,jde1-5)*c_de1o(iin,jed + jde1-5)
     1          + a(jde1-2,jde1-4)*c_de1o(iin,jed + jde1-4)
     1          + a(jde1-2,jde1-3)*c_de1o(iin,jed + jde1-3)
     1          + a(jde1-2,jde1-2)*c_de1o(iin,jed + jde1-2)
     1          + a(jde1-2,jde1-1)*c_de1o(iin,jed + jde1-1)
C      write (35,9400) i, jde1-2, b_test(jde1-2), b(jde1-2)
C*********************************************************************
C
C
      j = jed + jde1 - 1
C
      a(jde1-1,jde1-5) = -0.25d0*dfd_outer(zda(j))*Bde1io2o(j)
      a(jde1-1,jde1-4) = (4.0d0/3.0d0)*dfd_outer(zda(j))*Bde1io2o(j)
      a(jde1-1,jde1-3) = -3.0d0*dfd_outer(zda(j))*Bde1io2o(j)
      a(jde1-1,jde1-2) = 4.0d0*dfd_outer(zda(j))*Bde1io2o(j)
      a(jde1-1,jde1-1) = (-25.0d0/12.0d0)*(Bde1io1i(j)*(Kde1i/Kde1o)
     1               + Bde1io1o(j))-(25.0d0/12.0d0)*dfd_outer(zda(j))
     1               * Bde1io2o(j)
C
      b(jde1-1) = Bde1io1i(j)*(0.25d0*cde1ia(i-4,j)-(4.0d0/3.0d0)
     1     * cde1ia(i-3,j)+3.0d0*cde1ia(i-2,j)-4.0d0*cde1ia(i-1,j))
     1     - Bde1io1o(j)*(4.0d0*cde1oa(i+1,j)-3.0d0*cde1oa(i+2,j)
     1     + (4.0d0/3.0d0)*cde1oa(i+3,j)-0.25d0*cde1oa(i+4,j))

C
C*********************************************************************
C
```

```
      b_test(jde1-1) = a(jde1-1,jde1-5)*c_de1o(iin,jed + jde1-5)
     1          + a(jde1-1,jde1-4)*c_de1o(iin,jed + jde1-4)
     1          + a(jde1-1,jde1-3)*c_de1o(iin,jed + jde1-3)
     1          + a(jde1-1,jde1-2)*c_de1o(iin,jed + jde1-2)
     1          + a(jde1-1,jde1-1)*c_de1o(iin,jed + jde1-1)
C      write (35,9400) i, jde1-1, b_test(jde1-1), b(jde1-1)
C*********************************************************************
C
      do 6200, k = jed + 1, jed + jde1 - 1
         x(k-jed) = c_de1o(iin,k)
6200      continue
C
      do 6300, k = 1, jde1 - 1
         sum = 0.0d0
         do 6400, l = 1, jde1 - 1
            sum = sum + a(k,l)*x(l)
6400     continue
C         write (39, 8000) i, sum, b(k)
6300  continue
C*********************************************************************
C
C
      call lu(jdim,jde1-1,iscrat,a,detlog,idsgn)
      call back(jdim,jde1-1,iscrat,a,b)
C
      do 1164, j = jed + 1, jed + jde1 - 1
         cde1oa(i,j) = b(j-jed)
1164  continue
C
C
C De1 right outer boundary
C ````````````````````````
      i = iin + iout
C
      do 1166, j = jed + 1, jed + jde1 - 1
C
      cde1oa(i,j) = (48.0d0*cde1oa(i-1,j)-36.0d0*cde1oa(i-2,j)
     1   + 16.0d0*cde1oa(i-3,j)-3.0d0*cde1oa(i-4,j))
     1   / 25.0d0
C      cde1oa(i,j) = 0.0d0
1166  continue
C
C
C r-direction boundaries in De2
C `````````````````````````````
C
C Solution for concentration by LU decomposition
C and back substitution
C
C Initialize coefficients of A:
C
      do 5170, k = 1, jdim
         do 1168, l = 1, jdim
            a(k,l) = 0.0d0
1168     continue
         b(k) = 0.0d0
         iscrat(k) = 0.0d0
```

```
5170  continue
C
C Fill in coeff. values corresponding to unknowns:
C
      i = 0
C
      j = jed + jde1 + 1
      a(1,1) = (25.0d0/12.0d0)*(Bde2l1(j)+Bde2l2(j))-Bde2l3(j)
      a(1,2) = -4.0d0*Bde2l2(j)
      a(1,3) = 3.0d0*Bde2l2(j)
      a(1,4) = (-4.0d0/3.0d0)*Bde2l2(j)
      a(1,5) = 0.25d0*Bde2l2(j)
C
      b(1) = Bde2l1(j)*(4.0d0*cde2ia(i+1,j)-3.0d0*cde2ia(i+2,j)
     1     + (4.0d0/3.0d0)*cde2ia(i+3,j)-0.25d0*cde2ia(i+4,j))
     1     - Bde2l4(j)*cors(j)
C
C*********************************************************************
C
      b_test(1) = a(1,1)*c_de2i(0,jed+jde1+1)
     1          + a(1,2)*c_de2i(0,jed+jde1+2)
     1          + a(1,3)*c_de2i(0,jed+jde1+3)
     1          + a(1,4)*c_de2i(0,jed+jde1+4)
     1          + a(1,5)*c_de2i(0,jed+jde1+5)
C      write (35, 7960)
C      write (35,9400) i, 1, b_test(1), b(1)
C*********************************************************************
C
C
      j = jed + jde1 + 2
      a(2,1) = 0.25d0*Bde2l2(j)
      a(2,2) = (25.0d0/12.0d0)*Bde2l1(j)+(10.0d0/12.0d0)
     1         * Bde2l2(j)-Bde2l3(j)
      a(2,3) = -1.5d0*Bde2l2(j)
      a(2,4) = 0.5d0*Bde2l2(j)
      a(2,5) = (-1.0d0/12.0d0)*Bde2l2(j)
C
      b(2) = Bde2l1(j)*(4.0d0*cde2ia(i+1,j)-3.0d0*cde2ia(i+2,j)
     1     + (4.0d0/3.0d0)*cde2ia(i+3,j)-0.25d0*cde2ia(i+4,j))
     1     - Bde2l4(j)*cors(j)
C
C*********************************************************************
C
      b_test(2) = a(2,1)*c_de2i(0,jed+jde1+1)
     1          + a(2,2)*c_de2i(0,jed+jde1+2)
     1          + a(2,3)*c_de2i(0,jed+jde1+3)
     1          + a(2,4)*c_de2i(0,jed+jde1+4)
     1          + a(2,5)*c_de2i(0,jed+jde1+5)
C      write (35,9400) i, 2, b_test(2), b(2)
C*********************************************************************
C
C
      do 1172, j = jed + jde1 + 3, jed + jde1 + jde2 - 3
C
         a(j-jed-jde1,j-jed-jde1-2) = (1.0d0/12.0d0)*(-1.0d0)
     1                              * Bde2l2(j)
         a(j-jed-jde1,j-jed-jde1-1) = (1.0d0/12.0d0)*8.0d0*Bde2l2(j)
```

```
         a(j-jed-jde1,j-jed-jde1) = (25.0d0/12.0d0)*Bde2l1(j)
     1                            - Bde2l3(j)
         a(j-jed-jde1,j-jed-jde1+1) = (1.0d0/12.0d0)*(-8.0d0)
     1                             * Bde2l2(j)
         a(j-jed-jde1,j-jed-jde1+2) = (1.0d0/12.0d0)*1.0d0*Bde2l2(j)
C
         b(j-jed-jde1) = Bde2l1(j)*(4.0d0*cde2ia(i+1,j)-3.0d0
     1                 * cde2ia(i+2,j)
     1     + (4.0d0/3.0d0)*cde2ia(i+3,j)-0.25d0*cde2ia(i+4,j))
     1     - Bde2l4(j)*cors(j)
C
1172  continue
C
C*********************************************************************
C
      do 1173, j = jed + jde1 + 3, jed + jde1 + jde2 - 3
         b_test(j-jed-jde1) = a(j-jed-jde1,j-jed-jde1-2)*c_de2i(0,j-2)
     1                 + a(j-jed-jde1,j-jed-jde1-1)*c_de2i(0,j-1)
     1                 + a(j-jed-jde1,j-jed-jde1)*c_de2i(0,j)
     1                 + a(j-jed-jde1,j-jed-jde1+1)*c_de2i(0,j+1)
     1                 + a(j-jed-jde1,j-jed-jde1+2)*c_de2i(0,j+2)
C         write (35,9400) i, j-jed-jde1,b_test(j-jed-jde1),b(j-jed-
jde1)
1173  continue
C*********************************************************************
C
C
      j = jed + jde1 + jde2 - 2
      a(jde2-2,jde2-5) = (1.0d0/12.0d0)*Bde2l2(j)
      a(jde2-2,jde2-4) = -0.5d0*Bde2l2(j)
      a(jde2-2,jde2-3) = 1.50d0*Bde2l2(j)
      a(jde2-2,jde2-2) = (25.0d0/12.0d0)*Bde2l1(j)
     1            -(10.0d0/12.0d0) * Bde2l2(j)-Bde2l3(j)
      a(jde2-2,jde2-1) = -0.25d0*Bde2l2(j)
C
      b(jde2-2) = Bde2l1(j)*(4.0d0*cde2ia(i+1,j)-3.0d0
     1              * cde2ia(i+2,j)+(4.0d0/3.0d0)*cde2ia(i+3,j)
     1              - 0.25d0*cde2ia(i+4,j))-Bde2l4(j)*cors(j)
C
C*********************************************************************
C
      b_test(jde2-2) = a(jde2-2,jde2-5)*c_de2i(0,jed+jde1+jde2-5)
     1          + a(jde2-2,jde2-4)*c_de2i(0,jed+jde1+jde2-4)
     1          + a(jde1-2,jde2-3)*c_de2i(0,jed+jde1+jde2-3)
     1          + a(jde2-2,jde2-2)*c_de2i(0,jed+jde1+jde2-2)
     1          + a(jde2-2,jde2-1)*c_de2i(0,jed+jde1+jde2-1)
C      write (35,9400) i, jde2-2, b_test(jde2-2), b(jde2-2)
C*********************************************************************
C
C
      j = jed + jde1 + jde2 - 1
      a(jde2-1,jde2-5) = -0.25d0*Bde2l2(j)
      a(jde2-1,jde2-4) = (4.0d0/3.0d0)*Bde2l2(j)
      a(jde2-1,jde2-3) = -3.0d0*Bde2l2(j)
      a(jde2-1,jde2-2) = 4.0d0*Bde2l2(j)
      a(jde2-1,jde2-1) = (25.0d0/12.0d0)*(Bde2l1(j)
     1                          - Bde2l2(j))-Bde2l3(j)
```

```
C
      b(jde2-1) = Bde2l1(j)*(4.0d0*cde2ia(i+1,j)-3.0d0
     1              * cde2ia(i+2,j)+(4.0d0/3.0d0)*cde2ia(i+3,j)
     1              - 0.25d0*cde2ia(i+4,j))-Bde2l4(j)*cors(j)
C
C*****************************************************************
C
      b_test(jde2-1) = a(jde2-1,jde2-5)*c_de2i(0,jed + jde1+jde2-5)
     1          + a(jde2-1,jde2-4)*c_de2i(0,jed + jde1+jde2-4)
     1          + a(jde2-1,jde2-3)*c_de2i(0,jed + jde1+jde2-3)
     1          + a(jde2-1,jde2-2)*c_de2i(0,jed + jde1+jde2-2)
     1          + a(jde2-1,jde2-1)*c_de2i(0,jed + jde1+jde2-1)
C      write (35,9400) i, jde2-1, b_test(jde2-1), b(jde2-1)
C*****************************************************************
C
C      write (39, 7960)
      do 6500, k = jed + jde1 + 1, jed + jde1 + jde2 - 1
         x(k-jed-jde1) = c_de2i(0,k)
6500  continue
C
      do 6700, k = 1, jde2 - 1
         sum = 0.0d0
         do 6600, l = 1, jde2 - 1
            sum = sum + a(k,l)*x(l)
6600     continue
C         write (39, 8000) i, sum, b(k)
6700  continue
C*****************************************************************
C
C
      call lu(jdim,jde2-1,iscrat,a,detlog,idsgn)
      call back(jdim,jde2-1,iscrat,a,b)
C
      do 1174, j = jed + jde1 + 1, jed + jde1 + jde2 - 1
         cde2ia(i,j) = b(j-jed-jde1)
C         cde2ia(i,j) = 1.0d0
1174  continue
C
C
C De2 inner/outer tissue boundary
C ````````````````````````````````
C
      i = iin
C
C Inner region
      j = jed + jde1 + 1
C
      a(1,1) = (-25.0d0/12.0d0)*(Bde2io1i(j)+Bde2io1o(j)*(Kde2o/Kde2i))
     1       + (25.0d0/12.0d0)*dfd_outer(zda(j))*Bde2io2i(j)
      a(1,2) = -4.0d0*dfd_outer(zda(j))*Bde2io2i(j)
      a(1,3) = 3.0d0*dfd_outer(zda(j))*Bde2io2i(j)
      a(1,4) = (-4.0d0/3.0d0)*dfd_outer(zda(j))*Bde2io2i(j)
      a(1,5) = 0.25d0*dfd_outer(zda(j))*Bde2io2i(j)
C
      b(1) = Bde2io1i(j)*(0.25d0*cde2ia(i-4,j)-(4.0d0/3.0d0)
     1     * cde2ia(i-3,j)+3.0d0*cde2ia(i-2,j)-4.0d0*cde2ia(i-1,j))
     1     - Bde2io1o(j)*(4.0d0*cde2oa(i+1,j)-3.0d0*cde2oa(i+2,j)
```

```
     1     + (4.0d0/3.0d0)*cde2oa(i+3,j)-0.25d0*cde2oa(i+4,j))
C
C*********************************************************************
C
C      open (unit = 35, file = 'test_b.txt')
       b_test(1) = a(1,1)*c_de2i(iin,jed+jde1+1)
     1           + a(1,2)*c_de2i(iin,jed+jde1+2)
     1           + a(1,3)*c_de2i(iin,jed+jde1+3)
     1           + a(1,4)*c_de2i(iin,jed+jde1+4)
     1           + a(1,5)*c_de2i(iin,jed+jde1+5)
C      write (35,9400) i, 1, b_test(1), b(1)
C*********************************************************************
C
C
       j = jed + jde1 + 2
C
       a(2,1) = 0.25d0*dfd_outer(zda(j))*Bde2io2i(j)
       a(2,2) = (-25.0d0/12.0d0)*(Bde2io1i(j)+Bde2io1o(j)
     1       * (Kde2o/Kde2i))+(10.0d0/12.0d0)*dfd_outer(zda(j))
     1       * Bde2io2i(j)
       a(2,3) = -1.5d0*dfd_outer(zda(j))*Bde2io2i(j)
       a(2,4) = 0.5d0*dfd_outer(zda(j))*Bde2io2i(j)
       a(2,5) = -(1.0d0/12.0d0)*dfd_outer(zda(j))*Bde2io2i(j)
C
       b(2) = Bde2io1i(j)*(0.25d0*cde2ia(i-4,j)-(4.0d0/3.0d0)
     1     * cde2ia(i-3,j)+3.0d0*cde2ia(i-2,j)-4.0d0*cde2ia(i-1,j))
     1     - Bde2io1o(j)*(4.0d0*cde2oa(i+1,j)-3.0d0*cde2oa(i+2,j)
     1     + (4.0d0/3.0d0)*cde2oa(i+3,j)-0.25d0*cde2oa(i+4,j))
C
C*********************************************************************
C
       b_test(2) = a(2,1)*c_de2i(iin,jed+jde1+1)
     1           + a(2,2)*c_de2i(iin,jed+jde1+2)
     1           + a(2,3)*c_de2i(iin,jed+jde1+3)
     1           + a(2,4)*c_de2i(iin,jed+jde1+4)
     1           + a(2,5)*c_de2i(iin,jed+jde1+5)
C      write (35,9400) i, 2, b_test(2), b(2)
C*********************************************************************
C
C
       do 1176, j = jed + jde1 + 3, jed + jde1 + jde2 - 3
C
          a(j-jed-jde1,j-jed-jde1-2) = (1.0d0/12.0d0)*(-1.0d0)
     1                               * Bde2io2i(j)
          a(j-jed-jde1,j-jed-jde1-1) = (1.0d0/12.0d0)*8.0d0
     1                               * Bde2io2i(j)
          a(j-jed-jde1,j-jed-jde1)   = (-25.0d0/12.0d0)*(Bde2io1i(j)
     1                               + Bde2io1o(j)*(Kde2o/Kde2i))
          a(j-jed-jde1,j-jed-jde1+1) = (1.0d0/12.0d0)*(-8.0d0)
     1                               * Bde2io2i(j)
          a(j-jed-jde1,j-jed-jde1+2) = (1.0d0/12.0d0)*(1.0d0)
     1                               * Bde2io2i(j)
C
         b(j-jed-jde1) = Bde2io1i(j)*(0.25d0*cde2ia(i-4,j)-(4.0d0/3.0d0)
     1      * cde2ia(i-3,j)+3.0d0*cde2ia(i-2,j)-4.0d0*cde2ia(i-1,j))
     1      - Bde2io1o(j)*(4.0d0*cde2oa(i+1,j)-3.0d0*cde2oa(i+2,j)
     1      + (4.0d0/3.0d0)*cde2oa(i+3,j)-0.25d0*cde2oa(i+4,j))
```

```
1176  continue
C
C*********************************************************************
C
      do 1178, j = jed + jde1 + 3, jed + jde1 + jde2 - 3
         b_test(j-jed-jde1) = a(j-jed-jde1,j-jed-jde1-2)*c_de2i(iin,j-
2)
     1                 + a(j-jed-jde1,j-jed-jde1-1)*c_de2i(iin,j-1)
     1                 + a(j-jed-jde1,j-jed-jde1)*c_de2i(iin,j)
     1                 + a(j-jed-jde1,j-jed-jde1+1)*c_de2i(iin,j+1)
     1                 + a(j-jed-jde1,j-jed-jde1+2)*c_de2i(iin,j+2)
C         write (35,9400) i, j-jed-jde1,b_test(j-jed-jde1),b(j-jed-
jde1)
1178  continue
C*********************************************************************
C
C
      j = jed + jde1 + jde2 - 2
C
      a(jde2-2,jde2-5) = (1.0d0/12.0d0)*dfd_outer(zda(j))*Bde2io2i(j)
      a(jde2-2,jde2-4) = -0.5d0*dfd_outer(zda(j))*Bde2io2i(j)
      a(jde2-2,jde2-3) = 1.5d0*dfd_outer(zda(j))*Bde2io2i(j)
      a(jde2-2,jde2-2) = (-25.0d0/12.0d0)*(Bde2io1i(j)+Bde2io1o(j)
     1               * (Kde2o/Kde2i))-(10.0d0/12.0d0)*dfd_outer(zda(j))
     1               * Bde2io2i(j)
      a(jde2-2,jde2-1) = -0.25d0*dfd_outer(zda(j))*Bde2io2i(j)
C
      b(jde2-2) = Bde2io1i(j)*(0.25d0*cde2ia(i-4,j)-(4.0d0/3.0d0)
     1     * cde2ia(i-3,j)+3.0d0*cde2ia(i-2,j)-4.0d0*cde2ia(i-1,j))
     1     - Bde2io1o(j)*(4.0d0*cde2oa(i+1,j)-3.0d0*cde2oa(i+2,j)
     1     + (4.0d0/3.0d0)*cde2oa(i+3,j)-0.25d0*cde2oa(i+4,j))
C
C*********************************************************************
C
      b_test(jde2-2) = a(jde2-2,jde2-5)*c_de2i(iin,jed+jde1+jde2-5)
     1          + a(jde2-2,jde2-4)*c_de2i(iin,jed+jde1+jde2-4)
     1          + a(jde1-2,jde2-3)*c_de2i(iin,jed+jde1+jde2-3)
     1          + a(jde2-2,jde2-2)*c_de2i(iin,jed+jde1+jde2-2)
     1          + a(jde2-2,jde2-1)*c_de2i(iin,jed+jde1+jde2-1)
C      write (35,9400) i, jde2-2, b_test(jde2-2), b(jde2-2)
C*********************************************************************
C
C
      j =  jed + jde1 +jde2 - 1
C
      a(jde2-1,jde2-5) = -0.25d0*dfd_outer(zda(j))*Bde2io2i(j)
      a(jde2-1,jde2-4) = (4.0d0/3.0d0)*dfd_outer(zda(j))*Bde2io2i(j)
      a(jde2-1,jde2-3) = -3.0d0*dfd_outer(zda(j))*Bde2io2i(j)
      a(jde2-1,jde2-2) = 4.0d0*dfd_outer(zda(j))*Bde2io2i(j)
      a(jde2-1,jde2-1) = (-25.0d0/12.0d0)*(Bde2io1i(j)+Bde2io1o(j)
     1               * (Kde2o/Kde2i))-(25.0d0/12.0d0)*dfd_outer(zda(j))
     1               * Bde2io2i(j)
C
      b(jde2-1) = Bde2io1i(j)*(0.25d0*cde2ia(i-4,j)-(4.0d0/3.0d0)
     1     * cde2ia(i-3,j)+3.0d0*cde2ia(i-2,j)-4.0d0*cde2ia(i-1,j))
     1     - Bde2io1o(j)*(4.0d0*cde2oa(i+1,j)-3.0d0*cde2oa(i+2,j)
```

```
     1     + (4.0d0/3.0d0)*cde2oa(i+3,j)-0.25d0*cde2oa(i+4,j))

C
C*********************************************************************
C
      b_test(jde2-1) = a(jde2-1,jde2-5)*c_de2i(iin,jed + jde1+jde2-5)
     1          + a(jde2-1,jde2-4)*c_de2i(iin,jed + jde1+jde2-4)
     1          + a(jde2-1,jde2-3)*c_de2i(iin,jed + jde1+jde2-3)
     1          + a(jde2-1,jde2-2)*c_de2i(iin,jed + jde1+jde2-2)
     1          + a(jde2-1,jde2-1)*c_de2i(iin,jed + jde1+jde2-1)
C      write (35,9400) i, jde2-1, b_test(jde2-1), b(jde2-1)
C*********************************************************************
C
      do 6800, k = jed + jde1 + 1, jed + jde1 + jde2 - 1
         x(k-jed-jde1) = c_de2i(iin,k)
6800  continue
C
      do 7000, k = 1, jde2 - 1
         sum = 0.0d0
         do 6900, l = 1, jde2 - 1
            sum = sum + a(k,l)*x(l)
6900     continue
C         write (39, 8000) i, sum, b(k)
7000  continue
C*********************************************************************
C
C
      call lu(jdim,jde2-1,iscrat,a,detlog,idsgn)
      call back(jdim,jde2-1,iscrat,a,b)
C
      do 1186, j = jed + jde1 + 1, jed + jde1 + jde2 - 1
         cde2ia(i,j) = b(j-jed-jde1)
1186  continue
C
C Outer region
      j = jed + jde1 + 1
C
      a(1,1) = (-25.0d0/12.0d0)*(Bde2io1i(j)*(Kde2i/Kde2o)+Bde2io1o(j))
     1       + (25.0d0/12.0d0)*dfd_outer(zda(j))*Bde2io2o(j)
      a(1,2) = -4.0d0*dfd_outer(zda(j))*Bde2io2o(j)
      a(1,3) = 3.0d0*dfd_outer(zda(j))*Bde2io2o(j)
      a(1,4) = (-4.0d0/3.0d0)*dfd_outer(zda(j))*Bde2io2o(j)
      a(1,5) = 0.25d0*dfd_outer(zda(j))*Bde2io2o(j)
C
      b(1) = Bde2io1i(j)*(0.25d0*cde2ia(i-4,j)-(4.0d0/3.0d0)
     1     * cde2ia(i-3,j)
     1     + 3.0d0*cde2ia(i-2,j)-4.0d0*cde2ia(i-1,j))
     1     - Bde2io1o(j)*(4.0d0*cde2oa(i+1,j)-3.0d0*cde2oa(i+2,j)
     1     + (4.0d0/3.0d0)*cde2oa(i+3,j)-0.25d0*cde2oa(i+4,j))
C
C*********************************************************************
C
C      open (unit = 35, file = 'test_b.txt')
      b_test(1) = a(1,1)*c_de2o(iin,jed+jde1+1)
     1          + a(1,2)*c_de2o(iin,jed+jde1+2)
     1          + a(1,3)*c_de2o(iin,jed+jde1+3)
     1          + a(1,4)*c_de2o(iin,jed+jde1+4)
```

```
     1          + a(1,5)*c_de2o(iin,jed+jde1+5)
C      write (35,9400) i, 1, b_test(1), b(1)
C*****************************************************************
C
C
      j = jed +jde1 + 2
C
      a(2,1) = 0.25d0*dfd_outer(zda(j))*Bde2io2o(j)
      a(2,2) = (-25.0d0/12.0d0)*(Bde2io1i(j)*(Kde2i/Kde2o)
     1       + Bde2io1o(j))+(10.0d0/12.0d0)*dfd_outer(zda(j))
     1       * Bde2io2o(j)
      a(2,3) = -1.5d0*dfd_outer(zda(j))*Bde2io2o(j)
      a(2,4) = 0.5d0*dfd_outer(zda(j))*Bde2io2o(j)
      a(2,5) = -(1.0d0/12.0d0)*dfd_outer(zda(j))*Bde2io2o(j)
C
      b(2) = Bde2io1i(j)*(0.25d0*cde2ia(i-4,j)-(4.0d0/3.0d0)
     1     * cde2ia(i-3,j)
     1     + 3.0d0*cde2ia(i-2,j)-4.0d0*cde2ia(i-1,j))
     1     - Bde2io1o(j)*(4.0d0*cde2oa(i+1,j)-3.0d0*cde2oa(i+2,j)
     1     + (4.0d0/3.0d0)*cde2oa(i+3,j)-0.25d0*cde2oa(i+4,j))
C
C*****************************************************************
C
      b_test(2) = a(2,1)*c_de2o(iin,jed+jde1+1)
     1          + a(2,2)*c_de2o(iin,jed+jde1+2)
     1          + a(2,3)*c_de2o(iin,jed+jde1+3)
     1          + a(2,4)*c_de2o(iin,jed+jde1+4)
     1          + a(2,5)*c_de2o(iin,jed+jde1+5)
C      write (35,9400) i, 2, b_test(2), b(2)
C*****************************************************************
C
C
      do 1188, j = jed + jde1 + 3, jed + jde1 + jde2 - 3
C
       a(j-jed-jde1,j-jed-jde1-2) = (1.0d0/12.0d0)*(-1.0d0)*Bde2io2o(j)
       a(j-jed-jde1,j-jed-jde1-1) = (1.0d0/12.0d0)*8.0d0*Bde2io2o(j)
       a(j-jed-jde1,j-jed-jde1)   = (-25.0d0/12.0d0)*(Bde2io1i(j)
     1                            * (Kde2i/Kde2o)+Bde2io1o(j))
       a(j-jed-jde1,j-jed-jde1+1) = (1.0d0/12.0d0)*(-8.0d0)*Bde2io2o(j)
       a(j-jed-jde1,j-jed-jde1+2) = (1.0d0/12.0d0)*(1.0d0)*Bde2io2o(j)
C
       b(j-jed-jde1) = Bde2io1i(j)*(0.25d0*cde2ia(i-4,j)-(4.0d0/3.0d0)
     1     * cde2ia(i-3,j)+3.0d0*cde2ia(i-2,j)-4.0d0*cde2ia(i-1,j))
     1     - Bde2io1o(j)*(4.0d0*cde2oa(i+1,j)-3.0d0*cde2oa(i+2,j)
     1     + (4.0d0/3.0d0)*cde2oa(i+3,j)-0.25d0*cde2oa(i+4,j))
1188  continue
C
C*****************************************************************
C
      do 5190, j = jed + jde1 + 3, jed + jde1 + jde2 - 3
         b_test(j-jed-jde1) = a(j-jed-jde1,j-jed-jde1-2)*c_de2o(iin,j-
2)
     1                + a(j-jed-jde1,j-jed-jde1-1)*c_de2o(iin,j-1)
     1                + a(j-jed-jde1,j-jed-jde1)*c_de2o(iin,j)
     1                + a(j-jed-jde1,j-jed-jde1+1)*c_de2o(iin,j+1)
     1                + a(j-jed-jde1,j-jed-jde1+2)*c_de2o(iin,j+2)
C         write (35,9400) i,j-jed-jde1,b_test(j-jed-jde1),b(j-jed-jde1)
```

```
5190  continue
C*********************************************************************
C
C
      j = jed + jde1 + jde2 - 2
C
      a(jde2-2,jde2-5) = (1.0d0/12.0d0)*dfd_outer(zda(j))*Bde2io2o(j)
      a(jde2-2,jde2-4) = -0.5d0*dfd_outer(zda(j))*Bde2io2o(j)
      a(jde2-2,jde2-3) = 1.5d0*dfd_outer(zda(j))*Bde2io2o(j)
      a(jde2-2,jde2-2) = (-25.0d0/12.0d0)*(Bde2io1i(j)*(Kde2i/Kde2o)
     1               + Bde2io1o(j))-(10.0d0/12.0d0)*dfd_outer(zda(j))
     1               * Bde2io2o(j)
      a(jde2-2,jde2-1) = -0.25d0*dfd_outer(zda(j))*Bde2io2o(j)
C
      b(jde2-2) = Bde2io1i(j)*(0.25d0*cde2ia(i-4,j)-(4.0d0/3.0d0)
     1     * cde2ia(i-3,j)+3.0d0*cde2ia(i-2,j)-4.0d0*cde2ia(i-1,j))
     1     - Bde2io1o(j)*(4.0d0*cde2oa(i+1,j)-3.0d0*cde2oa(i+2,j)
     1     + (4.0d0/3.0d0)*cde2oa(i+3,j)-0.25d0*cde2oa(i+4,j))
C
C*********************************************************************
C
      b_test(jde2-2) = a(jde2-2,jde2-5)*c_de2o(iin,jed+jde1+jde2-5)
     1          + a(jde2-2,jde2-4)*c_de2o(iin,jed + jde1+jde2-4)
     1          + a(jde2-2,jde2-3)*c_de2o(iin,jed + jde1+jde2-3)
     1          + a(jde2-2,jde2-2)*c_de2o(iin,jed + jde1+jde2-2)
     1          + a(jde2-2,jde2-1)*c_de2o(iin,jed + jde1+jde2-1)
C      write (35,9400) i, jde2-2, b_test(jde2-2), b(jde2-2)
C*********************************************************************
C
C
      j = jed + jde1 + jde2 - 1
C
      a(jde2-1,jde2-5) = -0.25d0*dfd_outer(zda(j))*Bde2io2o(j)
      a(jde2-1,jde2-4) = (4.0d0/3.0d0)*dfd_outer(zda(j))*Bde2io2o(j)
      a(jde2-1,jde2-3) = -3.0d0*dfd_outer(zda(j))*Bde2io2o(j)
      a(jde2-1,jde2-2) = 4.0d0*dfd_outer(zda(j))*Bde2io2o(j)
      a(jde2-1,jde2-1) = (-25.0d0/12.0d0)*(Bde2io1i(j)*(Kde2i/Kde2o)
     1               + Bde2io1o(j))-(25.0d0/12.0d0)*dfd_outer(zda(j))
     1               * Bde2io2o(j)
C
      b(jde2-1) = Bde2io1i(j)*(0.25d0*cde2ia(i-4,j)-(4.0d0/3.0d0)
     1     * cde2ia(i-3,j)+3.0d0*cde2ia(i-2,j)-4.0d0*cde2ia(i-1,j))
     1     - Bde2io1o(j)*(4.0d0*cde2oa(i+1,j)-3.0d0*cde2oa(i+2,j)
     1     + (4.0d0/3.0d0)*cde2oa(i+3,j)-0.25d0*cde2oa(i+4,j))

C
C*********************************************************************
C
      b_test(jde2-1) = a(jde2-1,jde2-5)*c_de2o(iin,jed + jde1+jde2-5)
     1          + a(jde2-1,jde2-4)*c_de2o(iin,jed + jde1+jde2-4)
     1          + a(jde2-1,jde2-3)*c_de2o(iin,jed + jde1+jde2-3)
     1          + a(jde2-1,jde2-2)*c_de2o(iin,jed + jde1+jde2-2)
     1          + a(jde2-1,jde2-1)*c_de2o(iin,jed + jde1+jde2-1)
C      write (35,9400) i, jde2-1, b_test(jde2-1), b(jde2-1)
C*********************************************************************
C
      do 7100, k = jed + jde1 + 1, jed + jde1 + jde2 - 1
```

```
         x(k-jed-jde1) = c_de2o(iin,k)
7100  continue
C
      do 7300, k = 1, jde2 - 1
         sum = 0.0d0
         do 7200, l = 1, jde2 - 1
            sum = sum + a(k,l)*x(l)
7200     continue
C         write (39, 8000) i, sum, b(k)
7300  continue
C*********************************************************************
C
C
      call lu(jdim,jde2-1,iscrat,a,detlog,idsgn)
      call back(jdim,jde2-1,iscrat,a,b)
C
      do 1198, j = jed + jde1 + 1, jed + jde1 + jde2 - 1
         cde2oa(i,j) = b(j-jed-jde1)
1198  continue
C
C
C De2 right outer boundary
C ````````````````````````
      i = iin + iout
C
      do 1920, j = jed + jde1 + 1, jed + jde1 + jde2 - 1
      cde2oa(i,j) = (48.0d0*cde2oa(i-1,j)-36.0d0*cde2oa(i-2,j)
     1   + 16.0d0*cde2oa(i-3,j)-3.0d0*cde2oa(i-4,j))
     1   / 25.0d0
C      cde2oa(i,j) = 0.0d0
1920  continue
C
C
C r-direction boundaries in Hd
C ````````````````````````````
C
C Initialize coefficients of A:
C
      do 1990, k = 1, jdim
         do 1980, l = 1, jdim
            a(k,l) = 0.0d0
1980     continue
         b(k) = 0.0d0
         iscrat(k) = 0.0d0
1990  continue
C
C Fill in coeff. values corresponding to unknowns:
C
      i = 0
C
      j = jed + jde1 + jde2 + 1
      a(1,1) = (25.0d0/12.0d0)*(Bhdl1(j)+Bhdl2(j))-Bhdl3(j)
      a(1,2) = -4.0d0*Bhdl2(j)
      a(1,3) = 3.0d0*Bhdl2(j)
      a(1,4) = (-4.0d0/3.0d0)*Bhdl2(j)
      a(1,5) = 0.25d0*Bhdl2(j)
C
```

```
      b(1) = Bhdl1(j)*(4.0d0*chdia(i+1,j)-3.0d0*chdia(i+2,j)
     1     + (4.0d0/3.0d0)*chdia(i+3,j)-0.25d0*chdia(i+4,j))
     1     - Bhdl4(j)*cors(j)
C
C*****************************************************************
C
      b_test(1) = a(1,1)*c_hdi(0,jed+jde1+jde2+1)
     1          + a(1,2)*c_hdi(0,jed+jde1+jde2+2)
     1          + a(1,3)*c_hdi(0,jed+jde1+jde2+3)
     1          + a(1,4)*c_hdi(0,jed+jde1+jde2+4)
     1          + a(1,5)*c_hdi(0,jed+jde1+jde2+5)
C      write (35, 7970)
C      write (35,9400) i, 1, b_test(1), b(1)
C*****************************************************************
C
C
      j = jed + jde1 + jde2 + 2
      a(2,1) = 0.25d0*Bhdl2(j)
      a(2,2) = (25.0d0/12.0d0)*Bhdl1(j)+(10.0d0/12.0d0)
     1         * Bhdl2(j)-Bhdl3(j)
      a(2,3) = -1.5d0*Bhdl2(j)
      a(2,4) = 0.5d0*Bhdl2(j)
      a(2,5) = (-1.0d0/12.0d0)*Bhdl2(j)
C
      b(2) = Bhdl1(j)*(4.0d0*chdia(i+1,j)-3.0d0*chdia(i+2,j)
     1     + (4.0d0/3.0d0)*chdia(i+3,j)-0.25d0*chdia(i+4,j))
     1     - Bhdl4(j)*cors(j)
C
C*****************************************************************
C
      b_test(2) = a(2,1)*c_hdi(0,jed+jde1+jde2+1)
     1          + a(2,2)*c_hdi(0,jed+jde1+jde2+2)
     1          + a(2,3)*c_hdi(0,jed+jde1+jde2+3)
     1          + a(2,4)*c_hdi(0,jed+jde1+jde2+4)
     1          + a(2,5)*c_hdi(0,jed+jde1+jde2+5)
C      write (35,9400) i, 2, b_test(2), b(2)
C*****************************************************************
C
C
      do 2000, j = jed + jde1 + jde2 + 3, jed + jde1 + jde2 + jhd - 3
C
         a(j-jed-jde1-jde2,j-jed-jde1-jde2-2) = (1.0d0/12.0d0)*(-1.0d0)
     1                                          * Bhdl2(j)
         a(j-jed-jde1-jde2,j-jed-jde1-jde2-1) =
     1                                    (1.0d0/12.0d0)*8.0d0*Bhdl2(j)
         a(j-jed-jde1-jde2,j-jed-jde1-jde2) =
     1                               (25.0d0/12.0d0)*Bhdl1(j)-Bhdl3(j)
         a(j-jed-jde1-jde2,j-jed-jde1-jde2+1) =
     1                                  (1.0d0/12.0d0)*(-8.0d0)*Bhdl2(j)
         a(j-jed-jde1-jde2,j-jed-jde1-jde2+2) =
     1                                    (1.0d0/12.0d0)*1.0d0*Bhdl2(j)
C
         b(j-jed-jde1-jde2) = Bhdl1(j)*(4.0d0*chdia(i+1,j)-3.0d0
     1                        * chdia(i+2,j)
     1     + (4.0d0/3.0d0)*chdia(i+3,j)-0.25d0*chdia(i+4,j))
     1     - Bhdl4(j)*cors(j)
2000  continue
```

```
C
C*********************************************************************
C
      do 2001, j = jed + jde1 + jde2 + 3, jed + jde1 + jde2 + jhd - 3
         b_test(j-jed-jde1-jde2) = a(j-jed-jde1-jde2,j-jed-jde1-jde2-2)
     1                           * c_hdi(0,j-2)
     1     + a(j-jed-jde1-jde2,j-jed-jde1-jde2-1)*c_hdi(0,j-1)
     1     + a(j-jed-jde1-jde2,j-jed-jde1-jde2)*c_hdi(0,j)
     1     + a(j-jed-jde1-jde2,j-jed-jde1-jde2+1)*c_hdi(0,j+1)
     1     + a(j-jed-jde1-jde2,j-jed-jde1-jde2+2)*c_hdi(0,j+2)
C         write (35,9400) i, j-jed-jde1-jde2,b_test(j-jed-jde1-jde2),
C     1                   b(j-jed-jde1-jde2)
2001  continue
C*********************************************************************
C
C
      j = jed + jde1 + jde2 + jhd- 2
      a(jhd-2,jhd-5) = (1.0d0/12.0d0)*Bhdl2(j)
      a(jhd-2,jhd-4) = -0.5d0*Bhdl2(j)
      a(jhd-2,jhd-3) = 1.50d0*Bhdl2(j)
      a(jhd-2,jhd-2) = (25.0d0/12.0d0)*Bhdl1(j)
     1            -(10.0d0/12.0d0) * Bhdl2(j)-Bhdl3(j)
      a(jhd-2,jhd-1) = -0.25d0*Bhdl2(j)
C
      b(jhd-2) = Bhdl1(j)*(4.0d0*chdia(i+1,j)-3.0d0
     1              * chdia(i+2,j)+(4.0d0/3.0d0)*chdia(i+3,j)
     1              - 0.25d0*chdia(i+4,j))-Bhdl4(j)*cors(j)
C
C*********************************************************************
C
      b_test(jhd-2) = a(jhd-2,jhd-5)*c_hdi(0,jed+jde1+jde2+jhd-5)
     1          + a(jhd-2,jhd-4)*c_hdi(0,jed+jde1+jde2+jhd-4)
     1          + a(jhd-2,jhd-3)*c_hdi(0,jed+jde1+jde2+jhd-3)
     1          + a(jhd-2,jhd-2)*c_hdi(0,jed+jde1+jde2+jhd-2)
     1          + a(jhd-2,jhd-1)*c_hdi(0,jed+jde1+jde2+jhd-1)
C      write (35,9400) i, jhd-2, b_test(jhd-2), b(jhd-2)
C*********************************************************************
C
C
      j = jed + jde1 + jde2 + jhd - 1
      a(jhd-1,jhd-5) = -0.25d0*Bhdl2(j)
      a(jhd-1,jhd-4) = (4.0d0/3.0d0)*Bhdl2(j)
      a(jhd-1,jhd-3) = -3.0d0*Bhdl2(j)
      a(jhd-1,jhd-2) = 4.0d0*Bhdl2(j)
      a(jhd-1,jhd-1) = (25.0d0/12.0d0)*(Bhdl1(j)
     1                          - Bhdl2(j))-Bhdl3(j)
C
      b(jhd-1) = Bhdl1(j)*(4.0d0*chdia(i+1,j)-3.0d0
     1              * chdia(i+2,j)+(4.0d0/3.0d0)*chdia(i+3,j)
     1              - 0.25d0*chdia(i+4,j))-Bhdl4(j)*cors(j)
C
C*********************************************************************
C
      b_test(jhd-1) = a(jhd-1,jhd-5)*c_hdi(0,jed+jde1+jde2+jhd-5)
     1          + a(jhd-1,jhd-4)*c_hdi(0,jed+jde1+jde2+jhd-4)
     1          + a(jhd-1,jhd-3)*c_hdi(0,jed+jde1+jde2+jhd-3)
     1          + a(jhd-1,jhd-2)*c_hdi(0,jed+jde1+jde2+jhd-2)
```

```
     1          + a(jhd-1,jhd-1)*c_hdi(0,jed+jde1+jde2+jhd-1)
C      write (35,9400) i, jhd-1, b_test(jhd-1), b(jhd-1)
C*********************************************************************
C
C      write (39, 7970)
      do 7400, k = jed + jde1 + jde2 + 1, jed + jde1 + jde2 + jhd - 1
         x(k-jed-jde1-jde2) = c_hdi(0,k)
7400  continue
C
      do 7600, k = 1, jhd - 1
         sum = 0.0d0
         do 7500, l = 1, jhd - 1
            sum = sum + a(k,l)*x(l)
7500     continue
C         write (39, 8000) i, sum, b(k)
7600  continue
C*********************************************************************
C
C
      call lu(jdim,jhd-1,iscrat,a,detlog,idsgn)
      call back(jdim,jhd-1,iscrat,a,b)
C
      do 2010, j = jed + jde1 + jde2 + 1, jed + jde1 + jde2 + jhd - 1
         chdia(i,j) = b(j-jed-jde1-jde2)
C         chdia(i,j) = 1.0d0
2010  continue
C
C
C Hd inner/outer tissue boundary
C ``````````````````````````````
      i = iin
C
C Inner region
      j = jed + jde1 + jde2 + 1
C
      a(1,1) = (-25.0d0/12.0d0)*(Bhdio1i(j)+Bhdio1o(j)*(Khdo/Khdi))
     1       + (25.0d0/12.0d0)*dfd_outer(zda(j))*Bhdio2i(j)
      a(1,2) = -4.0d0*dfd_outer(zda(j))*Bhdio2i(j)
      a(1,3) = 3.0d0*dfd_outer(zda(j))*Bhdio2i(j)
      a(1,4) = (-4.0d0/3.0d0)*dfd_outer(zda(j))*Bhdio2i(j)
      a(1,5) = 0.25d0*dfd_outer(zda(j))*Bhdio2i(j)
C
      b(1) = Bhdio1i(j)*(0.25d0*chdia(i-4,j)-(4.0d0/3.0d0)
     1     * chdia(i-3,j)+3.0d0*chdia(i-2,j)-4.0d0*chdia(i-1,j))
     1     - Bhdio1o(j)*(4.0d0*chdoa(i+1,j)-3.0d0*chdoa(i+2,j)
     1     + (4.0d0/3.0d0)*chdoa(i+3,j)-0.25d0*chdoa(i+4,j))
C
C*********************************************************************
C
C      open (unit = 35, file = 'test_b.txt')
      b_test(1) = a(1,1)*c_hdi(iin,jed+jde1+jde2+1)
     1          + a(1,2)*c_hdi(iin,jed+jde1+jde2+2)
     1          + a(1,3)*c_hdi(iin,jed+jde1+jde2+3)
     1          + a(1,4)*c_hdi(iin,jed+jde1+jde2+4)
     1          + a(1,5)*c_hdi(iin,jed+jde1+jde2+5)
C      write (35,9400) i, 1, b_test(1), b(1)
```

```
C***********************************************************************
C
C
      j = jed + jde1 + jde2 + 2
C
      a(2,1) = 0.25d0*dfd_outer(zda(j))*Bhdio2i(j)
      a(2,2) = (-25.0d0/12.0d0)*(Bhdio1i(j)+Bhdio1o(j)
     1       * (Khdo/Khdi))+(10.0d0/12.0d0)*dfd_outer(zda(j))
     1       * Bhdio2i(j)
      a(2,3) = -1.5d0*dfd_outer(zda(j))*Bhdio2i(j)
      a(2,4) = 0.5d0*dfd_outer(zda(j))*Bhdio2i(j)
      a(2,5) = -(1.0d0/12.0d0)*dfd_outer(zda(j))*Bhdio2i(j)
C
      b(2) = Bhdio1i(j)*(0.25d0*chdia(i-4,j)-(4.0d0/3.0d0)
     1     * chdia(i-3,j)+3.0d0*chdia(i-2,j)-4.0d0*chdia(i-1,j))
     1     - Bhdio1o(j)*(4.0d0*chdoa(i+1,j)-3.0d0*chdoa(i+2,j)
     1     + (4.0d0/3.0d0)*chdoa(i+3,j)-0.25d0*chdoa(i+4,j))
C
C***********************************************************************
C
      b_test(2) = a(2,1)*c_hdi(iin,jed+jde1+jde2+1)
     1          + a(2,2)*c_hdi(iin,jed+jde1+jde2+2)
     1          + a(2,3)*c_hdi(iin,jed+jde1+jde2+3)
     1          + a(2,4)*c_hdi(iin,jed+jde1+jde2+4)
     1          + a(2,5)*c_hdi(iin,jed+jde1+jde2+5)
C      write (35,9400) i, 2, b_test(2), b(2)
C***********************************************************************
C
C
      do 3000, j = jed + jde1 + jde2 + 3, jed + jde1 + jde2 + jhd - 3
C
         a(j-jed-jde1-jde2,j-jed-jde1-jde2-2) = (1.0d0/12.0d0)*(-1.0d0)
     1                                * Bhdio2i(j)
         a(j-jed-jde1-jde2,j-jed-jde1-jde2-1) = (1.0d0/12.0d0)*8.0d0
     1                                * Bhdio2i(j)
         a(j-jed-jde1-jde2,j-jed-jde1-jde2) = (-25.0d0/12.0d0)
     1                           *(Bhdio1i(j)+ Bhdio1o(j)*(Khdo/Khdi))
         a(j-jed-jde1-jde2,j-jed-jde1-jde2+1) = (1.0d0/12.0d0)*(-8.0d0)
     1                                * Bhdio2i(j)
         a(j-jed-jde1-jde2,j-jed-jde1-jde2+2) = (1.0d0/12.0d0)*(1.0d0)
     1                                * Bhdio2i(j)
C
        b(j-jed-jde1-jde2) = Bhdio1i(j)*(0.25d0*chdia(i-4,j)
     1                     - (4.0d0/3.0d0)*chdia(i-3,j)
     1                     + 3.0d0*chdia(i-2,j)-4.0d0*chdia(i-1,j))
     1     - Bhdio1o(j)*(4.0d0*chdoa(i+1,j)-3.0d0*chdoa(i+2,j)
     1     + (4.0d0/3.0d0)*chdoa(i+3,j)-0.25d0*chdoa(i+4,j))
3000  continue
C
C***********************************************************************
C
      do 3010, j = jed + jde1 + jde2 + 3, jed + jde1 + jde2 + jhd - 3
         b_test(j-jed-jde1-jde2) =
     1              a(j-jed-jde1-jde2,j-jed-jde1-jde2-2)*c_hdi(iin,j-
2)
     1            + a(j-jed-jde1-jde2,j-jed-jde1-jde2-1)*c_hdi(iin,j-
1)
```

```
     1             + a(j-jed-jde1-jde2,j-jed-jde1-jde2)*c_hdi(iin,j)
     1             + a(j-jed-jde1-jde2,j-jed-jde1-
jde2+1)*c_hdi(iin,j+1)
     1             + a(j-jed-jde1-jde2,j-jed-jde1-
jde2+2)*c_hdi(iin,j+2)
C         write (35,9400) i, j-jed-jde1-jde2, b_test(j-jed-jde1-jde2),
C     1                   b(j-jed-jde1-jde2)
3010  continue
C*********************************************************************
C
C
      j = jed + jde1 + jde2 + jhd - 2
C
      a(jhd-2,jhd-5) = (1.0d0/12.0d0)*dfd_outer(zda(j))*Bhdio2i(j)
      a(jhd-2,jhd-4) = -0.5d0*dfd_outer(zda(j))*Bhdio2i(j)
      a(jhd-2,jhd-3) = 1.5d0*dfd_outer(zda(j))*Bhdio2i(j)
      a(jhd-2,jhd-2) = (-25.0d0/12.0d0)*(Bhdio1i(j)+Bhdio1o(j)
     1               * (Khdo/Khdi))-(10.0d0/12.0d0)*dfd_outer(zda(j))
     1               * Bhdio2i(j)
      a(jhd-2,jhd-1) = -0.25d0*dfd_outer(zda(j))*Bhdio2i(j)
C
      b(jhd-2) = Bhdio1i(j)*(0.25d0*chdia(i-4,j)-(4.0d0/3.0d0)
     1     * chdia(i-3,j)+3.0d0*chdia(i-2,j)-4.0d0*chdia(i-1,j))
     1     - Bhdio1o(j)*(4.0d0*chdoa(i+1,j)-3.0d0*chdoa(i+2,j)
     1     + (4.0d0/3.0d0)*chdoa(i+3,j)-0.25d0*chdoa(i+4,j))
C
C*********************************************************************
C
      b_test(jhd-2) = a(jhd-2,jhd-5)*c_hdi(iin,jed+jde1+jde2+jhd-5)
     1          + a(jhd-2,jhd-4)*c_hdi(iin,jed+jde1+jde2+jhd-4)
     1          + a(jhd-2,jhd-3)*c_hdi(iin,jed+jde1+jde2+jhd-3)
     1          + a(jhd-2,jhd-2)*c_hdi(iin,jed+jde1+jde2+jhd-2)
     1          + a(jhd-2,jhd-1)*c_hdi(iin,jed+jde1+jde2+jhd-1)
C      write (35,9400) i, jhd-2, b_test(jhd-2), b(jhd-2)
C*********************************************************************
C
C
      j =  jed + jde1 +jde2 + jhd - 1
C
      a(jhd-1,jhd-5) = -0.25d0*dfd_outer(zda(j))*Bhdio2i(j)
      a(jhd-1,jhd-4) = (4.0d0/3.0d0)*dfd_outer(zda(j))*Bhdio2i(j)
      a(jhd-1,jhd-3) = -3.0d0*dfd_outer(zda(j))*Bhdio2i(j)
      a(jhd-1,jhd-2) = 4.0d0*dfd_outer(zda(j))*Bhdio2i(j)
      a(jhd-1,jhd-1) = (-25.0d0/12.0d0)*(Bhdio1i(j)+Bhdio1o(j)
     1               * (Khdo/Khdi))-(25.0d0/12.0d0)*dfd_outer(zda(j))
     1               * Bhdio2i(j)
C
      b(jhd-1) = Bhdio1i(j)*(0.25d0*chdia(i-4,j)-(4.0d0/3.0d0)
     1     * chdia(i-3,j)+3.0d0*chdia(i-2,j)-4.0d0*chdia(i-1,j))
     1     - Bhdio1o(j)*(4.0d0*chdoa(i+1,j)-3.0d0*chdoa(i+2,j)
     1     + (4.0d0/3.0d0)*chdoa(i+3,j)-0.25d0*chdoa(i+4,j))

C
C*********************************************************************
C
      b_test(jhd-1) = a(jhd-1,jhd-5)*c_hdi(iin,jed + jde1+jde2+jhd-5)
     1          + a(jhd-1,jhd-4)*c_hdi(iin,jed + jde1+jde2+jhd-4)
```

```
     1          + a(jhd-1,jhd-3)*c_hdi(iin,jed + jde1+jde2+jhd-3)
     1          + a(jhd-1,jhd-2)*c_hdi(iin,jed + jde1+jde2+jhd-2)
     1          + a(jhd-1,jhd-1)*c_hdi(iin,jed + jde1+jde2+jhd-1)
C      write (35,9400) i, jhd-1, b_test(jhd-1), b(jhd-1)
C*********************************************************************
C
      do 7700, k = jed + jde1 + jde2 + 1, jed + jde1 + jde2 + jhd - 1
         x(k-jed-jde1-jde2) = c_hdi(iin,k)
7700  continue
C
      do 7900, k = 1, jhd - 1
         sum = 0.0d0
         do 7800, l = 1, jhd - 1
            sum = sum + a(k,l)*x(l)
7800     continue
C         write (39, 8000) i, sum, b(k)
7900  continue
C*********************************************************************
C
C
      call lu(jdim,jhd-1,iscrat,a,detlog,idsgn)
      call back(jdim,jhd-1,iscrat,a,b)
C
      do 3020, j = jed + jde1 + jde2 + 1, jed + jde1 + jde2 + jhd - 1
         chdia(i,j) = b(j-jed-jde1-jde2)
3020  continue
C
C Outer region
      j = jed + jde1 + jde2 + 1
C
      a(1,1) = (-25.0d0/12.0d0)*(Bhdio1i(j)*(Khdi/Khdo)+Bhdio1o(j))
     1       + (25.0d0/12.0d0)*dfd_outer(zda(j))*Bhdio2o(j)
      a(1,2) = -4.0d0*dfd_outer(zda(j))*Bhdio2o(j)
      a(1,3) = 3.0d0*dfd_outer(zda(j))*Bhdio2o(j)
      a(1,4) = (-4.0d0/3.0d0)*dfd_outer(zda(j))*Bhdio2o(j)
      a(1,5) = 0.25d0*dfd_outer(zda(j))*Bhdio2o(j)
C
      b(1) = Bhdio1i(j)*(0.25d0*chdia(i-4,j)-(4.0d0/3.0d0)
     1     * chdia(i-3,j)
     1     + 3.0d0*chdia(i-2,j)-4.0d0*chdia(i-1,j))
     1     - Bhdio1o(j)*(4.0d0*chdoa(i+1,j)-3.0d0*chdoa(i+2,j)
     1     + (4.0d0/3.0d0)*chdoa(i+3,j)-0.25d0*chdoa(i+4,j))
C
C*********************************************************************
C
C      open (unit = 35, file = 'test_b.txt')
      b_test(1) = a(1,1)*c_hdo(iin,jed+jde1+jde2+1)
     1          + a(1,2)*c_hdo(iin,jed+jde1+jde2+2)
     1          + a(1,3)*c_hdo(iin,jed+jde1+jde2+3)
     1          + a(1,4)*c_hdo(iin,jed+jde1+jde2+4)
     1          + a(1,5)*c_hdo(iin,jed+jde1+jde2+5)
C      write (35,9400) i, 1, b_test(1), b(1)
C*********************************************************************
C
C
      j = jed + jde1 + jde2 + 2
C
```

```
      a(2,1) = 0.25d0*dfd_outer(zda(j))*Bhdio2o(j)
      a(2,2) = (-25.0d0/12.0d0)*(Bhdio1i(j)*(Khdi/Khdo)
     1       + Bhdio1o(j))+(10.0d0/12.0d0)*dfd_outer(zda(j))
     1       * Bhdio2o(j)
      a(2,3) = -1.5d0*dfd_outer(zda(j))*Bhdio2o(j)
      a(2,4) = 0.5d0*dfd_outer(zda(j))*Bhdio2o(j)
      a(2,5) = -(1.0d0/12.0d0)*dfd_outer(zda(j))*Bhdio2o(j)
C
      b(2) = Bhdio1i(j)*(0.25d0*chdia(i-4,j)-(4.0d0/3.0d0)
     1     * chdia(i-3,j)
     1     + 3.0d0*chdia(i-2,j)-4.0d0*chdia(i-1,j))
     1     - Bhdio1o(j)*(4.0d0*chdoa(i+1,j)-3.0d0*chdoa(i+2,j)
     1     + (4.0d0/3.0d0)*chdoa(i+3,j)-0.25d0*chdoa(i+4,j))
C
C*********************************************************************
C
      b_test(2) = a(2,1)*c_hdo(iin,jed+jde1+jde2+1)
     1          + a(2,2)*c_hdo(iin,jed+jde1+jde2+2)
     1          + a(2,3)*c_hdo(iin,jed+jde1+jde2+3)
     1          + a(2,4)*c_hdo(iin,jed+jde1+jde2+4)
     1          + a(2,5)*c_hdo(iin,jed+jde1+jde2+5)
C      write (35,9400) i, 2, b_test(2), b(2)
C*********************************************************************
C
C
      do 3030, j = jed + jde1 + jde2 + 3, jed + jde1 + jde2 + jhd  - 3
C
       a(j-jed-jde1-jde2,j-jed-jde1-jde2-2) =
     1                                  (1.0d0/12.0d0)*(-
1.0d0)*Bhdio2o(j)
       a(j-jed-jde1-jde2,j-jed-jde1-jde2-1) =
     1                                    (1.0d0/12.0d0)*8.0d0*Bhdio2o(j)
       a(j-jed-jde1-jde2,j-jed-jde1-jde2) =
     1                                       (-25.0d0/12.0d0)*(Bhdio1i(j)
     1                                        * (Khdi/Khdo)+Bhdio1o(j))
       a(j-jed-jde1-jde2,j-jed-jde1-jde2+1) =
     1                                   (1.0d0/12.0d0)*(-8.0d0)*Bhdio2o(j)
       a(j-jed-jde1-jde2,j-jed-jde1-jde2+2) =
     1                                  (1.0d0/12.0d0)*(1.0d0)*Bhdio2o(j)
C
       b(j-jed-jde1-jde2) = Bhdio1i(j)*(0.25d0*chdia(i-4,j)
     1                    - (4.0d0/3.0d0)
     1     * chdia(i-3,j)+3.0d0*chdia(i-2,j)-4.0d0*chdia(i-1,j))
     1     - Bhdio1o(j)*(4.0d0*chdoa(i+1,j)-3.0d0*chdoa(i+2,j)
     1     + (4.0d0/3.0d0)*chdoa(i+3,j)-0.25d0*chdoa(i+4,j))
3030  continue
C
C*********************************************************************
C
      do 3040, j = jed + jde1 + jde2 + 3, jed + jde1 + jde2 + jhd - 3
         b_test(j-jed-jde1-jde2) =
     1              a(j-jed-jde1-jde2,j-jed-jde1-jde2-2)*c_hdo(iin,j-2)
     1            + a(j-jed-jde1-jde2,j-jed-jde1-jde2-1)*c_hdo(iin,j-1)
     1            + a(j-jed-jde1-jde2,j-jed-jde1-jde2)*c_hdo(iin,j)
     1            + a(j-jed-jde1-jde2,j-jed-jde1-jde2+1)*c_hdo(iin,j+1)
     1            + a(j-jed-jde1-jde2,j-jed-jde1-jde2+2)*c_hdo(iin,j+2)
C         write (35,9400) i,j-jed-jde1-jde2,b_test(j-jed-jde1-jde2),
```

```
C     1                   b(j-jed-jde1-jde2)
3040  continue
C*********************************************************************
C
C
      j = jed + jde1 + jde2 + jhd - 2
      a(jhd-2,jhd-5) = (1.0d0/12.0d0)*dfd_outer(zda(j))*Bhdio2o(j)
      a(jhd-2,jhd-4) = -0.5d0*dfd_outer(zda(j))*Bhdio2o(j)
      a(jhd-2,jhd-3) = 1.5d0*dfd_outer(zda(j))*Bhdio2o(j)
      a(jhd-2,jhd-2) = (-25.0d0/12.0d0)*(Bhdio1i(j)*(Khdi/Khdo)
     1               + Bhdio1o(j))-(10.0d0/12.0d0)*dfd_outer(zda(j))
     1               * Bhdio2o(j)
      a(jhd-2,jhd-1) = -0.25d0*dfd_outer(zda(j))*Bhdio2o(j)
C
      b(jhd-2) = Bhdio1i(j)*(0.25d0*chdia(i-4,j)-(4.0d0/3.0d0)
     1     * chdia(i-3,j)+3.0d0*chdia(i-2,j)-4.0d0*chdia(i-1,j))
     1     - Bhdio1o(j)*(4.0d0*chdoa(i+1,j)-3.0d0*chdoa(i+2,j)
     1     + (4.0d0/3.0d0)*chdoa(i+3,j)-0.25d0*chdoa(i+4,j))
C
C*********************************************************************
C
      b_test(jhd-2) = a(jhd-2,jhd-5)*c_hdo(iin,jed+jde1+jde2+jhd-5)
     1          + a(jhd-2,jhd-4)*c_hdo(iin,jed + jde1+jde2+jhd-4)
     1          + a(jhd-2,jhd-3)*c_hdo(iin,jed + jde1+jde2+jhd-3)
     1          + a(jhd-2,jhd-2)*c_hdo(iin,jed + jde1+jde2+jhd-2)
     1          + a(jhd-2,jhd-1)*c_hdo(iin,jed + jde1+jde2+jhd-1)
C      write (35,9400) i, jhd-2, b_test(jhd-2), b(jhd-2)
C*********************************************************************
C
C
      j = jed + jde1 + jde2 + jhd - 1
C
      a(jhd-1,jhd-5) = -0.25d0*dfd_outer(zda(j))*Bhdio2o(j)
      a(jhd-1,jhd-4) = (4.0d0/3.0d0)*dfd_outer(zda(j))*Bhdio2o(j)
      a(jhd-1,jhd-3) = -3.0d0*dfd_outer(zda(j))*Bhdio2o(j)
      a(jhd-1,jhd-2) = 4.0d0*dfd_outer(zda(j))*Bhdio2o(j)
      a(jhd-1,jhd-1) = (-25.0d0/12.0d0)*(Bhdio1i(j)*(Khdi/Khdo)
     1               + Bhdio1o(j))-(25.0d0/12.0d0)*dfd_outer(zda(j))
     1               * Bhdio2o(j)
C
      b(jhd-1) = Bhdio1i(j)*(0.25d0*chdia(i-4,j)-(4.0d0/3.0d0)
     1     * chdia(i-3,j)+3.0d0*chdia(i-2,j)-4.0d0*chdia(i-1,j))
     1     - Bhdio1o(j)*(4.0d0*chdoa(i+1,j)-3.0d0*chdoa(i+2,j)
     1     + (4.0d0/3.0d0)*chdoa(i+3,j)-0.25d0*chdoa(i+4,j))

C
C*********************************************************************
C
      b_test(jhd-1) = a(jhd-1,jhd-5)*c_hdo(iin,jed + jde1+jde2+jhd-5)
     1          + a(jhd-1,jhd-4)*c_hdo(iin,jed + jde1+jde2+jhd-4)
     1          + a(jhd-1,jhd-3)*c_hdo(iin,jed + jde1+jde2+jhd-3)
     1          + a(jhd-1,jhd-2)*c_hdo(iin,jed + jde1+jde2+jhd-2)
     1          + a(jhd-1,jhd-1)*c_hdo(iin,jed + jde1+jde2+jhd-1)
C      write (35,9400) i, jhd-1, b_test(jhd-1), b(jhd-1)
C*********************************************************************
C
      do 7910, k = jed + jde1 + jde2 + 1, jed + jde1 + jde2 + jhd - 1
```

```
         x(k-jed-jde1-jde2) = c_hdo(iin,k)
7910  continue
C
      do 7930, k = 1, jhd - 1
         sum = 0.0d0
         do 7920, l = 1, jhd - 1
            sum = sum + a(k,l)*x(l)
7920     continue
C         write (39, 8000) i, sum, b(k)
7930  continue
C
7940  format ('Epidermis')
7950  format ('Dermis 1')
7960  format ('Dermis 2')
7970  format ('Hypodermis')
8000  format (i3,1x,d23.16,1x,d23.16)
C*****************************************************************
C
C
      call lu(jdim,jhd-1,iscrat,a,detlog,idsgn)
      call back(jdim,jhd-1,iscrat,a,b)
C
      do 3050, j = jed + jde1 + jde2 + 1, jed + jde1 + jde2 + jhd - 1
         chdoa(i,j) = b(j-jed-jde1-jde2)
3050  continue
C
C
C Hd right outer boundary
C ```````````````````````
      i = iin + iout
C
      do 2190, j = jed + jde1 + jde2 + 1, jed + jde1 + jde2 + jhd - 1
      chdoa(i,j) = (48.0d0*chdoa(i-1,j)-36.0d0*chdoa(i-2,j)
     1   + 16.0d0*chdoa(i-3,j)-3.0d0*chdoa(i-4,j))
     1   / 25.0d0
C       chdoa(i,j) = 0.0d0
2190  continue
C
C
C z-direction boundaries in Ed
C ````````````````````````````
C
C Ed inner region top surface
C ```````````````````````````
      j = 0
C
      do 1170, i = 0, iin
        cedib(i) = cedia(i,j+1)
1170  continue
C
C n iterations
C ````````````
      n = 0
10    n = n + 1
C
      do 1180, i = 2, iin - 2
      cedib_new(i) = (Bsced1i(i)*(0.25d0*cedia(i,j+4)-(4.0d0/3.0d0)
```

```
     1   * cedia(i,j+3)+3.0d0*cedia(i,j+2)-4.0d0*cedia(i,j+1))
     1   + (1.0d0/12.0d0)*Bsced2i(i)*(cedib(i-2)-8.0d0
     1   * cedib(i-1)+8.0d0*cedib(i+1)-cedib(i+2))-Bsced4(i)*cds(i))
     1   / (-Bsced3i(i)-(25.0d0/12.0d0)*Bsced1i(i))
C
1180  continue
C
      i = 1
      cedib_new(i) = (Bsced1i(i)*(0.25d0*cedia(i,j+4)-(4.0d0/3.0d0)
     1   * cedia(i,j+3)+3.0d0*cedia(i,j+2)-4.0d0*cedia(i,j+1))
     1   + Bsced2i(i)*((1.0d0/12.0d0)*cedib(i+3)-0.5d0*cedib(i+2)
     1   + 1.5d0*cedib(i+1)-0.25d0*cedib(i-1))-Bsced4(i)*cds(i))
     1   / (-(25.0d0/12.0d0)*Bsced1i(i)+(10.0d0/12.0d0)
     1   * Bsced2i(i)-Bsced3i(i))
C
      i = iin - 1
      cedib_new(i) = (Bsced1i(i)*(0.25d0*cedia(i,j+4)-(4.0d0/3.0d0)
     1   * cedia(i,j+3)+3.0d0*cedia(i,j+2)-4.0d0*cedia(i,j+1))
     1   + Bsced2i(i)*(-(1.0d0/12.0d0)*cedib(i-3)+0.5d0*cedib(i-2)
     1   - 1.5d0*cedib(i-1)+0.25d0*cedib(i+1))-Bsced4(i)*cds(i))
     1   / (-(25.0d0/12.0d0)*Bsced1i(i)-(10.0d0/12.0d0)
     1   * Bsced2i(i)-Bsced3i(i))
C
      i = iin
      cedib_new(i) = (Bsced1i(i)*(0.25d0*cedia(i,j+4)-(4.0d0/3.0d0)
     1   * cedia(i,j+3)+3.0d0*cedia(i,j+2)-4.0d0*cedia(i,j+1))
     1   + Bsced2i(i)*(0.25d0*cedib(i-4)-(4.0d0/3.0d0)*cedib(i-3)
     1   + 3.0d0*cedib(i-2)-4.0d0*cedib(i-1))
     1   - Bsced4(i)*cds(i)) / ((25.0d0/12.0d0)*(-Bsced2i(i)
     1   - Bsced1i(i))-Bsced3i(i))
C
      maxdiff = 0.0d0
      do 1190, i = 1, iin
         temp = abs(cedib_new(i) - cedib(i))
         if (temp .gt. maxdiff) then
            maxdiff = temp
         end if
1190  continue
C
      if (maxdiff .gt. tol) then
         do 1200, i = 1, iin
            cedib(i) = cedib_new(i)
1200     continue
         go to 10
      else
         do 1210, i = 1, iin
            cedia(i,j) = cedib_new(i)
C            cedia(i,j) = 1.0d0
1210     continue
C
C        i = iin
C        cedia(i,j) = 0.0d0
C
      end if
C
C
C Ed outer region top surface
```

```
C ``````````````````````````
      do 1280, i = iin, iin + iout
        cedob(i) = cedoa(i,j+1)
1280  continue
C
C n iterations
C ````````````
      n = 0
20    n = n + 1
C
      do 1290, i = iin + 2, iin + iout - 2
C
      cedob_new(i) = (Bsced1o(i)*(0.25d0*cedoa(i,j+4)-(4.0d0/3.0d0)
     1   * cedoa(i,j+3)+3.0d0*cedoa(i,j+2)-4.0d0*cedoa(i,j+1))
     1   + (1.0d0/12.0d0)*Bsced2o(i)*(cedob(i-2)-8.0d0
     1   * cedob(i-1)+8.0d0*cedob(i+1)-cedob(i+2))-Bsced4(i)*cds(i))
     1   / (-Bsced3o(i)-(25.0d0/12.0d0)*Bsced1o(i))
C
1290  continue
C
      i = iin + 1
C
      cedob_new(i) = (Bsced1o(i)*(0.25d0*cedoa(i,j+4)-(4.0d0/3.0d0)
     1   * cedoa(i,j+3)+3.0d0*cedoa(i,j+2)-4.0d0*cedoa(i,j+1))
     1   + Bsced2o(i)*((1.0d0/12.0d0)*cedob(i+3)-0.5d0*cedob(i+2)
     1   + 1.5d0*cedob(i+1)-0.25d0*cedob(i-1))-Bsced4(i)*cds(i))
     1   / (-(25.0d0/12.0d0)*Bsced1o(i)+(10.0d0/12.0d0)
     1   * Bsced2o(i)-Bsced3o(i))
C
      i = iin + iout - 1
C
      cedob_new(i) = (Bsced1o(i)*(0.25d0*cedoa(i,j+4)-(4.0d0/3.0d0)
     1   * cedoa(i,j+3)+3.0d0*cedoa(i,j+2)-4.0d0*cedoa(i,j+1))
     1   + Bsced2o(i)*(-(1.0d0/12.0d0)*cedob(i-3)+0.5d0*cedob(i-2)
     1   - 1.5d0*cedob(i-1)+0.25d0*cedob(i+1))-Bsced4(i)*cds(i))
     1   / (-(25.0d0/12.0d0)*Bsced1o(i)-(10.0d0/12.0d0)
     1   * Bsced2o(i)-Bsced3o(i))
C
      i = iin
C
      cedob_new(i) = (Bsced1o(i)*(0.25d0*cedoa(i,j+4)-(4.0d0/3.0d0)
     1   * cedoa(i,j+3)+3.0d0*cedoa(i,j+2)-4.0d0*cedoa(i,j+1))
     1   + Bsced2o(i)*(-0.25d0*cedob(i+4)+(4.0d0/3.0d0)*cedob(i+3)
     1   - 3.0d0*cedob(i+2)+4.0d0*cedob(i+1))
     1   - Bsced4(i)*cds(i)) / ((25.0d0/12.0d0)*(Bsced2o(i)
     1   - Bsced1o(i))-Bsced3o(i))
C
      maxdiff = 0.0d0
      do 1300, i = iin, iin + iout - 1
         temp = abs(cedob_new(i) - cedob(i))
         if (temp .gt. maxdiff) then
            maxdiff = temp
         end if
1300  continue
C
      if (maxdiff .gt. tol) then
         do 1310, i = iin, iin + iout - 1
```

```
            cedob(i) = cedob_new(i)
1310     continue
         go to 20
      else
         do 1320, i = iin, iin + iout - 1
            cedoa(i,j) = cedob_new(i)
C            cedoa(i,j) = 1.0d0
C
1320     continue
C
C         i = iin
C         cedoa(i,j) = 1.0d0
      end if
C
C
C Ed inner region Ed/De1 boundary
C ````````````````````````````````
C
      j = jed
C
      do 1220, i = 0, iin
         cedic(i) = cedia(i,j-1)
1220  continue
C
C n iterations
C ````````````
      n = 0
15    n = n + 1
C
      do 1230, i = 2, iin - 2
      cedic_new(i) = (Bedde11i(i)*(4.0d0*cedia(i,j-1)-3.0d0
     1   * cedia(i,j-2)+(4.0d0/3.0d0)*cedia(i,j-3)-0.25d0
     1   * cedia(i,j-4))-Bedde12i(i)*(0.25d0*cde1ia(i,j+4)
     1   - (4.0d0/3.0d0)*cde1ia(i,j+3)+3.0d0*cde1ia(i,j+2)-4.0d0
     1   * cde1ia(i,j+1))+(1.0d0/12.0d0)*Bedde13i(i)*(cedic(i-2)
     1   - 8.0d0*cedic(i-1)+8.0d0*cedic(i+1)-cedic(i+2)))
     1   / ((25.d0/12.0d0)*(Bedde11i(i)+Bedde12i(i)
     1   * (Kde1i/Kedi)))
C
1230  continue
C
      i = 1
      cedic_new(i) = (Bedde11i(i)*(4.0d0*cedia(i,j-1)-3.0d0
     1   * cedia(i,j-2)+(4.0d0/3.0d0)*cedia(i,j-3)-0.25d0
     1   * cedia(i,j-4))-Bedde12i(i)*(0.25d0*cde1ia(i,j+4)
     1   - (4.0d0/3.0d0)*cde1ia(i,j+3)+3.0d0*cde1ia(i,j+2)-4.0d0
     1   * cde1ia(i,j+1))+Bedde13i(i)*((1.0d0/12.0d0)*cedic(i+3)
     1   - 0.5d0*cedic(i+2)+1.5d0*cedic(i+1)-0.25d0
     1   * cedic(i-1))) / ((25.0d0/12.0d0)*(Bedde11i(i)
     1   + Bedde12i(i)*(Kde1i/Kedi))+(10.0d0/12.0d0)*Bedde13i(i))
C
      i = iin - 1
      cedic_new(i) = (Bedde11i(i)*(4.0d0*cedia(i,j-1)-3.0d0
     1   * cedia(i,j-2)+(4.0d0/3.0d0)*cedia(i,j-3)-0.25d0
     1   * cedia(i,j-4))-Bedde12i(i)*(-4.0d0*cde1ia(i,j+1)+3.0d0
     1   * cde1ia(i,j+2)-(4.0d0/3.0d0)*cde1ia(i,j+3)+0.25d0
     1   * cde1ia(i,j+4))+Bedde13i(i)*(-(1.0d0/12.0d0)*cedic(i-3)
```

```
     1   + 0.5d0*cedic(i-2)-1.5d0*cedic(i-1)+0.25d0
     1   * cedic(i+1))) / ((25.0d0/12.0d0)*(Bedde11i(i)
     1   + Bedde12i(i)*(Kde1i/Kedi))-(10.0d0/12.0d0)*Bedde13i(i))
C
      i = iin
      cedic_new(i) = (Bedde11i(i)*(4.0d0*cedia(i,j-1)-3.0d0
     1   * cedia(i,j-2)+(4.0d0/3.0d0)*cedia(i,j-3)-0.25d0
     1   * cedia(i,j-4))-Bedde12i(i)*(0.25d0*cde1ia(i,j+4)+3.0d0
     1   * cde1ia(i,j+2)-(4.0d0/3.0d0)*cde1ia(i,j+3)-4.0d0
     1   * cde1ia(i,j+1))+Bedde13i(i)*(-4.0d0*cedic(i-1)
     1   + 3.0d0*cedic(i-2)-(4.0d0/3.0d0)*cedic(i-3)+0.25d0
     1   * cedic(i-4))) / ((25.0d0/12.0d0)*(Bedde11i(i)
     1   + Bedde12i(i)*(Kde1i/Kedi)-Bedde13i(i)))
C
      maxdiff = 0.0d0
      do 1240, i = 1, iin
         temp = abs(cedic_new(i) - cedic(i))
         if (temp .gt. maxdiff) then
            maxdiff = temp
         end if
1240  continue
C
      if (maxdiff .gt. tol) then
         do 1250, i = 1, iin
            cedic(i) = cedic_new(i)
1250     continue
         go to 15
      else
         do 1260, i = 1, iin
            cedia(i,j) = cedic_new(i)
C            cedia(i,j) = 0.0d0
1260     continue
C
C      i = iin
C      cedia(i,j) = 0.0d0
      end if
C
C
C Ed outer region Ed/De1 boundary
C ````````````````````````````````
C
      do 1330, i = iin, iin + iout
         cedoc(i) = cedoa(i,j-1)
1330  continue
C
C n iterations
C ````````````
      n = 0
25    n = n + 1
C
      do 1340, i = iin + 2, iin + iout - 2
        cedoc_new(i) = (Bedde11o(i)*(4.0d0*cedoa(i,j-1)-3.0d0
     1   * cedoa(i,j-2)+(4.0d0/3.0d0)*cedoa(i,j-3)-0.25d0
     1   * cedoa(i,j-4))-Bedde12o(i)*(0.25d0*cde1oa(i,j+4)
     1   - (4.0d0/3.0d0)*cde1oa(i,j+3)+3.0d0*cde1oa(i,j+2)-4.0d0
     1   * cde1oa(i,j+1))+(1.0d0/12.0d0)*Bedde13o(i)*(cedoc(i-2)
     1   - 8.0d0*cedoc(i-1)+8.0d0*cedoc(i+1)-cedoc(i+2)))
```

```
     1   / ((25.d0/12.0d0)*(Bedde11o(i)+Bedde12o(i)
     1   * (Kde1o/Kedo)))
C
1340  continue
C
      i = iin + 1
      cedoc_new(i) = (Bedde11o(i)*(4.0d0*cedoa(i,j-1)-3.0d0
     1   * cedoa(i,j-2)+(4.0d0/3.0d0)*cedoa(i,j-3)-0.25d0
     1   * cedoa(i,j-4))-Bedde12o(i)*(0.25d0*cde1oa(i,j+4)
     1   - (4.0d0/3.0d0)*cde1oa(i,j+3)+3.0d0*cde1oa(i,j+2)-4.0d0
     1   * cde1oa(i,j+1))+Bedde13o(i)*((1.0d0/12.0d0)*cedoc(i+3)
     1   - 0.5d0*cedoc(i+2)+1.5d0*cedoc(i+1)-0.25d0
     1   * cedoc(i-1))) / ((25.0d0/12.0d0)*(Bedde11o(i)
     1   + Bedde12o(i)*(Kde1o/Kedo))+(10.0d0/12.0d0)*Bedde13o(i))
C
      i = iin + iout - 1
C
      cedoc_new(i) = (Bedde11o(i)*(4.0d0*cedoa(i,j-1)-3.0d0
     1   * cedoa(i,j-2)+(4.0d0/3.0d0)*cedoa(i,j-3)-0.25d0
     1   * cedoa(i,j-4))-Bedde12o(i)*(-4.0d0*cde1oa(i,j+1)+3.0d0
     1   * cde1oa(i,j+2)-(4.0d0/3.0d0)*cde1oa(i,j+3)+0.25d0
     1   * cde1oa(i,j+4))+Bedde13o(i)*(-(1.0d0/12.0d0)*cedoc(i-3)
     1   + 0.5d0*cedoc(i-2)-1.5d0*cedoc(i-1)+0.25d0
     1   * cedoc(i+1))) / ((25.0d0/12.0d0)*(Bedde11o(i)
     1   + Bedde12o(i)*(Kde1o/Kedo))-(10.0d0/12.0d0)*Bedde13o(i))
C
      i = iin
C
      cedoc_new(i) = (Bedde11o(i)*(4.0d0*cedoa(i,j-1)-3.0d0
     1   * cedoa(i,j-2)+(4.0d0/3.0d0)*cedoa(i,j-3)-0.25d0
     1   * cedoa(i,j-4))-Bedde12o(i)*(0.25d0*cde1oa(i,j+4)+3.0d0
     1   * cde1oa(i,j+2)-(4.0d0/3.0d0)*cde1oa(i,j+3)-4.0d0
     1   * cde1oa(i,j+1))+Bedde13o(i)*(4.0d0*cedoc(i+1)
     1   - 3.0d0*cedoc(i+2)+(4.0d0/3.0d0)*cedoc(i+3)-0.25d0
     1   * cedoc(i+4))) / ((25.0d0/12.0d0)*(Bedde11o(i)
     1   + Bedde12o(i)*(Kde1o/Kedo)+Bedde13o(i)))
C
      maxdiff = 0.0d0
      do 1350, i = iin, iin + iout - 1
         temp = abs(cedoc_new(i) - cedoc(i))
         if (temp .gt. maxdiff) then
            maxdiff = temp
         end if
1350  continue
C
      if (maxdiff .gt. tol) then
         do 1360, i = iin, iin + iout - 1
            cedoc(i) = cedoc_new(i)
1360     continue
         go to 25
      else
         do 1370, i = iin, iin + iout - 1
            cedoa(i,j) = cedoc_new(i)
C            cedoa(i,j) = 0.0d0
1370     continue
C
C         i = iin
```

```
C         cedoa(i,j) = 1.0d0
      end if
C
C
C z-direction boundaries in De1
C ````````````````````````````
C De1 inner region Ed/De1 boundary
C ````````````````````````````````
C
      j = jed
C
      do 1390, i = 0, iin
         cde1ib(i) = cde1ia(i,j+1)
1390  continue
C
C n iterations
C ````````````
      n = 0
30    n = n + 1
C
      do 1400, i = 2, iin - 2
      cde1ib_new(i) = (Bedde11i(i)*(4.0d0*cedia(i,j-1)-3.0d0
     1   * cedia(i,j-2)+(4.0d0/3.0d0)*cedia(i,j-3)-0.25d0
     1   * cedia(i,j-4))-Bedde12i(i)*(-4.0d0*cde1ia(i,j+1)+3.0d0
     1   * cde1ia(i,j+2)-(4.0d0/3.0d0)*cde1ia(i,j+3)+0.25d0
     1   * cde1ia(i,j+4))+(1.0d0/12.0d0)*Bedde14i(i)*(cde1ib(i-2)
     1   - 8.0d0*cde1ib(i-1)+8.0d0*cde1ib(i+1)-cde1ib(i+2)))
     1   / ((25.d0/12.0d0)*(Bedde12i(i)+Bedde11i(i)
     1   * (Kedi/Kde1i)))
C
1400  continue
C
      i = 1
      cde1ib_new(i) = (Bedde11i(i)*(4.0d0*cedia(i,j-1)-3.0d0
     1   * cedia(i,j-2)+(4.0d0/3.0d0)*cedia(i,j-3)-0.25d0
     1   * cedia(i,j-4))-Bedde12i(i)*(0.25d0*cde1ia(i,j+4)
     1   - (4.0d0/3.0d0)*cde1ia(i,j+3)+3.0d0*cde1ia(i,j+2)-4.0d0
     1   * cde1ia(i,j+1))+Bedde14i(i)*((1.0d0/12.0d0)*cde1ib(i+3)
     1   - 0.5d0*cde1ib(i+2)+1.5d0*cde1ib(i+1)-0.25d0*cde1ib(i-1)))
     1   / ((25.0d0/12.0d0)*(Bedde11i(i)*(Kedi/Kde1i)
     1   + Bedde12i(i))+(10.0d0/12.0d0)*Bedde14i(i))
C
      i = iin - 1
      cde1ib_new(i) = (Bedde11i(i)*(4.0d0*cedia(i,j-1)-3.0d0
     1   * cedia(i,j-2)+(4.0d0/3.0d0)*cedia(i,j-3)-0.25d0
     1   * cedia(i,j-4))-Bedde12i(i)*(-4.0d0*cde1ia(i,j+1)+3.0d0
     1   * cde1ia(i,j+2)-(4.0d0/3.0d0)*cde1ia(i,j+3)+0.25d0
     1   * cde1ia(i,j+4))+Bedde14i(i)*(-(1.0d0/12.0d0)*cde1ib(i-3)
     1   + 0.5d0*cde1ib(i-2)-1.5d0*cde1ib(i-1)+0.25d0
     1   * cde1ib(i+1))) / ((25.0d0/12.0d0)*(Bedde12i(i)
     1   + Bedde11i(i)*(Kedi/Kde1i))-(10.0d0/12.0d0)*Bedde14i(i))
C
      i = iin
      cde1ib_new(i) = (Bedde11i(i)*(4.0d0*cedia(i,j-1)-3.0d0
     1   * cedia(i,j-2)+(4.0d0/3.0d0)*cedia(i,j-3)-0.25d0
     1   * cedia(i,j-4))-Bedde12i(i)*(0.25d0*cde1ia(i,j+4)+3.0d0
     1   * cde1ia(i,j+2)-(4.0d0/3.0d0)*cde1ia(i,j+3)-4.0d0
```

```
     1   * cde1ia(i,j+1))+Bedde14i(i)*(-4.0d0*cde1ib(i-1)
     1   + 3.0d0*cde1ib(i-2)-(4.0d0/3.0d0)*cde1ib(i-3)+0.25d0
     1   * cde1ib(i-4))) / ((25.0d0/12.0d0)*(Bedde12i(i)
     1   + Bedde11i(i)*(Kedi/Kde1i)-Bedde14i(i)))
C
      maxdiff = 0.0d0
      do 1410, i = 1, iin
         temp = abs(cde1ib_new(i) - cde1ib(i))
         if (temp .gt. maxdiff) then
            maxdiff = temp
         end if
1410  continue
C
      if (maxdiff .gt. tol) then
         do 1420, i = 1, iin
            cde1ib(i) = cde1ib_new(i)
1420     continue
         go to 30
      else
         do 1430, i = 1, iin
            cde1ia(i,j) = cde1ib_new(i)
C            cde1ia(i,j) = 0.0d0
1430     continue
C
C         i = iin
C         cde1ia(i,j) = 0.0d0
      end if
C
C
C De1 outer region Ed/De1 boundary
C ````````````````````````````````
C
      do 1550, i = iin, iin + iout
        cde1ob(i) = cde1oa(i,j+1)
1550  continue
C
C n iterations
C ````````````
      n = 0
50    n = n + 1
C
      do 1560, i = iin + 2, iin + iout - 2
         cde1ob_new(i) = (Bedde11o(i)*(4.0d0*cedoa(i,j-1)-3.0d0
     1   * cedoa(i,j-2)+(4.0d0/3.0d0)*cedoa(i,j-3)-0.25d0
     1   * cedoa(i,j-4))-Bedde12o(i)*(-4.0d0*cde1oa(i,j+1)+3.0d0
     1   * cde1oa(i,j+2)-(4.0d0/3.0d0)*cde1oa(i,j+3)+0.25d0
     1   * cde1oa(i,j+4))+(1.0d0/12.0d0)*Bedde14o(i)*(cde1ob(i-2)
     1   - 8.0d0*cde1ob(i-1)+8.0d0*cde1ob(i+1)-cde1ob(i+2)))
     1   / ((25.d0/12.0d0)*(Bedde12o(i)+Bedde11o(i)
     1   * (Kedo/Kde1o)))
C
1560  continue
C
      i = iin + 1
      cde1ob_new(i) = (Bedde11o(i)*(4.0d0*cedoa(i,j-1)-3.0d0
     1   * cedoa(i,j-2)+(4.0d0/3.0d0)*cedoa(i,j-3)-0.25d0
     1   * cedoa(i,j-4))-Bedde12o(i)*(-4.0d0*cde1oa(i,j+1)+3.0d0
```

```
     1   * cde1oa(i,j+2)-(4.0d0/3.0d0)*cde1oa(i,j+3)+0.25d0
     1   * cde1oa(i,j+4))+Bedde14o(i)*((1.0d0/12.0d0)*cde1ob(i+3)
     1   - 0.5d0*cde1ob(i+2)+1.5d0*cde1ob(i+1)-0.25d0
     1   * cde1ob(i-1))) / ((25.0d0/12.0d0)*(Bedde12o(i)
     1   + Bedde11o(i)*(Kedo/Kde1o))+(10.0d0/12.0d0)*Bedde14o(i))
C
      i = iin + iout - 1
      cde1ob_new(i) = (Bedde11o(i)*(4.0d0*cedoa(i,j-1)-3.0d0
     1   * cedoa(i,j-2)+(4.0d0/3.0d0)*cedoa(i,j-3)-0.25d0
     1   * cedoa(i,j-4))-Bedde12o(i)*(-4.0d0*cde1oa(i,j+1)+3.0d0
     1   * cde1oa(i,j+2)-(4.0d0/3.0d0)*cde1oa(i,j+3)+0.25d0
     1   * cde1oa(i,j+4))+Bedde14o(i)*(-(1.0d0/12.0d0)*cde1ob(i-3)
     1   + 0.5d0*cde1ob(i-2)-1.5d0*cde1ob(i-1)+0.25d0
     1   * cde1ob(i+1))) / ((25.0d0/12.0d0)*(Bedde12o(i)
     1   + Bedde11o(i)*(Kedo/Kde1o))-(10.0d0/12.0d0)*Bedde14o(i))
C
      i = iin
      cde1ob_new(i) = (Bedde11o(i)*(4.0d0*cedoa(i,j-1)-3.0d0
     1   * cedoa(i,j-2)+(4.0d0/3.0d0)*cedoa(i,j-3)-0.25d0
     1   * cedoa(i,j-4))-Bedde12o(i)*(-4.0d0*cde1oa(i,j+1)+3.0d0
     1   * cde1oa(i,j+2)-(4.0d0/3.0d0)*cde1oa(i,j+3)+0.25d0
     1   * cde1oa(i,j+4))+Bedde14o(i)*(-0.25d0*cde1ob(i+4)
     1   + (4.0d0/3.0d0)*cde1ob(i+3)-3.0d0*cde1ob(i+2)+4.0d0
     1   * cde1ob(i+1))) / ((25.0d0/12.0d0)*(Bedde12o(i)
     1   + Bedde11o(i)*(Kedo/Kde1o)+Bedde14o(i)))
C
      maxdiff = 0.0d0
      do 1570, i = iin, iin + iout - 1
         temp = abs(cde1ob_new(i) - cde1ob(i))
         if (temp .gt. maxdiff) then
            maxdiff = temp
         end if
1570  continue
C
      if (maxdiff .gt. tol) then
         do 1580, i = iin, iin + iout - 1
            cde1ob(i) = cde1ob_new(i)
1580     continue
         go to 50
      else
         do 1590, i = iin, iin + iout - 1
            cde1oa(i,j) = cde1ob_new(i)
C            cde1oa(i,j) = 1.0d0
1590     continue
C
C         i = iin
C         cde1oa(i,j) = 1.0d0
      end if
C
C
C De1 inner region De1/De2 boundary
C ````````````````````````````````
      j = jed + jde1
C
      do 1490, i = 0, iin
         cde1ic(i) = cde1ia(i,j-1)
1490  continue
```

```
C
C n iterations
C ````````````
      n=0
45    n = n + 1
C
      do 1500, i = 2, iin - 2
      cde1ic_new(i) = (Bde1de21i(i)*(4.0d0*cde1ia(i,j-1)-3.0d0
     1   * cde1ia(i,j-2)+(4.0d0/3.0d0)*cde1ia(i,j-3)-0.25d0
     1   * cde1ia(i,j-4))-Bde1de22i(i)*(0.25d0*cde2ia(i,j+4)
     1   - (4.0d0/3.0d0)*cde2ia(i,j+3)+3.0d0*cde2ia(i,j+2)-4.0d0
     1   * cde2ia(i,j+1))+(1.0d0/12.0d0)*Bde1de23i(i)*(cde1ic(i-2)
     1   - 8.0d0*cde1ic(i-1)+8.0d0*cde1ic(i+1)-cde1ic(i+2)))
     1   / ((25.d0/12.0d0)*(Bde1de21i(i)+Bde1de22i(i)
     1   * (Kde2i/Kde1i)))
C
1500  continue
C
      i = 1
      cde1ic_new(i) = (Bde1de21i(i)*(4.0d0*cde1ia(i,j-1)-3.0d0
     1   * cde1ia(i,j-2)+(4.0d0/3.0d0)*cde1ia(i,j-3)-0.25d0
     1   * cde1ia(i,j-4))-Bde1de22i(i)*(0.25d0*cde2ia(i,j+4)
     1   - (4.0d0/3.0d0)*cde2ia(i,j+3)+3.0d0*cde2ia(i,j+2)-4.0d0
     1   * cde2ia(i,j+1))+Bde1de23i(i)*((1.0d0/12.0d0)*cde1ic(i+3)
     1   - 0.5d0*cde1ic(i+2)+1.5d0*cde1ic(i+1)-0.25d0
     1   * cde1ic(i-1))) / ((25.0d0/12.0d0)*(Bde1de21i(i)
     1   + Bde1de22i(i)*(Kde2i/Kde1i))+(10.0d0/12.0d0)*Bde1de23i(i))
C
      i = iin - 1
      cde1ic_new(i) = (Bde1de21i(i)*(4.0d0*cde1ia(i,j-1)-3.0d0
     1   * cde1ia(i,j-2)+(4.0d0/3.0d0)*cde1ia(i,j-3)-0.25d0
     1   * cde1ia(i,j-4))-Bde1de22i(i)*(-4.0d0*cde2ia(i,j+1)+3.0d0
     1   * cde2ia(i,j+2)-(4.0d0/3.0d0)*cde2ia(i,j+3)+0.25d0
     1   * cde2ia(i,j+4))+Bde1de23i(i)*(-(1.0d0/12.0d0)*cde1ic(i-3)
     1   + 0.5d0*cde1ic(i-2)-1.5d0*cde1ic(i-1)+0.25d0
     1   * cde1ic(i+1))) / ((25.0d0/12.0d0)*(Bde1de21i(i)
     1   + Bde1de22i(i)*(Kde2i/Kde1i))-(10.0d0/12.0d0)*Bde1de23i(i))
C
      i = iin
      cde1ic_new(i) = (Bde1de21i(i)*(4.0d0*cde1ia(i,j-1)-3.0d0
     1   * cde1ia(i,j-2)+(4.0d0/3.0d0)*cde1ia(i,j-3)-0.25d0
     1   * cde1ia(i,j-4))-Bde1de22i(i)*(0.25d0*cde2ia(i,j+4)+3.0d0
     1   * cde2ia(i,j+2)-(4.0d0/3.0d0)*cde2ia(i,j+3)-4.0d0
     1   * cde2ia(i,j+1))+Bde1de23i(i)*(-4.0d0*cde1ic(i-1)
     1   + 3.0d0*cde1ic(i-2)-(4.0d0/3.0d0)*cde1ic(i-3)+0.25d0
     1   * cde1ic(i-4))) / ((25.0d0/12.0d0)*(Bde1de21i(i)
     1   + Bde1de22i(i)*(Kde2i/Kde1i)-Bde1de23i(i)))
C
      maxdiff = 0.0d0
      do 1510, i = 1, iin
         temp = abs(cde1ic_new(i) - cde1ic(i))
         if (temp .gt. maxdiff) then
            maxdiff = temp
         end if
1510  continue
C
      if (maxdiff .gt. tol) then
```

```
         do 1520, i = 1, iin
            cde1ic(i) = cde1ic_new(i)
1520     continue
         go to 45
      else
         do 1530, i = 1, iin
            cde1ia(i,j) = cde1ic_new(i)
C            cde1ia(i,j) = 0.0d0
1530    continue
C
C        i = iin
C        cde1ia(i,j) = 0.0d0
      end if
C
C
C De1 outer region De1/De2 boundary
C ````````````````````````````````
C
      do 1600, i = iin, iin + iout
         cde1oc(i) = cde1oa(i,j-1)
1600  continue
C
C n iterations
C ````````````
      n = 0
55    n = n + 1
C
      do 1610, i = iin + 2, iin + iout - 2
      cde1oc_new(i) = (Bde1de21o(i)*(4.0d0*cde1oa(i,j-1)-3.0d0
     1   * cde1oa(i,j-2)+(4.0d0/3.0d0)*cde1oa(i,j-3)-0.25d0
     1   * cde1oa(i,j-4))-Bde1de22o(i)*(0.25d0*cde2oa(i,j+4)
     1   - (4.0d0/3.0d0)*cde2oa(i,j+3)+3.0d0*cde2oa(i,j+2)-4.0d0
     1   * cde2oa(i,j+1))+(1.0d0/12.0d0)*Bde1de23o(i)*(cde1oc(i-2)
     1   - 8.0d0*cde1oc(i-1)+8.0d0*cde1oc(i+1)-cde1oc(i+2)))
     1   / ((25.d0/12.0d0)*(Bde1de21o(i)+Bde1de22o(i)
     1   * (Kde2o/Kde1o)))
1610  continue
C
      i = iin + 1
      cde1oc_new(i) = (Bde1de21o(i)*(4.0d0*cde1oa(i,j-1)-3.0d0
     1   * cde1oa(i,j-2)+(4.0d0/3.0d0)*cde1oa(i,j-3)-0.25d0
     1   * cde1oa(i,j-4))-Bde1de22o(i)*(0.25d0*cde2oa(i,j+4)
     1   - (4.0d0/3.0d0)*cde2oa(i,j+3)+3.0d0*cde2oa(i,j+2)-4.0d0
     1   * cde2oa(i,j+1))+Bde1de23o(i)*((1.0d0/12.0d0)*cde1oc(i+3)
     1   - 0.5d0*cde1oc(i+2)+1.5d0*cde1oc(i+1)-0.25d0
     1   * cde1oc(i-1))) / ((25.0d0/12.0d0)*(Bde1de21o(i)
     1   + Bde1de22o(i)*(Kde2o/Kde1o))+(10.0d0/12.0d0)
     1   * Bde1de23o(i))
C
      i = iin + iout - 1
      cde1oc_new(i) = (Bde1de21o(i)*(4.0d0*cde1oa(i,j-1)-3.0d0
     1   * cde1oa(i,j-2)+(4.0d0/3.0d0)*cde1oa(i,j-3)-0.25d0
     1   * cde1oa(i,j-4))-Bde1de22o(i)*(-4.0d0*cde2oa(i,j+1)+3.0d0
     1   * cde2oa(i,j+2)-(4.0d0/3.0d0)*cde2oa(i,j+3)+0.25d0
     1   * cde2oa(i,j+4))+Bde1de23o(i)*(-(1.0d0/12.0d0)*cde1oc(i-3)
     1   + 0.5d0*cde1oc(i-2)-1.5d0*cde1oc(i-1)+0.25d0
     1   * cde1oc(i+1))) / ((25.0d0/12.0d0)*(Bde1de21o(i)
```

```
     1   + Bde1de22o(i)*(Kde2o/Kde1o))-(10.0d0/12.0d0)*Bde1de23o(i))
C
      i = iin
      cde1oc_new(i) = (Bde1de21o(i)*(4.0d0*cde1oa(i,j-1)-3.0d0
     1   * cde1oa(i,j-2)+(4.0d0/3.0d0)*cde1oa(i,j-3)-0.25d0
     1   * cde1oa(i,j-4))-Bde1de22o(i)*(0.25d0*cde2oa(i,j+4)+3.0d0
     1   * cde2oa(i,j+2)-(4.0d0/3.0d0)*cde2oa(i,j+3)-4.0d0
     1   * cde2oa(i,j+1))+Bde1de23o(i)*(4.0d0*cde1oc(i+1)
     1   - 3.0d0*cde1oc(i+2)+(4.0d0/3.0d0)*cde1oc(i+3)-0.25d0
     1   * cde1oc(i+4))) / ((25.0d0/12.0d0)*(Bde1de21o(i)
     1   + Bde1de22o(i)*(Kde2o/Kde1o)+Bde1de23o(i)))
C
      maxdiff = 0.0d0
      do 1620, i = iin, iin + iout - 1
         temp = abs(cde1oc_new(i) - cde1oc(i))
         if (temp .gt. maxdiff) then
            maxdiff = temp
         end if
1620  continue
C
      if (maxdiff .gt. tol) then
         do 1630, i = iin, iin + iout - 1
            cde1oc(i) = cde1oc_new(i)
1630  continue
         go to 55
      else
         do 1640, i = iin, iin + iout - 1
            cde1oa(i,j) = cde1oc_new(i)
C            cde1oa(i,j) = 0.0d0
1640     continue
C
C         i = iin
C         cde1oa(i,j) = 1.0d0
      end if
C
C
C De2 inner region De1/De2 boundary
C ````````````````````````````````
      j = jed + jde1
C
      do 1660, i = 0, iin
         cde2ib(i) = cde2ia(i,j+1)
1660  continue
C
C n iterations
C ````````````
      n = 0
60    n = n + 1
C
      do 1670, i = 2, iin - 2
      cde2ib_new(i) = (Bde1de21i(i)*(4.0d0*cde1ia(i,j-1)-3.0d0
     1   * cde1ia(i,j-2)+(4.0d0/3.0d0)*cde1ia(i,j-3)-0.25d0
     1   * cde1ia(i,j-4))-Bde1de22i(i)*(-4.0d0*cde2ia(i,j+1)+3.0d0
     1   * cde2ia(i,j+2)-(4.0d0/3.0d0)*cde2ia(i,j+3)+0.25d0
     1   * cde2ia(i,j+4))+(1.0d0/12.0d0)*Bde1de24i(i)*(cde2ib(i-2)
     1   - 8.0d0*cde2ib(i-1)+8.0d0*cde2ib(i+1)-cde2ib(i+2)))
     1   / ((25.d0/12.0d0)*(Bde1de22i(i)+Bde1de21i(i)
```

```
     1   * (Kde1i/Kde2i)))
C
1670  continue
C
      i = 1
      cde2ib_new(i) =  (Bde1de21i(i)*(4.0d0*cde1ia(i,j-1)-3.0d0
     1   * cde1ia(i,j-2)+(4.0d0/3.0d0)*cde1ia(i,j-3)-0.25d0
     1   * cde1ia(i,j-4))-Bde1de22i(i)*(0.25d0*cde2ia(i,j+4)
     1   - (4.0d0/3.0d0)*cde2ia(i,j+3)+3.0d0*cde2ia(i,j+2)-4.0d0
     1   * cde2ia(i,j+1))+Bde1de24i(i)*((1.0d0/12.0d0)*cde2ib(i+3)
     1   - 0.5d0*cde2ib(i+2)+1.5d0*cde2ib(i+1)-0.25d0*cde2ib(i-1)))
     1   / ((25.0d0/12.0d0)*(Bde1de21i(i)*(Kde1i/Kde2i)
     1   + Bde1de22i(i))+(10.0d0/12.0d0)*Bde1de24i(i))
C
      i = iin - 1
      cde2ib_new(i) = (Bde1de21i(i)*(4.0d0*cde1ia(i,j-1)-3.0d0
     1   * cde1ia(i,j-2)+(4.0d0/3.0d0)*cde1ia(i,j-3)-0.25d0
     1   * cde1ia(i,j-4))-Bde1de22i(i)*(-4.0d0*cde2ia(i,j+1)+3.0d0
     1   * cde2ia(i,j+2)-(4.0d0/3.0d0)*cde2ia(i,j+3)+0.25d0
     1   * cde2ia(i,j+4))+Bde1de24i(i)*(-(1.0d0/12.0d0)*cde2ib(i-3)
     1   + 0.5d0*cde2ib(i-2)-1.5d0*cde2ib(i-1)+0.25d0*cde2ib(i+1)))
     1   / ((25.0d0/12.0d0)*(Bde1de22i(i)+Bde1de21i(i)
     1   * (Kde1i/Kde2i))-(10.0d0/12.0d0)*Bde1de24i(i))
C
      i = iin
      cde2ib_new(i) = (Bde1de21i(i)*(4.0d0*cde1ia(i,j-1)-3.0d0
     1   * cde1ia(i,j-2)+(4.0d0/3.0d0)*cde1ia(i,j-3)-0.25d0
     1   * cde1ia(i,j-4))-Bde1de22i(i)*(0.25d0*cde2ia(i,j+4)+3.0d0
     1   * cde2ia(i,j+2)-(4.0d0/3.0d0)*cde2ia(i,j+3)-4.0d0
     1   * cde2ia(i,j+1))+Bde1de24i(i)*(-4.0d0*cde2ib(i-1)
     1   - (4.0d0/3.0d0)*cde2ib(i-3)+3.0d0*cde2ib(i-2)+0.25d0
     1   * cde2ib(i-4))) / ((25.0d0/12.0d0)*(Bde1de22i(i)
     1   + Bde1de21i(i)*(Kde1i/Kde2i)-Bde1de24i(i)))
C
      maxdiff = 0.0d0
      do 1680, i = 1, iin
         temp = abs(cde2ib_new(i) - cde2ib(i))
         if (temp .gt. maxdiff) then
            maxdiff = temp
         end if
1680  continue
C
      if (maxdiff .gt. tol) then
         do 1690, i = 1, iin
            cde2ib(i) = cde2ib_new(i)
1690     continue
         go to 60
      else
         do 1700, i = 1, iin
            cde2ia(i,j) = cde2ib_new(i)
C            cde2ia(i,j) = 1.0d0
1700     continue
C
C         i = iin
C         cde2ia(i,j) = 0.0d0
      end if
C
```

```
C
C De2 outer region De1/De2 boundary
C ````````````````````````````````
C
      do 1820, i = iin, iin + iout
        cde2ob(i) = cde2oa(i,j+1)
1820  continue
C
C n iterations
C ````````````
      n = 0
75    n = n + 1
C
      do 1830, i = iin + 2, iin + iout - 2
         cde2ob_new(i) = (Bde1de21o(i)*(4.0d0*cde1oa(i,j-1)-3.0d0
     1   * cde1oa(i,j-2)+(4.0d0/3.0d0)*cde1oa(i,j-3)-0.25d0
     1   * cde1oa(i,j-4))-Bde1de22o(i)*(-4.0d0*cde2oa(i,j+1)+3.0d0
     1   * cde2oa(i,j+2)-(4.0d0/3.0d0)*cde2oa(i,j+3)+0.25d0
     1   * cde2oa(i,j+4))+(1.0d0/12.0d0)*Bde1de24o(i)*(cde2ob(i-2)
     1   - 8.0d0*cde2ob(i-1)+8.0d0*cde2ob(i+1)-cde2ob(i+2)))
     1   / ((25.d0/12.0d0)*(Bde1de22o(i)+Bde1de21o(i)
     1   * (Kde1o/Kde2o)))
C
1830  continue
C
      i = iin + 1
      cde2ob_new(i) = (Bde1de21o(i)*(4.0d0*cde1oa(i,j-1)-3.0d0
     1   * cde1oa(i,j-2)+(4.0d0/3.0d0)*cde1oa(i,j-3)-0.25d0
     1   * cde1oa(i,j-4))-Bde1de22o(i)*(-4.0d0*cde2oa(i,j+1)+3.0d0
     1   * cde2oa(i,j+2)-(4.0d0/3.0d0)*cde2oa(i,j+3)+0.25d0
     1   * cde2oa(i,j+4))+Bde1de24o(i)*((1.0d0/12.0d0)*cde2ob(i+3)
     1   - 0.5d0*cde2ob(i+2)+1.5d0*cde2ob(i+1)-0.25d0
     1   * cde2ob(i-1))) / ((25.0d0/12.0d0)*(Bde1de22o(i)
     1   + Bde1de21o(i)*(Kde1o/Kde2o))+(10.0d0/12.0d0)
     1   * Bde1de24o(i))
C
      i = iin + iout - 1
      cde2ob_new(i) = (Bde1de21o(i)*(4.0d0*cde1oa(i,j-1)-3.0d0
     1   * cde1oa(i,j-2)+(4.0d0/3.0d0)*cde1oa(i,j-3)-0.25d0
     1   * cde1oa(i,j-4))-Bde1de22o(i)*(-4.0d0*cde2oa(i,j+1)+3.0d0
     1   * cde2oa(i,j+2)-(4.0d0/3.0d0)*cde2oa(i,j+3)+0.25d0
     1   * cde2oa(i,j+4))+Bde1de24o(i)*(-(1.0d0/12.0d0)*cde2ob(i-3)
     1   + 0.5d0*cde2ob(i-2)-1.5d0*cde2ob(i-1)+0.25d0
     1   * cde2ob(i+1))) / ((25.0d0/12.0d0)*(Bde1de22o(i)
     1   + Bde1de21o(i)*(Kde1o/Kde2o))-(10.0d0/12.0d0)*Bde1de24o(i))
C
      i = iin
      cde2ob_new(i) = (Bde1de21o(i)*(4.0d0*cde1oa(i,j-1)-3.0d0
     1   * cde1oa(i,j-2)+(4.0d0/3.0d0)*cde1oa(i,j-3)-0.25d0
     1   * cde1oa(i,j-4))-Bde1de22o(i)*(-4.0d0*cde2oa(i,j+1)+3.0d0
     1   * cde2oa(i,j+2)-(4.0d0/3.0d0)*cde2oa(i,j+3)+0.25d0
     1   * cde2oa(i,j+4))+Bde1de24o(i)*(-0.25d0*cde2ob(i+4)
     1   + (4.0d0/3.0d0)*cde2ob(i+3)-3.0d0*cde2ob(i+2)+4.0d0
     1   * cde2ob(i+1))) / ((25.0d0/12.0d0)*(Bde1de22o(i)
     1   + Bde1de21o(i)*(Kde1o/Kde2o)+Bde1de24o(i)))
C
      maxdiff = 0.0d0
```

```
      do 1840, i = iin, iin + iout - 1
         temp = abs(cde2ob_new(i) - cde2ob(i))
         if (temp .gt. maxdiff) then
            maxdiff = temp
         end if
1840  continue
C
      if (maxdiff .gt. tol) then
         do 1850, i = iin, iin + iout - 1
            cde2ob(i) = cde2ob_new(i)
1850     continue
         go to 75
      else
         do 1860, i = iin, iin + iout - 1
            cde2oa(i,j) = cde2ob_new(i)
C            cde2oa(i,j) = 1.0d0
1860     continue
C
C         i = iin
C         cde2oa(i,j) = 1.0d0
      end if
C
C
C De2 inner region De2/Hd boundary
C ````````````````````````````````
      j = jed + jde1 + jde2
C
      do 1760, i = 0, iin
         cde2ic(i) = cde2ia(i,j-1)
1760  continue
C
C n iterations
C ````````````
      n = 0
70    n = n + 1
C
      do 1770, i = 2, iin - 2
      cde2ic_new(i) = (Bde2hd1i(i)*(4.0d0*cde2ia(i,j-1)-3.0d0
     1   * cde2ia(i,j-2)+(4.0d0/3.0d0)*cde2ia(i,j-3)-0.25d0
     1   * cde2ia(i,j-4))-Bde2hd2i(i)*(0.25d0*chdia(i,j+4)+3.0d0
     1   * chdia(i,j+2)-(4.0d0/3.0d0)*chdia(i,j+3)-4.0d0
     1   * chdia(i,j+1))+(1.0d0/12.0d0)*Bde2hd3i(i)*(cde2ic(i-2)
     1   - 8.0d0*cde2ic(i-1)+8.0d0*cde2ic(i+1)-cde2ic(i+2)))
     1   / ((25.d0/12.0d0)*(Bde2hd1i(i)+Bde2hd2i(i)
     1   * (Khdi/Kde2i)))
C
1770  continue
C
      i = 1
      cde2ic_new(i) = (Bde2hd1i(i)*(4.0d0*cde2ia(i,j-1)-3.0d0
     1   * cde2ia(i,j-2)+(4.0d0/3.0d0)*cde2ia(i,j-3)-0.25d0
     1   * cde2ia(i,j-4))-Bde2hd2i(i)*(0.25d0*chdia(i,j+4)
     1   - (4.0d0/3.0d0)*chdia(i,j+3)+3.0d0*chdia(i,j+2)-4.0d0
     1   * chdia(i,j+1))+Bde2hd3i(i)*((1.0d0/12.0d0)*cde2ic(i+3)
     1   - 0.5d0*cde2ic(i+2)+1.5d0*cde2ic(i+1)-0.25d0
     1   * cde2ic(i-1))) / ((25.0d0/12.0d0)*(Bde2hd1i(i)
     1   + Bde2hd2i(i)*(Khdi/Kde2i))+(10.0d0/12.0d0)*Bde2hd3i(i))
```

```
C
      i = iin - 1
      cde2ic_new(i) = (Bde2hd1i(i)*(4.0d0*cde2ia(i,j-1)-3.0d0
     1   * cde2ia(i,j-2)+(4.0d0/3.0d0)*cde2ia(i,j-3)-0.25d0
     1   * cde2ia(i,j-4))-Bde2hd2i(i)*(-4.0d0*chdia(i,j+1)+3.0d0
     1   * chdia(i,j+2)-(4.0d0/3.0d0)*chdia(i,j+3)+0.25d0
     1   * chdia(i,j+4))+Bde2hd3i(i)*(-(1.0d0/12.0d0)*cde2ic(i-3)
     1   + 0.5d0*cde2ic(i-2)-1.5d0*cde2ic(i-1)+0.25d0*cde2ic(i+1)))
     1   / ((25.0d0/12.0d0)*(Bde2hd1i(i)+Bde2hd2i(i)
     1   * (Khdi/Kde2i))-(10.0d0/12.0d0)*Bde2hd3i(i))
C
      i = iin
      cde2ic_new(i) = (Bde2hd1i(i)*(4.0d0*cde2ia(i,j-1)-3.0d0
     1   * cde2ia(i,j-2)+(4.0d0/3.0d0)*cde2ia(i,j-3)-0.25d0
     1   * cde2ia(i,j-4))-Bde2hd2i(i)*(0.25d0*chdia(i,j+4)+3.0d0
     1   * chdia(i,j+2)-(4.0d0/3.0d0)*chdia(i,j+3)-4.0d0
     1   * chdia(i,j+1))+Bde2hd3i(i)*(-4.0d0*cde2ic(i-1)
     1   + 3.0d0*cde2ic(i-2)-(4.0d0/3.0d0)*cde2ic(i-3)+0.25d0
     1   * cde2ic(i-4))) / ((25.0d0/12.0d0)*(Bde2hd1i(i)
     1   + Bde2hd2i(i)*(Khdi/Kde2i)-Bde2hd3i(i)))
C
      maxdiff = 0.0d0
      do 1780, i = 1, iin
         temp = abs(cde2ic_new(i) - cde2ic(i))
         if (temp .gt. maxdiff) then
            maxdiff = temp
         end if
1780  continue
C
      if (maxdiff .gt. tol) then
         do 1790, i = 1, iin
            cde2ic(i) = cde2ic_new(i)
1790     continue
         go to 70
      else
         do 1800, i = 1, iin
            cde2ia(i,j) = cde2ic_new(i)
C            cde2ia(i,j) = 0.0d0
1800    continue
C
C         i = iin
C         cde2ia(i,j) = 0.0d0
      end if
C
C
C De2 outer region De2/Hd boundary
C ````````````````````````````````
C
         do 1870, i = iin, iin + iout
            cde2oc(i) = cde2oa(i,j-1)
1870     continue
C
C n iterations
C ````````````
      n = 0
80    n = n + 1
C
```

```
      do 1880, i = iin + 2, iin + iout - 2
      cde2oc_new(i) = (Bde2hd1o(i)*(4.0d0*cde2oa(i,j-1)-3.0d0
     1   * cde2oa(i,j-2)+(4.0d0/3.0d0)*cde2oa(i,j-3)-0.25d0
     1   * cde2oa(i,j-4))-Bde2hd2o(i)*(0.25d0*chdoa(i,j+4)+3.0d0
     1   * chdoa(i,j+2)-(4.0d0/3.0d0)*chdoa(i,j+3)-4.0d0
     1   * chdoa(i,j+1))+(1.0d0/12.0d0)*Bde2hd3o(i)*(cde2oc(i-2)
     1   - 8.0d0*cde2oc(i-1)+8.0d0*cde2oc(i+1)-cde2oc(i+2)))
     1   / ((25.d0/12.0d0)*(Bde2hd1o(i)+Bde2hd2o(i)
     1   * (Khdo/Kde2o)))
C
1880  continue
C
      i = iin + 1
      cde2oc_new(i) = (Bde2hd1o(i)*(4.0d0*cde2oa(i,j-1)-3.0d0
     1   * cde2oa(i,j-2)+(4.0d0/3.0d0)*cde2oa(i,j-3)-0.25d0
     1   * cde2oa(i,j-4))-Bde2hd2o(i)*(0.25d0*chdoa(i,j+4)
     1   - (4.0d0/3.0d0)*chdoa(i,j+3)+3.0d0*chdoa(i,j+2)-4.0d0
     1   * chdoa(i,j+1))+Bde2hd3o(i)*((1.0d0/12.0d0)*cde2oc(i+3)
     1   - 0.5d0*cde2oc(i+2)+1.5d0*cde2oc(i+1)-0.25d0
     1   * cde2oc(i-1))) / ((25.0d0/12.0d0)*(Bde2hd1o(i)
     1   + Bde2hd2o(i)*(Khdo/Kde2o))+(10.0d0/12.0d0)
     1   * Bde2hd3o(i))
C
      i = iin + iout - 1
      cde2oc_new(i) = (Bde2hd1o(i)*(4.0d0*cde2oa(i,j-1)-3.0d0
     1   * cde2oa(i,j-2)+(4.0d0/3.0d0)*cde2oa(i,j-3)-0.25d0
     1   * cde2oa(i,j-4))-Bde2hd2o(i)*(-4.0d0*chdoa(i,j+1)+3.0d0
     1   * chdoa(i,j+2)-(4.0d0/3.0d0)*chdoa(i,j+3)+0.25d0
     1   * chdoa(i,j+4))+Bde2hd3o(i)*(-(1.0d0/12.0d0)*cde2oc(i-3)
     1   + 0.5d0*cde2oc(i-2)-1.5d0*cde2oc(i-1)+0.25d0
     1   * cde2oc(i+1))) / ((25.0d0/12.0d0)*(Bde2hd1o(i)
     1   + Bde2hd2o(i)*(Khdo/Kde2o))-(10.0d0/12.0d0)*Bde2hd3o(i))
C
      i = iin
      cde2oc_new(i) = (Bde2hd1o(i)*(4.0d0*cde2oa(i,j-1)-3.0d0
     1   * cde2oa(i,j-2)+(4.0d0/3.0d0)*cde2oa(i,j-3)-0.25d0
     1   * cde2oa(i,j-4))-Bde2hd2o(i)*(0.25d0*chdoa(i,j+4)+3.0d0
     1   * chdoa(i,j+2)-(4.0d0/3.0d0)*chdoa(i,j+3)-4.0d0
     1   * chdoa(i,j+1))+Bde2hd3o(i)*(4.0d0*cde2oc(i+1)
     1   + (4.0d0/3.0d0)*cde2oc(i+3)-3.0d0*cde2oc(i+2)-0.25d0
     1   * cde2oc(i+4))) / ((25.0d0/12.0d0)*(Bde2hd1o(i)
     1   + Bde2hd2o(i)*(Khdo/Kde2o)+Bde2hd3o(i)))
C
      maxdiff = 0.0d0
      do 1890, i = iin, iin + iout - 1
         temp = abs(cde2oc_new(i) - cde2oc(i))
         if (temp .gt. maxdiff) then
            maxdiff = temp
         end if
1890  continue
C
      if (maxdiff .gt. tol) then
         do 1900, i = iin, iin + iout - 1
            cde2oc(i) = cde2oc_new(i)
1900     continue
         go to 80
      else
```

```
         do 1910, i = iin, iin + iout - 1
            cde2oa(i,j) = cde2oc_new(i)
C            cde2oa(i,j) = 0.0d0
1910     continue
C
C         i = iin
C         cde2oa(i,j) = 1.0d0
      end if
C
C
C Hd inner region De2/Hd boundary
C ````````````````````````````````
C
      do 1930, i = 0, iin
         chdib(i) = chdia(i,j+1)
1930  continue
C
C n iterations
C ````````````
      n = 0
85    n = n + 1
C
      do 1940, i = 2, iin - 2
      chdib_new(i) = (Bde2hd1i(i)*(4.0d0*cde2ia(i,j-1)-3.0d0
     1   * cde2ia(i,j-2)+(4.0d0/3.0d0)*cde2ia(i,j-3)-0.25d0
     1   * cde2ia(i,j-4))-Bde2hd2i(i)*(-4.0d0*chdia(i,j+1)+3.0d0
     1   * chdia(i,j+2)-(4.0d0/3.0d0)*chdia(i,j+3)+0.25d0
     1   * chdia(i,j+4))+(1.0d0/12.0d0)*Bde2hd4i(i)*(chdib(i-2)
     1   - 8.0d0*chdib(i-1)+8.0d0*chdib(i+1)-chdib(i+2)))
     1   / ((25.0d0/12.0d0)*(Bde2hd2i(i)+Bde2hd1i(i)
     1   * (Kde2i/Khdi)))
1940  continue
C
      i = 1
      chdib_new(i) = (Bde2hd1i(i)*(4.0d0*cde2ia(i,j-1)-3.0d0
     1   * cde2ia(i,j-2)+(4.0d0/3.0d0)*cde2ia(i,j-3)-0.25d0
     1   * cde2ia(i,j-4))-Bde2hd2i(i)*(0.25d0*chdia(i,j+4)
     1   - (4.0d0/3.0d0)*chdia(i,j+3)+3.0d0*chdia(i,j+2)-4.0d0
     1   * chdia(i,j+1))+Bde2hd4i(i)*((1.0d0/12.0d0)*chdib(i+3)
     1   - 0.5d0*chdib(i+2)+1.5d0*chdib(i+1)-0.25d0*chdib(i-1)))
     1   / ((25.0d0/12.0d0)*(Bde2hd1i(i)*(Kde2i/Khdi)
     1   + Bde2hd2i(i))+(10.0d0/12.0d0)*Bde2hd4i(i))

C
      i = iin - 1
      chdib_new(i) = (Bde2hd1i(i)*(4.0d0*cde2ia(i,j-1)-3.0d0
     1   * cde2ia(i,j-2)+(4.0d0/3.0d0)*cde2ia(i,j-3)-0.25d0
     1   * cde2ia(i,j-4))-Bde2hd2i(i)*(-4.0d0*chdia(i,j+1)+3.0d0
     1   * chdia(i,j+2)-(4.0d0/3.0d0)*chdia(i,j+3)+0.25d0
     1   * chdia(i,j+4))+Bde2hd4i(i)*(-(1.0d0/12.0d0)*chdib(i-3)
     1   + 0.5d0*chdib(i-2)-1.5d0*chdib(i-1)+0.25d0*chdib(i+1)))
     1   / ((25.0d0/12.0d0)*(Bde2hd2i(i)+Bde2hd1i(i)
     1   * (Kde2i/Khdi))-(10.0d0/12.0d0)*Bde2hd4i(i))
C
      i = iin
      chdib_new(i) = (Bde2hd1i(i)*(4.0d0*cde2ia(i,j-1)-3.0d0
     1   * cde2ia(i,j-2)+(4.0d0/3.0d0)*cde2ia(i,j-3)-0.25d0
```

```
     1   * cde2ia(i,j-4))-Bde2hd2i(i)*(0.25d0*chdia(i,j+4)+3.0d0
     1   * chdia(i,j+2)-(4.0d0/3.0d0)*chdia(i,j+3)-4.0d0
     1   * chdia(i,j+1))+Bde2hd4i(i)*(-4.0d0*chdib(i-1)
     1   - (4.0d0/3.0d0)*chdib(i-3)+3.0d0*chdib(i-2)+0.25d0
     1   * chdib(i-4))) / ((25.0d0/12.0d0)*(Bde2hd2i(i)
     1   + Bde2hd1i(i)*(Kde2i/Khdi)-Bde2hd4i(i)))
C
      maxdiff = 0.0d0
      do 1950, i = 1, iin
         temp = abs(chdib_new(i) - chdib(i))
         if (temp .gt. maxdiff) then
            maxdiff = temp
         end if
1950  continue
C
      if (maxdiff .gt. tol) then
         do 1960, i = 1, iin
            chdib(i) = chdib_new(i)
1960     continue
         go to 85
      else
         do 1970, i = 1, iin
            chdia(i,j) = chdib_new(i)
C            chdia(i,j) = 1.0d0
1970     continue
C
C         i = iin
C         chdia(i,j) = 0.0d0
      end if
C
C
C Hd outer region De2/Hd boundary
C ````````````````````````````````
C
      do 2090, i = iin, iin + iout
        chdob(i) = chdoa(i,j+1)
2090  continue
C
C n iterations
C ````````````
      n = 0
100   n = n + 1
C
      do 2100, i = iin + 2, iin + iout - 2
         chdob_new(i) = (Bde2hd1o(i)*(4.0d0*cde2oa(i,j-1)-3.0d0
     1   * cde2oa(i,j-2)+(4.0d0/3.0d0)*cde2oa(i,j-3)-0.25d0
     1   * cde2oa(i,j-4))-Bde2hd2o(i)*(-4.0d0*chdoa(i,j+1)+3.0d0
     1   * chdoa(i,j+2)-(4.0d0/3.0d0)*chdoa(i,j+3)+0.25d0
     1   * chdoa(i,j+4))+(1.0d0/12.0d0)*Bde2hd4o(i)*(chdob(i-2)
     1   - 8.0d0*chdob(i-1)+8.0d0*chdob(i+1)-chdob(i+2)))
     1   / ((25.0d0/12.0d0)*(Bde2hd2o(i)+Bde2hd1o(i)
     1   * (Kde2o/Khdo)))
C
2100  continue
C
      i = iin + 1
      chdob_new(i) = (Bde2hd1o(i)*(4.0d0*cde2oa(i,j-1)-3.0d0
```

```
     1   * cde2oa(i,j-2)+(4.0d0/3.0d0)*cde2oa(i,j-3)-0.25d0
     1   * cde2oa(i,j-4))-Bde2hd2o(i)*(-4.0d0*chdoa(i,j+1)+3.0d0
     1   * chdoa(i,j+2)-(4.0d0/3.0d0)*chdoa(i,j+3)+0.25d0
     1   * chdoa(i,j+4))+Bde2hd4o(i)*((1.0d0/12.0d0)*chdob(i+3)
     1   - 0.5d0*chdob(i+2)+1.5d0*chdob(i+1)-0.25d0
     1   * chdob(i-1))) / ((25.0d0/12.0d0)*(Bde2hd2o(i)
     1   + Bde2hd1o(i)*(Kde2o/Khdo))+(10.0d0/12.0d0)*Bde2hd4o(i))
C
      i = iin + iout - 1
      chdob_new(i) = (Bde2hd1o(i)*(4.0d0*cde2oa(i,j-1)-3.0d0
     1   * cde2oa(i,j-2)+(4.0d0/3.0d0)*cde2oa(i,j-3)-0.25d0
     1   * cde2oa(i,j-4))-Bde2hd2o(i)*(-4.0d0*chdoa(i,j+1)+3.0d0
     1   * chdoa(i,j+2)-(4.0d0/3.0d0)*chdoa(i,j+3)+0.25d0
     1   * chdoa(i,j+4))+Bde2hd4o(i)*(-(1.0d0/12.0d0)*chdob(i-3)
     1   + 0.5d0*chdob(i-2)-1.5d0*chdob(i-1)+0.25d0
     1   * chdob(i+1))) / ((25.0d0/12.0d0)*(Bde2hd2o(i)
     1   + Bde2hd1o(i)*(Kde2o/Khdo))-(10.0d0/12.0d0)*Bde2hd4o(i))
C
      i = iin
      chdob_new(i) = (Bde2hd1o(i)*(4.0d0*cde2oa(i,j-1)-3.0d0
     1   * cde2oa(i,j-2)+(4.0d0/3.0d0)*cde2oa(i,j-3)-0.25d0
     1   * cde2oa(i,j-4))-Bde2hd2o(i)*(-4.0d0*chdoa(i,j+1)+3.0d0
     1   * chdoa(i,j+2)-(4.0d0/3.0d0)*chdoa(i,j+3)+0.25d0
     1   * chdoa(i,j+4))+Bde2hd4o(i)*(-0.25d0*chdob(i+4)
     1   + (4.0d0/3.0d0)*chdob(i+3)-3.0d0*chdob(i+2)+4.0d0
     1   * chdob(i+1))) / ((25.0d0/12.0d0)*(Bde2hd2o(i)
     1   + Bde2hd1o(i)*(Kde2o/Khdo)+Bde2hd4o(i)))
C
      maxdiff = 0.0d0
      do 2110, i = iin, iin + iout - 1
         temp = abs(chdob_new(i) - chdob(i))
         if (temp .gt. maxdiff) then
            maxdiff = temp
         end if
2110  continue
C
      if (maxdiff .gt. tol) then
         do 2120, i = iin, iin + iout - 1
            chdob(i) = chdob_new(i)
2120     continue
         go to 100
      else
         do 2130, i = iin, iin + iout - 1
            chdoa(i,j) = chdob_new(i)
C            chdoa(i,j) = 1.0d0
2130     continue
C
C         i = iin
C         chdoa(i,j) = 1.0d0
      end if
C
C
C Hd inner region bottom boundary
C ````````````````````````````````
      j = jed + jde1 + jde2 + jhd
C
      do 2030, i = 0, iin
```

```
        chdic(i) = chdia(i,j-1)
2030  continue
C
C n iterations
C ````````````
      n = 0
95    n = n + 1
C
      do 2040, i = 2, iin - 2
C
      chdic_new(i) = (Bhdsub1i(i)*(4.0d0*chdia(i,j-1)-3.0d0
     1   * chdia(i,j-2)+(4.0d0/3.0d0)*chdia(i,j-3)-0.25d0
     1   * chdia(i,j-4))+(1.0d0/12.0d0)*Bhdsub2i(i)*(chdic(i-2)
     1   - 8.0d0*chdic(i-1)+8.0d0*chdic(i+1)-chdic(i+2))
     1   + Bhdsub4(i)*csub)
     1   / ((25.0d0/12.0d0)*Bhdsub1i(i)+Bhdsub3i(i))
C
2040  continue
C
      i = 1
      chdic_new(i) = (Bhdsub1i(i)*(4.0d0*chdia(i,j-1)-3.0d0
     1   * chdia(i,j-2)+(4.0d0/3.0d0)*chdia(i,j-3)-0.25d0
     1   * chdia(i,j-4))+Bhdsub2i(i)*((1.0d0/12.0d0)*chdic(i+3)-0.5d0
     1   * chdic(i+2)+1.5d0*chdic(i+1)-0.25d0*chdic(i-1))
     1   + Bhdsub4(i)*csub)
     1   / ((25.0d0/12.0d0)*Bhdsub1i(i)+(10.0d0/12.0d0)*Bhdsub2i(i)
     1   + Bhdsub3i(i))
C
      i = iin - 1
      chdic_new(i) = (Bhdsub1i(i)*(4.0d0*chdia(i,j-1)-3.0d0
     1   * chdia(i,j-2)+(4.0d0/3.0d0)*chdia(i,j-3)-0.25d0
     1   *chdia(i,j-4))+Bhdsub2i(i)*(-(1.0d0/12.0d0)*chdic(i-3)+0.5d0
     1   * chdic(i-2)-1.5d0*chdic(i-1)+0.25d0*chdic(i+1))+Bhdsub4(i)
     1   * csub)
     1   / ((25.0d0/12.0d0)*Bhdsub1i(i)-(10.0d0/12.0d0)*Bhdsub2i(i)
     1   + Bhdsub3i(i))
C
      i = iin
      chdic_new(i) = (Bhdsub1i(i)*(4.0d0*chdia(i,j-1)-3.0d0
     1   * chdia(i,j-2)+(4.0d0/3.0d0)*chdia(i,j-3)-0.25d0
     1   * chdia(i,j-4))+Bhdsub2i(i)*(-4.0d0*chdic(i-1)+3.0d0
     1   * chdic(i-2)-(4.0d0/3.0d0)*chdic(i-3)+0.25d0*chdic(i-4))
     1   + Bhdsub4(i)*csub)
     1   / ((25.0d0/12.0d0)*(Bhdsub1i(i)-Bhdsub2i(i))
     1   + Bhdsub3i(i))
C
      maxdiff = 0.0d0
      do 2050, i = 1, iin
         temp = abs(chdic_new(i) - chdic(i))
         if (temp .gt. maxdiff) then
            maxdiff = temp
         end if
2050  continue
C
      if (maxdiff .gt. tol) then
         do 2060, i = 1, iin
            chdic(i) = chdic_new(i)
```

```
2060     continue
         go to 95
      else
         do 2070, i = 1, iin
            chdia(i,j) = chdic_new(i)
C            chdia(i,j) = 0.0d0
2070     continue
C
C         i = iin
C         chdia(i,j) = 0.0d0
      end if
C
C
C Hd outer region bottom boundary
C ```````````````````````````````
C
      do 2140, i = iin, iin + iout
        chdoc(i) = chdoa(i,j-1)
2140  continue
C
C n iterations
C ````````````
      n = 0
105   n = n + 1
C
      do 2150, i = iin + 2, iin + iout - 2
      chdoc_new(i) = (Bhdsub1o(i)*(4.0d0*chdoa(i,j-1)-3.0d0
     1   * chdoa(i,j-2)+(4.0d0/3.0d0)*chdoa(i,j-3)-0.25d0
     1   * chdoa(i,j-4))+(1.0d0/12.0d0)*Bhdsub2o(i)*(chdoc(i-2)
     1   - 8.0d0*chdoc(i-1)+8.0d0*chdoc(i+1)-chdoc(i+2))
     1   + Bhdsub4(i)*csub)
     1   / ((25.0d0/12.0d0)*Bhdsub1o(i)+Bhdsub3o(i))
C
2150  continue
C
      i = iin + 1
      chdoc_new(i) = (Bhdsub1o(i)*(4.0d0*chdoa(i,j-1)-3.0d0
     1   * chdoa(i,j-2)+(4.0d0/3.0d0)*chdoa(i,j-3)-0.25d0
     1   * chdoa(i,j-4))+Bhdsub2o(i)*((1.0d0/12.0d0)*chdoc(i+3)-0.5d0
     1   * chdoc(i+2)+1.5d0*chdoc(i+1)-0.25d0*chdoc(i-1))
     1   + Bhdsub4(i)*csub)
     1   / ((25.0d0/12.0d0)*Bhdsub1o(i)+(10.0d0/12.0d0)*Bhdsub2o(i)
     1   + Bhdsub3o(i))
C
      i = iin + iout - 1
      chdoc_new(i) = (Bhdsub1o(i)*(4.0d0*chdoa(i,j-1)-3.0d0
     1   * chdoa(i,j-2)+(4.0d0/3.0d0)*chdoa(i,j-3)-0.25d0
     1   *chdoa(i,j-4))+Bhdsub2o(i)*(-(1.0d0/12.0d0)*chdoc(i-3)+0.5d0
     1   * chdoc(i-2)-1.5d0*chdoc(i-1)+0.25d0*chdoc(i+1))+Bhdsub4(i)
     1   * csub)
     1   / ((25.0d0/12.0d0)*Bhdsub1o(i)-(10.0d0/12.0d0)*Bhdsub2o(i)
     1   + Bhdsub3o(i))
C
      i = iin
      chdoc_new(i) = (Bhdsub1o(i)*(4.0d0*chdoa(i,j-1)-3.0d0
     1   * chdoa(i,j-2)+(4.0d0/3.0d0)*chdoa(i,j-3)-0.25d0
     1   * chdoa(i,j-4))+Bhdsub2o(i)*(4.0d0*chdoc(i+1)-3.0d0
```

```
     1   * chdoc(i+2)+(4.0d0/3.0d0)*chdoc(i+3)-0.25d0*chdoc(i+4))
     1   + Bhdsub4(i)*csub)
     1   / ((25.0d0/12.0d0)*(Bhdsub1o(i)+Bhdsub2o(i))
     1   + Bhdsub3o(i))
C
      maxdiff = 0.0d0
      do 2160, i = iin, iin + iout - 1
         temp = abs(chdoc_new(i) - chdoc(i))
         if (temp .gt. maxdiff) then
            maxdiff = temp
         end if
2160  continue
C
      if (maxdiff .gt. tol) then
         do 2170, i = iin, iin + iout - 1
            chdoc(i) = chdoc_new(i)
2170     continue
         go to 105
      else
         do 2180, i = iin, iin + iout - 1
            chdoa(i,j) = chdoc_new(i)
C            chdoa(i,j) = 0.0d0
2180     continue
C
C         i = iin
C         chdoa(i,j) = 1.0d0
      end if
C
C
C Corner nodes
C ````````````
C Ed corner top left
C ``````````````````
      j = 0
      i = 0
C
      cedia(i,j) = (Bsced1i(i)*(0.25d0*cedia(i,j+4)-(4.0d0/3.0d0)
     1   * cedia(i,j+3)+3.0d0*cedia(i,j+2)-4.0d0*cedia(i,j+1))
     1   + Bsced2i(i)*(4.0d0*cedia(i+1,j)-3.0d0*cedia(i+2,j)
     1   + (4.0d0/3.0d0)*cedia(i+3,j)-0.25d0*cedia(i+4,j))
     1   - Bsced4(i)*cds(i))
     1   / ((25.0d0/12.0d0)*(-Bsced1i(i)+Bsced2i(i))
     1   - Bsced3i(i))
C      cedia(i,j) = 1.0d0
C
C Ed corner top right
C ```````````````````
      i = iin + iout
C
      cedoa(i,j) = (Bsced1o(i)*(0.25d0*cedoa(i,j+4)-(4.0d0/3.0d0)
     1   * cedoa(i,j+3)+3.0d0*cedoa(i,j+2)-4.0d0*cedoa(i,j+1))
     1   + Bsced2o(i)*(0.25d0*cedoa(i-4,j)-(4.0d0/3.0d0)
     1   * cedoa(i-3,j)+3.0d0*cedoa(i-2,j)-4.0d0*cedoa(i-1,j))
     1   - Bsced4(i)*cds(i)) / ((25.0d0/12.0d0)*(-Bsced2o(i)
     1   - Bsced1o(i))-Bsced3o(i))
C      cedoa(i,j) = 1.0d0
C      cedoa(i,j) = 0.0d0
```

```
C
C Ed corner bottom left
C ``````````````````````
      j = jed
      i = 0
C
      cedia(i,j) = (Bedde11i(i)*(4.0d0*cedia(i,j-1)-3.0d0
     1   * cedia(i,j-2)+(4.0d0/3.0d0)*cedia(i,j-3)-0.25d0
     1   * cedia(i,j-4))-Bedde12i(i)*(0.25d0*cde1ia(i,j+4)
     1   - (4.0d0/3.0d0)*cde1ia(i,j+3)+3.0d0*cde1ia(i,j+2)-4.0d0
     1   * cde1ia(i,j+1))+Bedde13i(i)*(4.0d0*cedia(i+1,j)
     1   - 3.0d0*cedia(i+2,j)+(4.0d0/3.0d0)*cedia(i+3,j)-0.25d0
     1   * cedia(i+4,j))) / ((25.0d0/12.0d0)*(Bedde11i(i)
     1   + Bedde12i(i)*(Kde1i/Kedi)+Bedde13i(i)))
C      cedia(i,j) = 1.0d0
C      cedia(i,j) = 0.0d0
C
C Ed corner bottom right
C ``````````````````````
      i = iin + iout
C
      cedoa(i,j) = (Bedde11o(i)*(4.0d0*cedoa(i,j-1)-3.0d0
     1   * cedoa(i,j-2)+(4.0d0/3.0d0)*cedoa(i,j-3)-0.25d0
     1   * cedoa(i,j-4))-Bedde12o(i)*(0.25d0*cde1oa(i,j+4)+3.0d0
     1   * cde1oa(i,j+2)-(4.0d0/3.0d0)*cde1oa(i,j+3)-4.0d0
     1   * cde1oa(i,j+1))+Bedde13o(i)*(-4.0d0*cedoa(i-1,j)
     1   + 3.0d0*cedoa(i-2,j)-(4.0d0/3.0d0)*cedoa(i-3,j)+0.25d0
     1   * cedoa(i-4,j))) / ((25.0d0/12.0d0)*(Bedde11o(i)
     1   + Bedde12o(i)*(Kde1o/Kedo)-Bedde13o(i)))
C      cedoa(i,j) = 0.0d0
C
C
C De1 corner top left
C ``````````````````````
      j = jed
      i = 0
C
      cde1ia(i,j) = (Bedde11i(i)*(4.0d0*cedia(i,j-1)-3.0d0
     1   * cedia(i,j-2)+(4.0d0/3.0d0)*cedia(i,j-3)-0.25d0
     1   * cedia(i,j-4))-Bedde12i(i)*(-4.0d0*cde1ia(i,j+1)+3.0d0
     1   * cde1ia(i,j+2)-(4.0d0/3.0d0)*cde1ia(i,j+3)+0.25d0
     1   * cde1ia(i,j+4))+Bedde14i(i)*(-0.25d0*cde1ia(i+4,j)
     1   + (4.0d0/3.0d0)*cde1ia(i+3,j)-3.0d0*cde1ia(i+2,j)+4.0d0
     1   * cde1ia(i+1,j))) / ((25.0d0/12.0d0)*(Bedde12i(i)
     1   + Bedde11i(i)*(Kedi/Kde1i)+Bedde14i(i)))
C      cde1ia(i,j) = 1.0d0
C      cde1ia(i,j) = 0.0d0
C
C De1 corner top right
C ``````````````````````
      i = iin + iout
      cde1oa(i,j) = (Bedde11o(i)*(4.0d0*cedoa(i,j-1)-3.0d0
     1   * cedoa(i,j-2)+(4.0d0/3.0d0)*cedoa(i,j-3)-0.25d0
     1   * cedoa(i,j-4))-Bedde12o(i)*(0.25d0*cde1oa(i,j+4)+3.0d0
     1   * cde1oa(i,j+2)-(4.0d0/3.0d0)*cde1oa(i,j+3)-4.0d0
     1   * cde1oa(i,j+1))+Bedde14o(i)*(-4.0d0*cde1oa(i-1,j)
     1   + 3.0d0*cde1oa(i-2,j)-(4.0d0/3.0d0)*cde1oa(i-3,j)+0.25d0
```

```
     1   * cde1oa(i-4,j))) / ((25.0d0/12.0d0)*(Bedde12o(i)
     1   + Bedde11o(i)*(Kedo/Kde1o)-Bedde14o(i)))
C      cde1oa(i,j) = 0.0d0
C
C
C De1 corner bottom left
C ``````````````````````
      j = jed + jde1
      i = 0
C
      cde1ia(i,j) = (Bde1de21i(i)*(4.0d0*cde1ia(i,j-1)-3.0d0
     1   * cde1ia(i,j-2)+(4.0d0/3.0d0)*cde1ia(i,j-3)-0.25d0
     1   * cde1ia(i,j-4))-Bde1de22i(i)*(0.25d0*cde2ia(i,j+4)
     1   - (4.0d0/3.0d0)*cde2ia(i,j+3)+3.0d0*cde2ia(i,j+2)-4.0d0
     1   * cde2ia(i,j+1))+Bde1de23i(i)*(4.0d0*cde1ia(i+1,j)
     1   - 3.0d0*cde1ia(i+2,j)+(4.0d0/3.0d0)*cde1ia(i+3,j)-0.25d0
     1   * cde1ia(i+4,j))) / ((25.0d0/12.0d0)*(Bde1de21i(i)
     1   + Bde1de22i(i)*(Kde2i/Kde1i)+Bde1de23i(i)))
C      cde1ia(i,j) = 1.0d0
C      cde1ia(i,j) = 0.0d0
C
C De1 corner bottom right
C ```````````````````````
      i = iin + iout
C
      cde1oa(i,j) = (Bde1de21o(i)*(4.0d0*cde1oa(i,j-1)-3.0d0
     1   * cde1oa(i,j-2)+(4.0d0/3.0d0)*cde1oa(i,j-3)-0.25d0
     1   * cde1oa(i,j-4))-Bde1de22o(i)*(0.25d0*cde2oa(i,j+4)+3.0d0
     1   * cde2oa(i,j+2)-(4.0d0/3.0d0)*cde2oa(i,j+3)-4.0d0
     1   * cde2oa(i,j+1))+Bde1de23o(i)*(-4.0d0*cde1oa(i-1,j)
     1   + 3.0d0*cde1oa(i-2,j)-(4.0d0/3.0d0)*cde1oa(i-3,j)+0.25d0
     1   * cde1oa(i-4,j))) / ((25.0d0/12.0d0)*(Bde1de21o(i)
     1   + Bde1de22o(i)*(Kde2o/Kde1o)-Bde1de23o(i)))
C      cedoa(i,j) = 0.0d0
C
C De2 corner top left
C ```````````````````
      j = jed + jde1
      i = 0
C
      cde2ia(i,j) = (Bde1de21i(i)*(4.0d0*cde1ia(i,j-1)-3.0d0
     1   * cde1ia(i,j-2)+(4.0d0/3.0d0)*cde1ia(i,j-3)-0.25d0
     1   * cde1ia(i,j-4))-Bde1de22i(i)*(-4.0d0*cde2ia(i,j+1)+3.0d0
     1   * cde2ia(i,j+2)-(4.0d0/3.0d0)*cde2ia(i,j+3)+0.25d0
     1   * cde2ia(i,j+4))+Bde1de24i(i)*(-0.25d0*cde2ia(i+4,j)
     1   + (4.0d0/3.0d0)*cde2ia(i+3,j)-3.0d0*cde2ia(i+2,j)+4.0d0
     1   * cde2ia(i+1,j))) / ((25.0d0/12.0d0)*(Bde1de22i(i)
     1   + Bde1de21i(i)*(Kde1i/Kde2i)+Bde1de24i(i)))
C      cde2ia(i,j) = 1.0d0
C
C De2 corner top right
C ````````````````````
      i = iin + iout
C
      cde2oa(i,j) = (Bde1de21o(i)*(4.0d0*cde1oa(i,j-1)-3.0d0
     1   * cde1oa(i,j-2)+(4.0d0/3.0d0)*cde1oa(i,j-3)-0.25d0
     1   * cde1oa(i,j-4))-Bde1de22o(i)*(0.25d0*cde2oa(i,j+4)+3.0d0
```

```
     1   * cde2oa(i,j+2)-(4.0d0/3.0d0)*cde2oa(i,j+3)-4.0d0
     1   * cde2oa(i,j+1))+Bde1de24o(i)*(-4.0d0*cde2oa(i-1,j)
     1   + 3.0d0*cde2oa(i-2,j)-(4.0d0/3.0d0)*cde2oa(i-3,j)+0.25d0
     1   * cde2oa(i-4,j))) / ((25.0d0/12.0d0)*(Bde1de22o(i)
     1   + Bde1de21o(i)*(Kde1o/Kde2o)-Bde1de24o(i)))
C      cde2oa(i,j) = 0.0d0
C
C De2 corner bottom left
C ``````````````````````
      j = jed + jde1 + jde2
      i = 0
C
      cde2ia(i,j) = (Bde2hd1i(i)*(4.0d0*cde2ia(i,j-1)-3.0d0
     1   * cde2ia(i,j-2)+(4.0d0/3.0d0)*cde2ia(i,j-3)-0.25d0
     1   * cde2ia(i,j-4))-Bde2hd2i(i)*(0.25d0*chdia(i,j+4)+3.0d0
     1   * chdia(i,j+2)-(4.0d0/3.0d0)*chdia(i,j+3)-4.0d0
     1   * chdia(i,j+1))+Bde2hd3i(i)*(4.0d0*cde2ia(i+1,j)
     1   + (4.0d0/3.0d0)*cde2ia(i+3,j)-3.0d0*cde2ia(i+2,j)-0.25d0
     1   * cde2ia(i+4,j))) / ((25.0d0/12.0d0)*(Bde2hd1i(i)
     1   + Bde2hd2i(i)*(Khdi/Kde2i)+Bde2hd3i(i)))
C      cde2ia(i,j) = 1.0d0
C
C De2 corner bottom right
C ```````````````````````
      i = iin + iout
C
      cde2oa(i,j) = (Bde2hd1o(i)*(4.0d0*cde2oa(i,j-1)-3.0d0
     1   * cde2oa(i,j-2)+(4.0d0/3.0d0)*cde2oa(i,j-3)-0.25d0
     1   * cde2oa(i,j-4))-Bde2hd2o(i)*(0.25d0*chdoa(i,j+4)+3.0d0
     1   * chdoa(i,j+2)-(4.0d0/3.0d0)*chdoa(i,j+3)-4.0d0
     1   * chdoa(i,j+1))+Bde2hd3o(i)*(-4.0d0*cde2oa(i-1,j)
     1   + 3.0d0*cde2oa(i-2,j)-(4.0d0/3.0d0)*cde2oa(i-3,j)+0.25d0
     1   * cde2oa(i-4,j))) / ((25.0d0/12.0d0)*(Bde2hd1o(i)
     1   + Bde2hd2o(i)*(Khdo/Kde2o)-Bde2hd3o(i)))
C      cde2oa(i,j) = 0.0d0
C
C Hd corner top left
C ``````````````````
      j = jed + jde1 + jde2
      i = 0
C
      chdia(i,j) = (Bde2hd1i(i)*(4.0d0*cde2ia(i,j-1)-3.0d0
     1   * cde2ia(i,j-2)+(4.0d0/3.0d0)*cde2ia(i,j-3)-0.25d0
     1   * cde2ia(i,j-4))-Bde2hd2i(i)*(-4.0d0*chdia(i,j+1)+3.0d0
     1   * chdia(i,j+2)-(4.0d0/3.0d0)*chdia(i,j+3)+0.25d0
     1   * chdia(i,j+4))+Bde2hd4i(i)*(-0.25d0*chdia(i+4,j)
     1   + (4.0d0/3.0d0)*chdia(i+3,j)-3.0d0*chdia(i+2,j)+4.0d0
     1   * chdia(i+1,j))) / ((25.0d0/12.0d0)*(Bde2hd2i(i)
     1   + Bde2hd1i(i)*(Kde2i/Khdi)+Bde2hd4i(i)))
C      chdia(i,j) = 1.0d0
C
C Hd corner top right
C ```````````````````
      i = iin + iout
C
      chdoa(i,j) = (Bde2hd1o(i)*(4.0d0*cde2oa(i,j-1)-3.0d0
     1   * cde2oa(i,j-2)+(4.0d0/3.0d0)*cde2oa(i,j-3)-0.25d0
```

```
     1   * cde2oa(i,j-4))-Bde2hd2o(i)*(0.25d0*chdoa(i,j+4)+3.0d0
     1   * chdoa(i,j+2)-(4.0d0/3.0d0)*chdoa(i,j+3)-4.0d0
     1   * chdoa(i,j+1))+Bde2hd4o(i)*(-4.0d0*chdoa(i-1,j)
     1   + 3.0d0*chdoa(i-2,j)-(4.0d0/3.0d0)*chdoa(i-3,j)+0.25d0
     1   * chdoa(i-4,j))) / ((25.0d0/12.0d0)*(Bde2hd2o(i)
     1   + Bde2hd1o(i)*(Kde2o/Khdo)-Bde2hd4o(i)))
C      chdoa(i,j) = 0.0d0
C
C Hd corner bottom left
C ``````````````````````
      j = jed + jde1 + jde2 + jhd
      i = 0
C
      chdia(i,j) = (Bhdsub1i(i)*(4.0d0*chdia(i,j-1)-3.0d0
     1   * chdia(i,j-2)+(4.0d0/3.0d0)*chdia(i,j-3)-0.25d0
     1   * chdia(i,j-4))+Bhdsub2i(i)*(4.0d0*chdia(i+1,j)-3.0d0
     1   * chdia(i+2,j)+(4.0d0/3.0d0)*chdia(i+3,j)-0.25d0*chdia(i+4,j))
     1   + Bhdsub4(i)*csub)
     1   / ((25.0d0/12.0d0)*(Bhdsub1i(i)+Bhdsub2i(i))
     1   + Bhdsub3i(i))
C      chdia(i,j) = 1.0d0
C      chdia(i,j) = 0.0d0
C
C Hd corner bottom right
C ``````````````````````
      i = iin + iout
C
      chdoa(i,j) = (Bhdsub1o(i)*(4.0d0*chdoa(i,j-1)-3.0d0
     1   * chdoa(i,j-2)+(4.0d0/3.0d0)*chdoa(i,j-3)-0.25d0
     1   * chdoa(i,j-4))+Bhdsub2o(i)*(-4.0d0*chdoa(i-1,j)+3.0d0
     1   * chdoa(i-2,j)-(4.0d0/3.0d0)*chdoa(i-3,j)+0.25d0*chdoa(i-4,j))
     1   + Bhdsub4(i)*csub)
     1   / ((25.0d0/12.0d0)*(Bhdsub1o(i)-Bhdsub2o(i))
     1   + Bhdsub3o(i))
C      chdoa(i,j) = 0.0d0
C
7050  format (/,'Time=', d23.16)
9300  format (i3,1x,i3,1x,i3,1x,d23.16,1x,d23.16,1x,d23.16,1x,d23.16)
9350  format (i3,1x,i3,1x,d23.16,1x,d23.16)
9400  format (i3, 1x, i3,1x,d23.16,1xd23.16)
9450  format ('Dermis 1')
9500  format (i3,1x,d23.16,1x,d23.16,1x,d23.16)
C
      return
      end
C
C
      subroutine donorsolconc
      implicit double precision (a - z)
      integer i, idim, jdim, iin, iout, jmininf
      integer jed, jde1, jde2, jhd, j
      parameter (idim = 500, jdim = 500)
      parameter (pi = 3.141592654d0)
C
      dimension cedia(0:idim,0:jdim)
      dimension cedoa(0:idim,0:jdim)
      dimension cde1ia(0:idim,0:jdim)
```

```
      dimension cde1oa(0:idim,0:jdim)
      dimension cde2ia(0:idim,0:jdim)
      dimension cde2oa(0:idim,0:jdim)
      dimension chdia(0:idim,0:jdim)
      dimension chdoa(0:idim,0:jdim)
      dimension xia(0:idim), zda(0:jdim)
      dimension fval(0:idim), dfval(0:idim)
      dimension cds(0:idim), A1(0:idim), A2(0:idim)
      dimension t1(0:idim), t3(0:idim)
      dimension m(0:idim)
C
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
      common /xizetaval/ xia, zda
      common /concarrays/ cedia, cedoa, cde1ia, cde1oa, cde2ia,
     1                             cde2oa, chdia, chdoa
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
      common /f_values/ fval, dfval
      common /time/ t
      common /erfcarg/ m
      common /donorsoldata/ I_der, t1, t2, t3, t4, t5, t6, t7
      common /dsconctemp/ cds
      common /dsparam/ k, h, A, jmininf
      common /dsparam2/ t7ed, t7de1, t7de2
      common /dsparam3/ k_ed, k_de1, k_de2_2, k_hd
C
C      common /test/ Idered1,Idered2,Idered3,Idered4
C      common /test/ Iderde1, test1Iderde1, test2Iderde1
C
C
C Volume of donor solution over skin tissue
C ````````````````````````````````````````
      h = 100.0d0
      A = 1000.0d0
C
C Bottom limit of infundibulum
      jmininf = 36
C
C
C Term t_1
C ````````
C
      XI0_i = (xia(0)*(rd_max-fval(0))+fval(0))
     1    * (rd_max-fval(0))
     1    + (xia(iin)*(rd_max-fval(0))+fval(0))
     1    * (rd_max-fval(0))
      XI1_i = 0.0d0
      XI2_i = 0.0d0
C
      do 100, i = 1, iin - 1
         if (mod(i,2) .eq. 0) then
            XI2_i = XI2_i+((xia(i)*(rd_max-fval(0))+fval(0))
     1          * (rd_max-fval(0)))
```

```
         else
            XI1_i = XI1_i+((xia(i)*(rd_max-fval(0))+fval(0))
     1          * (rd_max-fval(0)))
         end if
100   continue
C
      t1i = hxi_in*(XI0_i+2.0d0*XI2_i+4.0d0*XI1_i)/3.0d0
C
      XI0_o = (xia(iin)*(rd_max-fval(0))+fval(0))
     1      * (rd_max-fval(0))
     1      + (xia(iin+iout)*(rd_max-fval(0))+fval(0))
     1      * (rd_max-fval(0))
      XI1_o = 0.0d0
      XI2_o = 0.0d0
C
      do 110, i = iin + 1, iin + iout - 1
         if (mod(i,2) .eq. 0) then
            XI2_o = XI2_o+((xia(i)*(rd_max-fval(0))+fval(0))
     1          * (rd_max-fval(0)))
         else
            XI1_o = XI1_o+((xia(i)*(rd_max-fval(0))+fval(0))
     1          * (rd_max-fval(0)))
         end if
110   continue
C
      t1o = hxi_out*(XI0_o+2.0d0*XI2_o+4.0d0*XI1_o)/3.0d0
C
      j = 0
      do 120, i = 0, iin + iout
         t1(i) = (2.0d0*pi*Pscsol(xia(i),zda(j))/Ksolref)
     1           * (t1i + t1o)
120   continue
C
C
C Evaluation of time derivative
C ````````````````````````````
      tt = t + 0.0001d0
C
C Epidermis
C
      XI0ed = erfcomp(zda(jed),t)*(fval(jed))**2
     1      + erfcomp(zda(0),t)*(fval(0))**2
      XI1ed = 0.0d0
      XI2ed = 0.0d0
C
      do 130, j = 1, jed - 1
         if (mod(j,2) .eq. 0) then
            XI2ed = XI2ed + erfcomp(zda(j),t)*(fval(j))**2
         else
            XI1ed = XI1ed + erfcomp(zda(j),t)*(fval(j))**2
         end if
130   continue
C
      inted_1 = hzd*(XI0ed+2.0d0*XI2ed+4.0d0*XI1ed)/3.0d0
C
C
      XI0ed = erfcomp(zda(jed),tt)*(fval(jed))**2
```

```
     1      + erfcomp(zda(0),tt)*(fval(0))**2
      XI1ed = 0.0d0
      XI2ed = 0.0d0
C
      do 140, j = 1, jed - 1
         if (mod(j,2) .eq. 0) then
            XI2ed = XI2ed+erfcomp(zda(j),tt)*(fval(j))**2
         else
            XI1ed = XI1ed+erfcomp(zda(j),tt)*(fval(j))**2
         end if
140   continue
C
      inted_2 = hzd*(XI0ed+2.0d0*XI2ed+4.0d0*XI1ed)/3.0d0
C
      Idered = (inted_2 - inted_1) / 0.0001d0
C
C
C Dermis 1
C
      XI0de1 = erfcomp(zda(jed+jde1),t)*(fval(jed+jde1))**2
     1       + erfcomp(zda(jed),t)*(fval(jed))**2
      XI1de1 = 0.0d0
      XI2de1 = 0.0d0
C
      do 150, j = jed + 1, jed + jde1 - 1
         if (mod(j,2) .eq. 0) then
            XI2de1 = XI2de1 + erfcomp(zda(j),t)*(fval(j))**2
         else
            XI1de1 = XI1de1 + erfcomp(zda(j),t)*(fval(j))**2
         end if
150   continue
C
      intde1_1 = hzd1*(XI0de1+2.0d0*XI2de1+4.0d0*XI1de1)/3.0d0
C
C
      XI0de1 = erfcomp(zda(jed+jde1),tt)*(fval(jed+jde1))**2
     1       + erfcomp(zda(jed),tt)*(fval(jed))**2
      XI1de1 = 0.0d0
      XI2de1 = 0.0d0
C
      do 155, j = jed + 1, jed + jde1 - 1
         if (mod(j,2) .eq. 0) then
            XI2de1 = XI2de1+erfcomp(zda(j),tt)*(fval(j))**2
         else
            XI1de1 = XI1de1+erfcomp(zda(j),tt)*(fval(j))**2
         end if
155   continue
C
      intde1_2 = hzd1*(XI0de1+2.0d0*XI2de1+4.0d0*XI1de1)/3.0d0
C
      Iderde1 = (intde1_2 - intde1_1) / 0.0001d0
C
C
C Dermis 2
C
      XI0de2 = erfcomp(zda(jed+jde1),t)*(fval(jed+jde1))**2
     1       + erfcomp(zda(jmininf),t)*(fval(jmininf))**2
```

```
      XI1de2 = 0.0d0
      XI2de2 = 0.0d0
C
      do 160, j = jed +jde1 + 1, jmininf - 1
         if (mod(j,2) .eq. 0) then
            XI2de2 = XI2de2 + erfcomp(zda(j),t)*(fval(j))**2
         else
            XI1de2 = XI1de2 + erfcomp(zda(j),t)*(fval(j))**2
         end if
160   continue
C
      intde2_1 = hzd2*(XI0de2+2.0d0*XI2de2+4.0d0*XI1de2)/3.0d0
C
C
      XI0de2 = erfcomp(zda(jed+jde1),tt)*(fval(jed+jde1))**2
     1       + erfcomp(zda(jmininf),tt)*(fval(jmininf))**2
      XI1de2 = 0.0d0
      XI2de2 = 0.0d0
C
      do 165, j = jed + jde1 + 1, jmininf - 1
         if (mod(j,2) .eq. 0) then
            XI2de2 = XI2de2+erfcomp(zda(j),tt)*(fval(j))**2
         else
            XI1de2 = XI1de2+erfcomp(zda(j),tt)*(fval(j))**2
         end if
165   continue
C
      intde2_2 = hzd2*(XI0de2+2.0d0*XI2de2+4.0d0*XI1de2)/3.0d0
C
      Iderde2 = (intde2_2 - intde2_1) / 0.0001d0
C
C
      Idertot = (pi*Ksebref/Ksolref)*(Idered + Iderde1 + Iderde2)
C
C
C Term t2
C `````````
C
      XI0ed = P_infund(jed)*erfcomp(zda(jed),t)*fval(jed)
     1      * sqrt(1.0d0+(dfval(jed))**2)
     1      + P_infund(0)*erfcomp(zda(0),t)*fval(0)
     1      * sqrt(1.0d0+(dfval(0))**2)
      XI1ed = 0.0d0
      XI2ed = 0.0d0
C
      do 170, j = 1, jed - 1
         if (mod(j,2) .eq. 0) then
            XI2ed = XI2ed+(P_infund(j)*erfcomp(zda(j),t)*fval(j)
     1            * sqrt(1.0d0+(dfval(j))**2))
         else
            XI1ed = XI1ed+(P_infund(j)*erfcomp(zda(j),t)*fval(j)
     1            * sqrt(1.0d0+(dfval(j))**2))
         end if
170   continue
C
      t2ed = hzd*(XI0ed+2.0d0*XI2ed+4.0d0*XI1ed)/3.0d0
C
```

```
C
      XI0de1 = P_infund(jed+jde1)*erfcomp(zda(jed+jde1),t)
     1       * fval(jed+jde1)
     1       * sqrt(1.0d0+(dfval(jed+jde1))**2)
     1       + P_infund(jed)*erfcomp(zda(jed),t)*fval(jed)
     1       * sqrt(1.0d0+(dfval(jed))**2)
      XI1de1 = 0.0d0
      XI2de1 = 0.0d0
C
      do 180, j = jed + 1, jed + jde1 - 1
         if (mod(j,2) .eq. 0) then
            XI2de1 = XI2de1+(P_infund(j)*erfcomp(zda(j),t)
     1             * fval(j)
     1             * sqrt(1.0d0+(dfval(j))**2))
         else
            XI1de1 = XI1de1+(P_infund(j)*erfcomp(zda(j),t)
     1             * fval(j)
     1             * sqrt(1.0d0+(dfval(j))**2))
         end if
180   continue
C
      t2de1 = hzd1*(XI0de1+2.0d0*XI2de1+4.0d0*XI1de1)/3.0d0
C
      XI0de2 = P_infund(jmininf)*erfcomp(zda(jmininf),t)
     1       * fval(jmininf)
     1       * sqrt(1.0d0+(dfval(jmininf))**2)
     1       + P_infund(jed+jde1)*erfcomp(zda(jed+jde1),t)
     1       * fval(jed+jde1)
     1       * sqrt(1.0d0+(dfval(jed+jde1))**2)
      XI1de2 = 0.0d0
      XI2de2 = 0.0d0
C
      do 190, j = jed+jde1+1, jmininf-1
         if (mod(j,2) .eq. 0) then
            XI2de2 = XI2de2+(P_infund(j)*erfcomp(zda(j),t)
     1             * fval(j)
     1             * sqrt(1.0d0+(dfval(j))**2))
         else
            XI1de2 = XI1de2+(P_infund(j)*erfcomp(zda(j),t)
     1             * fval(j)
     1             * sqrt(1.0d0+(dfval(j))**2))
         end if
190   continue
C
      t2de2 = hzd2*(XI0de2+2.0d0*XI2de2+4.0d0*XI1de2)/3.0d0
C
      t2 = (2.0d0*pi/Ksolref)*(t2ed + t2de1 + t2de2)
C
C Term t3
C ```````
      XI0_i = cedia(0,0)*((xia(0)*(rd_max-fval(0))+fval(0))
     1      * (rd_max-fval(0)))
     1      + cedia(iin,0)*((xia(iin)*(rd_max-fval(0))
     1      + fval(0))*(rd_max-fval(0)))
      XI1_i = 0.0d0
      XI2_i = 0.0d0
C
```

```
      do 210, i = 1, iin - 1
         if (mod(i,2) .eq. 0) then
            XI2_i = XI2_i+(cedia(i,0)*((xia(i)*(rd_max-fval(0))
     1            + fval(0))*(rd_max-fval(0))))
         else
            XI1_i = XI1_i+(cedia(i,0)*((xia(i)*(rd_max-fval(0))
     1            + fval(0))*(rd_max-fval(0))))
         end if
210   continue
C
      t3i = hxi_in*(XI0_i+2.0d0*XI2_i+4.0d0*XI1_i)/3.0d0
C
      XI0_o = cedoa(iin,0)*((xia(iin)*(rd_max-fval(0))
     1      + fval(0))*(rd_max-fval(0)))
     1      + cedoa(iin+iout,0)*((xia(iin+iout)*(rd_max-fval(0))
     1      + fval(0))*(rd_max-fval(0)))
      XI1_o = 0.0d0
      XI2_o = 0.0d0
C
      do 220, i = iin + 1, iin + iout - 1
         if (mod(i,2) .eq. 0) then
            XI2_o = XI2_o+(cedoa(i,0)*((xia(i)*(rd_max-fval(0))
     1            + fval(0))*(rd_max-fval(0))))
         else
            XI1_o = XI1_o+(cedoa(i,0)*((xia(i)*(rd_max-fval(0))
     1            + fval(0))*(rd_max-fval(0))))
         end if
220   continue
C
      t3o = hxi_out*(XI0_o+2.0d0*XI2_o+4.0d0*XI1_o)/3.0d0
C
      j = 0
      do 230, i = 0, iin+iout
        t3(i) = Pscsol(xia(i),zda(j)) * ((t3i/Kedi)+(t3o/Kedo))
230   continue
C
C
C Term t4 (inf/ed boundary)
C ````````````````````````
      XI0 = P_infund(jed)*cedia(0,jed)*fval(jed)
     1      * sqrt(1.0d0+(dfval(jed))**2)
     1      + P_infund(0)*cedia(0,0)*fval(0)
     1      * sqrt(1.0d0+(dfval(0))**2)
      XI1 = 0.0d0
      XI2 = 0.0d0
C
      do 240, j = 1, jed - 1
        if (mod(j,2) .eq. 0) then
            XI2 = XI2+(P_infund(j)*cedia(0,j)*fval(j)
     1            * sqrt(1.0d0+(dfval(j))**2))
         else
            XI1 = XI1+(P_infund(j)*cedia(0,j)*fval(j)
     1            * sqrt(1.0d0+(dfval(j))**2))
         end if
240   continue
C
      t4 = (1.0d0/Kedi)*(hzd*(XI0+2.0d0*XI2+4.0d0*XI1)/3.0d0)
```

```
C
C Term t5 (inf/de1 boundary)
C ``````````````````````````
      XI0 = P_infund(jed+jde1)*cde1ia(0,jed+jde1)
     1    * fval(jed+jde1)
     1    * sqrt(1.0d0+(dfval(jed+jde1))**2)
     1    + P_infund(jed)*cde1ia(0,jed)*fval(jed)
     1    * sqrt(1.0d0+(dfval(jed))**2)
      XI1 = 0.0d0
      XI2 = 0.0d0
C
      do 250, j = jed + 1, jed + jde1 - 1
        if (mod(j,2) .eq. 0) then
            XI2 = XI2+(P_infund(j)*cde1ia(0,j)*fval(j)
     1           * sqrt(1.0d0+(dfval(j))**2))
         else
            XI1 = XI1+(P_infund(j)*cde1ia(0,j)*fval(j)
     1           * sqrt(1.0d0+(dfval(j))**2))
         end if
250   continue
C
      t5 = (1.0d0/Kde1i)*(hzd1*(XI0+2.0d0*XI2+4.0d0*XI1)/3.0d0)
C
C Term t6 (inf/de2 boundary)
C ``````````````````````````
      XI0 = P_infund(jmininf)*cde2ia(0,jmininf)*fval(jmininf)
     1    * sqrt(1.0d0+(dfval(jmininf))**2)
     1    + P_infund(jed+jde1)*cde2ia(0,jed+jde1)
     1    * fval(jed+jde1)
     1    * sqrt(1.0d0+(dfval(jed+jde1))**2)
      XI1 = 0.0d0
      XI2 = 0.0d0
C
      do 260, j = jed+jde1+1, jmininf-1
        if (mod(j,2) .eq. 0) then
            XI2 = XI2+(P_infund(j)*cde2ia(0,j)*fval(j)
     1           * sqrt(1.0d0+(dfval(j))**2))
         else
            XI1 = XI1+(P_infund(j)*cde2ia(0,j)*fval(j)
     1           * sqrt(1.0d0+(dfval(j))**2))
         end if
260   continue
C
      t6 = (1.0d0/Kde2i)*(hzd2*(XI0+2.0d0*XI2+4.0d0*XI1)/3.0d0)
C
C Term t7
C ```````
      XI0ed = erfcomp(zda(jed),t)*(fval(jed))**2
     1      + erfcomp(zda(0),t)*(fval(0))**2
      XI1ed = 0.0d0
      XI2ed = 0.0d0
C
      do 270, j = 1, jed-1
        if (mod(j,2) .eq. 0) then
            XI2ed = XI2ed + erfcomp(zda(j),t)*(fval(j))**2
         else
            XI1ed = XI1ed + erfcomp(zda(j),t)*(fval(j))**2
```

```
         end if
270   continue
C
      t7ed = hzd*(XI0ed+2.0d0*XI2ed+4.0d0*XI1ed)/3.0d0
C
      XI0de1 = erfcomp(zda(jed+jde1),t)*(fval(jed+jde1))**2
     1       + erfcomp(zda(jed),t)*(fval(jed))**2
      XI1de1 = 0.0d0
      XI2de1 = 0.0d0
C
      do 280, j = jed+1, jed+jde1-1
        if (mod(j,2) .eq. 0) then
            XI2de1 = XI2de1 + erfcomp(zda(j),t)*(fval(j))**2
         else
            XI1de1 = XI1de1 + erfcomp(zda(j),t)*(fval(j))**2
         end if
280   continue
C
      t7de1 = hzd1*(XI0de1+2.0d0*XI2de1+4.0d0*XI1de1)/3.0d0
C
      XI0de2 = erfcomp(zda(jmininf),t) * (fval(jmininf))**2
     1       + erfcomp(zda(jed+jde1),t)*(fval(jed+jde1))**2
      XI1de2 = 0.0d0
      XI2de2 = 0.0d0
C
      do 290, j = jed+jde1+1, jmininf-1
        if (mod(j,2) .eq. 0) then
            XI2de2 = XI2de2 + erfcomp(zda(j),t)*(fval(j))**2
         else
            XI1de2 = XI1de2 + erfcomp(zda(j),t)*(fval(j))**2
         end if
290   continue
C
      t7de2 = hzd2*(XI0de2+2.0d0*XI2de2+4.0d0*XI1de2)/3.0d0
C
      t7 = pi*(Ksebref/Ksolref)*(t7ed+t7de1+t7de2)
      V = h*A+pi*(Ksebref/Ksolref)*(t7ed+t7de1+t7de2)
C
C  Donor solution concentration
C ````````````````````````````
C
      do 300, i = 0, iin + iout
         A1(i) = t1(i) + Idertot + t2
         A2(i) = (2*pi)*(t3(i)+t4+t5+t6)
         cds(i) = (A2(i)/A1(i))+(1.0d0-(A2(i)/A1(i)))
     1          * exp(t*(-A1(i)/V))
300   continue
C
      return
      end
C
C
      subroutine testcds
      implicit double precision (a - z)
      integer i, idim, jdim, iin, iout, jmininf
      integer jed, jde1, jde2, jhd
      parameter (idim = 500, jdim = 500)
```

```
      parameter (pi = 3.141592654d0)
C
      dimension cds(0:idim), lhs(0:idim)
      dimension testterm1(0:idim),testterm2(0:idim),
     1          testterm3(0:idim)
C
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
      common /avgconcdata/ num_edi, num_edo, num_de1i, num_de1o,
     1        num_de2i, num_de2o, num_hdi, num_hdo
      common /avgconcdata2/ den_edi, den_edo, den_de1i, den_de1o,
     1        den_de2i, den_de2o, den_hdi, den_hdo
      common /dsconctemp/ cds
      common /dsparam/ k, h, A, jmininf
      common /dsparam2/ t7ed, t7de1, t7de2
      common /dsparam3/ k_ed, k_de1, k_de2_2, k_hd
      common /testcdsdata/ lhs, rhs, testterm1, testterm2,
     1                     testterm3
C
C Left hand side inner and outer tissue
C ````````````````````````````````````
      do 100, i = 0, iin + iout
         testterm1(i) = h*A*cds(i)
         testterm2(i) = pi*(Ksebref/Ksolref)*(t7ed+t7de1+t7de2)
     1           * cds(i)
         testterm3(i) = 2.0d0*pi*(num_edi+num_edo+num_de1i+num_de1o
     1           + num_de2i+num_de2o+num_hdi+num_hdo)
         lhs(i) = testterm1(i)+testterm2(i)+testterm3(i)
100   continue
C
C Right hand side inner and outer tissue
C ````````````````````````````````````
      rhs = 1.0d0*h*A
C
      return
      end
C
C
      SUBROUTINE LU(ND,N,IPIV,A,DETLOG,IDSGN)
      IMPLICIT REAL*8 (A-H,O-Z)
      IMPLICIT INTEGER*4 (I-N)
      DIMENSION IPIV(ND),A(ND,ND)
      COMMON/COUNT/LUCOUNT,IBCOUNT,IFCOUNT
      LUCOUNT=LUCOUNT+1
C
C      Triangular decomposition by Gaussian elimination with partial
C      pivoting
C
       IF(N.EQ.1) GO TO 100
       IPIV(N)=N
       IDSGN=1
       N1=N-1
       DO 10 I=1,N1
         X=A(I,I)
```

```
          IF(X.LT.0.0)X=-X
          IPIV(I)=I
          I1=I+1
          DO 11 J=I1,N
              Y=A(J,I)
              IF(Y.LT.0.0)Y=-Y
              IF(Y.LE.X)GO TO 11
              X=Y
              IPIV(I)=J
11        CONTINUE
          IF(IPIV(I).EQ.I)GO TO 14
             IDSGN=-IDSGN
          K=IPIV(I)
          DO 12 J=I,N
              X=A(I,J)
              A(I,J)=A(K,J)
12        A(K,J)=X
14        DO 10 J=I1,N
C              IF(A(I,I).EQ.0.0)A(I,I)=1.0E-60
              X=-A(J,I)/A(I,I)
              A(J,I)=X
              DO 10 K=I1,N
10      A(J,K)=A(J,K)+X*A(I,K)
C
C       Calculate logarithm of determinant
C
100       DETLOG=0.0
        DO 20 I=1,N
          IF(A(I,I).GT.0.0)GOTO 20
          IF(A(I,I).EQ.0.0)A(I,I)=1.0E-60
          IF(A(I,I).EQ.0.0)IDSGN=0
          IDSGN=-IDSGN
20       DETLOG=DETLOG+DLOG10(DABS(A(I,I)))
        RETURN
        END
        SUBROUTINE BACK(ND,N,IPIV,A,V)
        IMPLICIT REAL*8 (A-H,O-Z)
        IMPLICIT INTEGER*4 (I-N)
        DIMENSION IPIV(ND),A(ND,ND),V(ND)
        COMMON/COUNT/LUCOUNT,IBCOUNT,IFCOUNT
        IBCOUNT=IBCOUNT+1
C
C       Solution of Linear Equation by back-substitution after
C       decomposition
C
        IF(N.EQ.1) GO TO 100
        N1=N-1
        DO 10 I=1,N1
          I1=I+1
          K=IPIV(I)
          IF(K.EQ.I)GO TO 11
          X=V(I)
          V(I)=V(K)
          V(K)=X
11         DO 10 J=I1,N
10      V(J)=V(J)+A(J,I)*V(I)
C        IF(A(N,N).EQ.0.0)A(N,N)=1.0E-60
```

```
       V(N)=V(N)/A(N,N)
       DO 15 II=2,N
         I=N+1-II
         I1=I+1
         DO 16 J=I1,N
16       V(I)=V(I)-A(I,J)*V(J)
C         IF(A(I,I).EQ.0.0)A(I,I)=1.0E-60
15     V(I)=V(I)/A(I,I)
       RETURN
C
100     V(1)=V(1)/A(1,1)
       RETURN
       END
C
C
C ***************************************************
C Evaluation of average concentration in volume of skin
C tissue surrounding the hair follicle.
C Double integrals are evaluated using the composite
C Simpson's rule, following the algorithm in "Numerical
C Analysis" (p.176).
C ***************************************************
C
      subroutine avgconc
      implicit double precision (a - z)
      integer i, j, idim, jdim, iin, iout
      integer jed, jde1, jde2, jhd, m
      integer imin, imax, jmin, jmax, jmin, jmininf
      parameter (idim = 500, jdim = 500)
      parameter (pi = 3.141592654d0)
C
      dimension xia(0:idim), zda(0:jdim)
C
      dimension cedia(0:idim,0:jdim)
      dimension cedoa(0:idim,0:jdim)
      dimension cde1ia(0:idim,0:jdim)
      dimension cde1oa(0:idim,0:jdim)
      dimension cde2ia(0:idim,0:jdim)
      dimension cde2oa(0:idim,0:jdim)
      dimension chdia(0:idim,0:jdim)
      dimension chdoa(0:idim,0:jdim)
      dimension fval(0:idim), dfval(0:idim)
      dimension fcut(0:idim)
      dimension cors(0:idim)
      dimension r1(0:idim), r2(0:idim)
      dimension cds(0:idim)
C
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
      common /xizetaval/ xia, zda
      common /concarrays/ cedia, cedoa, cde1ia, cde1oa, cde2ia,
     1                             cde2oa, chdia, chdoa
      common /f_values/ fval, dfval
      common /cuticle/ fcut
      common /time/ t
```

```
      common /avgconc_values/ ac_ed, ac_de
      common /avgconcdata/ num_edi, num_edo, num_de1i, num_de1o,
     1        num_de2i, num_de2o, num_hdi, num_hdo
      common /avgconcdata2/ den_edi, den_edo, den_de1i, den_de1o,
     1        den_de2i, den_de2o, den_hdi, den_hdo
      common /inf_conc/ cors
      common /avginfconc/ ac_inf,num_inf_ed,den_inf_ed,
     1       num_inf_de1,den_inf_de1, num_inf_de2, den_inf_de2
      common /avg_left/ ac_ors
      common /dsconctemp/ cds
C
C Integral limits
C ````````````````
      imin = 0
      imax = iin
      jmin = 22
      jmininf = 36
      jmax = 0
C
C
C stepsizes in z direction: hzd(ed), hzd1(de1), hzd2(de2)
C stepsize in r direction: hr
C
      do 10, j = 0, jed + jde1 + jde2 + jhd
         r1(j) = fcut(j)
         r2(j)= fval(j)
10    continue
C
C
C ed part of infundibulum
C ***********************
C
C Evaluation of numerator
C ```````````````````````
C
      m = 1
C
      J1 = 0.0d0
      J2 = 0.0d0
      J3 = 0.0d0
C
      do 20, j = 0, jed
         hr = (r2(j)-r1(j))/(2.0d0*dble(m))
         K1 = cors(j)*r1(j) + cors(j)*r2(j)
         K2 = 0.0d0
         K3 = 0.0d0
C
         do 15, i = 1, 2*m-1
            r = r1(j) + dble(i)*hr
            Z = cors(j) * r
C
            if (mod(i,2) .eq. 0) then
               K2 = K2 + Z
            else
               K3 = K3 + Z
            end if
C
```

```
15       continue
C
         L = (K1+2.0d0*K2+4.0d0*K3)*hr/3.0d0

         if (j .eq. 0 .or. j .eq. jed) then
            J1 = J1 + L
         else if (mod(j,2) .eq. 0) then
            J2 = J2 + L
         else
            J3 = J3 + L
         end if
C
20    continue
C
      num_inf_ed = (J1+2.0d0*J2+4.0d0*J3)*hzd/3.0d0
C
C Evaluation of denominator
C ``````````````````````````
C
      J1 = 0.0d0
      J2 = 0.0d0
      J3 = 0.0d0
C
      do 30, j = 0, jed
         hr = (r2(j)-r1(j))/(2.0d0*dble(m))
         K1 = r1(j) + r2(j)
         K2 = 0.0d0
         K3 = 0.0d0
C
         do 25, i = 1, 2*m-1
            r = r1(j) + dble(i)*hr
            Z = r
C
            if (mod(i,2) .eq. 0) then
               K2 = K2 + Z
            else
               K3 = K3 + Z
            end if
C
25       continue
C
         L = (K1+2.0d0*K2+4.0d0*K3)*hr/3.0d0

         if (j .eq. 0 .or. j .eq. jed) then
            J1 = J1 + L
         else if (mod(j,2) .eq. 0) then
            J2 = J2 + L
         else
            J3 = J3 + L
         end if
C
30    continue
C
      den_inf_ed = (J1+2.0d0*J2+4.0d0*J3)*hzd/3.0d0
C
C
C de1 part of infundibulum
```

```
C ************************
C
C Evaluation of numerator
C ```````````````````````
C
      J1 = 0.0d0
      J2 = 0.0d0
      J3 = 0.0d0
C
      do 40, j = jed, jed + jde1
         hr = (r2(j)-r1(j))/(2.0d0*dble(m))
         K1 = cors(j)*r1(j) + cors(j)*r2(j)
         K2 = 0.0d0
         K3 = 0.0d0
C
         do 35, i = 1, 2*m-1
            r = r1(j) + dble(i)*hr
            Z = cors(j) * r
C
            if (mod(i,2) .eq. 0) then
               K2 = K2 + Z
            else
               K3 = K3 + Z
            end if
C
35       continue
C
         L = (K1+2.0d0*K2+4.0d0*K3)*hr/3.0d0

         if (j .eq. jed .or. j .eq. jed+jde1) then
            J1 = J1 + L
         else if (mod(j,2) .eq. 0) then
            J2 = J2 + L
         else
            J3 = J3 + L
         end if
C
40    continue
C
      num_inf_de1 = (J1+2.0d0*J2+4.0d0*J3)*hzd1/3.0d0
C
C Evaluation of denominator
C `````````````````````````
C
      J1 = 0.0d0
      J2 = 0.0d0
      J3 = 0.0d0
C
      do 50, j = jed, jed + jde1
         hr = (r2(j)-r1(j))/(2.0d0*dble(m))
         K1 = r1(j) + r2(j)
         K2 = 0.0d0
         K3 = 0.0d0
C
         do 45, i = 1, 2*m-1
            r = r1(j) + dble(i)*hr
            Z = r
```

```
C
            if (mod(i,2) .eq. 0) then
               K2 = K2 + Z
            else
               K3 = K3 + Z
            end if
C
45       continue
C
         L = (K1+2.0d0*K2+4.0d0*K3)*hr/3.0d0

         if (j .eq. jed .or. j .eq. jed+jde1) then
            J1 = J1 + L
         else if (mod(j,2) .eq. 0) then
            J2 = J2 + L
         else
            J3 = J3 + L
         end if
C
50    continue
C
      den_inf_de1 = (J1+2.0d0*J2+4.0d0*J3)*hzd1/3.0d0
C
C
C de2 part of infundibulum
C ************************
C
C Evaluation of numerator
C ```````````````````````
C
      J1 = 0.0d0
      J2 = 0.0d0
      J3 = 0.0d0
C
      do 60, j = jed+jde1, jmin
         hr = (r2(j)-r1(j))/(2.0d0*dble(m))
         K1 = cors(j)*r1(j) + cors(j)*r2(j)
         K2 = 0.0d0
         K3 = 0.0d0
C
         do 55, i = 1, 2*m-1
            r = r1(j) + dble(i)*hr
            Z = cors(j) * r
C
            if (mod(i,2) .eq. 0) then
               K2 = K2 + Z
            else
               K3 = K3 + Z
            end if
C
55       continue
C
         L = (K1+2.0d0*K2+4.0d0*K3)*hr/3.0d0

         if (j .eq. jed+jde1 .or. j .eq. jmin) then
            J1 = J1 + L
         else if (mod(j,2) .eq. 0) then
```

```
            J2 = J2 + L
         else
            J3 = J3 + L
         end if
C
60    continue
C
      num_inf_de2 = (J1+2.0d0*J2+4.0d0*J3)*hzd2/3.0d0
C
C
C Evaluation of denominator
C ``````````````````````````
C
      J1 = 0.0d0
      J2 = 0.0d0
      J3 = 0.0d0
C
      do 70, j = jed+jde1, jmin
         hr = (r2(j)-r1(j))/(2.0d0*dble(m))
         K1 = r1(j) + r2(j)
         K2 = 0.0d0
         K3 = 0.0d0
C
         do 65, i = 1, 2*m-1
            r = r1(j) + dble(i)*hr
            Z = r
C
            if (mod(i,2) .eq. 0) then
               K2 = K2 + Z
            else
               K3 = K3 + Z
            end if
C
65       continue
C
         L = (K1+2.0d0*K2+4.0d0*K3)*hr/3.0d0

         if (j .eq. jed+jde1 .or. j .eq. jmin) then
            J1 = J1 + L
         else if (mod(j,2) .eq. 0) then
            J2 = J2 + L
         else
            J3 = J3 + L
         end if
C
70    continue
C
      den_inf_de2 = (J1+2.0d0*J2+4.0d0*J3)*hzd2/3.0d0
C
C
C Average concentration in infundibulum
C ************************************
C
      ac_inf = (num_inf_ed+num_inf_de1+num_inf_de2)
     1       / (den_inf_ed+den_inf_de1+den_inf_de2)
C
C
```

```
C
C Average concentration in epidermis inner tissue
C ***********************************************
C
C Evaluation of numerator
C ```````````````````````
      J1 = 0.0d0
      J2 = 0.0d0
      J3 = 0.0d0
C
      do 110, i = 0, iin
         K1 = cedia(i,0)*(rd_max-fval(0))*(xia(i)*(rd_max-fval(0))
     1      + fval(0))
     1      + cedia(i,jed)*(rd_max-fval(jed))*(xia(i)*(rd_max-
fval(jed))
     1      + fval(jed))
         K2 = 0.0d0
         K3 = 0.0d0
C
         do 100, j = 1, jed - 1
C
            Z = cedia(i,j)*(rd_max-fval(j))*(xia(i)
     1        * (rd_max-fval(j)) + fval(j))
C
            if (mod(j,2) .eq. 0) then
               K2 = K2 + Z
            else
               K3 = K3 + Z
            end if
100      continue
C
         L = (K1+2.0d0*K2+4.0d0*K3)*hzd/3.0d0
C
         if (i .eq. 0 .or. i .eq. iin) then
            J1 = J1 + L
         else if (mod(i,2) .eq. 0) then
            J2 = J2 + L
         else
            J3 = J3 + L
         end if
C
110   continue
C
      num_edi = (J1+2.0d0*J2+4.0d0*J3)*hxi_in/3.0d0
C
C
C Evaluation of denominator
C `````````````````````````
      J1 = 0.0d0
      J2 = 0.0d0
      J3 = 0.0d0
C
      do 130, i = 0, iin
C
         K1 = (rd_max-fval(0))*(xia(i)*(rd_max-fval(0)) + fval(0))
     1      + (rd_max-fval(jed))*(xia(i)*(rd_max-fval(jed)) +
fval(jed))
```

```
         K2 = 0.0d0
         K3 = 0.0d0
C
         do 120, j = 1, jed - 1
            Z = (rd_max-fval(j))*(xia(i)*(rd_max-fval(j)) + fval(j))
            if (mod(j,2) .eq. 0) then
               K2 = K2 + Z
            else
               K3 = K3 + Z
            end if
120      continue
C
         L = (K1+2.0d0*K2+4.0d0*K3)*hzd/3.0d0
C
         if (i .eq. 0 .or. i .eq. iin) then
            J1 = J1 + L
         else if (mod(i,2) .eq. 0) then
            J2 = J2 + L
         else
            J3 = J3 + L
         end if
C
130   continue
C
      den_edi = (J1+2.0d0*J2+4.0d0*J3)*hxi_in/3.0d0
C      print*, 'den_edi=', den_edi
C
C
C Volume of ed inner region (compare value to 2*pi*value of den_edi)
C ````````````````````````````````````````````````````````````````````
C
      XI0_1 = (fval(0))**2 + (fval(jed))**2
      XI1_1 = 0.0d0
      XI2_1 = 0.0d0
C
      do 140, j = 1, jed - 1
         if (mod(j,2) .eq. 0) then
            XI2_1 = XI2_1 + (fval(j))**2
         else
            XI1_1 = XI1_1 + (fval(j))**2
         end if
140   continue
C
      XI_1 = hzd*(XI0_1 + 2.0d0*XI2_1 + 4.0d0*XI1_1) / 3.0d0
C
C
      XI0_2 = (xia(iin)*(rd_max-fval(0))+fval(0))**2
     1      + (xia(iin)*(rd_max-fval(jed))+fval(jed))**2
      XI1_2 = 0.0d0
      XI2_2 = 0.0d0
C
      do 150, j = 1, jed - 1
         if (mod(j,2) .eq. 0) then
            XI2_2 = XI2_2 + (xia(iin)*(rd_max-fval(j))+fval(j))**2
         else
            XI1_2 = XI1_2 + (xia(iin)*(rd_max-fval(j))+fval(j))**2
         end if
```

```
150   continue
C
      XI_2 = hzd*(XI0_2 + 2.0d0*XI2_2 + 4.0d0*XI1_2) / 3.0d0
C
      V_edi = pi*(XI_2 - XI_1)
C
C      print*, 'V_edi=', V_edi
C
C
C Average concentration in epidermis outer tissue
C ********************************************
C
C Evaluation of numerator
C ~~~~~~~~~~~~~~~~~~~~~~~
      J1 = 0.0d0
      J2 = 0.0d0
      J3 = 0.0d0
C
      do 170, i = iin, iin + iout
         K1 = cedoa(i,0)*(rd_max-fval(0))*(xia(i)*(rd_max-fval(0))
     1      + fval(0))
     1      + cedoa(i,jed)*(rd_max-fval(jed))*(xia(i)*(rd_max-
fval(jed))
     1      + fval(jed))
         K2 = 0.0d0
         K3 = 0.0d0
C
         do 160, j = 1, jed - 1
C
            Z = cedoa(i,j)*(rd_max-fval(j))*(xia(i)
     1        * (rd_max-fval(j)) + fval(j))
C
            if (mod(j,2) .eq. 0) then
               K2 = K2 + Z
            else
               K3 = K3 + Z
            end if
160      continue
C
         L = (K1+2.0d0*K2+4.0d0*K3)*hzd/3.0d0
C
         if (i .eq. iin .or. i .eq. iin + iout) then
            J1 = J1 + L
         else if (mod(i,2) .eq. 0) then
            J2 = J2 + L
         else
            J3 = J3 + L
         end if
C
170   continue
C
      num_edo = (J1+2.0d0*J2+4.0d0*J3)*hxi_out/3.0d0
C
C
C Evaluation of denominator
C ~~~~~~~~~~~~~~~~~~~~~~~~~
      J1 = 0.0d0
```

```
      J2 = 0.0d0
      J3 = 0.0d0
C
      do 190, i = iin, iin + iout
C
         K1 = (rd_max-fval(0))*(xia(i)*(rd_max-fval(0)) + fval(0))
     1      + (rd_max-fval(jed))*(xia(i)*(rd_max-fval(jed)) +
fval(jed))
         K2 = 0.0d0
         K3 = 0.0d0
C
         do 180, j = 1, jed - 1
            Z = (rd_max-fval(j))*(xia(i)*(rd_max-fval(j)) + fval(j))
            if (mod(j,2) .eq. 0) then
               K2 = K2 + Z
            else
               K3 = K3 + Z
            end if
180      continue
C
         L = (K1+2.0d0*K2+4.0d0*K3)*hzd/3.0d0
C
         if (i .eq. iin .or. i .eq. iin + iout) then
            J1 = J1 + L
         else if (mod(i,2) .eq. 0) then
            J2 = J2 + L
         else
            J3 = J3 + L
         end if
C
190   continue
C
      den_edo = (J1+2.0d0*J2+4.0d0*J3)*hxi_out/3.0d0
C
C
C Volume of ed outer region (compare value to 2*pi*value of den_edo)
C ````````````````````````````````````````````````````````````````
C
      XI0_3 = (xia(iin+iout)*(rd_max-fval(0))+fval(0))**2
     1      + (xia(iin+iout)*(rd_max-fval(jed))+fval(jed))**2
      XI1_3 = 0.0d0
      XI2_3 = 0.0d0
C
      do 200, j = 1, jed - 1
         if (mod(j,2) .eq. 0) then
            XI2_3 = XI2_3 + (xia(iin+iout)*(rd_max-fval(j))+fval(j))**2
         else
            XI1_3 = XI1_3 + (xia(iin+iout)*(rd_max-fval(j))+fval(j))**2
         end if
200   continue
C
      XI_3 = hzd*(XI0_3 + 2.0d0*XI2_3 + 4.0d0*XI1_3) / 3.0d0
C
      V_edo = pi*XI_3 - pi*XI_2
C
C      print*, 'V_edo=', V_edo
C
```

```
C
C Dermis 1 inner tissue
C *********************
C
C Evaluation of numerator
C ```````````````````````
      J1 = 0.0d0
      J2 = 0.0d0
      J3 = 0.0d0
C
      do 220, i = 0, iin
         K1 = cde1ia(i,jed)*(rd_max-fval(jed))*(xia(i)
     1      * (rd_max-fval(jed)) + fval(jed))
     1      + cde1ia(i,jed+jde1)*(rd_max-fval(jed+jde1))
     1      * (xia(i)*(rd_max-fval(jed+jde1))+fval(jed+jde1))
         K2 = 0.0d0
         K3 = 0.0d0
C
         do 210, j = jed + 1, jed + jde1 - 1
C
            Z = cde1ia(i,j)*(rd_max-fval(j))*(xia(i)
     1        * (rd_max-fval(j)) + fval(j))
C
            if (mod(j,2) .eq. 0) then
               K2 = K2 + Z
            else
               K3 = K3 + Z
            end if
210      continue
C
         L = (K1+2.0d0*K2+4.0d0*K3)*hzd1/3.0d0
C
         if (i .eq. 0 .or. i .eq. iin) then
            J1 = J1 + L
         else if (mod(i,2) .eq. 0) then
            J2 = J2 + L
         else
            J3 = J3 + L
         end if
C
220   continue
C
      num_de1i = (J1+2.0d0*J2+4.0d0*J3)*hxi_in/3.0d0
C
C
C Evaluation of denominator
C `````````````````````````
      J1 = 0.0d0
      J2 = 0.0d0
      J3 = 0.0d0
C
      do 240, i = 0, iin
C
         K1 = (rd_max-fval(jed))*(xia(i)*(rd_max-fval(jed))+fval(jed))
     1      + (rd_max-fval(jed+jde1))*(xia(i)*(rd_max-fval(jed+jde1))
     1      + fval(jed+jde1))
         K2 = 0.0d0
```

```
         K3 = 0.0d0
C
         do 230, j = jed + 1, jed + jde1 - 1
            Z = (rd_max-fval(j))*(xia(i)*(rd_max-fval(j)) + fval(j))
            if (mod(j,2) .eq. 0) then
               K2 = K2 + Z
            else
               K3 = K3 + Z
            end if
230      continue
C
         L = (K1+2.0d0*K2+4.0d0*K3)*hzd1/3.0d0
C
         if (i .eq. 0 .or. i .eq. iin) then
            J1 = J1 + L
         else if (mod(i,2) .eq. 0) then
            J2 = J2 + L
         else
            J3 = J3 + L
         end if
C
240   continue
C
      den_de1i = (J1+2.0d0*J2+4.0d0*J3)*hxi_in/3.0d0
C      print*, 'den_de1i=', den_de1i
C
C
C Volume of de1 inner region (compare value to 2*pi*value of den_de1i)
C ````````````````````````````````````````````````````````````````````
C
      XI0_1 = (fval(jed))**2 + (fval(jed+jde1))**2
      XI1_1 = 0.0d0
      XI2_1 = 0.0d0
C
      do 250, j = jed + 1, jed + jde1 - 1
         if (mod(j,2) .eq. 0) then
            XI2_1 = XI2_1 + (fval(j))**2
         else
            XI1_1 = XI1_1 + (fval(j))**2
         end if
250   continue
C
      XI_1 = hzd1*(XI0_1 + 2.0d0*XI2_1 + 4.0d0*XI1_1) / 3.0d0
C
C
      XI0_2 = (xia(iin)*(rd_max-fval(jed))+fval(jed))**2
     1      + (xia(iin)*(rd_max-fval(jed+jde1))+fval(jed+jde1))**2
      XI1_2 = 0.0d0
      XI2_2 = 0.0d0
C
      do 260, j = jed + 1, jed + jde1 - 1
         if (mod(j,2) .eq. 0) then
            XI2_2 = XI2_2 + (xia(iin)*(rd_max-fval(j))+fval(j))**2
         else
            XI1_2 = XI1_2 + (xia(iin)*(rd_max-fval(j))+fval(j))**2
         end if
260   continue
```

```
C
      XI_2 = hzd1*(XI0_2 + 2.0d0*XI2_2 + 4.0d0*XI1_2) / 3.0d0
C
      V_de1i = pi*(XI_2 - XI_1)
C
C      print*, 'V_de1i=', V_de1i
C
C Dermis 1 outer tissue
C *********************
C
C Evaluation of numerator
C ```````````````````````
      J1 = 0.0d0
      J2 = 0.0d0
      J3 = 0.0d0
C
      do 280, i = iin, iin + iout
         K1 = cde1oa(i,jed)*(rd_max-fval(jed))*(xia(i)
     1      * (rd_max-fval(jed))+fval(jed))
     1      + cde1oa(i,jed+jde1)*(rd_max-fval(jed+jde1))*(xia(i)
     1      * (rd_max-fval(jed+jde1))+fval(jed+jde1))
         K2 = 0.0d0
         K3 = 0.0d0
C
         do 270, j = jed + 1, jed + jde1 - 1
C
            Z = cde1oa(i,j)*(rd_max-fval(j))*(xia(i)
     1        * (rd_max-fval(j)) + fval(j))
C
            if (mod(j,2) .eq. 0) then
               K2 = K2 + Z
            else
               K3 = K3 + Z
            end if
270      continue
C
         L = (K1+2.0d0*K2+4.0d0*K3)*hzd1/3.0d0
C
         if (i .eq. iin .or. i .eq. iin + iout) then
            J1 = J1 + L
         else if (mod(i,2) .eq. 0) then
            J2 = J2 + L
         else
            J3 = J3 + L
         end if
C
280   continue
C
      num_de1o = (J1+2.0d0*J2+4.0d0*J3)*hxi_out/3.0d0
C
C
C Evaluation of denominator
C `````````````````````````
      J1 = 0.0d0
      J2 = 0.0d0
      J3 = 0.0d0
C
```

```
      do 300, i = iin, iin + iout
C
         K1 = (rd_max-fval(jed))*(xia(i)*(rd_max-fval(jed))+fval(jed))
     1      + (rd_max-fval(jed+jde1))*(xia(i)*(rd_max-fval(jed+jde1))
     1      + fval(jed+jde1))
         K2 = 0.0d0
         K3 = 0.0d0
C
         do 290, j = jed + 1, jed + jde1 - 1
            Z = (rd_max-fval(j))*(xia(i)*(rd_max-fval(j)) + fval(j))
            if (mod(j,2) .eq. 0) then
               K2 = K2 + Z
            else
               K3 = K3 + Z
            end if
290      continue
C
         L = (K1+2.0d0*K2+4.0d0*K3)*hzd1/3.0d0
C
         if (i .eq. iin .or. i .eq. iin + iout) then
            J1 = J1 + L
         else if (mod(i,2) .eq. 0) then
            J2 = J2 + L
         else
            J3 = J3 + L
         end if
C
300   continue
C
      den_de1o = (J1+2.0d0*J2+4.0d0*J3)*hxi_out/3.0d0
C
C
C Volume of de1 outer region (compare value to 2*pi*value of den_de1o)
C ``````````````````````````````````````````````````````````````````````
C
      XI0_3 = (xia(iin+iout)*(rd_max-fval(jed))+fval(jed))**2
     1      + (xia(iin+iout)*(rd_max-fval(jed+jde1))+fval(jed+jde1))
     1      **2
      XI1_3 = 0.0d0
      XI2_3 = 0.0d0
C
      do 310, j = jed + 1, jed + jde1 - 1
         if (mod(j,2) .eq. 0) then
            XI2_3 = XI2_3 + (xia(iin+iout)*(rd_max-fval(j))+fval(j))**2
         else
            XI1_3 = XI1_3 + (xia(iin+iout)*(rd_max-fval(j))+fval(j))**2
         end if
310   continue
C
      XI_3 = hzd1*(XI0_3 + 2.0d0*XI2_3 + 4.0d0*XI1_3) / 3.0d0
C
      V_de1o = pi*XI_3 - pi*XI_2
C
C      print*, 'V_de1o=', V_de1o
C
C
C Dermis 2 inner tissue
```

```
C **********************
C
C Evaluation of numerator
C ```````````````````````
      J1 = 0.0d0
      J2 = 0.0d0
      J3 = 0.0d0
C
      do 330, i = 0, iin
C
         K1 = cde2ia(i,jed+jde1)*(rd_max-fval(jed+jde1))*(xia(i)
     1      * (rd_max-fval(jed+jde1)) + fval(jed+jde1))
     1      + cde2ia(i,jmin)*(rd_max-fval(jmin))
     1      * (xia(i)*(rd_max-fval(jmin))+fval(jmin))
C
         K2 = 0.0d0
         K3 = 0.0d0
C
         do 320, j = jed + jde1 + 1, jmin - 1
C
            Z = cde2ia(i,j)*(rd_max-fval(j))*(xia(i)
     1        * (rd_max-fval(j)) + fval(j))
C
            if (mod(j,2) .eq. 0) then
               K2 = K2 + Z
            else
               K3 = K3 + Z
            end if
320      continue
C
         L = (K1+2.0d0*K2+4.0d0*K3)*hzd2/3.0d0
C
         if (i .eq. 0 .or. i .eq. iin) then
            J1 = J1 + L
         else if (mod(i,2) .eq. 0) then
            J2 = J2 + L
         else
            J3 = J3 + L
         end if
C
330   continue
C
      num_de2i = (J1+2.0d0*J2+4.0d0*J3)*hxi_in/3.0d0
C
C
C Evaluation of denominator
C ```````````````````````````
      J1 = 0.0d0
      J2 = 0.0d0
      J3 = 0.0d0
C
      do 340, i = 0, iin
C
         K1 = (rd_max-fval(jed+jde1))*(xia(i)*(rd_max-fval(jed+jde1))
     1      + fval(jed+jde1))
     1      + (rd_max-fval(jmin))*(xia(i)
     1      * (rd_max-fval(jmin)) + fval(jmin))
```

```
C
         K2 = 0.0d0
         K3 = 0.0d0
C
         do 335, j = jed + jde1 + 1, jmin - 1
C
            Z = (rd_max-fval(j))*(xia(i)*(rd_max-fval(j)) + fval(j))
            if (mod(j,2) .eq. 0) then
               K2 = K2 + Z
            else
               K3 = K3 + Z
            end if
335      continue
C
         L = (K1+2.0d0*K2+4.0d0*K3)*hzd2/3.0d0
C
         if (i .eq. 0 .or. i .eq. iin) then
            J1 = J1 + L
         else if (mod(i,2) .eq. 0) then
            J2 = J2 + L
         else
            J3 = J3 + L
         end if
C
340   continue
C
      den_de2i = (J1+2.0d0*J2+4.0d0*J3)*hxi_in/3.0d0
C      print*, 'den_de2i=', den_de2i
C
C
C Volume of de2 inner region (compare value to 2*pi*value of den_de2i)
C ``````````````````````````````````````````````````````````````````````
C
      XI0_1 = (fval(jed+jde1))**2+(fval(jed+jde1+jde2))**2
      XI1_1 = 0.0d0
      XI2_1 = 0.0d0
C
      do 350, j = jed + jde1 + 1, jed + jde1 + jde2 - 1
         if (mod(j,2) .eq. 0) then
            XI2_1 = XI2_1 + (fval(j))**2
         else
            XI1_1 = XI1_1 + (fval(j))**2
         end if
350   continue
C
      XI_1 = hzd2*(XI0_1 + 2.0d0*XI2_1 + 4.0d0*XI1_1) / 3.0d0
C
C
      XI0_2 = (xia(iin)*(rd_max-fval(jed+jde1))+fval(jed+jde1))**2
     1      + (xia(iin)*(rd_max-fval(jed+jde1+jde2))
     1      + fval(jed+jde1+jde2))**2
      XI1_2 = 0.0d0
      XI2_2 = 0.0d0
C
      do 360, j = jed + jde1 + 1, jed + jde1 + jde2 - 1
         if (mod(j,2) .eq. 0) then
            XI2_2 = XI2_2 + (xia(iin)*(rd_max-fval(j))+fval(j))**2
```

```
         else
            XI1_2 = XI1_2 + (xia(iin)*(rd_max-fval(j))+fval(j))**2
         end if
360   continue
C
      XI_2 = hzd2*(XI0_2 + 2.0d0*XI2_2 + 4.0d0*XI1_2) / 3.0d0
C
      V_de2i = pi*(XI_2 - XI_1)
C
C      print*, 'V_de2i=', V_de2i
C
C Dermis 2 outer tissue
C *********************
C
C Evaluation of numerator
C ```````````````````````
      J1 = 0.0d0
      J2 = 0.0d0
      J3 = 0.0d0
C
      do 380, i = iin, iin + iout
C
         K1 = cde2oa(i,jed+jde1)*(rd_max-fval(jed+jde1))*(xia(i)
     1      * (rd_max-fval(jed+jde1))+fval(jed+jde1))
     1      + cde2oa(i,jed+jde1+jde2)*(rd_max-fval(jed+jde1+jde2))
     1      * (xia(i)
     1      * (rd_max-fval(jed+jde1+jde2))+fval(jed+jde1+jde2))
         K2 = 0.0d0
         K3 = 0.0d0
C
         do 370, j = jed + jde1 + 1, jed + jde1 + jde2 - 1
C
            Z = cde2oa(i,j)*(rd_max-fval(j))*(xia(i)
     1        * (rd_max-fval(j)) + fval(j))
C
            if (mod(j,2) .eq. 0) then
               K2 = K2 + Z
            else
               K3 = K3 + Z
            end if
370      continue
C
         L = (K1+2.0d0*K2+4.0d0*K3)*hzd2/3.0d0
C
         if (i .eq. iin .or. i .eq. iin + iout) then
            J1 = J1 + L
         else if (mod(i,2) .eq. 0) then
            J2 = J2 + L
         else
            J3 = J3 + L
         end if
C
380   continue
C
      num_de2o = (J1+2.0d0*J2+4.0d0*J3)*hxi_out/3.0d0
C
C
```

```
C Evaluation of denominator
C ````````````````````````
      J1 = 0.0d0
      J2 = 0.0d0
      J3 = 0.0d0
C
      do 400, i = iin, iin + iout
C
         K1 = (rd_max-fval(jed+jde1))*(xia(i)*(rd_max-fval(jed+jde1))
     1      + fval(jed+jde1))
     1      + (rd_max-fval(jed+jde1+jde2))*(xia(i)
     1      * (rd_max-fval(jed+jde1+jde2))+fval(jed+jde1+jde2))
         K2 = 0.0d0
         K3 = 0.0d0
C
         do 390, j = jed + jde1 + 1, jed + jde1 + jde2 - 1
            Z = (rd_max-fval(j))*(xia(i)*(rd_max-fval(j)) + fval(j))
            if (mod(j,2) .eq. 0) then
               K2 = K2 + Z
            else
               K3 = K3 + Z
            end if
390      continue
C
         L = (K1+2.0d0*K2+4.0d0*K3)*hzd2/3.0d0
C
         if (i .eq. iin .or. i .eq. iin + iout) then
            J1 = J1 + L
         else if (mod(i,2) .eq. 0) then
            J2 = J2 + L
         else
            J3 = J3 + L
         end if
C
400   continue
C
      den_de2o = (J1+2.0d0*J2+4.0d0*J3)*hxi_out/3.0d0
C
C
C Volume of de2 outer region (compare value to 2*pi*value of den_de2o)
C ````````````````````````````````````````````````````````````````````
C
      XI0_3 = (xia(iin+iout)*(rd_max-fval(jed+jde1))+fval(jed+jde1))
     1      **2
     1      + (xia(iin+iout)*(rd_max-fval(jed+jde1+jde2))
     1      + fval(jed+jde1+jde2))**2
      XI1_3 = 0.0d0
      XI2_3 = 0.0d0
C
      do 410, j = jed + jde1 + 1, jed + jde1 + jde2 - 1
         if (mod(j,2) .eq. 0) then
            XI2_3 = XI2_3 + (xia(iin+iout)*(rd_max-fval(j))+fval(j))**2
         else
            XI1_3 = XI1_3 + (xia(iin+iout)*(rd_max-fval(j))+fval(j))**2
         end if
410   continue
C
```

```
      XI_3 = hzd2*(XI0_3 + 2.0d0*XI2_3 + 4.0d0*XI1_3) / 3.0d0
C
      V_de2o = pi*XI_3 - pi*XI_2
C
C      print*, 'V_de2o=', V_de2o
C
C
C Hypodermis inner tissue
C ***********************
C
C Evaluation of numerator
C ```````````````````````
      J1 = 0.0d0
      J2 = 0.0d0
      J3 = 0.0d0
C
      do 430, i = 0, iin
C
         K1 = chdia(i,jed+jde1+jde2)*(rd_max-fval(jed+jde1+jde2))
     1      * (xia(i)
     1      * (rd_max-fval(jed+jde1+jde2)) + fval(jed+jde1+jde2))
     1      + chdia(i,jed+jde1+jde2+jhd)
     1      * (rd_max-fval(jed+jde1+jde2+jhd))
     1      * (xia(i)*(rd_max-
fval(jed+jde1+jde2+jhd))+fval(jed+jde1+jde2
     1      + jhd))
         K2 = 0.0d0
         K3 = 0.0d0
C
         do 420, j = jed+jde1+jde2+1, jed+jde1+jde2+jhd-1
C
            Z = chdia(i,j)*(rd_max-fval(j))*(xia(i)
     1        * (rd_max-fval(j)) + fval(j))
C
            if (mod(j,2) .eq. 0) then
               K2 = K2 + Z
            else
               K3 = K3 + Z
            end if
420      continue
C
         L = (K1+2.0d0*K2+4.0d0*K3)*hzd3/3.0d0
C
         if (i .eq. 0 .or. i .eq. iin) then
            J1 = J1 + L
         else if (mod(i,2) .eq. 0) then
            J2 = J2 + L
         else
            J3 = J3 + L
         end if
C
430   continue
C
      num_hdi = (J1+2.0d0*J2+4.0d0*J3)*hxi_in/3.0d0
C
C
C Evaluation of denominator
```

```
C ``````````````````````
      J1 = 0.0d0
      J2 = 0.0d0
      J3 = 0.0d0
C
      do 450, i = 0, iin
C
         K1 = (rd_max-fval(jed+jde1+jde2))*(xia(i)*(rd_max
     1      - fval(jed+jde1+jde2))+fval(jed+jde1+jde2))
     1      + (rd_max-fval(jed+jde1+jde2+jhd))*(xia(i)
     1      * (rd_max-fval(jed+jde1+jde2+jhd))
     1      + fval(jed+jde1+jde2+jhd))
         K2 = 0.0d0
         K3 = 0.0d0
C
         do 440, j = jed+jde1+jde2+1, jed+jde1+jde2+jhd-1
            Z = (rd_max-fval(j))*(xia(i)*(rd_max-fval(j)) + fval(j))
            if (mod(j,2) .eq. 0) then
               K2 = K2 + Z
            else
               K3 = K3 + Z
            end if
440      continue
C
         L = (K1+2.0d0*K2+4.0d0*K3)*hzd3/3.0d0
C
         if (i .eq. 0 .or. i .eq. iin) then
            J1 = J1 + L
         else if (mod(i,2) .eq. 0) then
            J2 = J2 + L
         else
            J3 = J3 + L
         end if
C
450   continue
C
      den_hdi = (J1+2.0d0*J2+4.0d0*J3)*hxi_in/3.0d0
C
C
C Volume of hd inner region (compare value to 2*pi*value of den_hdi)
C ``````````````````````````````````````````````````````````````````````
C
      XI0_1 = (fval(jed+jde1+jde2))**2
     1      + (fval(jed+jde1+jde2+jhd))**2
      XI1_1 = 0.0d0
      XI2_1 = 0.0d0
C
      do 460, j = jed+jde1+1+jde2, jed+jde1+jde2+jhd-1
         if (mod(j,2) .eq. 0) then
            XI2_1 = XI2_1 + (fval(j))**2
         else
            XI1_1 = XI1_1 + (fval(j))**2
         end if
460   continue
C
      XI_1 = hzd3*(XI0_1 + 2.0d0*XI2_1 + 4.0d0*XI1_1) / 3.0d0
C
```

```
C
      XI0_2 = (xia(iin)*(rd_max-fval(jed+jde1+jde2))
     1      + fval(jed+jde1+jde2))**2
     1      + (xia(iin)*(rd_max-fval(jed+jde1+jde2+jhd))
     1      + fval(jed+jde1+jde2+jhd))**2
      XI1_2 = 0.0d0
      XI2_2 = 0.0d0
C
      do 470, j = jed+jde1+jde2+1, jed+jde1+jde2+jhd-1
         if (mod(j,2) .eq. 0) then
            XI2_2 = XI2_2 + (xia(iin)*(rd_max-fval(j))+fval(j))**2
         else
            XI1_2 = XI1_2 + (xia(iin)*(rd_max-fval(j))+fval(j))**2
         end if
470   continue
C
      XI_2 = hzd3*(XI0_2 + 2.0d0*XI2_2 + 4.0d0*XI1_2) / 3.0d0
C
      V_hdi = pi*(XI_2 - XI_1)
C
C      print*, 'V_hdi=', V_hdi
C
C Hypodermis outer tissue
C ***********************
C
C Evaluation of numerator
C ```````````````````````
      J1 = 0.0d0
      J2 = 0.0d0
      J3 = 0.0d0
C
      do 490, i = iin, iin + iout
C
         K1 = chdoa(i,jed+jde1+jde2)*(rd_max-fval(jed+jde1+jde2))
     1      * (xia(i)
     1      * (rd_max-fval(jed+jde1+jde2))+fval(jed+jde1+jde2))
     1      + chdoa(i,jed+jde1+jde2+jhd)
     1      * (rd_max-fval(jed+jde1+jde2+jhd))*(xia(i)
     1      * (rd_max-fval(jed+jde1+jde2+jhd))+fval(jed+jde1+jde2+jhd))
         K2 = 0.0d0
         K3 = 0.0d0
C
         do 480, j = jed+jde1+jde2+1, jed+jde1+jde2+jhd-1
C
            Z = chdoa(i,j)*(rd_max-fval(j))*(xia(i)
     1        * (rd_max-fval(j)) + fval(j))
C
            if (mod(j,2) .eq. 0) then
               K2 = K2 + Z
            else
               K3 = K3 + Z
            end if
480      continue
C
         L = (K1+2.0d0*K2+4.0d0*K3)*hzd3/3.0d0
C
         if (i .eq. iin .or. i .eq. iin + iout) then
```

```
            J1 = J1 + L
         else if (mod(i,2) .eq. 0) then
            J2 = J2 + L
         else
            J3 = J3 + L
         end if
C
490   continue
C
      num_hdo = (J1+2.0d0*J2+4.0d0*J3)*hxi_out/3.0d0
C
C
C Evaluation of denominator
C ``````````````````````````
      J1 = 0.0d0
      J2 = 0.0d0
      J3 = 0.0d0
C
      do 510, i = iin, iin + iout
C
         K1 = (rd_max-fval(jed+jde1+jde2))*(xia(i)
     1      * (rd_max-fval(jed+jde1+jde2))
     1      + fval(jed+jde1+jde2))
     1      + (rd_max-fval(jed+jde1+jde2+jhd))*(xia(i)
     1      * (rd_max-fval(jed+jde1+jde2+jhd))
     1      + fval(jed+jde1+jde2+jhd))
         K2 = 0.0d0
         K3 = 0.0d0
C
         do 500, j = jed+jde1+jde2+1, jed+jde1+jde2+jhd-1
            Z = (rd_max-fval(j))*(xia(i)*(rd_max-fval(j)) + fval(j))
            if (mod(j,2) .eq. 0) then
               K2 = K2 + Z
            else
               K3 = K3 + Z
            end if
500      continue
C
         L = (K1+2.0d0*K2+4.0d0*K3)*hzd3/3.0d0
C
         if (i .eq. iin .or. i .eq. iin + iout) then
            J1 = J1 + L
         else if (mod(i,2) .eq. 0) then
            J2 = J2 + L
         else
            J3 = J3 + L
         end if
C
510   continue
C
      den_hdo = (J1+2.0d0*J2+4.0d0*J3)*hxi_out/3.0d0
C
C
C Volume of hd outer region (compare value to 2*pi*value of den_hdo)
C ```````````````````````````````````````````````````````````````````
C
      XI0_3 = (xia(iin+iout)*(rd_max-fval(jed+jde1+jde2))
```

```
     1      + fval(jed+jde1+jde2))**2
     1      + (xia(iin+iout)*(rd_max-fval(jed+jde1+jde2+jhd))
     1      + fval(jed+jde1+jde2+jhd))**2
      XI1_3 = 0.0d0
      XI2_3 = 0.0d0
C
      do 520, j = jed+jde1+jde2+1, jed+jde1+jde2+jhd-1
         if (mod(j,2) .eq. 0) then
            XI2_3 = XI2_3 + (xia(iin+iout)*(rd_max-fval(j))+fval(j))**2
         else
            XI1_3 = XI1_3 + (xia(iin+iout)*(rd_max-fval(j))+fval(j))**2
         end if
520   continue
C
      XI_3 = hzd3*(XI0_3 + 2.0d0*XI2_3 + 4.0d0*XI1_3) / 3.0d0
C
      V_hdo = pi*XI_3 - pi*XI_2
C
C      print*, 'V_hdo=', V_hdo
C
C Average concentrations for comparison with Grams et al's results
C ````````````````````````````````````````````````````````````````
      ac_edi = num_edi/den_edi
C      ac_edo = num_edo/(den_edi+den_edo)
      ac_ed = ac_edi
C
      ac_de1i = num_de1i/(den_de1i+den_de2i)
      ac_de2i = num_de2i/(den_de1i+den_de2i)
      ac_de = ac_de1i + ac_de2i
C
C      ac_de1i = num_de1i/(den_de1i+den_de1o+den_de2i+den_de2o)
C      ac_de1o = num_de1o/(den_de1i+den_de1o+den_de2i+den_de2o)
C      ac_de2i = num_de2i/(den_de1i+den_de1o+den_de2i+den_de2o)
C      ac_de2o = num_de2o/(den_de1i+den_de1o+den_de2i+den_de2o)
C      ac_de = ac_de1i + ac_de1o + ac_de2i + ac_de2o
C
C      ac_hdi = num_hdi/(den_hdi+den_hdo)
C      ac_hdo = num_hdo/(den_hdi+den_hdo)
C      ac_hd = ac_hdi + ac_hdo
C
C
C Calculation of average concentration at ORS / skin layers interface
C ********************************************************************
C
C ORS/Ed interface
C ````````````````
C
      XI0 = cedia(0,jed)*fval(jed)*sqrt(1.0d0+(dfval(jed))**2)
     1    + cedia(0,0)*fval(0)*sqrt(1.0d0+(dfval(0))**2)
      XI1 = 0.0d0
      XI2 = 0.0d0
C
      do 530, j = 1, jed - 1
         if (mod(j,2) .eq. 0) then
            XI2 = XI2 + cedia(0,j)*fval(j)*sqrt(1.0d0+(dfval(j))**2)
         else
            XI1 = XI1 + cedia(0,j)*fval(j)*sqrt(1.0d0+(dfval(j))**2)
```

```
         end if
530   continue
C
      num_ors_ed = hzd*(XI0+2.0d0*XI2+4.0*XI1)/3.0d0
C
C
      XI0 = fval(jed)*sqrt(1.0d0+(dfval(jed))**2)
     1    + fval(0)*sqrt(1.0d0+(dfval(0))**2)
      XI1 = 0.0d0
      XI2 = 0.0d0
C
      do 540, j = 1, jed - 1
         if (mod(j,2) .eq. 0) then
            XI2 = XI2 + fval(j)*sqrt(1.0d0+(dfval(j))**2)
         else
            XI1 = XI1 + fval(j)*sqrt(1.0d0+(dfval(j))**2)
         end if
540   continue
C
      den_ors_ed = hzd*(XI0+2.0d0*XI2+4.0*XI1)/3.0d0
C
C
C ORS/De1 interface
C ``````````````````
C
      XI0 = cde1ia(0,jed+jde1)*fval(jed+jde1)*sqrt(1.0d0
     1    + (dfval(jed+jde1))**2)
     1    + cde1ia(0,jed)*fval(jed)*sqrt(1.0d0+(dfval(jed))**2)
      XI1 = 0.0d0
      XI2 = 0.0d0
C
      do 550, j = jed + 1, jed + jde1 - 1
         if (mod(j,2) .eq. 0) then
            XI2 = XI2 + cde1ia(0,j)*fval(j)*sqrt(1.0d0+(dfval(j))**2)
         else
            XI1 = XI1 + cde1ia(0,j)*fval(j)*sqrt(1.0d0+(dfval(j))**2)
         end if
550   continue
C
      num_ors_de1 = hzd1*(XI0+2.0d0*XI2+4.0*XI1)/3.0d0
C
C
      XI0 = fval(jed+jde1)*sqrt(1.0d0+(dfval(jed+jde1))**2)
     1    + fval(jed)*sqrt(1.0d0+(dfval(jed))**2)
      XI1 = 0.0d0
      XI2 = 0.0d0
C
      do 560, j = jed + 1, jed + jde1 - 1
         if (mod(j,2) .eq. 0) then
            XI2 = XI2 + fval(j)*sqrt(1.0d0+(dfval(j))**2)
         else
            XI1 = XI1 + fval(j)*sqrt(1.0d0+(dfval(j))**2)
         end if
560   continue
C
      den_ors_de1 = hzd1*(XI0+2.0d0*XI2+4.0*XI1)/3.0d0
C
```

```
C
C ORS/De2 interface
C ``````````````````
C
      XI0 = cde2ia(0,jmin)*fval(jmin)*sqrt(1.0d0+(dfval(jmin))**2)
     1    + cde2ia(0,jed+jde1)*fval(jed+jde1)*sqrt(1.0d0
     1    + (dfval(jed+jde1))**2)
      XI1 = 0.0d0
      XI2 = 0.0d0
C
      do 570, j = jed + jde1 + 1, jmin - 1
         if (mod(j,2) .eq. 0) then
            XI2 = XI2 + cde2ia(0,j)*fval(j)*sqrt(1.0d0+(dfval(j))**2)
         else
            XI1 = XI1 + cde2ia(0,j)*fval(j)*sqrt(1.0d0+(dfval(j))**2)
         end if
570   continue
C
      num_ors_de2 = hzd2*(XI0+2.0d0*XI2+4.0*XI1)/3.0d0
C
C
      XI0 = fval(jmin)*sqrt(1.0d0+(dfval(jmin))**2)
     1    + fval(jed+jde1)*sqrt(1.0d0+(dfval(jed+jde1))**2)
      XI1 = 0.0d0
      XI2 = 0.0d0
C
      do 580, j = jed + jde1 + 1, jmin - 1
         if (mod(j,2) .eq. 0) then
            XI2 = XI2 + fval(j)*sqrt(1.0d0+(dfval(j))**2)
         else
            XI1 = XI1 + fval(j)*sqrt(1.0d0+(dfval(j))**2)
         end if
580   continue
C
      den_ors_de2 = hzd2*(XI0+2.0d0*XI2+4.0*XI1)/3.0d0
C
C
      ac_ors = (num_ors_ed+num_ors_de1+num_ors+de2)
     1       / (den_ors_ed+den_ors_de1+den_ors_de2)
C
C      ac_ors_ed = num_ors_ed / den_ors_ed
C      ac_ors_de = (num_ors_de1+num_ors_de2)
C     1          / (den_ors_de1+den_ors_de2)
C
      return
      end
C
C
C ****************************************************
C Error function for evaluation of concentration in ORS
C ****************************************************
C
      double precision function erfcomp(z, t)
      implicit double precision (a - z)
      integer idim, jdim
      parameter (idim = 500, jdim = 500)
C
```

```
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
C
C Constants
C `````````
      a1 = 0.254829592d0
      a2 = -0.284496736d0
      a3 = 1.421413741d0
      a4 = -1.453152027d0
      a5 = 1.061405429d0
      p = 0.3275911d0
C
      ztoped = 0.0d0
C
      arg = (ztoped-z)/(2.0d0*(Dsebum*t)**0.5)
C
      s = 1.0d0/(1.0d0+p*arg)
C
      erfcomp = (a1*s+a2*(s)**(2)+a3
     1          * (s)**(3)+ a4*(s)**(4)
     1          + a5*(s)**(5))*exp(-(arg)**(2))
C
      return
      end
C
C
C ************************************************
C Approximation of complementary error function with
C argument m = (z(surface)-z(j))/(2(Dt)^0.5)
C ************************************************
C
      subroutine errorfunction
      implicit double precision (a-z)
      integer i, j, idim, jdim, iin, iout
      integer jed, jde1, jde2, jhd
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      dimension m(0:idim,0:jdim)
      dimension s(0:idim,0:jdim)
      dimension erfc(0:idim,0:jdim)
C
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /xizetaval/ xia, zda
      common /time/ t
C
      open (unit = 80, file = 'erfc.txt')
      write (80, 7000)
      write (80,7050) t
      write (80, 7100)
C
C Constants
C `````````
      a1 = 0.254829592d0
      a2 = -0.284496736d0
```

```
      a3 = 1.421413741d0
      a4 = -1.453152027d0
      a5 = 1.061405429d0
      p = 0.3275911d0
C
C All skin layers - inner tissue
C ````````````````````````````````
C Argument of erfc
C ````````````````
      j = 0
      ztoped = zda(j)
C
      do 1050, i = 0, iin
      do 1000, j = 0, jed + jde1 + jde2 + jhd
         m(i,j) = (ztoped-zda(j))/(2.0d0*(Dedi(xia(i),zda(j))*t)
     1          **(0.5d0))
C
C Function s
C ``````````
         s(i,j) = 1.0d0/(1.0d0+p*m(i,j))
C
C erfc(m(i,j)) approximation
C ````````````````````````````
         erfc(i,j) = (a1*s(i,j)+a2*(s(i,j))**(2.0d0)+a3
     1             * (s(i,j))**(3.0d0)+ a4*(s(i,j))**(4.0d0)
     1             + a5*(s(i,j))**(5.0d0))*exp(-(m(i,j))**(2.0d0))
C
         write (80,9100) i, j, m(i,j), erfc(i,j)
C
1000  continue
1050  continue
      write (80, 7150)
C
C All skin layers - outer tissue
C ````````````````````````````````
      do 1150, i = iin, iin + iout
      do 1100, j = 0, jed + jde1 + jde2 + jhd
         m(i,j) = (ztoped-zda(j))/(2.0d0*(Dedi(xia(i),zda(j))*t)
     1          **(0.5d0))
         s(i,j) = 1.0d0/(1.0d0+p*m(i,j))
         erfc(i,j) = (a1*s(i,j)+a2*(s(i,j))**(2.0d0)+a3
     1             * (s(i,j))**(3.0d0)+ a4*(s(i,j))**(4.0d0)
     1             + a5*(s(i,j))**(5.0d0))*exp(-(m(i,j))**(2.0d0))
C
         write (80,9100) i, j, m(i,j), erfc(i,j)
C
1100  continue
1150  continue
C
C Formats
C
7000  format (2(/),'Values of concentration from c = c(surface)
     1       *erfc(m)')
7050  format (/,'Time = ', d23.16)
7100   format (/,'Inner tissue', 2(/), t3, 'i', t8, 'j',
     1       t24, 'c = erfc(m)')
7150  format (/,'Outer tissue', 2(/), t3, 'i', t8, 'j',
```

```
     1        t24, 'm(i,j)', t50, 'c = erfc(m)')
9100  format (i3, t6, i3, t12, d23.16, t40, d23.16)
C
      return
      end
C
C
C *************************
C Functions left Ed boundary
C *************************
C
      double precision function f_Bedl1(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim, iin, iout
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /steps_radial/ hxi_in, hxi_out
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /xizetaval/ xia, zda
C
      f_Bedl1 = ((-Dedi(xia(i),zda(j))/(1.0d0+(dfd_outer(zda(j)))
     1      **2)**(1.0d0/2.0d0))*((1.0d0/(rd_max-fd_outer(zda(j))))
     1      - dfd_outer(zda(j))*dxidzeta(xia(i),zda(j))))/hxi_in
C
      return
      end
C
C
      double precision function f_Bedl2(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      f_Bedl2 = ((-Dedi(xia(0),zda(j))/(1.0d0+(dfd_outer(zda(j)))
     1      **2)**(1.0d0/2.0d0))*dfd_outer(zda(j)))/hzd
C
      return
      end
C
C
      double precision function f_Bedl3(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
C
      f_Bedl3 = Porsed(i,j)/Kedi
C
```

```
      return
      end
C
C
      double precision function f_Bedl4(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
C
      f_Bedl4 = Porsed(i,j)/Korsed
C
      return
      end
C
C
C ******************************
C Functions for Sc / Ed boundary
C ******************************
C
      double precision function f_Bsced1i(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      f_Bsced1i = Dedi(xia(i),zda(j))/hzd
C
      return
      end
C
C
      double precision function f_Bsced1o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      f_Bsced1o = Dedo(xia(i),zda(j))/hzd
C
      return
      end
C
C
      double precision function f_Bsced2i(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
```

```
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_radial/ hxi_in, hxi_out
C
      f_Bsced2i = (Dedi(xia(i),zda(j))/hxi_in)*dxidzeta(xia(i),zda(j))
C
      return
      end
C
C
      double precision function f_Bsced2o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /steps_radial/ hxi_in, hxi_out
      common /xizetaval/ xia, zda
C
      f_Bsced2o = (Dedo(xia(i),zda(j))/hxi_out)*dxidzeta(xia(i),zda(j))
C
      return
      end
C
C
      double precision function f_Bsced3i(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
C
      f_Bsced3i = Pscsol(xia(i),zda(j))/Kedi
C
      return
      end
C
C
      double precision function f_Bsced3o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
C
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
C
      f_Bsced3o = Pscsol(xia(i),zda(j))/Kedo
```

```
C
      return
      end
C
C
      double precision function f_Bsced4(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
C
      f_Bsced4 = Pscsol(xia(i),zda(j))/Ksolref
C
      return
      end
C
C
C ***********************************
C Functions for hd / sublayer boundary
C ***********************************
C
      double precision function f_Bhdsub1i(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      f_Bhdsub1i = Dhdi(xia(i),zda(j))/hzd3
C
      return
      end
C
C
      double precision function f_Bhdsub1o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      f_Bhdsub1o = Dhdo(xia(i),zda(j))/hzd3
C
      return
      end
C
C
      double precision function f_Bhdsub2i(i,j)
```

```
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /steps_radial/ hxi_in, hxi_out
      common /xizetaval/ xia, zda
C
      f_Bhdsub2i = (Dhdi(xia(i),zda(j))/hxi_in)
     1          * dxidzeta(xia(i),zda(j))
C
      return
      end
C
C
      double precision function f_Bhdsub2o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /steps_radial/ hxi_in, hxi_out
      common /xizetaval/ xia, zda
C
      f_Bhdsub2o = (Dhdo(xia(i),zda(j))/hxi_out)
     1          * dxidzeta(xia(i),zda(j))
C
      return
      end
C
C
      double precision function f_Bhdsub3i(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
C
      f_Bhdsub3i = Psubsol(xia(i),zda(j))/Khdi
C
      return
      end
C
C
      double precision function f_Bhdsub3o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
```

```
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
C
      f_Bhdsub3o = Psubsol(xia(i),zda(j))/Khdo
C
      return
      end
C
C
      double precision function f_Bhdsub4(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
C
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
C
      f_Bhdsub4 = Psubsol(xia(i),zda(j))/Ksubref
C
      return
      end
C
C
C **************
C Permeabilities
C **************
C
      double precision function Pscsol(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
C
      if (xi .gt. 0.33d0) then
         Pscsol = 1.0d-6
      else
         Pscsol = 0.0003611d0
      end if
C
      return
      end
C
C
      double precision function Psubsol(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
C
      Psubsol = 0.000001d0
```

```
C
      return
      end
C
C
      double precision function Porsed(i,j)
      implicit double precision (a - z)
      integer i, j
C
      Porsed = P_ors(j)
C
      return
      end
C
C
      double precision function Porsde1(i,j)
      implicit double precision (a - z)
      integer i, j
C
      Porsde1 = P_ors(j)
C
      return
      end
C
C
      double precision function Porsde2(i,j)
      implicit double precision (a - z)
      integer i, j
C
      Porsde2 = P_ors(j)
C
      return
      end
C
C
      double precision function Porshd(i,j)
      implicit double precision (a - z)
      integer i, j
C
      Porshd = P_ors(j)
C
      return
      end
C
C
      double precision function P_ors(j)
      implicit double precision (a - z)
      integer j
C
      P_ors = P_infund(j) + P_duct(j)
C
      return
      end
C
C
      double precision function P_infund(l)
      implicit double precision (a - z)
```

```
      integer idim, jdim, l
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
C
      z = zda(l)
      if (z .ge. -10.0d0) then
C*******************************************************C
C Hair follicle boundary is permeable
C
C         P_infund = 1.0d0/(324.0d0 * z + 3600.0d0)
         P_infund = 1.0d0/(249.0d0 * z + 2770.0d0)
C*******************************************************C
C         P_infund = 0.0d0
C*******************************************************C
      else
         P_infund = 0.0d0
      end if
C
      return
      end
C
C
      double precision function P_duct(j)
      implicit double precision (a - z)
      integer idim, jdim, j
C
      parameter (idim = 500, jdim = 500)
      parameter (pi = 3.141592654d0)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
C
C
C Assumes 1 sebaceous gland / hair follicle
C
      z = zda(j)
      sigma = 1.0d0
      z_mean = -5.0d0
C      P_duct = ((0.069d0)/sqrt(2.0d0*pi*sigma**2))
C     1       * EXP(-((z-z_mean)**2)/(2.0d0*sigma**2))
      P_duct = 0.0d0
C
      return
      end
C
C
C ******************************
C Functions for Ed / De1 boundary
C ******************************
C
      double precision function f_Bedde11i(i,j)
      implicit double precision (a - z)
```

```
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      f_Bedde11i = Dedi(xia(i),zda(j))/hzd
C
      return
      end
C
C
      double precision function f_Bedde11o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      f_Bedde11o = Dedo(xia(i),zda(j))/hzd
C
      return
      end
C
C
      double precision function f_Bedde12i(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      f_Bedde12i = Dde1i(xia(i),zda(j))/hzd1
C
      return
      end
C
C
      double precision function f_Bedde12o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      f_Bedde12o = Dde1o(xia(i),zda(j))/hzd1
C
      return
      end
C
```

```
C
      double precision function f_Bedde13i(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /steps_radial/ hxi_in, hxi_out
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
      common /xizetaval/ xia, zda
C
      f_Bedde13i = dxidzeta(xia(i),zda(j))*((Dedi(xia(i),zda(j))
     1         /hxi_in)
     1         - (Dde1i(xia(i),zda(j))/hxi_in)*(Kde1i/Kedi))
C
      return
      end
C
C
      double precision function f_Bedde13o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /steps_radial/ hxi_in, hxi_out
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
      common /xizetaval/ xia, zda
C
      f_Bedde13o = dxidzeta(xia(i),zda(j))*((Dedo(xia(i),zda(j))
     1         /hxi_out)
     1         - (Dde1o(xia(i),zda(j))/hxi_out)*(Kde1o/Kedo))
C
      return
      end
C
C
      double precision function f_Bedde14i(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /steps_radial/ hxi_in, hxi_out
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
      common /xizetaval/ xia, zda
C
      f_Bedde14i = dxidzeta(xia(i),zda(j))
     1         * (-(Dde1i(xia(i),zda(j))/hxi_in)
     1         + (Dedi(xia(i),zda(j))/hxi_in)*(Kedi/Kde1i))
C
```

```
C
      return
      end
C
C
      double precision function f_Bedde14o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /steps_radial/ hxi_in, hxi_out
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
      common /xizetaval/ xia, zda
C
      f_Bedde14o=dxidzeta(xia(i),zda(j))
     1        * (-(Dde1o(xia(i),zda(j))/hxi_out)
     1        + (Dedo(xia(i),zda(j))/hxi_out)*(Kedo/Kde1o))
C
      return
      end
C
C
C ************************************
C Functions for Ed inner/outer boundary
C ************************************
C
      double precision function f_Bedio1i(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim, iin, iout
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /steps_radial/ hxi_in, hxi_out
C
      f_Bedio1i = ((Dedi(xia(i),zda(j))
     1          / (sqrt(1.0d0+(dfd_outer(zda(j)))**2)))
     1          * ((1.0d0/(rd_max-fd_outer))
     1          - dfd_outer(zda(j))*dxidzeta(xia(i),zda(j))))
     1          / hxi_in
C
      return
      end
C
C
      double precision function f_Bedio1o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim, iin, iout
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
```

```
      common /steps_radial/ hxi_in, hxi_out
C
      f_Bedio1o = ((Dedo(xia(i),zda(j))
     1          / (sqrt(1.0d0+(dfd_outer(zda(j)))**2)))
     1          * ((1.0d0/(rd_max-fd_outer))
     1          - dfd_outer(zda(j))*dxidzeta(xia(i),zda(j))))
     1          / hxi_out
C
      return
      end
C
C
      double precision function f_Bedio2i(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim, iin, iout
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
C
      f_Bedio2i = (1.0d0/hzd)*(Dedi(xia(i),zda(j))
     1          / sqrt(1.0d0+(dfd_outer(zda(j)))**2))
     1          *(1.0d0-(Kedo/Kedi))
C
      return
      end
C
C
      double precision function f_Bedio2o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim, iin, iout
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
C
      f_Bedio2o = (1.0d0/hzd)*(Dedo(xia(i),zda(j))
     1          / sqrt(1.0d0+(dfd_outer(zda(j)))**2))
     1          *((Kedi/Kedo)-1.0d0)
C
      return
      end
C
C
C ***************************
C Functions left de1 boundary
C ***************************
```

```
C
      double precision function f_Bde1l1(i,j)
      implicit double precision (a - z)
      integer i, j, iin, iout, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /steps_radial/ hxi_in, hxi_out
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /xizetaval/ xia, zda
C
      f_Bde1l1 = ((-Dde1i(xia(i),zda(j))/(1.0d0+(dfd_outer(zda(j)))
     1      **2)**(1.0d0/2.0d0))*((1.0d0/(rd_max-fd_outer(zda(j))))
     1      - dfd_outer(zda(j))*dxidzeta(xia(i),zda(j))))/hxi_in
C
      return
      end
C
C
      double precision function f_Bde1l2(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      f_Bde1l2 = ((-Dde1i(xia(i),zda(j))/(1.0d0+(dfd_outer(zda(j)))
     1      **2)**(1.0d0/2.0d0))*dfd_outer(zda(j)))/hzd1
C
      return
      end
C
C
      double precision function f_Bde1l3(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
C
      f_Bde1l3 = Porsde1(i,j)/Kde1i
C
      return
      end
C
C
      double precision function f_Bde1l4(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
```

```
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
C
      f_Bde1l4 = Porsde1(i,j)/Korsde1
C
      return
      end
C
C
C *************************
C Functions left de2 boundary
C *************************
C
      double precision function f_Bde2l1(i,j)
      implicit double precision (a - z)
      integer i, j, iin , iout, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /steps_radial/ hxi_in, hxi_out
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /xizetaval/ xia, zda
C
      f_Bde2l1 = ((-Dde2i(xia(i),zda(j))/(1.0d0+(dfd_outer(zda(j)))
     1      **2)**(1.0d0/2.0d0))*((1.0d0/(rd_max-fd_outer(zda(j))))
     1      - dfd_outer(zda(j))*dxidzeta(xia(i),zda(j))))/hxi_in
C
      return
      end
C
C
      double precision function f_Bde2l2(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      f_Bde2l2 = ((-Dde2i(xia(i),zda(j))/(1.0d0+(dfd_outer(zda(j)))
     1      **2)**(1.0d0/2.0d0))*dfd_outer(zda(j)))/hzd2
C
      return
      end
C
C
      double precision function f_Bde2l3(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
```

```
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
C
      f_Bde2l3 = Porsde2(i,j)/Kde2i
C
      return
      end
C
C
      double precision function f_Bde2l4(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
C
      f_Bde2l4 = Porsde2(i,j)/Korsde2
C
      return
      end
C
C
C *************************
C Functions left hd boundary
C *************************
C
      double precision function f_Bhdl1(i,j)
      implicit double precision (a - z)
      integer i, j, iin , iout, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /steps_radial/ hxi_in, hxi_out
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /xizetaval/ xia, zda
C
      f_Bhdl1 = ((-Dhdi(xia(i),zda(j))/(1.0d0+(dfd_outer(zda(j)))
     1      **2)**(1.0d0/2.0d0))*((1.0d0/(rd_max-fd_outer(zda(j))))
     1      - dfd_outer(zda(j))*dxidzeta(xia(i),zda(j))))/hxi_in
C
      return
      end
C
C
      double precision function f_Bhdl2(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
```

```
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      f_Bhdl2 = ((-Dhdi(xia(i),zda(j))/(1.0d0+(dfd_outer(zda(j)))
     1      **2)**(1.0d0/2.0d0))*dfd_outer(zda(j)))/hzd3
C
      return
      end
C
C
      double precision function f_Bhdl3(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
C
      f_Bhdl3 = Porshd(i,j)/Khdi
C
      return
      end
C
C
      double precision function f_Bhdl4(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
C
      f_Bhdl4 = Porshd(i,j)/Korshd
C
      return
      end
C
C
C ******************************
C Functions for de1 / de2 boundary
C ******************************
C
      double precision function f_Bde1de21i(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
```

```
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      f_Bde1de21i = Dde1i(xia(i),zda(j))/hzd1
C
      return
      end
C
C
      double precision function f_Bde1de21o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      f_Bde1de21o = Dde1o(xia(i),zda(j))/hzd1
C
      return
      end
C
C
      double precision function f_Bde1de22i(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      f_Bde1de22i = Dde2i(xia(i),zda(j))/hzd2
C
      return
      end
C
C
      double precision function f_Bde1de22o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      f_Bde1de22o = Dde2o(xia(i),zda(j))/hzd2
C
      return
      end
C
C
      double precision function f_Bde1de23i(i,j)
      implicit double precision (a - z)
```

```
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /steps_radial/ hxi_in, hxi_out
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
      common /xizetaval/ xia, zda
C
      f_Bde1de23i = dxidzeta(xia(i),zda(j))
     1          *((Dde1i(xia(i),zda(j))/hxi_in)
     1          -(Dde2i(xia(i),zda(j))/hxi_in)*(Kde2i/Kde1i))
C
      return
      end
C
C
      double precision function f_Bde1de23o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /steps_radial/ hxi_in, hxi_out
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
      common /xizetaval/ xia, zda
C
      f_Bde1de23o = dxidzeta(xia(i),zda(j))
     1          *((Dde1o(xia(i),zda(j))/hxi_out)
     1          -(Dde2o(xia(i),zda(j))/hxi_out)*(Kde2o/Kde1o))
C
      return
      end
C
C
      double precision function f_Bde1de24i(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /steps_radial/ hxi_in, hxi_out
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
      common /xizetaval/ xia, zda
C
      f_Bde1de24i=dxidzeta(xia(i),zda(j))
     1         * (-(Dde2i(xia(i),zda(j))/hxi_in)
     1         + (Dde1i(xia(i),zda(j))/hxi_in)*(Kde1i/Kde2i))
C
      return
      end
C
```

```
C
      double precision function f_Bde1de24o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /steps_radial/ hxi_in, hxi_out
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
      common /xizetaval/ xia, zda
C
      f_Bde1de24o=dxidzeta(xia(i),zda(j))
     1         * (-(Dde2o(xia(i),zda(j))/hxi_out)
     1         + (Dde1o(xia(i),zda(j))/hxi_out)*(Kde1o/Kde2o))
C
      return
      end
C
C
C ********************************
C Functions for de2 / hd boundary
C ********************************
C
      double precision function f_Bde2hd1i(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/ hzd, hzd1, hzd2, hzd3
C
      f_Bde2hd1i = Dde2i(xia(i),zda(j))/hzd2
C
      return
      end
C
C
      double precision function f_Bde2hd1o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/ hzd, hzd1, hzd2, hzd3
C
      f_Bde2hd1o = Dde2o(xia(i),zda(j))/hzd2
C
      return
      end
C
C
      double precision function f_Bde2hd2i(i,j)
      implicit double precision (a - z)
```

```
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/ hzd, hzd1, hzd2, hzd3
C
      f_Bde2hd2i = Dhdi(xia(i),zda(j))/hzd3
C
      return
      end
C
C
      double precision function f_Bde2hd2o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /steps_axial/ hzd, hzd1, hzd2, hzd3
C
      f_Bde2hd2o = Dhdo(xia(i),zda(j))/hzd3
C
      return
      end
C
C
      double precision function f_Bde2hd3i(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /steps_radial/ hxi_in, hxi_out
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
      common /xizetaval/ xia, zda
C
      f_Bde2hd3i = dxidzeta(xia(i),zda(j))
     1         * ((Dde2i(xia(i),zda(j))/hxi_in)
     1         - (Dhdi(xia(i),zda(j))/hxi_in)*(Khdi/Kde2i))
C
      return
      end
C
C
      double precision function f_Bde2hd3o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /steps_radial/ hxi_in, hxi_out
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
```

```
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
      common /xizetaval/ xia, zda
C
      f_Bde2hd3o = dxidzeta(xia(i),zda(j))
     1         *((Dde2o(xia(i),zda(j))/hxi_out)
     1         -(Dhdo(xia(i),zda(j))/hxi_out)*(Khdo/Kde2o))
C
      return
      end
C
C
      double precision function f_Bde2hd4i(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /steps_radial/ hxi_in, hxi_out
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
      common /xizetaval/ xia, zda
C
      f_Bde2hd4i = dxidzeta(xia(i),zda(j))
     1         * (-(Dhdi(xia(i),zda(j))/hxi_in)
     1         + (Dde2i(xia(i),zda(j))/hxi_in)*(Kde2i/Khdi))
C
      return
      end
C
C
      double precision function f_Bde2hd4o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /steps_radial/ hxi_in, hxi_out
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
      common /xizetaval/ xia, zda
C
      f_Bde2hd4o =dxidzeta(xia(i),zda(j))
     1         * (-(Dhdo(xia(i),zda(j))/hxi_out)
     1         + (Dde2o(xia(i),zda(j))/hxi_out)*(Kde2o/Khdo))
C
      return
      end
C
C
C ************************************
C Functions for de1 inner/outer boundary
C ************************************
C
      double precision function f_Bde1io1i(i,j)
      implicit double precision (a - z)
```

```
      integer i, j, idim, jdim, iin, iout
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /steps_radial/ hxi_in, hxi_out
C
      f_Bde1io1i = ((Dde1i(xia(i),zda(j))
     1          / (sqrt(1.0d0+(dfd_outer(zda(j)))**2)))
     1          * ((1.0d0/(rd_max-fd_outer))
     1          - dfd_outer(zda(j))*dxidzeta(xia(i),zda(j))))
     1          / hxi_in
C
      return
      end
C
C
      double precision function f_Bde1io1o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim, iin, iout
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /steps_radial/ hxi_in, hxi_out
C
      f_Bde1io1o = ((Dde1o(xia(i),zda(j))
     1          / (sqrt(1.0d0+(dfd_outer(zda(j)))**2)))
     1          * ((1.0d0/(rd_max-fd_outer))
     1          - dfd_outer(zda(j))*dxidzeta(xia(i),zda(j))))
     1          / hxi_out
C
      return
      end
C
C
      double precision function f_Bde1io2i(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim, iin, iout
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
C
      f_Bde1io2i = (1.0d0/hzd1)*(Dde1i(xia(i),zda(j))
     1          / sqrt(1.0d0+(dfd_outer(zda(j)))**2))
     1          *(1.0d0-(Kde1o/Kde1i))
C
      return
      end
```

```
C
C
      double precision function f_Bde1io2o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim, iin, iout
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
C
      f_Bde1io2o = (1.0d0/hzd1)*(Dde1o(xia(i),zda(j))
     1          / sqrt(1.0d0+(dfd_outer(zda(j)))**2))
     1          *((Kde1i/Kde1o)-1.0d0)
C
      return
      end
C
C
C ************************************
C Functions for de2 inner/outer boundary
C ************************************
C
      double precision function f_Bde2io1i(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim, iin, iout
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /steps_radial/ hxi_in, hxi_out
C
      f_Bde2io1i = ((Dde2i(xia(i),zda(j))
     1          / (sqrt(1.0d0+(dfd_outer(zda(j)))**2)))
     1          * ((1.0d0/(rd_max-fd_outer))
     1          - dfd_outer(zda(j))*dxidzeta(xia(i),zda(j))))
     1          / hxi_in
C
      return
      end
C
C
      double precision function f_Bde2io1o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim, iin, iout
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /steps_radial/ hxi_in, hxi_out
C
```

```
      f_Bde2io1o = ((Dde2o(xia(i),zda(j))
     1          / (sqrt(1.0d0+(dfd_outer(zda(j)))**2)))
     1          * ((1.0d0/(rd_max-fd_outer))
     1          - dfd_outer(zda(j))*dxidzeta(xia(i),zda(j))))
     1          / hxi_out
C
      return
      end
C
C
      double precision function f_Bde2io2i(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim, iin, iout
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
C
      f_Bde2io2i = (1.0d0/hzd2)*(Dde2i(xia(i),zda(j))
     1          / sqrt(1.0d0+(dfd_outer(zda(j)))**2))
     1          *(1.0d0-(Kde2o/Kde2i))
C
      return
      end
C
C
      double precision function f_Bde2io2o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim, iin, iout
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
C
      f_Bde2io2o = (1.0d0/hzd2)*(Dde2o(xia(i),zda(j))
     1          / sqrt(1.0d0+(dfd_outer(zda(j)))**2))
     1          *((Kde2i/Kde2o)-1.0d0)
C
      return
      end
C
C
C ************************************
C Functions for hd inner/outer boundary
C ************************************
C
      double precision function f_Bhdio1i(i,j)
```

```
      implicit double precision (a - z)
      integer i, j, idim, jdim, iin, iout
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /steps_radial/ hxi_in, hxi_out
C
      f_Bhdio1i = ((Dhdi(xia(i),zda(j))
     1          / (sqrt(1.0d0+(dfd_outer(zda(j)))**2)))
     1          * ((1.0d0/(rd_max-fd_outer))
     1          - dfd_outer(zda(j))*dxidzeta(xia(i),zda(j))))
     1          / hxi_in
C
      return
      end
C
C
      double precision function f_Bhdio1o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim, iin, iout
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /steps_radial/ hxi_in, hxi_out
C
      f_Bhdio1o = ((Dhdo(xia(i),zda(j))
     1          / (sqrt(1.0d0+(dfd_outer(zda(j)))**2)))
     1          * ((1.0d0/(rd_max-fd_outer))
     1          - dfd_outer(zda(j))*dxidzeta(xia(i),zda(j))))
     1          / hxi_out
C
      return
      end
C
C
      double precision function f_Bhdio2i(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim, iin, iout
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
C
      f_Bhdio2i = (1.0d0/hzd3)*(Dhdi(xia(i),zda(j))
     1          / sqrt(1.0d0+(dfd_outer(zda(j)))**2))
     1          *(1.0d0-(Khdo/Khdi))
C
      return
```

```
      end
C
C
      double precision function f_Bhdio2o(i,j)
      implicit double precision (a - z)
      integer i, j, idim, jdim, iin, iout
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
      common /boundarydata/ L0, Kedi, Kde1i, Kde2i, Khdi, Kedo,
     1      Kde1o, Kde2o, Khdo, csol, Ksolref, csub, Ksubref,
     1      Korsed, Korsde1, Korsde2, Korshd, Ksebref, Dsebum
C
      f_Bhdio2o = (1.0d0/hzd3)*(Dhdo(xia(i),zda(j))
     1          / sqrt(1.0d0+(dfd_outer(zda(j)))**2))
     1          *((Khdi/Khdo)-1.0d0)
C
      return
      end
C
C
C ****************************************
C Functions for exact calculation of Laplacian
C ****************************************
C
      double precision function rdf(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:idim)
C
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
C
      rdf = fd_outer(zeta) + xi*(rd_max-fd_outer(zeta))
C
      return
      end
C
C
      double precision function zdf(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:idim)
C
      common /xizetaval/ xia, zda
C
      zdf = zeta
C
      return
      end
```

```
C
C
C *********
C Functions
C *********
C
C Derivative coefficient functions
C
      double precision function a20edi(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
C
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a20edi = Dedi(xi,zeta)*((dxidzeta(xi,zeta))**2)
     1    + Dedi(xi,zeta)/((rd_max-fd_outer(zeta))**2)
C
      return
      end
C
      double precision function a20edo(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
C
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a20edo = Dedo(xi,zeta)*((dxidzeta(xi,zeta))**2)
     1    + Dedo(xi,zeta)/((rd_max-fd_outer(zeta))**2)
C
      return
      end
C
      double precision function a20de1i(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
C
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a20de1i = Dde1i(xi,zeta)*((dxidzeta(xi,zeta))**2)
```

```
     1    + Dde1i(xi,zeta)/((rd_max-fd_outer(zeta))**2)
C
      return
      end
C
      double precision function a20de1o(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
C
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a20de1o = Dde1o(xi,zeta)*((dxidzeta(xi,zeta))**2)
     1    + Dde1o(xi,zeta)/((rd_max-fd_outer(zeta))**2)
C
      return
      end
C
      double precision function a20de2i(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
C
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a20de2i = Dde2i(xi,zeta)*((dxidzeta(xi,zeta))**2)
     1    + Dde2i(xi,zeta)/((rd_max-fd_outer(zeta))**2)
C
      return
      end
C
      double precision function a20de2o(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
C
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a20de2o = Dde2o(xi,zeta)*((dxidzeta(xi,zeta))**2)
     1    + Dde2o(xi,zeta)/((rd_max-fd_outer(zeta))**2)
C
      return
```

```
      end
C
      double precision function a20hdi(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
C
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a20hdi = Dhdi(xi,zeta)*((dxidzeta(xi,zeta))**2)
     1    + Dhdi(xi,zeta)/((rd_max-fd_outer(zeta))**2)
C
      return
      end
C
      double precision function a20hdo(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
C
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a20hdo = Dhdo(xi,zeta)*((dxidzeta(xi,zeta))**2)
     1    + Dhdo(xi,zeta)/((rd_max-fd_outer(zeta))**2)
C
      return
      end
C
      double precision function a10edi(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
C
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a10edi = Dedi(xi,zeta)/(xi*((rd_max-fd_outer(zeta))**2)
```

```
     1    + fd_outer(zeta)*(rd_max-fd_outer(zeta)))
     1    + dDed10i(xi,zeta)/((rd_max-fd_outer(zeta))**2)
     1    + dxidzeta(xi,zeta)*dDed01i(xi,zeta)
     1    + Dedi(xi,zeta)*d2xidzeta2(xi,zeta)
     1    + dDed01i(xi,zeta)*((dxidzeta(xi,zeta))**2)
     1    + Dedi(xi,zeta)*dxidzeta(xi,zeta)*d2xidxidzeta(xi,zeta)
C
      return
      end
C
      double precision function a10edo(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
C
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a10edo = Dedo(xi,zeta)/(xi*((rd_max-fd_outer(zeta))**2)
     1    + fd_outer(zeta)*(rd_max-fd_outer(zeta)))
     1    + dDed10o(xi,zeta)/((rd_max-fd_outer(zeta))**2)
     1    + dxidzeta(xi,zeta)*dDed01o(xi,zeta)
     1    + Dedo(xi,zeta)*d2xidzeta2(xi,zeta)
     1    + dDed01o(xi,zeta)*((dxidzeta(xi,zeta))**2)
     1    + Dedo(xi,zeta)*dxidzeta(xi,zeta)*d2xidxidzeta(xi,zeta)
C
      return
      end
C
      double precision function a10de1i(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
C
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a10de1i = Dde1i(xi,zeta)/(xi*((rd_max-fd_outer(zeta))**2)
     1    + fd_outer(zeta)*(rd_max-fd_outer(zeta)))
     1    + dDde110i(xi,zeta)/((rd_max-fd_outer(zeta))**2)
     1    + dxidzeta(xi,zeta)*dDde101i(xi,zeta)
     1    + Dde1i(xi,zeta)*d2xidzeta2(xi,zeta)
     1    + dDde101i(xi,zeta)*((dxidzeta(xi,zeta))**2)
     1    + Dde1i(xi,zeta)*dxidzeta(xi,zeta)*d2xidxidzeta(xi,zeta)
C
```

```
      return
      end
C
      double precision function a10de1o(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
C
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a10de1o = Dde1o(xi,zeta)/(xi*((rd_max-fd_outer(zeta))**2)
     1    + fd_outer(zeta)*(rd_max-fd_outer(zeta)))
     1    + dDde110o(xi,zeta)/((rd_max-fd_outer(zeta))**2)
     1    + dxidzeta(xi,zeta)*dDde101o(xi,zeta)
     1    + Dde1o(xi,zeta)*d2xidzeta2(xi,zeta)
     1    + dDde101o(xi,zeta)*((dxidzeta(xi,zeta))**2)
     1    + Dde1o(xi,zeta)*dxidzeta(xi,zeta)*d2xidxidzeta(xi,zeta)
C
      return
      end
C
      double precision function a10de2i(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
C
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a10de2i = Dde2i(xi,zeta)/(xi*((rd_max-fd_outer(zeta))**2)
     1    + fd_outer(zeta)*(rd_max-fd_outer(zeta)))
     1    + dDde210i(xi,zeta)/((rd_max-fd_outer(zeta))**2)
     1    + dxidzeta(xi,zeta)*dDde201i(xi,zeta)
     1    + Dde2i(xi,zeta)*d2xidzeta2(xi,zeta)
     1    + dDde201i(xi,zeta)*((dxidzeta(xi,zeta))**2)
     1    + Dde2i(xi,zeta)*dxidzeta(xi,zeta)*d2xidxidzeta(xi,zeta)
C
      return
      end
C
      double precision function a10de2o(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
```

```
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
C
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a10de2o = Dde2o(xi,zeta)/(xi*((rd_max-fd_outer(zeta))**2)
     1    + fd_outer(zeta)*(rd_max-fd_outer(zeta)))
     1    + dDde210o(xi,zeta)/((rd_max-fd_outer(zeta))**2)
     1    + dxidzeta(xi,zeta)*dDde201o(xi,zeta)
     1    + Dde2o(xi,zeta)*d2xidzeta2(xi,zeta)
     1    + dDde201o(xi,zeta)*((dxidzeta(xi,zeta))**2)
     1    + Dde2o(xi,zeta)*dxidzeta(xi,zeta)*d2xidxidzeta(xi,zeta)
C
      return
      end
C
      double precision function a10hdi(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
C
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a10hdi = Dhdi(xi,zeta)/(xi*((rd_max-fd_outer(zeta))**2)
     1    + fd_outer(zeta)*(rd_max-fd_outer(zeta)))
     1    + dDhd10i(xi,zeta)/((rd_max-fd_outer(zeta))**2)
     1    + dxidzeta(xi,zeta)*dDhd01i(xi,zeta)
     1    + Dhdi(xi,zeta)*d2xidzeta2(xi,zeta)
     1    + dDhd01i(xi,zeta)*((dxidzeta(xi,zeta))**2)
     1    + Dhdi(xi,zeta)*dxidzeta(xi,zeta)*d2xidxidzeta(xi,zeta)
C
      return
      end
C
      double precision function a10hdo(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
C
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
```

```
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a10hdo = Dhdo(xi,zeta)/(xi*((rd_max-fd_outer(zeta))**2)
     1    + fd_outer(zeta)*(rd_max-fd_outer(zeta)))
     1    + dDhd10o(xi,zeta)/((rd_max-fd_outer(zeta))**2)
     1    + dxidzeta(xi,zeta)*dDhd01o(xi,zeta)
     1    + Dhdo(xi,zeta)*d2xidzeta2(xi,zeta)
     1    + dDhd01o(xi,zeta)*((dxidzeta(xi,zeta))**2)
     1    + Dhdo(xi,zeta)*dxidzeta(xi,zeta)*d2xidxidzeta(xi,zeta)
C
      return
      end
C
      double precision function a02edi(xi,zeta)
      implicit double precision (a - z)
C
      a02edi = Dedi(xi,zeta)
C
      return
      end
C
C
      double precision function a02edo(xi,zeta)
      implicit double precision (a - z)
C
      a02edo = Dedo(xi,zeta)
C
      return
      end
C
C
      double precision function a02de1i(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
C
      a02de1i = Dde1i(xi,zeta)
C
      return
      end
C
C
      double precision function a02de1o(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
C
      a02de1o = Dde1o(xi,zeta)
```

```
C
      return
      end
C
C
      double precision function a02de2i(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
C
      a02de2i = Dde2i(xi,zeta)
C
      return
      end
C
C
      double precision function a02de2o(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
C
      a02de2o = Dde2o(xi,zeta)
C
      return
      end
C
C
      double precision function a02hdi(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
C
      a02hdi = Dhdi(xi,zeta)
C
      return
      end
C
C
      double precision function a02hdo(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      common /mesh_i/ xi_in, rd_max, iin, iout
```

```
      common /mesh_j/ jed, jde1, jde2, jhd
C
      a02hdo = Dhdo(xi,zeta)
C
      return
      end
C
C
      double precision function a01edi(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a01edi = dDed01i(xi,zeta)+dDed10i(xi,zeta)*dxidzeta(xi,zeta)
C
      return
      end
C
C
      double precision function a01edo(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a01edo = dDed01o(xi,zeta)+dDed10o(xi,zeta)*dxidzeta(xi,zeta)
C
      return
      end
C
C
      double precision function a01de1i(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
```

```
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a01de1i = dDde101i(xi,zeta)+dDde110i(xi,zeta)*dxidzeta(xi,zeta)
C
      return
      end
C
C
      double precision function a01de1o(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a01de1o = dDde101o(xi,zeta)+dDde110o(xi,zeta)*dxidzeta(xi,zeta)
C
      return
      end
C
C
      double precision function a01de2i(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a01de2i = dDde201i(xi,zeta)+dDde210i(xi,zeta)*dxidzeta(xi,zeta)
C
      return
      end
C
C
      double precision function a01de2o(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
```

```
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a01de2o = dDde201o(xi,zeta)+dDde210o(xi,zeta)*dxidzeta(xi,zeta)
C
      return
      end
C
C
      double precision function a01hdi(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a01hdi = dDhd01i(xi,zeta)+dDhd10i(xi,zeta)*dxidzeta(xi,zeta)
C
      return
      end
C
C
      double precision function a01hdo(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a01hdo = dDhd01o(xi,zeta)+dDhd10o(xi,zeta)*dxidzeta(xi,zeta)
C
      return
      end
C
C
      double precision function a11edi (xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
```

```
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a11edi = 2.0d0*Dedi(xi,zeta)*dxidzeta(xi,zeta)
     1      * d2xidxidzeta(xi,zeta)
C
      return
      end
C
C
      double precision function a11edo (xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a11edo = 2.0d0*Dedo(xi,zeta)*dxidzeta(xi,zeta)
     1      * d2xidxidzeta(xi,zeta)
C
      return
      end
C
C
      double precision function a11de1i(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a11de1i = 2.0d0*Dde1i(xi,zeta)*dxidzeta(xi,zeta)
     1       * d2xidxidzeta(xi,zeta)
C
      return
      end
C
C
      double precision function a11de1o(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
```

```
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a11de1o = 2.0d0*Dde1o(xi,zeta)*dxidzeta(xi,zeta)
     1       * d2xidxidzeta(xi,zeta)
C
      return
      end
C
C
      double precision function a11de2i(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a11de2i = 2.0d0*Dde2i(xi,zeta)*dxidzeta(xi,zeta)
     1       * d2xidxidzeta(xi,zeta)
C
      return
      end
C
C
      double precision function a11de2o(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a11de2o = 2.0d0*Dde2o(xi,zeta)*dxidzeta(xi,zeta)
     1       * d2xidxidzeta(xi,zeta)
C
      return
      end
C
C
      double precision function a11hdi(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
```

```
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a11hdi = 2.0d0*Dhdi(xi,zeta)*dxidzeta(xi,zeta)
     1      * d2xidxidzeta(xi,zeta)
C
      return
      end
C
C
      double precision function a11hdo(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout, jed, jde1, jde2, jhd,
     1        idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
      common /steps_radial/ hxi_in, hxi_out
      common /steps_axial/  hzd, hzd1, hzd2, hzd3
C
      a11hdo = 2.0d0*Dhdo(xi,zeta)*dxidzeta(xi,zeta)
     1      * d2xidxidzeta(xi,zeta)
C
      return
      end
C
C
C Derivatives of diffusivities w.r.t. zeta
C
      double precision function dDed01i(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /param/ deltat, deltah, ratek_edi, ratek_edo,
     1       ratek_de1i, ratek_de1o, ratek_de2i, ratek_de2o,
     1       ratek_hdi, ratek_hdo
C
      dDed01i = (Dedi(xi,zeta+deltah)-Dedi(xi,zeta-deltah))
     1         / (2.0d0*deltah)
C
      return
      end
C
      double precision function dDed01o(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim
```

```
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /param/ deltat, deltah, ratek_edi, ratek_edo,
     1       ratek_de1i, ratek_de1o, ratek_de2i, ratek_de2o,
     1       ratek_hdi, ratek_hdo
C
      dDed01o = (Dedo(xi,zeta+deltah)-Dedo(xi,zeta-deltah))
     1         / (2.0d0*deltah)
C
      return
      end
C
C
      double precision function dDde101i(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /param/ deltat, deltah, ratek_edi, ratek_edo,
     1       ratek_de1i, ratek_de1o, ratek_de2i, ratek_de2o,
     1       ratek_hdi, ratek_hdo
C
      dDde101i = (Dde1i(xi,zeta+deltah)-Dde1i(xi,zeta-deltah))
     1    / (2.0d0*deltah)
C
      return
      end
C
      double precision function dDde101o(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /param/ deltat, deltah, ratek_edi, ratek_edo,
     1       ratek_de1i, ratek_de1o, ratek_de2i, ratek_de2o,
     1       ratek_hdi, ratek_hdo
C
      dDde101o = (Dde1o(xi,zeta+deltah)-Dde1o(xi,zeta-deltah))
     1    / (2.0d0*deltah)
C
      return
      end
C
      double precision function dDde201i(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /param/ deltat, deltah, ratek_edi, ratek_edo,
```

```
     1       ratek_de1i, ratek_de1o, ratek_de2i, ratek_de2o,
     1       ratek_hdi, ratek_hdo
C
      dDde201i = (Dde2i(xi,zeta+deltah)-Dde2i(xi,zeta-deltah))
     1         / (2.0d0*deltah)
C
C
      return
      end
C
      double precision function dDde201o(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /param/ deltat, deltah, ratek_edi, ratek_edo,
     1       ratek_de1i, ratek_de1o, ratek_de2i, ratek_de2o,
     1       ratek_hdi, ratek_hdo
C
      dDde201o = (Dde2o(xi,zeta+deltah)-Dde2o(xi,zeta-deltah))
     1         / (2.0d0*deltah)
C
C
      return
      end
C
      double precision function dDhd01i(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /param/ deltat, deltah, ratek_edi, ratek_edo,
     1       ratek_de1i, ratek_de1o, ratek_de2i, ratek_de2o,
     1       ratek_hdi, ratek_hdo
C
      dDhd01i = (Dhdi(xi,zeta+deltah)-Dhdi(xi,zeta-deltah))
     1         / (2.0d0*deltah)
C
      return
      end
C
      double precision function dDhd01o(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /param/ deltat, deltah, ratek_edi, ratek_edo,
     1       ratek_de1i, ratek_de1o, ratek_de2i, ratek_de2o,
     1       ratek_hdi, ratek_hdo
C
      dDhd01o = (Dhdo(xi,zeta+deltah)-Dhdo(xi,zeta-deltah))
```

```
     1         / (2.0d0*deltah)
C
      return
      end
C
C Derivatives of diffusivities w.r.t. xi
C
      double precision function dDed10i(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /param/ deltat, deltah, ratek_edi, ratek_edo,
     1       ratek_de1i, ratek_de1o, ratek_de2i, ratek_de2o,
     1       ratek_hdi, ratek_hdo
C
      dDed10i = (Dedi(xi+deltah,zeta)-Dedi(xi-deltah,zeta))
     1         / (2.0d0*deltah)
C
      return
      end
C
      double precision function dDed10o(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /param/ deltat, deltah, ratek_edi, ratek_edo,
     1       ratek_de1i, ratek_de1o, ratek_de2i, ratek_de2o,
     1       ratek_hdi, ratek_hdo
C
      dDed10o = (Dedo(xi+deltah,zeta)-Dedo(xi-deltah,zeta))
     1         / (2.0d0*deltah)
C
      return
      end
C
      double precision function dDde110i(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /param/ deltat, deltah, ratek_edi, ratek_edo,
     1       ratek_de1i, ratek_de1o, ratek_de2i, ratek_de2o,
     1       ratek_hdi, ratek_hdo
C
      dDde110i = (Dde1i(xi+deltah,zeta)-Dde1i(xi-deltah,zeta))
     1         / (2.0d0*deltah)
C
      return
      end
```

```
C
      double precision function dDde110o(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /param/ deltat, deltah, ratek_edi, ratek_edo,
     1       ratek_de1i, ratek_de1o, ratek_de2i, ratek_de2o,
     1       ratek_hdi, ratek_hdo
C
      dDde110o = (Dde1o(xi+deltah,zeta)-Dde1o(xi-deltah,zeta))
     1         / (2.0d0*deltah)
C
      return
      end
C
      double precision function dDde210i(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /param/ deltat, deltah, ratek_edi, ratek_edo,
     1       ratek_de1i, ratek_de1o, ratek_de2i, ratek_de2o,
     1       ratek_hdi, ratek_hdo
C
      dDde210i = (Dde2i(xi+deltah,zeta)-Dde2i(xi-deltah,zeta))
     1         / (2.0d0*deltah)
C
      return
      end
C
      double precision function dDde210o(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /param/ deltat, deltah, ratek_edi, ratek_edo,
     1       ratek_de1i, ratek_de1o, ratek_de2i, ratek_de2o,
     1       ratek_hdi, ratek_hdo
C
      dDde210o = (Dde2o(xi+deltah,zeta)-Dde2o(xi-deltah,zeta))
     1         / (2.0d0*deltah)
C
      return
      end
C
      double precision function dDhd10i(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim
      parameter (idim = 500, jdim = 500)
C
```

```
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /param/ deltat, deltah, ratek_edi, ratek_edo,
     1       ratek_de1i, ratek_de1o, ratek_de2i, ratek_de2o,
     1       ratek_hdi, ratek_hdo
C
      dDhd10i = (Dhdi(xi+deltah,zeta)-Dhdi(xi-deltah,zeta))
     1       / (2.0d0*deltah)
C
      return
      end
C
      double precision function dDhd10o(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /param/ deltat, deltah, ratek_edi, ratek_edo,
     1       ratek_de1i, ratek_de1o, ratek_de2i, ratek_de2o,
     1       ratek_hdi, ratek_hdo
C
      dDhd10o = (Dhdo(xi+deltah,zeta)-Dhdo(xi-deltah,zeta))
     1       / (2.0d0*deltah)
C
      return
      end
C
C Diffusivities as functions of dimensionless
C non-orthogonal coordinates
C
      double precision function Dedi(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim, iin, iout,
     1        jed, jde1, jde2, jhd
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
C
      rd = xi*(rd_max-fd_outer(zeta))+fd_outer(zeta)
      zd = zeta
      Dedi = Dedi_d(rd,zd)
C
      return
      end
C
C
      double precision function Dedo(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim, iin, iout,
     1        jed, jde1, jde2, jhd
      parameter (idim = 500, jdim = 500)
C
```

```
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
C
      rd = xi*(rd_max-fd_outer(zeta))+fd_outer(zeta)
      zd = zeta
      Dedo = Dedo_d(rd,zd)
C
      return
      end
C
C
      double precision function Dde1i(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim, iin, iout,
     1        jed, jde1, jde2, jhd
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
C
      rd = xi*(rd_max-fd_outer(zeta))+fd_outer(zeta)
      zd = zeta
      Dde1i = Dde1i_d(rd,zd)
C
      return
      end
C
C
      double precision function Dde1o(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim, iin, iout,
     1        jed, jde1, jde2, jhd
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
C
      rd = xi*(rd_max-fd_outer(zeta))+fd_outer(zeta)
      zd = zeta
      Dde1o = Dde1o_d(rd,zd)
C
      return
      end
C
C
      double precision function Dde2i(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim, iin, iout,
     1        jed, jde1, jde2, jhd
      parameter (idim = 500, jdim = 500)
C
```

```
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
C
      rd = xi*(rd_max-fd_outer(zeta))+fd_outer(zeta)
      zd = zeta
      Dde2i = Dde2i_d(rd,zd)
C
      return
      end
C
C
      double precision function Dde2o(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim, iin, iout,
     1        jed, jde1, jde2, jhd
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
C
      rd = xi*(rd_max-fd_outer(zeta))+fd_outer(zeta)
      zd = zeta
      Dde2o = Dde2o_d(rd,zd)
C
      return
      end
C
C
      double precision function Dhdi(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim, iin, iout,
     1        jed, jde1, jde2, jhd
      parameter (idim = 500, jdim = 500)
C
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
C
      rd = xi*(rd_max-fd_outer(zeta))+fd_outer(zeta)
      zd = zeta
      Dhdi = Dhdi_d(rd,zd)
C
      return
      end
C
C
      double precision function Dhdo(xi,zeta)
      implicit double precision (a - z)
      integer idim, jdim, iin, iout,
     1        jed, jde1, jde2, jhd
      parameter (idim = 500, jdim = 500)
C
```

```
      dimension xia(0:idim), zda(0:jdim)
      common /xizetaval/ xia, zda
      common /mesh_i/ xi_in, rd_max, iin, iout
      common /mesh_j/ jed, jde1, jde2, jhd
C
      rd = xi*(rd_max-fd_outer(zeta))+fd_outer(zeta)
      zd = zeta
      Dhdo = Dhdo_d(rd,zd)
C
      return
      end
C
C
C Diffusivities as functions of dimensionless orthogonal
C coordinates
C
      double precision function Dedi_d(rd,zd)
      implicit double precision (a - z)
C
      Dedi_d = 0.0152d0
C
      return
      end
C
C
      double precision function Dedo_d(rd,zd)
      implicit double precision (a - z)
C
      Dedo_d = 0.0152d0
C
      return
      end
C
      double precision function Dde1i_d(rd,zd)
      implicit double precision (a - z)
C
      Dde1i_d = 0.152d0
C
      return
      end
C
C
      double precision function Dde1o_d(rd,zd)
      implicit double precision (a - z)
C
      Dde1o_d = 0.152d0
C
      return
      end
C
C
      double precision function Dde2i_d(rd,zd)
      implicit double precision (a - z)
C
      Dde2i_d = 0.111d0
C
      return
```

```
      end
C
C
      double precision function Dde2o_d(rd,zd)
      implicit double precision (a - z)
C
      Dde2o_d = 0.152d0
C
      return
      end
C
      double precision function Dhdi_d(rd,zd)
      implicit double precision (a - z)
C
      Dhdi_d = 0.0027d0
C
      return
      end
C
C
      double precision function Dhdo_d(rd,zd)
      implicit double precision (a - z)
C
      Dhdo_d = 0.0027d0
C
      return
      end
C
C Dim'less test function c(xi,zeta)
C
      double precision function c(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout
C
      common /mesh_i/ xi_in, rd_max, iin, iout
C
      rd = xi*(rd_max-fd_outer(zeta)) + fd_outer(zeta)
      zd = zeta
      c = c_d(rd,zd)
C
      return
      end
C
C
      double precision function c_d(rd,zd)
      implicit double precision (a - z)
      integer iin, iout
C
      common /mesh_i/ xi_in, rd_max, iin, iout
C
      c_d = 0.5d0*((rd-fd_outer(zd))/(rd_max-fd_outer(zd)))
     1    - 1.0d0*zd + 1.0d0
C
      return
      end
C
C
```

```
C Derivatives dxi/dzeta
C
      double precision function dxidzeta(xi,zeta)
C
      implicit double precision (a - z)
      integer iin, iout
C
      common /mesh_i/ xi_in, rd_max, iin, iout
C
      dxidzeta = dfd_outer(zeta)*((xi-1.0d0)
     1         / (rd_max-fd_outer(zeta)))
C
      return
      end
C
C
C Derivatives d2xi/dzeta2
C
C
      double precision function d2xidzeta2(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout
C
      common /mesh_i/ xi_in, rd_max, iin, iout
C
      d2xidzeta2 = ((xi-1.0d0)/(rd_max-fd_outer(zeta)))
     1    * (d2fd_outer(zeta)+((dfd_outer(zeta))**2)
     1    / (rd_max*fd_outer(zeta)))
C
      return
      end
C
C
      double precision function d2xidxidzeta(xi,zeta)
      implicit double precision (a - z)
      integer iin, iout
C
      common /mesh_i/ xi_in, rd_max, iin, iout
C
      d2xidxidzeta = dfd_outer(zeta)
     1             / ((rd_max-fd_outer(zeta))**2)
C
      return
      end
C
C
      double precision function d2fd_outer(zeta)
      implicit double precision (a - z)
C
      common /param/ deltat, deltah, ratek_edi, ratek_edo,
     1       ratek_de1i, ratek_de1o, ratek_de2i, ratek_de2o,
     1       ratek_hdi, ratek_hdo
C
      d2fd_outer = (fd_outer(zeta+deltah)-2.0d0*fd_outer(zeta)
     1            + fd_outer(zeta-deltah)) / deltah**2
C
      return
```

```
      end
C
C
      double precision function dfd_outer(zeta)
      implicit double precision (a - z)
C
      common /param/ deltat, deltah, ratek_edi, ratek_edo,
     1       ratek_de1i, ratek_de1o, ratek_de2i, ratek_de2o,
     1       ratek_hdi, ratek_hdo
C
      dfd_outer = (fd_outer(zeta+deltah)-fd_outer(zeta-deltah))
     1          / (2.0d0*deltah)
C
      return
      end
C
C
C Function fd_outer
C
      double precision function fd_outer(zeta)
      implicit double precision (a - z)
C
      fd_outer = f_or_o(zeta)
C
      return
      end
C
C Cuticle of hair shaft
C
      double precision function fd_cu(zeta)
      implicit double precision (a - z)
C
      fd_cu = f_cu_o(zeta)
C
      return
      end
C
C
        subroutine setup_geom
*setup for follicular model geometry
*
*
*
*Johannes M. Nitsche, sabbatical leave at Procter & Gamble Miami Valley
*Laboratories, fall semester 1998
*
*
*
*terminal hair (normal hair or hair from hairy region of balding
scalp),
*anagen phase
*
*
*
*diam           fully developed hair shaft diameter, given in microns
*length         total length of hair shaft/follicle, given in mm
*
```

```
*all lengths made dimensionless using characteristic length of 100
*microns
*
*
*
*glossary:
*
*dimensions (first letter)
*
*       a       radius
*       z       z-coordinate
*       t       thickness
*       l       length
*       k       decay length for smoothing function
*
*tissue layers or regions (_subscript)
*
*       ge      general
*       hs      hair shaft
*       me      medulla of hair shaft
*       pa      dermal papilla
*       co      cortex of hair shaft
*       cu      cuticle of hair shaft
*       in      infundibulum (sebum-filled gap)
*       ir      inner root sheath
*       ic      cuticle of inner root sheath
*       hu      Huxley's layer of inner root sheath
*       he      Henle's layer of inner root sheath
*       or      outer root sheath
*       ct      dermal sheath ("ct" for "connective tissue")
*       in      infundibulum
*       va      vascularization
*       ex      tissue outside follicle ("ex" for "exterior tissue")
*
*       sc      stratum corneum
*       ed      viable epidermis
*       de      dermis
*       hd      hypodermis
*
*       bulb    hair bulb
*       tot     total (length)
*
*other affixes (_second subscript)
*
*       i       inner surface of tissue layer
*       o       outer surface of tissue layer
*       u       upper surface of tissue layer
*       l       lower surface of tissue layer
*       s       surface
*
*functions (first letter)
*
*       f       radius as a function of z     in cylindrical
coordinates
*       g       radius as a function of theta in spherical
coordinates
*
```

```
*
*
*input file:
*
*       data.geom.txt   diam (in microns), (subcutaneous) length (in
mm)
*
*
*
*output files:
*
*       out.1.geom.txt  listing of geometrical parameters
*
*       out.2.geom.txt  graphics file for cross-sectional view
*
*
*
*main outcomes:
*
*functions
*       f_me_o(z)
*       f_pa_o(z), g_pa_o(theta)
*       f_co_i(z), g_co_i(theta)
*       f_co_o(z), g_co_o(theta)
*       f_cu_i(z), g_cu_i(theta)
*       f_cu_o(z), g_cu_o(theta)
*       f_in_i(z)
*       f_in_o(z)
*       f_ic_i(z), g_ic_i(theta)
*       f_ic_o(z), g_ic_o(theta)
*       f_hu_i(z), g_hu_i(theta)
*       f_hu_o(z), g_hu_o(theta)
*       f_he_i(z), g_he_i(theta)
*       f_he_o(z), g_he_o(theta)
*       f_or_i(z), g_or_i(theta)
*       f_or_o(z), g_or_o(theta)
*       f_ct_i(z), g_ct_i(theta)
*       f_ct_o(z), g_ct_o(theta)
*       f_va_s(z), g_va_s(theta)
*       f_ex_i(z), g_ex_i(theta)
*
*parameters
*       z_ed_l = z_de_u
*       z_in(3)
*       z_hd_u
*       z_pa(0)
*
*
*
*declarations,
etc.....................................................
*
        implicit double precision (a - z)
        parameter (pi = 3.1415926535898d0)
*
*
        dimension a_hs(0:4), z_hs(0:3), k_hs(1:2)
```

```
        dimension a_pa(0:2), z_pa(0:1)
        dimension a_me(0:2), z_me(0:2), k_me(1:2)
        dimension t_in(0:3), z_in(0:3), k_in(1:3)
        dimension t_ic(0:3), z_ic(0:2)
        dimension t_hu(0:3), z_hu(0:2)
        dimension t_he(0:3), z_he(0:2)
        dimension t_or(0:6), z_or(0:5), k_or(1:4)
        dimension t_ct(0:4), z_ct(0:3), k_ct(1:2)
        dimension t_va(0:4), z_va(0:3), k_va(1:2)
*
*
        common / geom_ge / diam, length, theta_bulb, l_tot
        common / geom_hs / a_hs, z_hs, k_hs
        common / geom_pa / a_pa, z_pa
        common / geom_me / a_me, z_me, k_me
        common / geom_cu / t_cu
        common / geom_in / t_in, z_in, k_in
        common / geom_ic / t_ic, z_ic, k_ic
        common / geom_hu / t_hu, z_hu, k_hu
        common / geom_he / t_he, z_he, k_he
        common / geom_or / t_or, z_or, k_or
        common / geom_ct / t_ct, z_ct, k_ct
        common / geom_va / t_va, z_va, k_va, z_va_s
        common / geom_ex / a_ex
        common / geom_sc / z_sc_u, z_sc_l
        common / geom_ed / z_ed_u, z_ed_l
        common / geom_de / z_de_u, z_de_l
        common / geom_hd / z_hd_u
*
*
*
***
*
*hair shaft diameter (in microns) and subcutaneous length (in
mm).......
*
        open (unit = 20, file = 'data.geom.txt')
        read (20, *) diam, length
        close (20)
c
c Added 01.05.05
c
       open (unit = 12, file = 'output.2.geom.txt')
       write (12, 9000)

C
c      do 600, length = 2, 6, 2
c       do 500, diam = 40, 120, 40

C     print*, length, diam
      write (12, 5000) length, diam
*
        a_hs(0) = diam / 2.0d0 / 100.0d0
        l_tot = length * 1000.0d0 / 100.0d0

*
```

```
*dimensions of different tissue layers according to approximate rules
of
*thumb.....................................................................
.
*
*factor for smoothing functions
*
        factor_sw = 0.33d0
*
*hair shaft (outermost surface, i.e., outer surface of hair shaft
*cuticle)
*
        a_hs(1) = a_hs(0)
        a_hs(2) = 1.3d0 * a_hs(0)
        a_hs(3) = 2.0d0 * a_hs(0)
        a_hs(4) = 0.9d0 * a_hs(3)
        z_hs(0) = 0.0d0
        z_hs(1) = -0.5d0 * l_tot
        z_hs(2) = -l_tot + 4.0d0 * a_hs(3)
        z_hs(3) = -l_tot
        k_hs(1) = factor_sw * min(z_hs(0) - z_hs(1), z_hs(1) - z_hs(2))
        k_hs(2) = factor_sw * min(z_hs(1) - z_hs(2), z_hs(2) - z_hs(3))
        theta_bulb = pi / 6.0d0
*
*dermal papilla
*
        a_pa(0) = 0.05d0 * a_hs(3)
        a_pa(1) = 0.5d0 * a_hs(3)
        a_pa(2) = 0.7d0 * a_hs(3)
        z_pa(0) = -l_tot + 1.0d0 * a_hs(3)
        z_pa(1) = -l_tot
*
*medulla
*
        a_me(0) = 3.0d0 / 100.0d0
        a_me(1) = a_me(0)
        a_me(2) = a_pa(0)
        z_me(0) = 0.0d0
        z_me(1) = z_pa(0) + 1.0d0 * a_hs(3)
        z_me(2) = z_pa(0)
        k_me(1) = factor_sw * min(z_me(0) - z_me(1), z_me(1) - z_me(2))
        k_me(2) = factor_sw * min(z_me(1) - z_me(2), z_pa(0) - z_pa(1))
*
*cuticle of hair shaft
*
        t_cu = 3.0d0 / 100.0d0
*
*infundibulum
*
        t_in(0) = 2.0d0 * a_hs(0)
        t_in(1) = 0.3d0 * a_hs(0)
        t_in(2) = 0.3d0 * a_hs(0)
*
        z_in(0) = 0.0d0
        z_in(1) = -4.0d0 * a_hs(0)
        z_in(3) = -1.0d0 * 1000.0d0 / 100.0d0
        z_in(2) = z_in(3) + 4.0 * a_hs(0)
```

```
        k_in(1) = factor_sw * min(z_in(0) - z_in(1), z_in(1) - z_in(2))
        k_in(2) = factor_sw * min(z_in(1) - z_in(2), z_in(2) - z_in(3))
*
*cuticle of inner root sheath
*
        t_ic(0) = 4.0d0 / 100.0d0
        t_ic(1) = t_ic(0)
        t_ic(2) = 2.0d0 / 100.0d0
        t_ic(3) = t_ic(2)
        z_ic(0) = z_in(3)
        z_ic(1) = -l_tot + 4.0d0 * a_hs(3)
        z_ic(2) = -l_tot
        k_ic    = factor_sw * min(z_ic(0) - z_ic(1), z_ic(1) - z_ic(2))
*
*Huxley's layer of inner root sheath
*
        t_hu(0) = 12.0d0 / 100.0d0
        t_hu(1) = t_hu(0)
        t_hu(2) = 6.0d0 / 100.0d0
        t_hu(3) = t_hu(2)
        z_hu(0) = z_in(3)
        z_hu(1) = -l_tot + 4.0d0 * a_hs(3)
        z_hu(2) = -l_tot
        k_hu    = factor_sw * min(z_hu(0) - z_hu(1), z_hu(1) - z_hu(2))
*
*Henle's layer of inner root sheath
*
        t_he(0) = 8.0d0 / 100.0d0
        t_he(1) = t_he(0)
        t_he(2) = 4.0d0 / 100.0d0
        t_he(3) = t_he(2)
        z_he(0) = z_in(3)
        z_he(1) = -l_tot + 4.0d0 * a_hs(3)
        z_he(2) = -l_tot
        k_he    = factor_sw * min(z_he(0) - z_he(1), z_he(1) - z_he(2))
*
*infundibulum (revisited)
*
        t_in(3) = t_ic(0) + t_hu(0) + t_he(0)
        k_in(3) = factor_sw * min(z_in(2) - z_in(3), z_he(0) - z_he(1),
     $          z_hu(0) - z_hu(1), z_ic(0) - z_ic(1))
*
*outer root sheath
*
        t_or(0) = 100.0d0 / 100.0d0
        t_or(1) =  20.0d0 / 100.0d0
        t_or(2) =  20.0d0 / 100.0d0
        t_or(3) =  70.0d0 / 100.0d0
        t_or(4) =  20.0d0 / 100.0d0
        t_or(5) =   6.0d0 / 100.0d0
        t_or(6) =   6.0d0 / 100.0d0
        z_or(0) =   0.0d0
        z_or(1) = -10.0d0 * a_hs(0)
        z_or(2) = -25.0d0 * a_hs(0)
        z_or(3) = -l_tot + 0.33d0 * l_tot
        z_or(4) = -l_tot + 4.0d0 * a_hs(3)
        z_or(5) = -l_tot
```

```
        k_or(1) = factor_sw * min(z_or(0) - z_or(1), z_or(1) - z_or(2))
        k_or(2) = factor_sw * min(z_or(1) - z_or(2), z_or(2) - z_or(3))
        k_or(3) = factor_sw * min(z_or(2) - z_or(3), z_or(3) - z_or(4))
        k_or(4) = factor_sw * min(z_or(3) - z_or(4), z_or(4) - z_or(5))
*
*dermal sheath
*
        t_ct(0) = 10.0d0 / 100.0d0
        t_ct(1) = 10.0d0 / 100.0d0
        t_ct(2) = 20.0d0 / 100.0d0
        t_ct(3) = 20.0d0 / 100.0d0
        t_ct(4) = 2.0d0 * t_ct(3)
        z_ct(0) = 0.0d0
        z_ct(1) = z_in(3)
        z_ct(2) = -l_tot + 0.33d0 * l_tot
        z_ct(3) = -l_tot
        k_ct(1) = factor_sw * min(z_ct(0) - z_ct(1), z_ct(1) - z_ct(2))
        k_ct(2) = factor_sw * min(z_ct(1) - z_ct(2), z_ct(2) - z_ct(3))
*
*vascular surface (if any)
*
        t_va(0) = 0.0d0
        t_va(1) = 0.0d0
        t_va(2) = 0.0d0
        t_va(3) = 0.0d0
        t_va(4) = 0.0d0
        z_va(0) = 0.0d0
        z_va(1) = z_in(3)
        z_va(2) = -l_tot + 0.33d0 * l_tot
        z_va(3) = -l_tot
        k_va(1) = factor_sw * min(z_va(0) - z_va(1), z_va(1) - z_va(2))
        k_va(2) = factor_sw * min(z_va(1) - z_va(2), z_va(2) - z_va(3))
*
*----------
        z_va_s  = -300.0d0 / 100.0d0
*----------
*
*stratum corneum
*
        z_sc_u = 0.0d0
        z_sc_l = 0.0d0
*
*viable epidermis
*
        z_ed_u = 0.0d0
        z_ed_l = -100.0d0 / 100.0d0
C
C Changed by YD, 0824/05
C        z_ed_l = -40.0d0 / 100.0d0
C
*
*dermis
*
        z_de_u = z_ed_l
        z_de_l = z_de_u - 2000.0d0 / 100.0d0
C
C Changed by YD, 08/24/05
```

```
C        z_de_l = z_de_u - 300.0d0 / 100.0d0
C
C        z_de_l = z_de_u - 130.0d0 / 100.0d0
C
*
*hypodermis
*
        z_hd_u = z_de_l
*
*write geometrical
parameters.....................................
*
        open (unit = 11, file = 'output.1.geom.txt')
*
        write (11, 7900) 'diam, length'
        write (11, 8000) diam, length
*
        write (11, 7900) 'theta_bulb, l_tot'
        write (11, 8000) theta_bulb, l_tot
*
        write (11, 7900) 'factor_sw'
        write (11, 8000) factor_sw
*
        write (11, 7900) 'hs'
        write (11, 8000) a_hs(0), a_hs(1), a_hs(2), a_hs(3), a_hs(4)
        write (11, 8000) z_hs(0), z_hs(1), z_hs(2), z_hs(3)
        write (11, 8100)          k_hs(1), k_hs(2)
*
        write (11, 7900) 'me'
        write (11, 8000) a_me(0), a_me(1), a_me(2)
        write (11, 8000) z_me(0), z_me(1), z_me(2)
        write (11, 8100)          k_me(1), k_me(2)
*
        write (11, 7900) 'pa'
        write (11, 8000) a_pa(0), a_pa(1), a_pa(2)
        write (11, 8000) z_pa(0), z_pa(1)
*
        write (11, 7900) 'cu'
        write (11, 8000) t_cu
*
        write (11, 7900) 'in'
        write (11, 8000) t_in(0), t_in(1), t_in(2), t_in(3)
        write (11, 8000) z_in(0), z_in(1), z_in(2), z_in(3)
        write (11, 8100)          k_in(1), k_in(2), k_in(3)
*
        write (11, 7900) 'ic'
        write (11, 8000) t_ic(0), t_ic(1), t_ic(2), t_ic(3)
        write (11, 8000) z_ic(0), z_ic(1), z_ic(2)
        write (11, 8100)          k_ic
*
        write (11, 7900) 'hu'
        write (11, 8000) t_hu(0), t_hu(1), t_hu(2), t_hu(3)
        write (11, 8000) z_hu(0), z_hu(1), z_hu(2)
        write (11, 8100)          k_hu
*
        write (11, 7900) 'he'
        write (11, 8000) t_he(0), t_he(1), t_he(2), t_he(3)
```

```
        write (11, 8000) z_he(0), z_he(1), z_he(2)
        write (11, 8100)          k_he
*
        write (11, 7900) 'or'
        write (11, 8000) t_or(0), t_or(1), t_or(2), t_or(3), t_or(4),
     $          t_or(5), t_or(6)
        write (11, 8000) z_or(0), z_or(1), z_or(2), z_or(3), z_or(4),
     $          z_or(5)
        write (11, 8100)          k_or(1), k_or(2), k_or(3), k_or(4)
*
        write (11, 7900) 'ct'
        write (11, 8000) t_ct(0), t_ct(1), t_ct(2), t_ct(3), t_ct(4)
        write (11, 8000) z_ct(0), z_ct(1), z_ct(2), z_ct(3)
        write (11, 8100)          k_ct(1), k_ct(2)
*
        write (11, 7900) 'va'
        write (11, 8000) t_va(0), t_va(1), t_va(2), t_va(3), t_va(4)
        write (11, 8000) z_va(0), z_va(1), z_va(2), z_va(3)
        write (11, 8100)          k_va(1), k_va(2)
*
        write (11, 7900) 'z_va_s'
        write (11, 8000) z_va_s
        write (11, 7900) 'z_ed_u, z_ed_l'
        write (11, 8000) z_ed_u, z_ed_l
        write (11, 7900) 'z_de_u, z_de_l'
        write (11, 8000) z_de_u, z_de_l
        write (11, 7900) 'z_hd_u'
        write (11, 8000) z_hd_u
*
        close (11)
*
*prepare graphics for cross-sectional
view.............................
*
C
C
* Modified 01/05/05

*        open (unit = 12, file = 'output.2.geom.txt')
*        write (12, 9000)


*** Added by YD 09/06/05
***
*
*
*cortex of hair shaft
*
        write (12, 9100)
        step = 1.1d0 * l_tot / 1000.0d0
        do 1000, z = -l_tot, 0.1d0 * l_tot + 0.5d0 * step, step
                write (12, 9200) f_co_i(z), z
1000            continue
C
C        do 1000, j = 0, jed + jde1 + jde2 + jhd
C                 zeta = zda(j)
C            write(12, 9200) f_co_i(zeta), zeta
```

```
C1000    continue
C
        write (12, 9300)
*
C
        write (12, 9100)
        step = (pi - theta_bulb - 0.5d0 * pi) / 60.0d0
        do 1002, theta = 0.5d0 * pi, pi - theta_bulb + 0.5d0 * step,
     $          step
                write (12, 9200) g_co_i(theta) * sin(theta),
     $                  -l_tot + g_co_i(theta) * cos(theta)
1002            continue
        write (12, 9300)
*
        write (12, 9100)
        step = 1.1d0 * l_tot / 1000.0d0
        do 1004, z = -l_tot, 0.1d0 * l_tot + 0.5d0 * step, step
                write (12, 9200) f_co_o(z), z
1004            continue
C
C
C        do 1004, j = 0, jed + jde1 + jde2 + jhd
C        zeta = zda(j)
C           write(12, 9200) f_co_o(zeta), zeta
C1004    continue
C
C
        write (12, 9300)
*
        write (12, 9100)
        step = (pi - theta_bulb - 0.5d0 * pi) / 60.0d0
        do 1006, theta = 0.5d0 * pi, pi - theta_bulb + 0.5d0 * step,
     $          step
                write (12, 9200) g_co_o(theta) * sin(theta),
     $                  -l_tot + g_co_o(theta) * cos(theta)
1006            continue
        write (12, 9300)
*
        write (12, 9100)
        theta = pi - theta_bulb
        r_i = g_co_i(theta)
        r_o = g_co_o(theta)
        do 1008, tmp = 0.0d0, 1.001d0, 1.0d0
                r = r_i + tmp * (r_o - r_i)
                write (12, 9200) r * sin(theta),
     $                  -l_tot + r * cos(theta)
1008            continue
        write (12, 9300)
*
*cuticle of hair shaft
*
        write (12, 9100)
        step = 1.1d0 * l_tot / 1000.0d0
        do 1100, z = -l_tot, 0.1d0 * l_tot + 0.5d0 * step, step
                write (12, 9200) f_cu_i(z), z
1100            continue
C
```

```
C        do 1100, j = 0, jed + jde1 + jde2 + jhd
C                zeta = zda(j)
C            write(12, 9200) f_cu_i(zeta), zeta
C1100    continue

C
        write (12, 9300)
*
        write (12, 9100)
        step = (pi - theta_bulb - 0.5d0 * pi) / 60.0d0
        do 1102, theta = 0.5d0 * pi, pi - theta_bulb + 0.5d0 * step,
     $          step
                write (12, 9200) g_cu_i(theta) * sin(theta),
     $                  -l_tot + g_cu_i(theta) * cos(theta)
1102            continue
        write (12, 9300)
*
        write (12, 9100)
C
C *********************
C Added by YD 06/06/06
        write (12, 9116)
C *********************
C
C
        step = 1.1d0 * l_tot / 1000.0d0
        do 1104, z = -l_tot, 0.1d0 * l_tot + 0.5d0 * step, step
                write (12, 9200) f_cu_o(z), z
1104            continue
C
C        do 1104, j = 0, jed + jde1 + jde2 + jhd
C                zeta = zda(j)
C            write(12, 9200) f_cu_o(zeta), zeta
C1104         continue
C
C
        write (12, 9300)
*
        write (12, 9100)
C
C *********************
C Added by YD 06/06/06
        write (12, 9117)
C *********************
C
        step = (pi - theta_bulb - 0.5d0 * pi) / 60.0d0
        do 1106, theta = 0.5d0 * pi, pi - theta_bulb + 0.5d0 * step,
     $          step
                write (12, 9200) g_cu_o(theta) * sin(theta),
     $                  -l_tot + g_cu_o(theta) * cos(theta)
1106            continue
        write (12, 9300)
*
        write (12, 9100)
        theta = pi - theta_bulb
        r_i = g_cu_i(theta)
        r_o = g_cu_o(theta)
```

```
        do 1108, tmp = 0.0d0, 1.001d0, 1.0d0
                r = r_i + tmp * (r_o - r_i)
                write (12, 9200) r * sin(theta),
     $          -l_tot + r * cos(theta)
1108            continue
        write (12, 9300)
*
*cuticle of inner root sheath
*
        write (12, 9100)
        step = (z_in(3) + l_tot) / 1000.0d0
        do 1200, z = -l_tot, z_in(3) + 0.5d0 * step, step
                write (12, 9200) f_ic_i(z), z
1200            continue
C
C        do 1200, j = 0, jed + jde1 + jde2 + jhd
C                  zeta = zda(j)
C            write(12, 9200) f_ic_i(zeta), zeta
C1200    continue
C
C
        write (12, 9300)
*
        write (12, 9100)
        step = (pi - theta_bulb - 0.5d0 * pi) / 60.0d0
        do 1202, theta = 0.5d0 * pi, pi - theta_bulb + 0.5d0 * step,
     $          step
                write (12, 9200) g_ic_i(theta) * sin(theta),
     $                  -l_tot + g_ic_i(theta) * cos(theta)
1202            continue
        write (12, 9300)
*
        write (12, 9100)
* Added 01.11.05
        write (12, 9111)
*
        step = (z_in(3) + l_tot) / 1000.0d0
        do 1204, z = -l_tot, z_in(3) + 0.5d0 * step, step
                write (12, 9200) f_ic_o(z), z
1204            continue
C
C        do 1204, j = 0, jed + jde1 + jde2 + jhd
C                  zeta = zda(j)
C            write(12, 9200) f_ic_o(zeta), zeta
C1204    continue
C
C
        write (12, 9300)
*
        write (12, 9100)
* Added 01.11.05
        write (12, 9112)
*
        step = (pi - theta_bulb - 0.5d0 * pi) / 60.0d0
        do 1206, theta = 0.5d0 * pi, pi - theta_bulb + 0.5d0 * step,
     $          step
                write (12, 9200) g_ic_o(theta) * sin(theta),
```

```
     $                  -l_tot + g_ic_o(theta) * cos(theta)
1206            continue
        write (12, 9300)
*
        write (12, 9100)
        theta = pi - theta_bulb
        r_i = g_ic_i(theta)
        r_o = g_ic_o(theta)
        do 1208, tmp = 0.0d0, 1.001d0, 1.0d0
                r = r_i + tmp * (r_o - r_i)
                write (12, 9200) r * sin(theta),
     $          -l_tot + r * cos(theta)
1208            continue
        write (12, 9300)
*
        write (12, 9100)
        z = z_in(3)
        r_i = f_ic_i(z)
        r_o = f_ic_o(z)
        do 1209, tmp = 0.0d0, 1.001d0, 1.0d0
                r = r_i + tmp * (r_o - r_i)
                write (12, 9200) r, z
1209            continue
        write (12, 9300)
*
*Huxley's layer of inner root sheath
*
        write (12, 9100)
        step = (z_in(3) + l_tot) / 1000.0d0
        do 1300, z = -l_tot, z_in(3) + 0.5d0 * step, step
                write (12, 9200) f_hu_i(z), z
1300            continue
C
C        do 1300, j = 0, jed + jde1 + jde2 + jhd
C                  zeta = zda(j)
C            write(12, 9200) f_hu_i(zeta), zeta
C1300    continue
C
C
        write (12, 9300)
*
        write (12, 9100)
        step = (pi - theta_bulb - 0.5d0 * pi) / 60.0d0
        do 1302, theta = 0.5d0 * pi, pi - theta_bulb + 0.5d0 * step,
     $          step
                write (12, 9200) g_hu_i(theta) * sin(theta),
     $                  -l_tot + g_hu_i(theta) * cos(theta)
1302            continue
        write (12, 9300)
*
        write (12, 9100)
* Added 01.10.05
      write (12, 9109)
*
        step = (z_in(3) + l_tot) / 1000.0d0
        do 1304, z = -l_tot, z_in(3) + 0.5d0 * step, step
                write (12, 9200) f_hu_o(z), z
```

```
1304            continue
C
C        do 1304, j = 0, jed + jde1 + jde2 + jhd
C                 zeta = zda(j)
C            write(12,9200) f_hu_o(zeta), zeta
C1304    continue
C
C
        write (12, 9300)
*
        write (12, 9100)
* Added 01.10.05
      write (12, 9110)
*
        step = (pi - theta_bulb - 0.5d0 * pi) / 60.0d0
        do 1306, theta = 0.5d0 * pi, pi - theta_bulb + 0.5d0 * step,
     $          step
                write (12, 9200) g_hu_o(theta) * sin(theta),
     $          -l_tot + g_hu_o(theta) * cos(theta)
1306            continue
        write (12, 9300)
*
        write (12, 9100)
        theta = pi - theta_bulb
        r_i = g_hu_i(theta)
        r_o = g_hu_o(theta)
        do 1308, tmp = 0.0d0, 1.001d0, 1.0d0
                r = r_i + tmp * (r_o - r_i)
                write (12, 9200) r * sin(theta),
     $          -l_tot + r * cos(theta)
1308            continue
        write (12, 9300)
*
        write (12, 9100)
        z = z_in(3)
        r_i = f_hu_i(z)
        r_o = f_hu_o(z)
        do 1309, tmp = 0.0d0, 1.001d0, 1.0d0
                r = r_i + tmp * (r_o - r_i)
                write (12, 9200) r, z
1309            continue
        write (12, 9300)
*
*Henle's layer of inner root sheath
*
        write (12, 9100)
* Added 01.11.5
      write (12, 9115)
*
        step = (z_in(3) + l_tot) / 1000.0d0
        do 1400, z = -l_tot, z_in(3) + 0.5d0 * step, step
                write (12, 9200) f_he_i(z), z
1400            continue
C
C        do 1400, j = 0, jed + jde1 + jde2 + jhd
C                 zeta = zda(j)
C            write(12, 9200) f_he_i(zeta), zeta
```

```
C1400    continue
C
C
        write (12, 9300)
*
        write (12, 9100)
        step = (pi - theta_bulb - 0.5d0 * pi) / 60.0d0
        do 1402, theta = 0.5d0 * pi, pi - theta_bulb + 0.5d0 * step,
     $          step
                write (12, 9200) g_he_i(theta) * sin(theta),
     $                  -l_tot + g_he_i(theta) * cos(theta)
1402            continue
        write (12, 9300)
*
        write (12, 9100)
*
* Added 01.10.05
      write (12, 9107)
*
        step = (z_in(3) + l_tot) / 1000.0d0
        do 1404, z = -l_tot, z_in(3) + 0.5d0 * step, step
                write (12, 9200) f_he_o(z), z
1404            continue
C
C        do 1404, j = 0, jed + jde1 + jde2 + jhd
C                  zeta = zda(j)
C             write(12, 9200) f_he_o(zeta), zeta
C1404    continue
C
C
        write (12, 9300)
*
        write (12, 9100)
* Added 01.10.05
      write (12, 9108)
*
        step = (pi - theta_bulb - 0.5d0 * pi) / 60.0d0
        do 1406, theta = 0.5d0 * pi, pi - theta_bulb + 0.5d0 * step,
     $          step
                write (12, 9200) g_he_o(theta) * sin(theta),
     $                  -l_tot + g_he_o(theta) * cos(theta)
1406            continue
        write (12, 9300)
*
        write (12, 9100)
        theta = pi - theta_bulb
        r_i = g_he_i(theta)
        r_o = g_he_o(theta)
        do 1408, tmp = 0.0d0, 1.001d0, 1.0d0
                r = r_i + tmp * (r_o - r_i)
                write (12, 9200) r * sin(theta),
     $          -l_tot + r * cos(theta)
1408            continue
        write (12, 9300)
*
        write (12, 9100)
        z = z_in(3)
```

```
        r_i = f_he_i(z)
        r_o = f_he_o(z)
        do 1409, tmp = 0.0d0, 1.001d0, 1.0d0
                r = r_i + tmp * (r_o - r_i)
                write (12, 9200) r, z
1409            continue
        write (12, 9300)
*
*outer root sheath
*
        write (12, 9100)
* Added 01.10.05
        write (12, 9105)
*
        step = l_tot / 1000.0d0
        do 1500, z = -l_tot, 0.0d0 + 0.5d0 * step, step
                write (12, 9200) f_or_i(z), z
1500            continue
C
C        do 1500, j = 0, jed + jde1 + jde2 + jhd
C                 zeta = zda(j)
C            write (12, 9200) f_or_i(zeta), zeta
C1500    continue
C
C        do 1501, j = 0, jed + jde1 + jde2 + jhd
C           zeta = zda(j)
C           write (12, 9200) f_or(zeta), zeta
C1501    continue
***
C
C
        write (12, 9300)
*
        write (12, 9100)
* Added 01.10.05
      write (12, 9106)
*
        step = (pi - theta_bulb - 0.5d0 * pi) / 60.0d0
        do 1502, theta = 0.5d0 * pi, pi - theta_bulb + 0.5d0 * step,
     $          step
                write (12, 9200) g_or_i(theta) * sin(theta),
     $                  -l_tot + g_or_i(theta) * cos(theta)
1502            continue
        write (12, 9300)
*
**********08.11.2004
        write (12, 9101)
**********08.11.2004
        step = (z_ed_l + l_tot) / 1000.0d0
        do 1504, z = -l_tot, z_ed_l + 0.5d0 * step, step
                write (12, 9200) f_or_o(z), z
1504    continue
C
C        do 1504, j = 0, jed + jde1 + jde2 + jhd
C                 zeta = zda(j)
C                 f_bdry(j) = f_or_o(zeta)
C                 print*, j, f_bdry(j)
```

```
C1504    continue
C
        write (12, 9300)
*
********** Added 11.22.04
C     open (unit=13, file = 'zetacoord.txt')
C     do 1505, j = 0, 136
C           read(13,*) zda(j)
C1505       continue
*
C     open (unit=14, file = 'forovalues.txt')
C     do 1802, j = 0, jed + jde1 + jde2 + jhd
C           write(14,9500) f_or_o(zda(j)), zda(j)
C1802       continue
**********
*
**********08.11.2004
        write (12, 9102)
**********08.11.2004
        step = (pi - theta_bulb - 0.5d0 * pi) / 60.0d0
        do 1506, theta = 0.5d0 * pi, pi - theta_bulb + 0.5d0 * step,
     $          step
                write (12, 9200) g_or_o(theta) * sin(theta),
     $                  -l_tot + g_or_o(theta) * cos(theta)
1506            continue
        write (12, 9300)
*
        write (12, 9100)
        theta = pi - theta_bulb
        r_i = g_or_i(theta)
        r_o = g_or_o(theta)
        do 1507, tmp = 0.0d0, 1.001d0, 1.0d0
                r = r_i + tmp * (r_o - r_i)
                write (12, 9200) r * sin(theta), -l_tot + r *
cos(theta)
1507            continue
        write (12, 9300)
*
        write (12, 9100)
        z = z_ed_u
        r_i = f_or_i(z)
        r_o = l_tot
        do 1508, tmp = 0.0d0, 1.001d0, 0.1d0
                r = r_i + tmp * (r_o - r_i)
                write (12, 9200) r, z
1508            continue
        write (12, 9300)
*
        write (12, 9100)
        z = z_ed_l
        r_i = f_or_o(z)
        r_o = l_tot
        do 1509, tmp = 0.0d0, 1.001d0, 0.1d0
                r = r_i + tmp * (r_o - r_i)
                write (12, 9200) r, z
1509            continue
        write (12, 9300)
```

```
*
*dermal sheath, dermal papilla and medulla
*
        write (12, 9100)
        step = (z_ct(1) + l_tot) / 1000.0d0
        do 1600, z = -l_tot, z_ct(1) + 0.5d0 * step, step
                write (12, 9200) f_ct_i(z), z
1600            continue
C
C        do 1600, j = 0, jed + jde1 + jde2 + jhd
C                 zeta = zda(j)
C            write(12, 9200) f_ct_i(zeta), zeta
C1600    continue
C
C
        write (12, 9300)
*
        write (12, 9100)
        step = (pi - theta_bulb - 0.5d0 * pi) / 60.0d0
        do 1601, theta = 0.5d0 * pi, pi - theta_bulb + 0.5d0 * step,
     $          step
                write (12, 9200) g_ct_i(theta) * sin(theta),
     $                  -l_tot + g_ct_i(theta) * cos(theta)
1601            continue
        write (12, 9300)
*
**********08.11.2004
        write (12, 9103)
**********08.11.2004
*
* Added 01.11.05
      write (12, 9113)
*
        step = (z_ct(1) + l_tot) / 1000.0d0
        do 1602, z = -l_tot, z_ct(1) + 0.5d0 * step, step
                write (12, 9200) f_ct_o(z), z
1602            continue
C
C        do 1602, j = 0, jed + jde1 + jde2 + jhd
C                 zeta = zda(j)
C            write(12, 9200) f_ct_o(zeta), zeta
C1602    continue
C
        write (12, 9300)
*
**********08.11.2004
        write (12, 9104)
**********08.11.2004
*
*     Added 01.11.05
      write (12, 9114)
*
        step = (pi - 0.5d0 * pi) / 60.0d0
        do 1603, theta = 0.5d0 * pi, pi + 0.5d0 * step, step
                write (12, 9200) g_ct_o(theta) * sin(theta),
     $          -l_tot + g_ct_o(theta) * cos(theta)
1603            continue
```

```
        write (12, 9300)
*
        write (12, 9100)
        z = z_ct(1)
        r_i = f_ct_i(z)
        r_o = f_ct_o(z)
        do 1604, tmp = 0.0d0, 1.001d0, 1.0d0
                r = r_i + tmp * (r_o - r_i)
                write (12, 9200) r, z
1604            continue
        write (12, 9300)
*
        write (12, 9100)
        step = 1.1d0 * l_tot / 1000.0d0
        do 1605, z = -l_tot, 0.1d0 * l_tot + 0.5d0 * step, step
                write (12, 9200) f_co_i(z), z
1605            continue
C
C        do 1605, j = 0, jed + jde1 + jde2 + jhd
C                  zeta = zda(j)
C            write(12, 9200) f_co_i(zeta), zeta
C1605    continue
C
        write (12, 9300)
*
        write (12, 9100)
        step = (pi - theta_bulb - 0.5d0 * pi) / 60.0d0
        do 1606, theta = 0.5d0 * pi, pi - theta_bulb + 0.5d0 * step,
     $          step
                write (12, 9200) g_co_i(theta) * sin(theta),
     $                   -l_tot + g_co_i(theta) * cos(theta)
1606            continue
        write (12, 9300)
*
        write (12, 9100)
        theta = pi - theta_bulb
        r_i = g_co_i(theta)
        r_o = g_ct_i(theta)
        do 1607, tmp = 0.0d0, 1.001d0, 1.0d0
                r = r_i + tmp * (r_o - r_i)
                write (12, 9200) r * sin(theta), -l_tot + r *
cos(theta)
1607            continue
        write (12, 9300)
*
*vascular surface
*
        write (12, 9100)
        step = (z_va_s + l_tot) / 1000.0d0
        do 1700, z = -l_tot, z_va_s + 0.5d0 * step, step
                write (12, 9200) f_va_s(z), z
1700            continue
C
C        do 1700, j = 0, jed + jde1 + jde2 + jhd
C                  zeta = zda(j)
C            write(12, 9200) f_va_s(zeta), zeta
C1700    continue
```

```
C
        write (12, 9300)
*
        write (12, 9100)
        z = z_va_s
        r_i = f_va_s(z)
        r_o = l_tot
        do 1702, tmp = 0.0d0, 1.001d0, 0.1d0
                r = r_i + tmp * (r_o - r_i)
                write (12, 9200) r, z
1702            continue
        write (12, 9300)
*
*lower boundary of dermis
*
        write (12, 9100)
        z = z_de_l
        r_i = f_ct_o(z)
        r_o = l_tot
        do 1800, tmp = 0.0d0, 1.001d0, 0.1d0
                r = r_i + tmp * (r_o - r_i)
                write (12, 9200) r, z
1800            continue
        write (12, 9300)
*
        write (12, 9400)
        close (12)
C
C
C
c500    continue
c600   continue


*
*formats.....................................................
.
*
* Format 5000 added 01.05.05
*
5000  format (/, 'length=', d23.16, 3x, 'diam=', d23.16)
*
7900    format (a)
8000    format (f9.4,2x,f9.4,2x,f9.4,2x,f9.4,2x,f9.4,2x,f9.4,2x,f9.4)
8100    format (    11x,f9.4,2x,f9.4,2x,f9.4,2x,f9.4)
*
9000    format (' '/' ')
9100    format ('solid')
**********08.11.2004
9101    format ('f_or_o')
9102    format ('g_or_o')
9103    format ('f_ct_o')
9104    format ('g_ct_o')
9105  format ('f_or_i')
9106    format ('g_or_i')
9107  format ('f_he_o')
9108  format ('g_he_o')
```

```
9109  format ('f_hu_o')
9110  format ('g_hu_o')
9111  format ('f_ic_o')
9112  format ('g_ic_o')
9113  format ('f_ct_o')
9114  format ('g_ct_o')
9115  format ('f_he_i')
9116    format ('f_cu_o')
9117    format ('g_cu_o')
**********08.11.2004
9200    format (d21.14,3x,d21.14)
9300    format ('1.0d32 0.0d0')
9400    format ('stop')
********** Added 11.22.2004
9500  format (d23.16,3x,d23.16)
********** Added by YD 09/06/0
9900    format (i3,3x,d23.16)
**********
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function f_hs(z)
*hair shaft, outermost radius (or cuticle of hair shaft, outer radius)
*cylindrical coordinates
*
*declarations,
etc.................................................
*
        implicit double precision (a - z)
        dimension a_hs(0:4), z_hs(0:3), k_hs(1:2)
        common / geom_hs / a_hs, z_hs, k_hs
*
*definition.................................................
.
*
        f_hs_1 = a_hs(0) + (a_hs(1) - a_hs(0)) / (z_hs(1) - z_hs(0))
     $          * (z - z_hs(0))
        f_hs_2 = a_hs(1) + (a_hs(2) - a_hs(1)) / (z_hs(2) - z_hs(1))
     $          * (z - z_hs(1))
        f_hs_3 = a_hs(2) + (a_hs(3) - a_hs(2)) / (z_hs(3) - z_hs(2))
     $          * (z - z_hs(2))
        f_hs =    f_hs_1        * (0.5d0 + 0.5d0 * tanh((z - z_hs(1))
     $                                             / k_hs(1)))
     $          + f_hs_2        * (0.5d0 - 0.5d0 * tanh((z - z_hs(1))
     $                                             / k_hs(1)))
     $                          * (0.5d0 + 0.5d0 * tanh((z - z_hs(2))
     $                                             / k_hs(2)))
     $          + f_hs_3        * (0.5d0 - 0.5d0 * tanh((z - z_hs(2))
     $                                             / k_hs(2)))
*
        return
        end
```

```
*
*
*
*----*----==========---------==========---------==========----------
==
        double precision function g_hs(theta)
*hair shaft, outermost radius (or cuticle of hair shaft, outer radius)
*spherical coordinates
*
*declarations,
etc.....................................................
*
        implicit double precision (a - z)
        parameter (pi = 3.1415926535898d0)
        dimension a_hs(0:4), z_hs(0:3), k_hs(1:2)
        common / geom_ge / diam, length, theta_bulb, l_tot
        common / geom_hs / a_hs, z_hs, k_hs
*
*definition.............................................................
.
*
        j_hs = f_hs(-l_tot)
        g_hs = j_hs  + (a_hs(4) - j_hs)
     $          / (cos(pi - theta_bulb))**2
     $          * (cos(theta          ))**2
*
        return
        end
*
*
*
*----*----==========---------==========---------==========----------
==
        double precision function f_cu_i(z)
*cuticle of hair shaft, inner radius
*cylindrical coordinates
*
*declarations,
etc.....................................................
*
        implicit double precision (a - z)
        common / geom_cu / t_cu
*
*
        f_cu_i  = f_hs(z) - t_cu
*
        return
        end
*
*
*
*----*----==========---------==========---------==========----------
==
        double precision function g_cu_i(theta)
*cuticle of hair shaft, inner radius
*spherical coordinates
*
```

```
*declarations,
etc.....................................................
*
        implicit double precision (a - z)
        common / geom_cu / t_cu
*
        g_cu_i = g_hs(theta) - t_cu
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function f_cu_o(z)
*cuticle of hair shaft, outer radius
*cylindrical coordinates
*
        implicit double precision (a - z)
*
        f_cu_o  = f_hs(z)
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function g_cu_o(theta)
*cuticle of hair shaft, outer radius
*spherical coordinates
*
        implicit double precision (a - z)
*
        g_cu_o = g_hs(theta)
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function f_in_i(z)
*infundibulum (sebum-filled gap), inner radius
*cylindrical coordinates
*
        implicit double precision (a - z)
*
        f_in_i = f_cu_o(z)
*
        return
        end
*
*
```

```
*
*----*----==========---------==========---------==========---------
==
        double precision function f_co_i(z)
*cortex of hair shaft, inner radius
*cylindrical coordinates
*
*declarations,
etc.....................................................
*
        implicit double precision (a - z)
        dimension a_pa(0:2), z_pa(0:1)
        dimension a_me(0:2), z_me(0:2), k_me(1:2)
*
        common / geom_pa / a_pa, z_pa
        common / geom_me / a_me, z_me, k_me
*
*definition.............................................................
.
*
        f_me_1 = a_me(0) + (a_me(1) - a_me(0)) / (z_me(1) - z_me(0))
     $          * (z - z_me(0))
        f_me_2 = a_me(1) + (a_me(2) - a_me(1)) / (z_me(2) - z_me(1))
     $          * (z - z_me(1))
        f_pa_1 = a_pa(0) + (a_pa(1) - a_pa(0)) / (z_pa(1) - z_pa(0))
     $          * (z - z_pa(0))
        f_co_i =  f_me_1        * (0.5d0 + 0.5d0 * tanh((z - z_me(1))
     $                                                 / k_me(1)))
     $          + f_me_2        * (0.5d0 - 0.5d0 * tanh((z - z_me(1))
     $                                                 / k_me(1)))
     $                          * (0.5d0 + 0.5d0 * tanh((z - z_me(2))
     $                                                 / k_me(2)))
     $          + f_pa_1        * (0.5d0 - 0.5d0 * tanh((z - z_me(2))
     $                                                 / k_me(2)))
*
        return
        end
*
*
*
*----*----==========---------==========---------==========---------
==
        double precision function g_co_i(theta)
*cortex of hair shaft, inner radius
*spherical coordinates
*
*declarations,
etc.....................................................
*
        implicit double precision (a - z)
        parameter (pi = 3.1415926535898d0)
        dimension a_pa(0:2), z_pa(0:1)
        common / geom_ge / diam, length, theta_bulb, l_tot
        common / geom_pa / a_pa, z_pa
*
*definition.............................................................
.
```

```
*
        j_co_i = f_co_i(-l_tot)
        g_co_i = j_co_i + (a_pa(2) - j_co_i)
     $          / (cos(pi - theta_bulb))**2
     $          * (cos(theta           ))**2
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function f_pa_o(z)
*dermal papilla, (outer) radius
*cylindrical coordinates
*
        implicit double precision (a - z)
*
        f_pa_o = f_co_i(z)
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function g_pa_o(theta)
*dermal papilla, (outer) radius
*spherical coordinates
*
        implicit double precision (a - z)
*
        g_pa_o = g_co_i(theta)
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function f_me_o(z)
*medulla of hair shaft, (outer) radius
*cylindrical coordinates
*
        implicit double precision (a - z)
*
        f_me_o = f_co_i(z)
*
        return
        end
*
*
*
```

```
*----*----==========---------==========---------=========----------
==
        double precision function f_co_o(z)
*cortex of hair shaft, outer radius
*cylindrical coordinates
*
        implicit double precision (a - z)
*
        f_co_o = f_cu_i(z)
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function g_co_o(theta)
*cortex of hair shaft, outer radius
*spherical coordinates
*
        implicit double precision (a - z)
*
        g_co_o = g_cu_i(theta)
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function f_or_i(z)
*outer root sheath, inner radius
*cylindrical coordinates
*
*declarations,
etc.....................................................
*
        implicit double precision (a - z)
*
        dimension t_in(0:3), z_in(0:3), k_in(1:3)
        dimension t_ic(0:3), z_ic(0:2)
        dimension t_hu(0:3), z_hu(0:2)
        dimension t_he(0:3), z_he(0:2)
        common / geom_in / t_in, z_in, k_in
        common / geom_ic / t_ic, z_ic, k_ic
        common / geom_hu / t_hu, z_hu, k_hu
        common / geom_he / t_he, z_he, k_he
*
*definition.............................................................
.
*
*infundibulum, thickness
*
        f_in_1 = t_in(0) + (t_in(1) - t_in(0)) / (z_in(1) - z_in(0))
     $          * (z - z_in(0))
```

```
         f_in_2 = t_in(1) + (t_in(2) - t_in(1)) / (z_in(2) - z_in(1))
     $           * (z - z_in(1))
         f_in_3 = t_in(2) + (t_in(3) - t_in(2)) / (z_in(3) - z_in(2))
     $           * (z - z_in(2))
*
*cuticle of inner root sheath, thickness
*
         f_ic_1 = t_ic(0) + (t_ic(1) - t_ic(0)) / (z_ic(1) - z_ic(0))
     $           * (z - z_ic(0))
         f_ic_2 = t_ic(1) + (t_ic(2) - t_ic(1)) / (z_ic(2) - z_ic(1))
     $           * (z - z_ic(1))
*
*Huxley's layer of inner root sheath, thickness
*
         f_hu_1 = t_hu(0) + (t_hu(1) - t_hu(0)) / (z_hu(1) - z_hu(0))
     $           * (z - z_hu(0))
         f_hu_2 = t_hu(1) + (t_hu(2) - t_hu(1)) / (z_hu(2) - z_hu(1))
     $           * (z - z_hu(1))
*
*Henle's layer of inner root sheath, thickness
*
         f_he_1 = t_he(0) + (t_he(1) - t_he(0)) / (z_he(1) - z_he(0))
     $           * (z - z_he(0))
         f_he_2 = t_he(1) + (t_he(2) - t_he(1)) / (z_he(2) - z_he(1))
     $           * (z - z_he(1))
*
*outer root sheath, inner surface
*
         f_or_i = f_hs(z)
     $           + f_in_1        * (0.5d0 + 0.5d0 * tanh((z - z_in(1))
     $                                                / k_in(1)))
     $           + f_in_2        * (0.5d0 - 0.5d0 * tanh((z - z_in(1))
     $                                                / k_in(1)))
     $                           * (0.5d0 + 0.5d0 * tanh((z - z_in(2))
     $                                                / k_in(2)))
     $           + f_in_3        * (0.5d0 - 0.5d0 * tanh((z - z_in(2))
     $                                                / k_in(2)))
     $                           * (0.5d0 + 0.5d0 * tanh((z - z_in(3))
     $                                                / k_in(3)))
     $           + f_ic_1        * (0.5d0 - 0.5d0 * tanh((z - z_in(3))
     $                                                / k_in(3)))
     $                           * (0.5d0 + 0.5d0 * tanh((z - z_ic(1))
     $                                                / k_ic   ))
     $           + f_ic_2        * (0.5d0 - 0.5d0 * tanh((z - z_ic(1))
     $                                                / k_ic   ))
     $           + f_hu_1        * (0.5d0 - 0.5d0 * tanh((z - z_in(3))
     $                                                / k_in(3)))
     $                           * (0.5d0 + 0.5d0 * tanh((z - z_hu(1))
     $                                                / k_hu   ))
     $           + f_hu_2        * (0.5d0 - 0.5d0 * tanh((z - z_hu(1))
     $                                                / k_hu   ))
     $           + f_he_1        * (0.5d0 - 0.5d0 * tanh((z - z_in(3))
     $                                                / k_in(3)))
     $                           * (0.5d0 + 0.5d0 * tanh((z - z_he(1))
     $                                                / k_he   ))
     $           + f_he_2        * (0.5d0 - 0.5d0 * tanh((z - z_he(1))
     $                                                / k_he   ))
```

```
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function g_or_i(theta)
*outer root sheath, inner radius
*spherical coordinates
*
*declarations,
etc.....................................................
*
        implicit double precision (a - z)
        parameter (pi = 3.1415926535898d0)
        dimension t_ic(0:3), z_ic(0:2)
        dimension t_hu(0:3), z_hu(0:2)
        dimension t_he(0:3), z_he(0:2)
        common / geom_ge / diam, length, theta_bulb, l_tot
        common / geom_ic / t_ic, z_ic, k_ic
        common / geom_hu / t_hu, z_hu, k_hu
        common / geom_he / t_he, z_he, k_he
*
*definition.............................................................
.
*
        j_or_i = f_or_i(-l_tot)
        g_or_i = j_or_i + (g_hs(theta) + t_ic(3) + t_hu(3) + t_he(3)
     $          - j_or_i)
     $          / (cos(pi - theta_bulb))**2
     $          * (cos(theta          ))**2
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function f_in_o(z)
*infundibulum (sebum-filled gap), outer radius
*cylindrical coordinates
*
        implicit double precision (a - z)
*
        f_in_o = f_or_i(z)
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function f_ic(z)
```

```
*cuticle of inner root sheath, thickness
*cylindrical coordinates
*
*declarations,
etc.................................................
*
        implicit double precision (a - z)
        dimension t_ic(0:3), z_ic(0:2)
*
        common / geom_ic / t_ic, z_ic, k_ic
*
*definition.............................................................
.
*
        f_ic_1 = t_ic(0) + (t_ic(1) - t_ic(0)) / (z_ic(1) - z_ic(0))
     $          * (z - z_ic(0))
        f_ic_2 = t_ic(1) + (t_ic(2) - t_ic(1)) / (z_ic(2) - z_ic(1))
     $          * (z - z_ic(1))
        f_ic =    f_ic_1        * (0.5d0 + 0.5d0 * tanh((z - z_ic(1))
     $                                                 / k_ic   ))
     $          + f_ic_2        * (0.5d0 - 0.5d0 * tanh((z - z_ic(1))
     $                                                 / k_ic   ))
*
        return
        end
*
*
*
*----*----==========---------==========---------==========----------
==
        double precision function g_ic(theta)
*cuticle of inner root sheath, thickness
*spherical coordinates
*
*declarations,
etc.................................................
*
        implicit double precision (a - z)
        parameter (pi = 3.1415926535898d0)
        dimension t_ic(0:3), z_ic(0:2)
        common / geom_ge / diam, length, theta_bulb, l_tot
        common / geom_ic / t_ic, z_ic, k_ic
*
*definition.............................................................
.
*
        j_ic = f_ic(-l_tot)
        g_ic = j_ic + (t_ic(3) - j_ic)
     $          / (cos(pi - theta_bulb))**2
     $          * (cos(theta          ))**2
*
        return
        end
*
*
*
```

```
*----*----==========---------==========---------=========----------
==
        double precision function f_hu(z)
*Huxley's layer of inner root sheath, thickness
*cylindrical coordinates
*
*declarations,
etc.....................................................
*
        implicit double precision (a - z)
        dimension t_hu(0:3), z_hu(0:2)
*
        common / geom_hu / t_hu, z_hu, k_hu
*
*definition.............................................................
.
*
        f_hu_1 = t_hu(0) + (t_hu(1) - t_hu(0)) / (z_hu(1) - z_hu(0))
     $          * (z - z_hu(0))
        f_hu_2 = t_hu(1) + (t_hu(2) - t_hu(1)) / (z_hu(2) - z_hu(1))
     $          * (z - z_hu(1))
        f_hu =    f_hu_1        * (0.5d0 + 0.5d0 * tanh((z - z_hu(1))
     $                                                 / k_hu   ))
     $          + f_hu_2        * (0.5d0 - 0.5d0 * tanh((z - z_hu(1))
     $                                                 / k_hu   ))
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function g_hu(theta)
*Huxley's layer of inner root sheath, thickness
*spherical coordinates
*
*declarations,
etc.....................................................
*
        implicit double precision (a - z)
        parameter (pi = 3.1415926535898d0)
        dimension t_hu(0:3), z_hu(0:2)
        common / geom_ge / diam, length, theta_bulb, l_tot
        common / geom_hu / t_hu, z_hu, k_hu
*
*definition.............................................................
.
*
        j_hu = f_hu(-l_tot)
        g_hu = j_hu + (t_hu(3) - j_hu)
     $          / (cos(pi - theta_bulb))**2
     $          * (cos(theta          ))**2
*
        return
        end
*
```

```
*
*
*----*----==========---------==========---------==========---------
==
        double precision function f_he(z)
*Henle's layer of inner root sheath, thickness
*cylindrical coordinates
*
*declarations,
etc.....................................................
*
        implicit double precision (a - z)
        dimension t_he(0:3), z_he(0:2)
*
        common / geom_he / t_he, z_he, k_he
*
*definition..............................................................
.
*
        f_he_1 = t_he(0) + (t_he(1) - t_he(0)) / (z_he(1) - z_he(0))
     $          * (z - z_he(0))
        f_he_2 = t_he(1) + (t_he(2) - t_he(1)) / (z_he(2) - z_he(1))
     $          * (z - z_he(1))
        f_he =    f_he_1        * (0.5d0 + 0.5d0 * tanh((z - z_he(1))
     $                                                 / k_he   ))
     $          + f_he_2        * (0.5d0 - 0.5d0 * tanh((z - z_he(1))
     $                                                 / k_he   ))
*
        return
        end
*
*
*
*----*----==========---------==========---------==========---------
==
        double precision function g_he(theta)
*Henle's layer of inner root sheath, thickness
*spherical coordinates
*
*declarations,
etc.....................................................
*
        implicit double precision (a - z)
        parameter (pi = 3.1415926535898d0)
        dimension t_he(0:3), z_he(0:2)
        common / geom_ge / diam, length, theta_bulb, l_tot
        common / geom_he / t_he, z_he, k_he
*
*definition..............................................................
.
*
        j_he = f_he(-l_tot)
        g_he = j_he + (t_he(3) - j_he)
     $          / (cos(pi - theta_bulb))**2
     $          * (cos(theta          ))**2
*
        return
```

```
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function f_ic_i(z)
*cuticle of inner root sheath, inner radius
*cylindrical coordinates
*
        implicit double precision (a - z)
*
        f_ic_i = f_hs(z)
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function g_ic_i(theta)
*cuticle of inner root sheath, inner radius
*spherical coordinates
*
        implicit double precision (a - z)
*
        g_ic_i = g_hs(theta)
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function f_ic_o(z)
*cuticle of inner root sheath, outer radius
*cylindrical coordinates
*
        implicit double precision (a - z)
*
        f_ic_o = f_hs(z) + f_ic(z)
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function g_ic_o(theta)
*cuticle of inner root sheath, outer radius
*spherical coordinates
*
        implicit double precision (a - z)
*
```

```
        g_ic_o = g_hs(theta) + g_ic(theta)
*
        return
        end
*
*
*
*----*----==========---------==========---------==========----------
==
        double precision function f_he_i(z)
*Henle's layer of inner root sheath, inner radius
*cylindrical coordinates
*
        implicit double precision (a - z)
*
        f_he_i = f_or_i(z) - f_he(z)
*
        return
        end
*
*
*
*----*----==========---------==========---------==========----------
==
        double precision function g_he_i(theta)
*Henle's layer of inner root sheath, inner radius
*spherical coordinates
*
        implicit double precision (a - z)
*
        g_he_i = g_or_i(theta) - g_he(theta)
*
        return
        end
*
*
*
*----*----==========---------==========---------==========----------
==
        double precision function f_he_o(z)
*Henle's layer of inner root sheath, outer radius
*cylindrical coordinates
*
        implicit double precision (a - z)
*
        f_he_o = f_or_i(z)
*
        return
        end
*
*
*
*----*----==========---------==========---------==========----------
==
        double precision function g_he_o(theta)
*Henle's layer of inner root sheath, outer radius
*spherical coordinates
```

```
*
        implicit double precision (a - z)
*
        g_he_o = g_or_i(theta)
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function f_hu_i(z)
*Huxley's layer of inner root sheath, inner radius
*cylindrical coordinates
*
        implicit double precision (a - z)
*
        f_hu_i = f_ic_o(z)
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function g_hu_i(theta)
*Huxley's layer if inner root sheath, inner radius
*spherical coordinates
*
        implicit double precision (a - z)
*
        g_hu_i = g_ic_o(theta)
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function f_hu_o(z)
*Huxley's layer of inner root sheath, outer radius
*cylindrical coordinates
*
        implicit double precision (a - z)
*
        f_hu_o = f_he_i(z)
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
```

```
        double precision function g_hu_o(theta)
*Huxley's layer of inner root sheath, outer radius
*spherical coordinates
*
        implicit double precision (a - z)
*
        g_hu_o = g_he_i(theta)
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function f_or(z)
*outer root sheath, thickness
*cylindrical coordinates
*
*declarations,
etc.....................................................
*
        implicit double precision (a - z)
        dimension t_or(0:6), z_or(0:5), k_or(1:4)
*
        common / geom_or / t_or, z_or, k_or
*
*definition.............................................................
.
*
        f_or_1 = t_or(0) + (t_or(1) - t_or(0)) / (z_or(1) - z_or(0))
     $          * (z - z_or(0))
        f_or_2 = t_or(1) + (t_or(2) - t_or(1)) / (z_or(2) - z_or(1))
     $          * (z - z_or(1))
        f_or_3 = t_or(2) + (t_or(3) - t_or(2)) / (z_or(3) - z_or(2))
     $          * (z - z_or(2))
        f_or_4 = t_or(3) + (t_or(4) - t_or(3)) / (z_or(4) - z_or(3))
     $          * (z - z_or(3))
        f_or_5 = t_or(4) + (t_or(5) - t_or(4)) / (z_or(5) - z_or(4))
     $          * (z - z_or(4))
        f_or =    f_or_1        * (0.5d0 + 0.5d0 * tanh((z - z_or(1))
     $                                             / k_or(1)))
     $          + f_or_2        * (0.5d0 - 0.5d0 * tanh((z - z_or(1))
     $                                             / k_or(1)))
     $                          * (0.5d0 + 0.5d0 * tanh((z - z_or(2))
     $                                             / k_or(2)))
     $          + f_or_3        * (0.5d0 - 0.5d0 * tanh((z - z_or(2))
     $                                             / k_or(2)))
     $                          * (0.5d0 + 0.5d0 * tanh((z - z_or(3))
     $                                             / k_or(3)))
     $          + f_or_4        * (0.5d0 - 0.5d0 * tanh((z - z_or(3))
     $                                             / k_or(3)))
     $                          * (0.5d0 + 0.5d0 * tanh((z - z_or(4))
     $                                             / k_or(4)))
     $          + f_or_5        * (0.5d0 - 0.5d0 * tanh((z - z_or(4))
     $                                             / k_or(4)))
*
```

```
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function g_or(theta)
*outer root sheath, thickness
*spherical coordinates
*
*declarations,
etc.....................................................
*
        implicit double precision (a - z)
        parameter (pi = 3.1415926535898d0)
        dimension t_or(0:6), z_or(0:5), k_or(1:4)
        common / geom_ge / diam, length, theta_bulb, l_tot
        common / geom_or / t_or, z_or, k_or
*
*definition.............................................................
.
*
        j_or = f_or(-l_tot)
        g_or = j_or + (t_or(6) - j_or)
     $          / (cos(pi - theta_bulb))**2
     $          * (cos(theta          ))**2
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function f_or_o(z)
*outer root sheath, outer radius
*cylindrical coordinates
*
        implicit double precision (a - z)
*
        f_or_o = f_or_i(z) + f_or(z)
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function g_or_o(theta)
*outer root sheath, outer radius
*spherical coordinates
*
        implicit double precision (a - z)
*
        g_or_o = g_or_i(theta) + g_or(theta)
```

```
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function f_ct(z)
*dermal sheath, thickness
*cylindrical coordinates
*
*declarations,
etc.....................................................
*
        implicit double precision (a - z)
        dimension t_ct(0:4), z_ct(0:3), k_ct(1:2)
*
        common / geom_ct / t_ct, z_ct, k_ct
*
*definition.............................................................
.
*
        f_ct_1 = t_ct(0) + (t_ct(1) - t_ct(0)) / (z_ct(1) - z_ct(0))
     $          * (z - zct0)
        f_ct_2 = t_ct(1) + (t_ct(2) - t_ct(1)) / (z_ct(2) - z_ct(1))
     $          * (z - zct1)
        f_ct_3 = t_ct(2) + (t_ct(3) - t_ct(2)) / (z_ct(3) - z_ct(2))
     $          * (z - zct2)
        f_ct =    f_ct_1        * (0.5d0 + 0.5d0 * tanh((z - z_ct(1))
     $                                              / k_ct(1)))
     $          + f_ct_2        * (0.5d0 - 0.5d0 * tanh((z - z_ct(1))
     $                                              / k_ct(1)))
     $                          * (0.5d0 + 0.5d0 * tanh((z - z_ct(2))
     $                                              / k_ct(2)))
     $          + f_ct_3        * (0.5d0 - 0.5d0 * tanh((z - z_ct(2))
     $                                              / k_ct(2)))
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function g_ct(theta)
*dermal sheath, thickness
*spherical coordinates
*
*declarations,
etc.....................................................
*
        implicit double precision (a - z)
        parameter (pi = 3.1415926535898d0)
        dimension t_ct(0:4), z_ct(0:3), k_ct(1:2)
        common / geom_ge / diam, length, theta_bulb, l_tot
        common / geom_ct / t_ct, z_ct, k_ct
```

```
*
*definition.....................................................
.
*
        j_ct = f_ct(-l_tot)
        g_ct = j_ct + (t_ct(4) - j_ct)
     $          / (cos(pi   ))**2
     $           * (cos(theta))**2
*
        return
        end
*
*
*
*----*----==========---------==========---------==========----------
==
        double precision function f_ct_i(z)
*dermal sheath, inner radius
*cylindrical coordinates
*
        implicit double precision (a - z)
*
        f_ct_i = f_or_o(z)
*
        return
        end
*
*
*
*----*----==========---------==========---------==========----------
==
        double precision function g_ct_i(theta)
*dermal sheath, inner radius
*spherical coordinates
*
        implicit double precision (a - z)
*
        g_ct_i = g_or_o(theta)
*
        return
        end
*
*
*
*----*----==========---------==========---------==========----------
==
        double precision function f_ct_o(z)
*dermal sheath, outer radius
*cylindrical coordinates
*
        implicit double precision (a - z)
*
        f_ct_o = f_or_o(z) + f_ct(z)
*
        return
        end
*
```

```
*
*
*----*----==========---------==========---------==========---------
==
        double precision function g_ct_o(theta)
*dermal sheath, outer radius
*spherical coordinates
*
        implicit double precision (a - z)
*
        g_ct_o = g_or_o(theta) + g_ct(theta)
*
        return
        end
*
*
*
*----*----==========---------==========---------==========---------
==
        double precision function f_va(z)
*vascular surface, thickness of gap (from outer surface of dermal
*sheath)
*cylindrical coordinates
*
*declarations,
etc.....................................................
*
        implicit double precision (a - z)
        dimension t_va(0:4), z_va(0:3), k_va(1:2)
        common / geom_va / t_va, z_va, k_va, z_va_s
*
*definition.............................................................
.
*
        f_va_1 = t_va(0) + (t_va(1) - t_va(0)) / (z_va(1) - z_va(0))
     $          * (z - z_va(0))
        f_va_2 = t_va(1) + (t_va(2) - t_va(1)) / (z_va(2) - z_va(1))
     $          * (z - z_va(1))
        f_va_3 = t_va(2) + (t_va(3) - t_va(2)) / (z_va(3) - z_va(2))
     $          * (z - z_va(2))
        f_va =    f_va_1        * (0.5d0 + 0.5d0 * tanh((z - z_va(1))
     $                                                 / k_va(1)))
     $          + f_va_2        * (0.5d0 - 0.5d0 * tanh((z - z_va(1))
     $                                                 / k_va(1)))
     $                          * (0.5d0 + 0.5d0 * tanh((z - z_va(2))
     $                                                 / k_va(2)))
     $          + f_va_3        * (0.5d0 - 0.5d0 * tanh((z - z_va(2))
     $                                                 / k_va(2)))
*
        return
        end
*
*
*
*----*----==========---------==========---------==========---------
==
        double precision function g_va(theta)
```

```
*vascular surface, thickness of gap (from outer surface of dermal
*sheath)
*spherical coordinates
*
*declarations,
etc.....................................................
*
        implicit double precision (a - z)
        parameter (pi = 3.1415926535898d0)
        dimension t_va(0:4), z_va(0:3), k_va(1:2)
        common / geom_ge / diam, length, theta_bulb, l_tot
        common / geom_va / t_va, z_va, k_va, z_va_s
*
*definition.............................................................
.
*
        j_va = f_va(-l_tot)
        g_va = j_va + (t_va(3) - j_va)
     $          / (cos(pi   ))**2
     $          * (cos(theta))**2
*
        return
        end
*
*
*
*----*----==========---------==========---------==========----------
==
        double precision function f_va_s(z)
*vascular surface, radius
*cylindrical coordinates
*
        implicit double precision (a - z)
*
        f_va_s = f_ct_o(z) + f_va(z)
*
        return
        end
*
*
*
*----*----==========---------==========---------==========----------
==
        double precision function g_va_s(theta)
*vascular surface, radius
*spherical coordinates
*
        implicit double precision (a - z)
*
        g_va_s = g_ct_o(theta) + g_va(theta)
*
        return
        end
*
*
*
```

```
*----*----==========---------==========---------=========----------
==
        double precision function f_ex_i(z)
*tissue ouside follicle, inner radius
*cylindrical coordinates
*
        implicit double precision (a - z)
*
        f_ex_i = f_ct_o(z)
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        double precision function g_ex_i(theta)
*tissue ouside follicle, inner radius
*spherical coordinates
*
        implicit double precision (a - z)
*
        g_ex_i = g_ct_o(theta)
*
        return
        end
*
*
*
*----*----==========---------==========---------=========----------
==
        subroutine setup_prop
*setup for follicular model properties
*
*
*
*Johannes M. Nitsche, sabbatical leave at Procter & Gamble Miami Valley
*Laboratories, fall semester 1998
*
*
*
*partition coefficients, diffusion/dispersion coefficients, membrane
*permeabilities, and other tissue and material properties
*
*
*
*all quantities made dimensionless using
*       characteristic length           100 microns = 0.01 cm
*       characteristic diffusivity      10^-5 cm^2/s
*
*water is used as reference fluid for all partition coefficients
*
*
*
*glossary:
*
```

```
*variables
*
*       mw      molecular weight
*       k       partition coefficient (concentration / concentration
*                       in aqueous solution)
*       p       membrane permeability coefficient
*       dmol    molecular diffusivity
*
*tissue layers or regions, or materials (_subscript)
*
*       oct     octanol
*       veh     vehicle
*       lip     lipid pathway through stratum corneum
*       pol     polar pathway through stratum corneum
*
*       ex      tissue outside follicle ("ex" for "exterior tissue")
*       ed      epidermis
*       de      dermis
*       hd      hypodermis
*
*other affixes (_second subscript)
*
*       d       double precision
*       i       integer
*       a       array (double precision)
*
*
*
*output file:
*
*       output.prop.txt         listing of tissue and material property
*                               parameters
*
*
*
*main outcomes:
*
*
*
*declarations,
etc.....................................................
*
        implicit double precision (a - z)
        common / prop_ge / mw, k_oct, k_veh
        common / prop_sc / p_lip, p_pol
        common / prop_ed / k_ed, dmol_ed
        common / prop_de / k_de, dmol_de
        common / prop_hd / k_hd, dmol_hd
*
*permeant and vehicle input parameters
*
        open (unit = 30, file = 'data.prop.txt')
        read (30, *) mw
        read (30, *) log_k_oct
        read (30, *) k_veh
        close (30)
        k_oct = 10.0d0**log_k_oct
```

```
*
*stratum corneum
permeability.....................................
*
        p_pol = 5.0d-6 * sqrt(300.0d0 / mw)
     $          * 1.0d-2 / 1.0d-5 / 3600.0d0
        p_lip = 10.0d0**(log_k_oct - 0.018d0 / 2.303d0 * mw - 2.87d0)
     $          * 1.0d-2 / 1.0d-5 / 3600.0d0
*
*epidermis.....................................................
.
*modeled as aqueous solution
*. . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . .
.
*
        k_ed = 1.0d0
*
*dermis........................................................
.
*modeled as aqueous solution
*. . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . .
.
*
        k_de = 1.0d0
*
*hypodermis
*modeled as octanol
*. . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . .
.
*
        k_hd = k_oct
*
*write tissue and material property parameters
*
        open (unit = 31, file = 'output.prop.txt')
        write (31, 7900) 'mw'
        write (31, 8000) mw
        write (31, 7900) 'log_k_oct'
        write (31, 8000) log_k_oct
        write (31, 7900) 'k_veh'
        write (31, 8000) k_veh
        write (31, 7900) 'sc: p_lip, p_pol'
        write (31, 8000) p_lip, p_pol
        write (31, 7900) 'ed: k_ed, dmol_ed'
        write (31, 8000) k_ed
        write (31, 7900) 'de: k_de, dmol_de'
        write (31, 8000) k_de
        write (31, 7900) 'hd: k_hd, dmol_hd'
        write (31, 8000) k_hd
        close (31)
*
*formats
*
7900    format (a)
8000    format (d21.14,2x,d21.14)
*
        return
```

```
        end
```

E.2 Data file “datamesh.txt” for mesh parameters

```
10
20
0.02240325870d0
50.0d0
10
10
40
30
1.0d0
2.0d0
17.0d0
30.0d0
```

E.3 Data file “pcparam.txt” for physico-chemical parameters

```
0.01d0
17.0d0
14.0d0
20.0d0
28.0d0
17.0d0
14.0d0
14.0d0
28.0d0
1.0d0
1.1d0
0.0d0
28.0d0
17.0d0
17.0d0
17.0d0
17.0d0
26.0d0
0.088d0
```

E.4 Data file “tparam.txt” for time parameter and volumetric clearance rate coefficients

```
0.01d0 0.0001d0 0.0d0 0.0d0 0.0370d0 0.0370d0 0.0370d0 0.0037d0
0.0370d0 0.0d0
```

E.5 Data file “data.geom.txt” for hair follicle parameters

```
50.0d0   4.0d0
```

F Asymptoticity of the approximation formula for the distance between the centerline and the surface of the helical tube (Eq. 160)

The asymptoticity of the approximation to the distance between the centerline and the surface of the helical tube is verified by checking that the difference between the exact distance and the approximation (Eq. 160) are bounded by an upper bound. Thus with d_{approx} and d_{exact} denoting the approximate and the exact distance, we want to show

$$\frac{\left| d_{\text{approx}} - d_{\text{exact}} \right|}{\varepsilon \, d_{\text{exact}}} \leq S \tag{F1}$$

Figures F-1 and F-2 show the values obtained from the left-hand-side of Eq. F1 as a function of log s/ν, for various values of the angle ν, for $\varepsilon = 0.01$ and $\varepsilon = 0.001$, respectively. These results show the term on the left-hand-side of Eq. F1 to be bounded by the supremum $S \approx 0.5$. The left-hand-side of Eq. F1 for $\nu = 0$ in Fig. F-1 reaches a maximum value equal to 0.502. The difference $|d_{\text{approx}} - d_{\text{exact}}|$ is $O(\varepsilon)$, thus d_{approx} is asymptotic to d_{exact}.

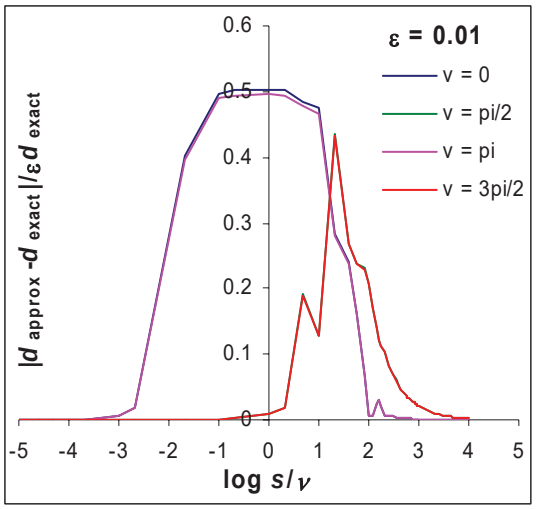


Figure F-1: Difference between the approximate and exact formula for the distance Eq. 160 as a function of $\log s/\nu$ for $\varepsilon = 0.01$ and varying angle ν. The curves for $\nu = \pi/2$ and $\nu = 3\pi/2$ overlap.

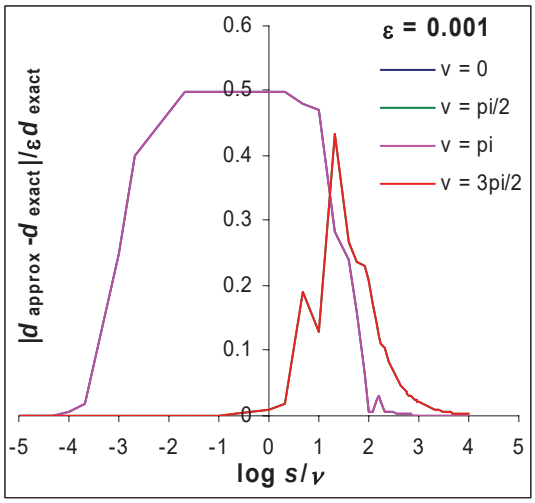


Figure F-2: Difference between the approximate and exact formula for the distance Eq. 160 as a function of $\log s/\nu$ for $\varepsilon = 0.01$ and varying angle ν. The curves for $\nu = 0$ and $\nu = \pi$ and for $\nu = \pi/2$ and $\nu = 3\pi/2$ overlap.

G Fortran code implementing the model of diffusion through and near an eccrine sweat duct

G.1 Main program

```
C Geometrical input parameters: R: helix radius
C                               P: helix pitch
C                       a: helical duct radius
C                               u: angle of rotation on surface
C                                  on surface of helix
C                       v: angle in meridional plane of helix
C                               t: arclength
C Function |x-x_0| called 'dist_'
C
C
C
      program main
      implicit double precision (a - z)
C
      call readinput
      call doubleint
C
      stop
      end
C
C
      subroutine readinput
      implicit double precision (a - z)
      parameter (pi = 3.141592654d0)
C
      common /geom/ R, eps, a, b_p, ni
      common /bc_param/ Aout, Bout, Kin, Kout, Din, Dout
      common /permeab/ P
C
      open (unit = 50,file = 'geom_param.txt',status = 'old')
      read (50,*) R, b, eps
      close (50)
C
      a = eps*R
      b_p = b/(2.0d0*pi)
      ni = sqrt(R**2+(b_p)**2)
C
      open (unit = 50,file = 'parameters.txt',status = 'old')
      read (50,*) Aout, Bout, Kin, Kout, Din, Dout
      close (50)
C
      open (unit = 52, file ='permeability.txt',status='old')
      read (52,*) P
      close (52)
```

```
C
      return
      end
C
C
      subroutine doubleint
      implicit double precision (a - z)
      integer Nt1, Nt2, Nt3, Nv, i, j, tdim, vdim
      parameter (pi = 3.141592654d0)
      parameter (tdim = 500, vdim = 500, jdim = 500)
C
      dimension wt1(0:tdim), wt2(0:tdim)
      dimension wt3(0:tdim), wv(1:vdim)
      dimension t1(0:tdim), t2(0:tdim)
      dimension t3(0:tdim), v(0:vdim)
C
      common /geom/ R, eps, a, b_p, ni
      common /bc_param/ Aout, Bout, Kin, Kout, Din, Dout
      common /permeab/ P
C
C
C Value of angle u
C
      u = 0.0d0
C
C
C dv integral
C ````````````
C Integration limits for dv integral
C
      vi = 0.0d0
      vf = 2.0d0*pi
C
C Number of subintervals for dv integral
C
      Nv = 120
C
C Stepsize for dv integral
C
      hv = (vf-vi)/dble(Nv)
C
C Array of weights for dv integral (equal weights)
C
      do 100, j = 1, Nv
         wv(j) = hv
100   continue
C
C
C dt integral
C ````````````
C Integration limits for dt integrals
C
      a1 = -1.0d0*eps
      b1 = 1.0d0*eps
      a2 = 1.0d0*eps
      b2 = 5.0d0
      a3 = -5.0d0
```

```
      b3 = -1.0d0*eps
C
C Number of subintervals:
C
      Nt1 = 500
      Nt2 = 500
      Nt3 = Nt2
C
C Stepsizes for dt integrals
C
      ht1 = (b1-a1) / dble(Nt1)
      ht2 = (b2-a2) / dble(Nt2)
      ht3 = (b3-a3) / dble(Nt3)
C
C Arrays of weights for Simpson's integrals
C
C     Weights for dt integrals
C
      wt1(0) = ht1 / 3.0d0
      wt1(Nt1) = ht1 / 3.0d0
C
      do 200, i = 1, Nt1-1, 2
         wt1(i) = 4.0d0 * ht1/3.0d0
200   continue
C
      do 300, i = 2, Nt1-2, 2
         wt1(i) = 2.0d0 * ht1/3.0d0
300   continue
C
      wt2(0) = ht2 / 3.0d0
      wt2(Nt2) = ht2 / 3.0d0
C
      do 400, i = 1, Nt2-1, 2
         wt2(i) = 4.0d0 * ht2/3.0d0
400   continue
C
      do 500, i = 2, Nt2-2, 2
         wt2(i) = 2.0d0 * ht2/3.0d0
500   continue
C
      wt3(0) = ht3 / 3.0d0
      wt3(Nt3) = ht3 / 3.0d0
C
      do 600, i = 1, Nt3-1, 2
         wt3(i) = 4.0d0 * ht3/3.0d0
600   continue
C
      do 700, i = 2, Nt3-2, 2
         wt3(i) = 2.0d0 * ht3/3.0d0
700   continue
C
C
C v angles
C ````````
C
      j = 0
      v(j) = 0
```

```
C
      do 900, j = 1, Nv
         v(j) = vi+(dble(j))*hv
900   continue
C
C
C Integrals dt
C ````````````
C
      sum1_3 = 0.0d0
      sum2_3 = 0.0d0
C
         do 800, i = 0, Nt3
            t3(i) = a3+(dble(i))*ht3
C
            sum1_3 = sum1_3 + (1.0d0/(4.0d0*pi*(dist(u,t3(i)))**3))
     1             * wt3(i)
C
            sum2_3 = sum2_3 + ((t3(i)/ni)*((t3(i)/ni)-SIN(t3(i)/ni))
     1             / (4.0d0*pi*(dist(u,t3(i)))**5)) * wt3(i)
C
800      continue
C
      sum1_1 = 0.0d0
      sum2_1 = 0.0d0
C
         do 1000, i = 0, Nt1
            t1(i) = a1+(dble(i))*ht1
C
            sum1_1 = sum1_1 + (1.0d0/(4.0d0*pi*(dist(u,t1(i)))**3))
     1             * wt1(i)
C
            sum2_1 = sum2_1 + ((t1(i)/ni)*((t1(i)/ni)-SIN(t1(i)/ni))
     1             / (4.0d0*pi*(dist(u,t1(i)))**5)) * wt1(i)
C
1000     continue
C
C
      sum1_2 = 0.0d0
      sum2_2 = 0.0d0
C
         do 1200, i = 0, Nt2
            t2(i) = a2+(dble(i))*ht2
C
            sum1_2 = sum1_2 + (1.0d0/(4.0d0*pi*(dist(u,t2(i)))**3))
     1             * wt2(i)
C
            sum2_2 = sum2_2 + ((t2(i)/ni)*((t2(i)/ni)-SIN(t2(i)/ni))
     1             / (4.0d0*pi*(dist(u,t2(i)))**5)) * wt2(i)
C
1200     continue
C
      I1_total = sum1_3 + sum1_1 + sum1_2
      I2_total = sum2_3 + sum2_1 + sum2_2
C
C
C Calculation of constants kap, F
```

```
C ````````````````````````````````

      c1 = ni*(P*(eps/Kout)+Din/R)
      c2 = -eps*P*I1_total*(R**2)/(Kout*ni)
      c3 = (Aout/Kout)*(eps*P*ni
     1   + Din*Kin*(b_p**2)/(R*ni))
C
      c4 = (Dout*R/ni)*(3.0d0*I2_total*((b_p)**2)
     1   - I1_total)
      c5 = Din*ni/R
      c6 = (Aout/ni)*(Dout*R+(Din*Kin*(b_p)**2)
     1   / (Kout*R))
C
      kap = (c6-(c3*c4/c2))/(c5-(c1*c4/c2))
C
      F = (c3-c1*kap)/c2
C
      print*, 'F=', F , 'kap=', kap
C
      return
      end
C
C
C Approximation of distance for evaluation of kap, F
C ````````````````````````````````````````````````````
C
      double precision function dist(u,t)
      implicit double precision (a - z)
C
      common /geom/ R, eps, a, b_p, ni
C
      dist = sqrt(2.0d0*(R**2)+(a**2)-2.0d0*(R**2)
     1     * COS(t/ni)+(b_p*t/ni)**2)
C
      return
      end
C
C
```

G.2 Datafile “parameters.txt” for constants A_{out}, B_{out} and physico-chemical parameters

```
0.02d0
1.0d0
1.0d0
1.0d0
0.455d0
0.152d0
```

G.3 Datafile “permeability.txt”

```
1.0d6
```

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