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A Simulation Study of Parameter Estimation in the One and Two Compartment Models

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Few attempts have been made to examine the statistical problems that the user of compartmental models must face. Some properties of the estimators of parameters for one and two compartmental models based on nonlinear estimation were studied through simulation. Of particular interest were the effect of the experimental design and the effect of different error structures on the empirical sampling distribution for the estimators. For the one compartment model it was found that nonlinear estimation yielded essentially unbiased estimators that were normally distributed unless the random error for the model was large. In the two compartment model simulations, bias appeared in the estimators to the extent that bimodal sampling distributions of the estimators were observed as the random error for the model was increased.

KEY WORDS: pharmacokinetic modelling; nonlinear estimation; one compartment model; two compartment model.

INTRODUCTION

Pharmacokinetic modelling has become a prominent feature of the analysis of studies in which the concentration of a drug in the blood (or urine) is determined over a period of time. The prominence of these models has been due to increasingly efficient computers; the availability of software packages, such as NONLIN (1), SAAM (2), AUTOAN (3), ESTRIP (4), and CSTRIP (5), and Pedersen's version of the Nelder and Mead algorithm (6);

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and the advent of efficacy and safety evaluation of drugs as a function of blood levels (7).

Pharmacokinetic models have a variety of uses. One of the most common is to predict plasma concentrations from single or multiple doses. Cooper and Simpson (8) describe a technique that enables a physician to determine individual patient dosage requirements of nortriptyline from a single 24-h blood sample. They showed that a strong correlation exists between the mean steady-state plasma level and the 24-h time point of the initial single-dose curve. Second, one can obtain information which will allow a better conceptualization of the mechanism of action of a drug. Boxenbaum and Riegelman (9) showed that the formation of acetylisoniazid, a metabolite of isoniazid, is slowed for those patients who are slow inactivators by comparing the rates of three metabolite urinary excretion curves. Third, one can also examine the effect of formulation changes or environmental factors (e.g., other medication) on the absorption of the drug. Benzathine penicillin G is an example of a slow release dosage form of penicillin which extends the duration of action of a single dose of the antibiotic (10). Sodium penicillin G, whether given orally or intramuscularly, does not demonstrate this slow release characteristic (11,12). These conclusions were made by comparing the half-lives of the two penicillins, which were determined from a one compartment model with first-order absorption and elimination. In addition, many other uses of pharmacokinetic models besides those cited here can be documented (3).

Fitting pharmacokinetic models is not without its problems. If $C(t)$, which denotes the concentration of drug in the body at time t, is expressed as

$$\sum_{i=1}^{n} f(k_1, \ldots, k_n) \exp(-k_i t)$$

Boxenbaum and his coauthors (13) found that it is important to examine the correlation between the coefficients, $f(k_1, \ldots, k_n)$, and the exponents, k_i; a high correlation reduces the desirability of obtaining parameter estimates. Hence, a reparameterization of the model which reduces the correlation between coefficients and exponents should be preferable. Another problem studied by Boxenbaum *et al.* is the bias of parameter estimators from nonlinear estimation. They performed simulations and found that the estimated standard error of parameter estimators can be two- to three-fold different from the true standard error and that the estimated standard error is more frequently underestimating rather than overestimating the true standard error.

Westlake (14) attacks the reliability of the parameter estimates and provides an example based upon a single simulation that shows estimates

obtained from blood levels are not reliable for predictors of tissue levels. Westlake (15) also claims that in most instances, very little faith can be placed in the estimated pharmacokinetic parameters *per se* and advises that confidence limits be reported. He then raises the question of whether or not planar limits are to be preferred to univariate limits. Planar limits are a series of confidence statements for the individual parameters based on the concept of tangent planes to the n-dimensional ellipsoid which describes the confidence region of the n parameters in the compartmental model. Westlake suggests the use of these planar limits because of correlations between parameter estimators. Some programs, such as NONLIN (1), calculate both types of limits.

The choice of starting values can also be a problem in pharmacokinetic modelling. Cobelli and Salvan (16) used simulations to investigate the effect of starting values on the final estimates of parameters and found that the effect was negligible if the initial guess deviated from −20 to 60% of the true value. Rodda *et al.* (17) also used simulations to investigate the effect of outliers on parameter estimates. They developed an estimation procedure that is less sensitive to outliers than classical least squares when the model is known and outliers are known to exist.

Westlake (15) stressed that few attempts have been made to examine the statistical and computation problems that the user of compartmental models must face. We will attempt to address some of these problems considering two models. For each we will study some of the properties of the estimators of compartmental model parameters through simulation. Of particular interest will be the effect of the experimental design (e.g., the number and spacing of sampling points) and the effect of different error structures on the empirical sampling distributions of the estimators. We will examine the bias of these estimators and the "normality" of their sampling distributions. In addition, we will compare the asymptotic standard error of each parameter estimator with its empirical counterpart and the asymptotic correlation coefficients between pairs of estimators to their empirical counterparts. We will also examine the univariate confidence limits for each parameter. Finally, we will compare the consistency of our results for the two models.

The first model to be studied is the one compartment open model (3) specified by the expression:

$$C(t) = \frac{k_a D}{V(k_a - k_e)}(e^{-k_e t} - e^{-k_a t})$$

henceforth called Model I, where $C(t)$ is the concentration of drug in the body at time t, D is the absorbed mass of drug, V is the apparent volume

of distribution of the central compartment, k_a is the absorption rate constant, and k_e is the elimination rate constant.

The second model to be studied is the following two compartment model (3):

$$C(t) = \frac{k_a D}{V}\left[\frac{(\alpha - k_{21})}{(\alpha-\beta)(k_a-\alpha)} e^{-\alpha t} + \frac{(k_{21}-\beta)}{(\alpha-\beta)(k_a-\beta)} e^{-\beta t} - \frac{(k_a-k_{21})}{(k_a-\alpha)(k_a-\beta)} e^{-k_a t}\right],$$

henceforth called Model II, where, in addition to those definitions above, k_{12} is the rate constant from the central to the peripheral compartment, k_{21} is the rate constant from the peripheral to the central compartment, $\alpha + \beta = k_e + k_{12} + k_{21}$, and $\alpha\beta = k_e k_{21}$.

SIMULATION FOR ONE COMPARTMENT MODEL (MODEL I)

For the simulation experiment the parameters D/V, k_a, and k_e for the one compartment model were specified to be 75 deq/liter, 1.5 h^{-1}, and 0.4 h^{-1}, respectively. Then for a given design and error structure, a random number generator was used to obtain sample values for a single simulation. These data were used to fit Model I to obtain estimates of D/V, k_a, k_e, asymptotic standard errors, and pairwise asymptotic correlation coefficients. The Marquardt method (18) was used to fit the data to the model. Starting values for the parameters were chosen from a grid search of a symmetric range around the true parameter values based upon the smallest weighted residual sum of squares.

Sample output from the NLIN procedure of SAS (79.3) (19) for a simulation of Model II is shown in Table I. Note that we obtain an ANOVA table, parameter estimates, asymptotic standard errors, univariate asymptotic 95% confidence intervals, and the asymptotic correlation coefficient matrix of the parameters. This simulation was repeated an additional 999 times making a total of 1000 data sets. As with the first simulation, NLIN was used to fit the sample data for each of the remaining 999 simulations.

Two designs were studied for Model I. Design 1 used the time points 0.5, 1.0, 1.5, 3.0, and 7.0 h. Design 2 used the time points 0.5, 1.0, 1.5, 2.0, 3.0, 5.0, 7.0, 9.0, and 11.0 h. These time points were chosen so as to sufficiently describe the shape of the curve. Four different error structures were used for $e(t)$ in the model $y(t) = C(t) + e(t)$ for each design. Case A corresponds to $e(t)$ being a random normal deviate with standard deviation

Table I. Sample Output from the NLIN Procedure of SAS (79.3)

Source	DF	Sum of squares	Mean square
Regression	5	0.36711507	0.07342301
Residual	9	0.00037015	0.00004113
Uncorrected total	14	0.36748522	
(Corrected total)	13	0.10435999	

Parameter	Estimate	Asymptotic std. error	Asymptotic 95% confidence interval Lower	Upper
P1	0.39422169	0.02705285	0.33302337	0.45542002
P2	2.99994190	0.33915833	2.23270592	3.76717788
P3	0.72440194	0.11627422	0.46136915	0.98743473
P4	0.03602138	0.00846431	0.01687362	0.05516914
P5	0.20172637	0.04207854	0.10653729	0.29691546

Asymptotic correlation matrix of the parameters

	P1	P2	P3	P4	P5
P1	1.000000	−0.944432	0.928093	0.423889	0.645034
P2	−0.944432	1.000000	−0.847580	−0.355421	−0.558078
P3	0.928093	−0.847580	1.000000	0.642628	0.859865
P4	0.423889	−0.355421	0.642628	1.000000	0.909492
P5	0.645034	−0.558078	0.859865	0.909492	1.000000

$\sigma(t) = 0.1$, for all t. Cases B, C, and D again let $e(t)$ be a random normal deviate but have $\sigma(t)$ proportional to drug concentration. For Case B, $\sigma(t) = 0.01C(t)$; for Case C, $\sigma(t) = 0.05C(t)$; and for Case D, $\sigma(t) = 0.1C(t)$. These relative errors are commonly seen in practice. When $\sigma(t)$ was proportional to drug concentration, a weighted least squares fit with the weights based upon the "true" level was obtained using NLIN.

Empirical sampling distributions for the estimators of D/V, k_a, k_e, and their pairwise asymptotic correlation coefficients were obtained from the 1000 simulations for each combination of design and error structure for Model I. The number of simulations (out of 1000) in which the true parameter value fell within the computed 95% confidence intervals specified by the parameter estimate and its asymptotic standard error was also observed.

For each parameter the mean and standard error of the 1000 estimates called the mean simulated value and the empirical standard error of simulated values, respectively, were computed. The mean simulated value was compared to the true parameter value. Percent bias, percent of mean squared error attributed to bias squared, and the root mean squared error

were expressed using the following:

$$\text{Bias} = \text{mean estimate} - \text{true value of parameter}$$

$$\%\ \text{Bias} = (\text{bias}/\text{true value of parameter}) \times 100\%$$

$$\text{MSE} = \text{RMSE}^2$$

$$\text{RMSE} = \left[\frac{1}{1000}\sum_{i=1}^{1000}(\hat{\mu}_i - \mu)^2\right]^{1/2}$$

where μ is the true value of a parameter. The empirical standard error was compared to the mean estimated asymptotic standard error from the 1000 simulations.

Similarly, the empirical correlation coefficient between pairs of parameter estimators was computed from the 1000 simulations. This value was compared to the mean estimated asymptotic correlation coefficient from the simulations. Also, the standard error of the estimated asymptotic correlation coefficient was obtained for each pair of parameters. A summary of these findings for Model I is presented here.

RESULTS OF SIMULATION MODEL I

Tables II and III display the results of the simulation study of Model I. For each parameter in each design and case of Model I, Table II displays the true parameter value, the % bias of the estimator, the mean and empirical standard error of the 1000 simulated values, the mean of the 1000 estimated asymptotic standard errors, the percent of times the true parameter value fell within 1000 sample univariate 95% confidence intervals, and a judgment regarding the distribution of the parameter estimates based upon a visual inspection of the frequency histogram.

Table III summarizes the results for the pairwise correlation coefficients for each design and case of Model I. Table III displays the mean of the estimated asymptotic correlation coefficients for the 1000 data sets, the empirical correlation coefficient for the parameter estimates from the 1000 simulated data sets, the standard error of the estimated asymptotic correlation coefficients, and a judgment regarding the distribution of estimated asymptotic correlation coefficients based upon a visual inspection of the frequency histogram.

Estimators of all parameters were unbiased for both designs when the error variance was not proportional to drug concentration (Table II, Case A, Designs 1 and 2). As the fraction of drug concentration which was included in the error increased from 1 to 5 to 10%, the bias increased from 0.1 to 1.8 to 7.2% for D/V and from 0.0 to 1.5 to 6.3% for k_e in Design

1. The increases in bias were less dramatic for both parameters in Design 2. For k_a, the bias increased from 0.0 to −2.0 to −6.0% for both designs. Root mean squared error was less for each parameter in Design 2 for a given Case than in Design 1. The percent of mean squared error attributed to bias squared was larger for each parameter in Design 2 for a given Case than in Design 1, if bias existed. The empirical standard error of the simulated values increased as the amount of drug proportional to the error increased for all three parameters. This pattern was followed in both designs. The standard errors were consistently smaller in Design 2 when compared with Design 1 for a given error structure. The mean asymptotic standard error of the simulated value was always equal to or smaller than its empirical counterpart. The univariate asymptotic 95% confidence intervals for the parameters contained the true parameter value from 88.5 to 95.9% of the time in actuality. The distributions of the parameter estimates were found to be "normallike" in both designs except for Case D, where skewness appeared for the distributions of D/V and k_e.

The empirical correlation coefficients of the parameters were found to be within 4.5% of the mean estimated asymptotic correlation (Table III). All of the distributions of correlation coefficients could be considered "normallike," with the exception of the distributions of correlation coefficients in Case D, which were skewed.

SIMULATION FOR TWO COMPARTMENT MODEL (MODEL II)

For this simulation experiment, the parameters D/V, k_a, α, β, and k_{21} for the two compartment model were specified to be 0.441 meq/liter, 2.389 h^{-1}, 0.914 h^{-1}, 0.0462 h^{-1}, and 0.25 h^{-1}, respectively, as in Westlake's paper (15). This simulation proceeded as it did for Model I.

Two designs were also studied for Model II. Design I consisted of the time points 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 6.0, 9.0, 12.0, 15.0, 18.0, 21.0, 24.0, 36.0, and 48.0 h. Design 2 used those time points in Design 1 along with the points 0.125, 0.375, 0.5625, 0.625, 0.6875, 0.8125, 0.875, 0.9375, 1.25, 1.75, 4.5, 7.5, 10.5, and 13.5 h. These times were chosen so as to sufficiently describe the shape of the curve. The same three error structures represented by Cases B, C, and D that were used for Model I were also used for this model. Case A was not used since the simulated concentrations were often negative for later sampling times. When $\sigma(t)$ was proportional to drug concentration, a weighted least squares fit with the weights based upon the "true" level was obtained using NLIN. Similar summarization of the 1000 simulations was done for this model as was done for Model I.

Table II. Results of One-Compartment Model Simulation (Model 1)[a]

Parameter	True value of parameter	Design: case	% Bias	$\%\left(\frac{\text{Bias}^2}{\text{MSE}}\right)$	Root mean squared error	Mean simulated value	Empirical standard error of simulated values	Mean estimated asymptotic standard error	% of simulated values within 95% confidence interval	Distribution of simulated values[b]
D/V	75.0	1:A	0.0	0.0	0.47	75.00	0.47	0.40	94.6	Normal
		1:B	0.1	0.4	0.90	75.06	0.90	0.78	95.2	Normal
		1:C	1.8	7.5	4.92	76.35	4.73	4.21	95.2	Normal
		1:D	7.2	17.5	12.89	80.39	11.71	9.52	95.1	Skewed right
		2:A	0.0	0.0	0.31	75.00	0.31	0.29	94.0	Normal
		2:B	0.1	2.0	0.42	75.06	0.42	0.42	95.6	Normal
		2:C	1.1	12.5	2.35	75.83	2.20	2.20	95.6	Normal
		2:D	3.3	22.6	5.24	77.49	4.61	4.59	96.0	Normal
k_a	1.5	1:A	0.0	0.0	0.02	1.50	0.02	0.01	94.5	Normal
		1:B	0.0	0.0	0.04	1.50	0.04	0.03	95.5	Normal
		1:C	−2.0	2.8	0.18	1.47	0.18	0.15	94.2	Normal
		1:D	−6.0	6.2	0.36	1.41	0.35	0.30	91.7	Normal
		2:A	0.0	0.0	0.01	1.50	0.01	0.01	93.6	Normal
		2:B	0.0	0.0	0.02	1.50	0.02	0.02	94.6	Normal
		2:C	−2.0	6.6	0.12	1.47	0.11	0.11	93.8	Normal
		2:D	−6.0	14.0	0.24	1.41	0.22	0.20	88.5	Normal

k_e	0.4	1:A	0.0	0.0	0.004	0.400	0.004	0.003	94.0	Normal
		1:B	0.0	0.0	0.004	0.400	0.004	0.004	95.4	Normal
		1:C	1.5	7.1	0.023	0.406	0.022	0.019	95.2	Normal
		1:D	6.3	17.0	0.061	0.425	0.055	0.044	94.3	Skewed right
		2:A	0.0	0.0	0.003	0.400	0.002	0.002	94.5	Normal
		2:B	0.0	0.0	0.002	0.400	0.001	0.001	95.9	Normal
		2:C	0.8	13.1	0.008	0.403	0.008	0.008	95.7	Normal
		2:D	2.5	23.9	0.021	0.410	0.018	0.017	95.8	Skewed right

[a] Design 1: 0.5, 1.0, 1.5, 3.0, and 7.0 h.
Design 2: 0.5, 1.0, 1.5, 2.0, 3.0, 5.0, 7.0, 9.0, and 11.0 h.
Case A: $\sigma(t) = 0.1$.
Case B: $\sigma(t) = 0.01C(t)$.
Case C: $\sigma(t) = 0.05C(t)$.
Case D: $\sigma(t) = 0.1C(t)$.
[b] Normal implies normallike.

Table III. Results of One-Compartment Model Simulation (Model I)[a]

Correlations	Design: Case	Mean of estimated asymptotic correlation coefficients	Empirical correlation coefficient	Standard error of estimated asymptotic correlation coefficients	Distribution of estimated asymptotic correlation coefficients[b]
$D/V, k_a$	1:A	−0.943	−0.944	0.002	Normal
	1:B	−0.851	−0.853	0.005	Normal
	1:C	−0.859	−0.848	0.025	Normal
	1:D	−0.849	−0.819	0.127	Skewed right
	2:A	−0.896	−0.903	0.002	Normal
	2:B	−0.589	−0.570	0.005	Normal
	2:C	−0.603	−0.576	0.025	Normal
	2:D	−0.624	−0.642	0.056	Skewed left
$D/V, k_e$	1:A	0.953	0.954	0.001	Normal
	1:B	0.914	0.915	0.003	Normal
	1:C	0.919	0.924	0.016	Normal
	1:D	0.915	0.949	0.058	Skewed left
	2:A	0.954	0.953	0.001	Normal
	2:B	0.833	0.827	0.002	Normal
	2:C	0.839	0.850	0.008	Normal
	2:D	0.845	0.852	0.021	Skewed right
k_a, k_e	1:A	−0.878	−0.886	0.003	Normal
	1:B	−0.853	−0.861	0.006	Normal
	1:C	−0.861	−0.848	0.031	Normal
	1:D	−0.852	−0.817	0.136	Skewed right
	2:A	−0.853	−0.854	0.003	Normal
	2:B	−0.767	−0.749	0.005	Normal
	2:C	−0.779	−0.755	0.025	Normal
	2:D	−0.795	−0.797	0.050	Normal

[a] Design 1: 0.5, 1.0, 1.5, 3.0, and 7.0 h.
Design 2: 0.5, 1.0, 1.5, 2.0, 3.0, 5.0, 7.0, 9.0, and 11.0 h.
Case A: $\sigma(t) = 0.1$.
Case B: $\sigma(t) = 0.01C(t)$.
Case C: $\sigma(t) = 0.05C(t)$.
Case D: $\sigma(t) = 0.1C(t)$.
[b] Normal implies normallike.

RESULTS OF SIMULATION MODEL II

Tables IV and V display the results of the simulation study of Model II. The format of these tables is similar to Tables II and III. The bias of the estimators increased from Case B to C to D as the error increased for both designs for the estimators D/V, k_a, and α (Table IV). The bias for the estimators D/V and α was positive (0.9–39% for D/V, 1.2–42.2% for α). The estimator of k_a demonstrated a negative bias (−1.1 to −25.7%) as it did in the one compartment model. The estimators of β and k_{21} each

showed a small positive bias (0–0.4% for β, 0.4–4.4% for k_{21}); however, the bias did not increase from Case B to C to D as it did for the estimators D/V, k_a and α (Table IV). Root mean squared error was smaller for each parameter in Design 2 for a given Case than in Design 1. With the exception of β and k_{21}, the percent of mean squared error attributed to bias squared was larger for each parameter in Design 2 for Cases B and C, and smaller for each parameter in Design 2 for Case D, than in Design 1.

As with the one compartment model, the empirical standard error of the simulated values, for all parameters, increased as the amount of drug proportional to the error, $e(t)$, defined by Cases B, C, and D, increased in both designs. However, the empirical standard error of the simulated values was considerably larger relative to the mean simulated value in the two compartment model. Not surprisingly, increasing the number of sampling time points, while keeping other variables constant, produced smaller standard errors. The mean estimated asymptotic standard error was larger or equal to its empirical counterpart for β and k_{21}. No generalities can be made for the other parameters. The percentages of times the true parameter value fell within the univariate 95% confidence interval ranged from 73.4 to 100.0%, a much larger range than in the one compartment model.

For the parameters D/V, k_a, and α, the distribution of estimated values was distinctly bimodal in Case D for both designs and in Case C for Design 1. The bimodal distribution degenerated to one which was skewed, in Case C for Design 2. Case B produced "normallike" distributions for both designs. When a bimodal sampling distribution existed for those estimators showing positive bias, i.e., D/V and α, the secondary mode was as much as 77% larger than the true parameter value (Table IV). For k_a, the secondary mode was 41% smaller than the true value in Design 2, Case D, and the primary mode was 41% smaller than the true value in Design 1, Case D. The distributions of the estimates of β and k_{21} were "normallike" in both designs regardless of the error structure considered.

For a given Design and Case, the empirical correlation coefficients and the mean of the estimated asymptotic correlation coefficients were more similar in value if the distribution of the estimated asymptotic correlation coefficients approached normality (Table V). In several instances when bimodal distributions existed, the two modes appeared on opposite sides of 0. When the correlation coefficient was between k_a and another parameter or between β and k_{21}, the distribution of estimated asymptotic correlation coefficients was skewed right, if skewness existed. For all other pairs of parameters, skewness, when it existed, was to the left. Distributions of correlations between D/V and α and between k_a and α were trimodal in Design 2, Case C. The distribution of estimated asymptotic correlation coefficients for parameter estimators with small bias were normal.

Table IV. Results of Two-Compartment Model Simulation (Model II)[a]

Parameter	True value of parameter	Design: Case	% Bias	$\%\left(\frac{\text{Bias}^2}{\text{MSE}}\right)$	Root mean squared error	Mean simulated value	Empirical standard error of simulated values	Mean estimated asymptotic standard error	% of simulated values within 95% confidence interval	Distribution of simulated values (frequency and value at high mode; frequency and value at low mode)[b]
D/V	0.441	1:B	1.0	10.1	0.01	0.4452	0.0125	0.0125	96.4	Normal
		1:C	18.5	50.4	0.11	0.5225	0.0807	0.1142	99.0	Bimodal (111, 0.480; 23, 0.672)
		1:D	39.0	40.6	0.27	0.6128	0.2076	0.1764	96.8	Bimodal (258, 0.540; 129, 0.720)
		2:B	0.9	17.0	0.01	0.4449	0.0086	0.0082	93.7	Normal
		2:C	14.8	65.6	0.08	0.5061	0.0471	0.0704	100.0	Skewed right
		2:D	24.3	37.8	0.17	0.5483	0.1375	0.0972	91.3	Bimodal (314, 0.480; 40, 0.750)
k_a	2.389	1:B	−1.1	7.9	0.10	2.362	0.092	0.092	95.6	Normal
		1:C	−16.2	54.3	0.52	2.002	0.355	0.494	93.5	Bimodal (66, 2.05; 39, 1.45)
		1:D	−25.7	64.9	0.76	1.774	0.452	0.613	73.4	Bimodal (77, 1.40; 59, 2.03)
		2:B	−1.1	15.1	0.07	2.363	0.061	0.058	93.1	Normal
		2:C	−15.0	73.5	0.42	2.030	0.216	0.329	93.5	Skewed left
		2:D	−18.7	56.8	0.59	1.943	0.388	0.415	77.7	Bimodal (65, 2.12; 30, 1.40)

α	0.914	1:B	1.3	9.7	0.04	0.926	0.037	0.037	96.2	Normal
		1:C	22.4	50.7	0.29	1.119	0.203	0.290	98.5	Bimodal (115, 1.015; 31, 1.505)
		1:D	42.2	43.4	0.59	1.300	0.441	0.411	93.6	Bimodal (167, 0.96; 62, 1.36)
		2:B	1.2	13.8	0.03	0.925	0.027	0.026	94.3	Normal
		2:C	19.5	65.5	0.22	1.092	0.129	0.197	98.9	Skewed right
		2:D	27.1	36.0	0.41	1.162	0.330	0.254	85.7	Bimodal (338, 0.96; 33, 1.62)
β	0.0462	1:B	0.0	0.0	0.0003	0.0462	0.0003	0.0003	94.6	Normal
		1:C	0.2	0.6	0.0013	0.0463	0.0013	0.0014	94.7	Normal
		1:D	0.0	0.0	0.0026	0.0462	0.0026	0.0028	96.5	Normal
		2:B	0.0	0.0	0.0002	0.0462	0.0002	0.0002	95.4	Normal
		2:C	0.4	2.9	0.0012	0.0464	0.0012	0.0012	96.1	Normal
		2:D	0.2	0.2	0.0023	0.0463	0.0023	0.0024	95.9	Normal
k_{21}	0.25	1:B	0.4	5.3	0.004	0.251	0.004	0.004	94.3	Normal
		1:C	3.2	18.0	0.019	0.258	0.017	0.020	95.0	Normal
		1:D	2.4	4.6	0.028	0.256	0.027	0.035	97.7	Normal
		2:B	0.4	7.8	0.004	0.251	0.003	0.003	94.5	Normal
		2:C	4.4	41.3	0.017	0.261	0.014	0.016	94.6	Normal
		2:D	2.0	5.2	0.022	0.255	0.021	0.028	98.6	Normal

[a] Design 1: 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 6.0, 9.0, 12.0, 15.0, 18.0, 21.0, 24.0, 36.0, and 48.0 h.
Design 2: 0.125, 0.25, 0.375, 0.5, 0.5625, 0.625, 0.6875, 0.75, 0.8125, 0.875, 0.9375, 1.0, 1.25, 1.75, 2.0, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5, 12.0, 13.5, 15.0, 18.0, 21.0, 24.0, 36.0, and 48.0 h.
Case B: $\sigma(t) = 0.01C(t)$.
Case C: $\sigma(t) = 0.05C(t)$.
Case D: $\sigma(t) = 0.1C(t)$.
[b] Normal implies normallike.

Table V. Results of Two-Compartment Model Simulation (Model II)[a]

Correlations	Design: Case	Mean of estimated asymptotic correlation coefficients	Empirical correlation coefficient	Standard error of estimated asymptotic correlation coefficients	Distribution of estimated asymptotic correlation coefficients (frequency and value at high mode; frequency and value at low mode)[b]
$D/V, k_a$	1:B	−0.964	−0.962	0.006	Normal
	1:C	−0.978	−0.901	0.014	Skewed right
	1:D	−0.955	−0.779	0.023	Skewed right
	2:B	−0.967	−0.969	0.004	Normal
	2:C	−0.981	−0.938	0.007	Bimodal (121, −0.987; 81, −0.972)
	2:D	−0.957	−0.886	0.014	Bimodal (95, −0.968; 70, −0.950)
$D/V, \alpha$	1:B	0.968	0.969	0.005	Normal
	1:C	0.980	0.963	0.012	Skewed left
	1:D	0.955	0.931	0.024	Skewed left
	2:B	0.964	0.968	0.004	Normal
	2:C	0.978	0.952	0.008	Trimodal (129, 0.987; 89, 0.980; 79, 0.971)
	2:D	0.948	0.978	0.019	Bimodal (101, 0.952; 98, 0.968)
$D/V, \beta$	1:B	0.237	0.219	0.002	Normal
	1:C	0.169	0.072	0.096	Bimodal (121, 0.255; 32, −0.015)
	1:D	0.057	−0.029	0.122	Bimodal (65, 0.150; 50, −0.060)
	2:B	0.270	0.269	0.001	Normal
	2:C	0.218	0.051	0.064	Skewed left
	2:D	0.116	0.039	0.118	Bimodal (83, 0.180; 30, −0.060)
$D/V, k_{21}$	1:B	0.671	0.670	0.005	Normal
	1:C	0.515	0.313	0.275	Bimodal (208, 0.700; 18, −0.070)
	1:D	0.198	0.065	0.377	Bimodal (67, 0.525; 33, −0.210)
	2:B	0.716	0.726	0.005	Normal
	2:C	0.642	0.349	0.152	Skewed left
	2:D	0.363	0.218	0.352	Bimodal (121, 0.595; 25, −0.210)
k_a, α	1:B	−0.926	−0.924	0.011	Normal
	1:C	−0.951	−0.868	0.025	Skewed right
	1:D	−0.887	−0.783	0.070	Skewed right
	2:B	−0.914	−0.920	0.010	Normal
	2:C	−0.946	−0.870	0.018	Trimodal (116, −0.963; 82, −0.945; 67, −0.924)
	2:D	−0.874	−0.849	0.046	Skewed right

k_a, β	1:B	−0.210	−0.194	0.002	Normal
	1:C	−0.147	−0.066	0.095	Bimodal (130, −0.210; 31, 0.045)
	1:D	−0.023	−0.010	0.130	Bimodal (66, −0.108; 47, 0.108)
	2:B	−0.241	−0.240	0.002	Normal
	2:C	−0.195	−0.003	0.062	Skewed right
	2:D	−0.081	−0.015	0.119	Bimodal (81, −0.120; 34, 0.120)
k_a, k_{21}	1:B	−0.621	−0.619	0.009	Normal
	1:C	−0.472	−0.298	0.277	Bimodal (207, −0.595; 19, 0.140)
	1:D	−0.122	−0.093	0.398	Bimodal (69, −0.455; 31, 0.315)
	2:B	−0.649	−0.657	0.009	Normal
	2:C	−0.586	−0.268	0.153	Skewed right
	2:D	−0.268	−0.137	0.363	Bimodal (118, −0.455; 23, 0.315)
α, β	1:B	0.322	0.307	0.008	Normal
	1:C	0.236	0.181	0.105	Bimodal (99, 0.330; 35, 0.030)
	1:D	0.160	0.097	0.111	Bimodal (78, 0.045; 64, 0.240)
	2:B	0.355	0.351	0.006	Normal
	2:C	0.283	0.170	0.070	Skewed left
	2:D	0.219	0.108	0.112	Bimodal (67, 0.288; 52, 0.036)
α, k_{21}	1:B	0.817	0.815	0.007	Normal
	1:C	0.642	0.530	0.276	Bimodal (195, 0.840; 19, 0.070)
	1:D	0.423	0.335	0.334	Bimodal (100, 0.750; 43, 0.090)
	2:B	0.857	0.859	0.004	Normal
	2:C	0.762	0.588	0.149	Skewed left
	2:D	0.585	0.380	0.311	Bimodal (152, 0.780; 26, 0.030)
β, k_{21}	1:B	0.654	0.654	0.004	Normal
	1:C	0.660	0.697	0.018	Skewed right
	1:D	0.678	0.703	0.027	Normal
	2:B	0.649	0.641	0.004	Normal
	2:C	0.642	0.674	0.013	Normal
	2:D	0.660	0.711	0.021	Normal

[a] Design 1: 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 6.0, 9.0, 12.0, 15.0, 18.0, 21.0, 24.0, 36.0, and 48.0 h.
Design 2: 0.125, 0.25, 0.375, 0.5, 0.5625, 0.625, 0.6875, 0.75, 0.8125, 0.875, 0.9375, 1.0, 1.25, 1.5, 1.75, 2.0, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5, 12.0, 13.5, 15.0, 18.0, 21.0, 24.0, 36.0, and 48.0 h.
Case B: $\sigma(t) = 0.01C(t)$.
Case C: $\sigma(t) = 0.05C(t)$.
Case D: $\sigma(t) = 0.1C(t)$.
[b] Normal implies normallike.

DISCUSSION

Three comments should be made at this point. First, no outliers were used in our simulation process. Second, we assume we are fitting our data to the "correct" model for accurate characterization of a dosage form. Third, we also assume our "correct" model has the "correct" weights associated with the observations at each time point. One can obtain information on the proper weighting in practice by obtaining replicate observations at each time point in a trial experiment. The weighting procedure is important since it may have a pronounced influence on bias in parameter estimation and on the type of distribution of the estimates.

We found that nonlinear estimation procedures for the one compartment model yielded essentially unbiased estimators that were normally distributed when the data points were subject to the three smallest error structures considered (Cases A, B, and C). Metzler (20) made similar conclusions after simulating the one compartment model 250 times with 12 time points and letting $e(t)$ be a random normal deviate with standard deviation, $\sigma(t)$, equaling $0.05C(t)$. In the case where $e(t)$ was a random normal deviate with standard deviation equaling $0.1C(t)$, the above statements do not hold as the estimators have larger bias and their distributions become skewed. For a given Case in Model I, there is no improvement in the bias of k_a in Design 2 when compared with the results in Design 1 as there is for D/V and k_e. This may be due to the selection of the time points.

With the exception of the smallest error structure considered, the results for the two compartment model showed estimators to have considerable bias. Estimators of α and D/V had substantial positive bias. The absorption rate constant, k_a, had a large negative bias. In Cases C and D for Design 1 and in Case C for Design 2, bimodal distributions were observed for the biased estimators. The distributions of correlation coefficients involving these parameters (D/V, α, k_a) with either α or k_{21} were bimodal.

In view of the unbiasedness of the estimators and the normality of the sampling distributions of the estimators in Cases A, B, and C for Model I, we found no reason to contradict the recommendation of Boxenbaum *et al.* (13) to perform t-tests to compare parameters. Also, using univariate confidence intervals for parameter estimates would seem to be appropriate in the three cases. When the error was large [Case D, $\sigma=0.1C(t)$], the confidence intervals for k_a were less than 95% accurate in the one compartment model. This suggests, in this case, that the use of planar limits is preferable, and the use of t-tests to compare parameters is questionable.

With large error, the accuracy of the univariate confidence intervals for the parameters D/V, k_a, and α in the two compartment model is also

suspect. Along with the lack of faith one places in estimates of the standard error for parameter estimators, the sometimes gross departures from normality of the sampling distributions of the parameter estimators suggest that performing t-tests to compare parameters in the two compartment model, as Boxenbaum *et al.* (13) have recommended, may be meaningless, except in Case B.

The bimodality of some of the distributions of correlation coefficients raises doubts as to how meaningful the correlations are. Thus, the importance placed upon them by Boxenbaum *et al.* (13) may be unwarranted. This bimodality also makes confidence ellipsoids appear to be less desirable than some have claimed (14). For parameters which had a bimodal sampling distribution, a bivariate plot of the two parameters in a correlation coefficient revealed two "balls" of points, each "ball" being centered at coordinates approximated by the modes of the distributions of the parameters themselves. This implies that two different sets of parameter values exist which yield approximately equivalent residual sums of squares. These simulations suggest that bimodality is more likely to occur when the amount of drug concentration proportional to error is large. Also, we used data obtained from one compartment to estimate parameters of a two compartment model. More information, such as urine data or blood data on the second compartment, would improve the quality of the parameter estimates. Clearly, further investigation of this problem seems warranted.

The conclusion for the two compartment model is that the bias in the estimates is effected minimally by the number of sampling time points and greatly by the error structure in the design. That is, the reduction in bias due to increasing the number of sampling points for a given error structure is small when compared to the reduction in bias due to reducing error for a given number of sampling points. The estimates of β in the two compartment model and k_e in the one compartment model are reasonably good. This is important since composite half-lives of elimination are based on these estimators of the elimination rate constants. In general, the relatively poor results for the two compartment model when compared to the one compartment model can be attributed to the higher correlations between parameters which existed in the two compartment model simulations and to the fact that data are obtained from only one compartment in the two compartment system.

It should be emphasized that our conclusions are based on results obtained for specific parameter values in specific designs, and any inferences obtained from our results should be viewed with appropriate caution. Therefore, further simulation studies may be worthwhile to confirm and expand our present knowledge.

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