Simulation of Mathematical Models for Public Health Problems

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THE USE of models, mechanical and mathematical, has a long and fruitful history in the health sciences. In the last few years, with the increasing availability of large electronic computers, activity and progress in this field have increased markedly. A great deal, however, can still be done in extending the application of models and their simulation in the many specialties of public health and its allied sciences.

The more complex a system or process is, the greater the promise of parametric or stochastic (probabilistic) models and of computer simulation in obtaining information about the role of the actions and interactions of a large number of variables in determining characteristics of the outcome.

A mathematical model, in general, consists of a number of mathematical statements (including definitions, postulates, equations, and rules) which describe the probabilistic behavior of random variables.

Approximation of Life Situation

Dr. Nooney (*1*), in discussing mathematical models, has introduced the space of "imagery" between reality and the model. This space is a simplification of the real-life situation and contains the major factors that predominate in determining the operation of the life situation and a description of their actions and interactions. The imagery space may also contain a "noise" variable which represents the sum total of the many factors, known and unknown, present in real life but which are minor or operate in a manner too little known to be included in the mathematical model.

If the model itself is considered as a series of "if . . ." statements, the results of its operation or simulation may be thought of as a series of "then . . ." statements. Whenever we can build a model for which the input of "if . . ." statements bears a relationship to a real-life situation, the resulting "then . . ." of the simulation procedure may lead to new conjectures, hypotheses, or means of interpretation of the process itself. The "if . . ." statements of the model may reflect past experience and may be altered to explore the effect of changes in operation of the system. By model simulation such changes (in management policy, for example) can be explored without interfering with a continuing program.

The ultimate usefulness of simulation based on a stochastic model depends on the extent to which the model corresponds to, and describes completely, some real-life situation. In the sense that a model ignores some contributing factors (or, as is frequently the case, averages

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over them), it involves approximation. This lack of completeness in representing all possible factors may limit the range of application of the simulated results but need not prevent the model from yielding useful information. Oversimplification and approximation are hardly unique to model building in the health sciences. It would be difficult for anyone to live a day without encountering the useful results of applications of the theorems of Euclidian geometry and of mechanical physics.

Simulation in the Health Sciences

Webster's Third New International Dictionary defines the word "simulate" as "to have the appearance of" and "to have the characteristics of." The program input of the simulation procedure for a stochastic model consists of the mathematical statements of the model as translated into operational machine language. In general, the computer is instructed to break the process down into its smallest elements and to generate a very large number of single observations on the basic random variables, to observe the outcomes, and to summarize them according to the plan of the model. For example, the pattern of outcomes in repeated independent tosses of 10 "fair" coins might be estimated by actually tossing 10 coins 100 times. If this manual simulation mechanism (the tossing method and the "fairness" of the coins) is adequate, the estimated results should conform closely to the binomial rule that, if the number of heads is x, then

$$\text{probability } (x=k)=\frac{10!}{k!\,(10-k)!}\left(\frac{1}{2}\right)^k\left(\frac{1}{2}\right)^{n-k} \quad \text{for } k=0,\ 1 \ldots 10.$$

A better representation of the binomial could be obtained in a much shorter time by computer simulation. This simulation might consist of the generation of 5-digit random numbers (00000 to 99999). The computer classifies each such number as a head if it is less than 5,000; otherwise, it is a tail. Each set of 10 random numbers yields an x value, the number of heads. It is the great speed with which these trials are made and the x results tabulated which makes computer simulation efficient both for this example and for much more complex operations.

There have been a number of examples of the use of simulation in epidemic theory (*2–5*). Many of these models are of greater complexity than the Reed-Frost process used in this paper to provide an example. Simulation in epidemiology holds real promise for the future.

Genetics, in which mathematical models can faithfully represent many situations of interest, offers many examples of computer simulation of stochastic processes (*6*, *7*). Levene and Dobzhansky (*8*) refer to "formidable analytic difficulties" overcome by use of what they call "bean bag genetics."

In the broad area of statistical theory, simulation of stochastic models (frequently called empirical sampling) has been used to study the sampling distributions of estimates, to estimate power functions, and to investigate the robustness of tests. Of particular interest here are studies related to bioassay, both fixed sample size and sequential (*9–11*), and to the estimation problem in followup studies (*12*).

Sheps and Perrin have discussed results of investigation of stochastic fertility models (*13*) and promise publication of a paper on a Monte Carlo investigation of a human fertility model.

Application of operations research methods to hospital studies has resulted in papers on utilization of hospital facilities (*14*, *15*), congestion in outpatient clinics (*16*), and the effect of admission policies on the hospital population. Thompson and associates at Yale University (*14*) state: "A maternity service simulator programmed for a large computer can provide hospital planners and administrators with predictive information about probable occupancy and consequently probable adequacy of various numbers and arrangements of maternity suite facilities." Fetter and Thompson conclude that computer simulation models "can and should play an important role in hospital administration" (*15*).

The Systems Research Group at Ohio State University, in a study of blood bank systems (*17*), state in their summary: "The simulation approach has proved to be an efficient method of studying blood-banking operations and is a unique example of the application of management science to community health systems. The flexibility of computer simulation permits experimenters to systematically alter community supply and demand characteristics and management decision rules to arrive at policies providing efficient service to the community. . . . Achievement of such understanding through direct manipulation of on-going systems is not safely possible in many instances and is prohibitive in terms of the time and cost that would be involved."

A most significant application of a different type is represented by the University of California and the Rand Corporation program entitled "Medical Use of Simulation Electronics" (MUSE) (*18*), which represents simulation of a physiological subsystem, the biochemical behavior of the blood. Dr. J. Maloney (*19*), in summarizing this program at the Fifth IBM Medical Symposium, points out that since computers are particularly helpful in handling systems with many variables and "there is no machine or system with as many variables as the human body, computers can be expected to be especially applicable to the problems of medicine." The MUSE program has been shown to be highly accurate and is, of course, free of laboratory and human errors. Alterations in response to simulated stresses in 56 blood constitutents can be calculated and printed out in 2 minutes. Maloney concludes that "The simulation of complex biological systems offers the greatest promise of the application of computers to medicine."

In the last few years computer simulation procedures have found application in psychiatry (*20*, *21*), carcinogenesis, learning theory (*22*), and neurology.

Simulation methods are not limited to game-playing on computers. E. Bogdanoff (*23*), in an article entitled "An Epidemiological Game: Simulation in Public Health," describes the simulation of health department action and response in the face of a supposed outbreak of rabies. The roles of the heads of the nursing, communicable disease, and sanitation branches were played by "gaming functionaries." The author outlined the purposes of the project:

(1) providing a simulation mechanism for public health functionaries to experience both unique and typical public health problems, thus gaining significant training in areas currently difficult to obtain;

(2) producing an instrument which is capable of providing an objective and efficient framework to analyze the operations of the public health system as it affects its environment;

(3) allowing for controlled experimental conditions, to study the use of various techniques used in simulation, and the processes of public health decision making, hence a tool to aid in the development of theory in both simulation and medicine.

Example of Simulation

One of the early and best-known examples of simulation of problems in public health is the mechanical model used by Lowell J. Reed and Wade Hampton Frost of Johns Hopkins University to illustrate the stochastic character of their epidemic model for closed and randomly mixing populations.

Assumptions

The Reed-Frost model, described by Abbey (*24*), is based on the following assumptions:

The infection is spread directly from infected individuals to others by a certain kind of contact (adequate contact) and in no other way.

Any non-immune individual in the group, after such contact with an infectious person in a given period, will develop the infection and will be infectious to others only within the following time period, after which he is wholly immune.

Each individual has a fixed probability of coming into adequate contact with any other specified individual in the group within one time interval, and this probability is the same for every member of the group.

The individuals are wholly segregated from others outside the group.

These conditions remain constant during the epidemic.

In application of the model to epidemics of recognizable disease it is necessary to make additional assumptions concerning the lengths of the infective and incubation periods and the absence of silent immunizing infections. When applying the model to a situation in which interest centers only on the occurrence of infection without distinction between overt and subclinical forms, these additional assumptions are relaxed; it is still necessary, however, to assume away (or average over) all differences in resistance, variability of dose, variability of length of infective period, all tendency of the population to congregate into sets, and the addition of new cases or susceptibles from the outside.

Specifications of the Model

Let

p=probability that any two persons in the population will make adequate con-contact within an interval.

Note that this single parameter summarizes: the behavior of the population members and the properties of the agent (mode of spread and infectivity), properties which determine what constitutes "adequate" contact. Note further that, on the average, each individual will make $p(N-1)$ adequate contacts and that some of these will be expended on susceptibles and immunes and perhaps some on infected persons.

Then, within the interval t to $t+1$,

$q=1-p$=the probability that any two individuals will fail to make adequate contact in an interval.

Let

C_t=the number of cases at time t,

and

S_t=the number of susceptibles at time t.

Then

q^{C_t}=probability that an individual avoids contact with all C_t cases,

and

$P=1-q^{C_t}$=probability that an individual fails to avoid all infected individuals and is exposed.

Then the expected (average) value of the number of new cases at time $t+1$ is

$$E(C_{t+1})=S_t(1-q^{C_t}).$$

C_{t+1} is a binomial random variable, and if we write

$$P=(1-q^{C_t}) \text{ and } Q=1-P,$$

then we have the familiar

$$E(C_{t+1})=S_tP \text{ and } \mathrm{Var}\ (C_{t+1})=S_tPQ$$

of the binomial.

The "Expected" Epidemic

The equation $C_{t+1}=S_t(1-q^{C_t})$ can be used to calculate the "expected" epidemic, that is, the epidemic in which, during each interval, the number of new cases is exactly equal to its expectation or to the number of cases expected on the average over a large number of such experiments. When we calculate the "expected" epidemic only, however, the probabilistic or stochastic nature of the model, or process, is not apparent in the result; nor is any measure of the random variation to be expected.

Role of Random Variation

Reed and Frost illustrated the random variation to be expected between one repetition of an epidemic trial and another by an ingenious model in which the cases (infected individuals), the susceptibles, and the immunes are represented by different-colored balls. Balls of a fourth color, called "blocks," were introduced to represent nonspecific impediments to adequate contact. The number of blocking balls introduced controls the value of the parameter p, or the probability of adequate contact between two individuals. The total population of balls is randomized (by vigorous shaking), and all the balls are poured into a narrow trough so that they form a single line. Any "susceptible" ball which is not separated from every "case" ball by at least one intervening block is considered to have had adequate contact with a case and is removed and replaced by a "case" ball. In addition, the "case" balls which were present at the beginning of the trial are replaced by "immunes":

Typical ordering of balls after randomization	*Replacements made before the next randomization*
Block	
Susceptible	
Susceptible	
Immune	
Susceptible	
Block	
Case	→ Immune
Immune	
Immune	
Block	
Susceptible	→ Case
Immune	
Susceptible	→ Case
Immune	
Case	→ Immune
Immune	
Block	

When the replacements have been accomplished, the entire process, including randomization, is repeated in order to find the observed number of new cases in the following period.

Those who have experimented with this model or with one like it may recall that on some occasions introduction of a single case failed to start an epidemic, while on other occasions chance would have it that the epidemic caught fire and eventually resulted in infection of the majority of the susceptible population.

Horiuchi and Sugiyama (*25*) in 1957 described results obtained by simulation with a mechanical model for the Reed-Frost epidemic. They described the simulation only as involving "chips and many shufflings." Using this method with a population of 100 susceptibles, for each of three contact rates (0.01, 0.02, and 0.04) they simulated 100 epidemics originating from introduction of a single case. They presented in graphic form the observed distributions of the total size of the epidemics. These results resemble very closely those in figure 1. The authors pointed out that, with the use of high-speed computers, many other interesting results could be obtained.

Although we were unaware of the work of Horiuchi and Sugiyama, it seemed that the simplest method of obtaining information about the probability distribution of the size would be computer simulation of the epidemic process. The existence of programs for generating random numbers and the ability of the computer to use random numbers to simulate binomial trials (or, in the two-agent model discussed later, trinomial trials (*26*)) made this approach appealing. (The specific subroutine used was described by E. D. Courant of Brookhaven National Laboratories, Upton, N.Y., June 1962.)

The 7094 IBM computer at Columbia University was programed by Varma to simulate the epidemic process. In the last computer run we made, 500 Reed-Frost epidemics were simulated for each of five conditions, These 2,500 epidemic trials required more than 3 million (very rough estimate) binomial trials as well as some 30,000 (also very rough estimate) calculations of the new probability of contact with a case $(1-q^{C_t})$. In addition, the machine printed out, for each of the five conditions and each of the five sets of 500 epidemics, the distribution of the epidemics by size (the number of cases of infection in a single epidemic); by duration (the number of time intervals during which the agent is present and spreading in the population); and by both size and dura-

Distribution of epidemics by number of cycles and number of cases per epidemic

Number of cycles per epidemic	Total epidemics	Number of cases per epidemic							
		1–9	10–119	120–129	130–139	140–149	150–159	160–169	170–179
Total	500	116	0	2	10	46	111	151	64
1	73	73							
2	29	29							
3	11	11							
4	3	3							
5	0								
6	0								
7	0								
8	2							2	
9	2					1			1
10	19				2	1	5	6	5
11	54				1	5	17	17	14
12	65				1	7	16	31	10
13	72			1		4	20	37	10
14	65			1	1	8	19	28	8
15	39				2	5	13	14	5
16	30				1	7	11	5	6
17	19					3	6	7	3
18	12				1	2	3	4	2
19	2				1	1			
20	1					1			
21	2					1	1		

tion. These results are summarized in the three figures and the table. The table shows the distribution of the 500 epidemics by the number of intervals or cycles per epidemic and by the number of cases per epidemic when the original susceptible population numbers 200, one infected case is originally introduced, the probable rate of adequate contact with an infected individual is 0.01, and the average number of contacts is 2.

The results of repeated trials of the Reed-Frost process are given in the figures. Figure 1 shows the distribution of size under three sets of conditions. Since one of the variables is the original number of susceptibles, S_o, the size has been expressed as a percentage of the population infected. In this first example the average number of contacts made by each infected individual per time period is held constant and equals 2. It is seen that the proportion of the epidemics which die out before they have involved more than 10 percent of the population is relatively constant over the three population sizes. As the original population of susceptibles increases, however, the sizes of epidemics which catch fire become more concentrated about the mode.

The distribution of duration times is given for the same three sets of conditions in figure 2. The effect of increasing the original number of susceptibles (still holding the average number of adequate contacts at two) is to increase the median (and mean) duration time.

Finally, in figure 3 the number of persons originally susceptible is held constant at $So=200$, while the contact rate increases. At the lowest contact rate ($p=0.005$) the large majority of the epidemics abort with very few cases, and none involves more than 60 of the 200 susceptibles. For $p=0.010$, the typical bimodal distribution shows the separation between the 20 percent of the epidemics affecting fewer than 10 persons and the remainder involving more than 120. Finally, for $p=0.020$,

Figure 1. Proportion of population becoming infected in 500 epidemics, with average number of contacts 2, for each of 3 population sizes

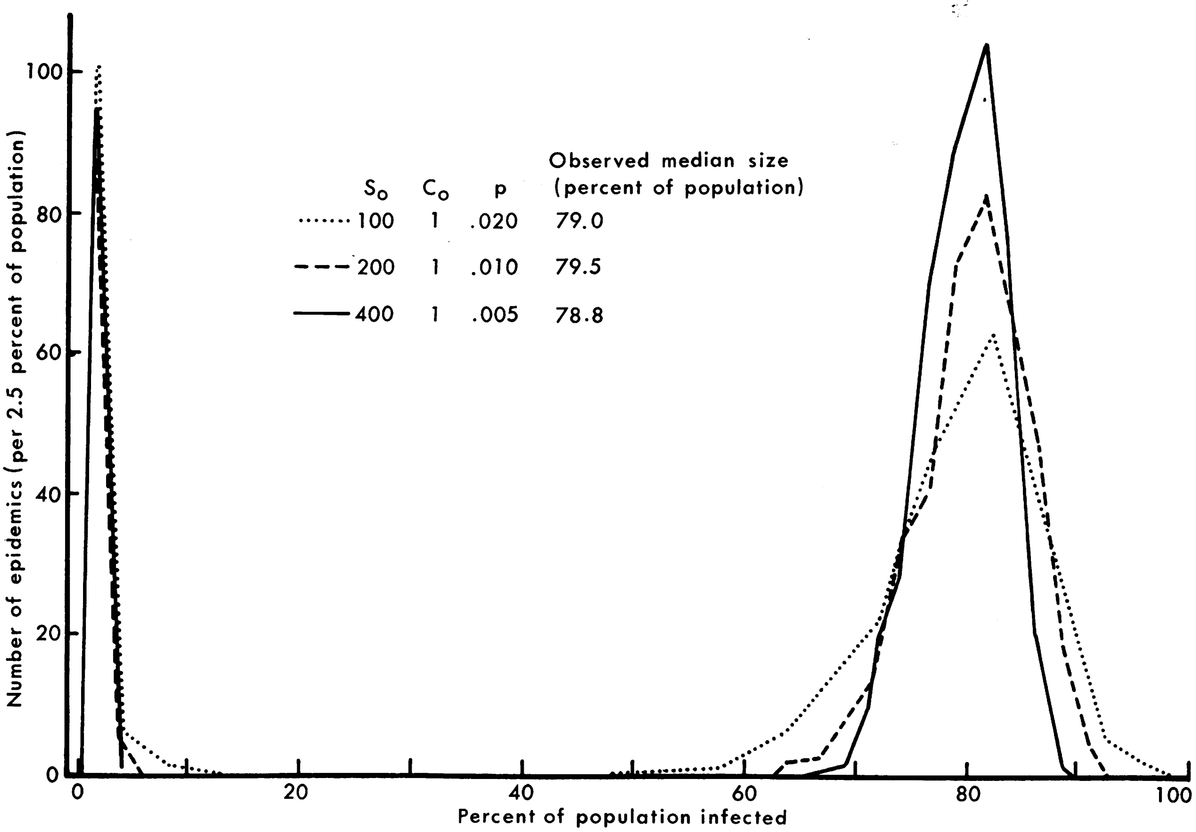
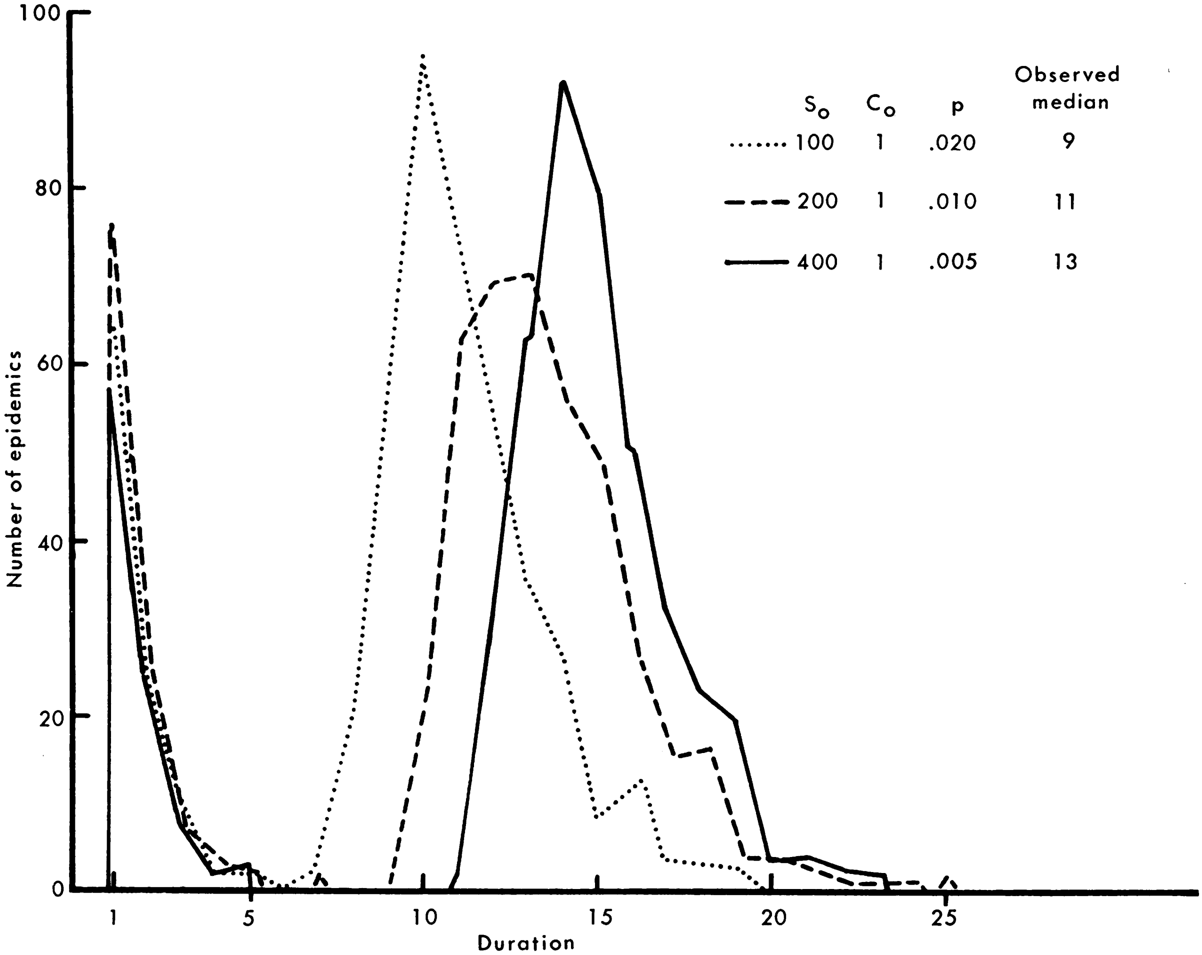


Figure 2. Duration period in 500 epidemics, with average number of contacts 2, for each of 3 population sizes



the highest contact rate, only 2 percent of the epidemics abort; the remainder sweep through 85 to 100 percent of the population.

Although the Reed-Frost epidemic model illustrated is a very simple one, it is characteristic of a class of problems (involving Markov processes) in which simulation is a most useful and efficient method. Here, each step (of going from one time interval to the next) is easily described analytically (as in the equation). It is, however, still difficult to make useful probability statements, analytically or numerically expressed, about the outcome of the entire sequence of steps. The random variables in the Reed-Frost model are binomial; each random number generated can be transformed into one observation on a variable with the desired distribution. Therefore the sampling efficiency (*27*) is maximum, in contrast, for example, to a system in which observations on an approximately normally distributed variable might be generated by using means of groups of random numbers.

The originial purpose in obtaining these size and duration distributions was to provide a basis for comparison with an epidemic involving two competing agents. Subsequently, however, the results have proved to be useful teaching material in conjunction with a Reed-Frost mechanical model.

Two-Agent Model

Around 1963 Dr. John Fox, chief of the epidemiology department, Public Health Research Institute of New York City, asked Elveback whether information relevant to the difficult problem of naturally occurring viral interference could be obtained through the use of theoretical models. The term "interference" refers to the partial or total suppression of infection with one virus because of already existing infection with a second. The theoretical model developed (*24*) represented the two-agent competitive risk situations as an extension of the model of Reed-Frost. On a desk calculator, the "expected" epidemic for the two-virus competitive situation was obtained and compared with the epidemic "expected" under the simple Reed-Frost model for the absence of an interfering agent. The two "expected" epidemics differed very little. These results were interesting but unsatisfying.

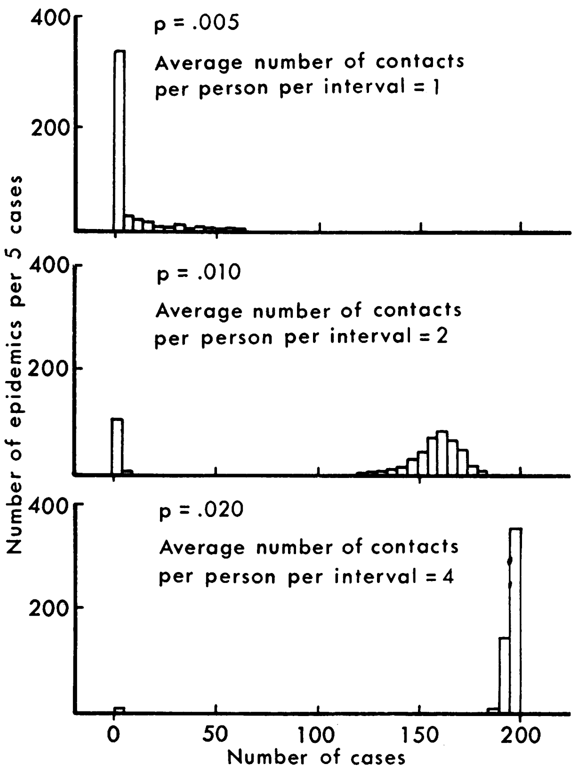
The comparison of real interest was that between the two probabilities, for the single-agent model and the two-agent model, that the epidemic would abort with fewer than, say, six cases. This comparison could be accomplished with a desk calculator, but by exceedingly tedious computations. It would be necessary to write down all paths to total sizes of 1, 2, 3, 4, and 5 and to compute the probability of each by repeated use of the simple binomial formulas. For the simple Reed-Frost epidemic for one agent, 16 paths are involved; for the two-agent epidemics there are many more. Even with a large high-speed computer, this method is unpromising, particularly if the entire probability distributions of the size are desired. We obtained the size and duration distributions by computer simulation for the two-agent epidemic under the assumption of complete interference. These distributions were found to differ from those presented in figures 1 and 2 only in trivial detail. These results enabled us to conclude that the detection and "demonstration of the operation of wholly naturally occurring viral interference would be very difficult indeed" (*26*).

Summary

The increasing availability of large electronic computers has given impetus to use of simulation of stochastic models to obtain information, otherwise inaccessible, on problems in public health and the medical sciences.

Many examples can be cited from the literature to illustrate the broad range of problems for which this statistical method proves useful and efficient. One example, taken from the Reed-Frost epidemic model, is given in detail, from the assumptions relating to the real-life situation to the mathematical model. Distributions of total number of cases and duration for repeated epidemics were obtained by computer simulation. An extension of this model was used in a study of viral interference between competing agents.

Figure 3. Size of epidemics in population of 200 susceptibles in 500 epidemics for each of 3 contact rates



DOCUMENTATION NOTE

Although we have not attempted extensive bibliographic research on computer simulation in biomedical problems, we have accumulated a rather large bibliography on the subject. Single copies of this are available through: Editor, *The New York Statistician* (official publication of the New York area chapter of the American Statistical Association), 765 Broad Street, Newark 1, N.J., at a cost of $1.

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Division of Hospital and Medical Facilities Reorganized

The Division of Hospital and Medical Facilities, Public Health Service, which has administered the Hill-Burton program of health facility construction since its inception in 1946, has been reorganized to reflect the broadened scope of its activities in connection with new programs established by 1963 and 1964 legislation.

The recent legislation not only extended and enlarged the Hill-Burton program, but gave the Division responsibility for administering construction grant programs providing aid for educational facilities for health professions and facilities for the mentally retarded. In addition, the Division is jointly responsible with other units of the Public Health Service for administering grant programs which would add to the nation's supply of comprehensive mental health centers and nurse training facilities.

Six branches comprise the new administrative framework:

- The Architectural, Engineering, and Equipment Branch provides leadership in the architectural and engineering aspects of all construction grant programs administered by the Division, and provides consultation and assistance to Federal and State officials, private organizations, and the general public regarding the planning, construction, and equipping of the facilities aided by these programs.
- The Educational Facilities Branch administers or cooperates in administering project grant programs concerned with the construction of teaching facilities for students working toward professional degrees in medicine, osteopathy, pharmacy, optometry, podiatry, dentistry, public health, and nursing. It also administers a project grant program for the construction of university-affiliated facilities for the mentally retarded which train the professional and technical personnel required for the care and treatment of the mentally retarded.
- The Health Facilities Services Branch administers and participates in research, study, consultation, and demonstration programs designed to improve organization, standards of operation, and use of health facilities and services. It also promotes the application of new concepts, standards, and practices.
- The Program Planning and Analysis Branch provides program planning and development assistance to the Division, particularly through statistical studies and data evaluation.
- The Research and Demonstration Grants Branch administers the extramural research and demonstration grant programs which relate to the social, administrative, clinical, organizational, and physical aspects of hospitals and other patient care facilities.
- The State Plans Branch directs the Hill-Burton program and other formula grant programs administered at the State level by an officially designated State agency. These include Federal aid for constructing hospitals, long-term care facilities including nursing homes, public health centers, diagnostic and treatment centers, rehabilitation facilities, State health laboratories, and community facilities for the mentally retarded. This branch also administers grants to assist in areawide planning for hospitals and related health facilities, and cooperates in administering the formula grant program for planning and constructing community mental health centers.