Kinetic Simulation by Digital Computer Using Graphic Display Techniques

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Abstract ☐ A method of simulating chemical and biological processes by means of computer-generated plots is described, and two examples are given. The essence of the procedure is the successive approximation of smooth computed curves to the experimental data points, by means of systematized parameter variation. The curves generated during the simulation procedure are monitored on a video display screen, and instantaneous human direction or intervention may be made by means of numerical command signals from a coupled keyboard-printer. Knowledge of the parameter values for the simulation curves best fitting the original data points provides valuable insight into the principles underlying the experimental process under investigation and furnishes a predictive and manipulative tool of some precision.

Keyphrases ☐ Pharmacokinetic, chemical kinetic simulation—graphic display method ☐ Computerized methods—kinetic analysis, simulated ☐ Drug distribution, *in vivo*—computerized simulation ☐ Diagram, computer program—kinetic simulation

Previous papers from these laboratories illustrated the utilization of computer procedures for on-line data acquisition and control of pharmacological experiments (1–3). The present paper reports on the use of computer procedures as a means of simulating experimental conditions, with the aim of gaining an insight into the mechanisms underlying specified chemical, physical, and biological processes, with a maximum of accuracy and a minimum of routine and repetitive experimentation.

The simulation procedure involves the building up of a series of smooth computer-generated curves to find those most closely approximating the line of best fit through the data values determined experimentally, when the latter are presented as a graphic plot. The simulation curves are built up and manipulated by means of systematic variation of the parameters in a series of specification equations (4–7).

Digital computer procedures offer the advantage of large internal data storage capacity and high speed of decision-making and calculation (8). Analog computer procedures, on the other hand, offer the advantage of a direct human interaction facility, favoring optimum parameter variation control (9, 10). Hybrid computer systems utilize the advantages of both procedures: the parameter optimization strategy is performed in the digital control unit, whereas the actual solution of the specification equations is developed in the analog component (11). The present system achieves this dual capacity by means of an interactive simulation program on a digital computer equipped with graphic display devices.

SYSTEM DESIGN

A flow chart of the basic operations performed in the simulation procedure is given in Fig. 1.

The problem is defined for the computer as a series of FORTRAN IV subroutines and is entered into the system on punched cards. These statements include the differential equations governing the curve forms specified and the techniques necessary for their solution (12–15). The fixed data (notably the experimental results) are also entered *via* punched card input.

Such factors as selection of the parameters to be considered, initial values for all variables, increment sizes to be adopted when changing variables, type of scale to be used for each graphic axis (*i.e.*, log or linear), range and limits of the axis-scale values, and required precision of numerical integration are entered by means of numerical command signals from the keyboard-printer (Fig. 1). For example, numerical instruction "08–100.0" specifies that the upper limit of the horizontal axis will be set equal to 100.0. These commands may be varied instantaneously and at will during the actual simulation procedure by entering new instructions *via* the keyboard.

The keyboard may also be used to take a shortcut in parameter variation in the light of the simulation results already displayed, or to change the graphic output from video display to hard copy on the mechanical plotter, or vice versa (Fig. 1).

EQUIPMENT

The simulations are performed on an IBM-1800 digital computer with 32K (16 bits) core storage and 2-μ sec. cycle time. The computer is equipped with digital input and output capabilities, including programmable electronic contacts, process interruption signal lines, and digital input sense lines. A Calcomp 565 incremental drum plotter is attached to the computer for hard copy output of graphical information. The plotter may be operated in on-line mode or by tape-spooling on one of four available tape drives.

The IBM-1800 is a disk-oriented data acquisition system and ideally suited for on-line simulations when time shared with other batch or process operations (16).

A Tektronix 611 bistable storage oscilloscope is used as the graphical display device in kinetic simulations (Fig. 2). The cathode ray tube has a resolution of 20 stored line pairs/cm. and 0.5-sec. erase time. The device is remotely controlled by programmable electronic contacts which command the write (Z-axis signal) and erase functions. Horizontal (X-axis) and vertical (Y-axis) deflections are obtained from 2 × 10 programmable electronic contacts, which are connected to the input of a digital-to-analog converter.

The converter was developed in this laboratory: it is of a simple ladder circuit design, giving a full-scale deflection of 1 v. and compatible with the standard IBM digital-to-analog converter.

PROCEDURE

The simulation program is written entirely in FORTRAN IV and is available on request.

The arithmetic statements specifying the set of differential equations are inserted at the start of the fourth-order Runge–Kutta subroutine (17). Where the statements refer to special subroutine functions, these functions are also compiled before initiating the
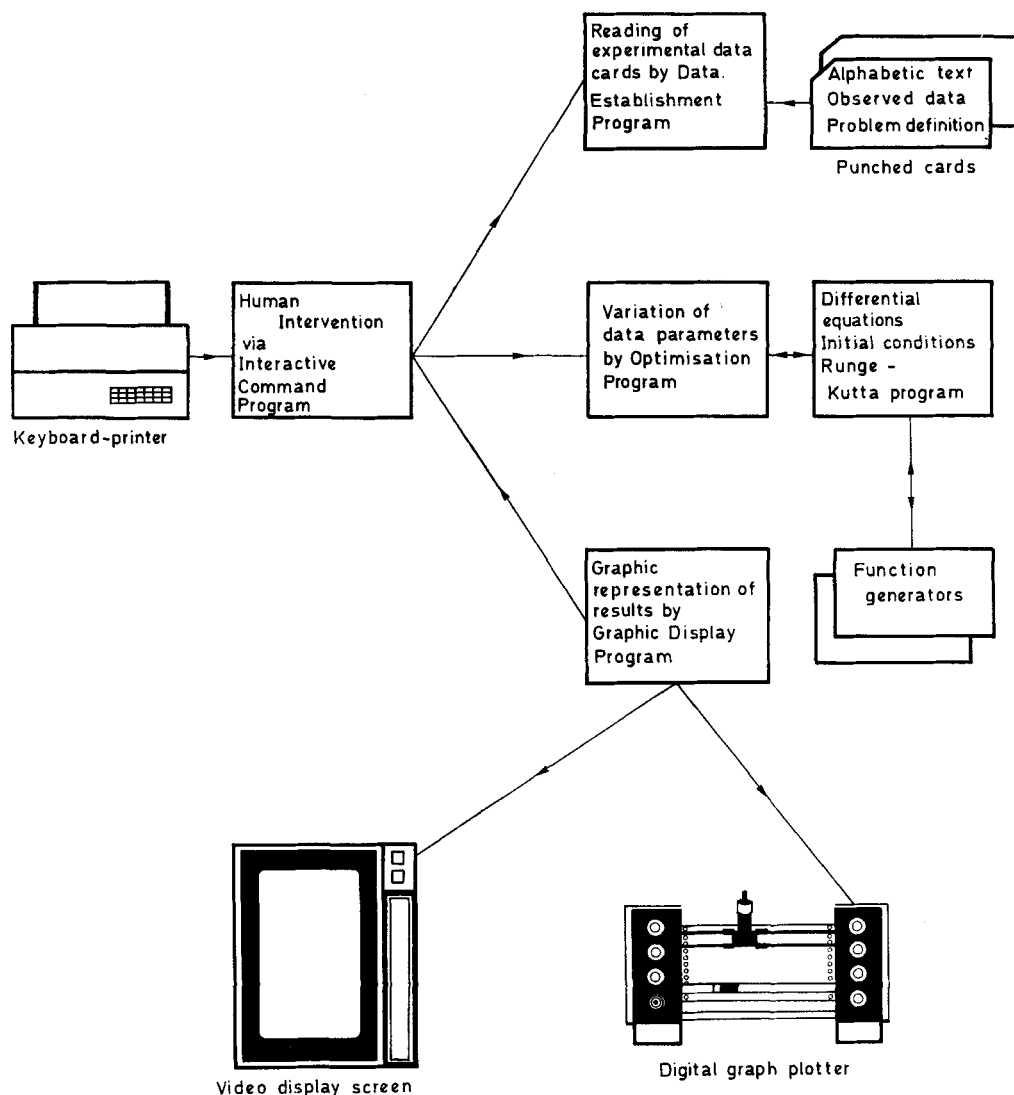
Figure 1—*Basic flowchart of the simulation procedure.*

simulation. Special nonlinear functions are available as in the Continuous Systems Modeling Program (CSMP) (18). The CSMP, however, does not provide for optimization of the parameters of a model.

For a problem involving the concentration of Compound X in a number of different intercommunicating compartments as a function of time, the fixed data input includes an alphabetic header (as in Figs. 3 and 4), the number of parameters (NP), the number of time values (NT), the number of compartments (NC) and all the time and concentration values, together with their standard errors and weight coefficients when these are available. The data are entered in the form of three matrixes of dimensions $NT \times NC$.

For each concentration value obtained experimentally (C^e), solution of the differential equations gives a computed value (C^c). The sum of the squares of the differences between C^e and C^c gives a measure of the goodness of fit of the simulation curve to the original data (C^e) values. The optimization program, therefore, computes the sum (Q) of the squared residuals, based on the initial (or previous) estimates of the parameter set $P_1, \ldots, P_K, \ldots, P_{NP}$, according to the formula:

$$Q = \frac{\sum_j \sum_i W_{ij}(C_{ij}^e - C_{ij}^c)^2}{\sum_j \sum_i W_{ij}} \qquad \text{(Eq. 1)}$$

where i denotes, in turn, each compartment specified; j denotes, in turn, each experimental time value specified; and W_{ij} represents the weight coefficient associated with the value C_{ij}^e. (The weight coefficients may be obtained by taking the reciprocals of the observed

concentration values or of the standard errors, or by using the weights specified on punched card input.)

If required, the optimization may be obtained from the sum of the squared *logarithmic* residuals:

$$Q = \frac{\sum_j \sum_i W_{ij} \left(\log \frac{C_{ij}^e}{C_{ij}^c} \right)^2}{\sum_j \sum_i W_{ij}} \qquad \text{(Eq. 2)}$$

This procedure has the merit of minimizing the squared relative deviations between fitted and observed values, and it represents a special method of weighting the data. The adequacies of the different weighting strategies were discussed recently by Mueller and Lieberman (19).

After calculation of the initial value for Q, the parameters selected for optimization are incremented by an amount ΔP_K (of which the magnitude may be varied by means of an appropriate command signal).

The new sum of squared residuals thus obtained is used for the estimation of the components of the gradient vector:

$$\frac{\partial Q}{\partial P_K} \cong$$

$$\frac{Q(P_1,\ldots,P_K + \Delta P_K,\ldots,P_{NP}) - Q(P_1,\ldots,P_K,\ldots,P_{NP})}{\Delta P_K} \quad \text{(Eq. 3)}$$

The components of the gradient vector (μ_k) are normalized by

Figure 2—*Keyboard entry device, incremental plotter, and visual display console used in connection with the IBM-1800 computer.*

means of the equation:

$$\mu_K = \frac{\partial Q}{\partial P_K} \Big/ \left[\sum_k \left(\frac{\partial Q}{\partial P_K} \right)^2 \right]^{1/2} \qquad \text{(Eq. 4)}$$

and new values of the parameters are computed from the relationship:

$$P_K{}' = P_K - \mu_K \beta \qquad \text{(Eq. 5)}$$

where β represents the step size in the parameter space. This procedure for automatic variation of the parameters was proposed by Giloi *et al.* (11) for a hybrid computer system.

```
BENZOYLATION OF NAPHTALENE,CHLOROBENZENE
         P        DP       MU
   1   21.10    .0100   -.9311     QP   -5.055
   2    .8995   .0100    .3647      Q   -5.055
                                   BET   .0100
                                   NI    10
```
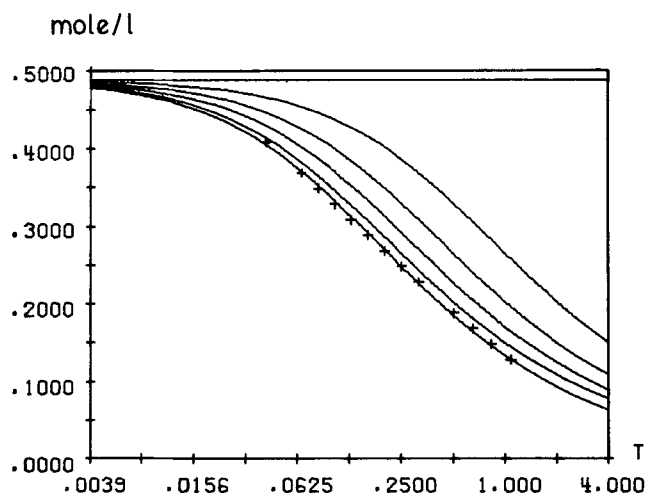
mole/l

Figure 3—*Computer-generated simulation plot for the progress of a chemical reaction (benzoylation of naphthalene). The vertical axis represents the concentration of naphthalene (moles/liter), and the horizontal axis represents the time (T) in hours. Crosses indicate the data values obtained experimentally. For explanation of alpha-numeric symbols, see text. The initial curve is uppermost, and each subsequent curve was computed with successively improved values of the parameters.*

```
PIMOZIDE (R6238)  SC BLD  BRN
         P        DP       MU
   1    .3724    .0001   -.9767     QP   -5.829
   2   1.509    .0001    .2146       Q   -5.831
                                    BET   .0010
                                    NI    10
```
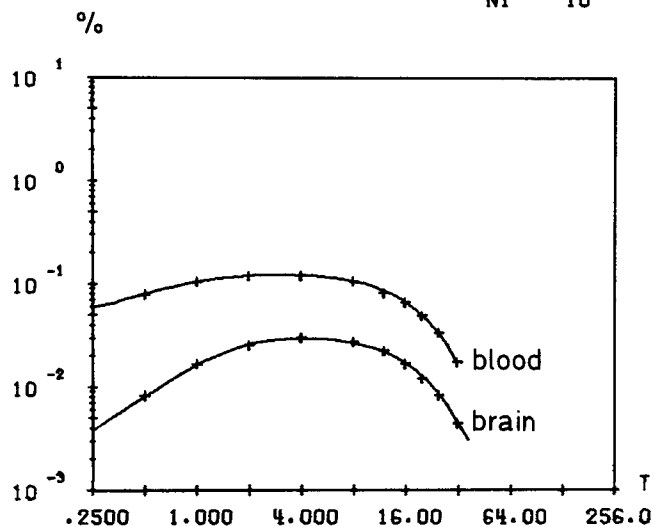
%

Figure 4—*Pharmacokinetic simulation of the level of the neuroleptic drug pimozide (R6238) in the brain (BRN) of rats, based on the known levels of drug in the blood (BLD). The vertical axis represents the brain level (as a percentage of the initial dose), and the horizontal axis represents the time in hours after subcutaneous (s.c.) injection of the drug. Crosses indicate the data values obtained experimentally. For explanation of alpha-numeric symbols, see text.*

Each parameter may be varied sequentially according to the Gauss-Seidel procedure (4). Alternatively, two or more of the available parameters may be varied simultaneously. The different weighting strategies and objective functions available in the optimizing algorithm permit optimization over several different compartments.

When the time–concentration functions of one or more compartments can be adequately approximated from the observed data by utilizing sums of exponential functions (20), gamma variates, polynomial expressions (21, 22), or other procedures, these functions and their derivatives may be used in the Runge-Kutta algorithm to develop solutions for other compartments.

When a solution has been obtained, it can be presented on a graphic display frame on the cathode ray tube or on the plotter as shown in Fig. 2. The display area includes an alphabetic zone (top line) and two numerical zones (next five lines)—one containing the actual parameter values (*P*), their increments (*DP*), and the
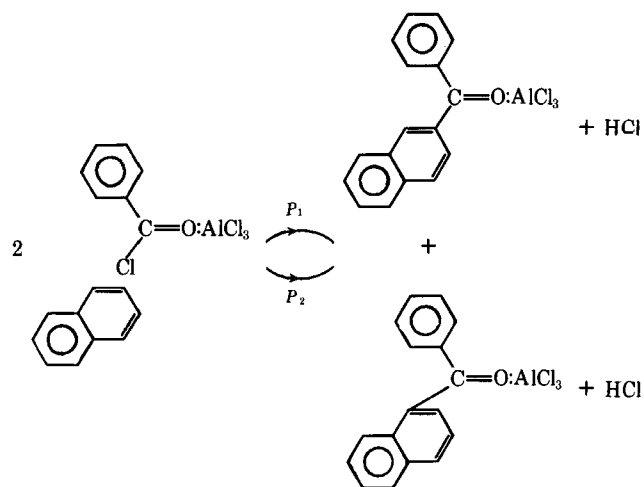
Scheme I—Benzoylation of naphthalene by means of the Friedel-Crafts reaction in chlorobenzene

normalized gradients (*MU*), and the other containing logarithmic values of the previous (*QP*) and actual (*Q*) sums of squared residuals, the step size in the parameter space (*BET*), and the number of integrations (*NI*) in the Runge–Kutta procedure.

The system permits visualization, on the same frame, of successive solutions for one compartment (Fig. 3) or parallel solutions for different compartments (Fig. 4).

Example 1—*Benzoylation of Naphthalene (Fig. 3)*—The simulation program was used to study the kinetics of the benzoylation of naphthalene in chlorobenzene (Scheme I) by the Friedel–Crafts reaction (23). The initial concentrations of the two reactants were both 0.488 mole/l. Experimental data on the progress of the reaction were obtained by withdrawing and analyzing samples of the reaction mixture at different times.

A good fit between the simulation curves and the experimental data was obtained using a third-order main reaction rate constant (P_1) of 21.10/hr. and a second-order parallel reaction rate constant (P_2) of 0.8995/hr. (Fig. 3).

Example 2—*Drug Distribution within the Body (Fig. 4)*—It is possible to study more complex kinetic models than the chemical reaction described previously by resolving them into a number of separate simulations, each involving only some of the compartments. An example is given here.

The distribution of the neuroleptic drug pimozide (R6238) was studied extensively in rats by radioisotopic labeling (24). Radioactivity levels of the nonmetabolized drug were recorded for the brain, blood, liver, urine, and feces at a number of time intervals after subcutaneous administration of the drug.

The first step in the solution of the blood–brain relationship was to derive a polynomial approximation by a least-squares method between blood concentration (C_{b1}) and log time (T) values. This function $F(T)$ was entered as a subroutine program and used to simulate the brain concentration (C_{br})–time function.

The problem was thus defined by the statement:

$$\dot{C}_{br} = P_1 F(T) - P_2 C_{br} \qquad \text{(Eq. 6)}$$

where P_1 represents the rate constant of uptake from the blood compartment, and P_2 represents the rate constant of elimination from the brain compartment. The initial concentrations were set equal to the best-fit concentration values for the smallest time interval after pimozide administration (0.25 hr.).

As Fig. 4 shows, the rate constant for the transfer of pimozide from blood to brain (P_1) was 0.3724/hr., and that for the reverse transfer (P_2) was 1.509/hr.

REFERENCES

(1) P. J. Lewi and C. J. E. Niemegeers, *Drug Inform. Bull.*, **4**, 108(1970).

(2) P. J. Lewi and C. J. E. Niemegeers, *Eur. J. Pharmacol.*, **11**, 361(1970).

(3) P. J. Lewi, C. J. E. Niemegeers, F. J. Verbruggen, W. W. Braet, D. G. Van Riel, and P. A. J. Janssen, *Arch. Int. Pharmacodyn. Ther.*, **187**, 249(1970).

(4) F. B. Hildebrand, in "Introduction to Numerical Analysis," McGraw-Hill, New York, N. Y., 1956, p. 439.

(5) M. Berman, in "Computers in Biomedical Research," vol. II, R. W. Stacy and B. Waxman, Eds., Academic, New York, N. Y., 1965, p. 173.

(6) J. B. Hazelrig, *Proc. Staff Meet. Mayo Clin.*, **39**, 841(1964).

(7) L. V. Avioli and M. Berman, *J. Appl. Physiol.*, **21**, 1688 (1966).

(8) E. Ackerman, E. H. Strickland, J. B. Hazelrig, and L. C. Gatewood, *Clin. Pharmacol. Ther.*, **8**, 170(1967).

(9) E. R. Garrett, R. C. Thomas, D. P. Wallach, and C. D. Alway, *J. Pharmacol. Exp. Ther.*, **130**, 106(1960).

(10) H. Röpke and J. Riemann, "Analog Computer in Chemie und Biologie," Springer Verlag, Berlin, West Germany, 1969, p. 45.

(11) W. Giloi, A. Kley, R. Herschel, G. Haussmann, and P. Wiesenthal, *Telefunken Z.*, **39**, 66(1963).

(12) J. G. Llaurado, *J. Appl. Physiol.*, **27**, 544(1969).

(13) A. Rescigno, *Ann. N.Y. Acad. Sci.*, **108**, Art. 1, 204(1963).

(14) G. Segre, *ibid.*, **96**, Art. 1, 913(1962).

(15) J. G. Wagner, *Clin. Pharmacol. Ther.*, **8**, 201(1967).

(16) R. K. Louden, in "Programming the IBM 1130 and 1800," Prentice-Hall, Englewood Cliffs, N. J., 1967, p. 41.

(17) S. D. Conte, in "Elementary Numerical Analysis," McGraw-Hill, New York, N. Y., 1965, p. 223.

(18) C. F. Evert and M. J. Randall, *J. Pharm. Sci.*, **59**, 403 (1970).

(19) F. W. Mueller and S. V. Lieberman, *ibid.*, **59**, 514(1970).

(20) J. B. Hazelrig, E. Ackerman, and J. W. Rosevaer, *Proc. Ann. Conf. Eng. Biol. Med. 16th*, **5**, 8(1963).

(21) P. J. Lewi, A. E. F. Chandler, D. G. Van Riel, P. J. Somers, F. T. N. Allewijn, J. G. H. Dony, and P. A. J. Janssen, *Drug Res.*, **20**, 684(1970).

(22) P. J. Lewi, J. J. P. Heykants, F. T. N. Allewijn, J. G. H. Dony, and P. A. J. Janssen, *ibid.*, **20**, 943(1970).

(23) M. Janssen, Ph.D. thesis, University of Louvain, Louvain, Belgium, 1967.

(24) P. J. Lewi and J. J. P. Heykants, to be published.

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