Formulation and Computation of Compartment Models

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Abstract □ In the formulation of compartment models for describing biological phenomena, two separate approaches have usually been employed for isotope dilution systems and systems for which no tracers are introduced. In the former, steady state is assumed to exist and small perturbations are introduced for solution of the system. In the latter, sets of simultaneous differential equations are solved for the complete time course of the drug kinetic system. For linear systems which can be described by first-order kinetics, it is shown that the isotope dilution problem can be cast into the more general approach of simultaneous linear differential equations and the restriction of steady state removed. Solutions to these equations are shown to be easily obtainable using the state-space approach. For systems in which linearity cannot be assumed, digital computer techniques are presented which greatly facilitate numerical solutions. These concepts are demonstrated with two examples. A third example shows how these concepts and others can be employed with isotope dilution to find the initial pool sizes and rate constants in a six-compartment system.

Keyphrases □ Models, compartment—formulation, computation □ Theoretical considerations—data fitting, models □ Kinetic equations—first-order model system □ Computer program—data fitting, models

The use of mathematical descriptions called models that seek to capture the essence of biological phenomena has been emerging over the last 20 years. These concepts have been widely reported in the literature from a general and theoretical point of view, as well as in relation to specific applications. Most frequently, some form of dynamic behavior has been of concern so that the areas of pharmacokinetics and radioactive tracers have been the major contributors of applications. From these sources two points of view have arisen. One is concerned with the dynamics of a system described by a set of differential equations and seeks to evaluate the time course of the substance as a steady state is approached. The other presumes that steady state exists and that small perturbations about this value are introduced in order to evaluate flow rates, dilution, *etc.* These two points of view have placed emphasis on different variables, and the formulation of the descriptions of the system behavior in terms of these different variables has given the appearance of different computational requirements. It will be shown for first-order systems that these differences are superficial and that new advances in computer algorithms and computing languages now provide conveniences not generally recognized or utilized in biological modeling.

COMPUTATION FOR COMPARTMENT MODELS

The observable behavior of the distribution, absorption, or elimination of drugs has led to the concept that a biological system can be treated as if there were boundaries called "compartments" which separate the system into parts and that the drug or other material is transferred from one compartment to another in conformance with first-order kinetics. This assumes that the rate of change of material is proportional to the amount of material that is present in the compartment. The application of Fick's law in the case of diffusion can lead to similar sets of linear first-order differential equations. Although the assumption of first-order kinetics, linearity, and rate coefficients that are constants is clearly a gross approximation of a complex biological phenomenon, the approach has proved beneficial in numerous instances when it is utilized with discretion and understanding. The assumptions are so widely accepted that one textbook (1) states: "Most drugs disappear from the body in this fashion."

The use of mathematical models as an aid to the better understanding of biological phenomena requires that some form of computation be executed. While there have been advances from time to time in the conceptual features of modeling, little attention seems to have been paid to keeping the computational procedures up-to-date and to making the techniques more attractive to the biological researchers who could take advantage of modeling as a tool. Basic to a dynamic model is the solution of a set of differential equations. This job has been variously relegated to the analog computer or the digital computer. The work that has been assigned to the digital computer has been that of solving the equations by the techniques of numerical integration, the computation of statistical parameters, or perhaps some curve fitting. Most laboratories seem to have developed their own libraries of programs associated with modeling and, except for utilizing some common language such as FORTRAN, they appear to have overlooked the availability of general-purpose programs such as CSMP (Continuous System Modeling Program) (2). It is hoped that this paper will suggest some new approaches to meeting the computational requirements of modeling and thus reduce the effort required in the utilization of models for biological systems.

The recent emergence of the ideas of organizing the description of systems characterized by sets of first-order differential equations under the heading of "state space" has fostered the development of algorithms (3) which provide analytical solutions. The user is not required to manipulate matrices or to use the Laplace transform. The algorithms may be programmed for digital computers and thus provide the proper analytical form and the associated coefficients in a more convenient fashion than most other methods. This is also the form most familiar to those applying compartment theory, and the approach should therefore have appeal to anyone interested in biological dynamics. The use of the state-space formulation of the equations has the added advantages that it identifies the basic assumptions of linearity and clarifies the use of superposition. The state-space method yields solutions in functional form which gives the opportunity of locating maxima by differentiation and permits comparisons in terms of time constants. When comparing the functional solutions with experimental data points, one need only evaluate the function at the specific points in question. All other points need not be computed. An analog computer or numerical integration technique would continuously evaluate the complete range of the solution. There is the disadvantage, however, that when the system parameters are altered, an entirely new state-space solution must be executed, but corresponding disadvantages are present in obtaining the solutions of numerical integration procedures. Thus there are trade-offs in the computational aspects of modeling, and it is desirable to have alternative techniques available so that one may select the tool that is most appropriate for the requirements. An analog computer run generates a continuous solution in the desired range.

The analog computer is convenient for use in matching models to data when the number of parameters to be changed is small, say five or less. However, to evaluate a single point, the analog computer must compute a continuous solution at least to the desired point. Digital programs such as CSMP to be illustrated here have been written to simulate the operation of the analog computer. They are in fact conveniently packaged numerical integration routines with the ability to be interspersed with FORTRAN statements. With this program, one may run successive cases and make decisions automatically at the end of each case for purposes of optimization or curve fitting. Good initial estimates of system parameters will reduce the number of successive runs required. These analog simulators usually incorporate nonlinear components and thus provide a convenient way of solving nonlinear differential equations without special programming. Here again the solutions are in the form of tables of values or digitally plotted curves rather than explicit functions of the independent parameter. Evaluation of specific data points requires computation of all previous points. As a means of illustrating the use of CSMP and later the state-space approach, a problem which has been published (4) in a nonlinear formulation requiring extensive special programming will be reviewed. However, the ramifications of the method go far beyond this particular application.

The usual problem in drug dynamics seeks to evaluate the time course of the amount of drug in the various compartments of interest. The initial conditions are usually assumed to be zero except in the compartment into which the drug is introduced. The resulting formulation is a dynamic system with the drug being distributed among the compartments and perhaps being eliminated from the system at several points. The conditions of steady state may not be of particular interest because steady state could be the condition in which all the drug has been cleared from the system. The length of time for the system to reach steady state may be prohibitively long for clinical verification. The point of interest may well be the early rates of the dynamic behavior, and there may be little concern with the final conditions of steady state.

In the case of the mathematical description of phenomena in which radioactive tracers are of interest, the emphasis has been on the small variations from an existing steady state. In fact an effort is made not to disturb the steady state appreciably. This concept of steady state in a biological system does not mean that there is no exchange of material among the compartments, but rather that the amount transferred into a compartment in a given unit of time is exactly the same as the amount which leaves the compartment in the given unit of time. Thus there can be a flow of material in the system, and the point of interest is in establishing the flow rates or pool sizes through dilution measurements. Radioactive tracers are suited to this task because they are not distinguishable by the body from the parent substance. Tracers may be injected in small enough quantities so as not to upset the equilibrium conditions and yet in sufficient amount so as to be measurable. The usual measurement is that of specific activity. Therefore, it was a natural approach to formulate the description in these well-known terms. The equations have been published (4) before and are of the general form:

$$S_i \frac{da_i}{dt} = \sum_{\substack{j=1 \\ j \neq i}}^{n} \rho_{ij}(a_j - a_i)$$

where a_i = specific activity, ρ_{ij} = flow constant, and S_i = compartment size (amount of parent substance).

This formulation is most convenient when the conditions of steady state are met. However, when one wishes to investigate the behavior in nonsteady state, it requires that the equations be viewed as having time-varying coefficients. A solution which leads to a form of the generalized Riccati-type equation can be found in the reference given. The solution was re-presented by Rescigno and Segre (5). The system solved in these references was a three-compartment closed system. The flow constants were assumed fixed with the exception of one which was specified as a function of time.

The general form of these equations can be derived from the equations that describe the same system with first-order kinetics (see *Appendix 1*). The specific activity parameter is introduced by defining specific activity as $a = R/S$, differentiating and substituting for the derivatives of R and S in the equations. Here R is the amount of radioactivity and S is the amount of parent substance. If S is assumed to be constant, it can be associated with the first-order rate constant to give a new coefficient ρ. However, if S changes with time and the new coefficients ρ are specified as constants, as in the example referred to, one is forced to allow the normally fixed-rate constant to vary. It is not clear what physical reality was intended to be represented in the example problem. Nevertheless, assume that a problem of this form is to be solved and its biological justification has been established. For the three-compartment closed system the equations for nonsteady state, when written in terms of specific activity, take the form:

$$S_1 \frac{da_1}{dt} = \rho_{12}(a_2 - a_1) + \rho_{13}(a_3 - a_1)$$

$$S_2 \frac{da_2}{dt} = \rho_{21}(a_1 - a_2) + \rho_{23}(a_3 - a_1)$$

$$S_3 \frac{da_3}{dt} = \rho_{31}(a_1 - a_3) + \rho_{32}(a_2 - a_3)$$

$$\frac{dS_1}{dt} = \rho_{12} - \rho_{21} + \rho_{13} - \rho_{31}$$

$$\frac{dS_2}{dt} = \rho_{21} - \rho_{12} + \rho_{23} - \rho_{32}$$

$$\frac{dS_3}{dt} = \rho_{31} - \rho_{13} + \rho_{32} - \rho_{23}$$

where S_i = amount of parent substance, a_i = specific activity, and ρ_{ij} = flow coefficients.

If some of the ρ's are functions of time, it is necessary to carry out the simultaneous solution of these six differential equations. Any suitable numerical integration algorithm may be used. However, the Continuous System Modeling Program is typical of the family of similar programs available for such solutions. The program shown in *Appendix 2* is all that is required to solve this problem. Problems of much greater complexity can be solved in the same fashion and require a minimum of effort or programming skill.

The formulation of the three-compartment closed system, when applied to a system with first-order kinetics, really falls into the more usual category of the nonsteady-state linear systems. Since in such systems the theorem of superposition is applicable, one may solve the equations for the behavior of the parent substance S, followed by the solution for the activity R. The division of the curve for R by that for S gives a curve of specific activity as a function of time. No assumption of steady state need be made in the formulation. The origins of the two curves which are to be divided may be offset relative to each other. That is to say, the system may be initially loaded with the unlabeled species so that all compartments have initial conditions or finite pool sizes at the time the radioactive tracer is introduced. In fact there may be little interest in how the system got to the condition which prevailed at the time of the introduction of the tracer. The subsequent values of specific activity are the important considerations. A complete example of a two-compartment closed model is carried out in the state-space form in *Appendix 3*. Note that the solution is in the form of a function of exponential terms. If the rate constants are known, they can be combined into numerical coefficients. Computer solutions of the state-space matrix $\bar{A}$, of course, require numerical values.

It commonly occurs that the rate constants of the system are not known and that an experiment must be conducted to evaluate these constants. Many papers have treated the problem of curve fitting of assumed functions or the iterative searching for unknown parameters. One of the basic uses of the tracer method is that of establishing pool size through the technique of introducing tracers and then computing the pool size from the dilution indicated by the specific activity. This is easily done in a single compartment or more complicated system, if the rate constants are known or where extensive measurements can be made. Unfortunately, in many systems some rate constants may be unknown or certain internal compartments are not accessible for measurement. The accompanying model considered in *Appendix 4* is one in which it was desired to establish the pool size existing at the time of the introduction of the tracer and none of the rate constants was known. The approach was one that could be of benefit in most drug metabolism studies. A model was established based on the best judgment of what might be appropriate and an analytical solution was derived. The state-space numerical solution would have yielded the final exponential form if rate constant values were given. Nevertheless, here it was desirable to identify

the terms of each coefficient comprising the final solution form, and a complete derivation was made. The derivation developed showed that it would be possible to determine the desired quantities from clinical test data. Then to demonstrate that the procedure was feasible, a simulation of the model using assumed parameters was run and data were taken on the model which corresponded to the clinical data expected from the actual experiment. Then from these data the pool size and rate constants were evaluated and shown to agree with the assumed values. One, of course, is not assured that the model is a unique representation of the biological phenomena, but if the experimental data indicates that the model is acceptable, then the parameters can be evaluated. Thus, in this fashion one can be assured that an experiment is feasible and that it will yield the desired parameters. Additional knowledge was gained regarding the requirements for data collection in the clinical experiment, the sensitivity of the parameters in the model was determined, and the general level of confidence regarding the experiment was raised.

While there is no completely general approach to this kind of modeling, this example utilizes relationships that might be overlooked in some situations. Rate constants were separated, based on the final value of the compartment measurements, and the use of a derivative of the analytical form of the solution yielded a transcendental equation that gave the sum of two rate constants. The fortuitous circumstances inherent in this model were that there was an output compartment directly linked to the input compartment and the fact that the parent drug could be assayed as well as the specific activity measured.

CONCLUSIONS

These considerations have shown that it is not necessary to formulate the tracer kinetics for systems governed by first-order linear differential equations in the form of nonlinear equations in order to evaluate the nonsteady-state behavior in terms of specific activity. The solutions may be obtained routinely through the use of the state-space formulation for the separate evaluations of the parent substance and the radioactive tracer, followed by a division of the curves or data points if specific activity is desired. Furthermore, if the case for nonlinear formulation of nonsteady-state conditions is justified on some biological grounds, the solution can be conveniently obtained through the use of a continuous system modeling program such as CSMP which provides a numerical integration algorithm and suitable selection of nonlinear elements. The model in *Appendix 4*, chosen to exhibit the procedures mentioned above, also exhibited other important features. Through the use of final value and curve fitting or solution of transcendental equations, the initial pool size was evaluated in a model of three internal compartments. The usual model in which dilution techniques are used through the measurement of specific activity to evaluate pool size consists of a single internal compartment linked to an external excretory compartment. An interesting problem exists in the extension of this approach to more complex systems.

It is to be noted that the formalism of postulating a model, assuming parameters, and executing trial runs to produce simulated clinical data, followed by the use of the data to check the previously assumed parameters, provides an assurance that the entire process is well defined. In this fashion the requirements for data collection and processing may be set forth well in advance of the clinical phase of the experimentation.

APPENDIX 1

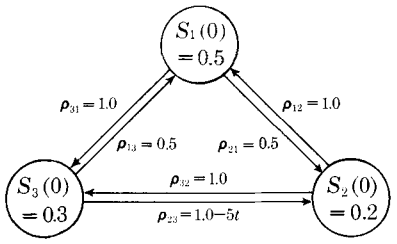
For an n-compartment, closed, first-order system, one can write

$$\frac{dS_i}{dt} = \sum_{\substack{j=1 \\ j\neq i}}^{n} K_{ij}S_j - \sum_{\substack{j=1 \\ j\neq i}}^{n} K_{ji}S_i \quad i = 1,2,\ldots,n$$

or

$$\frac{dS_i}{dt} = \sum_{\substack{j=1 \\ j\neq i}}^{n} K_{ij}S_j - K_{ji}S_i \quad i = 1,2,\ldots,n$$

where K_{ij} is the rate constant with units hours^{-1} for the transfer of substances S from compartment j to compartment i. S_i is the *total* amount of substance in compartment i with units of moles.



Scheme I—Three-compartment system.

One can write similar equations for the activity R_i of compartment i since the body will process labeled and unlabeled material in like manner. R has units of counts per minute.

$$\frac{dR_i}{dt} = \sum_{\substack{j=1 \\ j\neq i}}^{n} K_{ij}R_j - K_{ji}R_i \quad i = 1,2,\ldots,n$$

Specific activity a_i of compartment i is defined as

$$a_i = \frac{R_i}{S_i} \quad i = 1,2,\ldots,n$$

Differentiating,

$$\frac{da_i}{dt} = \frac{S_i(dR_i/dt) - R_i(dS_i/dt)}{S_i^2}$$

$$\frac{da_i}{dt} = \frac{1}{S_i}\frac{dR_i}{dt} - \frac{R_i}{S_i^2}\frac{dS_i}{dt}$$

Substituting for the derivatives of R_i and S_i results in

$$\frac{da_i}{dt} = \frac{1}{S_i}\sum_{\substack{j=1 \\ j\neq i}}^{n} K_{ij}R_j - K_{ji}R_i - \frac{R_i}{S_i^2}\sum_{\substack{j=1 \\ j\neq i}}^{n} K_{ij}S_j - K_{ji}S_i$$

$$\frac{da_i}{dt} = S_j\sum_{\substack{j=1 \\ j\neq i}}^{n} K_{ij}\frac{1}{S_i}\frac{R_j}{S_j} - K_{ji}\frac{1}{S_j}\frac{R_i}{S_i} - S_j\sum_{\substack{j=1 \\ j\neq i}}^{n} K_{ij}\frac{1}{S_i}\frac{R_i}{S_i} - K_{ji}\frac{1}{S_j}\frac{R_i}{S_i}$$

$$\frac{da_i}{dt} = S_j\sum_{\substack{j=1 \\ j\neq i}}^{n} \frac{K_{ij}}{S_i}a_j - \frac{K_{ji}}{S_j}a_i - \frac{K_{ij}}{S_i}a_i + \frac{K_{ji}}{S_j}a_i$$

$$S_i\frac{da_i}{dt} = \sum_{\substack{j=1 \\ j\neq i}}^{n} K_{ij}S_j(a_j - a_i)$$

If one defines $\rho_{ij} = K_{ij}S_j$ as a flow variable with variability due to S_j and not the rate constant K_{ij},

$$S_i\frac{da_i}{dt} = \sum_{\substack{j=1 \\ j\neq i}}^{n} \rho_{ij}(a_j - a_i)$$

If steady-state conditions exist, all S's will be constant and ρ becomes a constant.

APPENDIX 2

For the system in Scheme I with the substances S_i at steady state, it is desired to find the specific activities a_i of each compartment after injecting one unit of labeled material into Compartment 1 at $t = 0$. One cannot resort to known general solutions of linear differential equations (see *Appendix 3*) because the flow "constant" $\rho_{23} = 1 - 5t$ makes the differential equations which describe the system have time-varying coefficients. For the system in Scheme I, one can write for the specific activities:

$$\frac{da_1}{dt} = \frac{1}{S_1}[\rho_{12}(a_2 - a_1) + \rho_{13}(a_3 - a_1)]$$

$$\frac{da_2}{dt} = \frac{1}{S_2}[\rho_{21}(a_1 - a_2) + \rho_{23}(a_3 - a_2)]$$

$$\frac{da_3}{dt} = \frac{1}{S_3}[\rho_{31}(a_1 - a_3) + \rho_{32}(a_2 - a_3)]$$

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****CONTINUOUS SYSTEM MODELING PROGRAM****
      ***PROBLEM INPUT STATEMENTS***
LABEL    TRACER KINETICS EXAMPLE PAGE 148 SHEPPARD
PARAM  R12=1.0,R13=.5,R21=.5,R32=1.0,R31=1.0
       R23=1.-5.*TIME
       DA1=(R12*(A2-A1)+R13*(A3-A1))/S1
       DA2=(R21*(A1-A2)+R23*(A3-A2))/S2
       DA3=(R31*(A1-A3)+R32*(A2-A3))/S3
       DS1=0.
       DS2=-.5-5.*TIME
       DS3=.5+5.*TIME
       A1=INTGRL(1.,DA1)
       A2=INTGRL(0.,DA2)
       A3=INTGRL(0.,DA3)
       S1=INTGRL(.5,DS1)
       S2=INTGRL(.2,DS2)
       S3=INTGRL(.3,DS3)
TIMER OUTDEL=.01,FINTIM=.2,DELT=.0001
PRTPLT A1(0.,1.,S1)
PRTPLT A2(0.,1.,S2)
PRTPLT A3(0.,1.,S3)
END
STOP
```

Figure 1—*CSMP program.*

where ρ_{23} is time varying.

For the substance S_i in each compartment the equations are:

$$\frac{dS_1}{dt} = \rho_{12} + \rho_{13} - \rho_{21} - \rho_{31} = 0$$

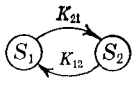
$$\frac{dS_2}{dt} = \rho_{21} + \rho_{23} - \rho_{12} - \rho_{32} = -0.5 - 5t$$

$$\frac{dS_3}{dt} = \rho_{31} + \rho_{32} - \rho_{13} - \rho_{23} = 0.5 + 5t$$

The six equations shown can be solved simultaneously in a straightforward manner with numerical techniques by using a digital computer language such as CSMP which simulates an analog computer. The simple CSMP program required to solve the above equations is shown in Fig. 1. Integration is performed by using the CSMP function "INTGRL(IC,X)", where IC is the initial condition and X is the function to be integrated. The functions to be integrated such as da_1/dt, which is shown in DA1 in Fig. 1, are defined by FORTRAN IV statements and/or with other CSMP functions. Plots of functions may be called for as well as function values at discrete points. Results of the above example are shown in Figs. 2–4. It is important to note that the above approach makes solutions easily obtainable for a large class of problems. The assumption of steady state, for instance, could be removed and add little complexity to the CSMP program.

APPENDIX 3

Consider a two-compartment, closed, first-order system with initial conditions $S_1(0)$ and $S_2(0)$:



As in *Appendix I*, one can write:

$$\frac{dS_1}{dt} = K_{12}S_2 - K_{21}S_1$$

$$\frac{dS_2}{dt} = K_{21}S_1 - K_{12}S_2 \qquad \text{(Eq. 1)}$$

or in matrix form

$$\begin{bmatrix}\dot{S}_1\\ \dot{S}_2\end{bmatrix} = \begin{bmatrix}-K_{21} & K_{12}\\ K_{21} & -K_{12}\end{bmatrix}\cdot\begin{bmatrix}S_1\\ S_2\end{bmatrix} \qquad \text{(Eq. 2)}$$

which may be written as

$$\dot{\bar{S}} = \bar{A}\bar{S}$$

These equations are in the form of the canonical state equations for which solutions are well known (3). The solution is

$$\bar{S} = e^{\bar{A}t}\bar{S}_0$$

where $\bar{S}_0$ is a constant column vector

$$\begin{bmatrix}S_1(0)\\ S_2(0)\end{bmatrix}$$

of initial conditions. The matrix $e^{\bar{A}t}$ is defined as

$$e^{\bar{A}t} = \bar{I} + \bar{A}t + \cdots + \frac{\bar{A}^K t^K}{K!} + \cdots$$

where $\bar{I}$ is an $n \times n$ identity matrix and $\bar{A}$ is an $n \times n$ constant matrix, which, for this example, are rate constants as in Eq. 2.

All that is necessary for a complete analytical solution to Eq. 1 is evaluating $e^{\bar{A}t}$. Several methods suited to computer implementation exist in the literature (3), but the method of Laplace transforms will be used here for convenience. It can be shown (3) that $e^{\bar{A}t}$ is the inverse Laplace transform of the matrix

$$[s\bar{I} - \bar{A}]^{-1}$$

where s is the Laplace variable and $\bar{I}$ is the identity matrix. One can write

$$[s\bar{I} - \bar{A}] = s\begin{bmatrix}1 & 0\\ 0 & 1\end{bmatrix} - \begin{bmatrix}-K_{21} & K_{12}\\ K_{21} & -K_{12}\end{bmatrix} = \begin{bmatrix}s + K_{21} & -K_{12}\\ -K_{21} & s + K_{12}\end{bmatrix}$$

Now,

$$[s\bar{I} - \bar{A}]^{-1} = \begin{bmatrix}\dfrac{(s + K_{12})}{s(s + K_{12} + K_{21})} & \dfrac{K_{12}}{s(s + K_{12} + K_{21})}\\ \dfrac{K_{21}}{s(s + K_{12} + K_{21})} & \dfrac{(s + K_{21})}{s(s + K_{12} + K_{21})}\end{bmatrix}$$

by normal methods. Taking the inverse Laplace transform yields[1]

$$L^{-1}([s\bar{I} - \bar{A}]^{-1}) = e^{\bar{A}t}$$

$$= \begin{bmatrix}\dfrac{K_{12}}{K_{12} + K_{21}} + \dfrac{K_{21}}{K_{12} + K_{21}}e^{-(K_{12}+K_{21})t}; & \dfrac{K_{12}}{K_{12} + K_{21}} - \dfrac{K_{12}}{K_{12} + K_{21}}e^{-(K_{12}+K_{21})t}\\ \dfrac{K_{21}}{K_{12} + K_{21}} - \dfrac{K_{21}}{K_{12} + K_{21}}e^{-(K_{12}+K_{21})t}; & \dfrac{K_{21}}{K_{12} + K_{21}} + \dfrac{K_{12}}{K_{12} + K_{21}}e^{-(K_{12}+K_{21})t}\end{bmatrix}$$

Thus the solutions for Eq. 2 can be written as

$$\begin{bmatrix}S_1\\ S_2\end{bmatrix} = \begin{bmatrix}\dfrac{K_{12}}{K_{12} + K_{21}} + \dfrac{K_{21}}{K_{12} + K_{21}}e^{-(K_{12}+K_{21})t}; & \dfrac{K_{12}}{K_{12} + K_{21}} - \dfrac{K_{12}}{K_{12} + K_{21}}e^{-(K_{12}+K_{21})t}\\ \dfrac{K_{21}}{K_{12} + K_{21}} - \dfrac{K_{21}}{K_{12} + K_{21}}e^{-(K_{12}+K_{21})t}; & \dfrac{K_{21}}{K_{12} + K_{21}} + \dfrac{K_{12}}{K_{12} + K_{21}}e^{-(K_{12}+K_{21})t}\end{bmatrix}\begin{bmatrix}S_1(0)\\ S_2(0)\end{bmatrix}$$

or

$$S_1 = S_1(0)\left[\frac{K_{12}}{K_{12} + K_{21}} + \frac{K_{21}}{K_{12} + K_{21}}e^{-(K_{12}+K_{21})t}\right] + S_2(0)\left[\frac{K_{12}}{K_{12} + K_{21}} - \frac{K_{12}}{K_{12} + K_{21}}e^{-(K_{12}+K_{21})t}\right]$$

$$S_2 = S_1(0)\left[\frac{K_{21}}{K_{12} + K_{21}} - \frac{K_{21}}{K_{12} + K_{21}}e^{-(K_{12}+K_{21})t}\right] + S_2(0)\left[\frac{K_{21}}{K_{12} + K_{21}} + \frac{K_{12}}{K_{12} + K_{21}}e^{-(K_{12}+K_{21})t}\right]$$

[1] A matrix of the type

$$\begin{bmatrix}1 & 0\\ 0 & 1\end{bmatrix}$$

is written as

$$\begin{bmatrix}1; & 0\\ 0; & 1\end{bmatrix}$$

because of format restrictions.

MINIMUM A1 VERSUS TIME MAXIMUM

TIME	A1	0.0 I	1.0000E 00 I	S1
0.0	1.0000E 00			5.0000E-01
1.0000E-02	9.7085E-01			5.0000E-01
2.0000E-02	9.4335E-01			5.0000E-01
3.0000E-02	9.1741E-01			5.0000E-01
4.0000E-02	8.9296E-01			5.0000E-01
5.0000E-02	8.6993E-01			5.0000E-01
6.0000E-02	8.4824E-01			5.0000E-01
7.0000E-02	8.2783E-01			5.0000E-01
8.0000E-02	8.0865E-01			5.0000E-01
9.0000E-02	7.9063E-01			5.0000E-01
1.0000E-01	7.7373E-01			5.0000E-01
1.1000E-01	7.5789E-01			5.0000E-01
1.2000E-01	7.4309E-01			5.0000E-01
1.3000E-01	7.2928E-01			5.0000E-01
1.4000E-01	7.1644E-01			5.0000E-01
1.5000E-01	7.0454E-01			5.0000E-01
1.6000E-01	6.9359E-01			5.0000E-01
1.7000E-01	6.8359E-01			5.0000E-01
1.8000E-01	6.7460E-01			5.0000E-01
1.9000E-01	6.6675E-01			5.0000E-01
2.0000E-01	6.6062E-01			5.0000E-01

Figure 2—$a_1(t)$ *from CSMP program.*

MINIMUM A2 VERSUS TIME MAXIMUM

TIME	A2	0.0 I	1.0000E 00 I	S2
0.0	0.0			2.0000E-01
1.0000E-02	2.4822E-02			1.9475E-01
2.0000E-02	4.9252E-02			1.8899E-01
3.0000E-02	7.3252E-02			1.8274E-01
4.0000E-02	9.6807E-02			1.7599E-01
5.0000E-02	1.1992E-01			1.6874E-01
6.0000E-02	1.4262E-01			1.6098E-01
7.0000E-02	1.6493E-01			1.5273E-01
8.0000E-02	1.8692E-01			1.4398E-01
9.0000E-02	2.0865E-01			1.3473E-01
1.0000E-01	2.3022E-01			1.2497E-01
1.1000E-01	2.5176E-01			1.1472E-01
1.2000E-01	2.7341E-01			1.0397E-01
1.3000E-01	2.9540E-01			9.2716E-02
1.4000E-01	3.1803E-01			8.0964E-02
1.5000E-01	3.4173E-01			6.8711E-02
1.6000E-01	3.6721E-01			5.5960E-02
1.7000E-01	3.9570E-01			4.2710E-02
1.8000E-01	4.2975E-01			2.8960E-02
1.9000E-01	4.7662E-01			1.4709E-02
2.0000E-01	6.4537E-01			−4.0663E-05

Figure 3—$a_2(t)$ *from CSMP program.*

MINIMUM A3 VERSUS TIME MAXIMUM

TIME	A3	0.0 I	1.0000E 00 I	S3
0.0	0.0			3.0000E-01
1.0000E-02	3.1908E-02			3.0525E-01
2.0000E-02	6.1143E-02			3.1099E-01
3.0000E-02	8.7954E-02			3.1724E-01
4.0000E-02	1.1258E-01			3.2399E-01
5.0000E-02	1.3522E-01			3.3123E-01
6.0000E-02	1.5607E-01			3.3898E-01
7.0000E-02	1.7531E-01			3.4723E-01
8.0000E-02	1.9310E-01			3.5598E-01
9.0000E-02	2.0959E-01			3.6522E-01
1.0000E-01	2.2491E-01			3.7497E-01
1.1000E-01	2.3918E-01			3.8522E-01
1.2000E-01	2.5252E-01			3.9596E-01
1.3000E-01	2.6504E-01			4.0721E-01
1.4000E-01	2.7684E-01			4.1896E-01
1.5000E-01	2.8802E-01			4.3120E-01
1.6000E-01	2.9868E-01			4.4395E-01
1.7000E-01	3.0893E-01			4.5720E-01
1.8000E-01	3.1891E-01			4.7095E-01
1.9000E-01	3.2883E-01			4.8519E-01
2.0000E-01	3.3933E-01			4.9994E-01

Figure 4—$a_3(t)$ *from CSMP program.*

If one does not know $S_1(0)$ and $S_2(0)$ but knows them at some time, t_1, earlier [e.g., 100 mg. of substance was injected into Compartment 1 with no initial substance in the system, then $S_1(t_1) = 100$ and $S_2(t_1) = 0$], one can use the above solutions with different initial conditions and evaluate at the later time which has been defined as zero to obtain $S_1(0)$ and $S_2(0)$.

If labeled substance is now injected into the system at $t = 0$, it is possible to write for the activities, as in *Appendix 1*,

$$\frac{dR_1}{dt} = K_{12}R_2 - K_{21}R_1$$

$$\frac{dR_2}{dt} = K_{21}R_1 - K_{12}R_2$$

The solutions to the above follow in the same manner as for the unlabeled substance S_1, *i.e.*,

$$R_1 = R_1(0)\left(\frac{K_{12}}{K_{12}+K_{21}} + \frac{K_{21}}{K_{12}+K_{21}}e^{-(K_{12}+K_{21})t}\right) + R_2(0)\left(\frac{K_{12}}{K_{12}+K_{21}} - \frac{K_{12}}{K_{12}+K_{21}}e^{-(K_{12}+K_{21})t}\right)$$

$$R_2 = R_1(0)\left(\frac{K_{21}}{K_{12}+K_{21}} - \frac{K_{12}}{K_{12}+K_{21}}e^{-(K_{12}+K_{21})t}\right) + R_2(0)\left(\frac{K_{21}}{K_{12}+K_{21}} + \frac{K_{12}}{K_{12}+K_{21}}e^{-(K_{12}+K_{21})t}\right)$$

The above solutions could be obtained by other methods, but the state-space method has the advantage of being easily relegated to a computer. One can now obtain a complete analytical solution for the specific activities simply by dividing:

$$a_1 = \frac{R_1}{S_1}$$

$$a_1 = \frac{R_1(0)\left(\frac{K_{12}}{K_{12}+K_{21}} + \frac{K_{21}}{K_{12}+K_{21}}e^{-(K_{12}+K_{21})t}\right) + R_2(0)\left(\frac{K_{12}}{K_{12}+K_{21}} - \frac{K_{12}}{K_{12}+K_{21}}e^{-(K_{12}+K_{21})t}\right)}{S_1(0)\left(\frac{K_{12}}{K_{12}+K_{21}} + \frac{K_{21}}{K_{12}+K_{21}}e^{-(K_{12}+K_{21})t}\right) + S_2(0)\left(\frac{K_{12}}{K_{12}+K_{21}} - \frac{K_{12}}{K_{12}+K_{21}}e^{-(K_{12}+K_{21})t}\right)}$$

and

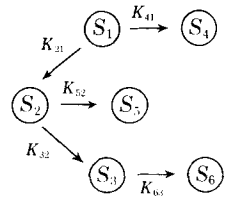
$$a_2 = \frac{R_2}{S_2}$$

$$a_2 = \frac{R_1(0)\left(\frac{K_{21}}{K_{12}+K_{21}} - \frac{K_{12}}{K_{12}+K_{21}}e^{-(K_{12}+K_{21})t}\right) + R_2(0)\left(\frac{K_{21}}{K_{12}+K_{21}} + \frac{K_{12}}{K_{12}+K_{21}}e^{-(K_{12}+K_{21})t}\right)}{S_1(0)\left(\frac{K_{21}}{K_{12}+K_{21}} - \frac{K_{21}}{K_{12}+K_{21}}e^{-(K_{12}+K_{21})t}\right) + S_2(0)\left(\frac{K_{21}}{K_{12}+K_{21}} + \frac{K_{12}}{K_{12}+K_{21}}e^{-(K_{12}+K_{21})t}\right)}$$

Note that the amount of radioactive drug injected must be added to $S_1(0)$ and $S_2(0)$ since S is defined as the total amount of drug present. Also note that the second term in the numerator of the a_i is zero if the labeled material is injected into Compartment 1 only, as is the usual case.

APPENDIX 4

In the following first-order compartment model each compartment contains an initial condition at time $t = 0$. Measurements are possible for Compartments 4, 5, and 6 only, and hence the initial conditions of Compartments 1, 2, and 3 are unknown. Also, all rate constants are unknown. It will be shown that all of the unknowns may be uniquely determined by using the method of isotope dilution.



One can write

$$\frac{dS_1}{dt} = -(K_{21} + K_{41})S_1$$

$$\frac{dS_2}{dt} = K_{21}S_1 - (K_{32} + K_{52})S_2$$

$$\frac{dS_3}{dt} = K_{32}S_2 - K_{63}S_3$$

The solutions to the above three equations are

$$S_1 = S_1(0)e^{-(K_{21}+K_{41})t}$$

$$S_2 = \frac{K_{21}S_1(0)}{(K_{52}+K_{32}) - (K_{21}+K_{41})}(e^{-(K_{21}+K_{41})t} - e^{(K_{32}+K_{52})t}) + S_2(0)e^{-(K_{32}+K_{52})t}$$

$$S_3 = S_3(0)e^{-K_{63}t} + \frac{K_{32}S_2(0)}{(K_{52}+K_{32}) - K_{63}}(e^{-K_{63}t} - e^{-(K_{52}+K_{32})t}) + K_{21}K_{32}S_1(0)\left(\frac{e^{-K_{63}t}}{(K_{52}+K_{32}-K_{63})(K_{41}+K_{21}-K_{63})} + \frac{e^{-(K_{32}+K_{52})t}}{(K_{63}-K_{32}-K_{52})(K_{41}+K_{21}-K_{32}-K_{52})} + \frac{e^{-(K_{41}+K_{21})t}}{(K_{63}-K_{41}-K_{21})(K_{52}+K_{32}-K_{41}-K_{21})}\right)$$

The above three equations describe the time dependency of mass.

Suppose an amount of labeled material is injected into Compartment 1 at $t = 0$. One can write rate equations for the amount of activity in each compartment as:

$$\frac{dR_1}{dt} = -(K_{41} + K_{21})R_1$$

$$\frac{dR_2}{dt} = K_{21}R_1 - (K_{52} + K_{32})R_2$$

$$\frac{dR_3}{dt} = K_{32}R_2 - K_{63}R_3$$

The solutions to the activity equations above are of the same form as the mass equation solutions except that no initial conditions of activity exist on any compartments except 1. Thus the solutions are

$$R_1 = R_1(0)e^{-(K_{21}+K_{41})t}$$

$$R_2 = \frac{K_{21}R_1(0)}{(K_{21}+K_{41}) - (K_{52}+K_{32})}(e^{-(K_{32}+K_{52})t} - e^{-(K_{21}+K_{41})t})$$

$$R_3 = K_{21}K_{32}R_1(0)\left(\frac{e^{-K_{63}t}}{(K_{52}+K_{32}-K_{63})(K_{21}+K_{41}-K_{63})} + \frac{e^{-(K_{32}+K_{52})t}}{(K_{63}-K_{32}-K_{52})(K_{21}+K_{41}-K_{32}-K_{52})} + \frac{e^{-(K_{21}+K_{41})t}}{(K_{63}-K_{41}-K_{21})(K_{32}+K_{52}-K_{41}-K_{21})}\right)$$

Now if specific activity is defined as

$$a = \frac{R}{S}$$

one has for Compartment 1

$$a_1 = \frac{R_1}{S_1} = \frac{R_1(0)\ e^{-(K_{41}+K_{21})t}}{S_1(0)\ e^{-(K_{41}+K_{21})t}}$$

which is a constant. $K_{41}S_1$ and $K_{41}R_1$ can be measured so that

$$a_1 = \frac{K_{41}R_1}{K_{41}S_1}$$

can be determined. Since $R_1(0)$ and a_1 are known,

$$S_1(0) = \frac{R_1(0)}{a_1}$$

which is one of the unknowns to be determined. Note that one must subtract that amount of labeled substance introduced from the above value.

In addition it is possible now also to evaluate K_{41} from

$$K_{41} = \frac{K_{41}S_1(0)}{S_1(0)}$$

K_{21} may be determined from a curve fitting of the $K_{41}S_1$ data with K_{41} as the only unknown. K_{21} could also be determined from the final values of Compartments 4, 5, and 6, *i.e.*,

$$\frac{K_{41}}{K_{21}} = \frac{S_4(\infty)}{S_5(\infty) + S_6(\infty)}$$

The sum $(K_{32} + K_{52})$ can be found from a curve fit of the $K_{52}R_2$ data with the sum as the only unknown or by solving a transcendental equation derived as

$$K_{52}R_2 = \frac{K_{52}K_{32}R_1(0)}{(K_{21} + K_{41}) - (K_{52} + K_{32})}\left(e^{-(K_{41}+K_{21})t} - e^{-(K_{32}+K_{52})t}\right)$$

$$\frac{dK_{52}R_2}{dt} = \frac{K_{52}K_{32}R_1(0)}{(K_{21} + K_{41}) - (K_{52} + K_{32})}\left(-(K_{41} + K_{21})\,e^{-(K_{41}+K_{21})t} + (K_{32} + K_{52})\,e^{-(K_{32}+K_{52})t}\right)$$

at the time T_m, $K_{52}R_2$ reaches its maximum and $(dK_{52}R_2/dt) = 0$. Thus

$$(K_{41} + K_{21})\,e^{-(K_{41}+K_{21})T_m} = (K_{32} + K_{52})\,e^{-(K_{32}+K_{52})T_m}$$

which is a transcendental equation which must be solved iteratively. All terms are known except the sum $(K_{32} + K_{52})$.

The sum $(K_{32} + K_{52})$ may now be split into its parts by making use of the relationship

$$\frac{K_{52}}{K_{32}} = \frac{S_5(\infty)}{S_6(\infty)}$$

and thus K_{52} and K_{32} are determined explicitly. One can now determine the unknown initial conditions, $S_2(0)$. It is possible to measure

$$K_{52}S_2 = K_{52}S_2(0)e^{-(K_{32}+K_{52})t} + \frac{K_{52}K_{21}S_1(0)}{(K_{32} + K_{52}) - (K_{41} + K_{21})}\left(e^{-(K_{41}+K_{21})t} - e^{-(K_{32}+K_{52})t}\right)$$

and thus at $t = 0$ one can be sure he is measuring $K_{52}S_2(0)$ alone. Since K_{52} is known,

$$S_2(0) = \frac{K_{52}S_2(0)}{K_{52}}$$

Only two unknowns remain for the system, $S_3(0)$ and K_{63}. K_{63} can be found with a curve fit of the measured $K_{63}R_3$ data with K_{63} as the only unknown, or one can solve another transcendental equation derived in a manner similar to the first.

From the $K_{63}S_3$ data at $t = 0$, one can find $K_{63}S_3(0)$ in the same manner as $K_{52}S_2(0)$ and hence

$$S_3(0) = \frac{K_{63}S_3(0)}{K_{63}}$$

Thus all unknowns have been uniquely determined. Two methods of evaluating several of the unknowns are possible and can be used as a check.

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