Complete solution of the three-compartment model in steady state after single injection of radioactive tracer

S. M. SKINNER, R. E. CLARK, N. BAKER AND R. A. SHIPLEY
Department of Chemistry and Chemical Engineering, Case Institute of Technology, the Radioisotope Service, Veterans Administration Hospital, and Departments of Biochemistry and Medicine, Western Reserve University School of Medicine, Cleveland, Ohio

SKINNER, S. M., R. E. CLARK, N. BAKER AND R. A. SHIPLEY. Complete solution of the three-compartment model in steady state after single injection of radioactive tracer. Am. J. Physiol. 166(2): 238-244. 1955.—Solutions of a general, three-compartment model in a nonisotopic steady state are developed. By means of these solutions, the investigator may analyze a great variety of kinetic flow relationships utilizing only algebraic procedures. Values of compartment sizes, rates of transport and specific activity-time curves are obtained for three typical hypothetical examples. Possible degrees of freedom and the use of parameters are examined. For those models where physical limitations prevent sufficient independent observations to allow completely determinate solutions, possible limiting values are established.

IN TRACER STUDIES of physiological and biochemical processes, the compartment or pool concept generally facilitates mathematical interpretation. The potential complexity of many models and the attending mathematical treatment often invites simplification to the point that much meaningful information is obscured or lost entirely in the final analysis. Recently, however, Robertson (1) has presented an excellent comprehensive review of more complex solutions. The present analysis is intended to simplify the mathematical treatment of a general nonrestricted three-compartment model when a single injection of isotope is made into one compartment. It provides a straightforward method of analysis for a great variety of models, whether physiological, biochemical or physical. Values sought are those for individual pool sizes and rates of transport.

The pool system to be treated, as shown in figure 1, includes all possible interconnections and routes of ingress and egress. By suppression of various channels of flow so that the corresponding constants are zero the general model can be converted into one of many restricted forms such as are illustrated in figure 2. Setting all values of ingress and egress to zero gives a closed model. General solutions for the model under consideration have been developed in the brilliant matrix treatment of Berman and Schoenfeld (2). The actual analysis of experimental data by matrix methods, however, becomes complex, especially in cases where the number of measurable parameters is smaller than the number of variables. In such an instance the computational effort may be prohibitive. In the present analysis an alternative direct method of obtaining the solution is carried through to the point at which only algebraic operations are necessary on the part of the experimenter.

FORMULATION OF FLOW EQUATIONS

The size of a compartment (labeled and unlabeled material) will be designated by $Q_i$ with its appropriate subscript, and the quantity of radioactive material instantaneously present in it by $q_i$. Flow produces a dependence of $q_i$ on time, commencing with the known initial conditions, and ending in the final equilibrium. No delay time or lag in mixing is assumed; the effects of such a delay may be treated by the introduction of additional compartments or by a more complex analysis. Let $k_{ij}$ be the value of the flow of total (labeled + unlabeled) material into compartment $i$ from compartment $j$, i.e. the quantity per unit time passing into $i$ from $j$. If compartment $j$ is of size $Q_j$ and contains $q_j$ labeled material, the fraction of $k_{ij}$ which is labeled material is $q_j/Q_j$ (specific activity), and the rate of de-
crease of labeled material in compartment $j$ by flow into
$i$ is $-(Q_j/Q_i + \lambda_i)$. This, with sign changed, is also the
rate of increase of labeled material in compartment $i$
by flow from $j$. The rate constant $\lambda_{ij}$ is defined by
$k_{ij}/Q_i$. Flow into the system, $I_i$, represents diluting
material of zero activity (see fig. 1). The flow equations
are:

$$\begin{align*}
pool 1: \frac{dQ_1}{dt} &= -\lambda_{11}Q_1 + \lambda_{12}Q_2 + \lambda_{13}Q_3 \\
pool 2: \frac{dQ_2}{dt} &= \lambda_{21}Q_1 - \lambda_{22}Q_2 + \lambda_{23}Q_3 \\
pool 3: \frac{dQ_3}{dt} &= \lambda_{31}Q_1 + \lambda_{32}Q_2 - \lambda_{33}Q_3
\end{align*}$$

where

$$\begin{align*}
\lambda_{11} &= \lambda_{12} + \lambda_{13} \\
\lambda_{22} &= \lambda_{23} + \lambda_{21} \\
\lambda_{33} &= \lambda_{32} + \lambda_{31} + \lambda_{34}
\end{align*}$$

**Boundary Conditions**

When a single dose of radioactive tracer ($q_{10}$) is in-
jected into compartment $i$ at $t = 0$:

$$q_i = q_{i0} + q_i = q_i = 0$$

The flow from one chamber to another need not be the
same as its reverse flow. If the total flow into each
chamber is the same as the total outflow (nonisotopic
steady state), the following conditions exist:

$$\begin{align*}
I_i + \lambda_{10}Q_2 + \lambda_{13}Q_3 &= \lambda_{10}Q_1 \\
I_j + \lambda_{20}Q_2 + \lambda_{23}Q_3 &= \lambda_{20}Q_2 \\
I_k + \lambda_{30}Q_2 + \lambda_{33}Q_3 &= \lambda_{30}Q_3
\end{align*}$$

As a consequence of experimental observations or
physiological inference other boundary conditions may
be established. For example, one or more of the flows
in figure 1 may be determinable or considered non-
existent. Perhaps the net flow or ratio of flows between
two compartments is known, or information is available
as to the size or size ratio of one or more compartments.

It is assumed that the $\lambda_{ij}$ are constant. Any deviation
from this assumption can be permitted only to the extent
that the solutions become approximations to the actual
behavior. In the most general mathematical treatment
the assumptions 3 need not apply, i.e. the total inflow
$k_{ij}$ of labeled and unlabeled material into a compart-
ment need not be equal to the total outflow (pool sizes
inconstant). The $Q_i$ of equations 3 would then be re-
placed by $Q_i(t)$. The treatment of this is not pursued in
the present paper.

**Solution of Equations**

Using Laplace transforms, it may be shown that
when no two $g_i$ are equal the solution of equations 1 for
the injection of a quantity $q_{10}$ of radioactive material
at $t = 0$ into the first compartment are:

$$\begin{align*}
\frac{q_1}{q_{10}} &= H_1e^{-\lambda t} + H_2e^{-\lambda t} + H_3e^{-\lambda t} \\
\frac{q_2}{q_{10}} &= K_1e^{-\lambda t} + K_2e^{-\lambda t} + K_3e^{-\lambda t} \\
\frac{q_3}{q_{10}} &= L_1e^{-\lambda t} + L_2e^{-\lambda t} + L_3e^{-\lambda t}
\end{align*}$$

where

$$\begin{align*}
H_i &= \frac{(-g_i + \lambda_{10})(-g_i + \lambda_{13}) - \lambda_2\lambda_{13}}{\Delta_t} \\
K_i &= \frac{(-g_i + \lambda_{20})(-g_i + \lambda_{23}) - \lambda_0\lambda_{23}}{\Delta_t} \\
L_i &= \frac{(-g_i + \lambda_{30})(-g_i + \lambda_{32}) - \lambda_0\lambda_{32}}{\Delta_t}
\end{align*}$$
S. M. SKINNER, R. F. CLARK, N. BAKER AND R. A. SHIPLEY

<table>
<thead>
<tr>
<th>TABLE I. Solutions of Examples 1, 2 and 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(A)</td>
</tr>
<tr>
<td>( Q_2/Q_1 )</td>
</tr>
<tr>
<td>( Q_3/Q_1 )</td>
</tr>
<tr>
<td>( 1/Q_1 )</td>
</tr>
<tr>
<td>( \lambda_{U2} )</td>
</tr>
<tr>
<td>( \lambda_{U3} )</td>
</tr>
<tr>
<td>( \lambda_{U23} )</td>
</tr>
<tr>
<td>( \lambda_{U31} )</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SOLUTION</th>
<th>( I )</th>
<th>( II )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( Q_2/Q_1 )</td>
<td>( C_3C_5(C_{10} - C_{11}) - C_8C_9C_{11} )</td>
<td>( 17 )</td>
</tr>
<tr>
<td>( Q_3/Q_1 )</td>
<td>( C_5C_4C_{11} )</td>
<td>( 16.6 )</td>
</tr>
<tr>
<td>( 1/Q_1 )</td>
<td>( C_{13}C_{14}C_{15} )</td>
<td>( 0.13 )</td>
</tr>
<tr>
<td>( \lambda_{U2} )</td>
<td>( C_4C_5C_6C_7C_8C_9C_{10}/C_2C_3C_4 )</td>
<td>( 0.0086 )</td>
</tr>
<tr>
<td>( \lambda_{U3} )</td>
<td>( C_3 )</td>
<td>( 0.26 )</td>
</tr>
<tr>
<td>( \lambda_{U23} )</td>
<td>( C_3C_2C_4C_5C_6C_7C_8C_9C_{10}/C_2C_3C_4 )</td>
<td>( 0.011 )</td>
</tr>
</tbody>
</table>

Ranges shown in part C are the limiting values obtained with possible variations in the parameters \( a \) and \( \theta \). Where two sets of values are shown, those in the lower left form a set, as do those in the upper right. Note that one of the limiting solutions of part C is that of part B.

\[
\begin{align*}
\lambda_1 &= \frac{(-g_1 + g_2)}{(-g_3 + g_4)} \\
\lambda_2 &= \frac{(-g_3 + g_4)}{(-g_1 + g_2)} \\
\lambda_3 &= \frac{(-g_1 + g_2)}{(-g_3 + g_4)}
\end{align*}
\]

The following identities emerge in the course of obtaining the solution:

\[
\begin{align*}
\Delta_1 &= (-g_1 + g_2)(-g_3 + g_4) \\
\Delta_2 &= (-g_2 + g_3)(-g_3 + g_4) \\
\Delta_3 &= (-g_1 + g_2)(-g_2 + g_3)
\end{align*}
\]

Samples from that compartment into which the radioactivity is initially injected, i.e. compartment 1, will al
most always be obtainable for analysis. If specific activity of the compartment at \( t = 0 \) is normalized to 1.0 and the ensuing time curve plotted as fractions of this initial value, the values of the slopes and intercepts will be those of \( g_i \) and \( H_i \) of equations 4. In particular, \( g_3 \) and \( H_3 \) would be, respectively, the slope and zero time intercept of the third component of the curve. The first two components of the curve, obtained by conventional curve peeling, yield \( g_1, g_2, H_1 \) and \( H_2 \). It is evident that \( H_1 = H_2 = 1.0 \).

In equations 4–8 the values of \( g_i \) and \( H_i \) are known while the \( \lambda_{ij} \) are to be determined. The \( K_i \) and \( L_i \) may be evaluated from equations 6 and 7 unless additional observations on compartments 2 and/or 3 are possible, under which circumstances these values may be observed as were \( H_i \). Equations 5 and 6 can be solved straightforwardly without the need for solving the cubic equations implicit in 8. In the subsequent equations relationships of observed values such as \( p_i \) and \( H_i \) are developed in terms of arbitrary constants, \( C \). Values of individual rate-constants \( \langle \lambda_{ij} \rangle \) and volumes \( \langle Q_i \rangle \) may then be expressed in terms of these constants.

**Compartment 1**

Two of equations 5 are independent. Thus, multiplying through by the denominators and subtracting:

\[
\lambda_1 - \lambda_2 = (g_3 - g_1) + (g_3 - g_2)H_3 = g_3 - g_2 - H_3 - C_1 \tag{9}
\]

from this and either equation of 5.

\[
\lambda_2 \lambda_3 - \lambda_3 \lambda_2 = (g_2 - g_1)(g_2 - g_3)H_2 - g_2^2 + C_2g_3 - C_4 \tag{10}
\]

Equations 8 now become:

\[
\lambda_1 = g_1 + g_2 + g_3 - C_1 = C_1
\]

\[
\lambda_2 \lambda_3 + \lambda_3 \lambda_2 - C_2 = C_2
\]

\[
\lambda_3 \lambda_1 + \lambda_1 \lambda_3 + \lambda_1 \lambda_2 + \lambda_2 \lambda_1 = -g_2g_3 + C_3C_2 = C_6
\]

\[
\lambda_3 \lambda_2 = g_2g_3 + C_3C_2 = C_6
\]

**Compartment 2**

When measurements relating to the second compartment are possible, two more relations are obtained:

\[
\lambda_2 = (g_3 - g_2)K_1 + (g_3 - g_1)K_2 = C_4 \tag{12}
\]

\[
\lambda_3 \lambda_2 + C_3 \lambda_2 = -(g_3 - g_1)(g_3 - g_2)K_1 + C_3K_2 = C_7 \tag{13}
\]

**Compartment 3**

Measured values of the \( L_i \) of compartment 3 would similarly yield:

\[
\lambda_3 = (g_3 - g_2)L_3 + (g_3 - g_1)L_2 = C_4 \tag{14}
\]

\[
\lambda_2 \lambda_3 + C_3 \lambda_2 = -(g_3 - g_1)(g_3 - g_2)L_3 + C_2L_3 = C_7 \tag{15}
\]

If either 12 and 13 or 14 and 15 are used with 11, the latter becomes simpler algebraically; if both are used, all equations become linear.

As in compartment 1 it is evident that only two of the three equations implied in each of 6 and 7 are independent. The specific activity-time curve in compartments 2 and 3 will be zero at \( t = 0 \), rise to a maximum, and decline exponentially. Thus \( 2KL_1 = \Sigma L_i = 0 \).

**Structure of Solutions**

Equations 9–15 are a set of simultaneous nonlinear equations which permit algebraic calculation of the
desired quantities. To them are added equations 3 and other boundary conditions which are applicable. The difference between the number of unknowns and the experimentally determinable quantities plus the number of boundary conditions is the measure of the degrees of freedom of the system. If each unknown is expressed by its ratio to a particular parameter, here chosen as \( Q_r \), the size of the first compartment, 14 unknowns remain to be determined: \( Q_2, Q_3 \), the six \( \lambda_{ij} \), the three \( \lambda_{ii} \), and the three \( I_i \).

Experimentally determinable quantities include those five from the first compartment, namely any two \( H_i \) and three \( g_i \) in equations 5 and 8. Measurements on additional pools, e.g. via excretion, would provide two additional quantities per pool, i.e. two \( K_i \) or two \( L_i \). The \( g_i \) will be the same in all three compartments. The steady state boundary conditions of equations 3 remove an additional three degrees of freedom.

When the number of unknowns is smaller than the number of equations, an equal number of unknowns and equations is selected and values are computed. Equations which incorporate the most trustworthy assumptions are preferred. If the remaining ones require alteration in order to achieve conformity, this would challenge the reasonableness of the model, the accuracy of part of the data, or the graphical fitting of the curve to the data.

When the number of variables exceeds the number of equations, the excess variables are chosen as arbitrary parameters, in the same manner as was done in reference 2. Instead of matrix methodology, however, the solution proceeds algebraically, treating the parameters as known quantities. Numerical work may be lightened by exercising ingenuity in the selection of the variables which will serve as parameters. After the complete solution has been obtained, the condition requiring that no \( \lambda_{j} \) or \( Q_r \) has a negative value is applied. This delimits areas in which the parameters may take their values. In the typical case, some of these last conditions include and are more stringent than others, so that the final results may depend upon only a few of the conditions of non-negativity.

EXAMPLES OF USE OF EQUATIONS

A. Strictly Determinate Models

1. Three compartments in line, with external flow. One of the more common models used in the analysis of the flow of tracer materials in biological systems is the scheme of three compartments in line. Although this is sometimes treated as a closed system, without flow to or from the model, biological systems frequently include components of turnover or replacement. Such a model, figure 2A, will be treated here. We assume physiological steady state and that measurement of activity can be made only in \( Q_r \) where the initial activity, \( q_10 \), is injected.

Under these conditions there are eight unknowns: \( Q_2, Q_3; \) and \( I_1, \lambda_{11}, \lambda_{12}, \lambda_{23}, \lambda_{3} \). The other \( I_i \) and \( \lambda_{ij} \) are zero. To solve for these eight, there exist the three boundary conditions 3, and the five expressions of 9, 10, and 11, so that the problem is completely determinate. Inserting the value of zero for the appropriate variables in the general equations, therefore, the eight equations are:

\[
\begin{align*}
I_1 + \lambda_{11}Q_1 &= \lambda_{12}Q_2 \\
\lambda_{12}Q_2 + \lambda_{23}Q_3 &= (\lambda_{12} + \lambda_{3})Q_2 \\
\lambda_{23}Q_3 &= (\lambda_{22} + \lambda_{23})Q_3 \\
\lambda_{11} + \lambda_{12} &= C_1 \\
\lambda_{12} \lambda_{23} - \lambda_{12} \lambda_{23} &= C_3 \\
\lambda_{11} &= C_4 \\
\lambda_{12} \lambda_{23} &= C_4 \\
\end{align*}
\]

If the analysis of an hypothetical decay curve in the first compartment furnishes the following values: \( g_1 = 0.577, g_2 = 0.0933, g_3 = 0.0080, H_1 = 0.841, H_2 = 0.131, H_3 = 0.028, \) and \( q_{10}/Q_1 = 53.5 \), the resulting
SOLUTION OF THREE-COMPARTMENT MODEL IN STEADY STATE

solution is shown in table 1A. With certain modifications of the general model a direct numerical substitution in equations 3, 9, 10 and 11 may be simpler than the algebraic formulation of $\lambda_{ij}$ and $Q_i$ in terms of the constants $C$.

Using the values (table 1A) of the variables, one may now compute the $K_i$ and the $L_i$, and therefore the time-wise course of specific activity in the second and third compartments. Figure 3A shows the specific activity in all three compartments semilogarithmically as a function of time.

2. One reserve compartment. The model used here is that of figure 2B, with $I_2$ and $Q_0$ equal to zero. In this case, the unknowns to be determined are:

$$Q_1, Q_2, \lambda_{12}, \lambda_{11}, \lambda_{13}, \lambda_{21}, \lambda_{22}, I_1$$

With the same two assumptions as in the first example, the equations available for solving the model are:

$$I_1 + \lambda_1Q_1 + \lambda_{21}Q_2 = \lambda_{13}Q_3$$
$$\lambda_{12}Q_1 = \lambda_{12}Q_2$$
$$\lambda_{13}Q_1 + \lambda_{13}Q_{3} = \lambda_{13}Q_{3}$$

As is evident from equations 9 and 10, the solution will involve a quadratic, and two solutions may be possible:

$$x_{22} = \frac{-\lambda_{13} + \sqrt{\lambda_{13}^2 - 4\lambda_{13}C}}{2\lambda_{13}}$$
$$x_{33} = \frac{-\lambda_{13} - \sqrt{\lambda_{13}^2 - 4\lambda_{13}C}}{2\lambda_{13}}$$

The two strictly determinate models computed above from the same set of experimental data both show sets of values which, under many circumstances, would be considered reasonable. In general, the fact that the experimental data provide reasonable values for one assumed model is not acceptable as proof that the model is the correct one. Before such a conclusion can be drawn, it would be necessary to examine the values obtained for a number of models, and to incorporate any additional information such as reasonableness from the point of view of physiological and chemical processes.

**B. Indeterminate Models**

Only one example is necessary to exhibit the method of using the data. The previous model will be used, including the inflow and outflow at the third compartment, as shown in figure 2B. If measurements of specific activity can be made only in the first compartment, there are 10 unknowns, namely $6 \lambda_{ij}, 2 I_i, Q_1$ and $Q_3$, but only 8 experimental data to fix the variables.

The two parameters chosen will be defined as

$$I_3/Q_3 = v, \lambda_{20} = w$$

Using the known data, there result the following equations:

$$\lambda_{21} + \lambda_{20} = C_1$$
$$\lambda_{02} = C_2$$
$$\lambda_{13} = C_3$$
$$\lambda_{21} + \lambda_{23} = C_4$$
$$\lambda_{02} + \lambda_{12} + \lambda_{03} = C_5$$

For example, if pool 1 in this hypothetical example is considered to be plasma, and pool 2, interstitial fluid (with the outflow $\lambda_{02}$ indicating irreversible flow into cells), and if the material under study is known to penetrate readily through capillaries, the data of figure 3B might be eliminated in favor of that of figure 3C. Pool 2 (fig. 3B) is excessively large, and its specific activity-time curve is markedly divergent from that of pool 1. Figure 4 indicates the variation in the size of compartments 2 and 3 as $g_2$ varies while $g_1$ and $g_3$ remain fixed. This graphically predicts the uncertainty in $Q_2$ and $Q_3$ resulting from errors in estimate of $g_2$. 

**FIG. 5. Allowable range of values for the parameters $v$ and $w$ of example 3, solution I.**

The two strictly determinate models computed above from the same set of experimental data both show sets of values which, under many circumstances, would be considered reasonable. In general, the fact that the experimental data provide reasonable values for one assumed model is not acceptable as proof that the model is the correct one. Before such a conclusion can be drawn, it would be necessary to examine the values obtained for a number of models, and to incorporate any additional information such as reasonableness from the point of view of physiological and chemical processes.
It may be noticed that the values of $\lambda_{11}$ do not depend upon $v$ or $w$. When $C_{12}$, $C_{13}$ are defined as $(C - C)/ \left( (C_{11} - C_{13}) \right)$, and $C = C_{10}/(C_{11} - C_{13})$, respectively, one obtains the relationships shown below and in table 1A.

\[
\begin{align*}
\lambda &= w \\
I_0/Q_1 &= v \\
\lambda &= C_{11} - w \\
\lambda &= C_{10}/\lambda = C_{10}/(C_{11} - w) \\
\lambda &= C_{12} = C - C_{10}/(C_{11} - w) \\
\lambda &= C_{13} - C_{11} - w)/[C_{10}(C_{11} - w) - C_{12}] \\
\lambda &= C_{11} - w = C_{10} - C_{12}/C_{11} - w) \\
Q_0/Q_1 &= \lambda_{11}/C_{11} = C_{10}/C_{11} - C_{12}/C_{11} - w) \\
Q_0/Q_1 &= \frac{v + \lambda_{11}}{C_{11}} = \frac{v}{C_{11}} + \frac{C_{10}}{C_{11}}(C_{11} + w) \\
I_0/Q_1 &= C_{10} - \frac{C_{12}}{C_{11} - w} - v \left( 1 - \frac{w}{C_{11}} \right)
\end{align*}
\]

To see how much variability in these quantities is introduced by permitting the flows $\lambda_{11}$ and $I_0$, the values of the $g_i$ and $H_i$ used in the last example are taken. In $20$, $a$ and $b$ require that

$$v \geq 0, \quad w \geq 0.$$ 

References