STOCHASTIC MODELS FOR THE DISTRIBUTION OF RADIOACTIVE MATERIAL IN A CONNECTED SYSTEM OF COMPARTMENTS

S. R. BERNARD
Oak Ridge National Laboratory

L. R. SHENTON
Oak Ridge National Laboratory

and

University of Georgia

V. R. RAO UPPULURI
Oak Ridge National Laboratory

1. Introduction

The purpose of this report is to consider the problem of nonuniform distribution of bone seeking radionuclides, such as the alkaline earth elements, and the effect of age on the retention of these radionuclides in organisms via a mathematical study of a compartmental system in which the connections between the compartments are random variables. In most compartmental studies it is generally assumed that the contents of the compartments are uniformly distributed (see for example, Sheppard and Householder [7], Berman and Schoenfeld [1], Hearon [4]). This is not a realistic assumption for the case of bone seeking elements such as radium, where it has been well demonstrated that hot spots of activity occur as many as 20 or 30 years after intake of $^{226}$Ra by man [5]. Rowland states that the concentrations in the hot spots exist in regions of bone where new mineral was laid down at the time the radium was acquired and that in this mineral the original concentration of Ra, expressed as the ratio of Ra to Ca, was essentially the same as the Ra to Ca ratio that existed in the blood plasma at the time the new mineral was formed. There is also a second type of distribution which is much lower in concentration and rather uniform. This is believed to be the result of an exchange process which continually transfers Ca and/or Ra atoms from blood to bone and back again and which is characterized by an unusually long time constant.

It is customary to think of bone tissue in terms of two types—the trabecular

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or spongy tissue and the cortical or hard bony material. A process called remodeling of these tissues takes place during life and this amounts to the erosion or resorption of one region of bone and the laying down or rebuilding in another region. It is during this process of absorption and resorption that "hot spots" are formed in bone.

There is a growing trend to consider turnover rates in bone in terms of at least two "subcompartments," trabecular bone and compact bone. The turnover rates in these two types of bone are observed to be different, faster in trabecular bone and much slower in the compact bone. Lucas has suggested that the biological half life for Ra in trabecular bone is about 7 to 14 years and twice as long in compact bone. Also, the hot spots of Ra would disappear from the bone after perhaps 200 years since by then the whole bone would be remodeled and turned over. How may we more adequately represent these phenomena in terms of a compartmental approach?

One way to gain more insight into this problem is to consider the bone-blood system as a set of $j$ randomly connected compartments; let the first compartment represent blood, in which the element is uniformly mixed, and the other $j - 1$ compartments represent bone. Take a subset of $r$ compartments, $r < j - 1$, and call these trabecular bone. Let the other $j - r - 1$ compartments be cortical bone. Assume that the flows between the blood and bone are random, that is, of the $j - 1$ compartments only one of them is connected to the blood in the interval $0$ to $t_1$, while in the interval $t_1$ to $t_2$, one of them is also connected but not necessarily the same one that was connected in the first interval of time, and so on, for other intervals of time. Thus, some of the $j - 1$ compartments trap the concentration that existed in the interval $0$ to $t_1$ (This represents the laying down of new bone.) They may release it at a later time (this represents the remodeling of bone), or they may never reopen and connect with the blood stream (this represents a hot spot), thereby maintaining the same concentration that existed at time $t_1$.

The above constitutes the general compartmental system we want to study. We need to determine the behavior of the system—what are the concentrations in a given compartment as a function of time—how long must one wait until a compartment releases the trapped material—how many randomly connected compartments are required to represent the available data on retention in bone? We find that these are difficult questions and that before we can get some answers to the general case we have to initiate our studies on a simpler system, namely, that of only two compartments with random flows. Here we gain some insight into the behavior of the general system. Thus, we begin by presenting the results of the study of this simpler model, which has been described by Bernard and Uppuluri [2]. They consider the radioactive material retained in animals (dogs, and so forth) by introducing an open system consisting of two compartments $S$ and $B$ which refer to the blood stream and the bone structure respectively.

Initially (time $t = 0$ or stage zero), the compartments hold unit mass of
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radioactive material (henceforth abbreviated to "material"), and compartment B holds zero mass, and the connecting valve is closed. At the end of a unit time interval $\Delta t$ (stage 1) there occurs a random event which determines the opening or closing of the valve connecting the two compartments. If the valve at the end of time $\Delta t$ is closed, then the amount of material in S is reduced by a factor $a$ (the attenuation factor). Thus, in this case the amount in S at the end of the first interval of time would be $a \times 1 = a$, whereas the amount in B is still zero. If, however, the valve opens at the end of time $\Delta t$, then the total amount in the two compartments is reduced by a factor $a$, and reapportioned in equal amounts between S and B. Thus, if the system has initially unit material in S and zero in B, then at the end of time $\Delta t$ the compartments contain the amounts shown in figure 2. The sketch at the left in figure 2 shows the result if the valve remains closed at the end of $\Delta t$ (with probability $1 - p$), and the one on the right, the result if the valve opens at the end of $\Delta t$ (with probability $p$). Similarly, the state of the compartments with respect to the amount of material held at the end of the second time interval $\Delta t$ can be constructed and will be seen to consist of four possibilities as shown in table I.

The scheme in table I could be continued so as to show the possible amounts of material in S and B at the end of $m$ intervals of time $\Delta t$. Clearly, there would be $2^m$ values for the amounts in S, B with corresponding probabilities, in this

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**Figure 1**

Two compartment model.

**Figure 2**

States of system after $\Delta t$.

Left: valve remains closed at end of $\Delta t$ with probability $1 - p$.

Right: valve opens at end of $\Delta t$ with probability $p$. 

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TABLE I

STATE OF THE SYSTEM AT END OF TIME 2Δt

<table>
<thead>
<tr>
<th>State of System at End of</th>
<th>Closed</th>
<th>Closed</th>
<th>Open</th>
<th>Open</th>
</tr>
</thead>
<tbody>
<tr>
<td>2Δt</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Probabilities</td>
<td>(1 - p)(1 - p)</td>
<td>(1 - p)p</td>
<td>p(1 - p)</td>
<td>p^2</td>
</tr>
<tr>
<td>Amount in S</td>
<td>a^2</td>
<td>1/2 a^2</td>
<td>1/4 a^2</td>
<td>1/4 a^2</td>
</tr>
<tr>
<td>Amount in B</td>
<td>0</td>
<td>1/2 a^2</td>
<td>1/4 a</td>
<td>1/4 a</td>
</tr>
<tr>
<td>Total amount in the system</td>
<td>a^2</td>
<td>a^2</td>
<td>1/4 a(a + 1)</td>
<td>a^2</td>
</tr>
</tbody>
</table>

branching process. We shall denote the amounts in S and B at the end of time mΔt by C_{S,m} and C_{B,m}, respectively; these are then random quantities obeying the following stochastic recursive relations [2]

\[ C_{S,m} = X_m \frac{a}{2} (C_{S,m-1} + C_{B,m-1}) + a (1 - X_m) C_{S,m-1}, \]

\[ C_{B,m} = X_m \frac{a}{2} (C_{S,m-1} + C_{B,m-1}) + (1 - X_m) C_{B,m-1}, \]

\( m = 1, 2, \ldots \), with \( C_{S,0} = 1, C_{B,0} = 0. \)

In these equations \( X_m \) is a random variable associated with the state of the valve at the end of the \( m \)th interval. If the valve is open, then \( X_m \) takes the value unity (probability \( p \)); if, however, the valve is closed, then \( X_m \) takes value zero (probability \( 1 - p \)). We thus see that the state of the system at time \( mΔt \) is ultimately related to the initial state, and this is succinctly expressed in matrix form by the equation

\[ \begin{bmatrix} C_{S,m} \\ C_{B,m} \end{bmatrix} = (\Gamma_1 \Gamma_{m-1} \cdots \Gamma_1) \begin{bmatrix} C_{S,0} \\ C_{B,0} \end{bmatrix} \]

where

\[ \Gamma_i = \begin{bmatrix} \frac{1}{4} a X_i + a (1 - X_i) & \frac{1}{4} a X_i \\ \frac{1}{4} a X_i & \frac{1}{4} a X_i + (1 - X_i) \end{bmatrix} \]

We note that in general the matrices \( \Gamma_i \) are noncommutative.

In a previous account of the subject [2], expressions were derived for the expected amounts in the system at time \( mΔt \). Our objective here is to extend this initial work and consider and discuss several further aspects centered around the following topics: (i) multicompartment systems; (ii) principles of mixing when several compartments are connected; (iii) association of the system with a branching process; (iv) higher moments of the amounts in the compartments at time \( mΔt \); and (v) feasibility studies.

We now discuss some of these in general terms and refer to them again in the sequel.

There are many varieties of multicompartment systems which are feasible in
the present situation. Some of these also occur in connection with tracer experiments in steady state systems and reference may be made to Sheppard and Householder [7] and Sheppard [6]. It is to be remembered that interest here centers mainly on the connectivity aspect of a system. One that is studied in some detail is the so called mammillary system shown in figure 3.

![Random Valve (connection) Peripheral Compartment Stream](image)

**FIGURE 3**

Mammillary system.
(Each peripheral compartment communicates with the stream.)

The amounts in the compartments at time $m\Delta t$ can be considered as components of a random vector $C_m$, the number of components being the same as the number of compartments (including the stream). In general, the sample space of $C_m$ can be defined recursively by products of matrices operating on $C_0$, but the description of the sample space at time $m\Delta t$ in closed form presents considerable difficulties. From another point of view the sample space description involves an evaluation of the iterates of an initial vector under a series of non-commutative linear transformations. This problem is greatly simplified when the attenuation factor is taken to be unity, but even here formulae relating to sample spaces for vectors of more than three components have proved intractable. Even a complete description of the sample space for two component vectors is out of reach.

The complete specification of a solution to a given system would demand the evaluation of the joint distribution of the components of $C_m$. Thus, being given the physical structure of a system (that is, the number of compartments and the connectivity complex), we also require the probabilistic structure associated with the valves. The general distributional problems are beyond the scope of this report and we confine ourselves to the evaluation of the means and covariances of the variates in $C_m$.

2. Description of the model

2.1. *The basic stochastic recursive relation*. The state of the system is represented by a $(j - 1)$-tuple, $j \geq 3$. Thus, if the first valve is open, the system is
represented by \( e_1 = (1, 0, \ldots, 0) \) and if the \( i \)th valve is open then the system is said to be in state \( e_i \) where \( e_i \) has unity as its \( i \)th component, all other components being zero. Clearly, the states \( e_1, e_2, \ldots, e_{j-1} \) are mutually exclusive and exhaustive. At any instant the system can be in one and only one of the states \( e_1, e_2, \ldots, e_{j-1} \).

Let \( \xi = (E_1, E_2, \ldots, E_{j-1}) \) denote a state of the system. For example \( \xi = (E_1, E_2, \ldots, E_{j-1}) = e_1 \) implies that \( E_1 = 1, E_2 = E_3 = \ldots = E_{j-1} = 0 \).

Let \( P\{\xi = e_i\} = p_i > 0 \) for \( i = 1, 2, \ldots, j - 1 \) and \( \sum_{i=1}^{j-1} p_i = 1 \).

Let \( C_{s,m} \) denote the amount of substance in the stream, and \( C_{i,m}, i = 1, 2, \ldots, j - 1 \), denote the amount of substance in the peripheral compartments at time \( m\Delta t \) for \( m = 1, 2, \ldots \). We shall suppose that the initial amounts are given as \( C_{s,0} = 1 \), and \( C_{i,0} = 0, i = 1, 2, \ldots, j - 1 \).

At any time \( m\Delta t \), if the system is in state \( e_i \), let us suppose that instantly the amount in the stream and \( i \)th peripheral compartment becomes

\[
C_{s,m} = \frac{j - 1}{j} a(C_{s,m-1} + C_{i,m-1}),
\]

(2.1)

\[
C_{i,m} = \frac{1}{j} a(C_{s,m-1} + C_{i,m-1}),
\]

and the amounts in the rest of the compartments remain the same as at time \( (m - 1)\Delta t \). This apportionment stems from the fact that the total amount in the communicating compartment and the stream is divided in proportion to their volumes—it being assumed that the volumes of the \( j - 1 \) peripheral compartments are the same, and the volume of the stream is \( j - 1 \) times that of any peripheral compartment.

This may be written as

\[
C_{s,m} = \frac{j - 1}{j} aE_1(C_{s,m-1} + C_{1,m-1}) + \frac{j - 1}{j} aE_2(C_{s,m-1} + C_{2,m-1})
\]

\[
\quad + \cdots + \frac{j - 1}{j} aE_{j-1}(C_{s,m-1} + C_{j-1,m-1}),
\]

\[
C_{1,m} = \frac{a}{j} E_1(C_{s,m-1} + C_{1,m-1}) + (E_2 + E_3 + \cdots + E_{j-1})C_{1,m-1},
\]

(2.2)

\[
C_{2,m} = E_1C_{2,m-1} + \frac{a}{j} E_2(C_{s,m-1} + C_{2,m-1})
\]

\[
\quad + (E_3 + E_4 + \cdots + E_{j-1})C_{2,m-1},
\]

\[
\vdots
\]

\[
C_{j-1,m} = (E_1 + E_2 + \cdots + E_{j-1})C_{j-1,m-1} + \frac{a}{j} E_{j-1}(C_{s,m-1} + C_{j-1,m-1}).
\]

We note that the random variates \( E_i \), with \( i = 1, 2, \ldots, j - 1 \), are assumed to be independent of time. The above can be compactly expressed as
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\[ C_{2,m} = \begin{bmatrix} \frac{i-1}{j} aE_1 & \frac{i-1}{j} aE_2 & \cdots & \frac{i-1}{j} aE_{j-1} \\ \vdots & \vdots & \ddots & \vdots \\ \frac{a}{j} E_1 & E + \left( \frac{a}{j} - 1 \right) E_2 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots \\ \frac{a}{j} E_{j-1} & 0 & \cdots & E + \left( \frac{a}{j} - 1 \right) E_{j-1} \end{bmatrix} C_{2,m-1} \]

where \( E = E_1 + E_2 + \cdots + E_{j-1} \) and \( m = 1, 2, \cdots \).

Let \( C_m \) denote the \( j \times 1 \) column vector with the \( i \)th component as \( C_{i,m} \) for \( i = 1, 2, \cdots, j-1 \), and \( T \) denote the random matrix

\[ T = E_1 A_1 + E_2 A_2 + E_3 A_3 + \cdots + E_{j-1} A_{j-1}, \]

where the \( j \times j \) matrix \( A_r = (b_{ij}^r) \), is given by

\[ b_{ij}^r = \begin{cases} \frac{j-1}{j} a, & \text{if } f = 1, \\ \frac{a}{j} & \text{if } f = r + 1, \\ 1 & \text{otherwise,} \end{cases} \]

if \( g = f \),

\[ \begin{cases} \frac{j-1}{j} a, & \text{if } f = 1, g = r + 1, \\ \frac{a}{j} & \text{if } f = r + 1, g = 1, \\ 0 & \text{otherwise,} \end{cases} \]

if \( g \neq f \).

It may be noted that in general \( A_r A_u \neq A_u A_r \).

Now (2.3) can be written as

\[ C_m = TC_{m-1}, \quad m = 1, 2, 3, \cdots, \]

which is the basic recursive relation, and being given \( C_0 \), this describes the system completely.

2.2. Sample space.

2.2.1. General case. This case may be described as the branching process (figure 4) where at each instant of time we have \( (j-1) \) possible linear transformations \( A_1, A_2, \cdots, A_{j-1} \) which can transform any \( j \times 1 \) vector \( u = (u_1, u_2, \cdots, u_j) \) of the previous stage into \( A_r u \) with probability \( p_i \) for \( i = 1, 2, \cdots, j-1 \).

The sample space after \( m \) independent trials is represented by the totality of \( j \) component vectors such as

\[ (A_1 A_{m-1} A_{j-1}) u_0, \quad A_r \in (A_1, A_2, \cdots, A_{j-1}), \]
$u_0$ is the initial $j \times 1$ vector of amounts in the system, and $r_1, r_2, \ldots, r_m$ is a partition of $m$, with the associated probability

\begin{equation}
(2.9) \quad p_1^0 \cdot p_2^0 \cdots p_m^0.
\end{equation}

It is understood that some of the $p$ may be equal, so that after $m$ trials we may have several entirely different realizations with the same probability.

Figure 4.

Illustration of branching process.

2.2.2. Sample Space when $j = 3$. As an illustration of the sample space we consider a three compartment system in which the peripheral compartments communicate with the stream with probabilities $p_1$ and $p_2$. We then have for the random amounts in the compartments at the $m$th stage

\begin{equation}
(2.10) \quad \begin{pmatrix}
C_{S,m} \\
C_{1,m} \\
C_{2,m}
\end{pmatrix} = \begin{pmatrix}
E_1 \begin{pmatrix} 2a & 2a & 0 \\ a & a & 0 \\ 0 & 0 & 1 \end{pmatrix} + E_2 \begin{pmatrix} 2a & 0 & 2a \\ 0 & 1 & 0 \\ a & 0 & a \end{pmatrix}
\end{pmatrix} \begin{pmatrix}
C_{S,m-1} \\
C_{1,m-1} \\
C_{2,m-1}
\end{pmatrix}
\end{equation}

$m = 1, 2, \ldots$.

Taking $a = 1$ introduces a further simplification, for now the matrices in (2.10) are not only stochastic but also idempotent. The sample space and associated probability structure may now be written in the form
(2.11) \((p_1A_1 + p_2A_2)(p_1A_1 + p_2A_2) \cdots (p_1A_1 + p_2A_2)C_0 = (p_1A_1 + p_2A_2)^mC_0\)

where the expression in (2.11) is to be evaluated with due regard to the fact that \(A_1\) and \(A_2\) are not commutative, and where

\[
(2.12) \quad A_1 = \begin{pmatrix} \frac{3}{2} & \frac{3}{2} & 0 \\ \frac{3}{2} & \frac{3}{2} & 0 \\ 0 & 0 & 1 \end{pmatrix}, \quad A_2 = \begin{pmatrix} \frac{3}{2} & 0 & \frac{3}{2} \\ 0 & 1 & 0 \\ \frac{3}{2} & 0 & \frac{3}{2} \end{pmatrix}.
\]

For example, we have from (2.11) with \(m = 2, 3, \ldots\),

\[
(2.13) \quad (p_1A_1 + p_2A_2)^2C_0 = (p_2p_1A_1 + p_1p_2A_1A_2 + p_2p_2A_1A_2A_1)C_0 \\
+ (p_2p_2A_2A_1A_2 + (p_2p_1 + p_1p_2)A_2A_1 + p_2A_2)C_0.
\]

These may be written as a sum of complementary terms. Thus,

\[
(2.14) \quad (p_1A_1 + p_2A_2)^2 = \Phi_2(p_1, p_2, A_1, A_2) + \Phi_2(p_2, p_1, A_2, A_1),
\]

where the second term is derived from the first by the interchange \(p_1 \leftrightarrow p_2\), \(A_1 \leftrightarrow A_2\); and similarly for the third power. We shall now prove a more general theorem.

**Theorem 2.1.** If \(A_1\) and \(A_2\) are two idempotent matrices (of the same order), then for any positive integer \(m\),

\[
(2.15) \quad (p_1A_1 + p_2A_2)^m = \Phi_m(p_1, p_2, A_1, A_2) + \Phi_m(p_2, p_1, A_2, A_1)
\]

where

(i) \(\Phi_m(p_1, p_2, A_1, A_2) = a^{(m)}(p_1, p_2)A_1 + a^{(m)}(p_1, p_2)A_1A_2 + a^{(m)}(p_1, p_2)A_1A_2A_1 + a^{(m)}(p_1, p_2)(A_1A_2)^2 + \cdots + a^{(m)}(p_1, p_2)(A_1A_2)^{m-2}A_2\),

(ii) \(\lambda = \left[\frac{m}{2}\right], \mu = m - 2\left[\frac{m}{2}\right] \) with \([x]\) referring to the greatest integer less than or equal to \(x\),

(iii) \(a^{(m)}_{2r}(p_1, p_2) = (p_1p_2)^r \sum_{s=0}^{m-2r} \binom{r + s - 1}{r - 1}(m - r - s - 1)p_1p_2^{m-2r-s}, \)

\(r = 1, 2, \ldots, \left[\frac{m}{2}\right]\),

\(= 0\) otherwise,

(iv) \(a^{(m)}_{2r+1}(p_1, p_2) = \begin{cases} p_1^{r+1}p_2^{m-2r-1} \binom{r + s}{r}(m - r - s - 2)p_1p_2^{m-2r-s-1}, & \text{if } r = 1, 2, \ldots, \left[\frac{m}{2} - 1\right] \\ p_1^{r+1}, & \text{if } r = 0, \\ 0 & \text{otherwise}, \end{cases}\)

and similar expressions for \(\Phi_m(p_2, p_1, A_2, A_1)\).

**Proof.** By induction, the cases for \(m = 2, 3\) are verified easily. We assume the formulae in (2.15) hold up to and including \(m\). Then
(2.16) \[(p_1 A_1 + p_2 A_2)^{m+1}
\]

and so

(2.17) \[a^{(m+1)}_{2r}(p_1, p_2) = p_1 a^{(m)}_{2r-1}(p_1, p_2) + p_2 a^{(m)}_{2r}(p_1, p_2), r = 1, 2, \ldots \left[\frac{m}{2} + \frac{1}{2}\right]\]

and

(2.18) \[a^{(m+1)}_{2r+1}(p_1, p_2) = p_1 a^{(m)}_{2r+1}(p_1, p_2) + p_1 a^{(m)}_{2r+1}(p_1, p_2), r = 1, 2, \ldots \left[\frac{m}{2}\right].\]

From (2.17) and (2.15),

(2.19) \[a^{(m+1)}_{2r}(p_1, p_2) = p_1 p_2 \sum_{s=0}^{m-2r+1} \binom{r + s - 1}{r - 1} \binom{m - r - s - 1}{r - 2} p_1^{m-2r-s+1} p_2^{m-2r-s+1} + p_1 p_2 \sum_{s=0}^{m-2r} \binom{r + s - 1}{r - 1} \binom{m - r - s - 1}{r - 1} p_1^{m-2r-s+1} p_2^{m-2r-s+1} = (p_1 p_2)^r \sum_{s=0}^{m-2r} p_1^{m-2r-s+1} \binom{r + s - 1}{r - 1} \binom{m - r - s}{r - 1} + (p_1 p_2)^r \binom{m - r}{r - 1} p_1^{m-2r+1},\]

since

(2.20) \[\binom{n + 1}{r} = \binom{n}{r} + \binom{n}{r - 1}.\]

(2.21) \[a^{(m+1)}_{2r+1}(p_1, p_2) = (p_1 p_2)^r \sum_{s=0}^{m-2r} \binom{r + s - 1}{r - 1} \binom{m - r - s}{r - 1} p_1^{m-2r-s+1} p_2^{m-2r-s+1}\]

which agrees with statement (iii) of the theorem with \((m + 1)\) for \(m\). Hence the formula is universally valid. Similarly, the formula for \(a^{(m+1)}_{2r+1}\) can be proved.

A proof using combinatorial analysis proceeds as follows. We have to evaluate probabilities associated with terms of the form \((A_1 A_2)^r (A_1 A_2)^r A_1\). For the probability of \((A_1 A_2)^r\) we consider the products

(2.22) \[A_1^r A_2^r A_1^s A_2^s \cdots A_1^t A_2^t,\]

where \(\sum_{j=1}^{r} (r_j + s_j) = m\), with \(r_j, s_j > 0\) and \(j = 1, 2, \ldots, r\).

Since each \(A_1\) and \(A_2\) in (2.22) occurs with an index of at least unity, the probability associated with this term is \((p_1 p_2)^r\) multiplied by the probability associated with

(2.23) \[A_1^r A_2^r A_1^s A_2^s \cdots A_1^t A_2^t,\]

where \(\sum_{j=1}^{r} (t_j + u_j) = m - 2r, t_j, u_j \geq 0,\) for \(j = 1, 2, \ldots, r\) and \(m - 2r \geq 0\).

The problem now reduces to a classical occupancy case. We require the number of ways in which \(m - 2r\) objects can be placed in \(r\) cells of one kind and \(r\) cells of another kind. Now \(s\) indistinguishable things can be placed in \(r\) cells in \(\binom{r + s - 1}{r - 1}\) ways (see, for example, Feller [3]). The two kinds of cells refer to \(A_1\) and \(A_2\), which in turn carry with them probabilities \(p_1\) and \(p_2\), respectively.
Since the \( m - 2r \) objects can be partitioned into categories with \( s \) belonging to \( A_1 \) and \( m - 2r - s \) belonging to \( A_2 \), where \( s = 0, 1, \ldots, m - 2r \), we have

\[
(2.24) \quad a^{(m)}_{2r} = (p_1 p_2)^r \sum_{s=0}^{m-2r} \binom{r+s-1}{r-1} \left( m - r - s - 1 \right) p_1 p_{2r-s-}, \\
\]  

\[ r = 1, 2, \ldots, \left\lfloor \frac{m}{2} \right\rfloor. \]

We treat \( (A_1 A_2)^r A_1 \) in a similar way considering the arrangements of \( m - 2r - 1 \) objects into \( r + 1 \) cells of one kind and \( r \) cells of another kind and verify statement (iv) of theorem 2.1.

In the special case when \( p_1 = p_2 = 1/2 \) the expressions for \( a^{(m)}_{2r} \) and \( a^{(m)}_{2r+1} \) may be simplified by using identities arising from the coefficient of \( t^{m-2r} \) in \( (1 - t)^r \) \((1 - t)^r(1 - t)^{r-1} \). We find

\[
(2.25) \quad a^{(m)}_{2r} = \left( \frac{m - 1}{m - 2r} \right)^{2m}, \quad a^{(m)}_{2r+1} = \left( \frac{m - 1}{m - 2r - 1} \right)^{2m},
\]

so that the probabilities associated with various vectors are binomial probabilities. The sample space itself is defined by

\[
(2.26) \quad (A_1 A_2)^r C_0, \quad (A_2 A_1)^r C_0, \quad r = 1, 2, \ldots, \left\lfloor \frac{m}{2} \right\rfloor,
\]

\[
(2.26) \quad (A_1 A_2)^r A_1 C_0, \quad (A_2 A_1)^r A_2 C_0, \quad r = 0, 1, \ldots, \left\lfloor \frac{m - 1}{2} \right\rfloor,
\]

where

\[
(2.27) \quad (A_1 A_2)^r = \begin{bmatrix} \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \end{bmatrix} - \frac{1}{3^r} \begin{bmatrix} \frac{1}{4} & -\frac{1}{4} & -\frac{1}{4} & -\frac{1}{4} \\ \frac{1}{4} & -\frac{1}{4} & -\frac{1}{4} & -\frac{1}{4} \\ \frac{1}{4} & -\frac{1}{4} & -\frac{1}{4} & -\frac{1}{4} \\ \frac{1}{4} & -\frac{1}{4} & -\frac{1}{4} & -\frac{1}{4} \end{bmatrix},
\]

\[
(2.27) \quad (A_1 A_2)^r A_1 = \begin{bmatrix} \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \end{bmatrix} + \frac{1}{3^r} \begin{bmatrix} \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \end{bmatrix},
\]

\[
(2.27) \quad (A_2 A_1)^r = \begin{bmatrix} \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \end{bmatrix} - \frac{1}{3^r} \begin{bmatrix} \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \end{bmatrix},
\]

\[
(2.27) \quad (A_2 A_1)^r A_2 = \begin{bmatrix} \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \end{bmatrix} + \frac{1}{3^r} \begin{bmatrix} \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \\ \frac{1}{4} & \frac{1}{4} & \frac{1}{4} & \frac{1}{4} \end{bmatrix}.
\]

Evidently the sample space in the limit, as \( m \to \infty \), reduces to \((1/2, 1/4, 1/4)\) irrespective of the initial amounts in the compartments.

2.3. Functional equation satisfied by the moment generating function. Let \( \tau' = (t_0, t_1, t_2, \ldots, t_{j-1}) \), and \( \phi_m (\tau') \) denote the moment generating function of
$C_m$ where $C_m$ is the column vector $(C_{s,m}, C_{1,m}, \cdots, C_{j-1,m})$ and $E$ denotes the expectation operator. Then by definition

$$\phi_m(\tau') = E \exp(\tau'C_m)$$

$$= E \exp\left\{ \left( \tau' \sum_{i=1}^{j-1} E_i A_i \right) C_{m-1} \right\}$$

$$= E \exp\left\{ \sum_{i=1}^{j-1} (E_i \tau'A_i) C_{m-1} \right\}.$$ 

Invoking the principle of independence, we therefore have

$$\phi_m(\tau') = \sum_{i=1}^{j-1} p_i E \exp(\tau'A_i C_{m-1})$$

where $\phi_0(\tau') = \exp(\tau'C_0)$ and $C_0$ is the vector referring to the initial amounts in the $j$ compartments. From the recursive relation (2.29) between the moment generating functions at the $m$th stage and $(m-1)$th stage, we can obtain expressions for the mean amount $\mu_m$ and covariances.

2.4. Mean amounts in the compartments.

2.4.1. General case. For the mean amounts in the system at the $m$th stage

$$\mu_m = E(C_m) = \sum_{i=1}^{j-1} p_i A_i \mu_{m-1}$$

$$= M^m C_0, \quad m = 1, 2, \ldots,$$

$$M = \begin{bmatrix}
\frac{a(j - 1)}{j} & \frac{a(j - 1)}{j} p_1 & \frac{a(j - 1)}{j} p_2 & \cdots & \frac{a(j - 1)}{j} p_{j-1} \\
\frac{a p_1}{j} & \frac{a p_1}{j} + 1 - p_1 & 0 & \cdots & 0 \\
\frac{a p_2}{j} & 0 & \frac{a p_2}{j} + 1 - p_2 & \cdots & 0 \\
\cdots & \cdots & \cdots & \cdots & \cdots \\
\frac{a p_{j-1}}{j} & 0 & 0 & \cdots & \frac{a p_{j-1}}{j} + 1 - p_{j-1}
\end{bmatrix}$$

and $\mu_0 = C_0$.

2.4.2. Eigenvalues of the first moment matrix. Since for the vector of mean values $\mu_m = M^m C_0$, for $m = 0, 1, 2, \cdots$, it is clear that a consideration of the eigenvalues of $M$ may be useful. Now the eigenvalues are roots of $f(\lambda) = 0$, where
is the expression arising from the expansion of the determinant $|M - \lambda I|$ by elements in its first row and first column. Now it may be seen that there is one eigenvalue located in each of the following intervals,

$$\lambda_{\text{max}} \sim 1 - \frac{je}{2(j - 1)} - \frac{\varepsilon^2 j}{2(j - 1)} - \frac{j^3}{8(j - 1)^4} \left( \sum_{i=1}^{j-1} 1 \right).$$

The interesting point here is that the first order term in $\lambda_{\text{max}}$ is independent of the $\mu_i$. 

2.4.3. Equiprobable case. In this case $p_1 = p_2 = \cdots = p_{j-1} = 1/(j - 1)$ with $j > 2$, so that from (2.30)

$$\mu_{s,m} = a \frac{j - 1}{j} \mu_{s,m-1} + a \sum_{i=1}^{j-1} \mu_{i,m-1},$$

$$\mu_{i,m} = a \frac{j - 1}{j(j - 1)} \mu_{s,m-1} + \theta \mu_{i,m-1}, \quad i = 1, 2, \cdots, j - 1,$$

where $m = 1, 2, \cdots$, and $\theta = a/j(j - 1) + (j - 2)/(j - 1)$. Clearly,

$$\mu_{i,m} - \mu_{k,m} = \theta(\mu_{i,m-1} - \mu_{k,m-1})$$

$$= \theta^m(C_{i,0} - C_{k,0}), \quad i, k = 1, 2, \cdots, (j - 1)$$

Hence if the $j - 1$ peripheral compartments contain the same amount initially, then their means are identical at any stage. This property is intuitively obvious. Hence, equation (2.35) for the means in the $j$ compartments reduces to the matrix equation

$$\begin{bmatrix} \mu_{s,m} \\ \mu_{i,m} \end{bmatrix} = \begin{bmatrix} a \frac{j - 1}{j} & a \frac{j - 1}{j} \\ a \frac{j - 1}{j(j - 1)} & \theta \end{bmatrix} \begin{bmatrix} \mu_{s,m-1} \\ \mu_{i,m-1} \end{bmatrix}$$

$$m = 1, 2, \cdots, i = 1, 2, \cdots, j - 1.$$
Thus,

\[
\begin{bmatrix}
\mu_{S,m} \\
\nu_{i,m}
\end{bmatrix} = \begin{bmatrix}
a(j-1)/j & a(j-1)/j \\
a/j & \theta
\end{bmatrix} \begin{bmatrix}
C_{S,0} \\
C_{i,0}
\end{bmatrix} \quad m = 1, 2, \ldots.
\]

If we now take \(C_{S,0} = u, C_{i,0} = (1 - u)/(j - 1),\) where \(i = 1, 2, \ldots, j - 1\) and \(0 \leq u \leq 1,\) and let \(\mu_{B,m} = \sum_{i=1}^{j-1} \mu_{i,m},\) then it is straightforward to show that

\[
\mu_{S,m} = \frac{a}{j} [1 + (j - 2)u] \theta_1 + u \theta_2,
\]

\[
\mu_{B,m} = \left[\frac{a}{j} u + \theta(1 - u)\right] \theta_1 + (1 - u) \theta_2,
\]

\[
\mu_{i,m} = \mu_{S,m} + \mu_{B,m}
\]

\[
= \left\{\frac{a}{j} [1 + (j - 1)u] + \theta(1 - u)\right\} \theta_1 + \theta_2,
\]

where

\[
\theta_1 = (\lambda_1 u - \lambda_2 u) / (\lambda_1 - \lambda_2),
\]

\[
\theta_2 = (\lambda_1 \lambda_2 - \lambda_2 \lambda_1) / (\lambda_1 - \lambda_2),
\]

and \(\lambda_1, \lambda_2\) are the eigenvalues of the reduced \(2 \times 2\) matrix, given by the roots of the equation

\[
\lambda^2 - \lambda \left[ \frac{a(j-1)}{j} + \theta \right] + \frac{a(j-2)}{j} = 0.
\]

2.4.4. Case when the system consists of two groups of equiprobable peripheral compartments. We now suppose that the \(j - 1\) peripheral compartments are such that \(n_1\) and \(n_2\) of them have probabilities \(r_1\) and \(r_2\), respectively, of opening. We let

\[
r_1 = \frac{\theta}{n_1}, \quad r_2 = \frac{1 - \theta}{n_2}, \quad 0 < \theta < 1, 0 \leq n_1 \leq j - 1,
\]

where \(n_1 + n_2 = j - 1.\) If in addition the expected amounts at the \(m\)th stage in the stream in the first group of \(n_1\) peripheral compartments and the second group of \(n_2\) peripheral compartments are denoted by \(\mu_{S,m}, n_1 \mu_{1,m}, n_2 \mu_{2,m}\), respectively, then from

\[
\begin{bmatrix}
\mu_{S,m} \\
n_1 \mu_{1,m} \\
n_2 \mu_{2,m}
\end{bmatrix} = \begin{bmatrix}
a(j-1)/j & a(j-1)/j & a(j-1)/j \\
a/j & a/j & a/j \\
a(1-\theta)/j & 0 & a/j
\end{bmatrix} \begin{bmatrix}
1 \\
r_1 + 1 - r_1 \\
r_2 + 1 - r_2
\end{bmatrix} \begin{bmatrix}
u \\
0 \\
0
\end{bmatrix}
\]

\[
= \begin{bmatrix}
u \\
0 \\
0
\end{bmatrix}
\]

\[
= \begin{bmatrix}
u \\
0 \\
0
\end{bmatrix}
\]
where initially $m = 0$, the amount in the stream is $u$, $0 \leq u \leq 1$, and the amount in each of the peripheral compartments is $(1 - u)/(j - 1)$.

2.4.5. Modified concentrations. At any time $m\Delta t$, if the system is in state $e_i$, let us suppose that instantly the amount in the stream becomes

$$C_{s,m} = \frac{a\beta(j - 1)}{\beta(j - 1) + 1} (C_{s,m-1} + C_{i,m-1}),$$

and the amount in the $i$th peripheral compartment becomes

$$C_{i,m} = \frac{a}{\beta(j - 1) + 1} (C_{s,m-1} + C_{i,m-1}),$$

where $\beta > 0$ and the amounts in the rest of the compartments remain the same as that at time $(m - 1)\Delta t$. This modified apportionment can be viewed as equivalent to a system consisting of a stream of volume $\beta V$ and the peripheral compartments of volume $V/(j - 1)$ each. This leads to the new system of recursive relations between the vectors $\mu_m$ and $\mu_{m-1}$,

$$\mu_{s,m} = K_1\mu_{s,m-1} + K_2 \sum_{i=1}^{j-1} p_i \mu_{i,m-1},$$

$$\mu_{i,m} = K_3 p_i \mu_{s,m-1} + [1 + (K_2 - 1)p_i] \mu_{i,m-1},$$

$$i = 1, 2, \ldots, j - 1, m = 1, 2, \ldots,$$

where $K_1 = a\beta(j - 1)/[1 + \beta(j - 1)]$ and $K_2 = a/[1 + \beta(j - 1)]$ and the initial amounts $\mu_{s,0}$ and $\mu_{i,0}$ are arbitrary.

2.5. Covariances.

2.5.1. General case. For the covariance (uncorrected) matrix $Q_m$ of the amounts in the system at the $m$th stage, we have

$$Q_m = E[C_mC'_m]$$

$$= E[TC_{m-1}'C_{m-1}T']$$

$$= E\left[\left(\sum_{i=1}^{j-1} E_t A_i \right)C_{m-1}'C_{m-1}' \left(\sum_{i=1}^{j-1} E_t A'_i \right)\right]$$

$$= \sum_{i=1}^{j-1} p_i A_i' Q_{m-1} A_i'$$

$$m = 1, 2, \ldots,$$

where $Q_0 = C_0 C'_0$. More explicitly, if we define the uncorrected covariances as

$$\mu_{ss,m} = E(C_{s,m}^2),$$

$$\mu_{si,m} = E(C_{s,m}C_{i,m}),$$

$$\mu_{ii,m} = E(C_{i,m}^2),$$

$$\mu_{ik,m} = E(C_{i,m}C_{k,m}),$$

$$i, k = 1, 2, \ldots, j - 1,$$
then

\[
\begin{align*}
\mu_{SS,m} &= a^2 \left( \frac{j - 1}{j} \right)^2 \left[ \mu_{SS,m} - 1 + 2 \sum_{i=1}^{j-1} p_i \mu_{Si,m} + \sum_{i=1}^{j-1} p_i \mu_{ii,m-1} \right], \\
\mu_{Si,m} &= \frac{a(j - 1)}{j} \left\{ a \frac{p_i \mu_{SS,m} - 1 + \left[ 1 + \left( \frac{2a}{j} - 1 \right) p_i \right] \mu_{Si,m} - 1}{j - 1} \right\} + \left( \frac{a}{j} - 1 \right) p_i \mu_{ii,m-1} + \sum_{k=1}^{j-1} p_k \mu_{ik,m-1}, \\
\mu_{ii,m} &= \left( \frac{a}{j} \right)^2 p_i \left[ \mu_{SS,m} - 1 + 2 \mu_{Si,m} + \mu_{ii,m} \right] + (1 - p_i) \mu_{ii,m}, \\
\mu_{ik,m} &= \frac{a}{j} \left( 2 p_i \mu_{Si,m} + p_k \mu_{Si,m} - 1 \right) + \left[ 1 + \left( \frac{a}{j} - 1 \right) (p_i + p_k) \right] \mu_{ik,m-1}, \quad i \neq k.
\end{align*}
\]

(2.49)

2.5.2. **Equi probable case.** In the equi probable case we now show that instead of \(j(j + 1)/2\) covariances, in general, there are only four distinct values, namely,

\[
\begin{align*}
&\text{(i) } \mu_{SS,m}, \\
&\text{(ii) } \mu_{Si,m} = \mu_{Sk,m}, \\
&\text{(iii) } \mu_{ii,m} = \mu_{kk,m}, \\
&\text{(iv) } \mu_{ik,m} = \mu_{rs,m}, \\&i \neq k, r \neq s,
\end{align*}
\]

(2.50)

for \(i, k, r, s = 1, 2, \ldots, j - 1\).

This is intuitively feasible, for when the communicating valves behave equivalently, probabilistically, it seems clear that at stage \(m\) the system consists of a random variable \(C_{S,m}\) for the stream and amounts \(X_1, X_2, \ldots, X_{j-1}\) for the peripheral compartments; the latter \(j - 1\) variates being identically distributed.

To prove that there are only four distinct covariances we write (2.49) as

\[
\begin{align*}
\mu_{Si,m} &= k_1 \mu_{Si,m-1} + k_2 \mu_{ii,m-1} + K_{i,m-1} + k_3, \\
\mu_{ii,m} &= m_1 \mu_{Si,m-1} + m_2 \mu_{ii,m-1} + \ell_3, \\
K_{i,m} &= m_3 \mu_{Si,m-1} + m_4 K_{i,m-1} + m_5, \\
&= m = 1, 2, \ldots, i = 1, 2, \ldots, j - 1
\end{align*}
\]

(2.51)

where \(k_1, k_2, k_3, \ell_1, \ell_2, \ell_3, m_1, m_2, m_3\) are constants independent of \(i\) and

\[
K_{i,m} = \sum_{k=1}^{j-1} \mu_{ik,m}.
\]

(2.52)

Equation (2.51) may be written

\[
\begin{bmatrix}
\mu_{Si,m} \\
K_{i,m} \\
\mu_{ii,m}
\end{bmatrix}
= \begin{bmatrix}
k_1 & k_2 & 1 \\
\ell_1 & \ell_2 & 0 \\
m_1 & 0 & 3
\end{bmatrix}
\begin{bmatrix}
\mu_{Si,m-1} \\
\mu_{ii,m-1} \\
K_{i,m-1}
\end{bmatrix}
+ \begin{bmatrix}
k_3 \\
\ell_3 \\
m_3
\end{bmatrix},
\]

(2.53)
or \( \Lambda_{i,m} = KA_{i,m-1} + L \), say. Hence,

\[
(2.54) \quad \Lambda_{i,m} = (I + K + K^2 + \cdots + K^{m-1})L + K^m \Lambda_{i,0},
\]

and \( \Lambda_{i,m} \) is independent of \( i \) if \( \Lambda_{i,0} \) is independent of \( i \). This can also be seen by using induction on equations (2.49).

We have thus indicated that the \( j \) compartment system with equiprobable communicating valves has only four distinct terms in its covariance structure, provided the initial amounts in the peripheral compartments are independent of the peripheral compartment description. From (2.49) it is now easily shown that

\[
(2.55)
\]

\[
\begin{bmatrix}
\mu_{i,i,m} & \mu_{i,j,m} & \mu_{i,m} \\
\mu_{j,i,m} & \mu_{j,j,m} & \mu_{j,m} \\
\mu_{m,i,m} & \mu_{m,j,m} & \mu_{m,m} \\
\end{bmatrix}
= 
\begin{bmatrix}
\frac{(j-1)^2}{j^2} & \frac{2(j-1)a^2}{j^2} & \frac{(j-1)^2a^2}{j^2} & 0 \\
\frac{a^2}{j^2} & \frac{a}{j} \left( \frac{2a}{j} + j - 2 \right) & \frac{a^2}{j^2} & \frac{a(j-2)}{j} \\
\frac{a^2}{j^2(j-1)} & \frac{2a^2}{j^2(j-1)} & \frac{a^2}{j^2} + j - 2 & 0 \\
0 & \frac{2a}{j(j-1)} & 0 & 1 + \frac{2}{j-1} \left( \frac{a}{j} - 1 \right) \\
\end{bmatrix}
\]

\[
\begin{bmatrix}
u^2 \\
\frac{u(1-u)}{j-1} \\
\frac{(1-u)^2}{j(j-1)^2} \\
\frac{(1-u)^2}{j(j-1)^2} \\
\end{bmatrix}
\]

\[m = 1, 2, \ldots, j = 3, 4, \ldots,\]

where the initial amounts are \( u \) in the stream and \( (1-u)/(j-1) \) in each peripheral compartment.

3. Further problems

3.1. General remarks. There are several possible directions for further research. The most interesting seem to be related to

(i) alternative models for a system,

(ii) models which involve a continuous time variable,

(iii) sample spaces and their definition and limits.

We discuss each of these briefly.

3.2. Other models. Different models from that considered can be constructed by changing the connectivity of the system, or the complex of communication, or the probability structure associated with the communicating valves.

A system with a different communicating complex would be the “catenary” system referred to by Sheppard and Householder [7]. In this, each peripheral compartment is connected to two neighboring compartments, with two exceptions; the first peripheral compartment is connected to the stream and its neighboring peripheral compartment, whereas the outermost peripheral compartment has only one connection which is to its neighbor. It is fairly clear that a system of this kind with a large number of compartments could retain material for long intervals of time—this could happen if initially all the material was located in the extreme peripheral compartment which communicated with its neighbor but rarely.
Other systems could consist of a combination of mammillary and catenary systems; here the possibilities are extensive.

With regard to a different probability structure than the one already discussed we mention the case where each valve operates independently of all others. To illustrate, consider a three compartment system such as figure 5, but where the communicating valves operate independently; thus, the first valve opens in a time interval $\Delta t$ with probability $p_1$ and remains closed with probability $1 - p_1$, whereas the second valve opens and closes with probabilities $p_2$ and $1 - p_2$, respectively. As before we associate with valves 1 and 2 random variables $X$ and $Y$, where for example, $X = 1$ if valve 1 is open and $X = 0$ if valve 1 is closed. The communicating valves now have four states which can be associated with the random variables $XY, X(1 - Y), (1 - X)Y, (1 - X)(1 - Y)$. Now let us assume the same concentration principle as was illustrated in section 2.1. Then the amounts in the three compartments at the time $m\Delta t$ are given by

$$
\begin{align*}
\begin{bmatrix}
    c_{S,m} \\
    c_{1,m} \\
    c_{2,m}
\end{bmatrix} &= \begin{bmatrix}
    a & a & a \\
    \frac{2}{2} & \frac{2}{2} & \frac{2}{2} \\
    a & a & a \\
    \frac{4}{4} & \frac{4}{4} & \frac{4}{4}
\end{bmatrix} X_m Y_m + X_m (1 - Y_m) \begin{bmatrix}
    2a & 2a & 0 \\
    \frac{2a}{3} & \frac{2a}{3} & 0 \\
    a & a & 0 \\
    \frac{3}{3} & \frac{3}{3} & 1
\end{bmatrix} \\
&+ (1 - X_m) Y_m \begin{bmatrix}
    0 & 0 & 0 \\
    0 & 0 & 0 \\
    \frac{a}{3} & 0 & \frac{a}{3}
\end{bmatrix} + (1 - X_m)(1 - Y_m) \begin{bmatrix}
    0 & 0 & 0 \\
    0 & 0 & 0 \\
    0 & 0 & 1
\end{bmatrix}
\end{align*}
$$

where $X_m, a$, and so forth, refer to the random variable occurring in the $m$th time interval. We can write (3.1) as
(3.2) \[ C_m = [X_n Y_m A_{11} + X_m(1 - Y_m)A_{12} + (1 - X_m)Y_m A_{21} + (1 - X_m)(1 - Y_m)A_{22}]C_{m-1}, \]
so that \( C_m \) is the ordered product
\[ C_m = \prod_{r=1}^{m} [X_r Y_r A_{11} + X_r(1 - Y_r)A_{12} + (1 - X_r)Y_r A_{21} + (1 - X_r)(1 - Y_r)A_{22}]C_s. \]
Mean amounts in the compartments and covariances can be worked out following the methods outlined in section 2. The sample space, however, is difficult to set out in closed form.

This type of model can be generalized so that there are \( j - 1 \) valves associated with the \( j - 1 \) independent random variates \( X_1, X_2, \cdots, X_{j-1} \), where, for example, \( X_i = 1 \) with probability \( p_i \) when valve \( i \) is open and \( X_i = 0 \) with probability \( 1 - p_i \) when valve \( i \) is closed.

Evidently with this type of model, since more than one valve can open at the same time, the material in the system would be expected to decay faster than would be the case with valves operating one at a time. Moreover, an increase in the number of peripheral compartments would scarcely alter the state of affairs.

3.3. Models operating in continuous time. We now consider a system acting over a time period \( m\Delta t = t \), where \( \Delta t \) is now taken to be small. It is relatively difficult now to produce a probabilistic complex which can be sustained for infinitesimal values of \( \Delta t \). Thus, a system in which one and only one valve opens during \( \Delta t \) entails conceptual difficulties. However, a system in which valves operate independently seems feasible. A natural structure is to assume that a valve opens in time \( \Delta t \) with probability \( p(t)\Delta t \), and closes with probability \( 1 - p(t)\Delta t \), where \( p(t) \) is a constant or a time dependent parameter. This structure is equivalent to assuming that the probability structure of the valves follows a Poisson process in time. We consider two systems from this point of view.

3.3.1. Two compartment system with "Poisson" communicating valves. Let the concentration exchange principle be that illustrated in section 2.1. Referring to figure 1 we assume that \( X_n \) is the random variable associated with the valve in the \( n \)th interval of time of duration \( \Delta t \). Let
\[ \Pr \{X_n = 1\} = p(t)\Delta t, \]
\[ \Pr \{X_n = 0\} = 1 - p(t)\Delta t, \]

(3.4)
to the first order of small quantities \( \Delta t \). Also, let \( C_S(t) \) and \( C_B(t) \) be the random amounts in the stream and peripheral compartments at time \( t \). Then,
\[ C_S(t + \Delta t) = \frac{1}{2} a X_n\Delta t[C_S(t) + C_B(t)] + a(1 - X_n\Delta t)C_S(t) \]
\[ C_B(t + \Delta t) = \frac{1}{2} a X_n\Delta t[C_S(t) + C_B(t)] + (1 - X_n\Delta t)C_B(t). \]

(3.5)
Now the "decay" factor $a = \exp (-k\Delta t)$; that is, in a small interval of time the amount of material in the stream (or in communication with the stream) suffers a reduction proportional to $\Delta t$. Now assuming independence of the random variables on the right side of (3.5), we take expectations to find

$$
\mu_s(t + \Delta t) = \frac{1}{2} e^{-k\Delta t} p(t) \Delta t [\mu_s(t) + \mu_B(t)] + e^{-k\Delta t} [1 - p(t)\Delta t] \mu_s(t),
$$

(3.6)

$$
\mu_B(t + \Delta t) = \frac{1}{2} e^{-k\Delta t} p(t) \Delta t [\mu_s(t) + \mu_B(t)] + [1 - p(t)\Delta t] \mu_B(t),
$$

so that when $\Delta t$ tends to zero we have

$$
\frac{d\mu_s(t)}{dt} = \frac{1}{2} p(t) \mu_B(t) - [k + \frac{1}{2} p(t)] \mu_s(t),
$$

(3.7)

$$
\frac{d\mu_B(t)}{dt} = \frac{1}{2} p(t) \mu_s(t) - \frac{1}{2} p(t) \mu_B(t).
$$

By elimination we have for the mean amounts in each compartment the differential equations

(3.8)

$$
\frac{d^2\mu_s(t)}{dt^2} + \left\{ p(t) + k + p(t) \frac{d}{dt} \frac{1}{p(t)} \right\} \frac{d\mu_B(t)}{dt} + \frac{1}{2} kp(t) \mu_B(t) = 0,
$$

$$
\frac{d^2\mu_B(t)}{dt^2} + \left\{ p(t) + k + p(t) \frac{d}{dt} \frac{1}{p(t)} \right\} \frac{d\mu_s(t)}{dt} + \frac{1}{2} kp(t) \left\{ 1 + \frac{1}{2} \frac{d}{dt} \frac{1}{p(t)} \right\} \mu_s(t) = 0.
$$

If at $t = 0$ the amounts in the stream and peripheral compartments are unity and zero, respectively, then from (3.7) the initial conditions for (3.8) are

$$
\mu_s(0) = 1, \quad \mu_B(0) = 0,
$$

(3.9)

$$
\frac{d\mu_s}{dt} \mid_{t=0} = - (k + \frac{1}{2} p(0)),
$$

$$
\frac{d\mu_B}{dt} \mid_{t=0} = \frac{1}{2} p(0).
$$

If $p(t)$ is independent of $t$, then $\mu_s(t)$ and $\mu_B(t)$ satisfy the second order linear differential equation with constant coefficients

(3.10)

$$
\frac{d^2y}{dt^2} + (k + p) \frac{dy}{dt} + \frac{1}{2} kp y = 0,
$$

so that using (3.9) the solution is

$$
\mu_s(t) = \left\{ \cosh \left( \frac{1}{2} Lt \right) - \frac{k}{L} \sinh \left( \frac{1}{2} Lt \right) \right\} \exp \left[ - \frac{1}{2} (k + p)t \right],
$$

(3.11)

$$
\mu_B(t) = \frac{p}{L} \sinh \left( \frac{1}{2} Lt \right) \exp \left[ - \frac{1}{2} (k + p)t \right].
$$

3.3.2. General case. Similarly a $j$ compartment model could be considered in which each communicating valve operates independently, the $i$th valve opening
in the $n$th time interval with probability $p_i(t)\Delta t$ and closing with probability $1 - p_i(t)\Delta t$. Solutions would consist of exponential sums provided $p_i(t)$ was independent of $t$.

However it must be remarked that whereas there is no difficulty in setting up expressions for higher moments, this is not the case in attempting expressions for the sample space.

3.4. Sample space problems. A detailed description of the sample space for a three compartment system when $a = 1$ is given in section 2.2.2, where it is shown that products of the matrices $A_1$ and $A_2$ can take one and only one of four forms (see (3.5)) whenever such a product is not degenerate (for example, since the $A$ are idempotent, a power of $A_1$ is called degenerate).

With a more general compartment model which has the property of connectivity, we can introduce a set of mutually exclusive events associated with the communicating valves. Each of these exclusive events $E_i$ is related to a phase of the system and to a matrix $A_n$, say; these events and matrices are set out for one system in section 2.1 and (2.2). Now if the decay factor $a$ is taken to be unity, then if $E_*$ occurs twice in succession the state of the system does not change. If $C_n$ is the state of the system at any time (or stage), we may write

$$A_1^2C_n = A_1C_n,$$

which gives an indication that the $A_1$ may be expected to be idempotent. In addition, it is not difficult to see that these matrices are asymptotically ($a \to 1$) stochastic. We have shown in section 3.2 that in general for the three compartment system that products of the matrices $A_1$ and $A_2$ in any order tend to one limiting value whenever the product is not degenerate, the product consisting of an infinite number of terms. Does this property in modified form hold with more general connected systems whenever the decay factor $a$ is taken to be unity?

The authors wish to put on record their indebtedness to Mrs. Barbara F. Bombay and Mr. John A. Carpenter of the Mathematics Division of Oak Ridge National Laboratory for assistance in the computational aspects of the problem.

◊ ◇ ◇ ◇ ◇

APPENDIX

Three Compartment Model

A.1. Description

The general ideas discussed in section 2 will now be considered in detail by reference to a system consisting of the stream and two peripheral compartments, $j = 3$ (see figure 5). Let the total volume of the peripheral compartments be equal to that of the stream, and let each of the two peripheral compartments be of the same volume. At any instant of time $m\Delta t$, $m = 1, 2, \cdots$, let $(E_1, E_2)$ refer to the state of the values between the stream and the two compartments; thus
if compartment 1 is in communication with the stream, then \((E_1, E_2) = (1, 0)\) with probability \(p_1 > 0\), and if compartment 2 is in communication with the stream, then \((E_1, E_2) = (0, 1)\) with probability \(1 - p_1 = p_2\). Let \(C_{s,m}, C_{1,m}, C_{2,m}\) denote the random amounts at the \(m\)th stage in the stream and the compartments 1 and 2, respectively. The state of the system initially \((m = 0)\) is assumed to be \(C'_0 = (C_{s,0}, C_{1,0}, C_{2,0}) = (u, v, 1 - u - v)\), where \(u, v \geq 0\) and \(u + v \leq 1\).

At any instant of time \(m\Delta t\), if the first compartment is in communication with the stream, that is, \((E_1, E_2) = (1, 0)\), then instantly the random amount in the stream becomes \(C_{s,m} = (2a/3)(C_{s,m-1} + C_{1,m-1})\) and the random amount in the first compartment becomes \(C_{1,m} = (a/3)(C_{s,m-1} + C_{1,m-1})\), and the random amount in the second compartment will be \(C_{2,m} = C_{2,m-1}\). Similar remarks apply if the second peripheral compartment is in communication with the stream.

We are thus led to the recursive relation

\[
C_m = \begin{bmatrix}
C_{s,m} \\
C_{1,m} \\
C_{2,m}
\end{bmatrix} = \begin{bmatrix}
\frac{2a}{3} & \frac{2a}{3} E_1 & \frac{2a}{3} E_2 \\
\frac{a}{3} E_1 & \frac{a}{3} E_1 + E_2 & 0 \\
\frac{a}{3} E_2 & 0 & \frac{a}{3} E_1 + E_1
\end{bmatrix} \begin{bmatrix}
C_{s,m-1} \\
C_{1,m-1} \\
C_{2,m-1}
\end{bmatrix}
\]

say, where \(T = E_1 A_1 + E_2 A_2\) and

\[
A_1 = \begin{bmatrix}
\frac{2a}{3} & \frac{2a}{3} & 0 \\
\frac{a}{3} & \frac{a}{3} & 0 \\
0 & 0 & 1
\end{bmatrix}, \quad A_2 = \begin{bmatrix}
\frac{2a}{3} & 0 & \frac{2a}{3} \\
0 & 1 & 0 \\
\frac{a}{3} & 0 & \frac{a}{3}
\end{bmatrix}
\]

### A.2. Sample space

Suppose the state of the system at the \(i\)th stage is \((E_1^{(i)}, E_2^{(i)})\). Then,

\[
C_m = (E_1^{(m)} A_1 + E_2^{(m)} A_2)(E_1^{(m-1)} A_1 + E_2^{(m-1)} A_2) \cdots (E_1^{(1)} A_1 + E_2^{(1)} A_2) C_0
\]

describes the sample space of \(C_m\), where we assume that \((E_1^{(i)}, E_2^{(i)})\) is independent of \((E_1^{(i-1)}, E_2^{(i-1)}), i = 1, 2, \ldots\). Thus, in particular if \(m = 2\),

\[
C_2 = (E_1^{(2)} E_1^{(1)} A_1^2 + E_1^{(2)} E_2^{(1)} A_1 A_2 + E_2^{(2)} E_1^{(1)} A_2 A_1 + E_2^{(2)} E_2^{(1)} A_2^2) C_0
\]
This appears as a branching process in figure 6 where the probabilities are indicated in parentheses.

![Diagram of branching process](https://example.com/diagram.png)

**Figure 6**
Illustration of branching process.

Table II represents the total probability associated with each distinct point in the sample space, of three different random variables, at the same stage. Table III gives the grouped distributions of the amount in stream at further stages. The multimodal characteristic of these distributions is noteworthy.

**TABLE II**

**Probability Distributions of the Amounts in the Stream and Peripheral Compartments for a Three Compartment System**

\[ a = 0.9, p_1 = 0.3, p_2 = 0.7, m = 5, C_0 = (1, 0, 0) \]

<table>
<thead>
<tr>
<th>Stream Amount</th>
<th>Probability</th>
<th>Total in the Peripheral Compartments Amount</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.26244</td>
<td>0.2436</td>
<td>0.19683</td>
<td>0.1705</td>
</tr>
<tr>
<td>0.31104</td>
<td>0.0882</td>
<td>0.30618</td>
<td>0.0777</td>
</tr>
<tr>
<td>0.32076</td>
<td>0.2331</td>
<td>0.31438</td>
<td>0.0441</td>
</tr>
<tr>
<td>0.32184</td>
<td>0.0882</td>
<td>0.32238</td>
<td>0.0777</td>
</tr>
<tr>
<td>0.32616</td>
<td>0.0441</td>
<td>0.32328</td>
<td>0.0441</td>
</tr>
<tr>
<td>0.33096</td>
<td>0.0882</td>
<td>0.33048</td>
<td>0.0441</td>
</tr>
<tr>
<td>0.35496</td>
<td>0.0441</td>
<td>0.33372</td>
<td>0.0441</td>
</tr>
<tr>
<td>0.39366</td>
<td>0.1705</td>
<td>0.33588</td>
<td>0.0441</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>1.0000</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Probability</th>
<th>Total Amount Amount</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.59049</td>
<td>0.1705</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.61236</td>
<td>0.0777</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.62604</td>
<td>0.0777</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.63066</td>
<td>0.0441</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.63144</td>
<td>0.0777</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.64476</td>
<td>0.0441</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.65124</td>
<td>0.0441</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.66066</td>
<td>0.0441</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.66114</td>
<td>0.0777</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.66204</td>
<td>0.0441</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.66366</td>
<td>0.0441</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.66456</td>
<td>0.0441</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>0.0441</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.66996</td>
<td>0.0441</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.67824</td>
<td>0.0441</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.69366</td>
<td>0.0777</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1.0000 1.0000
TABLE III

PROBABILITY DISTRIBUTION OF THE AMOUNT IN THE STREAM
FOR A THREE COMPARTMENT SYSTEM

\( a = 0.9, p_1 = 0.3, p_2 = 0.7 \)

<table>
<thead>
<tr>
<th>Interval</th>
<th>Probability</th>
<th>Interval</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.72 ≤ x &lt; 1.82</td>
<td>0.060462</td>
<td>1.52 ≤ x &lt; 1.62</td>
<td>0.042351</td>
</tr>
<tr>
<td>1.82 ≤ x ≤ 1.92</td>
<td>0.000000</td>
<td>1.62 ≤ x ≤ 1.72</td>
<td>0.000000</td>
</tr>
<tr>
<td>1.92 ≤ x ≤ 2.02</td>
<td>0.000000</td>
<td>1.72 ≤ x ≤ 1.82</td>
<td>0.000000</td>
</tr>
<tr>
<td>2.02 ≤ x ≤ 2.12</td>
<td>0.183687</td>
<td>1.82 ≤ x ≤ 1.92</td>
<td>0.140851</td>
</tr>
<tr>
<td>2.12 ≤ x ≤ 2.22</td>
<td>0.163942</td>
<td>1.92 ≤ x ≤ 2.02</td>
<td>0.185102</td>
</tr>
<tr>
<td>2.22 ≤ x ≤ 2.32</td>
<td>0.207477</td>
<td>2.02 ≤ x ≤ 2.12</td>
<td>0.192618</td>
</tr>
<tr>
<td>2.32 ≤ x ≤ 2.42</td>
<td>0.230281</td>
<td>2.12 ≤ x ≤ 2.22</td>
<td>0.261237</td>
</tr>
<tr>
<td>2.42 ≤ x ≤ 2.52</td>
<td>0.076439</td>
<td>2.22 ≤ x ≤ 2.32</td>
<td>0.099787</td>
</tr>
<tr>
<td>2.52 ≤ x ≤ 2.62</td>
<td>0.063341</td>
<td>2.32 ≤ x ≤ 2.42</td>
<td>0.064861</td>
</tr>
<tr>
<td>2.62 ≤ x ≤ 2.72</td>
<td>0.000000</td>
<td>2.42 ≤ x ≤ 2.52</td>
<td>0.000334</td>
</tr>
<tr>
<td>2.72 ≤ x ≤ 2.82</td>
<td>0.006683</td>
<td>2.52 ≤ x ≤ 2.62</td>
<td>0.000000</td>
</tr>
<tr>
<td>2.82 ≤ x ≤ 2.92</td>
<td>0.000000</td>
<td>2.62 ≤ x ≤ 2.72</td>
<td>0.000459</td>
</tr>
<tr>
<td>2.92 ≤ x ≤ 3.02</td>
<td>0.007519</td>
<td>2.72 ≤ x ≤ 2.82</td>
<td>0.000000</td>
</tr>
<tr>
<td></td>
<td>1.000000</td>
<td></td>
<td>2.82 ≤ x ≤ 2.92</td>
</tr>
</tbody>
</table>

A.3. Mean amounts in the system

We have

\( \mu_m = E(C_m) \)

\[ = E\{[E_1^{(m)}A_1 + E_2^{(m)}A_2] \cdots [E_1^{(m)}A_1 + E_2^{(m)}A_2]\}C_0 \]

\[ = \left\{ \prod_{1 \leq i \leq m} E[E_i^{(0)}A_1 + E_2^{(0)}A_2]\right\}C_0. \]

Hence, the mean vectors are given by

\[ \mu_m = M^mC_0, \quad m = 0, 1, \cdots, \]

where

\[ M = \begin{bmatrix} \frac{2a}{3} & \frac{2a}{3} & p_2 \\ \frac{a}{3} & \frac{a}{3} & p_1 + p_2 \\ \frac{a}{3} & 0 & \frac{a}{3}p_2 + p_1 \end{bmatrix} \]

\[ = \begin{bmatrix} 1 \frac{1}{2} \left[ 1 + \left( 1 - \frac{32}{9}p_1p_2 \right)^{1/2} \right] \\ \frac{1}{2} \left[ 1 - \left( 1 - \frac{32}{9}p_1p_2 \right)^{1/2} \right] \]
A.4. Illustrations

(i) Let \( a = 1 - \epsilon \) with \( \epsilon > 0 \) small quantity, \( p_1 = p_2 = 1/2 \), and \( \alpha_0 = (1, 0, 0.) \). Then,
\[
\mu_{s,m} \sim \frac{1}{2} \left( 1 - \frac{3}{4} \epsilon \right)^m + \frac{1}{2} \left( \frac{1}{3} \right)^m, \quad \lambda_1 \sim 1 - \frac{3}{4} \epsilon,
\]
\[
\mu_{1,m} \sim \frac{1}{4} \left( 1 - \frac{3}{4} \epsilon \right)^m - \frac{1}{4} \left( \frac{1}{3} \right)^m, \quad \lambda_2 \sim \frac{2}{3},
\]
\[
\mu_{2,m} \sim \frac{1}{4} \left( 1 - \frac{3}{4} \epsilon \right)^m - \frac{1}{4} \left( \frac{1}{3} \right)^m, \quad \lambda_3 \sim \frac{1}{3}.
\]

(ii) If \( p_2 \) is small, \( \lambda_1 \sim 1 - p_2(1 - a/3) \), and \( \lambda_2 \sim a + p_2[1/3 - 5a/9] \), then
\[
\lambda_3 \sim p_2 \left( \frac{2}{3} + \frac{2a}{9} \right),
\]
\[
\mu_{s,m} \sim \frac{2}{3} \lambda_2^m + \frac{1}{3} \lambda_3^m,
\]
\[
\mu_{1,m} \sim \frac{1}{3} (\lambda_2^m - \lambda_3^m),
\]
and \( \mu_{2,m} \) is of the order as \( p_2 \).

(iii) Let \( a = 0.9 \), \( p_1 = 0.2 \), \( p_2 = 0.8 \), \( \lambda_1 = 0.93 \), \( \lambda_2 = 0.80 \), and \( \lambda_3 = 0.17 \). Then
\[
\mu_{s,m} = 0.35 \lambda_1^m + 0.26 \lambda_2^m + 0.39 \lambda_3^m
\]
\[
\mu_{1,m} = 0.29 \lambda_1^m - 0.26 \lambda_2^m - 0.03 \lambda_3^m
\]
\[
\mu_{2,m} = 0.17 \lambda_1^m + 0.17 \lambda_2^m - 0.34 \lambda_3^m
\]
\[
\lambda_{l,m} = \mu_{s,m} + \mu_{1,m} + \mu_{2,m}
\]
\[
= 0.82 \lambda_1^m + 0.17 \lambda_2^m + 0.01 \lambda_3^m.
\]

REMARKS. It will be seen from (i) that when \( a \) is nearly unity and the two peripheral compartments are equiprobable \((p_1 = p_2)\), the mean amounts retained in the compartments are dominated by the largest eigenvalue \( \lambda = 1 - 3\epsilon/4 \), and as \( m \) increases the amounts become proportional to 2:1:1 (the compartmental volume distribution). If the connection between the stream and one of the peripheral compartments has a small probability of opening \((p_2 \) small), then the amount expected in this compartment at any time is of the same order as \( p_2 \). Moreover, the expected amount in the stream decays about as fast as \( 2a^m/3 \), and the amount in the peripheral compartment (from which is frequently connecting to the stream) decays with \( a^m/3 \).

In summary, if the attenuation term \( a \) is near unity then the mean amounts are the compartments decay almost independent of \( p_1 \) and \( p_2 \) (assuming neither of these small), whereas if one peripheral compartment has a rare chance of communicating with the stream the ultimate decay rate is dominated by the value of \( a \).
A.5. Covariance evaluation

An alternative to the recursive system described in (2.45) is to proceed from first principles and evaluate expressions such as

\[(A.5.1) \quad EC_{3,m}^2 = E\left(\frac{2a}{3} EC_{S,m-1} + \frac{2}{3} E_1 C_1, m - 1 + \frac{2a}{3} E_2 C_{2,m-1}\right)^2.\]

Now \((E_1, E_2)\) really refers to the probabilities interpretation of the communicating values at the \(m\)th stage, and so is independent of \((C_S,m-1, C_1, m-1, C_2,m-1)\).

Hence,

\[(A.5.2) \quad EC_{3,m} = p_1 E\left(\frac{2a}{3} C_{S,m-1} + \frac{2a}{3} C_{1,m-1}\right) + p_2 E\left(\frac{2a}{3} C_{S,m-1} + \frac{2a}{3} C_{2,m-1}\right)^2.\]

Treating \(E(C_{S,m}C_{S,1})\), and so forth, in a similar way, we find

\[(A.5.3)\]

\[
\begin{pmatrix}
\mu_{11,m} \\
\mu_{12,m} \\
\mu_{21,m} \\
\mu_{22,m} \\
\mu_{31,m} \\
\mu_{32,m} \\
\mu_{33,m}
\end{pmatrix} =
\begin{pmatrix}
\frac{4a^2}{9} p_1 & \frac{4a^2}{9} p_2 & \frac{8a^2}{9} p_1 & \frac{8a^2}{9} p_2 & 0 \\
\frac{a^2}{9} p_1 & \frac{a^2}{9} p_1 + p_2 & 0 & \frac{2a^2}{9} p_1 & 0 & 0 \\
\frac{a^2}{9} p_2 & 0 & \frac{a^2}{9} p_2 + p_1 & 0 & \frac{2a^2}{9} p_2 & 0 \\
\frac{2a^2}{9} p_1 & \frac{2a^2}{9} p_1 + 2a^2 p_3 & 0 & \frac{4a^2}{9} p_1 + \frac{2a^3}{9} p_2 & 0 & \frac{2a^2}{9} p_2 \\
\frac{2a^2}{9} p_2 & 0 & \frac{2a^2}{9} p_2 + 2a^2 p_3 & 0 & \frac{4a^2}{9} p_2 + \frac{2a^3}{9} p_1 & \frac{2a^2}{9} p_2 \\
0 & 0 & 0 & \frac{a}{3} p_2 & \frac{a}{3} p_1 & \frac{a}{3}
\end{pmatrix} \mu_{33,m-1}
\]

Using \(V_m\) for the column vector of covariances and \(V\) for the \(6 \times 6\) transition matrix, we have \(V_m = V^m V_0\) where \(V_0\) depends on the initial conditions.

**TABLE IV**

**Means and Standard Deviations for a Three Compartment System**

\(a = 0.9, p_1 = 0.3, p_2 = 0.7\)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Stream</th>
<th>Peripheral Compartment 1</th>
<th>Peripheral Compartment 2</th>
<th>Total Amount in the System</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>S.D.</td>
<td>Mean</td>
<td>S.D.</td>
</tr>
<tr>
<td>1</td>
<td>0.600</td>
<td>0.060</td>
<td>0.090</td>
<td>0.137</td>
</tr>
<tr>
<td>2</td>
<td>0.464</td>
<td>0.089</td>
<td>0.125</td>
<td>0.129</td>
</tr>
<tr>
<td>3</td>
<td>0.399</td>
<td>0.072</td>
<td>0.141</td>
<td>0.111</td>
</tr>
<tr>
<td>4</td>
<td>0.356</td>
<td>0.055</td>
<td>0.147</td>
<td>0.094</td>
</tr>
<tr>
<td>5</td>
<td>0.321</td>
<td>0.043</td>
<td>0.148</td>
<td>0.079</td>
</tr>
<tr>
<td>6</td>
<td>0.292</td>
<td>0.033</td>
<td>0.146</td>
<td>0.067</td>
</tr>
<tr>
<td>7</td>
<td>0.267</td>
<td>0.027</td>
<td>0.142</td>
<td>0.057</td>
</tr>
<tr>
<td>8</td>
<td>0.245</td>
<td>0.023</td>
<td>0.136</td>
<td>0.049</td>
</tr>
<tr>
<td>9</td>
<td>0.225</td>
<td>0.020</td>
<td>0.129</td>
<td>0.043</td>
</tr>
<tr>
<td>10</td>
<td>0.208</td>
<td>0.019</td>
<td>0.123</td>
<td>0.038</td>
</tr>
</tbody>
</table>
In concluding this section we remark that the means and standard deviations for the first ten stages of a particular system are given in table IV.

A.6. Feasibility of the model

A.6.1. Finding a model in agreement with a given set of data. Given that a set of data has been fitted with a function consisting of a sum of exponential terms, can a model be found in approximate agreement?

Now a number of examples of data in the literature are of the form

(A.6.1) \[ f(t) = de^{-kt} + (1-d)e^{-kt}, \quad 0 < d < 1, 0 < k_1 < k_2. \]

The following are typical (see, for example, Bernard and Uppuluri [2]):

(a) \[ f(t) = 0.65 \exp(-0.7t/240) + 0.35 \exp(-0.7t/6), \]
(b) \[ f(t) = 0.43 \exp(-0.7t/321) + 0.57 \exp(-0.7t/5), \]
(c) \[ f(t) = 0.28 \exp(-0.7t/224) + 0.72 \exp(-0.7t/3.2), \]
(d) \[ f(t) = 0.24 \exp(-0.7t/250) + 0.76 \exp(-0.7t/3), \]
(e) \[ f(t) = 0.16 \exp(-0.0002t) + 0.18 \exp(-0.0046t) + 0.26 \exp(-0.102t) + 0.40 \exp(-0.748t). \]

Here \( f(t) \) refers to the total amount of radiation retained in the system (of dogs) at time \( t \). The corresponding data for the bloodstream and regions of the bone are not available at the time of writing.

In general, solutions for the amounts in a \( j \) compartment system lead to sums of \( j \) exponential terms. However, there are exceptions which arise when a number of peripheral compartments behave identically; this will be the case when a number of the communicating valves operate with equal probabilities. A word of caution is, however, in order here. Identical peripheral compartments arise under equiprobable openings—the random amounts in these compartments are identically distributed variables; a particular realization at any time will show, in general, different amounts in the equivalent peripheral compartments.

Another important point refers to the initial conditions \( C_0 \) of the system. For the data in (a) to (e) the initial conditions are not known. We can experiment with two cases: (i) assume that there is a unit amount in the bloodstream; (ii) assume that there is a unit amount in the system, apportioned in unknown amounts among the stream and the peripheral compartments.

A.6.2. Solutions under the assumption that \( C_{S,0} = 1 \) and \( C_{i,0} = 0 \) for \( i = 1, 2, \ldots, j - 1 \). For data consisting of two exponential terms we consider the case with \( (j - 1) \) equiprobable peripheral compartments, so that the system
behaves, at least with respect to means, as a two compartment system. We have for the total amounts from (2.25)

\[(A.6.2) \quad \mu_{i,m} = \frac{(a - \lambda_2)\lambda_i^n + (\lambda_1 - a)\lambda_2^n}{\lambda_1 - \lambda_2},\]

where \(\lambda_1 > \lambda_2\) are the roots of

\[(A.6.3) \quad \lambda^2 - \lambda \left[ \frac{a(j^2 - 2j + 2)}{j(j - 1)} + \frac{j - 2}{j - 1} \right] + \frac{a(j - 2)}{j} = 0.\]

The stage \(m\) is related to the time \(t\) by \(m(\Delta t) = t\), and moreover, the experimentalists use the notation \(a = \exp(-k\Delta t)\).

Now let us suppose that (A.6.1) and (A.6.2) are identical; then we wish to decide whether admissible parameters of the model can be determined. The three unknowns \(j, k\), and \(\Delta t\) may be found from the equations

\[(A.6.4) \quad k_1 = (1/\Delta t) \ln(1/\lambda_1), \quad k_2 = (1/\Delta t) \ln(1/\lambda_2), \quad d = (a - \lambda_2)/(\lambda_1 - \lambda_2).\]

From (A.6.4) \(\lambda_2^n = \lambda_1^k\), and if we define \(k_2/k_1 = r (> 1)\) then

\[(A.6.5) \quad \lambda_2 = \lambda_1^r.\]

But now from (A.6.3) and (A.6.5),

\[(A.6.6) \quad \lambda_1 + \lambda_1^r = \frac{a(j^2 - 2j + 2)}{j(j - 1)} + \frac{j - 2}{j - 1}, \quad \lambda_1^{r+1} = \frac{a(j - 2)}{j}.\]

But also from (A.6.3) and (A.6.4)

\[(A.6.7) \quad a = \lambda_1^r(1 - d) + \lambda_0d.\]

Hence, eliminating \(j\) and \(a\) from (A.6.6) and (A.6.7) we have

\[(A.6.8) \quad (1 - \lambda_0)(1 - \lambda_1)\lambda_1^{r-1} = d(1 - d)(1 - \lambda_1^{r-1})^2.\]

For given values of \(r\) and \(d\) the equation (A.6.8) determines values of \(\lambda_1\), in general, more than one. However, it can be shown that there is at most one value of \(\lambda_1\) such that \(0 < \lambda_1 < 1\). For if

\[(A.6.9) \quad \psi(\lambda) = (1 - \lambda)(1 - \lambda^r)\lambda^{r-1}(1 - \lambda^{r-1})^2, \quad r > 1,\]

when \(\psi(0) = 0\), using L'Hospital's rule, we have \(\psi(1) = r/(r - 1)^2\). That \(\psi(1)\) is indeed the maximum value of the function in \((0, 1)\) is evident from continuity considerations. Hence, (A.6.8) can only have a solution if \(r(r - 1)^2\) exceeds \(d(1 - d)\). Referring to examples (a) through (d), we have the comparisons in table V.

Hence no parametrization of the model is feasible for these examples. A plausible reason for this lies in the fact that in the examples given in section A.6.1 one of the exponential terms in each case is near to unity, and this term
TABLE V

Comparisons of \( r/(r - 1)^2 \) and \( d(1 - d) \) for Examples (a) through (d)

<table>
<thead>
<tr>
<th>Example</th>
<th>( r/(r - 1)^2 )</th>
<th>( d(1 - d) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a)</td>
<td>0.026</td>
<td>0.23</td>
</tr>
<tr>
<td>(b)</td>
<td>0.016</td>
<td>0.25</td>
</tr>
<tr>
<td>(c)</td>
<td>0.014</td>
<td>0.20</td>
</tr>
<tr>
<td>(d)</td>
<td>0.012</td>
<td>0.18</td>
</tr>
</tbody>
</table>

does not appear with a small coefficient. This suggests that there is some mechanism in the system which leads to the retention of material for excessively long periods of time. In the theoretical model, if initially all the material is in the central compartment (blood stream), then material cannot help but be lost more or less rapidly. However, it seems intuitively clear that if initially material was stored in small amounts in a large number of peripheral compartments then it would be retained for much longer periods.

A.6.3. Solution when \( C_{S0} = u, C_{Si} = (1 - u)/(j - 1), i = 1, 2, \ldots, j - 1 \).

We thus turn our attention to case (ii) when initially there is an amount \( u \) in the stream and amounts \( (1 - u)/(j - 1) \) in each of the equiprobable peripheral compartments. In this case we have the parameters \( a, j, \Delta t, u \) (relating to the model) to align with the parameters \( d, k_1, k_2 \) of the fitted exponentials to the data. Here we have one degree of freedom which can be disposed of in various ways. A simple device is to decide on a value of \( \Delta t \) (= 1 say) and then find \( a, j, u \) from the three determining equations. Thus, from section A.6.1, we have

\[
\frac{1}{\lambda_1 - \lambda_2} \left\{ \frac{a}{j} [1 + (j - 1)u] + \theta(1 - u) - \lambda_2 \right\} = d
\]

where

\[
\theta = \frac{a}{j(j - 1)} + \frac{j - 2}{j - 1},
\]

which now determines the value of \( u \). Since \( a = \exp(-k\Delta t) \) where \( \Delta t \) is known, we see that \( k = \frac{[\ln(1/a)]}{\Delta t} \). Examples of this are given in table VI.

TABLE VIa

Theoretical Model from (A.2.1) Fitted to Experimental Data

Example (a): \( f(t) = 0.65 \exp(-0.7t/240) + 0.35 \exp(-0.7t/6) \)

<table>
<thead>
<tr>
<th></th>
<th>( \Delta t = 1 )</th>
<th>( \Delta t = 2 )</th>
<th>( \Delta t = 4 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eigenvalues</td>
<td>0.997, 0.890</td>
<td>0.994, 0.792</td>
<td>0.988, 0.627</td>
</tr>
<tr>
<td>Number of compartments</td>
<td>3135</td>
<td>826</td>
<td>233</td>
</tr>
<tr>
<td>Decay factor</td>
<td>0.888</td>
<td>0.788</td>
<td>0.623</td>
</tr>
<tr>
<td>Amount in S initially</td>
<td>0.360</td>
<td>0.361</td>
<td>0.363</td>
</tr>
</tbody>
</table>
BERNARD, SHENTON AND UPPULURI

TABLE VIIb

Example (b): \( f(t) = 0.24 \exp\left(-0.7t/250\right) + 0.76 \exp\left(-0.7t/3\right) \)

<table>
<thead>
<tr>
<th>( \Delta t )</th>
<th>Eigenvalues</th>
<th>Number of compartments</th>
<th>Decay factor</th>
<th>Amount in S initially</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.997, 0.793</td>
<td>1727</td>
<td>0.791</td>
<td>0.278</td>
</tr>
<tr>
<td>2</td>
<td>0.994, 0.629</td>
<td>483</td>
<td>0.626</td>
<td>0.759</td>
</tr>
<tr>
<td>4</td>
<td>0.989, 0.395</td>
<td>149</td>
<td>0.393</td>
<td>0.761</td>
</tr>
</tbody>
</table>

Evidently there is now no difficulty in determining the parameters for the equiprobable multicompartment model with arbitrary initial conditions and many parametrizations are possible. When data for the peripheral compartments becomes available it may be possible to select a unique model to fit experimental data.

REFERENCES