STOCHASTIC PARAMETERS IN COMPARTMENTAL SYSTEMS

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ABSTRACT

Let r_{ij} denote the probability that a particle in compartment j will reach (or enter) compartment i . We present several formulas for obtaining the r_{ij} in terms of the fractional transfer coefficients. The parameter are interesting for their own sake and they are also useful for obtaining qualitative properties of compartmental systems and for interpreting results already obtained. The reachability parameters also play a role in structural identification since they give us a new method for expressing the transfer function.

1. INTRODUCTION

A compartmental system may be defined as a system of n interacting populations. Each population is envisioned to be contained in a compartment (a compartment is a mathematical abstraction; it need not represent a physical space). Let $x_j(t)$ denote the mean number of individuals in compartment j of time $t \geq 0$. A common assumption is that the rate of flow of individuals from compartment j to compartment i is proportional to $x_j(t)$ and the constant of proportionality, $a_{ij} \geq 0$, is called the fractional transfer coefficient. A compartment may allow flow out of the system and into the system's environment. The rate of flow from compartment j to the environment is assumed proportional to $x_j(t)$ and the constant of proportionality, $a_{0j} \geq 0$, is called the excretion coefficient. The flow through compartments may be described by a digraph (directed graph) as illustrated in Fig. 1. It is customary to set

$$a_{jj} = -(a_{0j} + a_{1j} + \dots + a_{j-1j} + a_{j+1j} + \dots + a_{nj}) \quad (1.1)$$

and to define the compartmental matrix

$$A = \{a_{ij}\}_{i,j=1}^n \quad (1.2)$$

Then the dynamical system of equations takes the compact form

$$\dot{\underline{x}}(t) = A\underline{x}(t) \quad (1.3)$$

Two excellent accounts of compartmental theory may be found in Jacquez's book [1] and in Brown's recent survey article [2].

It has been noted by several authors [3-10], to mention a few, that the linear time-invariant system given in (1.3) admits a stochastic interpretation. In fact the compartmental matrix A may be regarded as the infinitesimal generator (also called the intensity matrix) of the transition matrix,

$$P(t) = e^{tA}, \quad (1.4)$$

of a Markovian stochastic process with continuous time parameter. The compartments are then the states of the system. The element $p_{ij}(t)$ gives us the probability that a particle is in compartment i at time t , having initiated the process in compartment j . There are two important notational differences which we must keep in mind in connecting compartmental and the stochastic theories:

- (i) The subscript ij denotes flow from j to i ,
- (ii) Compartmental systems need not be closed (i.e. flow out of the system is allowed) thus the columns of $P(t)$ need not sum to one.

It has been pointed out (e.g., in [11]) that the variations in the statistical distribution of the population sizes, for fixed t , are negligible for large populations. Brown [2] has suggested the number 300 as a guide, i.e. for population sizes much larger than 300 the statistical variations in population sizes may be ignored. In tracer studies, where extremely large numbers of molecules are present in each compartment, statistical distributions are not generally taken into account. Nevertheless, even in tracer dynamics, stochastic parameters have played a useful role. For instance, Saffer et al. [12] found that mean residence times

and absorption probabilities are very meaningful in describing the flow of radioactive tracer through the hepatic system. Another such example may be found in [13].

Stochastic parameters are also useful for interpreting and giving meaning to analytical results. For instance, it has been known for some time that the compartmental matrix A has the following two properties [14-16]:

- (i) If A is nonsingular then $-A^{-1}$ is nonnegative,
- (ii) A is nonsingular if and only if the system does not have traps (i.e. every particle, no matter which compartment it lies, has a path to the environment).

Recently it was pointed out in [10] that the element t_{ij} of the matrix

$$T = -A^{-1} \quad (1.5)$$

is the mean residence time that a particle spends in compartment i having initiated the system in compartment j . It is clear from this interpretation why t_{ij} is nonnegative. Moreover it is well-known in probability theory that the mean residence time, t_{ij} , is finite if and only if state i is transient and this statement is equivalent to assertion (ii).

It is also apparant from the above example that the introduction of stochastic parameters into compartmental theory has the potential advantage of aiding in uncovering relationships between parameters and thereby facilitating computations. We have in mind, in particular, the problem of structural identifiability, which was introduced into compartmental theory by Bellman and Astrom [17]. The problem involves displaying the transfer function matrix,

$$T(s) = (sI - A)^{-1} , \quad (1.6)$$

explicitly in terms of the nonzero elements of A . (A more precise statement is given in Section 6.)

The purpose of this paper is several fold. First we introduce a set of parameters r_{ij} , where $\{r_{ij}\}$ denotes the probability that a particle in compartment j will reach (or enter) compartment i . Then we relate the r_{ij} to the t_{ij} . In particular we derive the formula $t_{ij} = t_{ii}r_{ij}$ (which implies that $t_{ij} \leq t_{ii}$). Finally we show how the stochastic parameters are useful in constructing the transfer function elements of (1.6).

2. REACHABLE PROBABILITIES

In this section we define r_{ij} , the probability that a particle in compartment j reaches (or enters) compartment i . In the trivial case, $i = j$, we set

$$r_{ii} = 1, \quad i = 1, 2, \dots, n . \quad (2.1)$$

For $i \neq j$ there are several ways to express r_{ij} in terms of the coefficients a_{ij} . The first method is based on the digraph. We say that compartment j reaches compartment i if there is a path from j to i in the digraph of the system. Clearly

$$r_{ij} = 0, \quad i \text{ not reachable from } j . \quad (2.2)$$

For example in Fig. 1, $r_{i7} = 0$ if $i \neq 7$.

In more complex situations it is convenient to introduce the parameter

$$r(j \rightarrow i) = a_{ij} / |a_{jj}| \quad . \quad (2.3)$$

Let us recall from Eq. (1.1) that $|a_{jj}|x_j(t)$ is the total outflow from compartment j and $a_{ij}x_j(t)$ is that portion of the outflow which enters compartment i . Thus $r(j \rightarrow i)$ is the proportion of outflow from j which enters i . Stochastically, $r(i \rightarrow j)$ is the probability that a particle in j enters i when a transition occurs. (See [18], p. 6). In the event that the only path from j to i is the segment a_{ij} then

$$r_{ij} = r(j \rightarrow i) \quad (\text{single path of unit length}). \quad (2.4)$$

For instance in Fig. 1, $r_{21} = a_{21} / (a_{21} + a_{51})$.

Next we define the probability $r(\Gamma)$ that j reaches i along a sequence

$$\Gamma : j = m_1 \rightarrow m_2 \rightarrow \dots \rightarrow m_{q+1} = i \quad (2.5)$$

where

$$m_k \neq i \quad \text{for } k \leq q \quad . \quad (2.6)$$

$r(\Gamma)$ is the product of the probabilities of each transfer along the sequence, i.e.

$$r(\Gamma) = \prod_{k=1}^q r(m_k \rightarrow m_{k+1}) \quad . \quad (2.7)$$

Clearly if Γ is the only path from j to i , which does not pass through i , then $r_{ij} = r(\Gamma)$. For instance in Fig. 1, $r_{31} = r(1 \rightarrow 2)r(2 \rightarrow 3) =$

$$[a_{21}/(a_{21} + a_{51})][a_{32}/(a_{32} + a_{42})].$$

Finally we consider the most general case in which j reaches i along several sequences. We denote by U_{ij} the set of sequences (from j to i) of the form (2.5)-(2.6). Then r_{ij} is the sum of the probabilities for each sequence, i.e.

$$r_{ij} = \sum_{\Gamma \in U_{ij}} r(\Gamma) \quad (2.8)$$

For instance in Fig. 1, we have an infinite number of sequences from 6 to 7 which do not pass through $7: 6 \rightarrow 7, 6 \rightarrow 5 \rightarrow 6 \rightarrow 7, \dots, 6 \rightarrow 5 \rightarrow 6 \rightarrow \dots \rightarrow 6 \rightarrow 7, \dots$. Let Γ_k denote the sequence which traverses compartment 6 k times before entering 7. Then $r(\Gamma_k) = [r(6 \rightarrow 5)r(5 \rightarrow 6)]^k [r(6 \rightarrow 7)] = [r(6 \rightarrow 5)]^k r(6 \rightarrow 7)$. Thus $r_{76} = \sum_{k=0}^{\infty} r(\Gamma_k) = r(6 \rightarrow 7) \sum_{k=0}^{\infty} [r(6 \rightarrow 5)]^k = r(6 \rightarrow 7)[1 - r(6 \rightarrow 5)]^{-1} = a_{76}(a_{76} + a_{06})^{-1}$. It is interesting that the result is the same as that which would have been obtained if compartments 5 and 6 were considered as one compartment.

The cardinality of the set U_{ij} is infinite when the flow from j to i contains cycles. In such cases it is usually easier to calculate r_{ij} by formulas given in the next section.

3. CONNECTION WITH ABSORPTION PROBABILITIES

A compartment i is said to be absorbing if it is a trap. The equivalent conditions: $a_{ii} = 0, p_{ii}(t) \equiv 1$, both characterize an absorbing compartment. For instance in Fig. 1, compartment 7 is absorbing. In the case of an absorbing compartment, $i, p_{ij}(t)$ is the probability that a particle reaches i from j in a time increment of length t . Thus

$$r_{ij} = \lim_{t \rightarrow \infty} p_{ij}(t) \quad (i \text{ absorbing}) \quad . \quad (3.1)$$

Let us suppose, for convenience, that compartment n is absorbing. Then we can express A in the partitioned matrix form

$$A = \begin{bmatrix} E & F \\ G & H \end{bmatrix}, \quad (3.2)$$

where $E = \{a_{ij}\}_{i,j=1,n-1}$, $G = [a_{n1}, a_{n2}, \dots, a_{nn-1}]$, F is a $(n-1) \times 1$ matrix of zero entries and H is a 1×1 matrix whose entry is zero. By a known formula [19];

$$P(t) = e^{tA} = \begin{bmatrix} U(t) & F \\ V(t) & W \end{bmatrix}, \quad (3.3)$$

where $U(t) = e^{tE}$, W is the 1×1 matrix whose entry is one and $V(t) = G E^{-1}(U(t) - I)$. (I generally denotes an identity matrix). We are assuming here that E is nonsingular which is equivalent to assuming that the subsystem associated with E does not contain traps. The matrix $U(t)$ is also a submatrix of $P(t)$; in fact $u_{ij}(t) = p_{ij}(t)$ for $i, j = 1, \dots, n-1$. Since we are assuming that each compartment j ($j < n$) is transient (this equivalent to the assumption that E has no traps), $u_{ij}(t) \rightarrow 0$ as $t \rightarrow \infty$ and consequently

$$[r_{n1}, r_{n2}, \dots, r_{nn-1}] = \lim_{t \rightarrow \infty} V(t) = -G E^{-1} \quad (3.4)$$

For instance in Fig. 1, $[r_{71}, r_{72}, \dots, r_{76}] = -[0, 0, 0, 0, 0, a_{76}]E^{-1}$, where

$$E = \{a_{ij}\}_{i,j=1,6}.$$

In deriving formula (3.4) for r_{ij} we made the following assumption

- (i) $i = n$, the last compartment,
- (ii) i is absorbing.
- (iii) All other compartment $j = i$, are transient.

None of these assumptions are necessary. The first is simply notational since the compartments may be renumbered so that the compartment in question is numbered last. To eliminate the second restriction we define the matrix A^* by:

$$a_{ij}^* = a_{ij} \text{ if } j \neq n, \quad a_{in}^* = 0 \text{ (for all } i) \quad (3.5)$$

We notice that A^* represents a compartmental system in which compartment n is absorbing and that the sequences from j to n ($j \neq n$) are identical in the two systems. Thus $[r_{n1}, r_{n2}, \dots, r_{nn-1}] = [r_{n1}^*, r_{n2}^*, \dots, r_{nn-1}^*] = -G^*(E^*)^{-1} = -GE^{-1}$ (since $G^* = G$ and $E^* = E$). In other words formula (3.4) is valid without the absorbing assumption.

We now return to restriction (iii). For the sake of motivation let us consider Fig. 1. We notice that the direct application of formula (3.4) to compute r_{24} is not valid because compartment 7 is not transient, thereby violating condition (iii). On the other hand it is clear from the digraph that flow from 2 to 4 does not involve 7 at all and therefore we should eliminate compartment 7 from consideration in the application of formula (3.4) to compute r_{24} . In fact we need only be concerned with the subsystem containing the flow from 2 to 4.

To formulatize the above concept we define sybsystems as follows.

Let $C = \{n_1, n_2, \dots, n_q\}$ denote a subset of compartments. Let D be the

digraph of the entire system. We define the subdigraph $D(C)$ as the digraph which contains all sequences from j to i whenever both i and j belong to C . Thus the compartments in $D(C)$ consists of those compartments in C and those compartment which lie on a sequence connecting any pair of compartments in C . Moreover, the environment of $D(C)$ consists of the environment of D and all compartments exterior to $D(C)$. More precisely, let j be a compartment in $D(C)$ and let $B(C)$ be the set of all compartments in D which are not in $D(C)$, then the excretion coefficient of j in $D(C)$ is

$$a_{0j}^{(C)} = a_{0j} + \sum_{k \in B(C)} a_{kj} \quad (3.6)$$

For instance in Fig. 1, the digraphs of $D(\{2,4\})$ and $D(\{4\})$ are given in Figs. 2(a) and 2(b) respectively.

It is important to notice that the matrix $A(C)$, associated with $D(C)$, is always a submatrix of A . However not every submatrix of A corresponds to a subdigraph $D(C)$. We should notice also that if k belongs to a subsystem then all compartments which are mutually reachable with k also belong to the subsystem.

We now return to the problem of computing reachability probabilities. Let i be any compartment and let C be any subset of compartments which reach i and which also contains compartment i . Let $A(C)$ be the matrix associated with the subdigraph $D(C)$. Finally let $D^*(C)$ and $A^*(C)$ be the digraph and its associated matrix which are obtained by setting all outflows from compartment i equal to zero (as in (3.5)). We then notice that i is absorbing in $D^*(C)$ while all other compartments are transient in $D^*(C)$ since they all reach compartment i . Thus formula (3.4) is valid

for computing $r_{ij}(D^*(C))$, where we use the notation $r_{ij}(\Delta)$ to denote the probability that j reaches i in the digraph Δ . On the other hand from the above discussion we have that for any j in $D(C)$, which is different from i , $r_{ij} = r_{ij}(D) = r_{ij}(D(C)) = r_{ij}(D^*(C))$. Thus we may apply formula (3.4) to obtain r_{ij} but to the subsystem $D(C)$. The matrix E in the formula is now $E = \{a_{kj}\}$ where k and j range over all compartments in $D(C)$ except for i . When we multiply on the right by E we obtain the identity

$$\sum_{\substack{k \in D(C) \\ k \neq i}} r_{ik} a_{kj} = -a_{ij}, \quad j \in D(C), \quad j \neq i \quad (3.7)$$

which is valid for any subdigraph $D(C)$ of sequence from C to i . Let $q+1$ be the number of compartments in $D(C)$. Then (3.7) defines a system of q linear equations from which we can determine the q reachable probabilities, r_{ik} , $k \in D(C)$ and $k \neq i$ (the $q \times q$ submatrix of coefficients is the transpose of E , which is nonsingular).

As an illustration we refer to Fig. 1, with $i = 4$, $j = 2$ and $C = \{2, 4\}$. We recall that $D(C)$, given in Fig. 2(a), contains compartments 2, 3, and 4. In this case Eqs. (3.7) is $r_{42}a_{22} + r_{43}a_{32} = -a_{42}$ and $r_{42}a_{23} + r_{43}a_{33} = -a_{43}$. The two equations obtain a linear system which can be inverted to yield r_{42} and r_{43} . Since $a_{23} = 0$, and taking account of Eqs. (1.1), we obtain $r_{42} = r_{43} = 1$, which is obvious from the digraph (a particle in either 2 or 3 must reach 4).

As a second illustration we compute r_{67} . This time we choose $D(C)$ to be the subdigraph containing 5, 6 and 7. The linear system (3.7) is now $r_{75}a_{55} + r_{76}a_{65} = -a_{75}$ and $r_{75}a_{56} + r_{76}a_{66} = -a_{65}$. Inverting we obtain

r_{75} and r_{76} . We can verify that r_{76} , obtained in the way, coincides with the expression for r_{76} obtained earlier by summing an infinite series (see after Eq. (2.8)).

We now have two methods, given by formulas (2.8) and (3.7) for computing the reachability probabilities. A third formula is (4.6), given below.

4. CONNECTION WITH MEAN RESIDENCE TIMES

Let A be the matrix of fractional transfer coefficients for a compartmental system, or for a subsystem, which has not traps (equivalently, A is nonsingular). As we mentioned earlier (in the Introduction) the element t_{ij} of $T = -A^{-1}$ is the mean residence time that a particle spends in compartment i having initiated the system in compartment j .

In order to relate the mean residence times to the reachable probabilities we recall Eq. (3.7). Since $r_{ii} = 1$ we can write the equation in the form

$$\sum_{k \in D(C)} r_{ij} a_{kj} = 0, \quad j \neq i. \quad (4.1)$$

Suppose we set C to be the entire set of compartments which reach i (in which case every compartment in $D(C)$ is also in C). If k is not in C , i.e. k does not reach i , then $r_{ik} = 0$. Thus the subscript k in (4.1) may range over all compartments, i.e.

$$\sum_{k=1}^n r_{ij} a_{kj} = 0, \quad j \neq i. \quad (4.2)$$

We let R denote the matrix of reachable probabilities and we set

$$H = RA \quad (4.3)$$

According to (4.2) H is a diagonal matrix, i.e.

$$h_{ij} = 0, \quad i \neq j \quad .$$

Assuming A is nonsingular we multiply by A^{-1} on the right of (4.3) to obtain

$$R = HA^{-1} = -HT \quad .$$

Since H is diagonal, this gives

$$r_{ij} = -h_{ii}t_{ij} \quad . \quad (4.4)$$

In particular if we set $j = i$ we obtain $1 = r_{ii} = -h_{ii}t_{ii}$. Thus

$$h_{ii} = -t_{ii}^{-1} \quad . \quad (4.5)$$

Substituting (4.5) into (4.4) we obtain

$$r_{ij} = t_{ij}/t_{ii} \quad . \quad (4.6)$$

The identity (4.6) provides us with another method for obtaining the reachable probabilities. The formula is easier to state than either of the alternative formulas, (2.8) and (3.7). However, the formula is computationally less attractive because it involves the inversion of a matrix.

Identity (4.6), expressed in the form

$$t_{ij} = t_{ii}r_{ij} \quad , \quad (4.7)$$

may also be obtained by the following more intuitive argument. Suppose we have m particles in compartment j . Each has a probability r_{ij} of reaching compartment i so that the mean number reaching compartments i is $r_{ij}m$. Now each particle that enters i is expected to spend t_{ii} units in i , (prior to leaving the system) so that the total mean time in i for the m particles is $t_{ii}r_{ij}m$. On the other hand, each of the particles initiating in j is expected to spend t_{ij} units of time in i so that the total mean time in i for the m particles is $t_{ij}m$. That is $t_{ij}m = t_{ii}r_{ij}m$, which results in identity (4.7).

Identity (4.7), which shows that the mean time in compartment is proportional to the probability of reaching i , yields immediately,

$$t_{ij} \leq t_{ii} , \quad (4.8)$$

since $r_{ij} \leq 1$ (it is a probability). That is the particle maximizes its mean time spent in i by initiating in i rather than from some other compartment. The intuitive inequality provides another property of compartmental matrices.

It is interesting to consider identity (4.7) in the special case of a single exit system (also called an almost closed system) which is a system with one and only one exit to the environment, say from compartment i . More precisely we are considering a system such that

$$a_{0i} > 0, \quad a_{0k} = 0 \quad \text{if } k \neq i, \quad (\text{single exit}). \quad (4.9)$$

It has been pointed out that for a system satisfying (4.9), the i th row of A^{-1} (assuming A^{-1} exists) is constant. The proof of this statement (see

$$\sum_{k=1}^n r_{ik} a_{kj} = -\delta_{ij}/t_{ii} \quad , \quad (4.12)$$

which is valid for all compartmental systems (whether or not there are traps). In other words, $H = RA$ is a diagonal matrix whose i th diagonal entry is $-1/t_{ii}$ if i is transient and zero if i is recurrent. A possible application of formulas (4.7) and (4.12) are described in the next section.

Another way to compute the mean residence time t_{ii} was given by Rescigno and Gurpride [13] who argue as follows. Let τ_i be the "mean transit time through compartment i (also called the "first exit time" and the "turnover time") i.e. the time spent by the particle from its entry into the compartment to its next exit. It is well known that

$$\tau_i = -\frac{1}{a_{ii}} \quad , \quad (4.13)$$

assuming, of course, that $-a_{ii} > 0$ (i.e. the particle is allowed to leave). If there is no possibility of return to i then $t_{ii} = \tau_i$. In general, let r_i denote the probability of returning to i . Suppose m particles exist in compartment i at $t = 0$. Each particle is expected to spend τ_i units of time during its first passage through the compartment so that the total mean first transit time for all m particles is $m\tau_i$. The expected number of returning particles is $r_i m$ and so the total expected time for the second transit through the compartment is $rm\tau_i$; the third is $r_i^2 m\tau_i$ and so on. Thus the total mean residence time for the m particles is $m\tau_i + r_i m\tau_i + r_i^2 m\tau_i + \dots = m\tau_i/(1-r_i)$. Dividing by m we obtain the mean residence time in i for a single particle initiating in

in i , i.e.

$$t_{ii} = \tau_i / (1 - r_i) = -[a_{ii}(1 - r_i)]^{-1}. \quad (4.14)$$

We notice that if i is transient (i.e. $r_i < 1$) t_{ii} is finite while if i is recurrent ($r_i = 1$) t_{ii} is infinite, as we noted earlier. Formula (4.13) is derived in [13] however we remark here that

$$r_i = \sum_{k \neq i} r_{ik} r(i \rightarrow k) \quad (4.15)$$

and so we can express the formula (4.14) in the form

$$t_{ii} = -\{a_{ii}[1 - \sum_{k \neq i} r_{ik} r(i \rightarrow k)]\}^{-1} \quad (4.16)$$

In view of formulas (4.16) and (4.7) we see that all mean residence times t_{ij} are obtained from the set of n^2 parameters $\{a_{ii}\}$ and $\{r_{ij}\}_{i \neq j}$. In the event that the system contains traps some of the t_{ij} are infinite but if the system is without traps then the matrix T is well defined, nonsingular, and $A = -T^{-1}$ is also expressed in terms of the diagonal elements of A and the off-diagonal elements of R .

5. COMPUTATION OF THE TRANSFER FUNCTION

Suppose that an experiment is performed in which the flow initiates in compartment j and it is observed in compartment i (i may equal j). Compartment j is then called the input compartment and i is the output compartment. The transfer function for the input-output experiment is

[20], p. 320) does not involve probability theory however, in the light of identity (4.7), the result is equivalent to $r_{ij} = 1$ for all j . But this is obvious since every particle must pass through compartment i before it can exit the system. In other words the result is an immediate corollary of (4.7).

Let us now consider a compartmental matrix A but we do not assume A is nonsingular. Let

$$A(s) = A - sI$$

where s is a nonnegative number. We notice that, for fixed s , $A(s)$ represents a compartmental system in which the excretion and total outflow coefficients are

$$a_{0j}(s) = a_{0j} + s, \quad a_{jj}(s) = a_{jj} - s, \quad (4.10)$$

and all other fractional transfer coefficients are independent of s . If $s > 0$ then all compartments are exits and hence $A(s)$ is nonsingular. In view of formulas (4.2), (4.3) and (4.5), we obtain

$$\sum_{k=1}^n r_{ik}(s)a_{kj}(s) = -\delta_{ij}/t_{ii}(s). \quad (4.11)$$

where δ_{ij} is the kronecker delta symbol, i.e. $\delta_{ij} = 0$ if $i \neq j$ and $\delta_{ij} = 1$ if $i = j$. As $s \rightarrow 0$ $a_{kj}(s) \rightarrow a_{kj}$, $r_{ij}(s) \rightarrow r_{ik}$, $t_{ii}(s) \rightarrow t_{ii}$ if i is transient and $t_{ii}(s) \rightarrow +\infty$ if i is recurrent (nontransient). We adopt the convention $0 = 1/\infty$ and we take the limit as $s \rightarrow 0$ in (4.11) to obtain

$t_{ij}(s)$, the ij element of the matrix

$$T(s) = -(A-sI)^{-1} = -A^{-1}(s) \quad .$$

An important problem, which arises in structural identifiability (see the next section), is to express $t_{ij}(s)$ explicitly in terms of the a_{ij} elements. For large systems the inversion of $A(s)$ is cumbersome, however the computation may be facilitated by the use of stochastic parameters.

Let us recall, from the previous section, that for $s > 0$, $A(s)$ is a compartmental matrix such that all coefficients $a_{ij}(s) = a_{ij}$, except for the excretion and the total outflow coefficients which are given in (4.10). The transfer function $t_{ij}(s)$ may then be interpreted as a mean residence time. Suppose that the reachable probabilities $r_{ij}(s)$ can be determined without inverting an $n \times n$ matrix. Then we can apply formulas (4.7) and (4.16) to derive the formula

$$t_{ij}(s) = -\left[\sum_{k=1}^n r_{ik}(s)a_{ki}(s)\right]^{-1}r_{ij}(s) \quad . \quad (5.1)$$

As an illustration we consider the computation of $t_{17}(s)$ in Fig. 1. Since $a_{k7}(s) = 0$ for $k \neq 7$, $a_{77}(s) = -s$ and $r_{77}(s) = 1$, we see that

$$t_{71}(s) = r_{71}(s)/s \quad . \quad (5.2)$$

Moreover, it is clear from Fig. 1 that in order for a particle to reach 7 from 1 it must pass through compartments 2,4,5 and 6. Thus

$$r_{71}(s) = r_{76}(s)r_{65}(s)r_{54}(s)r_{42}(s)r_{21}(s) \quad . \quad (5.3)$$

Each of the reachable probabilities, except for $r_{76}(s)$, are easily

obtained from formula (2.8) since there only a finite number of sequence to sum over.

$$r_{21}(s) = a_{21}/[s + a_{21} + a_{51}] \quad . \quad (5.4)$$

$$r_{42}(s) = a_{42}/[s + a_{32} + a_{42}] + \{a_{43}/[s + a_{43}]\}\{a_{32}/[s + a_{32} + a_{42}]\} \quad . \quad (5.5)$$

$$r_{54}(s) = a_{54}/[s + a_{54}] \quad . \quad (5.6)$$

$$r_{65}(s) = a_{65}/[s + a_{65}] \quad . \quad (5.7)$$

Since there are an infinite number of sequences from 6 to 7 we apply formula (3.7) to compute $r_{76}(s)$ with $C = \{6,7\}$. In this case $D(C)$ is the subsystem formed by compartments 5,6 and 7 and formula (3.7) yields $r_{75}(s)(-s - a_{65}) + r_{76}(s)a_{65} = 0$ and $r_{75}(s)a_{56} + r_{76}(s)(-s - a_{56} - a_{76}) = -a_{65}$. The first equation expresses the fact that $r_{75}(s) = r_{76}(s)r_{65}(s)$, which is evident from the digraph. Substituting this result in the second equation yields

$$r_{76}(s) = a_{65}/[s + a_{56} + a_{76} - r_{65}(s)a_{56}] \quad . \quad (5.8)$$

We see from formulas (5.2)-(5.8) that $t_{71}(s)$ may be constructed without having to invert a 7×7 matrix by the error-prone Kramer's Rule. We should note the existence of other methods of obtaining the inverse of a compartmental matrix (see [21] and [22]).

6. CONNECTION WITH STRUCTURAL IDENTIFICATION

Suppose that an input-output experiment has been performed and we are attempting to estimate, from the observed data, a set of structural parameters $\theta = (\theta_1, \theta_2, \dots)$ (usually these are a subset of fractional transfer coefficients). We form an objective function $J(\theta)$, say as the sum of squares of the difference between observed and predicted values. We then attempt to minimize $J(\theta)$, say in a small region of parameter space where we suspect the solution is contained. This parameter estimation problem has led to several interesting mathematical pursuits, one of which is the structural identification problem. It is an important consideration in experimental design ([17]). The problem is to ascertain if detection of θ from the observed data is possible even under "ideal circumstances".

More precisely, suppose we know the transfer function, e.g. suppose it has the form

$$\tau(s) = \alpha \prod_j (s - \xi_j) / \prod_k (s - \pi_k)$$

with poles π_k and zeros ξ_j . These, along with the constant α , are collectively referred to as the transfer-function parameters and denoted by a vector, say σ . Suppose further that we know the correspondence between σ and θ , i.e., we know the map

$$\sigma = f(\theta)$$

where $f(\theta)$ is the (nonlinear) identification map. Then the input-output experiment is said to be structurally identifiable if $f(\theta)$ is locally

invertible ([17], [23]). The absence of structural identifiability means that not all of the unknown structural parameters θ_i uniquely exist in the transfer function and therefore the observed data does not contain all the information desired. Even if not all θ_i are identifiable the question of which combination of the θ_i are identifiable is of interest.

As an illustration we consider the identifiability of the fractional transfer coefficient a_{43} in Fig. 1 by performing the experiment which inputs in compartment 1 and observes in compartment 7. More specifically, we wish to determine if a_{43} can be uniquely determined from the zeros and poles of $t_{71}(s)$. If we consider the representation (5.2)-(5.8) we see that a_{43} occurs only in the expression (5.5). Moreover, it is clear that $-a_{43}$ is a pole of $r_{42}(s)$. It is conceivable that one of the other terms in the product (5.3) may have a zero ξ_i and it may happen that $\xi_i = -a_{43}$. If this occurs then $-a_{43}$ may be a removable singularity in $\tau_{71}(s)$. We may however take the point of view, held by Cobelli et al. [23] and others, that the possibility that $-a_{43}$ is a removable singularity is remote (more precisely, it occurs on a set of Lebesgue measure zero in parameter space) and say that $-a_{43}$ is structurally identifiable (at almost all points).

Of course there are ten other parameters in Fig. 1 to consider. Certainly the question of structural identifiability is facilitated by the representation (5.2)-(5.7) since the problem is broken up in terms of subsystems along the flow.

The problem of structural identifiability has turned out to be surprisingly difficult for large systems and no general solution is yet in sight (although there are plenty of partial results). It appears from

our example that the stochastic representations which we introduced above will bring further insight into the problem.

We end with an observation which is discussed more fully by Rescigno and Gurpride ([7], [13]) but in somewhat different terminology. Suppose that an experiment is performed with input and output both from compartment i . We may not know the complete structure of the system nor even how many compartments are involved. Nevertheless several parameters are structurally identifiable including: the total out flow coefficient a_{ij} , the mean transit time τ_i (formula (4.13)), the mean residence time t_{ii} and the probability of return r_i (formula (4.15)). In fact suppose we observe $x_i(t)$. Then it is clear from the differential equation, $\dot{x}_i(t) = a_{ii} x_i(t) + \sum_{k \neq i} a_{ik} x_k(t)$, and the initial conditions $x_k(0) = 0$, $k \neq i$ that $a_{ii} = \dot{x}(0)/x(0)$. Moreover $t_{ii} = \int_0^\infty x_i(t) dt / x_i(0)$. The remaining two parameters are obtainable from formulas (4.13) and (4.14).

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FIGURE LEGENDS

Figure 1 - Example of a Compartmental System

Figure 2 - Some subsystems of Fig. 1

- a. Flows from 2 to 4
- b. Flows from 4 to 4

Figure 1.

Figure 2.