RELATIONSHIP BETWEEN STOCHASTIC AND DIFFERENTIAL MODELS OF COMPARTMENTAL SYSTEMS

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ABSTRACT. This paper shows that the differential equations model for compartmental systems is consistent with a stochastic description. Consequently, we may employ either a differential equations or a stochastic formulation for either parameter identification, or for physical interpretation, as best suits the purpose. The differential equations parameters, the so-called fractional transfer coefficients, may be determined from the corresponding set of stochastic parameters and vice versa.

INTRODUCTION. This paper deals with mathematical models for compartmental systems to be used for parameter identification. Usually one employs the differential equations model [1] however sometimes we find a stochastic model [2]. The paper discusses the relationship between these modeling techniques.

We consider the differential equations model first. In the case of the "bolus input hypothesis", the model takes the form

$$\dot{X}(t) = AX(t), \quad X(0) = X_0 . \tag{1.1}$$

Here A is an $n \times n$ *compartmental matrix*. The elements of A, the so-called fractional transfer coefficients, have the following properties:

$$a_{ij} \geq 0 \ (i \neq j), \ \sum_{i=1}^{n} a_{ij} \leq 0 \quad (j = 1,2,\ldots,n). \tag{1.2}$$

The compartmental matrix A will be said to be *closed* if A has the additional property:

$$\sum_{i=1}^{m} a_{ij} = 0 \quad (j = 1,2,\ldots,n). \tag{1.3}$$

The vector $X(t)$ is called the *state* of the system at time $t \geq 0$. Its component $x_i(t)$ is the state of compartment i at time t. In general, $x_i(t)$ represent nonnegative physical quantities. For example in [2], $x_i(t)$ represents the percentage of Rose Bengal in compartment i at time t. The closure condition corresponds to the conservation law $\frac{d}{dt} \sum_{i=1}^{n} x_i(t) = 0$. Thus if initially the sum is

1, it will remain 1 for all $t > 0$.

For closed compartmental systems for which $\sum_{i=1}^{m} x_i(0) = 1$, the state vector $X(t)$ is a *probability vector*, ie. for each fixed $t > 0$ the components satisfy:

$$x_i \geq 0, \quad \sum_{i=1}^{m} x_i = 1. \tag{1.4}$$

Taking advantage of this property, the process may be considered from the stochastic point of view. Saffer et al [2] define the transition probability matrix $P(h)$ such that

$$X(t + h) = P(h)X(t) \tag{1.5}$$

and regard, for fixed time increment h, $X(nh)$, $n = 0,1,\ldots,$ as a Markov chain. The elements $p_{ij}(h)$ of $P(h)$ represent probabilities of going from compartment j to compartment i in time h.

One sees from the discussion of liver diseases [2] that the stochastic model is very handy for interpreting data. It is also convenient for parameter identification since one is dealing with a discrete process. On the other hand, the differential equations approach has nice analytical properties and the flow graph of A may have less segments than the corresponding stochastic matrix. Each modeling approach provides its own special insight into the physical problem.

This paper deals with the following question. Suppose data identifies, via the differential equations model, a compartmental matrix A, and via the stochastic model, a probability matrix P. How are P and A related? It develops that these matrices are

related by relatively simple formulas which permit computation of one from the other. This provides for more identification algorithms.

Leaving aside identification, one may take advantage of the relationship between the models to interpret compartmental parameters from the stochastic point of view. For example we are led to the interpretation of $-A^{-1}$ as the matrix whose $(i,j)^{\text{th}}$ entry is the mean time the process is in compartment i, having started in compartment j, before being excreted.

2. PROBABILITY AND COMPARTMENTAL MATRICES. Since we are relating probability matrices to compartmental matrices, we define a *probability vector*, X, as a column vector (rather than the more customary row vector) satisfying condition (1.4). A *probability matrix* is defined as a matrix such that each column is a probability vector. We do not require that a probability matrix be square, in fact a probability vector is a probability matrix with one column.

The following properties are well known [3] and are not difficult to verify.

Lemma 2.1. (i) The product of two probability matrices (whose dimensions are compatible for multiplication) is a probability matrix. (ii) The limit (if it exists) of probability matrices is a probability matrix.

Recall that a closed compartmental matrix was defined above to satisfy properties (1.2)-(1.3). The following simple connection between closed compartmental matrices and probability matrices was

essentially pointed out in [4].

Lemma 2.2. (i) Let A be an $n \times n$ closed compartmental matrix. Let $d = max\{|a_{ij}| : 1 \leq i, j \leq n\}$. Then

$$Q(h) \equiv I + hA, \quad 0 \leq h \leq d^{-1}, \tag{2.1}$$

is a probability matrix. (I denotes the identity matrix).

(ii) Let P be a probability matrix, then for all $h > 0$

$$A(h) = h^{-1}(P - I) \tag{2.2}$$

is a closed compartmental matrix.

Proof: (i) The column sums of $Q(h)$ are $1 + h \sum_{i=1}^{n} a_{ij} = 1$ by condition (1.3). The off-diagonal elements of $Q(h)$ are the off-diagonal elements of hA which are nonnegative by condition (1.2). Finally, the diagonal elements of $Q(h)$ are $1 + ha_{ii}$ which are nonnegative since $h \leq d^{-1}$. (ii) Since multiplication by positive scalars preserves the properties (1.2)-(1.3), it suffices to show that these properties are satisfied by $P - I$. But this is easy to verify.

Theorem 2.1. Let A be a closed compartmental matrix. Then

$$P(h) = exp(hA), \quad h \geq 0 \tag{2.3}$$

is a probability matrix.

Proof: It suffices to consider the case $h = 1$. Since hA is also a closed compartmental matrix.

We define the functions $f_n(s) = (1 + s/n)^n$, $n = 1,2,\ldots,$ and $f_\infty(s) = \exp(s)$. It is well known that $f_n(s) \to f_\infty(s)$ for all complex numbers s. Moreover, the derivatives $f_n^{(k)}(s) \to f_\infty^{(k)}(s)$, $k = 1,2,\ldots$. It follows (see [5], p. 606) that the corresponding matrices $f_n(A) = (I + A/n)^n$ converge to $f(A) = \exp(A)$. We know from Lemma 2.2(i) that $I + A/n$ is a probability matrix for n sufficiently large. Hence $(I + A/n)^n$ is a probability matrix, for large n, by Lemma 2.1(i). Finally, we apply Lemma 2.1(ii) to see that $\exp(A) = \lim_{n\to\infty} (I + A/n)^n$ is a probability matrix. This completes the proof.

3. RELATIONS BETWEEN STOCHASTIC AND DIFFERENTIAL PROCESSES. The following result is at the heart of the correspondence between the two models.

Theorem 3.1. (i) Let $X(t)$ be a solution to the differential system (1.1) where A is a closed compartmental matrix. Then there is a one parameter family of probability matrices $P(h)$, $h \geq 0$, such that Eq. (1.5) is satisfied and $P(h)$ is expressed in terms of A by Eq. (2.3). If $X(0)$ is a probability vector, then $X(t)$ is a probability vector for each $t > 0$. Conversely, (ii) let $X(t)$ be a solution to Eq. (1.5) where $P(h)$ is a one parameter family of probability matrices such that $P(h)$ is differentiable at

$h = 0$. Let

$$A = \dot{P}(0). \tag{3.1}$$

Then A is a closed compartmental matrix and $X(t)$ is a solution of the differential system (1.1).

Proof: (i) The solution to (1.1) is

$$X(t) = \exp(tA)X_0 . \tag{3.2}$$

Thus $X(t + h) = \exp((t + h)A)X_0 = \exp(hA)\exp(tA)X_0 = P(h)X(t)$ where $P(h)$ is a probability matrix by Theorem 2.1. If X_0 is a probability vector, then $X(t)$ is a probability vector in view of Eq. (3.2) and Lemma 2.1(i). (ii) Observe that $A = P(0) = \lim_{h \to 0} A(h)$ where $A(h)$ is given by Eq. (2.2). Since $A(h)$ is a closed compartmental matrix (Lemma 2.2(ii)) so is its limit A. Next observe from Eq. (1.5) that $X(t + h) = P(h)X(t)$ and $P(0)X(t) = X(t) = IX(t)$. Thus $h^{-1}(X(t + h) - X(t)) = A(h)X(t)$. Taking the limit as $h \to 0$ we obtain Eq. (1.1). This completes the proof.

The above result is well known in the context of semi-group theory (see [6], p. 231) but not in regards to the relationship between probability and compartmental matrices. The matrix A is called the infinitesimal generator of the semi-group $P(h)$. The following result is a paraphrase of Theorem 3.1 which emphasizes the modeling aspect.

Corollary 3.1. (i) Suppose a compartmental system is described by the differential equation model (1.1) where A is a closed compartmental matrix and X_0 is a probability vector. Then for each $h > 0$ and for each $t_0 \geq 0$ the system may be modeled as a Markov chain $X_{n+1} = P(h)X_n$ where $X_n = X(nh + t_0)$. Conversely, if the system may be modeled as a Markov chain in the above sense for each fixed $h > 0$, $t_0 \geq 0$ and if $P(h)$ is differentiable at $h = 0$, then the system may be modeled in terms of the differential system (1.1) where A is a closed compartmental matrix.

Remark 3.1. (flow graphs) In general the graph of $P(h)$ $(h > 0)$ exhibits more connections between compartments than the graph of A.. For example, if the fractional transfer coefficient $a_{ij} = 0$ then the graph of A has no path from compartment j to compartment i which does not intersect other compartments. However, as long as compartment i is reachable from compartment j along some path (which may intersect several intermediate compartments, the probability, $p_{ij}(h)$ of reaching compartment i from compartment j in time $h > 0$ is positive. On the other hand, we may observe from the expansion

$$P(h) = \exp(hA) = I + hA + h^2A^2/2! + \ldots \tag{3.3}$$

that for h small

$$P(h) \sim I + hA \ . \tag{3.4}$$

Notice that the graph of the approximation $I + hA \quad (h > 0)$ has the same connections between compartments as does the graph of A. This is because if there is no immediate path from j to i then $p_{ij}(h)$ is of order h^2 as $h \to 0$.

4. SYSTEMS WITH EXCRETIONS. We now consider an $n \times n$ compartmental matrix A which is not closed, i.e. there is at least one integer j such that

$$a_{0j} \equiv - \sum_{i=1}^{n} a_{ij} > 0 \ . \tag{4.1}$$

The positive quantity a_{0j} represents the *excretion* from compartment j into the external environment.

Let r denote the number of excretions. For the sake of simplicity of notation, we renumber (if necessary) the compartments so that the first r compartments exhibit excretions. In order to obtain an equivalent closed model of our system, we add r new compartments (traps) so that the i^{th} new compartment serves as the depository for the i^{th} excretion. The resulting compartmental matrix, which we call the *closure of* A (see Remark 8.1) and denote it by $\overline{A}$, is described as the partitioned matrix

$$\overline{A} = \begin{bmatrix} O_{rr} & E \\ O_{nr} & A \end{bmatrix} \ . \tag{4.2}$$

Here O_{rr} (resp. O_{nr}) denotes the $r \times r$ (resp. $n \times r$) matrix of zero entries and E is the $r \times n$ matrix such that

$$e_{ij} = a_{0j} \quad (i = j), \quad e_{ij} = 0 \quad (i \neq j) \ . \tag{4.3}$$

Notice that $\overline{A}$ is in block upper triangular form so we may apply Corollary 3.1 in [7] to obtain (for $h \geq 0$):

$$\overline{P}(h) = exp(h\overline{A}) = \begin{bmatrix} I_{rr} & S(h) \\ O_{nr} & P(h) \end{bmatrix} \tag{4.4}$$

where I_{rr} denotes the $r \times r$ identity matrix, $P(h) = exp(hA)$ as before and

$$S(h) = E \sum_{n=0}^{\infty} h^{n+1}A^n/(n+1)! \tag{4.5}$$

The series (4.4) always converges, and if A^{-1} exist, as is the case when A is excretory (see Theorem 4.1, below), then the series converges to

$$S(h) = EA^{-1}(P(h) - I) \ . \tag{4.6}$$

If h is small, then in view of the approximation (3.4)

$$S(h) \sim hE = h\ diag(a_{01}, a_{02}, \ldots, a_{0n}) \ . \tag{4.7}$$

Notice that $\overline{P}(h)$ is a probability matrix but $P(h)$ is not $(h > 0)$. However, the elements of $P(h)$ are elements of a probability matrix and have the properties.

$$p_{ij} \geq 0, \quad \sum_{j=1}^{n} p_{ij} \leq 1 \ . \tag{4.8}$$

Matrices having properties (4.8) will be called *PP (partial probability) matrices.*

Remarks 4.1. All the above results remain true when "probability" is replaced by "*PP*" and "closed compartmental" is replaced by "compartmental". That is, *PP* matrices correspond to compartmental matrices in the same fashion as probability matrices correspond to closed compartmental matrices.

The representation (4.4) is handy for applying some well known concepts from Markov chain theory [3].

A Markov chain is *absorbing* if it has one or more absorbing states and it is possible to reach an absorbing state from every state. In a corresponding fashion we define the differential process (1.1) to be *excretory* if there is at least one excretion and it is possible to reach an excreting compartment from every compartment (i.e. there are no traps). We will say that a probability (resp. compartmental matrix is absorbing (resp. excretory) if it is the transfer matrix (resp. matrix of fractional transfer coefficients) for an absorbing (resp. excretory) process.

Lemma 4.1. Let $h > 0$. Then $\overline{P}(h)$ is absorbing if and only if the corresponding compartmental matrix A is excretory.

Proof: The result follows from comparing the graphs of $\overline{A}$ and $\overline{P}(h)$. It is not difficult to show that a compartment i is reachable from compartment j if and only if the probability $\overline{p}_{ij}(h)$ of reaching i from j, in time h, is positive.

Lemma 4.2. Let $\overline{P}(h)$ be absorbing. Then

$$M(h) = (I - P(h))^{-1} \tag{4.9}$$

exists and is equal to the series $\sum_{n=0}^{\infty} P(nh)$.

Proof: The result is immediate from [8] (p. 106) and the fact that $P(nh) = P(h)^n$.

Lemma 4.3. The matrix M, given in (4.9), exists if and only if A^{-1} exists.

Proof: This follows directly from the spectral mapping Theorem (see [6], p. 227).

Lemma 4.4. Suppose A is excretory. Then A^{-1} exists.

Proof: We argue by the contrapositive. Suppose compartment k is not reachable to any excretory compartment. Let C be the set of all compartments reached from compartment k. Consider the solution $X(t)$ of the differential system (1.1) where the initial input $X(0)$ is given by $x_k(0) = 1$, $x_i(0) = 0$ if $i \neq k$. Let $s(t) = \sum_{i \in C} x_i(t)$. Then, since there is no excretion from the set of compartments C, $s(t) \equiv 1$, $t \geq 0$. On the other hand, we know from the theory of differential equations that $s(t)$ may be expressed as a sum of linearly independent modes $s(t) = \sum_{i=1}^{m} a_i f_i(t)$ where the amplitudes $a_i \neq 0$ $(i = 1,2,\ldots,n)$ and $f_i(t) = t^{n_i} \exp(\lambda_i t)$ for some non-negative integer n_i and some eigenvalue λ_i of A. But $\sum_{i=1}^{m} a_i f_i(t) - 1 \equiv 0$ implies that the set of functions

$(1, f_1(t), \ldots, f_n(t))$ are linearly dependent, which necessitates that 0 is among the eigenvalues λ_i. We conclude that A is singular.

Theorem 4.1. Let $h > 0$ be fixed. The following conditions are equivalent

(i) A is excretory.

(ii) $\overline{P}(h)$ is absorbing.

(iii) $M(h)$ exists

(iv) A^{-1} exists.

Proof: The proof results from Lemma's 4.1-4.4.

Remark 4.2. The results in Theorem 4.1 are not all new. Dr. John Jacquez conjectured that "a linear compartmental system has a trap if and only if zero is an eigenvalue of the associated compartmental matrix". This result, later proved by Fife [9], is equivalent to our "excretory if and only if invertible" result and, in particular, it contains Lemma 4.3, which is also proved in [10]. However, we have included an additional proof of Lemma 4.3 since it offers a somewhat different slant. For further results regarding traps see [11].

The matrix $M(h)$ is known as the *fundamental matrix* (corresponding to $\overline{P}(h)$). The elements $m_{ij}(h)$ of $M(h)$ may be interpreted as the mean number of iterations the Markov process is in compartment i, having started initially from compartment j, before the process enters an absorbing state (is excreted). The approximation (3.4) yields

$$M(h) \sim - h^{-1}A^{-1} \tag{4.10}$$

The matrices A, $P(h)$ and $M(h)$ are all functions of one another so that the knowledge of any one determines (with h known) the other two (even without the approximation (3.4)). An example will be presented in Section 5.

Another set of useful parameters is furnished by the matrix

$$G(h) = S(h)M(h) = -EA^{-1} .$$

The elements $g_{ij}(h)$ give us the probability that, starting in a transient compartment j, the Markov process will be excreted to compartment $n+i$, when it finally is excreted.

Remark 4.3. Notice that the approximation (4.10) implies that $-A^{-1}$ is nonnegative. This fact is directly deductible from the properties (1.2), however it is interesting to see it as a consequence of stochastic theory. The same observation applies to $exp(hA)$ $(h \geq 0)$ which, as a PP matrix, is also nonnegative.

Let $p_{ij}(t)$ denote the elements of $P(t)$. Then, in an infinitesimal interval $[t, t+\delta t)$, the mean time the process is in compartment i, having started in compartment j, before entering an absorbing compartment, is $p_{ij}(t)\delta t$. The total mean time the process stays in compartment i, having started in compartment j, before entering an absorbing compartment, is the $(i,j)^{\text{th}}$ element of

$$T \equiv \int_0^\infty P(t)dt = -A^{-1} . \tag{4.11}$$

The above integration may be obtained using the function-of-a-matrix representation (see [5], p. 606 or [6], p. 225).

$$\int_0^\infty P(t)dt = \int_0^\infty exp(tA)dt = \int_0^\infty \left[\frac{1}{2\pi i}\oint_C exp(\lambda t)(\lambda I - A)^{-1}d\lambda\right]dt =$$

$$\frac{1}{2\pi i}\oint_C \left[\int_0^\infty exp(\lambda t)dt\right](\lambda I - A)^{-1}d\lambda = \frac{1}{2\pi i}\oint_C -\lambda^{-1}(\lambda I - A)^{-1}d\lambda$$

(we choose the contour C in the left half plane so that $e^{\lambda t} \to 0$ as $t \to \infty$) $= -A^{-1}$.

We summarize the above result.

Theorem 4.2. Let A be excretory (equivalent to A^{-1} exists). Then the (i,j) element of $-A^{-1}$ is the mean time (w.r. to $\overline{P}(t)$) the process is in compartment i, having started in compartment j, before being excreted.

Remark 4.4. Employing the Riemann sum, for small increments of constant width h, to approximate the integral in (4.11) we obtain (See Lemma 4.2)

$$T \sim \sum_{n=0}^{\infty} P(nh)h = hM(h) . \tag{4.12}$$

Notice that the approximation (4.12), along with (4.11), yields (4.10).

Remark 4.5. Hearon [12] defines a conditional probability density for times of exit from the system, conditioned on the total number of particles which, leave the system. Using this density, he defines

the mean residence time μ_1 for the system. For the special case that excretion is from one and only one compartment, say compartment k, then $\mu_1 = \int_0^\infty t x_k(t)dt / \int_0^\infty x_k(t)dt$. Specializing further to the case that only one compartment is loaded, say compartment s, Hearon shows that μ_1 is the s column sum of $-A^{-1}$. This result is consistent with Theorem 4.2, for having started in compartment s, the total mean residence time in the system is the sum of mean times in each compartment. If the system has more than one excretion, the above formula for μ_1 as the ratio of two moments may no longer be valid. However we may still conclude from Theorem 4.2 that

Corollary 4.1. Given that an excretory system is loaded in a single compartment s, the mean residence time is the s column sum in $-A^{-1}$.

5. A LIVER MODEL. As an illustrative example we consider the model of the biliary system discussed in [2] and [4]. Here we have two transient compartments: blood (1) and liver (2). Rose Bengal (a radioactive substance) is injected into the blood and it is eventually excreted into either the urine, from the blood, or into the feces, from the liver. The compartmental matrix for the two compartment model is

$$A = \begin{array}{c} \\ b \\ \ell \end{array} \begin{array}{c} \begin{array}{cc} b & \ell \end{array} \\ \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix} \end{array} \qquad (5.1)$$

where none of the elements a_{ij} are zero and the excretions

$a_{0i} = -a_{1i} - a_{2i}$ $(i = 1,2)$ are positive. Since A is excretory it is invertible. (see Theorem 4.1).

The closure of A is given by

$$\overline{A} = \begin{array}{c} \\ u \\ f \\ b \\ \ell \end{array} \begin{array}{c} \begin{array}{cccc} u & f & b & \ell \end{array} \\ \left[\begin{array}{cccc} 0 & 0 & a_{01} & 0 \\ 0 & 0 & 0 & a_{02} \\ \hline 0 & 0 & a_{11} & a_{12} \\ 0 & 0 & a_{21} & a_{22} \end{array}\right] \end{array} . \tag{5.2}$$

Let time be measured in hours and let $\underline{h = 1 \ hour}$. Then, according to Eq. (4.4),

$$\overline{P} = \begin{array}{c} \\ u \\ f \\ b \\ \ell \end{array} \begin{array}{c} \begin{array}{cccc} u & f & b & \ell \end{array} \\ \left[\begin{array}{cccc} 1 & 0 & s_{11} & s_{12} \\ 0 & 1 & s_{21} & s_{22} \\ 0 & 0 & p_{11} & p_{12} \\ 0 & 0 & p_{21} & p_{22} \end{array}\right] \end{array} . \tag{5.3}$$

For simplicity of notation we have dropped the dependence on h. Saffer et al [2] adopted the stochastic model (5.3). However they assumed that S is diagonal which may be justified in the light of the approximation (4.7) if h is small. Now $h = 1$ hour may be considered small compared to their 72 hour observation period. Thus perhaps they may be justified in their approximation

$$S \sim E = \begin{bmatrix} a_{01} & 0 \\ 0 & a_{02} \end{bmatrix} . \tag{5.4}$$

For one patient (D.W., diagnosed as neonatal hepatitis) they estimated the fundamental matrix

$$M = \begin{bmatrix} 10 & 8 \\ 77 & 81 \end{bmatrix} . \tag{5.5}$$

They interpret (see Remark 4.4) (5.5) to mean that the mean number of hours in the blood before eventually ending up in the urine or feces having initially started from the blood is 10 and having initially started from the liver is 8. Similarly, they interpret the mean number of hours in the liver before eventually ending up in the urine or feces, having initially started from the blood is 77 and having initially started from the liver is 81.

It is an interesting numerical exercise to determine the compartmental matrix A corresponding to the fundamental matrix (5.5). Notice that

$$A = g(M) \quad \text{where} \quad g(\lambda) = \ln(1 - \lambda^{-1}) . \tag{5.6}$$

Let λ_1 and λ_2 be the eigenvalues of M. Using the interpolation method (see [5], pp. 607-612):

$$A = \frac{g(\lambda_1)}{\lambda_1 - \lambda_2} [M - \lambda_2 I] + \frac{g(\lambda_2)}{\lambda_2 - \lambda_1} [M - \lambda_1 I] ,$$

we obtain

$$A = \begin{bmatrix} -0.558 & 0.055 \\ 0.534 & -0.066 \end{bmatrix} . \tag{5.7}$$

If we use the approximation (4.10) we estimate

$$A \sim \begin{bmatrix} -0.418 & 0.041 \\ 0.397 & -0.052 \end{bmatrix} \tag{5.8}$$

which approximates (5.7) by about 25%. As for the excretions, the estimated values of S in [2] are: $(s_{11},s_{22}) = (0.020,0.010)$. From the matrix (5.7) one determines $(a_{01},a_{02}) = (0.024,0.011)$. The approximation (5.4), in this case, $(0.020,0.010) \sim (0.024,0.011)$ is accurate to within 17% (assuming that M given in Eq. (5.5) is correct).

The above calculations are meant as merely an illustration of how to compute one set of parameters from another and as a gauge of the approximation (3.4).

6. STOCHASTIC INTERPRETATION OF THE IMPULSE RESPONSE FUNCTION. We now consider the case of q $(q \geq 1)$ inputs, $u_1(t),u_2(t),\ldots,u_q(t)$, which occur over an interval of time. Suppose that the rate of flow into compartment i is given by $\sum_{j=1}^{q} b_{ij}u_j(t)$ where b_{ij} are positive constants. We also consider p $(p \geq 1)$ observations from the n compartments $y_i(t) = \sum_{j=1}^{n} c_{ij}x_j(t)$. The governing state equations then take the form (e.g., see [13]):

$$\dot{X}(t) = AX(t) + BU(t) \quad (t > 0), \quad X(0) = 0, \tag{6.1}$$

$$Y(t) = CX(t) \quad (t \geq 0) \tag{6.2}$$

where A is the $n \times n$ matrix of fractional transfer coefficients,

B is the $n \times q$ matrix of input constants b_{ij}, C is the $p \times n$ matrix of output constants c_{ij}, $X(t)$ is the state vector of compartmental states $x_i(t)$, $U(t)$ is the vector of inputs $u_i(t)$ and $Y(t)$ is the vector of observations $y_i(t)$. In systems theory [5], $Y(t)$ is referred to as the output vector.

Notice that we may integrate in Eq. (6.1) to obtain

$$X(t) = \int_0^t exp((t-s)A)B\ U(s)ds\ . \tag{6.3}$$

Suppose we set

$$U(s) = \delta(s)U_0, \quad X_0 = BU_0\ . \tag{6.4}$$

where $\delta(s)$ denotes the Dirac delta function and U_0 is a constant vector. Then, under conditions (6.4), $X(t)$ reduces to the solution (3.2) which corresponds to the "bolus input hypothesis". Thus the model (6.1)-(6.2) is more complete than the model (1.1) in that it allows for inputs over continuous time and exhibits the input/output pathways.

As an illustrative example we consider the injection $u_1(t) = \delta(t)$ (bolus input hypothesis) of Rose Bengal into the blood as discussed in Section 5. As outputs we have: y_1 (blood), y_2 (urine) and y_3 (feces). If we adopt the 2 compartmental model (5.1) we take

$$CAB = \begin{pmatrix} 1 & 0 \\ a_{01} & 0 \\ 0 & a_{02} \end{pmatrix} \begin{pmatrix} a_{11} & a_{12} \\ a_{21} & a_{22} \end{pmatrix} \begin{pmatrix} 1 \\ 0 \end{pmatrix}\ . \tag{6.5}$$

On the other hand, if we adopt the closed four compartmental model (5.2), we obtain

$$\bar{C}\bar{A}\bar{B} = \begin{pmatrix} 0 & 0 & 1 & 0 \\ 1 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 \end{pmatrix} \begin{pmatrix} 0 & 0 & a_{01} & 0 \\ 0 & 0 & 0 & a_{02} \\ 0 & 0 & a_{11} & a_{12} \\ 0 & 0 & a_{21} & a_{22} \end{pmatrix} \begin{pmatrix} 1 \\ 0 \\ 0 \\ 0 \end{pmatrix}. \quad (6.6)$$

Notice that certain parameters may appear either in the compartmental matrix or the output matrix, depending on how the problem is modeled.

Returning to the general case, suppose we multiply in Eq. (6.3) by C to obtain

$$Y(t) = \int_0^t \Phi(t - s)U(s)ds, \quad (6.7)$$

where the matrix,

$$\Phi(t) = C \exp(tA)B, \quad (6.8)$$

is the so-called impulse response function. Although there may be several ways to model the process, the impulse response function, which determines the input/output transfer, is independent of the particular compartmental model. In particular, for the liver problem, we have

$$\Phi(t) = C \exp(tA)B = \bar{C} \exp(t\bar{A})\bar{B} . \quad (6.9)$$

In the language of systems theory, the triplets (A,B,C) and

$(\overline{A},\overline{B},\overline{C})$ are said to be *realizations* of the impulse response function $\Phi(t)$.

Systems identification theory deals with the question of whether or not sufficient input-output information is available in order to determine the fractional transfer coefficients. One of the underlying principles which has been clearly pointed out by Bellman [14], is that all identifiable parameters must be identified through the impulse response function. For example, suppose in the liver model (for a particular patient) data is available only in the blood compartment. In this case $\Phi(t) = (1,0)exp(tA)\begin{pmatrix} 1 \\ 0 \end{pmatrix}$. It may be shown [15] that $\Phi(t) = \alpha_1 exp(\lambda_1 t) + \alpha_2 exp(\lambda_2 t)$ where (λ_1,λ_2) are eigenvalues of A and (α_1,α_2) are corresponding amplitudes. These decay parameters may be estimated from the data. Now $a_{11} = \Phi(0) = \alpha_1\lambda_1 + \alpha_2\lambda_2$ is identifiable. Also, from the trace $a_{11} + a_{22} = -\lambda_1 - \lambda_2$, we identify $a_{22} = -\lambda_1 - \lambda_2 - a_{11}$. From the determinant equation $a_{11}a_{22} - a_{12}a_{21} = \lambda_1\lambda_1$ we may also identify the product $a_{12}a_{21}$. However, it can be shown from results in [15], that neither a_{12} nor a_{21} is identifiable from blood samples alone but they are identifiable if we include either urine or feces samples.

Since the impulse response function plays an important role in the identification problem we would like to obtain a stochastic interpretation. For this purpose we employ the realization $(\overline{A},\overline{B},\overline{C})$ corresponding to the closed compartmental model. We recall from Theorem 2.1 that $\overline{P}(t) = exp(t\overline{A})$ is a probability matrix. Thus if $\overline{B}$ and $\overline{C}$ are also probability matrices, as in the case of (6.6), then $\Phi(t)$ is a probability matrix. *The elements* $\phi_{ij}(t)$ *may be inter-*

preted as the probability of reaching output i *from input* j *in time* t. The assumption that $\overline{B}$ is a probability matrix is not unreasonable and, in fact, is assumed in the work of Cobelli and Romanin-Jacur [13]. However, the output matrix is often not a probability matrix but it is a nonnegative matrix. Thus by appropriate normalization (e.g., dividing by the largest column sum) we may regard $\overline{C}$ as a *PP* matrix. It then follows (see Remark 4.1) that $\Phi(t)$ is a *PP* matrix and so we may still interpret the elements $\phi_{ij}(t)$ as stated above.

7. CONTINUOUS TO DISCRETE MODELS. We consider again the model (6.1)-(6.2). Let $h > 0$ be a fixed time increment and suppose the input

$$U(t) = U_n, \quad nh \leq t \leq (n + s)h, \tag{7.1}$$

where U_n is a constant, $n = 0,1,\ldots$. We set

$$X_n = X(nh), \quad Y_n = Y(nh), \quad n = 0,1,\ldots . \tag{7.2}$$

Then, from Eq. (6.3) we obtain $X_{n+1} = \int_0^{(n+1)h} \exp[((n + 1)h - s)A]BU(s)ds$

$$= \int_0^{nh} \exp[((n + 1)h - s)A]BU(s)ds + \int_{nh}^{(n+1)h} \exp[((n + 1)h - s)A]BU_n ds$$

$$= P(h)X_n + F(h)U_n,$$

$$F(h) = \left[\sum_{n=0}^{\infty} h^{n+1}A^n/(n + 1)!\right]B . \tag{7.3}$$

The series which occurs in Eq. (7.3) is the same series which occurs in Eq. (4.5). Recalling the observation made in Section 4, we have:

$$F(h) \sim hB \quad (h \sim 0), \tag{7.4}$$

$$F(h) = A^{-1}(P(h) - I)B \quad (A^{-1} \text{ exists}). \tag{7.5}$$

We see that under assumption (7.1), the model (6.1)-(6.2) may be expressed in discrete form:

$$X_{n+1} = P(h)X_n + F(h)U_n \quad (n=0,1,\ldots), \; X_0 = 0, \tag{7.6}$$

$$Y_n = CX_n \quad (n = 0,1,\ldots). \tag{7.7}$$

The discrete system (7.6)-(7.7) is in the standard systems-theory form. As in the continuous case, the equations may be combined:

$$Y_{n+1} = \sum_{i=1}^{n} \psi_{n-i}U_i \,, \quad (n = 0,1,\ldots), \tag{7.8}$$

where the discrete impulse response,

$$\psi_n = CP^n(h)F(h) = CP(nh)F(h) \quad (n = 0,1,\ldots). \tag{7.9}$$

Notice that for small h (see (7.4))

$$\psi_n \sim h\Phi(nh). \tag{7.10}$$

Stochastic interpretations for the matrices appearing in Eqs. (7.4) through (7.10) may be obtained by appealing to the results in Sections 2,3,4 and 6.

8. CONCLUSIONS. We have pointed out relationships between the differential equations and the stochastic approaches for modeling a

compartmental system. Moreover, we have touched on relationships between open and closed models and between continuous and discrete models. We see therefore that there lies a multitude of wars for modeling a physical system all of which are at our disposal. One of the advantages gained from the relationships between the differential equations and the stochastic models is that either one may be used for system identification purposes and either set of parameters may be computed from the other. Another advantage is gained in the stochastic interpretation of the physical process in terms of fractional transfer coefficients.

REMARK 8.1. Dr. John A. Jacquez has suggested defining the closure of A by collecting all excretions into a single compartment. Then the closure of A has only one more column and one more row than A. This would simplify the development in Section 4 and make its application to particular problems a little easier. On the other hand, when we want to keep track of the separate excretions, as in the liver model, the definition of closure given in Section 4 seems more appropriate.

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