ON MEAN RESIDENCE TIMES IN COMPARTMENTS

by

J. Eisenfeld[1]

Technical Report No. #106

May, 1979

[1]Department of Mathematics
University of Texas at Arlington and
Arlington, Texas 76019

Department of Medical Computer Science
University of Texas Health Science Center
at Dallas
Dallas, Texas 75235

ON MEAN RESIDENCE TIMES IN COMPARTMENTS

by

J. Eisenfeld[1]

ABSTRACT

This paper is concerned with a set of parameters which measure the mean time a random particle resides in individual compartments in response to a given load distribution. These parameters are related to other time parameters and to each other.

[1]Department of Mathematics
University of Texas at Arlington and
Arlington, Texas 76019

Department of Medical Computer Science
University of Texas Health Science Center at Dallas
Dallas, Texas 75235

ON MEAN RESIDENCE TIMES IN COMPARTMENTS

1. Introduction

Let A be the matrix of fractional transfer coefficients associated with a compartmental system. It was observed in [1] that the elements of $-A^{-1}$ (assuming A is invertible), denoted by τ_{ij}, admit to the following interpretation: τ_{ij} is the mean time in compartment i have loaded the system in compartment j. This interpretation appears to be very useful in providing further insight into the analysis of compartmental systems and deserves a more extensive discussion than that given in [1]. In this paper we extend the definition of mean times (in compartments) to systems for which the associated compartmental matrix is not necessary invertible and the extended definition includes arbitrary loading.

We also relate the compartment mean times with other time parameters. For example Hearon [2] defined the mean residence time (for the entire system). It is natural to ask if the sum of the mean times in each compartment coincides with Hearon's mean residence time. As this is indeed true, i.e., the definitions are consistant, and it seems natural to use the phrase, "compartmental mean residence time", CMRT to describe the portion of mean residence time spent in individual compartments. Other time parameters which are used for comparison are the mean first exit times and the relaxation times (or "half-lives"). We avoid the term "turn-over time" since this phrase has led to some confusion ([3]-[5]).

The second part of the paper deals with relationships between CMRT parameters, especially in finding conditions under which they have identical values. In particular our discussion helps to explain why different elements in the inverses of compartmental matrices are sometimes equal to each other, e.g. [6], p. 502.

We conclude with some suggestions for further studies.

2. Preliminaries

We have occasion to use both column vectors and row vectors; the latter will be distinguished from the former by the use of the transpose symbol "*". Following Hearon ([2],[7]) we reserve u to denote a column vector of ones, $u^* = [1,1,\ldots,1]$. The symbol 1_j denotes a vector with zero components except for one in the j position, i.e., $1_j^* = [0,0,\ldots,1,0,\ldots,0]$.

The initial vector or the load in compartmental systems is a vector x^o having nonnegative components. The load distribution vector is defined by $d = x^o/u^*x^o$. Since mean residence times depend only on the load distribution it is convenient to normalize so that $x^o = d$, i.e., we may assume that loss of generality that

$$u^*x^o = \sum_i x_i^o = 1 \quad . \tag{2.1}$$

We begin with a brief summary of compartmental systems which are discussed extensively in [8]. Time-invariant systems are modeled by systems of differential equations of the form

$$\dot{x} = Ax\,,\ x(0) = x^o \quad . \tag{2.2}$$

The compartmental matrix A consists of elements a_{ij} called the fractional transfer coefficients, i.e., $a_{ij}x_j$ $(i \neq j)$ is the inflow of tagged particles from j to i. The total outflow from j into other compartments and the systems environment is $-a_{jj}x_j$. The off-diagonal parameters a_{ij} are nonnegative since they correspond to inflows while the diagonal parameters a_{jj} are nonpositive since they measure outflows. Equation (2.2) is the statement of the fact that the rate of change of particles in each compartment is the difference between the inflows and the outflows.

The rate of excretion from compartment j into the systems environment is $a_{0j}x_j$ where

$$a_{0j} = -\sum_{i \neq 0} a_{ij} = |a_{jj}| - \sum_{i \neq j,0} a_{ij} \quad . \tag{2.3}$$

The nonnegative parameters a_{0j} are called the excretion coefficients. A compartment j is said to be excretory (or an exit) if $a_{0j} > 0$.

It is customary to describe compartmental systems in terms of their associated weighted digraphs (directed graphs) as in Fig. 1. The segment in the digraph which joins compartment j to compartment i and is directed from j to i corresponds to the fractional transfer coefficient a_{ij} $(i \neq j)$. In the case of open systems, i.e. systems having excretory compartments, an excretion a_{0j} is described by an arrow pointing away from excretory compartment j. Systems which are not open are said to be closed or traps. The outflow coefficients a_{ii} are not usually represented in the digraph since they are not positive quantities and are determined by Eq. (2.3). A sequence in a digraph is a set of directed line segments connecting a compartment j to a compartment i with all segments oriented in the direction from j to i. A path is a sequence which intersects each compartment along its route only once. Compartment j is said to reach compartment i if there is a path from j to i.

A compartmental system is said to strongly connected if each compartment reaches every other compartment in the system. In the event that the system is not strongly connected then its compartmental matrix is reducible, i.e. the compartments may be numbered in such a fashion so that A may be partitioned

$$A = \begin{bmatrix} E & O \\ G & H \end{bmatrix} \tag{2.4}$$

where O denotes a matrix of zeros. E and H are also compartmental matrices; they correspond to compartmental subsystems. Representations of the form (2.4) are not difficult to identify with the aid of the digraph. For example in Fig. 1, compartments $5,6,7$ do not reach compartment $1,2,3,4$. Thus $\{1,2,3,4\}$ and $\{5,6,7\}$ determine subsystems with associated compartmental matrices E and H respectively. The decomposition is not unique for we could also have, e.g., $\{1\}$ and $\{2,3,4,5,6,7\}$. If S is a subsystem of S_1 and S_2 is a subsystem of S_1 then S_2 is considered to be a subsystem of S. For example Fig. 1 has 24 (proper) subsystems two of which are given in Fig. 2. Notice that a segment from compartment j to compartment i becomes an excretion in regard to subsystem which contains j but not i and all excretions from the same compartment are lumped together. For example if E corresponds to the subsystem of Fig. 1 which contains only compartment 1 then $E = (a_{11})$ Recall that $a_{11} = -(a_{21} + a_{51})$. Thus in constructing Fig. 2(a) we join the segments associated with a_{21} and a_{51} to form the excretion coefficient $a_{21} + a_{51}$.

Mean residence times are closely related to the matrix

$$T = -A^{-1} \tag{2.5}$$

if the compartmental matrix A is invertible. Thus it is convenient to recall some well-known properties of inverses of compartmental matrices ([1],[2],[6],[9]).

Theorem 1. (i) The inverse of a compartmental matrix A exists if and only if there are no traps (closed subsystems), i.e., A^{-1} exists if and only if every compartment reaches at least one excretory compartment. Equivalently, (ii) the inverse of A exists if and only if for arbitrary loading x^{o}, the entire load is eventually excreted, i.e. $x(\infty) = 0$ or, in other words, the total washout

$$\sum_j \int_0^\infty a_{0j} x_j(t)dt = 1 \quad (= \sum_i x_i^o) \quad . \tag{2.6}$$

(iii) If A^{-1} exists then

$$T = \int_0^\infty P(t)dt \geq 0 \quad \text{(each element} \geq 0) \tag{2.7}$$

where

$$P(t) = e^{tA} \geq 0 \tag{2.8}$$

(iv) If A^{-1} exists then

$$T = \lim_{h \to 0} [I - P(h)]^{-1} \tag{2.9}$$

where I is the identity matrix.

In view of Theorem 1 (i) it is not difficult to see from the digraph which compartmental (subcompartmental) systems have invertible compartmental matrices. For example the compartmental matrix of Fig. 1 is not invertible because compartment 7 is a trap. However its subsystems which do contain compartment 7 have invertible associated compartmental martices.

3. Compartmental Mean Residence Time

To review the definition of CMRT given in [1] we assume for the moment that the compartmental matrix A is invertible. The CMRT τ_{ij}, i.e., the mean time in compartment i resulting from a load in compartment j (and only in j) is the (i,j) element of $T = -A^{-1}$. To obtain this interpretation of the elements of T, the element $p_{ij}(t)$ of (2.8) is regarded as the probability of the event that a particle exists in compartment i at the time t conditioned on its having started in compartment j. Such an interpretation is not uncommon, e.g., see [6],[10], [11]. If we "close the system" by adding one or more compartments to represent the systems environment and if we fix a small time interval h, then the process is approximated by an absorbing discrete Markov chain where $P(h)$ represents the transition probability matrix from nonabsorbing states to nonabsorbing states. The fundamental matrix for the discrete process is then $M(h) = [I - P(h)]^{-1}$; its elements $m_{ij}(h)$ give the mean number of visits to compartment i having started in compartment j. Since each visits occupies h units of time the mean time in i, having started in j, is $hm_{ij}(h)$. Letting h tend to zero we obtain the mean residence time as

$$\tau_{ij} = \lim_{h \to 0} hm_{ij}(h) \quad . \tag{3.1}$$

In view of Theorem (4.1) ((iii) and (iv)) τ_{ij} is also given by

$$\tau_{ij} = \int_0^\infty p_{ij}(t)dt = (T)_{ij} \tag{3.2}$$

and it gives the CMRT in i , conditioned on the load occuring only in compartment j .

We now consider an arbitrary load distribution x^o . The component x_j^o may be regarded as the probability that a random particles exists in compartment i at $t = 0$. In view of the above discussion, the CMRT in i conditioned on the load probability distribution x^o should be defined as

$$\tau_i(x^o) = \lim_{h \to 0} \sum_j hm_{ij}(h)x_j^o \tag{3.3}$$

which in view of Theorem 1 is also given by

$$\tau_i(x^o) = \sum_j \left(\int_0^\infty p_{ij}(t)dt\right)x_j^o = \sum_j \tau_{ij}x_j^o \quad . \tag{3.4}$$

We now remove the invertibility restriction. If A^{-1} does not exist then some CMRT parameters (3.4) will be infinite or undefined, however others may be defined. For example in Fig. 1, $\tau_i(x^o)$ is defined for all i (and for all x^o) except when $i = 7$. This is a consequence of the fact that all flows to a compartment i , $(i \neq 7)$ avoid the trap, compartment 7 . Even if $x_7^o > 0$ it contributes nothing to $\tau_i(x^o)$ since 7 does not reach i $(i \neq 7)$. It is not difficult to see, in general, that if a compartment j does not reach a compartment i then $p_{ij}(t) = 0$ for all t and $\tau_{ij} = 0$.

The CMRT parameters may be described in terms of subsystems. We define $S_i(x^o)$ as the smallest subsystem which contains all sequences from compartments j having $x_j^o > 0$ to compartment i . The corresponding subdigraph is denoted $D_i(x^o)$. For example if in Fig. 7 $x_1^o = 0$ but $x_2^o > 0$ then $D_4(x^o)$ is Fig. 2(b). The associated subcompartmental matrix is $A_i(x^o)$. In the event that $A_i(x^o)$ is invertible we define

$$T_i(x^o) = -A_i^{-1}(x^o) \quad . \tag{3.5}$$

It is clear from Theorem 1 (i) that $T_i(x^o)$ exists if and only if $S_i(x^o)$ does not contain traps. Moreover the CMRT parameter <u>$\tau_i(x^o)$ is defined if and only if $S_i(x^o)$ is free of traps</u>. For example if in Fig. 1 $x_1^o = 0$ and $x_2^o > 0$ then $\tau_4(x^o)$ is defined. Its value is

$$\tau_4(x^o) = \tau_{42}x_2^o + \tau_{43}x_3^o + \tau_{44}x_4^o \tag{3.6}$$

where

$$\tau_{42} = \tau_{43} = \tau_{44} = (a_{04} + a_{54})^{-1} \quad . \tag{3.7}$$

The τ_{ij}'s in (3.7) are the elements in the third row of $T_i(x^o)$. Later we explain why these elements are equal and we discuss relationships of this type.

In view of the fact that the CMRT parameter $\tau_i(x^o)$ depends only on the flows from loaded compartments to i, i.e. on the subsystem $S_i(x^o)$, it is permissible to replace the system by $S_i(x^o)$ when regarding this parameter. In other words we may assume, whenever convenient and without loss of generality, that the compartmental matrix is invertible in discussing a CMRT $\tau_i(x^o) < \infty$.

4. Comparison With Hearon's (System) Mean Residence Time

In defining mean residence time for a compartmental system, Hearon [2] made use of the function

$$\phi(t) = \sum_j a_{0j} x_j(t) \tag{4.1}$$

which is interpreted as the conditional probability density (recall from Theorem 1 (ii) that $\int_0^\infty \phi(t)dt = 1$) for times of exit from the system (see also [6],[10]). The mean residence time is then given by the first moment

$$\mu_1 = \sum_i \int_0^\infty t\phi(t)dt \tag{4.2}$$

In order to insure that the integral is finite for all load distributions Hearon required that the compartmental matrix A is invertible. This restriction is not essential since one can replace the system by the subsystem which is formed from the union of $S_i(x^o)$ where i runs over all compartments which are load reachable.

To express the parameter μ_1 in a form which is convenient for comparison we use the alternate formula

$$\phi(t) = -\sum_i \dot{x}_i \tag{4.3}$$

which results from the differential equations (2.2) and the conservation of mass equations (2.3). Insertion of (4.3) into (4.2) and integrating by parts (recall $x_i(\infty) = 0$) we have

$$\mu_1 = \sum_i \int_0^\infty x_i(t)dt \quad . \tag{4.4}$$

Solving the system of differential equations in the form $x(t) = \exp(tA)x^o = P(t)x^o$ we have

$$x_i(t) = \sum_j p_{ij}(t)x_j^o \quad . \tag{4.5}$$

Substituting (4.5) into (4.4), and taking account of (3.4), yields

$$\mu_1 = \sum_{ji} \tau_{ij}x_j^o = \sum_i \tau_i(x^o) \quad . \tag{4.6}$$

That is μ_1 is the sum of all CMRT's as anticipated.

5. First Exit Time

A particle existing in a compartment i at $t = 0$ may enter and exit compartment i several times. The duration of each visit is taken into account in the CMRT parameter τ_{ii}. That portion of mean residence time which occurs only up to the first exit from compartment i is given by ([12])

$$\gamma_i = 1/|a_{ii}| \tag{5.1}$$

where we recall that $|a_{ii}| = \sum_{k \neq i} a_{ki}$ represents the total out flow from compartment i. It seems natural to refer to γ_i as the mean first exit time from compartment i.

Suppose we consider the case of a compartment i which is not mutually reachable with any other compartment, e.g. compartment 2 in Fig. 1. In such cases the particle can exit only once and so it should turn out that

$$\gamma_i = \tau_{ii} \quad \text{(no return)} \quad . \tag{5.2}$$

To verify this we observe that "no return" compartments have the property that the subsystem $S_i(1_i)$, where 1_i is the unit vector defined in Section 2, consists of compartment i alone. The associated compartmental matrix $A_i(1_i)$ is the 1×1 matrix (a_{ii}) and $T_i(1_i) = -(1/a_{ii}) = |a_{ii}|^{-1}$. Thus the conclusion (5.2) results as an immediate consequence of expressing CMRT parameters in terms of subsystems.

6. Relaxation Times

An important case occurs when a component state i is expressed as an exponential sum of the form

$$x_i(t) = \sum_j \alpha_{ij} \exp(-t/\xi_j) \quad . \tag{6.1}$$

The positive quantities ξ_j are known as relaxation times (sometimes they are also referred to as half-lives in cases where no coupling exists between compartments). In view of the fact that $x_i(\infty) = 0$ the matrix $A_i(x^o)$ is invertible where x^o is the load. Thus $\tau_i(x^o)$ is defined and we will show that

$$\tau_i(x^o) = \sum_j \alpha_{ij} \xi_j \quad . \tag{6.2}$$

To see this we compare (4.5) with (3.4) and notice that $\tau_i(t) = \int_0^\infty x_i(t)dt$ and then we express $x_i(t)$ in terms of (6.1) to obtain the result, (6.2).

It is not difficult to show, using methods in [13] (pp. 607-612) that the coefficients α_{ij} are given by

$$\alpha_{ij} = 1_i^* Z_j x^o \tag{6.3}$$

where the component matrices (also called constituent matrices) Z_j are given by the Lagrange interpolating formula

$$Z_j = \sum_{k \neq j} (\lambda_k I - A) / \sum_{k \neq j} (\lambda_k - \lambda_j) \tag{6.4}$$

The λ_j are the eigenvalues of the compartmental matrix A ordered in such a fashion that $\xi_j = -\lambda_j^{-1}$ whenever $\lambda_j \neq 0$. Since software packages exist for estimating relaxation times and component matrices from observed data (e.g., [13]), formulas (6.1) and (6.3) offer a viable method for estimating the CMRT parameters which does not require prior estimates of the fractional transfer coefficients.

The relaxation times do not generally relate to individual compartments however in special cases it is possible to make an association. We consider in particular the two compartmental systems where the above formulas lead to the representations of the diagonal elements:

$$\tau_{11} = \alpha\xi_1 + (1-\alpha)\xi_2 \quad , \tag{6.5}$$

$$\tau_{22} = (1-\alpha)\xi_1 + \alpha\xi_2 \quad , \tag{6.6}$$

with α between zero and one. Thus the τ_{ii} are weighted averages of the ξ_i. If we number the compartments and the relaxation times so that

$$\tau_{11} < \tau_{22} \quad \text{and} \quad \xi_1 < \xi_2 \tag{6.7}$$

then we have the inequalities

$$\xi_1 < \tau_{11} < \tau_{22} < \xi_2 \quad . \tag{6.8}$$

Thus ξ_1 is a lower bound for the "fast" compartment and ξ_2 is an upper bound for the "slow" compartment.

Since the parameter α is of considerable importance (e.g., [15]) it seems worthwhile to list some equivalent formulas for representing it.

$$\begin{aligned}\alpha &= (\xi_2 - \tau_{11})/(\xi_2 - \xi_1) = (\tau_{22} - \xi_1)/(\xi_2 - \xi_1) \\ &= (a_{11} - \lambda_2)/(\lambda_1 - \lambda_2) = (\lambda_1 - a_{22})/(\lambda_1 - \lambda_2) \\ &= [\exp(-t/\xi_2) - p_{11}(t)]/[\exp(-t/\xi_2) - \exp(-t/\xi_1)] \\ &= [p_{22}(t) - \exp(-t/\xi_1)]/[\exp(-t/\xi_2) - \exp(-t/\xi_1)] \quad .\end{aligned}$$

These identities follow from the fact that functionally related matrices share identical components. Notice that the last two expressions involve t but the dependence on t cancels.

7. Inter CMRT Relationships

Having discussed how the CMRT relate to other time parameters we now consider how they relate to each other. The relationships we have in mind are illustrated in (3.7). We begin this discussion with an observation due to Anderson [16] in his study of SEC (Single-Exit Compartmental) systems.

An SEC system is defined to be a compartmental system having one and only one excretory compartment (called the exit) and (at least) one path from every compartment to the exit compartment. In particular the compartmental matrix is invertible. Anderson observed the following result.

Theorem 2 (Anderson). Let A be the compartmental matrix associated with an SEC system. Then if m is the exit compartment, the entries of row m in A^{-1} are identical and their common value is $-a_{0m}^{-1}$ where a_{0m} is the excretion coefficient form compartment m.

We note in passing that the converse of Theorem is also true, i.e. Theorem 3.

Theorem 3. Suppose A is a compartmental matrix having the property that $T = -A^{-1}$ has a constant row m, say $\tau_{mj} = \nu > 0$ for all j. Then A represents a SEC system where the excretion coefficient from the single-exit m is $a_{0m} = \nu^{-1}$. In particular T is allowed to have at most one constant row.

Proof: According to the hypothesis $\nu u^* = 1_m^* T$ where u and 1_m are defined in Section 2. Thus $u^*A = -\nu^{-1} 1_m^*$ which means, in view of (2.3), that

$$a_{0j} = 0\,, \quad j \neq m \quad \text{and} \quad a_{0m} = \nu^{-1} > 0 \quad . \tag{7.1}$$

That is m is the only exit compartment.

The proof of Theorem 3 is essentially the proof of Theorem 2 with the order of the steps reversed.

It follows immediately from Theorem 2 (and the normalization (2.1)) that the CMRT parameters given by (3.4), for the case of the single-exit, are independent of the load and their common value is

$$\tau_i(x^o) = a_{0m}^{-1} \quad \text{(single-exit, } m) \quad . \tag{7.2}$$

Such a conclusion might be anticipated from the fact that all particles must eventually enter m no matter where they start and there time in m is regulated by the excretion rate from m. The coincidence of the parameters in (3.7) occurs as a special case of (7.2).

As a second illustration we consider the unidirectional catenary system, given in Fig. 3, which appears e.g. in [6]. In this case all subsystems $S_i(x^o)$ are SEC systems. It follows immediately that T has the form

$$T = \begin{bmatrix} a_{21}^{-1} & 0 & 0 & \cdots & 0 \\ a_{32}^{-1} & a_{32}^{-1} & 0 & \cdots & 0 \\ \vdots & \vdots & \vdots & & \vdots \\ a_{0n}^{-1} & a_{0n}^{-1} & a_{0n}^{-1} & \cdots & a_{0n}^{-1} \end{bmatrix}$$

We now consider the following situation. Suppose we have three compartments of a compartmental system labeled j, m, p such that j reaches m, m reaches p and j must reach m. A case in point occurs in Fig. 1 taking $j = 2$, $m = 4$, $p = 6$. Although it seems intuitively clear, we show analytically that under these circumstances $\tau_{pj} = \tau_{pm}$. A more precise version of this statement is as follows.

Theorem 4. Let $S_m(1_j)$ be a SEC subsystem such that m reaches p where p is not in $S_m(1_j)$. Then $\tau_{pj} = \tau_{pm}$ (assuming they are defined).

Proof: Let $\tilde{A} = A_p(1_j)$ and $E = A_m(1_j)$ then E represents a SEC subsystem of $S_p(1_j)$. Thus $\tilde{A}$ may be expressed in the reducible form (with an appropriate numbering of compartments)

$$\tilde{A} = \begin{bmatrix} E & 0 \\ G & H \end{bmatrix}$$

and $\tilde{T} = \tilde{A}^{-1}$ is given by ([17] (p. 211))

$$\tilde{T} = \begin{bmatrix} -E^{-1} & 0 \\ T_{21} & -H^{-1} \end{bmatrix}, \quad T_{21} = H^{-1} G E^{-1} \quad . \tag{7.3}$$

Since $A_m(1_j)$ is SEC, its compartments can reach other compartments only by exiting from m. Thus G has the form

$$G = [0 : 0 : \ldots g]$$

where g is a column vector representing transfers from m to those compartments in $S_p(1_j)$ which are not in $S_m(1_j)$. It follows that GE^{-1} is independent of all rows of E^{-1} except the last row which, in view of the SEC property, has the form $-\nu u^*$ where $\nu > 0$. Thus GE^{-1} $= -\nu[g : g : \ldots : g]$ and consequently $T_{21} = -\nu[H^{-1}g : H^{-1}g : \ldots : H^{-1}g]$ has constant rows. Since both τ_{pj} and τ_{pm} are both members of one of these constant rows of T_{21} they necessarly coincide. This completes the proof.

Notice that the proof of Theorem 4 gives more information than that stated in the hypothesis however we prefer to keep they hypothesis simple so as not to obscure the main objective.

Theorem 4, applied several times to Fig. 1, yields $\tau_{52} = \tau_{53} = \tau_{54}$ and $\tau_{62} = \tau_{63} = \tau_{64}$.

We consider briefly DEC (Double-Exit Compartmental) Systems. Suppose r and m are the exit compartments and r reaches m but m does not reach r as in Fig. 1 where $r = 4$ and $m = 6$. Let $p(H,r)$ denote the probability that a particle in r reaches the subsystem represented by H. For the case under consideration, taking $H = A_m(1_m)$, we have [12] (p. 455)

$$p(H,r) = (|a_{rr}| - a_{0r})/|a_{rr}| \tag{7.4}$$

Notice that since H is SEC with exit m, $p(H,r)$ is also the probability that r reaches m. One might expect that

$$\tau_{mr} = \tau_{mm}p(H,r) = a_{0m}^{-1}p(H,r) \quad . \tag{7.5}$$

To verify (7.5) we stochastically interpret the matrix T_{21} occuring in (7.3). Now $Q = -GE^{-1}$ gives us the matrix of probabilities q_{kr} that a particle in compartment r of E (i.e. the subsystem represented by E) enters H through compartment k. Moreover $-H^{-1}$ is the matrix of CMRT parameters τ_{mk} 'from H to H'. Thus the elements of T are

$$\tau_{mr} = \sum_{k \in H} \tau_{mk}\, q_{kr} \quad . \qquad (m \in H,\, r \in E) \tag{7.6}$$

(notice that q_{kr} plays the role of x_k^o in (3.4)). Now in the case of (7.5) H represents a SEC system so that $\tau_{mk} = a_{0m}^{-1}$ for all k in H. In particular, $\tau_{mm} = a_{0m}^{-1}$ and (7.6) reduces to $\tau_{mr} = a_{0m}^{-1} \sum_{k \in H} q_{kr} = a_{0m}^{-1} p(H,r)$.

In Fig. 1 there are 3 DEC subsystems and we conclude from the above observations that $\tau_{64} = \tau_{66} a_{54} [a_{04} + a_{54}]^{-1} = [a_{06} + a_{76}]^{-1} a_{54} [a_{04} + a_{54}]^{-1}$, $\tau_{41} = \tau_{44} a_{21} [a_{21} + a_{51}]^{-1} = [a_{04} + a_{54}]^{-1} a_{21} [a_{21} + a_{61}]^{-1}$ and $\tau_{21} = \tau_{22} a_{21} [a_{21} + a_{51}]^{-1} = [a_{32} + a_{42}]^{-1} a_{21} [a_{21} + a_{51}]^{-1}$.

With the help of the stochastic interpretation it is not difficult to obtain further relationships like those stated above. It is hoped that such relationships will not only aid in constructing inverse matrices but they should be useful towards the analysis and identification of compartmental systems. Some related prospects for study are suggested below.

8. Suggestions for Further Studies

A. *Probability that j reaches i.* It should be evident from the discussion that $p(i,j) = \tau_{ij}/\tau_{ii}$ is the probability that j reaches i. For example in the case of a SEC where j is the exit, $p(i,j) = 1$ and Theorem 2 results. In the case of the situation occuring in (7.5), $p(m,r)$ is given by (7.4). Using the interpretation of $p(i,j)$ one should be able to uncover formulas for parameters $p(i,j)$ which are simpler than that given by Cramer's rule or by graph theoretic formulas ([17],[18]).

B. *Stochastic interpretation of the transfer function.* If A is a compartmental matrix then so is $A(s) = A - sI$ for $s > 0$ and all compartments of $A(s)$ are exits. Clearly $T(s) = -A^{-1}(s)$ exists. However the transfer function is related to the CMRT parameters corresponding to $T(s)$ Thus the interpretation of $T(s)$ should reflect on the structural identification problem.

C. *Mean passage time.* Another set of parameters that should be useful is the mean time of passage to particular compartments i when the system is not loaded in i.

FIGURE LEGENDS

Fig. 1 - Example of a Compartmental System

Fig. 2 - Some Subsystems of Fig. 1
  a. Flows from *1* to *1*
  b. Flows from *2* to *4*

Fig. 3 - Unidirectional Catenary System

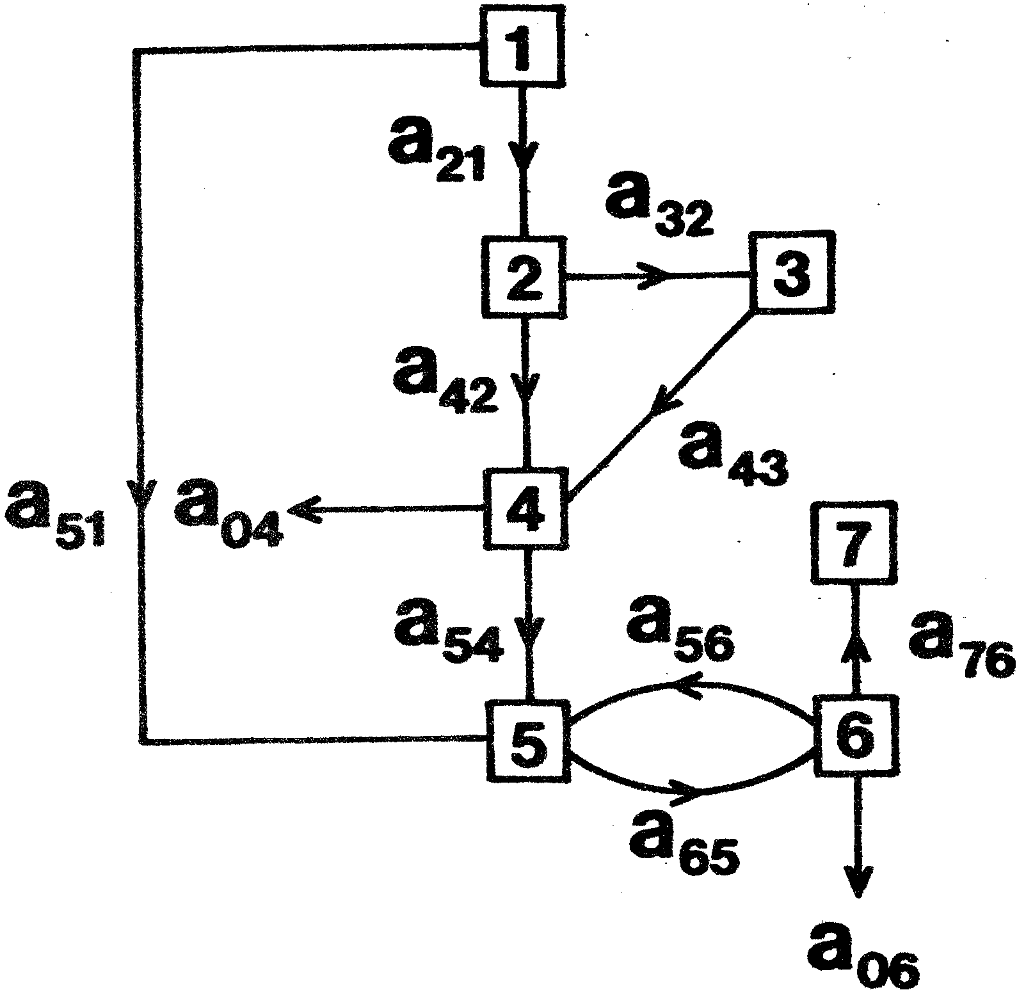

Figure 1

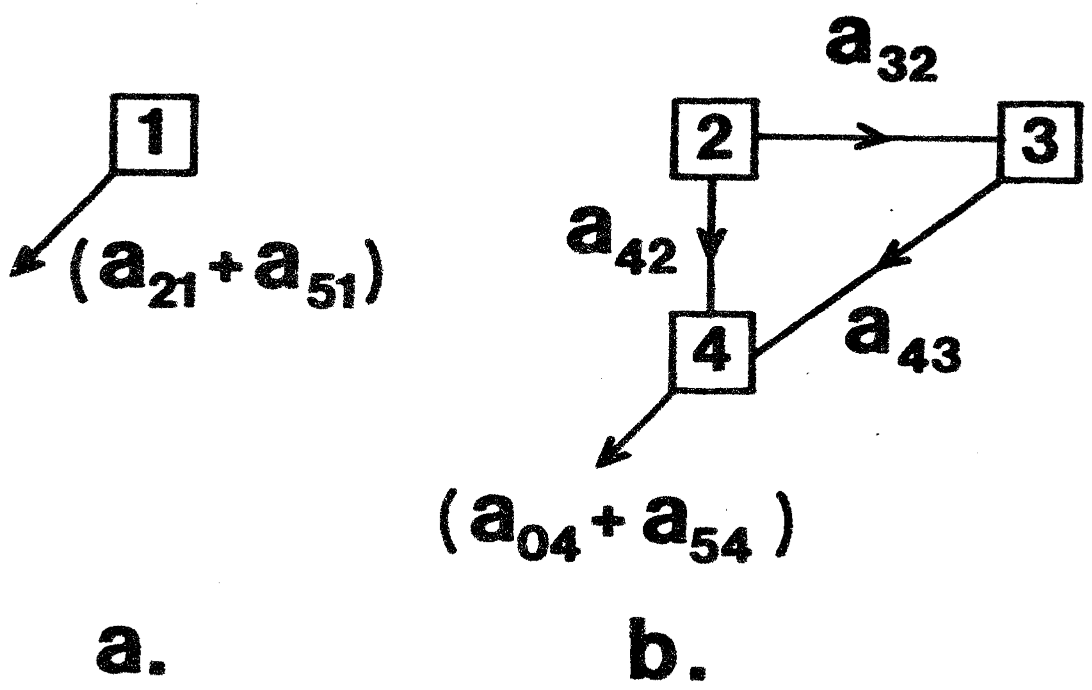

Figure 2

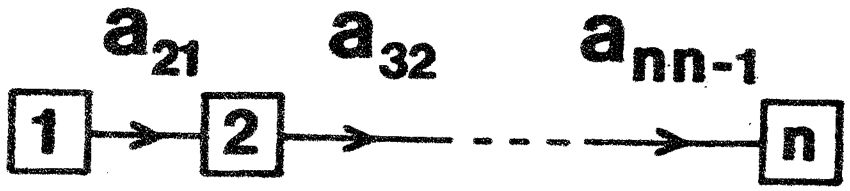

Figure 3

REFERENCES

[1] J. Eisenfeld, "Relationship between Stochastic and Differential Models of Compartmental Systems", *Math. Biosci.*, *43 :* 289-305 (1979).

[2] J. Z. Hearon, "Residence Times in Compartmental Systems and the Moments of a Certain Distribution", *Math. Biosci.*, *15 :* 69-77 (1972).

[3] G. L. Atkins, "Multicompartmental Models for Biological Systems", Methuen and Co., LTD, London, England, 1969.

[4] C. A. Mawson, "Meaning of 'Turnover' in Biochemistry", Nature, 176 : 317 (1955).

[5] M. Kleiber, "Meaning of 'Turnover' in Biochemistry", Nature, 175 : 342 (1955).

[6] C. W. Sheppard, "Stochastic Models for Tracer Experiments in the Circulation III. The Lumped Catenary System", *J. theor. Biol.*, *33 :* 491-515 (1971).

[7] J. Z. Hearon, "The Washout Curve in Tracer Kinetics", *Math. Biosci.*, *3 :* 31-39 (1968).

[8] J. A. Jacquez, "Compartmental Analyses in Biology and Medicine", Elsevier Publishing Co., Amsterdam, The Netherlands, (1972).

[9] D. Fife, "Which Linear Compartmental Systems Contain Traps?", *Math. Biosci.*, *14 :* 311-315 (1972).

[10] P. E. E. Bergner, "Tracer Dynamics : I. A Tentative Approach and Definition of Fundamental Concepts", *J. theor. Biol.*, *2 :* 120-140 (1961).

[11] S. I. Saffer, C. E. Mize, U. N. Bhat and S. A. Szygenda, "Use of Non-linear Programming and Stochastic Modeling in the Medical Evaluation of Normal-Abnormal Liver Function", *IEEE Trans. Biomed. Engineering*, *BME-23 :* 200-207 (1976).

[12] B. Singer and S. Spilerman, "Some Methodological Issues in the Analysis of Longitudinal Surveys", The Ann. Econom. Social Measurement 5 : 447-474 (1976).

[13] L. A. Zadeh and C. A. Desoer, "Linear Systems Theory : The State Space Approach", McGraw-Hill, New York, 1963.

[14] J. Estreicher, C. Revillard and J. Scherrer, "Compartmental Analysis-I : LINDE, A Program Using an Analytical Method of Integration with Constituent Matrices", *Comput. Biol. Med.*, *9 :* 49-65 (1979).

[15] P. Sejrsen, "Blood Flow in Cutaneous Tissue in Man Studied by Washout of Radioactive Xenon", Circulation Res. 25 : 215-229 (1969).

[16] D. H. Anderson, "The Volume Distribution in Single-Exit Compartmental Systems", in APPLIED NONLINEAR ANALYSIS, V. Lakshmikantham (ed.), Academic Press, New York, (1979) to appear.

[17] W. K. Chen, "Applied Graph Theory", North-Holland, New York, 1976 .

[18] A. Bossi, C. Cobelli, L. Colussi and G. Romanin Jacur, "A Method of Writing Symbolically the Transfer Matrix of a Compartmental Model", *Math. Biosci.*, *43* : 187-198 (1979).