ON IDENTIFIABILITY OF IMPULSE-RESPONSE IN
COMPARTMENTAL SYSTEMS

by

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GLOSSARY OF SYMBOLS

- T : transpose operation
 p : the number of outputs
 q : the number of inputs
 $u(t)$: the input vector
 $y(t)$: the output vector
 $x(t)$: the state vector
 $\phi(t)$: the impulse-response function
 $\hat{\phi}(s)$: the transfer function
 (A, B, C) : an arbitrary realization of the impulse-response function usually taken to be irreducible.
 (A_c, B_c, C_c) : a realization which corresponds to a compartmental model
 n : the number of compartments
 N : the McMillan degree
 s_k : integral transforms
 M_k : Markov parameters
 $w(t), W_k(t), h(t)$: method functions
 I_n : identity matrix of dimension n
 O : null matrix of arbitrary dimension
 H : an invertible matrix
 $(A_I, B_I, C_I), (A_Y, B_Y, C_Y)$: realizations
 U : controllability matrix
 V : observability matrix
 a_{ij}, a, b, c : fractional transfer (or excretion) coefficients
 $\Delta(\lambda)(\Delta(s))$: characteristic polynomial

a_k : coefficient in the characteristic polynomial

λ_k : arbitrary eigenvalue or a root of $\Delta(\lambda)$

λ_1 : specific eigenvalue, sometimes used to denote that only one eigenvalue is present

$\chi(\lambda)$: minimal polynomial

Z_{ki} : component matrix of A

R_{ki} : coefficient matrix in the minimal representation of $\phi(t)$

$\xi(\lambda)$: associated polynomial

J : minimal order of linear recursion relation

i, j, k, v : dummy indices

G : matrix appearing in s_k

$[0, T]$: interval containing data points

$\delta(t)$: Dirac delta function

$C_0^{(2N-1)}[0, T]$: space of method functions $w(t)$

$\tilde{\phi}(t)$: impulse-response function having s_k as its Markov parameters

W_k : Hankel matrix of $(M_0, M_1, \dots, M_k)$

Q : Hankel matrix of $(s_0, s_1, \dots, s_{2N-2})$

R : Hankel matrix of $(s_1, s_2, \dots, s_{2N-1})$

$(\tilde{A}, \tilde{B}, \tilde{C})$: irreducible realization constructed from the s_k

m_k : geometric multiplicity of λ_k

m : number of distinct eigenvalues

r_k : multiplicity of λ_k in the associated polynomial

r : number of distinct eigenvalues represented in the impulse-response function

$p_{ij}(s)/q_{ij}(s)$: elements of the transfer function represented as ratios of polynomials with no common factors

- $\tilde{U}$: controllability matrix for $(\tilde{A}, \tilde{B}, \tilde{C})$
- $\tilde{G}$: matrix appearing in s_k when $(\tilde{A}, \tilde{B}, \tilde{C})$ is used to represent s_k
- $f(\lambda)$: functional correspondence between A and G
- α_i : amplitudes occurring in the impulse-response function
- b, b_i : constants associated with a bolus input
- $v(t)$: a non-bolus input
- β_i : constants used in the construction of a method function
- $\rightarrow$: transfer
- $\rightarrow$: excretion
- $\rightarrow$: input
- $\rightarrow \bigcirc$: observation

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ABSTRACT

Structural identifiability in compartmental systems deals with the map from impulse-response parameters to model parameters. If the data is analyzed in terms of integral transforms s_k (Fourier, moments, etc) then we may study also the map from the s_k to impulse-response parameters. This paper is mainly concerned with the latter correspondence. In other words we discuss the possibility of removing (inadvertently or intentionally) decay terms in the process of forming integral transforms.

1. INTRODUCTION

The system identification problem (A_o, B_o, C_o, u, y) may be described as follows [1]. A_o is an $n \times n$ matrix representing the interactions of n compartments. The element a_{ij} is called the transfer coefficient from compartment j to compartment i . Some or all of the transfer coefficients are not known. In order to determine these parameters, an experiment is performed in which q inputs excite the compartments causing them to interact with each other. The q inputs are regarded as a column vector $u(t) = (u_1(t), u_2(t), \dots, u_q(t))^T$. (Here "T" means transpose). The paths by which the q inputs enter the n compartments is represented by a $n \times q$ matrix B_o . When the state (concentration, quantity, etc.), $x_i(t)$, of compartment i at time $t > 0$ is a response to the input $u(t)$ and only to $u(t)$, then $x(t) = (x_1(t), x_2(t), \dots, x_n(t))^T$ is determined by the system of differential equations

$$\dot{x}(t) = A_o x(t) + B_o u(t), t \geq 0, x(0) = 0. \quad (1.1)$$

It may not be possible to observe each individual state by itself, however there are observations $y(t) = (y_1(t), y_2(t), \dots, y_p(t))^T$ which are related to the states $x(t)$ through a system of linear equations

$$y(t) = C_o x(t), t > 0, \quad (1.2)$$

where C_o is a $p \times n$ matrix representing the paths from compartments to recording devices. The observations $y(t)$ are also called outputs.

Each input and each output may be sampled at discrete times. The sampling times may not be equally spaced and they may be different for each input or output. In any case we have a collection of data from which we wish to determine the unknown elements in A_o , and sometimes also the unknown elements in B_o and C_o . The process of determining the unknown parameters from the data is often referred to as parameter estimation. The most common procedures are based on the least squares principle. Such methods are capable of outputting numerical values independent of whether or not the problem actually has a solution. Instances in which the problem is not solvable are perhaps rare and physically uninteresting, nevertheless, the fact that such counterexamples do exist [3]-[4] presents a challenging mathematical problem.

The problem which we refer to as the identification problem, deals with the question of whether or not there is a set of formulas or algorithms, by which the unknown parameters may be uniquely determined from the data. This identification problem is separate from the estimation problem which takes into account such things as the distribution of noise in the data (random and nonrandom) and computer facilities (software and hardware). Certainly one would expect the investigations into the identification problem will lead to more effective estimation procedures.

Recent results on structural identifiability (e.g., [1]-[5]) have benefited from concepts in control theory, especially those developed by Kalman [6]. Bellman and Astrom [4] brought the identification into the control theory framework and showed the importance of impulse-response function (matrix)

$$\phi(t) = C_o e^{tA} C_o^T B_o . \quad (1.3)$$

Following [4] many authors have pursued the question of identifiability from the impulse-response function, or equivalently, from the transfer function

$$\hat{\phi}(s) = C_o [sI_n - A_o]^{-1} B_o \quad (1.4)$$

In the first part (Section 2) of this paper we discuss criteria for identifying the structural form and the McMillan degree of the impulse-response function. The section is needed in preparation for the latter part (Section 3).

The possibility of finding a unique solution to the problem depends not only on the structure of system but also on the operations which are performed on the data. We consider the case of a single-input/single-output system where we have the $y(t) = \int_0^t \phi(t-\tau)u(\tau)d\tau$. If we can take Laplace transforms then we can solve for $\hat{\phi}(s)$ in

$$\hat{y}(s) = \hat{\phi}(s)\hat{u}(s) . \quad (1.5)$$

If $y(t)$ and $u(t)$ are known analytically then the standard Laplace inversion formulas yield an analytic representation of $\phi(t)$. However in the real situation $y(t)$ and $u(t)$ are known only empirically and (1.5) does not provide an analytical representation of $\phi(t)$. Moreover the Laplace integrals, which require integration to infinite time, can not be formed. In such cases we may calculate a finite sequence of transforms [7]. Following Shinbrot [8], we view such transforms as integrals of the form

$$s_k = \int_0^t \phi(t) w_k(t) dt . \quad (1.6)$$

Depending on the choice of the method functions $w_k(t)$, the integrals (1.6) can be Fourier integrals, moments and etc. Not specifying the method functions exactly allows us to keep the discussion on a general plane, however we do specify the class of method functions. The main part of the paper (Section 3) deals with the question of constructability of the impulse-response function from transformed data, i.e., are any of the exponential terms in $\phi(t)$ lost or "filtered out" in the transform process? Sometimes appropriate filtering can be looked on as an advantage and hence necessary and sufficient for maintaining all exponential terms (or avoiding undesirable ones) are useful. Here again control theory concepts play an important role; they permit us to obtain formulas expressing an irreducible realization in terms of the integrals s_k .

2. STRUCTURE OF THE IMPULSE-RESPONSE FUNCTION

This section discusses methodology for analyzing the impulse-response function and develops concepts that are needed later.

A. Realizations. Suppose we know the impulse-response function a priori and wish to construct a compartmental model. For the sake of definiteness suppose $\phi(t) = \frac{1}{2}$. Then the model in Figure 1 whose compartmental matrices are

$$C, A, B = (\frac{1}{2}, \frac{1}{2}), \begin{bmatrix} -1 & 1 \\ 1 & -1 \end{bmatrix}, \begin{bmatrix} \frac{1}{2} \\ \frac{1}{2} \end{bmatrix} \quad (2.1)$$

has $\phi(t) = \frac{1}{2}$ as its impulse-response function i.e., it is a realization of $\phi(t) = \frac{1}{2}$. The realizations of an impulse-response function are not unique. In fact if (A, B, C) is one realization then any invertible matrix H , having the dimension of A , gives us another realization (A_1, B_1, C_1) , where

$$A_1 = H^{-1}AH, B_1 = H^{-1}B, C_1 = CH \quad (2.2)$$

For example suppose we take (A, B, C) as in (2.1) and

$$H = \begin{bmatrix} 1 & 1 \\ -1 & 1 \end{bmatrix}$$

then we obtain the realization

$$C_1, A_1, B_1 = (0, 1), \begin{bmatrix} -1 & 0 \\ 0 & 0 \end{bmatrix}, \begin{bmatrix} 0 \\ \frac{1}{2} \end{bmatrix} \quad (2.3)$$

which corresponds to the model in Fig. 2. Any two realizations which are related by a similarity transformation (i.e., a transformation of the form (2.2)) are said to be (algebraically) equivalent. Notice that Fig. 1 and Fig. 2 describe completely different processes but, from the systems theory point of view, they are equivalent because they have the same impulse-response function.

B. Irreducibility and the McMillan degree (N). The dimension of a realization (A, B, C) is the dimension of A , i.e., the number of compartments in a compartmental system. Realizations need not have the same dimension, e.g., for any number $\gamma \neq 0$, the 1×1 matrices

$$(A_\gamma, B_\gamma, C_\gamma) = ([0], [\gamma/2], [\gamma^{-1}]) \quad (2.4)$$

realize $\phi(t) = \frac{1}{2}$. Thus (2.1), (2.3), and the triplets (2.4) all realize the same impulse response function but (2.1) and (2.3) have dimension 2 while (2.4) have dimension 1.

The smallest dimension attained by realization is called the McMillan degree [9] of the impulse-response function. We always denote this integer by N . The realizations of order N are called irreducible. For example if $\phi(t) = \frac{1}{2}$ then $N = 1$ and the irreducible realizations are given in (2.4).

C. Controllability and observability. For time invariant system we

can define controllability and observability as follows ([6],[9],[10]). A realization of dimension n is said to be CC (completely controllable) if its controllability matrix $U = [B, AB, \dots, A^{n-1}B]$ is of full rank, i.e., if UU^T is invertible. The realization is said to be CO (completely observable) if its observability matrix $V = [C^T, C^T A^T, \dots, C^T (A^T)^{n-1}]^T$ has full rank, i.e., if $V^T V$ is invertible.

Kalman [6] showed that a realization is irreducible if and only if it is both CC and CO (see also [10]). Consider, e.g., the system in Figure 3. The model matrices are

$$C_c, A_c, B_c = (1, 1), \begin{bmatrix} -a & c \\ a & -b-c \end{bmatrix}, \begin{bmatrix} 1 \\ 0 \end{bmatrix}. \quad (2.5)$$

In this case U and V are invertible and hence this system is irreducible. Kalman [6] showed that an impulse-response is uniquely determined by its irreducible (CC and CO) part and this suggested to Bellman and Astrom [4] that "it is necessary to assume that the system is observable and controllable in the sense of Kalman". However this assertion requires modification since there are examples, such as in Figure 4, where the irreducible part contains all the unknown parameters. In fact the impulse-response function for Fig. 4,

$$\phi(t) = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \end{bmatrix} \exp\left[t \begin{bmatrix} -a & 0 & 0 \\ 0 & -b & 0 \\ a & b & 0 \end{bmatrix}\right] \begin{bmatrix} 1 & 0 \\ 0 & 1 \\ 0 & 0 \end{bmatrix} = \begin{bmatrix} e^{-at} & 0 \\ 0 & e^{-bt} \end{bmatrix}, \quad (2.6)$$

identifies the fractional transfer coefficients a and b . The fact that the model in Fig. 4 is not CO can be obtained either from its controllability matrix (which is of rank 2) or from graph theoretic considerations ([1],[2],[5]) since its trap is not output reachable.

Irreducibility is not sufficient for identifiability as noted by Delforge [3] using Fig. 3 as a counterexample. He noted that

$$\hat{\phi}(s) = \frac{s + a + b + c}{s^2 + (a + b + c)s + ab} \quad (2.7)$$

identifies only the lumped parameters $a + b + c$ and ab .

D. The associated polynomial. Kalman noted in [6] (see also [9] and [10]) that all irreducible realizations are equivalent. Thus if (A, B, C) is any irreducible realization the characteristic polynomial of A and the minimal polynomial of A is the same for all realizations. Thus these polynomials are determined by the impulse-response function only. For this reason we call these polynomials the characteristic polynomial of $\phi(t)$, denoted $\Delta(\lambda)$, and the minimal polynomial of $\phi(t)$, denoted $\chi(\lambda)$. For example if $\chi(\lambda) = e^{\lambda I} I_n$ where I_n is the $n \times n$ identity matrix, then an irreducible realization is $(I_n, \lambda_1 I_n, I_n)$. In this case $\Delta(\lambda) = (\lambda - \lambda_1)^n$ and $\chi(\lambda) = \lambda - \lambda_1$.

The minimal polynomial is useful in defining functions of a matrix [11]. In particular, if

$$\chi(\lambda) = \prod_{k=1}^m (\lambda - \lambda_k)^{m_k} \quad (2.8)$$

We define the associated polynomial of $\phi(t)$

$$\xi(\lambda) = \prod_{k=1}^n (\lambda - \lambda_k)^{r_k} . \quad (2.11)$$

Alternatively, we may define the associated polynomial by expressing each element in the transfer function matrix $\hat{\phi}_{ij}(s) = p_{ij}(s)/q_{ij}(s)$, where p_{ij} and q_{ij} have no common factors. Then ξ is the least common multiple the q_{ij} .

We have defined three polynomials corresponding to an impulse-response function which, in important cases, are all identical.

Theorem 1. In the single-input case ($q=1$) or in the single-output case ($p=1$), the characteristic polynomial, the minimal polynomial and the associated polynomial are identical, i.e.,

$$\Delta(\lambda) = X(\lambda) = \xi(\lambda) . \quad (2.12)$$

Proof. We see from the construction of ξ that ξ factors X and, of course, X factors Δ . Moreover all three polynomials are monic, i.e., the coefficient of the highest power is one. Thus it suffices to show that the degree of ξ is at least N , which is the degree of Δ . It is known ([6],[9],[10]) that for the cases $p=1$ or $q=1$ a realization of dimension having the degree of ξ exists and hence $\deg(\xi) \geq N$, since N is the smallest dimension possible. We conclude that $\deg(\xi) = N$ and all three polynomials are equal.

Notice that $\Delta = \chi$ means that the algebraic multiplicity of eigenvalues are also their geometric multiplicities, i.e., there can be no duplication of Jordan blocks. In a single-input experiment $\Delta = \chi$ is necessary for irreducibility. We may regard the condition $\Delta = \chi$ as disallowing redundancy of impulse-response mechanisms.

Notice also that $\Delta = \xi$ means that the impulse-response function expresses each eigenvalue λ_k to its algebraic multiplicity. In the case of a single-input/single output experiment with no resonance [12], i.e., the eigenvalues are simple ($r_k = 1$ for all k), then the number of exponential terms occurring in (2.9) is the same as the number of compartments provided that the model is irreducible. Resonance ($r_k > 1$) can be ruled out when the digraph is symmetric and has no cycles of order greater than two [13]. Such a situation occurs in the catenary system in Fig. 5. In view of the above remarks, the impulse response function for Fig. 5 has the form $\phi(t) = \sum_{i=1}^3 \alpha_i e^{\lambda_i t}$. One can conclude further from [14] that the amplitudes α_i are positive and the system is identifiable. Determining the form of ϕ is important from the point of view of estimation since we want to form the objective function so that it has a unique minimum.

In the multi-input/multi-output case ($q > 1, p > 1$) the conclusion of Theorem 1 may not hold. For example if $\phi(t) = e^{\lambda_1 t} I_n$ ($n > 1$), then $\Delta \neq \chi$ and $\Delta \neq \xi$.

Theorem 1 is useful for determining the McMillan degree. Consider the example in (2.7). Since the numerator and denominator of $\hat{\phi}(s)$ do not contain common factors we know that the denominator is the

associated polynomial. Hence the McMillan degree is two, i.e., is the system as irreducible as noted earlier. In simple models, such as (2.7), it is not difficult to determine, from the transfer coefficients, and combinations thereof, which are identifiable and also the McMillan degree of the system. An alternate approach to determining the identifiable parameters and the McMillan degree, which seems more convenient analytically, is through the Markov parameters.

E. Markov parameters and identification of the McMillan degree. The Markov parameters of an impulse-response $\phi(t)$ are its derivatives at $t = 0$, i.e., $M_k = \phi^{(k)}(0)$ [15]. The M_k are not independent and in fact satisfy a recursion relation of the form

$$M_{N+v} + \alpha_{N-1} M_{N-1+v} + \dots + \alpha_0 M_v = 0, v = 0, 1, \dots, \quad (2.9)$$

where 0 denotes a null matrix. To see this let the characteristic polynomial be

$$\Delta(\lambda) = \lambda^N + \alpha_{N-1} \lambda^{N-1} + \dots + \alpha_0 \quad (2.10)$$

If (A, B, C) is any realization then

$$M_k = CA^k B \quad (2.11)$$

If the realization is irreducible then it follows from the Cayley-

Hamilton Theorem that $CA^v[A^N + c_{N-1}A^{N-1} + \dots + c_0I_N]B = CA^vOB = 0$.

Having found that the Markov parameters satisfy a linear recursion relation of order N we might ask if such a relation of smaller order is possible. For example, if $\phi(t) = e^{\lambda_1 t} I_n$ then we have indeed a relation of order one, $M_{k+1} = -\lambda_1 M_k$ and hence (2.10) is not minimal ($n > 1$). However in all cases a minimal linear recursion relation does exist say, $M_{J+v} + d_{J-1}M_{J-1+v} + \dots + d_0M_v = 0$ where $J \leq N$. The first J of these equations (i.e., $v = 0, 1, \dots, J-1$) will determine the coefficients d_k uniquely and hence all M_k are expressible in terms of the first $2J M_k$. Thus $\phi(t)$ is expressible in terms of the first $2J M_k$. This observation allows us to obtain a lower bound on J and hence also on N .

Theorem 2. Let the Markov parameters M_k be regarded as functions of the model parameters. Suppose there is at least one M_k for $k \geq 2v-2$ which is independent of the Markov parameter M_k , $k \leq 2v-3$. Then the McMillan degree $N \geq v$.

We consider the following examples. In (2.5) we have $M_0 = 1$, $M_1 = 0$, $M_2 = -ab$. Thus M_2 is independent of M_0 and M_1 hence it must be that $N \geq 2$. Since $N \leq 2$ we conclude (once again) that $N = 2$.

As a second example we consider Figure 5. In this case $B_c^T = C_c = (0, 0, 1)$ and

$$A_0 = \begin{bmatrix} -a_{21} & a_{12} & 0 \\ a_{21} & (-a_{12}-a_{32}) & a_{23} \\ 0 & a_{32} & (-a_{03}-a_{23}) \end{bmatrix}. \quad (2.12)$$

Thus M_k is the $(3,3)$ element in $A_0^k, (A_0^k)_{33}$. It is easy to see from the digraph that M_4 contains the segment $a_{12}a_{21}$ but $M_k, k \leq 3$, are independent of a_{12} and a_{21} . Thus M_4 is independent of the earlier M_k in the sequence. We conclude that $N \geq 3$. Thus $N = 3$ and the system is irreducible.

In the above examples we are able to determine that N is at least as large as the dimension of the model n and hence conclude that $N = n$. We now consider how we may determine N for reducible systems. Such criteria can be found by consideration of the generalized Hankel matrices.

$$W_k = \begin{bmatrix} M_0 & M_1 & \dots & M_k \\ M_1 & M_2 & \dots & M_{k+1} \\ \vdots & \vdots & \ddots & \vdots \\ M_k & M_{k+1} & \dots & M_{2k} \end{bmatrix} \quad (2.13)$$

It is well known ([9],[10]) that the maximal ranks of these matrices is N and moreover, the maximal rank occurs when $k = N - 1$. To illustrate the usefulness of these facts in detecting N we consider the following examples.

Suppose we set $a_{23} = 0$ in (2.12). Then compartment 3 reaches only itself and hence $M_k = (-a_{03} - a_{23})^k$. In this case all W_k have rank 1 and thus $N = 1$. Next we set $a_{12} = 0$ in (2.12) while keeping all the other parameters a_{ij} positive. Now compartment 3 reaches itself and compartment 2 but not compartment 1. Thus M_2 contains the segment $a_{32}a_{23}$ which does not appear in M_0 and M_1 . We can conclude from Theorem 2 that N is at least two. To see that $N = 2$ we can construct W_2 , as a function of the a_{ij} , and show that its determinant is identically zero.

Although the analytic techniques mentioned above can be used to identify the McMillan degree we should point out that sometimes graph theoretic methods, which require no computation, are adequate. Consider the last two examples. If $a_{23} = 0$ in Fig. 5 then compartments 1 and 2 are not output reachable and hence they can be ignored [1]. Thus $N = 1$. In the case $a_{12} = 0$, compartment 1 can be ignored. Thus $N \leq 2$ and hence the calculation of the determinant of W_2 is not needed.

In any case there are methods for identifying N so that in the following section we may assume that N is known.

3. CONSTRUCTION OF AN IRREDUCIBLE REALIZATION

The data collected in an input/output experiment may be so dense that it may be regarded as continuous curves over an interval $[0, T]$ (e.g., Xenon washout [16] or fluorescence decay [17]). In such cases it is natural to analyse the data in terms of integral transforms (or finite sums which are regarded as integrals) of the form (1.6).

In order to keep the discussion on a general plane we do not wish to specify the method functions $w_k(t)$. However certain restrictions are convenient; for if we choose w_k appropriately then we can regard the transform integrals s_k as Markov parameters. The class of method functions will be defined in regard to the following considerations:

(i) the transforms s_k are obtainable as explicit expressions of integrals of $y(t)$ and $u(t)$,

(ii) if $(A, B, C,)$ is any realization of $\phi(t)$ then the integrals have the form

$$s_k = CA^kGB = CGA^kB \quad (3.1)$$

where G is a matrix having the dimension of A .

The class of method functions and the construction of an irreducible realization depend to some extent on the number and the type of inputs and outputs. We consider the problem in increasing order of difficulty.

A. Single-bolus-input/single-output. We consider the class of problems for which a unit of material enters the system in sufficiently short time

duration that it may be regarded to occur instantaneously. Let b_i be the amount of material which enters compartment i . Then $B_c = [b_1, b_2, \dots, b_n]^T$ is the initial state of the system. Suppose also that we have a single observation curve $y(t) = C_c x(t)$, $0 \leq t \leq T$. Such situations are common in radioactive tracer experiments [16]. The problem may be put into standard form,

$$\dot{x}(t) = A_c x(t) + B_c \delta(t), y(t) = C_c x(t), 0 \leq t \leq T, \quad (3.2)$$

where $\delta(t)$ is the Dirac delta function. In such cases $y(t) = \phi(t)$, i.e., the impulse-response is observed directly.

Let $C_0^{(2N-1)}[0, T]$ denote the space of functions which have $2N-1$ continuous derivatives on $[0, T]$ such that the first $2N-1$ derivatives vanish at the end-point. Here N is the McMillan degree. For any $w(t)$ in $C_0^{(2N-1)}[0, T]$ we form the finite sequence

$$s_k = (-1)^k \int_0^T \phi(t) w^{(k)}(t) dt, k = 0, 1, \dots, 2N-1. \quad (3.3)$$

In view of the end-point conditions on $w(t)$, we may integrate by parts to obtain the alternate form

$$s_k = \int_0^T \phi(t) w(t) dt. \quad (3.4)$$

If (A, B, C) is any irreducible realization then s_k has the form (3.1)

where

$$G = \int_0^T e^{tA} w(t) dt . \quad (3.5)$$

Thus the s_k have the same form as the Markov parameters except for the matrix G . In fact the s_k are the Markov parameters for the impulse-response function $\tilde{\phi}(t) = Ce^{tA}GB$. Since the recursion formula (2.10) is derived from the state matrix A , which is the same for both $\phi(t)$ and $\tilde{\phi}(t)$, we may conclude that the s_k satisfy the same recursion formula

$$s_{N+v} + c_{N-1}s_{N-1+v} + \dots + c_0s_v, \quad v = 0, 1, \dots, N-1 \quad (3.6)$$

We form the Hankel matrices

$$Q = \begin{bmatrix} s_0 & s_1 & \dots & s_{N-1} \\ s_1 & s_2 & \dots & s_N \\ \vdots & \vdots & \ddots & \vdots \\ s_{N-1} & s_N & \dots & s_{2N-2} \end{bmatrix}, \quad R = \begin{bmatrix} s_1 & s_2 & \dots & s_N \\ s_2 & s_3 & \dots & s_{N+1} \\ \vdots & \vdots & \ddots & \vdots \\ s_N & s_{N+1} & \dots & s_{2N-1} \end{bmatrix} \quad (3.7)$$

Notice that we can factor

$$R = \tilde{A}Q \quad (3.8)$$

where $\tilde{A}$ is the matrix

$$\tilde{A} = \begin{bmatrix} 0 & 1 & 0 & \dots & 0 & 0 \\ 0 & 0 & 1 & \dots & 0 & 0 \\ \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & \dots & 0 & 1 \\ -c_0 & -c_1 & -c_2 & \dots & -c_{N-2} & -c_{N-1} \end{bmatrix} \quad (3.9)$$

A matrix having the form given in (3.9) is said to be in row companion form. Its characteristic polynomial is $\Delta(\lambda)$. This suggests that $\tilde{A}$ may be similar to A which, in fact, is true provided G is invertible. To see this we observe from the form of s_k given in (3.1), that Q and R are expressible in the factored forms

$$Q = VGU, \quad R = VAGU (= VGAU) \quad (3.10)$$

where V and U are the observability and controllability matrices corresponding to the realization (A, B, C) . Substituting (3.10) into (3.8) and cancelling U we have $\tilde{A}VG = VAG$. If G is invertible then G cancels and we obtain

$$\tilde{A} = VAV^{-1} \quad (3.11)$$

i.e., $\tilde{A}$ is similar to A .

Assuming for the moment that G is invertible we proceed with the construction of $\tilde{B}$ and $\tilde{C}$. We know from [6] that if

$$\tilde{B} = [0, 0, \dots, 1]^T \quad (3.12)$$

then $(\tilde{A}, \tilde{B})$ is controllable, i.e.,

$$\tilde{U} = [\tilde{B}, \tilde{A}\tilde{B}, \dots, \tilde{A}^{N-1}\tilde{B}] \quad (3.13)$$

is invertible, and $\phi(t)$ has an irreducible realization of the form $(\tilde{A}, \tilde{B}, \tilde{C})$. To find $\tilde{C}$ we note that $s_k = \tilde{C}\tilde{G}\tilde{A}^{k-1}\tilde{B}$ and hence we obtain $[s_0, s_1, \dots, s_{N-1}] = \tilde{C}\tilde{G}\tilde{U}$. Now from (3.11), $\tilde{G} = \int_0^T e^{t\tilde{A}} w(t) dt$
 $= \int_0^T V e^{tA} V^{-1} w(t) dt = VGV^{-1}$ is invertible if G is invertible, which is what we are assuming. Thus

$$\tilde{C} = [s_0, s_1, \dots, s_{N-1}] \tilde{U}^{-1} \left[\int_0^T e^{t\tilde{A}} w(t) dt \right]^{-1} \quad (3.14)$$

is given in terms of known quantities.

Having found formulas for expressing an irreducible realization in terms of the s_k , we return to the question of the invertibility of

G . First we observe from (3.5) that $G = f(A)$ where $f(\lambda)$

$= \int_0^T e^{\lambda t} w(t) dt$. Thus by the Spectral Mapping Theorem [18] (p. 569), the eigenvalues of G are $\int_0^T e^{\lambda_k t} w(t) dt$ where λ_k are the roots of $\Delta(\lambda)$. Thus G is invertible if and only if

$$\int_0^T e^{\lambda_k t} w(t) dt \neq 0 \quad (\Delta(\lambda_k) = 0) \quad (3.15)$$

As long as $w(t)$ satisfies (3.15) the above formulas for the construction of an irreducible realization are valid.

Condition (3.15) is sufficient but is it necessary? We consider first an example. Suppose $\phi(t) = \alpha_1 e^{\lambda_1 t} + \alpha_2 e^{\lambda_2 t}$ and $\int_0^T e^{\lambda_1 t} w(t) dt = 0$. Then $s_k = \int_0^T \phi^{(k)}(t) w(t) dt = \alpha_2 \lambda_2^k \int_0^T e^{\lambda_2 t} w(t) dt$ does not contain α_1 or λ_1 . Clearly the impulse-response function can not be constructed from these s_k .

To deal with the general situation, we again regard (A, GB, C) as a realization of an impulse-response function $\tilde{\phi}(t)$. The controllability and observability matrices for (A, GB, C) are GU and V respectively. Thus the McMillan degree $\tilde{\phi}$ is N if and only if G is invertible, i.e., if and only condition (3.15) is satisfied. If (3.15) is not satisfied, the McMillan degree of $\tilde{\phi}$ is less than N and hence, by Theorem 1, does not express each λ_k to its geometric multiplicity. It follows that the lost multiplicities occur also in $s_k = \tilde{\phi}^{(k)}(0)$. We conclude that $\phi(t)$, which, by Theorem 1, expresses each λ_k to its geometric (as well as algebraic) multiplicity, can not be constructed from the s_k .

We summarize the above observations in Theorem 3.

Theorem 3. The method function $w(t)$, chosen from the space $C_0^{(2N-1)}[0, T]$, is admissible (i.e., it allows the construction of an irreducible realization) if and only if it satisfies condition (3.15).

It is interesting to see what happens when (3.15) is violated, say

$\int_0^T e^{\lambda_1 t} w(t) dt = 0$. We have already discussed an example in which λ_1 is a simple eigenvalue and we found that the decay mode $\alpha_1 e^{\lambda_1 t}$ is lost or

filtered out. Suppose $\phi(t) = (\alpha_1 + \alpha_2 t)e^{\lambda_1 t}$ where now $\alpha_2 te^{\lambda_1 t}$ is a resonant mode. Notice that s_k satisfies the linear recursion relation of order one, $s_{k+1} = -\lambda_1 s_k$. If we regard N as one (instead of its true value, two) then the construction procedure yields $\alpha_2 e^{\lambda_1 t}$. In fact the s_k correspond to the impulse-response $\alpha_2 e^{\lambda_1 t}$ with method function $tw(t)$. The resonant mode $\alpha_2 te^{\lambda_1 t}$ has been filtered out except for the amplitude α_2 which has been made to replace α_1 .

We might consider how these observations might be applied. There are situations in which a decay rate λ_1 is known from an earlier experiment, as in [19], (or it might result from noise in the system) and its presence interferes with the detection of the other decay rates. If λ_1 is simple we can filter it out by choosing $w(t)$ so as to satisfy $\int_0^T e^{\lambda_1 t} w(t) dt = 0$. If λ_1 is resonant of order ν , i.e. $t^\nu e^{\lambda_1 t}$ is present in $\phi(t)$, then we require $\int_0^T t^k e^{\lambda_1 t} w(t) dt = 0$ for $k \leq \nu$. This filtering idea has been studied in [20].

Suppose now that we want to identify λ_k , then we should be concerned that an unfortunate choice of $w(t)$ filters it out. The set of functions $w(t)$ such that $\int_0^T e^{\lambda_k t} w(t) dt$ is a proper subspace of $C_0^{(2N-1)}[0, T]$ for each k . Therefore in theory we may say that condition (3.15) is satisfied almost everywhere in $C_0^{(2N-1)}[0, T]$. The "almost everywhere" concept has already been introduced into the literature [5] to indicate a negligible subset as compared to the entire set. In practice however it may happen that $\int_0^T e^{\lambda_i t} w(t) dt$ is small compared to $\int_0^T e^{\lambda_j t} w(t) dt$ which makes the estimation of λ_i difficult. To avoid this

several choices of $w(t)$ should be used.

B. Single-bolus-input/multi-output. Fortunately the formalism in case A carries over to the multi-output case with only minor modification. We simply point out the differences. First $\phi(t)$ and e_k are now vectors and hence Q and R are generalized Hankel matrices of the s_k . Formula (3.8) no longer makes sense and it should be replaced by

$$Q^T R = \tilde{A} Q^T Q, \quad (3.16)$$

where $\tilde{A}$ is given by (3.9) as before. Assuming $w(t)$ is admissible, $\tilde{A}$ is uniquely determined from (3.16) in terms of the s_k . Moreover $\tilde{A} = H A H^{-1}$ where $H = (G U)^T (V^T V)$.

The matrix $\tilde{B}$ is defined exactly as before and $\tilde{C}$ is again defined through formula (3.14).

C. Single-input/multi-output. We no longer assume a bolus input only i.e., $u(t)$ has the more general form $u(t) = b\delta(t) + v(t)$ where b is a constant (possibly zero) and $v(t)$ occurs over a significant portion of $[0, T]$. The additional concern here is that $\phi(t)$ is no longer observed directly. Pointwise deconvolution to obtain $\phi(t)$ from $y(t)$ and $u(t)$ may be difficult especially if $u(t)$ vanishes at $t = 0$ and the data values near $t = 0$ are noisy (e.g., [17],[19]). In such situations we define $w(t)$ in terms of another function $h(t)$ by

$$w(t) = \int_0^{T-t} u(\tau) h(\tau+t) d\tau. \quad (3.17)$$

In order to insure that $w(t)$ belongs to $C_0^{(2N-1)}[0, T]$ we require that $h(t)$ has $2N-1$ continuous derivatives and satisfies the conditions

$$\int_0^T u(t)h^{(k)}(t)dt = h^{(k)}(T) = 0, \quad k = 0, 1, \dots, 2N-2. \quad (3.18)$$

Notice that in the bolus-input case $u(t) = \delta(t)$, (3.17) reduces to $w(t) = h(t)$. It is not difficult to verify that if s_k is defined in terms of $u(t)$ and $y(t)$ by

$$s_k = (-1)^k \int_0^T y(t)h^{(k)}(t)dt \quad (3.19)$$

then s_k is also given by $s_k = \int_0^T \phi^{(k)}(t)w(t)dt$ as before. Therefore we are back to cases A or B.

One method for constructing $h(t)$ is to set

$h(t) = (T-t)^{2N-1} \sum_{i=1}^{2N-1} \beta_i h_i(t)$ where $h_i(t)$ are chosen method functions ($t^i, \sin(it)$, etc.), $\beta_{2N-1} = 1$ and the other β_i are obtained by the conditions $\int_0^T w(t)h^{(k)}(t)dt = 0, \quad k \leq 2N-2$.

We conclude this case by presenting a result which is similar to one given in [4].

Theorem 4. Suppose that all compartments are observed, i.e., $C_c = I_n$, and the system is controllable. Then the compartmental matrix A_c is given in terms of the transforms s_k by

$$A_c = [s_1, s_2, \dots, s_n][s_0, s_1, \dots, s_{n-1}]^{-1}. \quad (3.20)$$

provided $w(t)$ is admissible.

Proof. Since $C_c = I_n$, $s_k = A_c^k G B_c (= G A_c^k B_c)$ and hence, $s_{k+1} = A_c s_k$. It follows that $A_c[s_0, s_1, \dots, s_{n-1}] = [s_1, s_2, \dots, s_n]$. Moreover, $[s_0, s_1, \dots, s_{n-1}] = G[B_c, A_c B_c, \dots, A_c^{n-1} B_c] = GU$ is invertible. The conclusion readily follows. In the case when the s_k are moment integrals (3.20) reduces to a similar formula given in [21].

D. Multi-inputs. Suppose now there are $q > 1$ inputs. We consider first possibilities for reducing to the single-input case.

Suppose it is possible to perform q separate experiments in which all but one input is activated in each experiment, then the impulse-response for q inputs is $\phi = [\phi_1, \phi_2, \dots, \phi_q]$, where ϕ_i is the impulse-response corresponding to the i th single-input experiment.

If the inputs occur simultaneously but do not interfere with one another, as in Fig. 4, we can still regard the experiment as separate single-input experiments.

In the general case of q inputs and p outputs we have input-output equations $\hat{y}_i(s) = \sum_{j=1}^q \hat{\phi}_{ij}(s) \hat{u}_j(s)$, $i = 1, 2, \dots, p$, with possibly pq unknowns. Thus we see why special constraint conditions, which are imposed by the digraph, are needed in order to discuss

the multi-input case.

The formalism given above may appear complicated due to the fact that it deals with a general class of problems. Specific cases need not be difficult to handle. We conclude with the example where

$\hat{\phi}(s) = (d_0 + d_1 s) / (s^2 + c_1 s + c_0)$. To find the c_k from the s_k we apply (3.8) which, in this case, reduces to $-(s_2, s_3)$

$= (c_0, c_1) \begin{bmatrix} s_0 & s_1 \\ s_1 & s_2 \end{bmatrix}$. Having obtained the c_k by inverting this

equation we form $\tilde{A}$. The Laplace transform of $e^{t\tilde{A}}$ is

$\begin{bmatrix} c_1 + s & 1 \\ -c_0 & s \end{bmatrix} / (s^2 + c_1 s + c_0)$. Thus by taking inverse Laplace trans-

forms we obtain $e^{t\tilde{A}}$. Next we carry out the integration $\int_0^T e^{t\tilde{A}} w(t) dt$

to obtain $\tilde{G}$. We then invert in $[s_0, s_1] = [d_0, d_1] \tilde{G} [\tilde{B}, \tilde{A}\tilde{B}]$ to find

the d_k where $\tilde{B} = \begin{bmatrix} 0 \\ 1 \end{bmatrix}$.

FIGURE LEGENDS

- Fig. 1 - Example of a compartmental system realizing $\phi(t) = \frac{1}{2}$.
- Fig. 2 - Example of a compartmental system realizing $\phi(t) = \frac{1}{2}$.
- Fig. 3 - Delforge's example: Irreducibility does not imply identifiability.
- Fig. 4 - Example showing identifiability does not imply irreducibility.
- Fig. 5 - Example used in illustrating identifiability of N .

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

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