INTERPRETATION OF TRACER DATA

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ABSTRACT The necessary and sufficient conditions for a particular compartment in an n-compartment system, under certain initial conditions, to be described by two exponential terms have been given by Mann and Gurpide (1969). These conditions are here derived in matrix-vector form, by an essentially algebraic process, under more general initial conditions. The existence of a certain constant is required by the Mann-Gurpide conditions. It is shown that that constant must be one of the real roots of a given matrix. Under certain restrictions, that constant is the unique largest real root of that matrix. Certain obvious sufficient conditions for the Mann-Gurpide conditions to hold are shown to be necessary in the case of symmetrizable systems.

INTRODUCTION

The conditions under which one or more compartments in an n-compartment system can be described by fewer than n exponentials are of some interest. A general study is complicated by the roles of structural features and conditional features which determine the phenomenon of lumping. For example when the matrix of the system is diagonable, a repeated root leads to lumping under all initial conditions (Hearon, 1963). On the other hand certain properties of connectivity or structure of the system lead to lumping under particular, but not arbitrary, initial conditions. Finally, if the initial vector of the system lies in a properly chosen subspace, lumping occurs regardless of structure or connectivity (Hearon, 1963).

For these reasons special examples of lumping, especially when the conditions are both necessary and sufficient, are of interest for the insight which they may afford into the general problem. In a recent paper Mann and Gurpide (1969) gave necessary and sufficient conditions for a particular compartment in an n-compartment system, under certain initial conditions, to be described by two exponentials. It is one purpose of this paper to derive the Mann-Gurpide conditions more directly under more general initial conditions. The conditions are obtained directly in a form which facilitates the further deductions and the discussion of special cases which are also given here.

PRELIMINARIES AND NOTATION

We consider a first-order differential system with matrix of real, constant coefficients. Most of the results which follow require no further assumptions, others require restrictions on the matrix appropriate to a compartmental matrix. Let the system be

$$\dot{f} = Kf, \tag{1}$$

where f is an n-dimensional column vector, $\dot{f} = df/dt$, and $K = [k_{ij}]$ is an n-square constant matrix. For any column vector v we denote the transpose of v by v^*. Partition f into f_1 and the vector x, where $x^* = [f_2, f_3, \cdots, f_n]$, and partition K as follows:

$$K = \begin{pmatrix} a & r^* \\ c & A \end{pmatrix},$$

where $a = k_{11}$, the row vector $r^* = [k_{12}, k_{13}, \cdots, k_{1n}]$, $c^* = [k_{21}, k_{31}, \cdots, k_{n1}]$, and A is the submatrix obtained from K by deleting the first row and column. We further define the scalar $y = r^*x$. Then equation 1 reads

$$\dot{f}_1 = af_1 + y \tag{2}$$

$$\dot{x} = f_1c + Ax \tag{3}$$

and further, it follows from equation 3 that

$$\dot{y} = (r^*c)f_1 + r^*Ax. \tag{4}$$

Finally we consider the initial conditions

$$f_1(0) = f_1^0$$

$$x(0) = kc, \tag{5}$$

where f_1^0 and k are arbitrary constants. The conditions of equations 5 with $k = 0$ are the initial conditions of Mann and Gurpide.

We say a function is two exponential (2-exp) if it is a linear combination of either exp $(\lambda_1 t)$ and exp $(\lambda_2 t)$, $\lambda_1 \neq \lambda_2$, or of exp (λt) and t exp (λt). We begin with a lemma first proved by Mann and Gurpide (1969).

Lemma 1

f_1 is 2-exp if and only if there exist constants α and β such that

$$\dot{f}_1 = af_1 + y$$

$$\dot{y} = \beta f_1 + \alpha y. \tag{6}$$

Proof. We observe that the first equation of equations 6 is just equation 2 and is always satisfied. It is obvious that if equation 6 holds, then f_1 is 2-exp. Conversely, assume f_1 to be 2-exp, say exp$(\lambda_1 t)$ and exp $(\lambda_2 t)$, $\lambda_1 \neq \lambda_2$. To produce α and β such that equations 6 hold, we have only to require that they be such that λ_1 and λ_2 are the roots of the matrix of equations 6. We have at once $a + \alpha = \lambda_1 + \lambda_2$ and $a\alpha - \beta = \lambda_1\lambda_2$, which determine α and β. Now suppose that f_1 consists of exp (λt) and t exp (λt). We now require α and β such that λ is a double root of the matrix of equations 6. Thus $a + \alpha = 2\lambda$ and $a\alpha - \beta = \lambda^2$. This completes the proof.

In the event that $k = 0$, the above case of the repeated root is of scant interest for real compartmental systems. For in this case we cannot have f_1 be 2-exp and y be nonnegative. To see this, suppose $f_1 = (p_1 + p_2 t) \exp(\lambda t)$. Then from the initial conditions we have $p_1 = f_1^0$ and from the initial value of $\dot{f}_1$ we have $p_2 = (a - \lambda) f_1^0 = (a - \lambda) p_1$. Substitution of the assumed form of f_1 into the first equation of equations 6 gives $y = (\lambda - a) p_2 t \exp(\lambda t)$, which results from the fact that $p_2 + (\lambda - a) p_1 = 0$. Now $2\lambda = a + \alpha$ and $\lambda^2 = a\alpha - \beta$ determine β as $\beta = -(\lambda - a)^2 \leqq 0$. A necessary condition for $y \geqq 0$ is that $\beta \geqq 0$ (Hearon, 1963, and references therein). Thus we must have $\beta = 0$. But then $\lambda = a$ which results in $y(t) = 0$, identically, and $f_1 = f_1^0 \exp(\lambda t)$, which is *not* 2-exp.

We next give an alternative derivation of the Mann-Gurpide conditions.

THEOREM I

f_1 is 2-exp, under all initial conditions of the form of equations 5, if and only if there exists an α such that $r^*(A - \alpha I)A^j c = 0$ for every integer $j \geqq 0$.

Necessity. Assume that f_1 is 2-exp. Then by lemma 1, there exist α and β such that equations 6 are satisfied. But equation 4 is always satisfied and equating equations 4 and 6 we have that

$$\beta f_1 + \alpha(r^* x) = (r^* c) f_1 + r^* A x \tag{7}$$

which holds identically in t for all initial conditions of the form of equations 5. In particular equation 7 holds at $t = 0$ and we obtain

$$(\beta - r^* c) f_1^0 = r^*(A - \alpha I) c k. \tag{8}$$

Since f_1^0 and k are independently variable and equation 8 must hold for all possible sets of values f_1^0 and k, we must have $\beta = r^* c$ and $r^*(A - \alpha I)c = 0$. Given that $\beta = r^* c$ it follows from equation 7 that $r^*(A - \alpha I)x = u^* x = 0$, identically in t, where $u^* = r^*(A - \alpha I)$. We now show by induction that for every integer $k \geqq 0$ we have $u^* A^k x = 0$, identically in t, and $u^* A^k c = 0$. To this end we assume that $u^* A^s x = 0$ for a given integer s and show that it follows that $u^* A^s c = 0$ and $u^* A^{s+1} x = 0$. Since we have just shown that $u^* A^s x = 0$ for $s = 0$, i.e. we have just proved that $u^* x = 0$, it follows that $u^* A^k x = 0$ and $u^* A^k c = 0$ for every integer $k \geqq 0$. So assume $u^* A^s x = 0$. Then $u^* A^s \dot{x} = 0$ and from equation 3,

$$(u^* A^s c) f_1 + u^* A^{s+1} x = 0,$$

identically in t and for all conditions of the form of equations 5. But since f_1^0 and k are independently variable, we must have $u^* A^s c = 0$ and $u^* A^{s+1} x = 0$.

Sufficiency. Subject to equations 5, the solution of equation 3 is

$$\begin{aligned} x &= e^{At} kc + \int_0^t e^{A\theta} c f_1(t - \theta)\, d\theta \\ &= k \sum_{p=0}^{\infty} A^p c \frac{t^p}{p!} + \int_0^t \sum_{p=0}^{\infty} A^p c \frac{\theta^p}{p!} f_1(t - \theta)\, d\theta, \end{aligned} \tag{9}$$

from which it follows that

$$u^*x = k \sum_{p=0}^{\infty} (u^*A^p c) \frac{t^p}{p!} + \int_0^t \sum_{p=0}^{\infty} (u^*A^p c) \frac{\theta^p}{p!} f_1(t - \theta)\, d\theta.$$

If $u^*A^k c = 0$ for $k = 0, 1, 2, \cdots$, then we have $u^*x = 0$, identically in t. But this means that $r^*Ax = \alpha r^*x = \alpha y$ and equation 4 reduces to the second equation of equations 6 with $\beta = r^*c$. It now follows from lemma 1 that f_1 is 2-exp.

We observe that the above argument can be shortened by noting that any function of A is a polynomial in A (Gantmacher, 1959 *a*). If $u^*A^k c = 0$ for $k = 0, 1, 2, \cdots$, then it follows at once that $u^* \exp (At)c = u^* \int_0^t \exp (A\theta) c f_1(t - \theta)\, d\theta = 0$ and hence $u^*x = 0$. We further note that if m is the degree of the minimum polynomial of A, then any power of A can be written as a polynomial in A of degree at most $m - 1$. Thus the condition of theorem 1 can be replaced by $u^*A^k c = 0$ for $k = 0, 1, 2, \cdots, m - 1$.

THEOREM II

Let $r^*(A - \alpha I)A^k c = 0$ for some α and $k = 0, 1, 2, \cdots$. Then if $r^*c \neq 0$, α is a root of A.

Proof. Suppose that α is not a root of A. Then $(A - \alpha I)^{-1}$ exists and can be written as a polynomial in $A - \alpha I$ which is obviously a polynomial in A. If $r^*(A - \alpha I)A^k c = 0$ for $k = 0, 1, 2, \cdots$, if follows that $r^*(A - \alpha I)p(A)c = 0$ for any polynomial $p(A)$. If we choose $p(A) = (A - \alpha I)^{-1}$, we then have $r^*c = 0$. Thus if α is not a root of A, then $r^*c = 0$ and the theorem is proved.

With some restrictions on A, the results in theorem II can be sharpened considerably. However, we require a lemma preparatory to proving the next theorem.

Lemma 2[1]

Let A be a real, square irreducible matrix with nonnegative off-diagonal elements. Then there is a number b such that $A + bI$ has a positive root μ_1 such that $\mu_1 > |\mu_k|$, where μ_k is any other root of A. Moreover, $\mu_1 = \alpha_1 + b$ where α_1 exceeds the real part of very other root of A.

Proof. Choose a $b > 0$ such that $A + bI$ has nonnegative entries; (Any $b \geqq \max |a_{ii}|$ will do). Then $A + bI$ is a nonnegative irreducible matrix. Let the roots of A be $\lambda_j = \alpha_j + i\beta_j$, where $i = \sqrt{-1}$. The roots of $A + bI$ are then $\mu_j = \lambda_j + b$. By a classical theorem (Gantmacher, 1959 *b*) $A + bI$ has a real positive root μ_1 such that $\mu_1 \geqq |\mu_k|$, where μ_k is any other root of $A + bI$. Thus $\mu_1 = \lambda_1 + b$ is real and hence λ_1 is real, i.e., $\lambda_1 = \alpha_1$. It can be shown straightforwardly that $\alpha_1 > \alpha_k$, where

[1] In the language of nonnegative matrices (Gantmacher, 1959 *b*), the lemma states that if A meets the conditions of the lemma, then there exists a b such that $A + bI$ is primitive.

α_k is the real part of any root of A other than λ_1 (Hearon, 1963). Suppose that for the value of b which we have chosen, equality holds in $\mu_1 \geqq |\mu_k|$ for some k, say $k = 2$. Then $(\alpha_1 + b)^2 = (\alpha_2 + b)^2 + \beta_2^2$. But since $\alpha_1 > \alpha_2$, it follows at once that for any $\epsilon > 0$, $(\alpha_1 + b + \epsilon)^2 > (\alpha_2 + b + \epsilon)^2 + \beta_2^2$. Thus $A + (b + \epsilon)I$ which has roots $\mu'_j = \mu_j + \epsilon$ has a *strictly dominant root* $\mu'_i > |\mu'_k|$.

THEOREM III

Let $r^*(A - \alpha I)A^k c = 0$ for some α and $k = 0, 1, 2, \cdots$. If $r^*c \neq 0$, $r \geqq 0$ and A is irreducible, then α is the maximum real root of A and exceeds the real part of every other root of A.

Proof. Let C be a matrix with a strictly dominant root, i.e., a root which strictly exceeds in modulus every other root. Then, given an arbitrary vector q_0, there are scale factors γ_i such that if $q_1, q_2, \cdots$ are defined by $Cq_0 = \gamma_1 q_1$, $Cq_1 = \gamma_2 q_2, \cdots$, then the sequence Cq_i, $i = 1, 2, \cdots$ converges to an eigenvector of C associated with the dominant root (Wilkinson, 1965). By lemma 2 $B = A + bI$ has a strictly dominant root for some b. Therefore the sequence $w_1 = Bc$, $w_2 = B^2c/\gamma_1$, $w_3 = B^3c/\gamma_1\gamma_2, \cdots$ converges to an eigenvector z of B associated with the dominant root. Since B^k is a polynomial in A, we have $r^*(A - \alpha I)B^k c = 0$ for $k = 0, 1, 2, \cdots$ and the sequence $r^*(A - \alpha I)w_k$, where $k = 1, 2, \cdots$, converges to $r^*(A - \alpha I)z = 0$. But z satisfies $Bz = (\alpha_1 + b)z = (A + bI)z = Az + bz$ and thus $Az = \alpha_1 z$, where, as in lemma 2, $\alpha_1 + b$ is the dominant root of B and $\alpha_1 > \alpha_k$ is the maximum real root of A. From $r^*(A - \alpha I)z = 0$ and $Az = \alpha_1 z$ we have $r^*z(\alpha_1 - \alpha) = 0$. But by a well-known theorem, the elements of z are nonzero and all of the same sign (Gantmacher, 1959 *b*). Hence $r^*z \neq 0$ and $\alpha = \alpha_1$, which completes the proof of the theorem.

It is worth noting that while the validity of theorem III obviously requires that $Bc \neq 0$, this can fail if and only if c is an eigenvector of A and $-b$ is a root of A. But we can always choose b such that this is not the case, even when c is an eigenvector of A. We must also rule out the trivial situation $A - \alpha I = 0$, which in fact can occur in a mammillary system which meets the Mann-Gurpide conditions.

We say that a matrix G is symmetrizable if there exists a positive definite matrix H such that GH is hermitian, i.e. $M = GH = M^*$, where M^* is the conjugate transpose of M. We then say that G is symmetrizable by H.

THEOREM IV

Let K be symmetrizable by a diagonal matrix. Then if $r^*(A - \alpha I)A^k c = 0$, for $k = 0, 1, 2, \cdots$, we have $Ac = \alpha c$ and $A^*r = \alpha r$.

Proof. If K is symmetrizable by H, then it is known (e.g. Hearon 1963, 1967) that there exists a positive definite T such that $T^{-1}KT$ is hermitian. According to the partitioning we have used for the matrix K of equation 1, we partition T as $T = \text{diag}(t_{11}, V)$ where V is a real, $(n - 1)$-square, diagonal matrix. It is known

(Hearon 1953, 1961) that t_{11} can be chosen arbitrarily and we take $t_{11} = 1$. This being the case it is readily verified (see Hearon, 1961) that if $T^{-1}KT$ is hermitian, we must have $V^{-1}AV = S = S^*$ and $Vr = V^{-1}c = v$, where the last equality defines v. If $r^*(A - \alpha I)A^k c = 0$ is written as $(r^*V)V^{-1}(A - \alpha I)V(V^{-1}A^kV)(V^{-1}c) = 0$, we clearly have $r^*V(S - \alpha I)S^kV^{-1}c = 0$ and hence $v^*(S - \alpha I)p(S)v = 0$ for any polynomial $p(S)$. We choose $p(S) = S - \alpha I = S^* - \alpha I$ (observe that α is real and S hermitian by construction) and obtain $v^*(S - \alpha I)(S^* - \alpha I)v = 0$. But this is the squared length of the vector $(S^* - \alpha I)v$ and hence $(S - \alpha I)v = (S^* - \alpha I)v = 0$. From $Sv = \alpha v$, the definition of S, and $v = V^{-1}c$, we obtain at once $Ac = \alpha c$. Similarly, from $S^*v = \alpha v$, the definition of S, and $v = Vr$, we obtain $A^*r = \alpha r$. The proof is complete.

DISCUSSION

Lemma 1 and theorem I entail essentially no restrictions on the matrix K. While the initial conditions of equations 5, which include those of Mann and Gurpide as a particular case, are rather special, they appear to be the most general under which theorem I will go through. It is a fact that equations 5 can be achieved under the washout conditions (Hearon, 1968) in a mammillary system, but this is rather trivial (see remarks following theorem III); and also under the washout conditions, with input into the first compartment only, in any system such that c is an eigenvector of A and A is nonsingular. For, from equation 3, the asymptotic vector $x(\infty)$ is given by[2] $x(\infty) = -f_1(\infty)A^{-1}c$ and if, for some $\lambda \neq 0$, $Ac = \lambda c$, then we have $x(\infty) = -f_1(\infty)c/\lambda$ which is a scalar multiple of c. The conditions of theorem I can be written $\alpha r^*A^kc = r^*A^{k+1}c$ and in this form, with due allowance for notation, we have equations 5 of Mann and Gurpide. They can also be put in the form $r^*A^kc = \alpha r^*A^{k-1}c = \alpha^2 r^*A^{k-2}c = \cdots = \alpha^k r^*c$.

The condition $r^*c \neq 0$ in theorem II is actually no restriction at all. For, if $r^*c = 0$, then $\beta = 0$ in the second equation of equations 6 and since the initial condition on y is $y(0) = r^*x(0) = kr^*c = 0$, it follows that $y(t) \equiv 0$ and f_1 is a single exponential. Thus in any case of interest we are entitled to the conclusion of theorem II, which tells us that if an α exists such that the conditions of theorem 1 are met, then α must be sought among the real roots of A. With the additional restrictions that the elements of r be nonnegative (a condition realized in *any* compartmental case) and that A be irreducible, theorem III tells that α is precisely the maximum real root of A.

It is obvious that if either $Ac = \alpha c$ or $r^*A = \alpha r^*$, the conditions of theorem I are met. Theorem IV thus means that in the symmetrizable case, the conditions of theorem I are met if and only if $Ac = \alpha c$ and $r^*A = \alpha r^*$. A large class of compartmental systems are symmetrizable. (Hearon, 1963) and certain linear systems of great physical interest are symmetrizable (Kramer, 1959; Shuler, 1959).

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[2] It can be shown (Hearon 1963; 1968) that for any actual compartmental case, $-A^{-1}$ is a nonnegative matrix and in such a case c is of course a nonnegative vector, and hence so is $x(\infty)$.

As noted above, it is *sufficient* for the conditions of theorem I to hold, that either c be an eigenvector of A or that r^* be a row eigenvector of A. In fact if either of these situations obtains, it is clear without knowledge of theorem I that f_1 is 2-exp. For, if $r^*A = \alpha r^*$, then equation 4 reduces at once to the second equation of equations 6 with $\beta = r^*c^*$. If $Ac = \alpha c$, then $\exp(At)c = \exp(\alpha t)c$ and equation 9 then reads

$$x = \exp(\alpha t)kc + \int_0^t \exp[\alpha(t - \theta)]cf_1(\theta)d\theta.$$

From this it follows that $\dot{x} = f_1 c + \alpha x$ and hence that $\dot{y} = (r^*c)f_1 + \alpha y$, which is the second equation of equations 6 with $\beta = r^*c$. We now show, by counter example, that neither $Ac = \alpha c$ nor $r^*A = \alpha r^*$ is *necessary* for f_1 to be 2-exp.

We consider K to be a compartmental matrix: the off-diagonal entries are nonnegative, the column sums are nonpositive, and the real part of each root is nonpositive. Then every principal submatrix of K will enjoy these properties. Let K be chosen such that A is in the form

$$A = \begin{pmatrix} A_1 & 0 \\ B_1 & C \end{pmatrix},$$

where A_1 and C are square and $B_1 \neq 0$, and $B_1 \geqq 0$. Accordingly the vectors c and r are partitioned as $c^* = (\gamma_1^*, \gamma_2^*)$ and $r^* = (\rho_1^*, \rho_2^*)$, where γ_1, γ_2, ρ_1 and ρ_2 are column vectors of appropriate dimensions. It is always possible[3] to choose α as a real root of A_1 and γ_1 such that $(A_1 - \alpha I)\gamma_1 = 0$ and to choose C such that C^{-1} and $(C - \alpha I)^{-1}$ exist and $-(C - \alpha I)^{-1}$ is nonnegative. Then we are clearly at liberty to choose the nonnegative vector γ_2 to be $\gamma_2 = -(C - \alpha I)^{-1}(B_1\gamma_1 - q)$ where q is a nonzero vector. Finally we choose $\rho_2 = 0$ and ρ_1 such that $\rho_1^*(A_1 - \alpha I) \neq 0$, which is possible since surely not every nonnegative vector is in the nullspace of $A_1^* - \alpha I$. We then have

$$(A - \alpha I)c = \begin{pmatrix} 0 \\ q \end{pmatrix} \neq 0 \tag{10}$$

as a direct result of $(A_1 - \alpha I)\gamma_1 = 0$ and $B_1\gamma_1 + (C - \alpha I)\gamma_2 = q$. Further,

$$r^*(A - \alpha I) = [\rho_1^*(A_1 - \alpha I), 0] \neq 0 \tag{11}$$

as a direct result of $\rho_1^*(A_1 - \alpha I) \neq 0$ and $\rho_2 = 0$. Thus c is not an eigenvector of A corresponding to the root α and r^* is not a row eigenvector corresponding to the

[3] Choose A_1 to be irreducible. Then by lemma 2, there is a b such that $A_1 + bI$ has a real root $\alpha_1 + b$ where α_1 is the maximum real root of A_1. Further (Gantmacher 1959 *b*), there is a positive eigenvector z such that $(A_1 + bI)z = (\alpha_1 + b)z$ and clearly $A_1 z = \alpha_1 z$. Thus we choose $\alpha = \alpha_1$ and $\gamma_1 = z$. C can be chosen nonsingular and such that the real parts of the roots of C are less than α. Then the real parts of the roots of $C - \alpha I$ are negative and (Hearon 1963; 1968) the matrix $-(C - \alpha I)^{-1}$ is nonnegative.

root α. However, as we now show, it is true for every integer $k \geqq 0$ that we have $r^*(A - \alpha I)A^k c = 0$. Straightforward multiplication will show that for every integer $k \geqq 0$, we have

$$A^k = \begin{pmatrix} A_1^k & 0 \\ B_k & C^k \end{pmatrix}, \tag{12}$$

where the character of B_k enters the ensuing argument in no way.[4] From equations 12 and 10 it follows that

$$A^k(A - \alpha I)c = (A - \alpha I)A^k c = \begin{pmatrix} 0 \\ C^k q \end{pmatrix} \neq 0. \tag{13}$$

But from equation 13 and $r^* = (\rho_1{}^*, 0)$ we plainly have $r^*(A - \alpha I)A^k c = 0$.

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[4] The B_k are given by $B_0 = 0$, $B_k = B_1 A_1^{k-1} + CB_{k-1}$, $k \geqq 1$.