APPLICATION OF RESULTS FROM LINEAR KINETICS TO THE HODGKIN-HUXLEY EQUATIONS

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ABSTRACT On the basis of its role in the analysis of mammillary compartmental systems, a matrix with non-zero elements in the first row, first column, and along the main diagonal and with zero elements elsewhere is called a mammillary matrix. It is pointed out that such matrices occur in a variety of biological problems including the linearized Hodgkin-Huxley equations (H-H). In considering whether such a linear system exhibits stability (all roots of the matrix with negative real parts) it is of interest to seek conditions, expressible in a simple manner in terms of the matrix elements, which lead to stability or instability. For the case when the diagonal elements, with the possible exception of the first, are negative (a condition physically guaranteed for the space-clamped axon) simple criteria for instability and stability are formulated in terms of the matrix elements. These criteria are derived by extending previous results from linear kinetics through appeal to a classical matrix theorem without recourse to the characteristic polynomial. The relation of these mathematical results to the work of Chandler, FitzHugh, and Cole on the space-clamped axon is discussed. The results are in no way restricted by the order of the matrix (which is four for the H-H equations) and other possible applications are noted.

Consider a so called mammillary compartmental system (1) consisting of a central compartment and $n - 1$ peripheral compartments. The matrix of the system of differential equations describing the system has non-zero elements in the first row and first column, and along the main diagonal. All other elements are zero. The matrix can thus be written

$$A = \begin{bmatrix} a & r \\ c & D \end{bmatrix} \qquad [1]$$

where r and c are a row and column, respectively, of $n - 1$ elements and D is a diagonal matrix, $D = \text{diag}\ (d_1, d_2, \ldots, d_{n-1})$. The same formal situation arises in the theory of blood-tissue exchange (2) and chemical kinetics (3). In all of the cases mentioned thus far, the elements of r and c are positive and the diagonal elements are negative. Given these conditions the nature of the roots of A and their relation to the elements $d_1, d_2, \ldots, d_{n-1}$ can be very simply characterized (4).

Consider now a non-linear system described by the equations

$$\begin{aligned} \dot{x}_1 &= f(x_1, x_2, \cdots, x_n) \\ \dot{x}_j &= g_j(x_1, x_j), \qquad j = 2, 3, \cdots, n \end{aligned} \qquad [2]$$

where the dot denotes differentiation with respect to time and as indicated f is a function of all of the variables and any g_j is a function only of x_1 and x_j. Assume that there exists a singular point (critical point and stationary point are other definitions) such that if $x_k = a_k$ for all k, then $\dot{x}_k = 0$ for all k. If equation [2] is expanded about this point up through linear terms there results, since $\partial g_j/\partial x_k$ is different from zero only when $k = 1$ and $k = j$,

$$\dot{x}_1 = \frac{d}{dt}(x_1 - a_1) = \sum_{k=1}^{n} f_k \cdot (x_k - a_k)$$

$$\dot{x}_j = \frac{d}{dt}(x_j - a_j) = g_{j1} \cdot (x_1 - a_1) + g_{jj} \cdot (x_j - a_j), \qquad j = 2, 3, \cdots, n$$

where f_k is $\partial f/\partial x_k$ evaluated at the singular point and g_{jk} is $\partial g_j/\partial x_k$ evaluated at the singular point. If we define $y_i = x_i - a_i$, $1 \leq i \leq n$, and y as the vector whose elements are the y_i, then the expanded equations can be written

$$\dot{y} = Ay \qquad [3]$$

where A is of the equation form [1] with $a = f_1$, the elements of the row r are $f_2, f_3, \ldots, f_n$, the elements of the column c are $g_{21}, g_{31}, \ldots, g_{n1}$, and the diagonal elements of D are $g_{22}, g_{33}, \ldots, g_{nn}$. With suitable numbering of the variables and $n = 4$ this is precisely the situation which obtains for the Hodgkin-Huxley equations as shown by Chandler, FitzHugh, and Cole (5) who studied the above linearization with special reference to the stability of a given singular point.

It is the purpose of this paper to show that certain previous results from linear kinetics can be brought to bear upon this stability problem. These results, although not as restrictive in practice as one would like, are obtained from known properties of matrices and are not readily seen by direct examination of the characteristic polynominal of the matrix.

We refer to a matrix of the equation form [1] as a mammillary matrix and for any such matrix, assuming D is not singular, we define an associated scalar quality, $H(A)$, as follows:

$$H(A) = a - rD^{-1}c. \qquad [4]$$

Now in the axon stability problem the elements of D are inherently negative. In most cases[1] the signs of the elements of r and c can be prescribed, but the character of

[1] At least over the ranges studied, the voltage dependence of the rate parameters α and β (see reference 5 for notation) is such that, with certain other considerations, the signs of the

these sign patterns (or what is more important the signs of the products $r_i c_i$) is such that these sign restrictions have not as yet been shown to be useful in determining the nature of the roots of A. However, some statements regarding the roots of A can still be made by exploiting techniques previously used (4).

Under the stated conditions, (D non-singular and the d_j negative), it can be shown that $H(A) > 0$ implies a positive root and hence instability. For, by a known determinantal identity (Note I; reference 6, p. 46; reference 7, p. 74) the determinant of A, denoted $|A|$, can be written as

$$|A| = |D|\ H(A) = \lambda_1\lambda_2 \cdots \lambda_n \qquad [5]$$

where the first equality is the identity cited and the second states the well known fact (reference 7, p. 88) that $|A|$ is the product of the characteristic roots, λ_j, $j = 1, 2, \ldots, n$, of A. Given that $d_j < 0$ for all j, equation [5] can be written

$$(-1)^{n-1}p_1 H(A) = (-1)^N p_2 \qquad [6]$$

where p_1 and p_2 are positive[2] and N is the number of negative roots. From equation [6], if $H(A) > 0$, then $n - 1$ and N must either be equal or differ by an even positive integer. If $N = n - 1$ there are $n - 1$ negative roots and the single remaining root must be positive. Thus assume

$$n - 1 - N = \rho \qquad [7]$$

where ρ is an even integer ≥ 2. If P and C are the number of positive and complex roots, respectively, then

$$n = N + P + C \qquad [8]$$

and from equations [7, 8]

$$n - N = P + C = \rho + 1 \qquad [9]$$

where $\rho + 1$ is an odd integer not less than 3. Since complex roots, if any, must occur in conjugate pairs, C is either zero or an even integer not exceeding ρ, and equation [9] shows that P cannot be zero but must be an odd integer. Thus we see that $H(A) > 0$ implies the existence of at least one positive root and hence instability.

On the other hand, if $H(A) < 0$, the same argument leads to $n - N = P + C = \rho$, and we are assured nothing but that P is even if it is not zero.

We now make use of the fact that the sum of a mammillary matrix and its transpose is again a mammillary matrix. Define the *symmetric* matrix B by

$$B = (A + A^T)/2 \qquad [10]$$

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elements of r and c can be fixed. The author is indebted to one of the referees for calling this point to his attention.

[2] If the negative d_i are written $d_j = -q_j$, q_j positive, then $p_1 = q_1 q_2 \ldots q_{n-1}$. If the real, negative roots are $-\alpha_i$, α_i positive, $i = 1, 2, \ldots, N$, then $p_2 = \alpha_1\alpha_2 \ldots \alpha_N T$ where T is the product of complex roots. Since complex roots, if any, must occur in conjugate pairs, T consists of a product of numbers of the form $\lambda\bar{\lambda}$, where $\bar{\lambda}$ is the complex conjugate of λ. Thus T is positive.

where A^T denotes the transpose of A. With A from equation [1], it is readily seen that B is a mammillary matrix and in fact the submatrix of order $n - 1$ in the lower right hand corner of B is the matrix D. It is well known that the roots of B are real (reference 7, p. 73). Let $\lambda_j = \alpha_j + i\beta_j$, where $i = \sqrt{-1}$, and α_j and β_j are real, be any root of A. It is a known theorem (8, 9) that if M and m are the maximum and minimum roots, respectively, of B, then

$$m \leq \alpha_j \leq M, \qquad j = 1, 2, \cdots, n \tag{11}$$

In fact this theorem is sufficiently simple to prove here (see Note II).

Therefore any condition which insures $M < 0$ will insure that every root of A has a negative real part. Thus any condition which implies $M < 0$ is a sufficient condition for stability. Based on a classical theorem (*cf.* reference 10 for discussion and references) which states that the roots of B are separated by the diagonal elements of D, it has been shown that M and $H(B)$ are of like sign (4). Thus $H(B) < 0$ implies $M < 0$, and is a sufficient condition for stability.

If $H(B)$ is written out from the definition of equation [10] we have after some simplification

$$H(B) = H(A) + Q \tag{12}$$

where the positive quantity Q is

$$Q = -\frac{1}{4} \sum_{i=1}^{n-1} (c_i - r_i)^2/d_i \tag{13}$$

and from the definition of $H(A)$,

$$H(A) = a - \sum_{i=1}^{n-1} r_i c_i/d_i \tag{14}$$

If $H(A) > 0$ then $H(B) > 0$ and the sufficient condition for stability is infringed. But it has been seen that $H(A) > 0$ implies instability, since this implies the existence of an odd number of positive roots. Thus $H(A) < 0$ is a necessary condition for stability. In particular if $r_i c_i \geq 0$ for all i, it is seen from equation [14] that $a < 0$ is necessary for stability since under these conditions $a \geq 0$ implies $H(A) > 0$. Thus we have

(i)	$H(A) > 0$	instability
(ii)	$Q > -H(A) > 0$	stability or instability
(iii)	$-H(A) > Q > 0$	stability

Considering $H(A)$ on the real line, the region to the right of zero is a region of instability; the region between zero and $-Q$ may be stable or unstable; the region to the left of $-Q$ is a region of stability.

According to computations by Dr. Richard FitzHugh,[3] the ambiguous region (ii) may be rather broad. However the sufficient conditions (i) and (iii) for stability and instability, respectively, are not difficult to apply and give a region guaranteeing instability, a region guaranteeing stability, and a region which must be explored in more numerical detail. As noted, $H(A) < 0$ is a *necessary* condition for stability.

We close by indicating some connections between this analysis and that of Chandler, FitzHugh, and Cole (5). Assume,[4] as these authors tacitly did, that no d_j is a root of A. Then application of the determinantal identity already cited (reference 6, p. 46) to the characteristic matrix, $A - \lambda I$, gives the characteristic equation in the form

$$|A - \lambda I| = |D - \lambda I'| \, [a - \lambda - r(D - \lambda I')^{-1}c] = |D - \lambda I'| \, H(A - \lambda I) = 0 \quad [15]$$

where I and I' are the identity matrices of order n and $n - 1$ respectively. Under the assumption that $D - \lambda I'$ is not singular, the roots of A are the zeroes of the function $H(A - \lambda I)$. Chandler, FitzHugh, and Cole take as the characteristic equation

$$-CH(A - \lambda I) = 0 \quad [16]$$

where $C > 0$ is the membrane capacity per unit area, and they write equation [16] as (their equation 9)

$$g + F(\lambda) = 0, \quad [17]$$

on the basis that $-Ca = g + g_\infty$, where g_∞ is the infinite frequency membrane conductance and g is the conductance in series with the membrane. The factored equation form [16] of the characteristic equation was obtained in a different way by Smith and Morales (2) and in still a different way by Sheppard and Householder (1), who established certain properties of the roots of A by studying the poles of $H(A - \lambda I)$. What has been discussed here, is the role which the sign and magnitude of the quantity $-CH(A) = g + F(0)$ plays in determining the stability of a singular point for the space-clamped axon. In particular it is seen (reference 5, equation 10) that

$$-CH(A) = g + F(0) = g + g_\infty + g_m + g_h + g_n = \Sigma g,$$

where g_m, g_h and g_n are defined in reference (5), and the condition $H(A) > 0$ of this paper can be replaced, since $C > 0$, by $\Sigma g < 0$.

We have dealt specifically with application of some properties of mammillary matrices to the axon stability problem. It is clear that this analysis is applicable to any system obeying equation [2] and such that $\partial g_j/\partial x_j = d_j < 0$. What is more, arguments such as those leading from equation [5] to equation [9] can still be used

[3] Personal communication.

[4] Actually it can be shown that $\lambda \neq d_j$, for any j, provided that $r_ic_i \neq 0$ for all i, and the d_j are distinct.

when the signs of the d_j are known whether or not they are all of like sign. Finally, although linear chemical systems (and we include actual linear systems and non-linear systems when we are concerned with tracer kinetics) and *closed* non-linear chemical systems are stable (10), an open non-linear chemical system may have more than one singular point and some of these may be unstable. To the extent that equation [2] is obeyed, the present analysis is applicable to such systems and possibly to certain analogues of such systems.

NOTE I

If we accept the fact (reference 7, p. 80) that for two square matrices, F and G, of the same order, it is true that $|GF| = |F|\cdot|G|$, then for the case in hand the determinantal identity referred to is easily proved. Take the matrix

$$G = \begin{bmatrix} 1 & -rD^{-1} \\ 0 & I' \end{bmatrix}$$

where 0 is a column of $n - 1$ zeroes and I' is the unit matrix of order $n - 1$. By expanding the determinant $|G|$ according to the elements of the first column it is readily verified that $|G| = 1\cdot|I'| = 1$. Therefore $|GA| = |A|$. By direct multiplication, with A from equation [1], the produce GA is

$$GA = \begin{bmatrix} a - rD^{-1}c & 0 \\ c & D \end{bmatrix} = \begin{bmatrix} H(A) & 0 \\ c & D \end{bmatrix}$$

where we have used the definition of equation [4]. Expansion of the determinant of this last matrix according to the elements of the first row gives $|GA| = |A| = |D|\, H(A)$, the first equality of equation [5], which was to be proved.

NOTE II

Consider an arbitrary square matrix A. Denote by A^* the conjugate transpose of A; *i.e.*, if $A = [a_{ij}]$ then $A^* = [\bar{a}_{ij}]^T$. Applied to a column vector x this notation means that x^* is a row vector, each element of which is the complex conjugate of the corresponding element of x. Let $\lambda = \alpha + i\beta$ be any root of A and x the corresponding characteristic vector. Then we have

(i) $$Ax = \lambda x$$

(ii) $$x^* A^* = \bar{\lambda} x^*$$

If (i) is multiplied from the left by $x^*/2$ and (ii) from the right by $x/2$, and the corresponding equations added, there results

(iii) $$x^* \frac{(A + A^*)}{2} x = x^* Bx = \alpha x^* x$$

Now the matrix $B = (A + A^*)/2$ is Hermitian (if A is real, $A^* = A^T$, and B is symmetric) and thus has real roots $M = \mu_1 \geq \mu_2 \geq \ldots \geq \mu_n = m$. The real number $\alpha = x^*Bx/x^*x$ lies in the field of B (*e.g.* see reference 9) and is thus contained in the interval (m,M) as will now be shown. Since B is Hermitian it is standard that there exists a matrix U, such that $U^* U = I$ and $U^* BU = \text{diag}\,(\mu_1, \mu_2, \ldots, \mu_n)$. Thus if in (iii) we substitute $x = Uy$ we obtain

$$\text{(iv)} \qquad \alpha = \sum \bar{y}_i y_i \mu_i / \sum \bar{y}_i y_i = \sum w_i \mu_i$$

where $w_i = \bar{y}_i y_i / \Sigma \bar{y}_i y_i$, and $\Sigma w_i = 1$. Therefore α is the weighted mean of the μ_i and cannot exceed M or be exceeded by m. For, if (iv) is written as $\Sigma w_i(\mu_i - \alpha) = 0$, it is seen, since $w_i \geq 0$, that both $\alpha > M$, which implies $\alpha > \mu_i$ for all i, and $\alpha < m$, which implies $\alpha < \mu_i$ for all i, lead to a contradiction. It is proved that $m \leq \alpha \leq M$.

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