THE PHYSICAL INTERPRETATION OF MATHEMATICAL MODELS FOR SODIUM PERMEABILITY CHANGES IN EXCITABLE MEMBRANES

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ABSTRACT This paper deals with the physical interpretation of existing mathematical models which describe the transient sodium conductance changes in excitable membranes. It is shown that there are clear limitations to the specificity of inferences which may be drawn about physical mechanism from the behavior of abstract models. Within these limitations, it is shown that a pronounced inactivation shift is not necessarily evidence for coupling between the events responsible for the rise and inactivation of the sodium conductance, but that the inactivation shift may be associated with an event whose rate explicitly depends on the rate of continuous voltage change or magnitude of instantaneous voltage change.

INTRODUCTION

An empirical quantitative description of the sodium permeability changes in nerve membrane was achieved over 20 years ago (Hodgkin and Huxley, 1952). The Hodgkin-Huxley mathematical model by no means implies a particular physical mechanism for the permeability changes, although the formal similarity to common statistical mechanical functions of some terms in the Hodgkin-Huxley equations has been noted (Agin, 1963). Various more or less explicit physical mechanisms for the transient sodium conductance changes, not formally related to the Hodgkin-Huxley equations, have been suggested (Goldman, 1971; Jakobsson, 1969; Moore and Jakobsson, 1971; Wei, 1971; Tasaki, 1968; Offner, 1972; Fishman et al., 1972). An alternative empirical mathematical model has also appeared (Hoyt, 1968). The fact that the Hoyt model behaves differently from the Hodgkin-Huxley model in slight but measurable ways (i.e., the inactivation shift) adds a new dimension of relevance to the basic question: what aspects of physical mechanism may be inferred from the form of an empirical mathematical model for a process? This paper deals with that question as it applies to existing models for sodium conductance change in excitable membranes.

PHYSICAL INTERPRETATION OF SETS OF COUPLED DIFFERENTIAL EQUATIONS

Consider a set of n coupled differential equations in n variables of the form:

$$\left.\begin{aligned} \dot{X}_1 &= f_1(X_1, \cdots, X_i, \cdots, X_n) \\ \dot{X}_i &= f_i(X_1, \cdots, X_i, \cdots, X_n) \\ \dot{X}_n &= f_n(X_1, \cdots, X_i, \cdots, X_n) \end{aligned}\right\}. \tag{1}$$

The models which have been proposed to simulate the behavior of nerve membranes are of this form. In the Hodgkin-Huxley model (Hodgkin and Huxley, 1952), for example, $n = 5$. The five time-varying quantities or X_i's are: I, V, m, n, and h. In the Hoyt model (Hoyt, 1968), n also equals 5. The X_i's are: I, V, ν, ω, and ν_k. A sometimes useful way of looking at such sets of equations is to interpret their behavior geometrically as sets of trajectories in an n-dimensional space (Lefschetz, 1957; FitzHugh, 1960). Physically, the experimenter alters the behavior of a nerve membrane by passing current from one side of it to the other. In the geometrical interpretation of the Hodgkin-Huxley or Hoyt equations, this means that the experimenter may control the system's position along the I axis, with its trajectory along the other four dimensions following from equations of the form 1. In this context, a voltage clamp experiment is viewed not as a different kind of stimulus from a current injection but as an injection of current just sufficient to maintain a constant voltage. A very important point follows from this geometrical analogy. Just as the trajectory of a particle through normal three-dimensional space is unaffected by the choice of coordinate system used to describe that space, so is the behavior of a nerve membrane model unaffected by the choice of coordinate system used to describe the five-dimensional space in which it exists. Because they are directly measurable, there seems no profit in any coordinate transformation involving the plane defined by I and V. In the remaining h, m, n space of the Hodgkin-Huxley axon there seems considerable evidence that the system's trajectory in the n direction (the potassium or late current) is not coupled by physical mechanism to the trajectory in the m-h plane (the sodium or early transient current). The corresponding statement is true of the Hoyt model, i.e., the trajectory in the ν_k direction is not coupled to its trajectory in the ν-ω plane. The important point to make at this juncture is that one may choose any one of an infinite number of coordinate systems to describe the m-h or ν-ω planes, and the system's trajectory as projected on those planes will be totally independent of that choice. Translating this statement back out of the geometrical analogy, one can refer to the system's trajectory projected on the m-h or ν-ω plane as the behavior of its sodium or fast transient system and can say that there are an infinite number of equivalent representations of both the Hodgkin-Huxley and Hoyt models for this system. By equivalent representations, I mean sets of equations with identical input-output characteristics. In this case, each equivalent representation of a fast transient system model will

give identical fast transient conductance or permeability behavior for a given voltage or sequence of voltages. The Hodgkin-Huxley and Hoyt equations for the fast transient conductance as presented by their authors can now be seen as but one each of an infinite number of equivalent representations of their respective model systems. This is a vital point for the physical interpretation of these models. Even if a particular mathematical model describes a system's behavior correctly, there is still no more than one representation in which the mathematical variables represent the discrete physical components of the system, and it is only from this representation that one may make inference about the nature of those components and their interactions with each other.

How does one achieve this particular physical representation, or judge when it has been achieved? Emphatically *not* solely by the criterion of fitting the system's experimentally determined behavior, because it has already been pointed out that there are an infinite number of representations which will do that equally well. One approach to achieving this physical representation is to build up the mathematical model directly from a postulated physical concept of the system components and how they interact with each other. A second approach is to treat the system as a black box and deduce its internal structure from its observed kinetics. Ultimately, both approaches will almost certainly have to be combined to give us a complete story of the molecular basis of excitability. The Hodgkin-Huxley and Hoyt equations for the fast transient system are compact descriptions of that system's observed kinetics and thus form a possible starting point for the second approach to achieving a physical representation, but they are *not* necessarily physical representations in themselves. To determine the physical significance of these models, one should consider also the equivalent representations which are related to the original equations by transformation of variables (or, in the geometrical interpretation, by phase-space coordinate transformations.).

APPLICATION OF VARIABLE TRANSFORMATIONS TO SPECIFIC MODELS FOR THE FAST TRANSIENT SYSTEM

The purpose of this paper is to apply the above general considerations to existing proposed models which represent the behavior of this system and suggest thereby what may and may not be inferred from these models about the physical processes underlying that behavior. Before going into the distinctions between these models, we should state what they have in common. The kinetics of the fast transient system are clearly voltage dependent, and so are the kinetics of all the proposed models. Another consensus belief about the sodium system is that there are two physical processes involved. This seems clear because the response to a step input (voltage is the input to this system) is, under a wide range of conditions, an output which has a transient peak (conductance is the output). One point of discussion has been whether these two underlying physical processes have independent kinetics or

whether they are kinetically coupled to each other. We would like to know further, in as much detail as possible, just what these physical processes are.

In this paper, I will mention three models of the sodium system which have been carried to the point of numerical computations. They are the classic Hodgkin-Huxley model, the more recently proposed Hoyt model, and the Moore-Jakobsson model (Moore and Jakobsson, 1971). The models, as represented by their authors are as follows:

The Hodgkin-Huxley model:

$$\left.\begin{aligned} g_{Na} &= g_{Na} m^3 h \\ dm/dt &= \alpha_m(1 - m) - \beta_m m \\ dh/dt &= \alpha_h(1 - h) - \beta_h h \end{aligned}\right\}. \tag{2}$$

α_m, β_m, α_h, β_h are the empirical functions of voltage.

The Hoyt model:

$$\left.\begin{aligned} g_{Na} &= f(\nu) \text{ } (f \text{ is an empirical monotonically increasing function of } \nu) \\ d\nu/dt &= -k_1(\omega - \omega_{eq}) - k_3(\nu - \nu_{eq}) \\ d\omega/dt &= -k_1(\omega - \omega_{eq}) \end{aligned}\right\}. \tag{3}$$

k_1, k_3, ν_{eq}, ω_{eq} are the empirical functions of voltage.

The Moore-Jakobsson model:

$$\left.\begin{aligned} P_{Na} &= \bar{P}_{Na} S_m \\ \frac{dS_m}{dt} &= \left\{ -\frac{k_m}{1 + K_c[Ca]_o} + k_{-m}[Ca]_o + k_h \right\} S_m \\ &\quad + \left\{ k_{-h} - \frac{k_m}{1 + K_c[Ca]_o} \right\} S_h + \frac{k_m}{1 + K_c[Ca]_o} \\ \frac{dS_h}{dt} &= k_{-h} S_h + k_h S_m \end{aligned}\right\}. \tag{4}$$

k_m, k_{-m}, k_h, k_{-h}, K_c are empirical functions of voltage; $[Ca]_o$ is external calcium ion concentration.

Let us look at these three models in the light of the general features of sets of coupled differential equations mentioned above. First, it might be noted again that each of these sets of equations is not a system, but rather a particular representation of a system. As such, it is but one of an infinite number of equivalent representations. Once one representation is set forth, any other equivalent representation may be generated by a transformation of variables. For example, the

Hodgkin-Huxley model, given the transformation $\xi = m^3h$, goes over to the equivalent representation in ξ and m:

$$\left.\begin{aligned} g_{Na} &= g_{Na}\xi \\ d\xi/dt &= \alpha_h(m^3 - \xi) - \beta_h\xi \\ &\quad + 3\,\alpha_m[(\xi/m) - \xi] - 3\,\beta_m\xi \\ dm/dt &= \alpha_m(1 - m) - \beta_m m \end{aligned}\right\} . \tag{5}$$

We should note some things about Eq. 5. Firstly, although the original Hodgkin-Huxley equations are cast in terms of the uncoupled variables m and h with g_{Na} being a function of both of them, the equivalent representation 5 is cast in terms of one independently varying quantity (m) and a quantity (ξ) which is coupled to the independent variable. Furthermore, the conductance is a function of the coupled variable only. In short, the representation 5 of the Hodgkin-Huxley model is coupled in just the same way as is the Hoyt model. This specific example points up an important general feature of representation of linear systems by sets of differential questions. This is that, in transformation from one equivalent representation to another, the state of coupledness or uncoupledness is not necessarily preserved This fact is well known and applied in the analysis of such diverse systems as electrical circuits, crystal lattices, chemical reactions, and quantum waves. Mathematical simplification is often achieved by finding the uncoupled representations. This process is sometimes called finding the normal modes, or diagonalizing the matrix, or finding the eigen-functions of a system.

A second point to note about Eqs. 5 is that, in contrast to m and h in the original Hodgkin-Huxley equations Eqs. 2, the variable ξ does not seem a plausible candidate for an actual physical variable, because it is difficult to think of a physical process represented by the equation describing its time-course.

At this point we can come to a conclusion and a direction for the rest of this paper. The conclusion is that the coupledness or uncoupledness of a particular set of equations, i.e., a representation, describing a phenomenon is *in itself* totally irrelevant to the question of whether the physical processes underlying that phenomenon are coupled or uncoupled. It may be, however, that one can judge based on the form of the equations whether a particular representation is more plausible than another as a candidate for the physical representation and, indeed, whether perhaps one representation is the most likely physical representation of all possibilities. Only to the extent that such judgments can be made, can the behavior of particular representations be evidence for the coupledness of physical processes. Let us investigate then the plausibility of ascribing physical reality to various equivalent representations of the models for the sodium system which have been proposed.

PHYSICAL INTERPRETATIONS OF MATHEMATICAL REPRESENTATIONS FOR THE FAST TRANSIENT SYSTEM

One question which might be dealt with here, since the author of the model does not answer it explicitly and since the answer is not obvious, is: what physical mechanism might be directly represented by the Hoyt equations? To deal with this question, first note that we can factor ω itself explicitly out of the equation for $\dot{\nu}$ and leave $\dot{\omega}$ only, giving $\dot{\nu} = \dot{\omega} - k_3(\nu - \nu_{eq})$.

Under voltage clamp conditions, the Hoyt equation for $\dot{\nu}$ may be written:

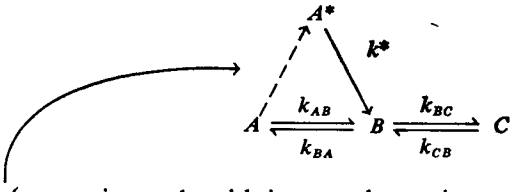
$$\dot{\nu} = -k_1(\omega_o - \omega_{eq})e^{-k_1 t} - k_3(\nu - \nu_{eq}). \tag{6}$$

Note the form of the first term on the right side of Eq. 6. It is a single exponential with an initial value dependent on the step size $(\omega_{eq} - \omega_o)$ and a time constant depending on voltage. This is just the form of the concentration of a transient excited state, whose population increase depends on how much energy is put into the membrane in a voltage step. In fact, the creation of such a state in the form of a nonequilibrium distribution of surface dipoles has previously been proposed by Wei (Wei, 1971) as a physical basis for the transient increase in sodium permeability.

It can be shown that the Hoyt equations may represent the addition of a transient excited state to the following scheme:

$$A \underset{k_{BA}}{\overset{k_{AB}}{\rightleftharpoons}} B \underset{k_{CB}}{\overset{k_{BC}}{\rightleftharpoons}} C; \qquad g_{Na} = f(B). \tag{7}$$

In scheme 7 state A is resting, state B is permeable or conductive, and state C is inactivated. On a depolarizing step, the model goes from A to C, with a transient increase in B. Adding a transient excited state to this scheme takes it to:



(occurs instantly with instant change in membrane ΔV). (8)

For a depolarizing clamp, it is reasonable to set the parameters k_{AB} and k_{BA} slower than 1 ms and $k_{CB} \ll k_{BC}$. In this event the differential equation for the time-course of B goes to:

$$dB/dt = k^* A_o^*(V, V_o)e^{-k^* t} - k_{BC}B. \tag{9}$$

Eq. 9 corresponds to Eq. 6 term-for-term in the following way: k^* is dependent on instantaneous voltage, corresponding to k_1 ; A_o^* depends on V and V_o and cor-

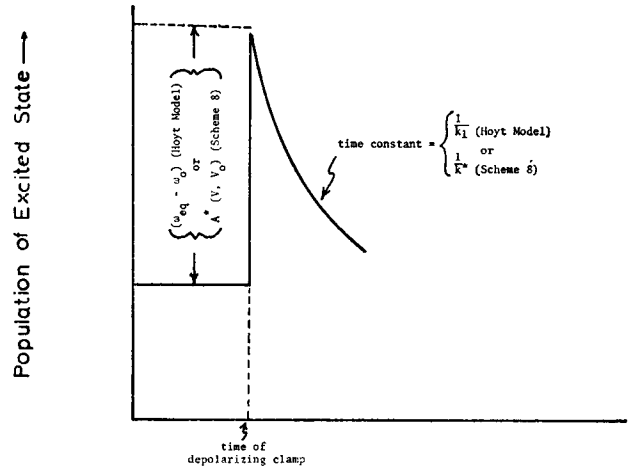


FIGURE 1 Concentration of transient excited state involved in one physical interpretation of Hoyt model for early transient current.

responds to $(\omega_{eq} - \omega_o)$, k_{BC} depends on instantaneous voltage, corresponding to k_3, and ν_{eq} corresponding to steady-state value of g_{Na} is near 0. B corresponds to ν, instantaneous value of g_{Na}. The time-course of the transient excited state concentration for a voltage clamp is shown in Fig. 1.

One very interesting feature of this interpretation of the Hoyt variables as physical quantities is that it leads to kinetics with explicit dependence on voltage change (scheme 8), rather than kinetics with a pure dependence on instantaneous voltage. This is a necessary consequence of one-way coupling. ($\dot{\omega}$ independent of ν but $\dot{\nu}$ dependent on ω). The only way that one-way coupling in a physical representation can be consistent with conservation of energy is for the quantity associated with the independent variable (note: the physical quantity A^* is precisely represented by $\dot{\omega}$ not ω) to be created directly from energy added to the system. In the fast transient permeability system the obvious energy source is the change in electric field.

It should be noted that the above treatment does not deal satisfactorily with the problem of physically interpreting the Hoyt equations under condition of a hyperpolarizing voltage step. Thus scheme 8 and Eq. 9 do not constitute a complete physical interpretation of the Hoyt equations but rather a possible mechanism to explain the special behavior of those equations under depolarizing voltage steps of various sizes.

Interestingly, the Hoyt equations do *not* represent, even indirectly, scheme 7:

$$A \underset{k_{BA}}{\overset{k_{AB}}{\rightleftharpoons}} B \underset{k_{CB}}{\overset{k_{BC}}{\rightleftharpoons}} C. \qquad (7)$$

It *is* possible however, by making a transformation of the form

$$\begin{cases} \nu = B \\ \omega = B + \alpha C \end{cases}$$

where α is a constant, to represent scheme 7 by the set of equations:

$$\left.\begin{aligned} d\nu/dt &= \alpha_{\nu\nu}(\nu - \nu_{eq}) - \alpha_{\nu\omega}(\omega - \omega_{eq}) \\ d\omega/dt &= \alpha_{\omega\omega}(\omega - \omega_{eq}) \end{aligned}\right\}. \tag{10}$$

At first glance, Eqs. 10 look like the Hoyt model, if one makes the substitutions:

$$\left.\begin{aligned} \alpha_{\nu\nu} &= k_3 \\ \alpha_{\nu\omega} &= k_1 \\ \alpha_{\omega\omega} &= k_1 \\ \nu_{eq} &= \nu_{eq} \\ \omega_{eq} &= \omega_{eq} \end{aligned}\right\}. \tag{11}$$

Unfortunately, the above substitutions cannot be made and still have the model represent scheme 7, because they involve setting simultaneously five parameters as empirical functions of voltage ($\alpha_{\nu\nu}$, $\alpha_{\nu\omega}$, $\alpha_{\omega\omega}$, ν_{eq} , ω_{eq}) and scheme 7 only has four parameters to set empirically (k_{AB} , k_{BA} , k_{BC} , k_{CB}). Since $\alpha_{\nu\nu}$, ν_{eq} , $\alpha_{\nu\omega}$, ω_{eq} , and $\alpha_{\omega\omega}$ in Eqs. 10 are all functions of (k_{AB} , k_{BA} , k_{BC} , k_{CB}) in scheme 7, only four of them can be used as independent empirical parameters and the fifth is a function of the other four. It is true that one can arrange the values of (k_{AB} , k_{BA} , k_{BC} , k_{CB}) so that $\alpha_{\nu\omega} = \alpha_{\omega\omega}$, as in the Hoyt model, but one cannot simultaneously do this and also independently choose empirical values for $\alpha_{\nu\nu}$, $\alpha_{\omega\omega}$, ω_{eq} , and ν_{eq} , as is done in the Hoyt model. At least, one cannot do this and still have a set of equations representing scheme 7.

The Hoyt equations may be transformed into variables which are independent at constant voltage. Under the transformation:

$$\mu = \nu + \left(\frac{k_1}{k_3 - k_1}\right)\omega,$$

the Hoyt equations go to:

$$\left.\begin{aligned} \dot{\omega} &= -k_1(\omega - \omega_{eq}) \\ \dot{\mu} &= -k_3(\mu - \mu_{eq}) + \omega \frac{d}{dV}\left[\frac{k_1}{k_3 - k_1}\right]\frac{dV}{dt} \\ g_{Na} &= f\left(\mu - \frac{k_1}{k_3 - k_1}\omega\right) \end{aligned}\right\}. \tag{12}$$

Considered as a physical representation, Eqs. 12 have some interesting qualities. It is uncoupled when the voltage is constant ($dV/dt = 0$) but coupled otherwise. The sodium conductance is a sum rather than a product of the two variables, sug-

gesting two parallel channels. The sign of the two terms in the expression for the conductance will be different. In general, the ω term will contribute a positive value while the μ term will contribute a negative value, and the ω term will relax with a fast time constant $(1/k_1)$ while the μ term will relax with a slow time constant $(1/k_8)$. Thus if we consider ω and μ as representative of physical channels, ω will give rise to the activation process while μ will give rise to inactivation and, since μ contributes a negative conductance, we must infer that in this representation the inactivation process involves active transport. In summary, we have in this representation of the Hoyt model the conductance as the sum of that of two parallel channels, a fast-relaxing activation channel through which sodium moves down its electrochemical gradient and a slow-relaxing inactivation channel, through which sodium is electrogenically pumped up its electrochemical gradient. There is no coupling between the two channels when the voltage is constant, but there is when the voltage is changing. Hence, the coupling mechanism requires energy, and the source of energy, as in scheme 8, is the membrane capacity.

It is also possible to transform the Hodgkin-Huxley equations into a form which suggests parallel channels, although as in the previous transformation of the Hodgkin-Huxley model the resultant formulation does not seem very plausible as a physical representation. Consider the transformation:

$$\left.\begin{aligned} \mu &= m + k_\mu h \\ \sigma &= m + k_\sigma h \end{aligned}\right\}, \tag{13}$$

where k_μ , k_σ are constants. Then the equations for the time-course of μ and σ are:

$$\left.\begin{aligned} \dot{\mu} &= \alpha_{\mu\mu}\mu + \alpha_{\mu\sigma}\sigma + \alpha_\mu \\ \dot{\sigma} &= \alpha_{\sigma\mu}\mu + \alpha_{\sigma\sigma}\sigma + \alpha_\sigma \end{aligned}\right\}, \tag{14}$$

where the α's are functions of α_m , β_m , α_h , β_h , k_σ , and k_μ ; and the sodium conductance is given by:

$$g_{Na} = g_{Na}\frac{[(k_\mu\sigma - k_\sigma\mu)^3(\mu - \sigma)]}{(k_\mu - k_\sigma)^4}. \tag{15}$$

If σ and μ are physical variables, Eqs. 14 show they are coupled and the fact that linear combinations of σ and μ appear in the expression 15 for the conductance suggest that these variables represent parallel pathways for ion flow. But it is difficult to develop a reasonable complete physical picture, corresponding to Eq. 15, for what physical entities the quantities μ and σ might represent.

The Moore-Jakobsson model, like the Hoyt model, has been presented by its authors in coupled form. Unlike the Hoyt model, however, it is derived from a

specific kinetic scheme, namely:

$$\begin{array}{c} \text{(fast)} \\ S_c \underset{k_{-r}[\mathrm{Ca}]_o}{\overset{k_r}{\rightleftharpoons}} S_r \underset{k_{-m}[\mathrm{Ca}]_o}{\overset{k_m}{\rightleftharpoons}} S_m \underset{k_{-h}}{\overset{k_h}{\rightleftharpoons}} S_h \\ \text{(fast)} \end{array} \qquad (16)$$

where $K_c = k_{-r}/k_r$, and where k_{-r} and k_{-m} are rate constants for calcium binding on to the sodium transfer site while k_r and k_m are rate constants for calcium unbinding. Because Eqs. 4 are derived from scheme 16, the calcium dependence of the coupling coefficients makes physical sense according to the law of mass action only if the mathematical variables in the physical representation are two of the three (S_m, S_h, and S_r). Hence, the Moore-Jakobsson model is inherently coupled, in a way that the Hodgkin-Huxley and Hoyt models are not either coupled or uncoupled. It might be possible to construct an uncoupled model using the basic calcium-binding hypothesis which underlies the Moore-Jakobsson model, but it would be much more complex. The coupled model is suggested quite naturally by the experimental fact that the turning on and inactivation parameters are shifted in the same direction for a given change in external calcium, a fact quite difficult to duplicate in any model which would combine calcium binding with uncoupled kinetics.

RELEVANCE TO EXPERIMENTAL DATA

The different mathematical models which have been proposed to describe the kinetics of fast transient permeability changes in excitable membranes, while all fitting the general time-course of this permeability as determined experimentally, differ in certain detailed ways in the type of behavior they predict. One of the possibly significant differential predictions concerns the dependence of the steady-state inactivation on the size of the test-pulse used to measure it.

Computed results have not shown a significant shift of inactivation with test-pulse size for the Hodgkin-Huxley or Moore-Jakobsson models but they have for the Hoyt model (Hoyt, 1968; Moore and Jakobsson, 1971). Thus far, it has not been conclusively determined to what extent these differential predictions reflect inherent characteristics of the forms of the equations, and to what extent the models' behavior with regard to the inactivation shift might be changed by changes in numerical parameters. Experimentally, the inactivation shift has been investigated in squid and *Myxicola* (Hoyt and Adelman, 1970; Goldman and Schauf, 1972). This paper has nothing to add to the issue of which model in fact fits the data better or best; it is rather concerned with physical interpretations of the models regardless of relative fit.

SUMMARY AND CONCLUSIONS

Because of the general properties of sets of coupled differential equations, it is not possible to say with certainty that the Hodgkin-Huxley and Hoyt models represent either coupled or uncoupled physical processes. All such arguments must rest on the plausibility as physical systems of particular representations of these models. By these criteria, it is shown that the Hoyt model may represent either fully coupled physical events or events which have a coupling coefficient which goes to zero when $dV/dt = 0$. In the physical schemes presented in this paper which are associated with each of these possibilities, there must be a mechanism with a rate dependent on voltage change, which implies some energy exchange between the sodium system and the membrane capacity. It is shown that the Hoyt equations do *not* represent a simple coupled kinetic scheme with pure voltage-dependent kinetics. The fact that the Moore-Jakobsson model, which does represent such a simple coupled kinetic scheme, does not (at least for the authors' original parameters) show a pronounced inactivation shift, seems further evidence that the existence of this shift is not a function of coupling per se (Jakobsson and Moore, 1971). One hypothesis concerning the physical basis for the inactivation shift, which would be consistent with the results presented in this paper, is that it might be due to a mechanism whose rate is explicitly related to voltage change. Such a mechanism might involve energy transfer between the sodium transfer site and the membrane capacitance. A preliminary report has been made of the results of adding such a mechanism directly to the Hodgkin-Huxley model (Jakobsson and Scudiero, 1973); the resultant model can display an inactivation shift or not, depending on parameter values. It is still entirely possible of course that a different hypothesis for the physical basis of the inactivation shift, consistent with pure voltage dependent rate constants, may be found.

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