INDEPENDENCE OF THE SODIUM AND POTASSIUM CONDUCTANCE CHANNELS

A KINETIC ARGUMENT

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ABSTRACT Tightly coupled models for the sodium and potassium conductance changes, in which the potassium "on" process is intimately related to the sodium "on" and "off" processes, are studied. It is shown that such coupled models are incapable of simultaneously showing the observed effects of conditioning potentials on sodium inactivation and on the translation of the potassium conductance in time. It is concluded that the primary mechanisms for the sodium and potassium channels are probably independent.

INTRODUCTION

In the original Hodgkin and Huxley (1952) model for the conductance changes of nerve fiber membranes, three completely independent variables (n, m, and h) were postulated to account for these changes. Their model can be called *completely uncoupled* since the differential equation describing any one of the three variables contains no terms involving the other two variables. The *HH* model is indicated schematically as case A of Fig. 1; the n process is shown in the first line, the m process in the second line, and the h process in the last line.

On the other hand, in models such as those of Mullins (1960) and Goldman (1964), the sodium (early) and potassium (delayed) conductance changes are described by coupled processes. Upon applying a depolarizing clamp the early high sodium conductance state is an unstable intermediate that must be passed through before the final high potassium conductance state can be reached. In such *completely coupled* models sodium inactivation and potassium activation are not independent of one another. These models are indicated schematically as case C of Fig. 1.

An intermediate type of model has also been described (Hoyt, 1963, 1968) in which the primary processes describing the activation of the potassium channel are considered to be independent of (not coupled to) those that describe the activation and inactivation of the sodium channel. The latter, however, are considered to be coupled together in such a way that the activated sodium state is an unstable inter-

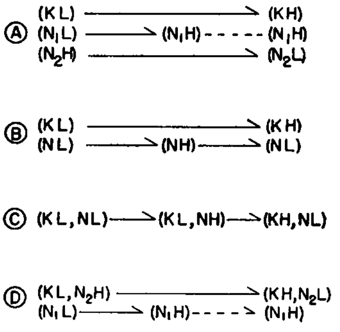

FIGURE 1 Classification of some models. *KL* and *KH* stand for low and high potassium conductance states, *NL* and *NH* for low and high sodium conductance states. Upon application of a depolarizing voltage clamp, the membrane is assumed to undergo the transitions shown by the arrows, from an initial resting state to a final depolarized state. (A) The completely uncoupled model of Hodgkin and Huxley. (B) Intermediate coupled model of Hoyt. (C) The completely coupled models of Mullins and Goldman. (D) An alternative intermediate coupled model.

mediate that must be passed through before the inactivated sodium state is reached. This intermediate model is shown as case B of Fig. 1.

Still another intermediate model is shown as case D of Fig. 1. Here the sodium activation process is decoupled from the sodium inactivation process but the latter is coupled to the potassium activation process (or maybe is identical to it).

Although not all possible models, including perhaps the "correct" one, can be categorized by placing them in one or another of the four classifications of Fig. 1, comparative judgments of the relative ability of models of these four classes to fit the known experimental behavior may lead to a better understanding of the underlying phenomena. A first step in this process of comparative judgment among the classes of Fig. 1 has already been taken. In this first step the question of no coupling (A or B) or of a coupling (C or D) of the potassium to the sodium system was bypassed. Rather the question was asked whether the sodium system is better represented by a coupled system (B or C) or by two uncoupled, independent processes (A or D). Theoretical analyses (Hoyt, 1968) and subsequent comparison with experiments (Hoyt and Adelman, 1970) have shown that sodium inactivation experiments are better described by a coupled sodium system (B or C) than by the independent sodium processes model (A or D).

If one thus rules out A and D, the question remains whether no primary coupling (B) or intimate primary coupling (C) exists between the mechanisms responsible for the sodium and potassium conductance changes. Arguments such as those based on the action of TEA (tetraethyl ammonium ion) on the potassium conductance alone and on the action of TTX (tetrodotoxin) on the sodium conductance alone (Mullins, 1968 *a*, *b*; Narahashi and Moore, 1968) provide strong presumptive, but not conclusive, evidence for discarding the completely coupled models (C). The remainder of this paper is concerned with the kinetic arguments that also can be used to rule out classification C, leaving B as best able, among these four, to describe nerve fiber behavior.

Throughout the above discussion and in what follows, the terms coupled and uncoupled are restricted to the description of the primary processes responsible for the conductance changes. Many secondary, second-order couplings are undoubtedly present, due for example to the fact that the sodium and potassium mechanisms, even if separate, are probably situated in closely contiguous regions of the membrane and therefore can interact, at least secondarily, by their mutual electrostatic and elastic effects on the intervening membrane. Such secondary couplings can produce second-order effects of one system on the other even if their primary processes are distinct. It is only the latter primary (qualitative) rather than second-order (quantitative) phenomena that are considered in what follows.

An experimental basis for distinguishing between B and C may lie in the effects of conditioning voltages, which affect the sodium and potassium conductance changes produced by depolarizing test clamps in strikingly different ways. For a given test clamp the magnitude of the peak sodium conductance is greatly affected by the conditioning potential, as shown by the typical inactivation curve. On the other hand, for a given test clamp the only effect of the conditioning potential on the monotonic rise of the potassium conductance to its steady-state level[1] is to translate the conductance-time curve along the time axis (Cole and Moore, 1960). We therefore now ask, is it possible for a completely coupled system (C of Fig. 1) to show correctly these two different conditioning effects on the intermediate sodium state and on the final potassium state? If the answer is "no" we will have added a very strong argument in favor of B over C. As an aid to the reader, in the next section two specific coupled systems are analyzed, one showing the correct potassium shift in time and the other the correct sodium inactivation, but neither showing both phenomena. In the following section a general treatment is applied to the wide class of linear coupled systems, first-order in time, and it is shown that no such system can satisfy both criteria at once. The restrictions of linearity and first-order in time are then removed and the same conclusions are shown to apply.

CONDITIONING IN TWO SPECIFIC COUPLED SYSTEMS

The HH-Armstrong Potassium System

As noted by Cole and Moore (1960) the property of translation in time is built into the HH, n^4, model. Since n itself satisfies a linear first-order equation it has solutions of the form

$$n = n_\infty - (n_\infty - n_0) \exp - (t/\tau_n). \qquad (1)$$

This can be rewritten as

$$n = n_\infty[1 - \exp - (t - t_0)/\tau_n], \qquad (2)$$

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[1] Throughout this paper the very long time-constant potassium inactivation described by Ehrenstein and Gilbert (1966) is neglected.

where the time shift, t_0, is related to the initial value, n_0 by

$$(n_0/n_\infty) = 1 - \exp\,(t_0/\tau_n). \tag{3}$$

Whether the potassium conductance is given by a fourth-power dependence

$$g_k = \bar{g}n_\infty{}^4[1 - \exp - (t - t_0)/\tau_n]^4,$$

a sixth- or a twenty-fifth-power dependence (Cole and Moore, 1960), or a less simply expressed monotonic dependence on n

$$g_k = \bar{g}f(n) = \bar{g}f(n_\infty[1 - \exp - (t - t_0)\tau_n])$$

(Hoyt, 1963), the only effect of changing the initial conditioning level, for a given fixed final level, is a shift (t_0) along the time axis, with no change of shape. This behavior results from the nature of the differential equation obyed by n.

Recently Armstrong (1969) has used a coupled-equations formulation of the HH n^4 model, adding to it a final step to describe the potassium inactivation produced by quaternary ammonium ions and omitting the very long time-constant inactivation of Ehrenstein and Gilbert (1966). The Armstrong formulation, omitting the inactivation states, is represented in Fig. 2 *a*, where the final-state *Y* represents the potassium-activated state. In terms of the model suggested by Hodgkin and Huxley (1952), *U* can be thought of as a site with no activating particles present, *V* a site with one activating particle, etc. The particular choice of the integral ratios shown for

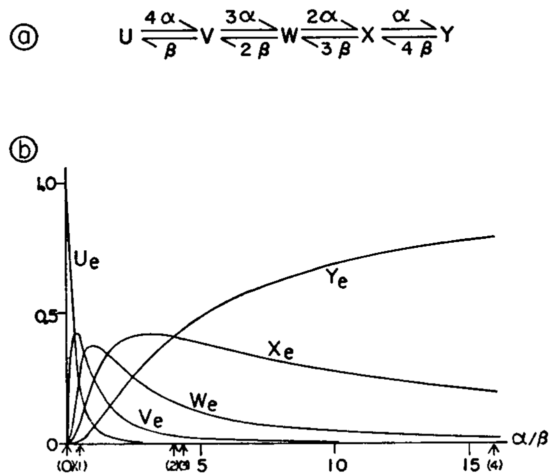

FIGURE 2 The Armstrong formulation of the Hodgkin and Huxley n^4 process. (*a*) The coupled system. (*b*) The dependence of the relative equilibrium values as functions of the rate constant ratio, α/β. The arrows and numbers in parentheses indicate the α/β values used in Fig. 3.

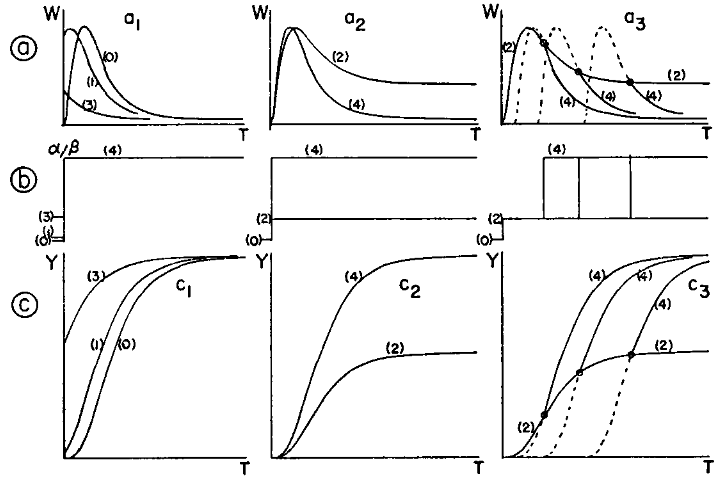

FIGURE 3 Time dependences of the Armstrong system of Fig. 2. Rows *a* and *c* show the *W* and *Y* states, respectively. The initial and final values of α/β are shown in row *b*. The numbers in parentheses refer to the numbered α/β values shown by arrows in Fig. 2 *b*. They are: (0) $\alpha/\beta = 0.0$; (1) $\alpha/\beta = 0.6$; (2) $\alpha/\beta = 4.0$; (3) $\alpha/\beta = 4.4$; (4) $\alpha/\beta = 16.0$. In column 2, the initial value of α/β is (0) throughout, and the final values are shown beside each curve. In column 3, α/β is first stepped from 0 to 2, followed at various later times by a step to 4. The dashed portions represent initial portions of curves 4 of column 2, translated in time by appropriate amounts.

the forward and back rate constants correctly weight the probabilities of the five states. The relative equilibrium probabilities of the five states are shown as functions of the rate constant ratio, α/β, in Fig. 2 *b*. This coupled-equation formulation, in which the final-state *Y* is associated with the high potassium conductance state, immediately raises the question whether the high sodium conductance state can be associated with one of the intermediate states such as *W* or *X*. That this is not possible is shown as follows.

As indicated by Armstrong (1969), the solution of the set of linear first-order equations that describe Fig. 2 *a* are most easily expressed in terms of the variable *n* where

$$n = n_\infty[1 - \exp - a(t - t_0)], \tag{4 a}$$

$$a = 1/\tau_n = \alpha + \beta, \tag{4 b}$$

$$n_\infty = (Y_\infty)^{1/4} = \alpha/(\alpha + \beta), \tag{4 c}$$

$$n_0 = (Y_0)^{1/4} = n_\infty(1 - \exp a\, t_0). \tag{4 d}$$

In terms of *n* the solutions for the five states are easily shown to be

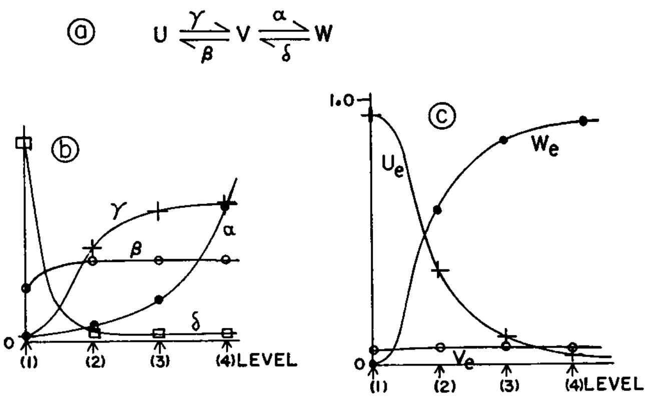

FIGURE 4 (*a*) A three-state system that shows inactivation. (*b*) Rate constant values at four different "voltage" levels. (*c*) Relative equilibrium values of the three states at the four "voltage" levels.

$$U = (1 - n)^4, \qquad (5\,a)$$

$$V = 4n(1 - n)^3, \qquad (5\,b)$$

$$W = 6n^2(1 - n)^2, \qquad (5\,c)$$

$$X = 4n^3(1 - n), \qquad (5\,d)$$

$$Y = n^4. \qquad (5\,e)$$

Substitution of Equation 4 *a* into Equations 5 shows that not only does the final-state Y have the property of translation in time, but so do all the intermediate states. This property is shown in Fig. 3 *a* and *c* for states W and Y. It is apparent that no intermediate state of this system can be associated with the sodium conductance; if an intermediate state rises to a peak and then falls, the magnitude of the peak is unaffected either by the initial level or by the final level (Fig. 3 *a*). On the other hand, the final state (Fig. 3 *c*) correctly shows the behavior demanded of the potassium conductance; changes in the initial level produce simple shifts in time and changes in the final level cause changes in the steady-state value approached at long times.

A Coupled System Showing Inactivation

Coupled systems can be formulated in which an intermediate state does show the correct changes of peak amplitude with conditioning and final-level changes, but only if the simple integral relationships among the rate constants shown in Fig. 2 *a* are discarded. Consider, for example, the three-state system shown in Fig. 4 *a*. The rate equations for this system, subject to the conservation condition

$$U + V + W = 1, \qquad (7\,a)$$

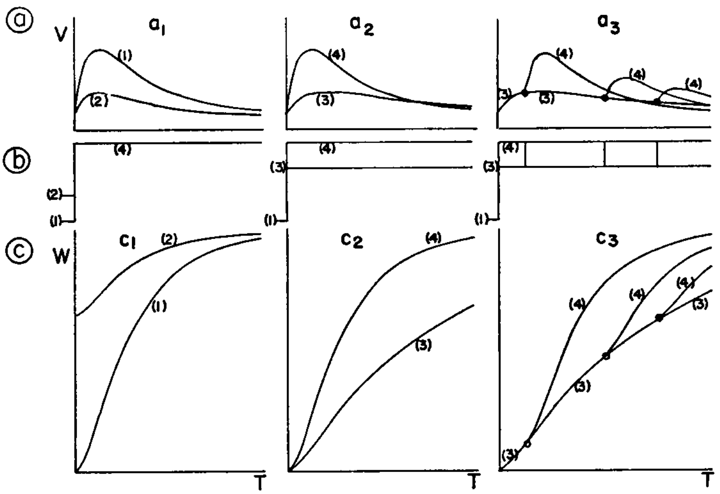

FIGURE 5 Time dependence of the *V* and *W* states of the three-state system of Fig. 4 *a*. Rows a and c show the time variations of the *V* and *W* states, respectively. Row b shows the initial and final levels used, from Fig. 4 *b*. In column 1, the final level is 4 throughout, and the initial level is shown beside each curve. In column 2, the initial level is 1 throughout and the final level is shown beside each curve. In column 3, the level is first stepped from 1 to 3, followed at various later times by a step to 4.

are

$$\dot{V} = -(\alpha + \beta + \gamma)V + (\delta - \gamma)W + \gamma, \qquad (7\,b)$$

$$\dot{W} = \alpha V - \delta W. \qquad (7\,c)$$

These coupled equations have solutions

$$V = V_\infty + V_1 e^{-\epsilon_1 t} + V_2 e^{-\epsilon_2 t}, \qquad (8\,a)$$

$$W = W_\infty + W_1 e^{-\epsilon_1 t} + W_2 e^{-\epsilon_2 t}, \qquad (8\,b)$$

where the reciprocal time constants are given by

$$\epsilon_{1,2} = \frac{(\alpha + \beta + \gamma + \delta) \pm \sqrt{(\alpha + \beta + \gamma + \delta)^2 - 4(\gamma\delta + \beta\delta + \alpha\gamma)}}{2}, \qquad (8\,c)$$

and the equilibrium values by

$$V_\infty = \gamma\delta/(\gamma\delta + \beta\delta + \alpha\gamma), \qquad (8\,d)$$

$$W_\infty = \alpha\gamma/(\gamma\delta + \beta\delta + \alpha\gamma). \qquad (8\,e)$$

The coefficients, V_1, V_2, W_1, W_2 are dependent on the initial values $V(0)$ and $W(0)$ as well as on the final state. The rate constants at four different voltage levels are assumed to have the relative values shown in Fig. 4 *b*. The corresponding equilibrium values for U, V, and W are shown in Fig. 4 *c*.[2]

The time-dependent behavior of V and W for clamps from one equilibrium level to another are shown in Fig. 5 *a* and *c*. It is obvious that by discarding the simple integral relationship of the system of Fig. 2 *a*, which for the three-state system of Fig. 4 *a* would be $\gamma = 2\alpha$ and $\delta = 2\beta$, inactivation of the intermediate state has been obtained (its peak value is now dependent on the initial level, Fig. 5 *a* 1 and 5 *a* 3), but this has been accompanied by a loss of the property of translation in time for the final-state W, Fig. 5 *c* 1 and 5 *c* 3. Therefore in the particular system of Figs. 4 and 5, while the intermediate V shows the correct qualitative behavior of a variable to be associated with the turning on and off of the sodium conductance, the final-state W shows a behavior that departs qualitatively from that required of a variable to be associated with the turn on of the potassium conductance.

LINEAR COUPLED SYSTEMS, FIRST-ORDER IN TIME

The above presentation shows that specific coupled systems can be chosen *either* to show the potassium-like conditioning property of a pure translation in time for the last state of the chain or to show the sodium-like conditioning property of a change in peak amplitude for an intermediate state of the chain. The question remains, is it possible to find a coupled system that shows *both* behaviors at once, and thus falls into classification C of Fig. 1?

Consider the $n + 1$ states, $x_0, x_1, x_2, \text{----}\ x_n$, coupled together by linear first-order processes. Four examples are shown in Fig. 6 *a*, *b*, *c*, *d*. Such systems are described by sets of n coupled first-order differential equations of the form

$$\begin{aligned}
\dot{x}_1 &= \alpha_{10} + \alpha_{11}x_1 + \alpha_{12}x_2 + \text{----} + \alpha_{1n}x_n\,, \\
\dot{x}_2 &= \alpha_{20} + \alpha_{21}x_1 + \alpha_{22}x_2 + \text{----} + \alpha_{2n}x_n\,, \\
&\ \vdots \\
\dot{x}_i &= \alpha_{i0} + \alpha_{i1}x_1 + \alpha_{i2}x_2 + \text{----} + \alpha_{in}x_n\,, \\
&\ \vdots \\
\dot{x}_n &= \alpha_{n0} + \alpha_{n1}x_1 + \alpha_{n2}x_2 + \text{----} + \alpha_{nn}x_n\,,
\end{aligned} \tag{9}$$

where it is assumed that the conservation equation, $x_0 + x_1 + x_2 + \text{----} + x_n = 1$, has been used to eliminate x_0 from these equations. The coupling constants, α_{ij} many of which will be zero, are combinations of the various forward and reverse rate constants; they are dependent only on the final state of the system, not its initial state. These first-order equations can be treated by methods similar to those employed with second-order coupled oscillator systems (Hoffman, 1955). The solution for the nth-state variable may be written

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[2] This simple system and its rate constants have been chosen with the intent merely to illustrate the qualitative phenomena; no quantitative significance is intended or implied.

$$x_n = x_{n\infty} + \sum_{j=1}^{n} x_{nj} \exp - (\epsilon_j t), \tag{10}$$

where the n decay constants (ϵ_1 ----- ϵ_n) are given by the roots of the determinantal equation

$$| \alpha_{ik} + \epsilon_j \delta_{ik} | = 0,$$

and the coefficients x_{nj} depend on the final and initial states. The solutions for the other state variables may be written

$$x_i = x_{i\infty} + \sum_{j=1}^{n} c_{ij} x_{nj} \exp - (\epsilon_j t), \tag{11}$$

where the *relative* coefficients, c_{ij}, can be shown to depend only on the coupling coefficients (α_{pq}) and therefore only on the final state. All information about the *initial* state is contained in the single set of n coefficients, x_{nj}, of Equation 10.

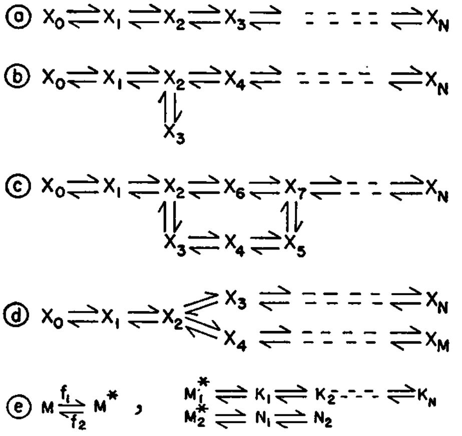

FIGURE 6 Different types of coupled systems. (*a*) Simple chain. (*b*) Chain with side chain. (*c*) Chain with side loop (*d*) Forked chain. (*e*) Indirect coupling, the rate constants f_1 and f_2 are assumed to be much greater than all other rate constants.

Consider next the approach of the system to the same final state from a different state. Equations 10 and 11 are then

$$x'_n = x_{n\infty} + \sum x'_{nj} \exp - (\epsilon_j t), \tag{12}$$

$$x'_i = x_{i\infty} + \sum c_{ij} x'_{nj} \exp - (\epsilon_j t). \tag{13}$$

(Note that the c_{ij} in Equations 11 and 13 are identical since the final states are the same.) Let us first assume that the rate constants, and therefore the coupling constants, have been chosen in such a way that x_n shows the potassium behavior of translation in time, i.e.,

$$x'_n(t) = x_n(t - t_0), \tag{14}$$

or

$$x_n' = x_{n\infty} + \sum x_{nj} \exp - \epsilon_j(t - t_0).$$

This obviously requires that

$$x_{nj}' = x_{nj} \exp (\epsilon_j t_0). \tag{15}$$

Substitution of Equation 15 into Equation 13 then also yields

$$x_i' = x_{i\infty} + \sum c_{ij} x_{nj} \exp - \epsilon_j(t - t_0). \tag{16}$$

Therefore not just for x_n but also for all x_i the only effect of a change in the initial conditions is a simple translation in time. Similarly, if we alternatively assume that x_i' is *not* a simple translation in time of x_i, i.e.

$$x_i'(t) \neq x_i(t - t_0), \tag{17}$$

then

$$x_{nj}' \neq x_{nj} \exp (\epsilon_n t_0)$$

and x_n' will also not show a simple time translation, i.e.

$$x_n' \neq x_n(t - t_0).$$

We therefore conclude that Equations 14 and 17 are mutually exclusive, and that one and the same coupled system cannot be used for both the potassium and the sodium channels.

It is thus clear that for *first-order linear* coupled systems of the straight chain variety, Fig. 6 *a*, any choice of rate constants that leads to the property of translation in time for the last member, X_N, imposes this same translation property upon *all* members of the chain. Further it is obvious that the same result holds if first-order side chains, loops, and branches are added at intermediate points of the chain, Fig. 6 *b*, *c*, *d*. It is thus impossible to describe the sodium and potassium mechanisms by a single first-order, linear, coupled system in which the open sodium channel is represented by an intermediate precursor (e.g. X_3) to the opening of the potassium channel (X_N) Fig. 6 *a*, or for a precursor (X_2) to potassium (X_N) to act also as a precursor to sodium (X_3) Fig. 6 *b*, *c*, *d*).

There is one sense in which the last sentence must be qualified. It is quite possible that a very rapid membrane transformation is the precursor of both subsequent K and Na processes, e.g. Fig. 6 *e*. If the rate constants f_1 and f_2 are very much larger than all other rate constants, M and M^* can be considered at all times to be in equilibrium, $M/M^* = f_1/f_2$. Since time constants describing the potassium and sodium conductance changes typically have values greater than 0.1 msec, a sufficient condition on f_1 and f_2 is

$$1/(f_1 + f_2) < 1\ \mu\text{sec}.$$

Under these conditions the kinetics of the upper chain can be made to show the property of translation in time, while the lower chain can be made to show the property of inactivation of an intermediate state. We classify the system of Fig. 6 *e* under category B since it can be thought of as postulating two *independent* systems, both affected separately by rapid changes in the membrane caused by a voltage clamp. Such very rapid membrane changes might be rotation of dipole groups, readjustment of Debye layers, release or additional binding of ions to membrane sites, etc. The last mentioned would be affected by the calcium concentration and might be used to explain the quite similar effects of Ca^{++} on the two channels. It might also be used to explain the effects of external K concentration on the sodium system (Adelman and Palti, 1969). Upon completion of these very rapid changes the upper and lower systems progress, independently, through their much slower sequence of changes.

In addition to the indirect coupling of Fig. 6 *e*, other weak secondary couplings may exist between the K and Na systems, as for example, mutual electrostatic effects due to close proximity in space. As mentioned earlier, such second-order couplings are neglected here, since our emphasis is on whether or not primary couplings of the types postulated in the Mullins (1960) and the Goldman (1964) models can exist.

GENERAL COUPLED SYSTEMS

The restriction to *linear* coupled systems is not essential to the conclusions of the previous section. Consider the coupled system described by the set of equations, first-order in time but not necessarily linear in the state variables x_i,

$$\dot{x}_i = f_i(x_1, x_2, \cdots x_n). \tag{18}$$

Supposing that the system has, at $t = T$, reached the state described by $x_i = X_i$, we expand the functions f_i in a Taylor's series about this state, using the new, small signal, state variables $z_i = x_i - X_i$, and $t' = t - T$. Discarding all those terms of higher power than the first, Equation 18 becomes

$$dz_i/dt' = \alpha_{i0} + \alpha_{i1}z_1 + \cdots + \alpha_{in}z_n, \tag{19}$$

valid for small t'. All the α_{ij}, except possibly the α_{i0}, coefficients again depend only on the final state. Over a small t' interval the argument of the last section may now be used on this system, with the same conclusion being reached, namely if one state variable, z_n, possesses the translation in time property all the other z_i do also; alternatively, if one z_j does not possess the translation property none of the other

z_i possess it. By piece-wise fitting such small linearized paths together, the same conclusions can be seen to hold for the behavior of the nonlinear system, for all times, as held for the linear system.

In addition to removal of the linear condition, it is also possible to remove the condition that the system obey equations that are first-order in time. If higher order derivatives than the first appear in the system equations additional time constants will be introduced, but the same two types of behavior will again be distinguishable; either all system variables possess the translation in time property or none possess it. It is worth noting that the set of n Equations 9 can be "reduced" by elimination to a set of m $(m < n)$ equations involving higher order than the first derivative. Alternatively, a set of m equations involving higher order than the first time derivative can be "expanded" to a set of $n > m$ equations involving just the first time derivative. This principle was used (Hoyt, 1963) to "expand" the postulated second-order sodium mechanism to two first-order coupled mechanisms. Analogously, the Armstrong (1969) coupled system expands the fourth-order HH system to four first-order coupled equations.

CONCLUSION

Based on the foregoing analyses, it is concluded that the two properties of translation of g_K in time and inactivation of the peak g_{Na} rule out tightly coupled models (such as C of Fig. 1). Combining this conclusion with the earlier one (Hoyt 1968; Hoyt and Adelman, 1970) that a tightly coupled model for g_{Na} better explains the sodium inactivation behavior than does the independent factor model (the m and h of Hodgkin and Huxley [1952]) leaves class B of Fig. 1 as the best able to fit the behavior of normal nerve fibers. This conclusion, based on kinetic analyses, is in agreement with the observation that TTX blocks the sodium channel but leaves the potassium channel unaffected, an observation hard to reconcile with a tightly coupled model.

Very central to the argument developed in this paper has been the assumption that the effect of initial conditions on the potassium system can be expressed as a simple translation in time. The experimental evidence for this assumption rests on the results presented by Cole and Moore (1960). In order to avoid the complications that arise in clamp records when sodium as well as potassium currents are present, Cole and Moore used the sodium reversal potential as the test potential. The translation in time property of the potassium system has therefore only been proved experimentally for a limited range of test potentials. Before the conclusions drawn in this paper can be accepted as valid, the experiments of Cole and Moore should be repeated over a wide range of test potentials; for example by using TTX to remove sodium currents, by using a sequence of external solutions in which different fractions of the normal sodium content of ASW is substituted by an inert cation such as Tris, or some other equivalent means.

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