A TRANSIENT EXCITED STATE MODEL FOR SODIUM PERMEABILITY CHANGES IN EXCITABLE MEMBRANES

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ABSTRACT In this paper we explore the properties of a mathematical model for the passive sodium permeability system of excitable membranes. This model is distinguished by the explicit inclusion of a rate constant which depends not on instantaneous voltage, but on rate of voltage change. Actually, the model is a rather modest modification of the Hodgkin-Huxley model, but displays some behaviors which the H-H model does not. Among these behaviors are a pronounced inactivation shift (for certain parameter values), a difference between inactivation time constant as measured by turning off of sodium current under sustained depolarization and as measured by double pulse experiments, skip runs under sustained current stimulation, and accommodation to slowly rising currents.

INTRODUCTION

The reason the voltage clamp technique for excitable membranes has been so fruitful is clearly that the state of the membrane permeability channels is primarily a function of voltage. This is reflected in the fact that in the highly successful Hodgkin-Huxley model (1952) the rate constants for permeability changes are functions of instantaneous voltage alone. To the extent that the Hodgkin-Huxley model successfully predicts the behavior of excitable membranes, the assumption of the membrane's pure voltage dependence seems well justified. On the other hand deviations of the membrane's behavior from the H-H model can lead us to question how exactly correct that assumption is, or whether some features of the membrane's behavior might be related to a process explicitly related to the membrane's voltage history or rate of voltage change. One way in which it has been suggested that actual nerve membranes may deviate from the Hodgkin-Huxley model is by the existence of a pronounced inactivation shift (Hoyt and Adelman, 1970; Goldman and Schauf, 1972), wherein the apparent steady-state sodium inactivation measured by double pulse experiments is a function of the size of the test pulse. Hoyt has reported an abstract model for the fast transient system with pure voltage dependent kinetics which also has this feature (Hoyt, 1968). It has been shown, however, that physical representations of the Hoyt

model can involve the existence of a rate constant dependent on dV/dt rather than V (Jakobsson, 1973). This suggests that further investigation of the effects of this sort of mechanism might be fruitful. Other investigators have also postulated the existence of a transient excited state in the excitation process (Wei, 1971; Jain et al., 1970).

In this paper we use the Hodgkin-Huxley model as a base-line state whose properties are well known, add to that model a fast transient turning-on process whose rate depends on dV/dt rather than V, and compute the results.

THE MODEL

For the fast transient, or sodium, conductance the Hodgkin-Huxley model is:

$$g_{Na} = \overline{g_{Na}} m^3 h, \tag{1}$$

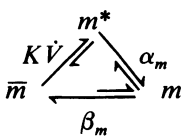
where m and h are described by the kinetic schemes:

$$\overline{m} \underset{\beta_m}{\overset{\alpha_m}{\rightleftharpoons}} m \tag{2}$$

$$\bar{h} \underset{\beta_h}{\overset{\alpha_h}{\rightleftharpoons}} h \tag{3}$$

where $\overline{m}$ denotes "not m" and $\bar{h}$ denotes "not h." The α's and β's are empirical voltage-dependent parameters determined by Hodgkin and Huxley.

In the modification presented in this paper, Eqs. 1 and 3 are unchanged, but 2 goes to:



(4)

where K is an empirical constant with units of millivolts^{-1}, and $\dot{V} \equiv dV/dt$.

The short arrows from m to m^*, $\overline{m}$ to m, and m^* to $\overline{m}$ are a formal recognition of the fact that all reaction steps are to some extent reversible. However, beyond this formal recognition we will not be much concerned with those reverse rate constants and will simply assume them much smaller than α_m and β_m. A clear implication of system 4 in terms of energy levels is that configuration m^* has more energy than configuration m which has more energy in turn than configuration $\overline{m}$. The reaction $\overline{m} \rightarrow m^*$ thus requires energy. It is natural for this reaction rate to be proportional to dV/dt, since dV/dt is just proportional to the average rate of change of potential energy of fixed charges within the membrane. Thus the scheme implies some mechanism whereby energy released from the membrane's electric field when the voltage is changed may be picked up by charged groups of the state $\overline{m}$, effecting its transition to m^*.

We leave the potassium, or slowly-rising, current unchanged from the Hodgkin-Huxley formulation:

$$g_K = \bar{g}_K n^4, \tag{5}$$

$$\bar{n} \underset{\beta_n}{\overset{\alpha_n}{\rightleftharpoons}} n \tag{6}$$

and also use the original Hodgkin-Huxley value for the leakage current.

For the rest of this paper, we will refer to the model introduced herein as the "m^*-model."

CALCULATIONAL AND COMPUTATIONAL METHODS

Voltage Clamp Case

The behavior of the kinetic systems 3, 4, and 6 can all be solved analytically for the case of the voltage clamp. The solutions to 3 and 6 are straightforward and well known from the original Hodgkin-Huxley work. For system 4, the solution is almost equally straightforward.

First note that in the case of the voltage clamp, there is an instantaneous transformation from the state $\bar{m}$ to the state m^*. The equations describing 4 are:

$$\mathrm{d}m^*/\mathrm{d}t = K\dot{V}\bar{m} - \alpha_m m^*, \tag{7}$$

$$\mathrm{d}m/\mathrm{d}t = \alpha_m m^* - \beta_m m, \tag{8}$$

adding the stoichiometric relationship:

$$1 = \bar{m} + m^* + m; \tag{9}$$

then Eqs. 9 and 7 go to:

$$\begin{aligned} \mathrm{d}m^*/\mathrm{d}t &= K\dot{V}(1 - m^* - m) - \alpha_m m^*, \quad \text{or} \\ \mathrm{d}m^*/\mathrm{d}t &= K\dot{V} - (K\dot{V} + \alpha_m)m^* - K\dot{V}m, \end{aligned} \tag{10}$$

so Eqs. 8 and 10 constitute the kinetic equations to be solved for m. We now have in the voltage clamp case (at least for an ideal clamp) a singularity. At the instant of clamp, $\dot{V} = \infty$. On the other hand, this occurs only for a time interval of zero duration, so the equations do not necessarily blow up. At the singularity, note that Eq. 10 goes to:

$$\mathrm{d}m^*/\mathrm{d}t = K(\mathrm{d}V/\mathrm{d}t)(1 - m^* - m),$$

or

$$dm^*/dt = K(dV/dt)(\bar{m}). \tag{11}$$

Also, at the singularity:

$$dm/dt \ll dm^*/dt. \tag{12}$$

Eqs. 12 and 9 together give, at the singularity:

$$d\bar{m}/dt = - dm^*/dt \tag{13}$$

Eq. 13 in 11 gives:

$$-d\bar{m}/dt = K(dV/dt)\bar{m}, \tag{14}$$

or, factoring out dt

$$-d\bar{m}/\bar{m} = K dV \tag{15}$$

in the singularity. The solution to Eq. 15 is:

$$\bar{m}\,|_{t_{0+}} = \bar{m}\,|_{t_{0-}} e^{-K\Delta V} \tag{16}$$

where $|_{t_{0-}}$ denotes the instant before step, and $|_{t_{0+}}$ denotes the instant after step; or, combining Eq. 16 with 13

$$m^*\,|_{t_{0+}} = m^*\,|_{t_{0-}} + \bar{m}\,|_{t_{0-}}(1 - e^{-K\Delta V}),$$

or, in terms of the variables in Eqs. 8 and 10,

$$m^*\,|_{t_{0+}} = m^*\,|_{t_{0-}} + (1 - m^* - m)\,|_{t_{0-}}(1 - e^{-K\Delta V}). \tag{17}$$

Obviously,

$$m\,|_{t_{0+}} = m\,|_{t_{0-}}. \tag{18}$$

Eqs.17 and 18 constitute the solutions for 8 and 10 in the singularity at the instant of a voltage step.

After the step change in voltage, $\dot{V} = 0$, so Eq.10 becomes:

$$dm^*/dt = -\alpha_m m^*, \tag{19}$$

which may be immediately solved to give:

$$m^* = m^*\,|_{t_{0+}} e^{-\alpha_m t}. \tag{20}$$

Substituting Eq. 20 in 8 and solving for m gives:

$$m = [(\alpha_m m^* |_{t0+})/(\beta_m - \alpha_m)]e^{-\alpha_m t} + (m_0 - [(\alpha_m m^* |_{t0+})/(\beta_m - \alpha_m)])e^{-\beta_m t}. \quad (21)$$

Eq. 21 gives the voltage clamp behavior of m when $\dot{V} = 0$.

It might be worth noting that Eqs. 8 and 19 together for m are formally identical to the Hoyt equations for ν if we make the identifications $m \rightarrow \nu$, $m^* \rightarrow \dot{\omega}$, and approximate $\nu_{eq} \simeq 0$. Also it should be noted that Eq. 21 always gives $m_\infty = 0$, a deviation from the Hodgkin-Huxley model but in agreement with the conclusions of Goldman and Schauf (1973) based on their data from *Myxicola* axons.

Non-Voltage Clamped Case

Just as with the Hodgkin-Huxley equations, so it is with this modification that the simulation of the space-clamped but not voltage-clamped membrane cannot be by analytical solution but rather requires numerical integration. In our case these computations were done on the University of Illinois IBM 360/75, using 360/CSMP programming language. 360/CSMP offers eight alternative schemes for numerical integration; we chose the Simpson's Rule method for most computations.[1] To check the accuracy of the Simpson's Rule procedure, the original SEAC simulations of repetitive firing behavior (Cole et al., 1955; Fitz-Hugh and Antosiewicz, 1959) and some of the original H-H space-clamped action potential simulations (Hodgkin and Huxley, 1952) were repeated. Agreement was essentially perfect.

RESULTS

Since much of the original motivation for this work was a desire to understand what might in fact be the basis for the inactivation shift, it is appropriate to display first the model's behavior in this regard. Results are shown in Fig. 1. In these simulations, as in all in this paper, the numerical value of K was chosen some positive constant when $\dot{V} > 0$ and 0 when $\dot{V} < 0$. The value of the constant was varied to demonstrate its effect on the results. It is easily shown that the larger the value of K the smaller the value of the inactivation shift and vice versa. If the clamp is begun from a long-standing hyperpolarized steady state, then before t_0 the m-system is almost entirely in $\overline{m}$ (scheme 4). The step may be thought of as acting by "kicking" a certain fraction of the m-system from the $\overline{m}$ to the m^*-state. If we step up by an amount ΔV, then the fraction kicked into m^* is just $(1 - e^{-K\Delta V})$. For all voltage steps where the $K\Delta V$ product is large, the fraction kicked up into m^* will be very close to unity and the simulated inactivation at V_0 will be given by the value of h_∞ at that voltage. On the other hand when the $K\Delta V$ product is not large there will be an apparent shift in the inactivation curve. Fig. 1 shows the model simulated inactivation curves as a function of test potential for $K = 0.04$. This value was chosen to give an inactivation shift of magnitude similar to that reported by Hoyt and Adelman (1970). Higher values of K give a less pronounced

[1] For the computations of Fig. 7, a fourth-order Runge-Kutta with variable interval was used.

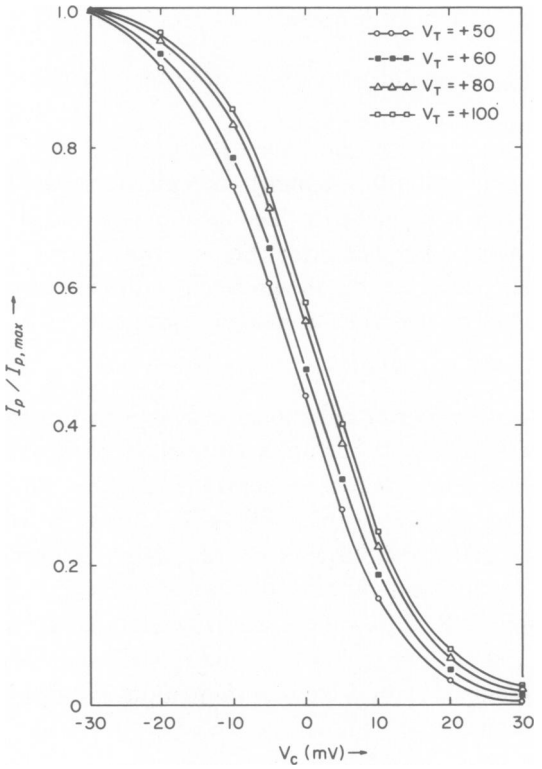


FIGURE 1 Inactivation shift calculated using the m^*, $K = 0.04$ model. (I_{Na}, peak/I_{Na}, peak$_{V_c=30}$) as a function of V_c (holding potential) for various values of V_t (test potential).

shift and in fact, the inactivation shift can be made almost arbitrarily small by increasing the value of K.

Although we have displayed in Fig. 1 a K to match the Hoyt-Adelman results, it's not clear what in fact is the best value of K with which to model the squid axon. To show this, we have simulated the Hoyt-Adelman measurement of inactivation shift on the m^*-model (with $\bar{g}_{Na} = 240$ mmho/cm^2 to give an I_{Na} typical of the Hoyt-Adelman results) with $K = 0.3$ in series with a resistance of 2.5 Ω-cm^2. This value of K does *not* give an inactivation shift if one assumes perfect voltage control across the membrane. The equivalent circuit is shown in Fig. 2. In this instance voltage across the membrane itself is not perfectly controlled, so the conductance equations are solved numerically on the digital computer, rather than analytically. The boundary condition is perfect voltage control across the membrane plus the resistance in series, with computed input current (I) corresponding to the experimentally measured current. The computed current from this equivalent circuit was analyzed to determine inactivation in just the way the Hoyt-Adelman data were (I_{peak} – leakage), and the results are shown in Fig. 3. The closeness of the match to the Hoyt-Adelman data (Hoyt and Adelman, 1970) is remarkable (especially see Figs. 5 and 6 of Hoyt and Adelman). Since values of series

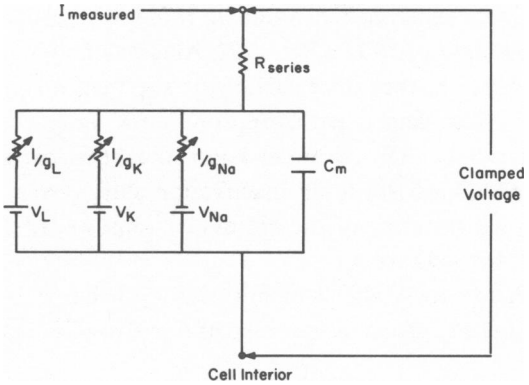


FIGURE 2 Equivalent circuit for excitable membrane in series with external resistance.

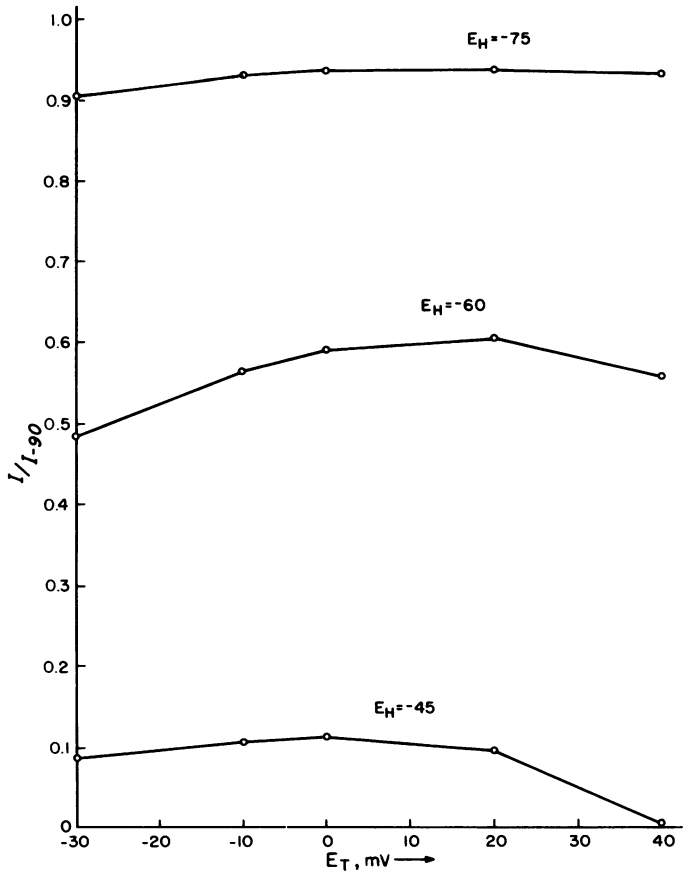


FIGURE 3 Peak current ratios at various values of absolute holding potential (E_h) and test potential (E_t). Simulated by m^*-model with $K = 0.3$, $\bar{g}_{Na} = 240$ mmho/cm^2 and $R_s = 2.5$ Ω-cm^2. Deviation of curves from straight horizontal line is equivalent to apparent inactivation shift. Other calculations by us and by J. W. Moore (personal communication) show that apparent inactivation shift due to series resistance is more pronounced the higher the values of series resistance and $\bar{g}_{Na}$.

resistance deduced from experimental results in squid axon range from 1 to 10 Ω-cm^2 (Armstrong, 1969; Hodgkin and Huxley, 1952; Adelman and Senft, 1973; Takashima and Schwan, 1974) it may be that all or part of the apparent inactivation shift in squid is a series-resistance effect, and that the appropriate K value for squid axon is substantially higher than 0.04. On the other hand, the *Myxicola* axon (Goldman and Schauf, 1972) seems to demonstrate an inactivation shift even when series-resistance compensated; analyzed in terms of the m^*-model, this would mean that *Myxicola* would be fit with a lower value of K.

The value of K also strongly affects repetitive firing behavior of the model under a sustained current stimulus. Over a large range of K and applied current, a great variety

TABLE I

SUMMARY OF THE CONSTANT CURRENT RESPONSE OF THE m^*-MODEL AS A FUNCTION OF STIMULUS CURRENT AND K

The Roman numerals represent the following general type of response: I, only one AP; II, only two APs; III, a short decremental train of regenerative responses including an initial full sized AP followed by potential oscillations of rapidly decreasing size; IV, a train of APs exhibiting a "skipping" phenomenon; V, a long train of APs whose amplitudes are only slowly decreasing. Heavy lines indicate boundaries between behavioral regions. Dotted lines are approximate boundaries.

K ↓ / current (μA/cm^2) →	7	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	90	100
0.4	I	I	I	I		I	I	I	I	I	I	I	I	I	I	I	I	I
0.5	I	I	I	I		I				I					II			II
0.55						I		I		I	II	II		II		II		II
0.6	I	I	I	I		I		I	II	II		II	II	II		II		II
0.65						I		I	II	II		IV	III	III		III		III
0.7	I	I	I	I		I	I	II	II	IV			IV			IV		III
0.8	I	I	I	I		I	II	IV	V	V			V			V		III
0.9	I	I	I	I	I	IV				V			V			V		III
1.0					II													
2.0	I	I	V	V		V				V			V		V			V
3.0	V	V	V	V		V				V			V		V			V

of repetitive firing type behavior was observed. This behavior is classified into five categories and the occurence of each as a function of K and applied current is given in Table I. Note that the appearance of repetitive firing at all only occurs at K greater than 0.4. Frequency of repetitive firing is only a weak function of current strength, as in the standard H-H axon. The "skipping" phenomenon (category III) bears some resemblance to the "skip runs" seen experimentally in squid axon in low external calcium (Guttman and Barnhill, 1970). This type of activity has not been reported for the standard H-H axon nor for any membrane model with pure voltage-dependent kinetics. Fig. 4 shows some results (voltage vs. time) of the constant current simulations.

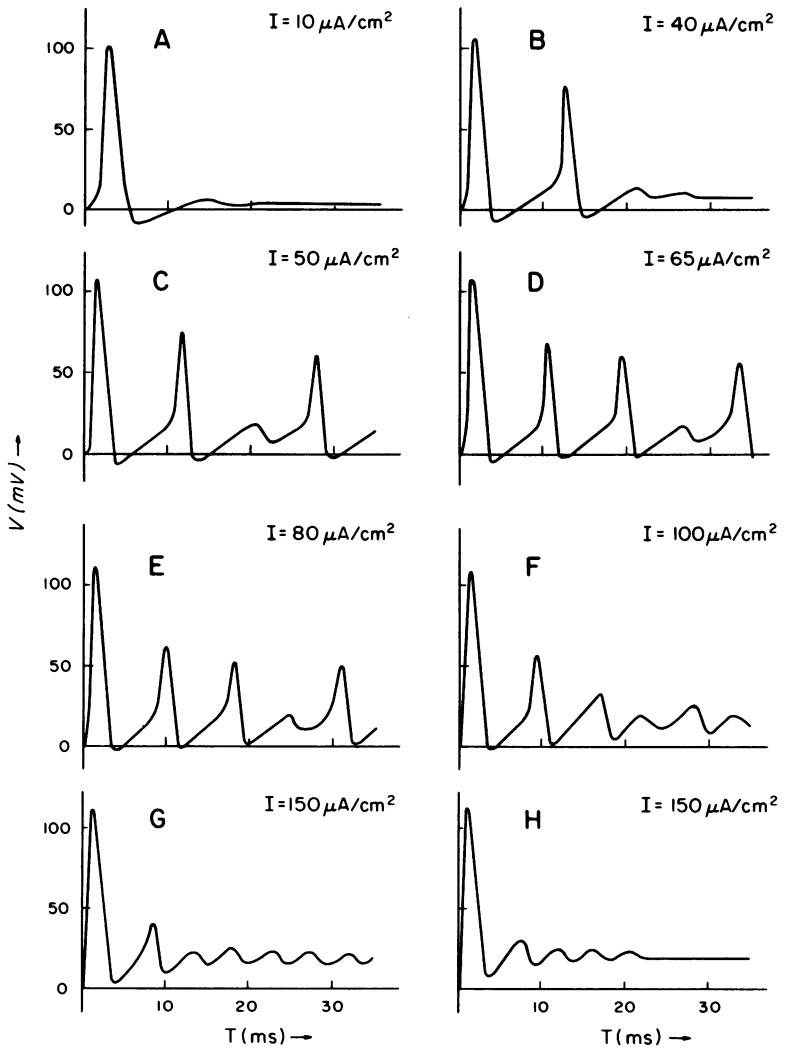


FIGURE 4 Voltage vs. time for current clamp of m^*-model at various steady depolarizing current densities. $K = 0.7$.

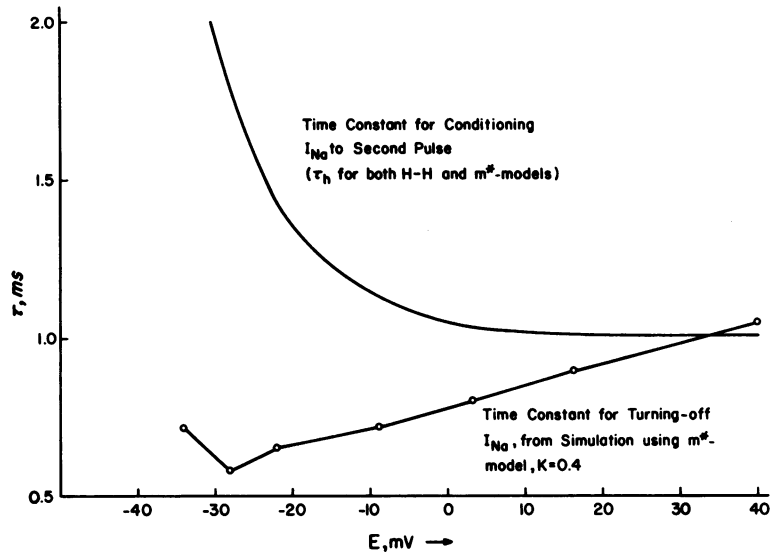


FIGURE 5 Comparison between time constants for turning-off of I_{Na} and true inactivation, as measured by double step, for m^*-model. Time constant for true inactivation is τ_h for both m^*- and H-H models, but time constant for I_{Na} turn-off is distinctly faster for m^*-model.

There are for various current densities with $K = 0.70$ and provide examples of all of the classes of behavior of Table I except V.

One of the features of the Hodgkin-Huxley model which matches closely experimental results on the squid axon is that the time course of turning off the sodium current at constant voltage is the same as the time course of inactivation of the sodium current as measured by double-pulse experiments. Goldman and Schauf (1973) however reported that in *Myxicola* the turning-off process was clearly faster than the inactivation process. In the m^*-model also the turning-off process is faster than the inactivation process, thus being more like *Myxicola* than squid in this respect. This is shown in Fig. 5. The reason for this behavior in the model is apparently the role that β_m plays in the turning-off process of the m^*-model, while it plays no such role in the H-H model. We have found that the m^*-model may be modified to match this feature of the H-H model and the squid axon by using a smaller value for β_m than the standard H-H value. We have also found that for the m^*-model to achieve a quantitative fit to published squid voltage clamp currents, both α_m and β_m must be modified. Further, the degree of modification depends on the value of K assumed. Since we have shown earlier in this paper that the appropriate value of K for squid is not determinable from the published data, we have foregone developing and presenting quantitative fits to the squid voltage clamp currents. (The above considerations are sufficient to make such quantitative fitting not very meaningful, but in addition to them we also found in our computations the further confounding factor that uncompensated series resistance can significantly alter the apparent time course with which the sodium current turns off.)

TABLE II

RESPONSE OF THE m^*-MODEL TO RAMP CURRENT STIMULATION AS A FUNCTION OF K

Stimulus	$K = 0.2$	$K = 0.4$	$K = 0.6$
$\mu A/cm^2/ms$			
0.20	Subthreshold	Subthreshold	Subthreshold
0.40	Subthreshold	Subthreshold	Subthreshold
0.60	Subthreshold	Subthreshold	Subthreshold
0.80	Subthreshold	Subthreshold	Subthreshold
1.00	Subthreshold	Subthreshold	AP
1.50	Subthreshold	AP	AP
2.00	Subthreshold	AP	AP
3.0	AP	AP	AP
8.0	AP	AP	AP
	$K = 0.8$	$K = 1.0$	$K = 2.0$
0.20	Subthreshold	Subthreshold	Subthreshold
0.40	Subthreshold	Subthreshold	AP
0.60	Subthreshold	AP	AP
0.80	AP	AP	AP

Another important category of behavior in neurons is accommodation, as demonstrated in experiments in which a current stimulus of linearly rising intensity is imposed on the membrane. The H-H model departs from the experimental behavior of the squid axon in this regard; no matter how slowly the current rises the H-H model ultimately fires a train of action potentials when the current gets high enough (FitzHugh, 1969). This may be understood in terms of the phase-space representation of the H-H equations as follows: at certain values of current the structure of the H-H phase-space contains a limit cycle and the model will give pulse trains at that current no matter how slowly it was turned on. Experimentally, however, the squid axon *does* accommodate to a slowly rising current (Hagiwara and Oomura, 1958). Table II shows the relevant data for the m^*-model. It is seen that for the values of K examined, which span the range of plausibility in modeling the squid axon, the m^*-model did accommodate to sufficiently slow ramp stimuli, in agreement with experiment. It is interesting that FitzHugh (FitzHugh, 1969) attempted to achieve this modification in the H-H accommodation behavior by introducing a dependence on I where we have used $\dot{V}$, since in the non-voltage clamped membrane $\dot{V}$ is proportional to I.

DISCUSSION AND SUMMARY

In discussing the above results, it is important first to make clear what is and is not attempted to be demonstrated in this paper. We have not attempted to demonstrate, and we do not suggest, that the m^*-model is a good candidate for the "true" kinetic scheme of the membrane, in the sense that its mathematical variables might correspond one-to-one with molecular entities. Rather the m^*-model, like the Hodgkin-Huxley model,

has more physical significance in the ways in which its behavior varies with physically definable conditions than in its detailed form. Thus, the fact that the Hodgkin-Huxley parameters are explicit functions of instantaneous voltage implies that the internal state of the membrane is primarily a function of instantaneous electric field within the membrane. On the other hand, to the extent that the m^* modification improves the performance of the H-H axon, it is legitimate to infer that it is at least possible that part of the state of the excitability mechanism depends on rate of *change* of membrane potential (dV/dt) rather than entirely on the instantaneous value of membrane potential (V).

To more specific points: it is firstly very significant that by varying K, it is possible to make the model either have a significant inactivation shift or not. The fact that the same model can have the shift or not depending on parameter values is a further demonstration that the existence of the shift is not related in a simple way to the form of the equations for the time dependence of the sodium conductance. (Jakobsson, 1973, Jakobsson and Moore, 1971). It might also be noted that the m^*-model does not fall neatly into either the "coupled" or "uncoupled" class as these terms have previously been used in the literature (Hoyt, 1968). The model is "coupled" in that the turning-on and turning-off of g_{Na} under sustained depolarization are mathematically coupled to each other via scheme 4 but it is simultaneously "uncoupled" in that the inactivation proceeds independently via scheme 3.

Another type of behavior which the m^*-model may or may not show, depending on choice of parameters, is a time course for sodium turn-off at constant voltage which is different from the time course for true sodium inactivation (removal of ability to respond to a second pulse) at the same voltage. Since *Myxicola* and the Hodgkin-Huxley model for the squid axon show different behavior in this regard, perhaps this model or a similar one may help to resolve this disparity.

The results on repetitive firing behavior are significant on two counts. In the first place, Table I shows a great variation in repetitive firing behavior when K is varied from 0.5 to 3.0 mV^{-1}. Since the fraction of the m-state kicked into the m^*-state at the time of clamp is $1 - e^{-K\Delta V}$, it is seen that the fractional variation of peak g_{Na} with K will be significant only at voltage depolarizing steps of a few millivolts, in which region the magnitude of g_{Na} is very small. Hence the simulated variation of voltage clamp data with K is very small, perhaps not experimentally discernible, over the range of K in which the repetitive firing behavior changes drastically. This fact may be significant in relation to the inability of the voltage-clamp derived H-H model to simulate more accurately than it does the repetitive-firing behavior of the squid axon. (Cole et al., 1955; Hagiwara and Oomura, 1958).

The second significant feature of the repetitive firing data is the presence of "skipped" action potentials (APs), an example of which is given in Fig. 4. The point here is that the skipping phenomenon may be seen in a model which has no slow process (time constant the order of several APs), such as potassium accumulation in the extracellular space (Frankenhaeuser and Hodgkin, 1956; Adelman and Senft, 1973).

One further way in which the m^*-model behaves differently from the H-H model is

that the m^*-model accommodates without firing APs to slowly-rising currents while the H-H model does not. It seems likely to us that this difference comes from the formal differences between the models, and that no reasonable alteration of parameters will make the m^*-model behave like the H-H in this regard.

Just as the H-H model, the m^*-model would require modification to fit data in which the axon membrane is treated in such a way as to cause inhibition of the turning-off of the sodium current. (Ulbricht, 1969; Chandler and Meves, 1970; Armstrong et al., 1973.) In the m^*-model however, *two* transitions would have to be suppressed simultaneously ($m \rightarrow \bar{m}$ and $h \rightarrow \bar{h}$) to have this effect.

Overall, it seems suggestive that the addition of a transient excited state to the Hodgkin-Huxley axon effects alterations in a variety of behaviors which have been cited as problems in the model's ability to fit the data (inactivation shift, repetitive firing, accommodation, and anomalies in determination of τ_h by single and double step experiments) and in general tends to make the model more capable of dealing with these phenomena. (It seems obligatory at this juncture to point out that the H-H axon is still far more remarkable for the variety of phenomena which it successfully simulates than for those which it does not. Indeed, as far as scientific theories are concerned, modification is the sincerest form of flattery. Any quantitative biological theory which is still worth modifying, rather than replacing totally, at the age of 22 years is a theory of considerable power.) We are still, however, some distance from a "true" physicochemical kinetic scheme for the permeability changes which will simultaneously correlate: (*a*) the normal voltage clamp and action potential data, (*b*) those areas in which the H-H axon has problems fitting the data, and (*c*) the various effects of external agents such as calcium, hydrogen ion, and drugs on the excitable membrane. In this paper we merely wish to suggest the possibility that an ultimate "true" kinetic scheme may have as one of its characteristics a transient excited state whose creation depends explicitly on voltage change.

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