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Potassium Conductance Models Related to an Interactive Subunit Membrane*

A. H. Bretag, B. R. Davis, and D. I. B. Kerr

School of Pharmacy, South Australian Institute of Technology,
and Departments of Electrical Engineering and Human Physiology and Pharmacology,
University of Adelaide, Adelaide, South Australia

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Summary. The properties of various potassium conductance models have been investigated using an analogue computer. It is shown that the experimental data of Hodgkin and Huxley can be fitted as satisfactorily by a cube (n^3) model of potassium conductance as it is by the Hodgkin-Huxley (n^4) and (n^6) models.

A planar subunit array structure for the membrane has been suggested, where the appearance of a potassium conducting channel depends upon a conformational change to an activated state in each of δ neighboring subunits. This system is described by the same mathematics as the Hodgkin-Huxley activating particle mechanism and so provides a physical basis for the power (n^δ) formulae. Introduction of interaction between subunits, such that a conformational change is prohibited unless an adjacent subunit is in the activated state, modifies the mathematics and enables simulation of the delayed potassium currents observed by Cole and Moore (*Biophys. J.* **1**:1, 1960). This innovation avoids the difficulties associated with the higher power ($\delta > 6$) models, by not requiring physical justification for large numbers of simultaneous events, while still providing a good fit to the experimental data. The interactive subunit models satisfactorily describe the potassium conductance changes which occur under voltage clamp or during an action potential.

To provide a physical basis for potassium conductance changes in the squid axon, Hodgkin and Huxley (1952*b*) suggested that potassium ions only cross the membrane when four charged particles move to a certain region of the membrane under the influence of the electric field. Taking n as the probability that one particle has moved to the correct position (Hodgkin, 1958), it follows that the potassium conductance g_K is described by

$$g_K = \bar{g}_K n^4 \tag{1}$$

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$\bar{g}_K$ being a constant with the dimensions of conductance/cm^2. The value of n is given by

$$\frac{dn}{dt} = \alpha_n(1-n) - \beta_n n \tag{2}$$

where α_n and β_n are voltage-dependent rate constants governing the movement of the activating particle. This model is hereafter termed the Hodgkin-Huxley model.

Use of the fourth power of n was dictated to simulate the characteristic delay in the increase of potassium conductance following a step depolarization, it being a property of the exponential solutions to such first-order equations as Eq. (2), that raising to a power produces a sigmoid time course.

Lewis (1964) has examined the general properties of this type of exponential raised to a power and has systematized our knowledge in relation to the delay and slope at the inflection point. In fact, Hodgkin and Huxley (1952*b*) themselves imagined that the extra delay provided by a sixth power might give a better fit to their data. Reasoning along these lines has since led to the suggestion of such extreme powers of n (Cole & Moore, 1960; FitzHugh, 1965) that the equations could no longer be interpreted in terms of the Hodgkin-Huxley activating particle model.

Several potassium conductance models, mathematically or physically different from those already described, have been introduced (Hoyt, 1963; Tille, 1965; Armstrong, 1969). All, however, seem to be similarly based upon the expedient of empirical curve fitting with only a secondary attempt at physical explanation. The consequently vague and incomplete physical models have given little impetus toward their further investigation. The only exceptions are the recent models of Hill and Chen (1972*b*) which could provide satisfactory explanations for many of the conductance characteristics. However, as we can show, it is unnecessary to complicate a straightforward subunit model by the addition of simultaneous, unrelated and not easily proven events.

In the present paper a physical model is described which is based upon a planar subunit array structure for the membrane with interaction between adjacent subunits. Similar membrane conductance models have appeared previously (Hechter, 1965; Schmitt & Davison, 1965; Changeux, 1970; Hill & Chen, 1971*a*, *b*) but either have not included an adequate mathematical evaluation of the physical processes that are involved or proved disappointing when simulation of experimental observations was attempted.

Special cases of our subunit array model exist which correspond to the models of Tille (1965) and of Hodgkin and Huxley (1952*b*), respectively, depending upon whether or not interaction is introduced.

Methods

We have derived a set of general equations describing potassium conductance (*see* Results) which can be written as follows:

$$g_K = \bar{g}_K n^\delta \tag{3}$$

$$\frac{dn}{dt} = \{\alpha_n(1-n) - \beta_n n\} f(n) \tag{4}$$

where

$$f(n) = 1-(1-n)^\gamma \tag{5}$$

while γ and δ take values according to the requirements of particular models.

These equations were solved for α_n and β_n using the EAI-580 analogue computer of the Computing Facility at the South Australian Institute of Technology. For computational purposes it was convenient to rewrite Eq. (4) as:

$$\frac{dn}{dt} = (\alpha_n + \beta_n)(n_\infty - n) f(n) \tag{4a}$$

where

$$n_\infty = \frac{\alpha_n}{\alpha_n + \beta_n}. \tag{6}$$

The equations could then be solved for $(\alpha_n + \beta_n)$ by fitting curves to the Hodgkin and Huxley (1952*b*) voltage-clamp data, having previously set n_∞ and chosen a suitable value for the initial condition n_0. Finally, α_n and β_n were determined from Eq. (6). Accuracy was not as much of a problem as Tille (1965) encountered when he solved similar equations by an analogue computer because the Eq. (4a) required, for solution, only one multiplier compared with Tille's three or more.

Solutions to Hodgkin and Huxley's (1952*b*) differential equations describing the space-clamped action potential were obtained by a modification of the Runge-Kutta method (Gill, 1951). The CDC 6400 digital computer of the University of Adelaide's Computing Science Centre was used for this purpose.

Standard parameters employed in the action potential computations were those given by Adrian, Chandler and Hodgkin (1970) for the squid axon, except that $\bar{g}_K$ was set at 36 mmho/cm^2 as in the original Hodgkin and Huxley (1952*b*) formulation.

Results

The Effects of the Power of n

An analysis of the results of Cole and Moore (1960) and those of Hodgkin and Huxley (1952*b*) has led us to conclusions similar to those of Hill and Chen (1972*a*, Appendix II). That is, that contrary to Cole and Moore

(1960), the potassium conductance curves for axon 17 of Hodgkin and Huxley (1952*b*) may be fitted by a cube (n^3) model of potassium conductance at least as well as the standard fourth power (n^4) or even sixth power (n^6) model provided that n_0 is appropriately adjusted. Values of α_n and β_n for each depolarization were obtained by fitting each conductance curve with an analogue computer solution of Eqs. (4a) and (6) as described in Methods. An excellent fit could be obtained for the cube (n^3) model by using $n_0 = 0.16$, compared to 0.215 as derived directly from Hodgkin and Huxley's value of 0.24 for the fourth power (n^4) model.

Manipulating n_0 in this way through quite a wide range can be justified from the lack of experimental knowledge of its true magnitude near the resting potential. Normally n_0 is calculated from resting potassium conductance, and at potentials close to the resting potential there is undoubted difficulty in obtaining a reliable experimental estimate of this parameter (Hodgkin & Huxley, 1952*a*).

Empirical equations describing the dependence of α_n and β_n on membrane potential were then determined. Employing a similar terminology to that of Adrian *et al.* (1970) these equations may be written as

$$\alpha_n = 4\bar{\alpha}_n f\{(\bar{V}_n - V)/4\} \tag{7}$$

where $f(x) = \dfrac{x}{e^x - 1}$ and V is membrane potential. Similarly,

$$\beta_n = \bar{\beta}_n \exp\{(\bar{V}_n - V)/\bar{W}\}. \tag{8}$$

The constants have the values

$$\bar{\alpha}_n = 0.00924 \text{ msec}^{-1}$$

$$\bar{\beta}_n = 0.148 \text{ msec}^{-1}$$

$$\bar{V}_n = -60.9 \text{ mV}$$

$$\bar{W} = 96 \text{ mV}.$$

These equations, together with Eqs. (3) and (4) where $\delta = 3$ and $f(n) = 1$, were then used as the cube model of potassium conductance and substituted for the Hodgkin-Huxley fourth power ($\delta = 4$) model in the space-clamped action potential equations. Computation resulted in the action potential shown in Fig. 1. Negligible changes in action potential shape attend the use of the cube ($\delta = 3$) model. But to obtain reasonably similar positive after-potentials while using the cube model it was found necessary

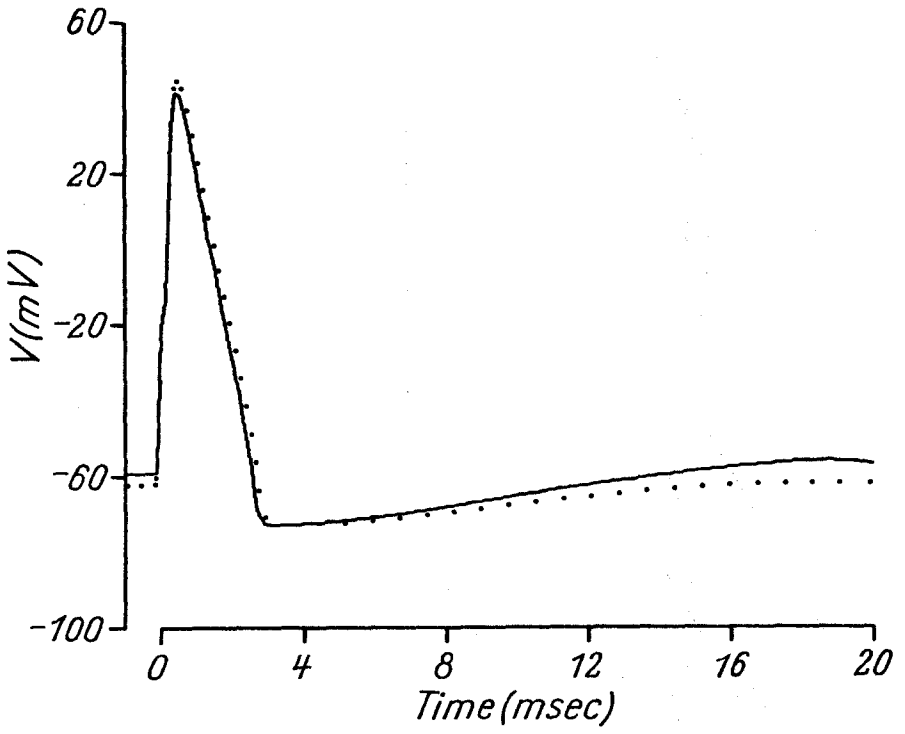

Fig. 1. Space-clamped action potential computed with the cube model of potassium conductance replacing the fourth power model. In this and later figures the dots indicate the time course of the standard Hodgkin-Huxley action potential wherever there is a difference of more than one line width

Table 1. Leakage conductance parameters employed in the action potential computations

	Model	V_L (mV)	g_L (mmho/cm^2)
Hodgkin-Huxley	$\delta=4$	−51.4	0.3
	$\delta=3$	−53.5	0.45
Tille	$\delta=1$, $\gamma=4$	−51.4	0.3
Interactive Subunit	$\delta=3$, $\gamma=6$	−53.5	0.45
	$\delta=4$, $\gamma=4$	−53.5	0.45

to adjust the leakage equilibrium potential and leakage conductance slightly (Table 1) within the ranges described by Hodgkin and Huxley (1952*b*).

The Membrane Subunit Model

There is a growing tendency to consider plasma membranes to be composed of subunits. The Davson-Danielli-Robertson (Robertson, 1964) concept of the continuous unit membrane has recently been challenged by

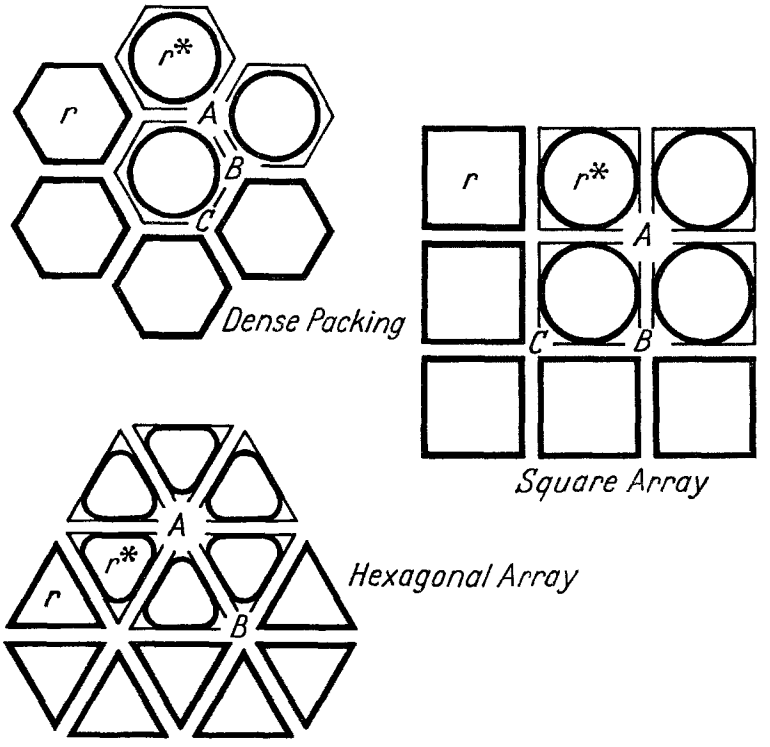

Fig. 2. Three possible array structures for a potassium conducting subunit membrane. The rounded form of a subunit indicates the activated state, r^*, which, when present in all subunits of a minimum functional group (all subunits adjacent to A), allows the formation of a conducting channel or pore at A

theories involving lipid micelles or globular proteins (Gent, Gregson, Gammack & Raper, 1964; Lucy, 1964; Hechter, 1965; Schmitt & Davison, 1965; Singer & Nicolson, 1972). However, although membrane proteins almost certainly exist in the α helical globular form (Finean, 1969; Korn, 1969) it is by no means certain that lipids are present in micellar form (Wilkins, Blaurock & Engelman, 1971). Nevertheless, membrane subunits of some kind are continually being observed using the electron-microscope (Benedetti & Emmelot, 1968; Changeux, 1970; Cartaud, Benedetti, Kasai & Changeux, 1971) and are consequently accepted for the purpose of the present model; the composition of the individual subunit need not be specified.

Our physical model for potassium conductance may be described as follows:

(1) The potassium conducting region of the membrane is composed of a planar array of subunits (Fig. 2). These subunits would probably be of the

size observed by electron-microscopy: of the order of 40- to 100-Å diameter. It is considered that the array would most likely be of the regular hexagonal, square or dense-packed configuration. Occasional imperfections in array structure have been observed microscopically (Benedetti & Emmelot, 1968) and these could explain leakage conductance.

(2) Each subunit may undergo a conformational change to state r^* compared to its complementary resting state, r. The rate and equilibrium constants for the change would be dependent on membrane potential, V. An exaggerated view of possible subunit conformation changes is shown in Fig. 2 where realignment of side chains or a contraction of the kind suggested by Schmitt and Davison (1965) is imagined to be responsible for the area differences.

(3) Other subunits may influence the ability of a particular subunit to change its conformation. Such interactions are well recognized in molecules of biological interest (Changeux, 1970). Any subunit can have γ influential neighbors where γ depends on the form of the array and on the distance over which the influence can be exerted.

(4) When a conformational change occurs in all members of a minimum functional group of neighboring subunits (i.e. δ subunits dependent on the arrangement), then a conducting channel or pore appears. (*Compare* Singer, 1971.) Conducting channels are shown as type A openings in the arrays (Fig. 2). Type B or C openings, where not all subunits of the surrounding minimum functional group are in state r^*, are generally considered inadequate for the passage of ions.

(5) The reversion of only one of such a group of subunits to its resting, r, conformation closes the channel.

(6) Transport through the conducting channel may occur by simple diffusion or by exposure of carrier systems if the channel is discontinuous.

(7) Ionic selectivity may be bestowed upon the conducting channel either by the dimensions of the channel or by exposure of specific carrier molecules.

(8) It is envisaged that patches of potassium conducting membrane, each comprising at least one functional group of subunits, are scattered throughout the excitable area of the membrane. Other similar subunit groups may form the basis for conductance changes in other ions. The particular subunits involved in potassium conductance changes might be called potassium subunits to distinguish them from neighboring sodium and other subunits.

Subunit Models Without Interaction. Consider a potassium conducting area. Let the probability of a subunit being in state r^*, be given by p. Then its probability of being in state r is $(1-p)$. Assuming first-order kinetics for random conformation changes among subunits,

$$\frac{dp}{dt} = A(1-p) - Bp \tag{9}$$

where A and B are rate constants for the conversions $r \rightarrow r^*$ and $r^* \rightarrow r$, respectively. Now, for a pore to appear at a site, all subunits in the surrounding minimum functional group (i.e. δ) must be in the state r^*. The probability for this is p^δ. Therefore, the expectation, E, of a pore appearing at any of the C possible pore sites within the array is,

$$E = Cp^\delta. \tag{10}$$

Since potassium conductance must depend upon E, it follows that g_K is proportional to p^δ.

Written in the more common terminology, these equations are identical to Eqs. (3) and (4) where $f(n) = 1$. For the square array ($\delta = 4$) this formulation is familiar as that of Hodgkin and Huxley (1952*b*).

The results of deriving appropriate voltage relationships for α_n and β_n and then computing the action potential for the dense-packed array where $\delta = 3$ has already been illustrated in comparison to the $\delta = 4$ Hodgkin-Huxley model (Fig. 1).

An action potential for the $\delta = 6$ model was not computed in view of the considerable effort involved in curve fitting, extracting appropriate α_n and β_n values, producing equations to describe the voltage dependence of α_n and β_n and finally computing the action potential. But it is surmised that any deviation in action potential shape due to $\delta = 6$ would also be negligible.

Interactive Subunit Models. The potassium conductance model of Hill and Chen (1971*a*) implies that a conformational change in a subunit is to some extent prohibited unless that subunit is changing to the state of its neighbors: simultaneous change therefore being preferred. By contrast, we envisage an interaction between the subunits of our model such that: (i) influence on conformational change is restricted to adjacent subunits (in this case, γ becomes the number of nearest neighbors); (ii) a subunit cannot undergo any conformational change unless it is situated adjacent to a subunit in state r^* (this could be explained by steric interference); and (iii) the states r and r^* may migrate from one subunit to an adjacent subunit of complementary state.

Consider a potassium conducting area. Let p be the probability of a subunit being in state r^*. Then its probability of being in state r is $(1-p)$ and the probability of at least one of γ adjacent subunits being in state r^* is $1-(1-p)^\gamma$. Now including the interaction defined in statements (ii) and (iii) above,

$$\frac{dp}{dt}=\{A(1-p)-Bp\}\{1-(1-p)^\gamma\}. \tag{11}$$

Although nearest neighbor interactions are necessary for the equation to have this form, our argument, like that of Tille, neglects correlations between different sites. Nevertheless, these are reasonable approximations, being of a kind used also in the description of other interactive processes, e.g. Onsager and Dupuis (1962) for the migration of defects in ice. An exact calculation which includes these correlations and compares the correct expression with this approximate one will be given in a later publication.

Periodic boundary conditions are assumed in the derivation of Eq. (11) (any subunit at one edge of the array is considered as though it were in contact with a corresponding subunit at the opposite edge of the same array). In this way all subunits are treated as equivalent (Hill & Chen, 1971*a*, *b*). Of course, in reality this will not be so and the magnitude of the boundary effect will depend upon the relative numbers of boundary and internal subunits. From the consideration that boundary subunits have less than γ nearest neighbors it is felt that the boundary effect could probably be approximated by some fractional reduction in γ. But since it seemed unlikely that the accuracy of the experimental data would enable fractional variations in γ to be confidently evaluated it did not appear worthwhile to include this added complexity in the model. Anyway, for a large array the effect would be quite small.

In these subunit models the probability of a pore being open depends upon the conformation of the minimum functional group and so potassium conductance is proportional to p^δ.

The equations of the interactive subunit model are therefore of the form of Eqs. (3) and (4).

Having defined the model mathematically, we then tested it for both the dense-packed ($\delta=3$, $\gamma=6$) and square array ($\delta=4$, $\gamma=4$) configurations by fitting curves to the conductance data as outlined in Methods. Appropriate choice of α_n, β_n, and n_0 again resulted in a good fit to the conductance curves for all depolarizations. This is illustrated in Fig. 3 for several depolarizations using the interactive dense-packed array model. Values of n_∞, n_0, and $(\alpha_n+\beta_n)$ for each depolarization are shown in Table 2.

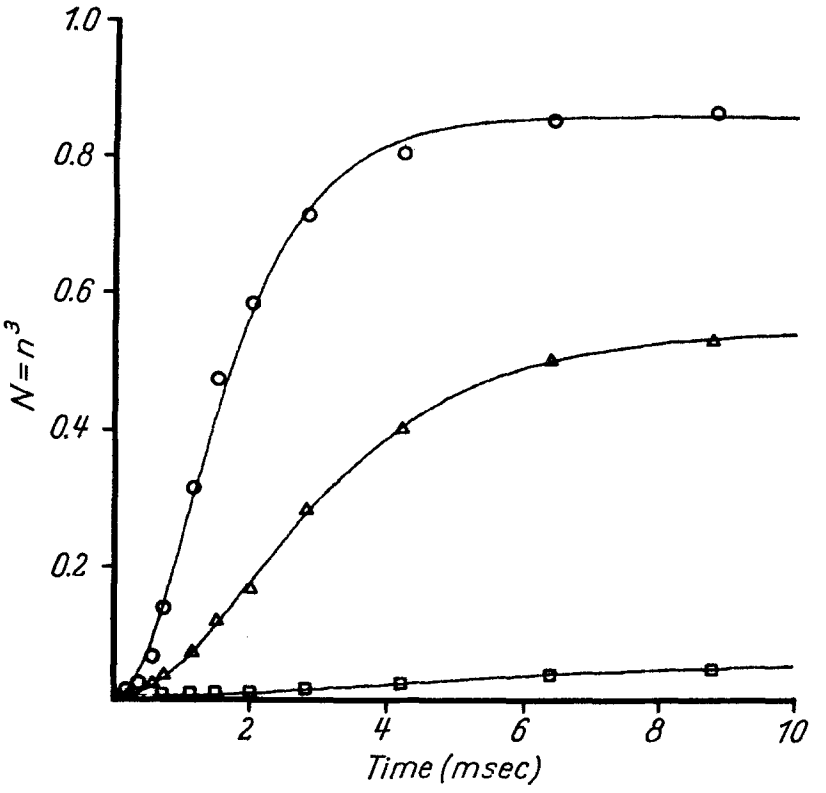

Fig. 3. Behavior of the co-operative, dense-packed array model: The potassium conductance data points are replotted from Fig. 3 of Hodgkin and Huxley (1952*b*) assuming $g_K = 24$ mmho/cm^2. Depolarizations are of 10 mV (□), 51 mV (△) and 109 mV (○) and the points are fitted by the ($\delta = 3$, $\gamma = 6$) model of potassium conductance. $N = n^3 = g_K/\bar{g}_K$

Table 2. Values of parameters employed in the solution of Eq. (4a) to give the curves fitted to the experimental data points in Fig. 3

Depolarization (mV)	10	51	109
n_∞	0.394	0.817	0.949
n_0	0.15	0.15	0.15
$\alpha_n + \beta_n$ (msec^{-1})	0.24	0.43	0.85

The precision of the Hodgkin and Huxley (1952*b*) conductance data, in conjunction with the unknown boundary effects mentioned above, would not justify any attempt to specify an exclusive array structure from these curve-fitting procedures. In our judgement both configurations tested appeared to fit the experimental data equally well.

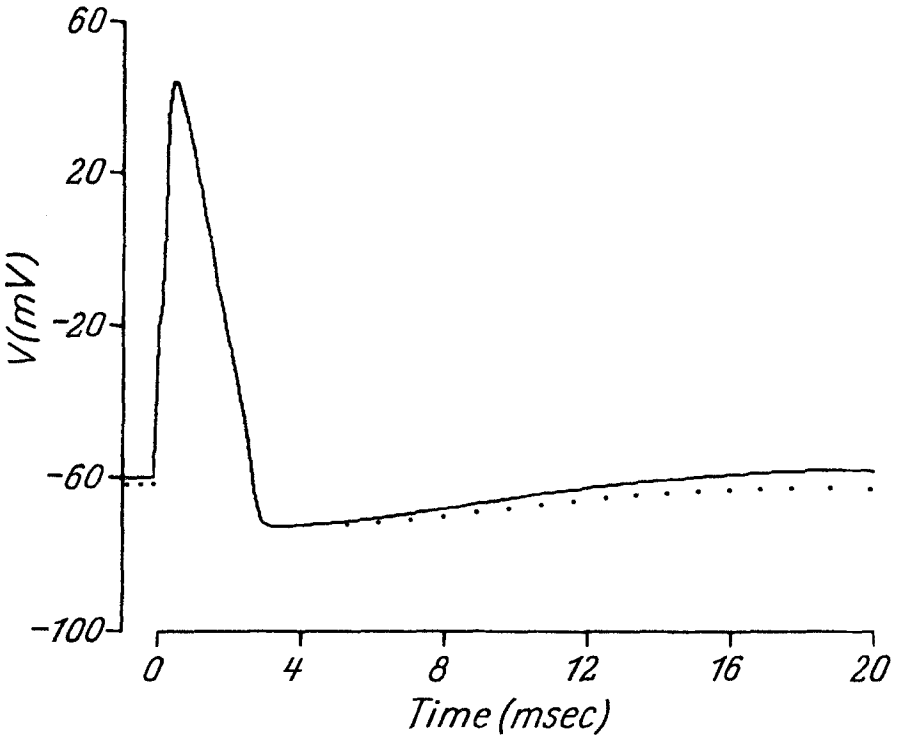

Fig. 4. Space-clamped action potential computed with the ($\delta=4$, $\gamma=4$) model of potassium conductance replacing the fourth power model

Voltage relationships for α_n and β_n derived as before a gain had thesame form as Eqs. (7) and (8). For the dense-packed array ($\delta=3$, $\gamma=6$)

$$\bar{\alpha}_n = 0.0074 \text{ msec}^{-1}$$

$$\bar{\beta}_n = 0.16 \text{ msec}^{-1}$$

$$\overline{V}_n = -62.4 \text{ mV}$$

$$\overline{W} = 83 \text{ mV}.$$

For the square array ($\delta=4$, $\gamma=4$)

$$\bar{\alpha}_n = 0.0081 \text{ msec}^{-1}$$

$$\bar{\beta}_n = 0.129 \text{ msec}^{-1}$$

$$\overline{V}_n = -64.8 \text{ mV}$$

$$\overline{W} = 94 \text{ mV}.$$

Action potentials computed after insertion of these values into Eqs. (3), (4), (5), (7) and (8) for the dense-packed array and the square array interactive subunit models were both closely similar to the standard Hodgkin-Huxley action potential, e.g. Fig. 4. It was, however, necessary to adjust leakage current parameters within the ranges described by Hodgkin and Huxley (1952*b*) to obtain reasonably similar after-potentials (Table 1).

With respect to the interactive subunit models, it is interesting to consider the situation where the circle of influence on conformation change in a particular subunit is very large ($\gamma \to \infty$). This means that the subunit may undergo a conformational change only if one of an infinite number of its neighbors is in state r^*. Obviously, this is the same as the requirement that none of its neighbors need be in state r^* or that there is no interaction between neighboring subunits. In fact, if $\gamma = \infty$ and $n > 0$, then $f(n) = 1$ [Eq. (5)] and under these conditions the interactive subunit models reduce to the simpler Hodgkin-Huxley models without interaction.

The Tille Model

If we consider the interactive subunit model and assume that the type C openings (Fig. 2), which would appear around a single subunit in state r^*, constitute a conducting channel (open pore), then the probability of a pore being open is given by Eq. (11). Since in this case the minimum functional group is just one subunit ($\delta = 1$), the result becomes identical to that of Tille (1965) for his pore interaction model. That is, potassium conductance is described by Eqs. (3) and (4) where $\delta = 1$ and γ depends on subunit (or equally, pore) arrangement. It should, however, be emphasized that Tille (1965) based his model on the movement of blocking particles into and out of the membrane in relation to interacting pores, rather than on conformation changes in subunits.

Tille employed curve-fitting procedures similar to those described in the present paper to obtain values of α_n and β_n and subsequently to derive the equations describing the dependence of α_n and β_n on membrane potential. For the square array these have the same form as Eqs. (7) and (8) but the constants have the values

$$\bar{\alpha}_n = 0.0079 \text{ msec}^{-1}$$

$$\bar{\beta}_n = 0.7082 \text{ msec}^{-1}$$

$$\overline{V}_n = -56.1 \text{ mV}$$

$$\overline{W} = 54 \text{ mV}.$$

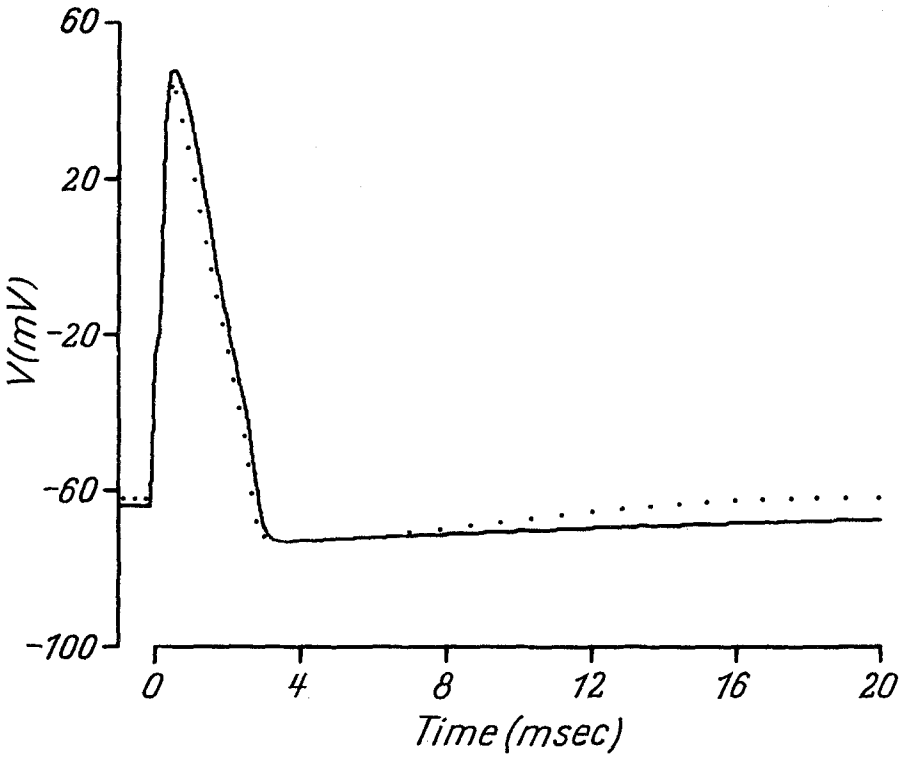

Fig. 5. Space-clamped action potential computed with the Tille ($\delta = 1$, $\gamma = 4$) model of potassium conductance replacing the fourth power model

The computed action potential resulting from the substitution of the Tille square array model ($\delta = 1$, $\gamma = 4$) for potassium conductance is shown in Fig. 5. Again deviations from the Hodgkin-Huxley ($\delta = 4$) model are only slight.

It might be noted that the shape of the action potential in Fig. 5 differs considerably from that calculated for the Tille model by Moore (1968). Our experience with such calculations provides no explanation for the aberrant resting potential nor the shape of the action potential in Moore's computation. Also of interest here is the resting potassium conductance which is higher in the Tille model and lower in the other interactive models than in the standard Hodgkin-Huxley model.

The Effects of Conditioning Hyperpolarization

As is well known (Cole & Moore, 1960), the long delay in the increase of the potassium conductance following a large hyperpolarizing prepulse

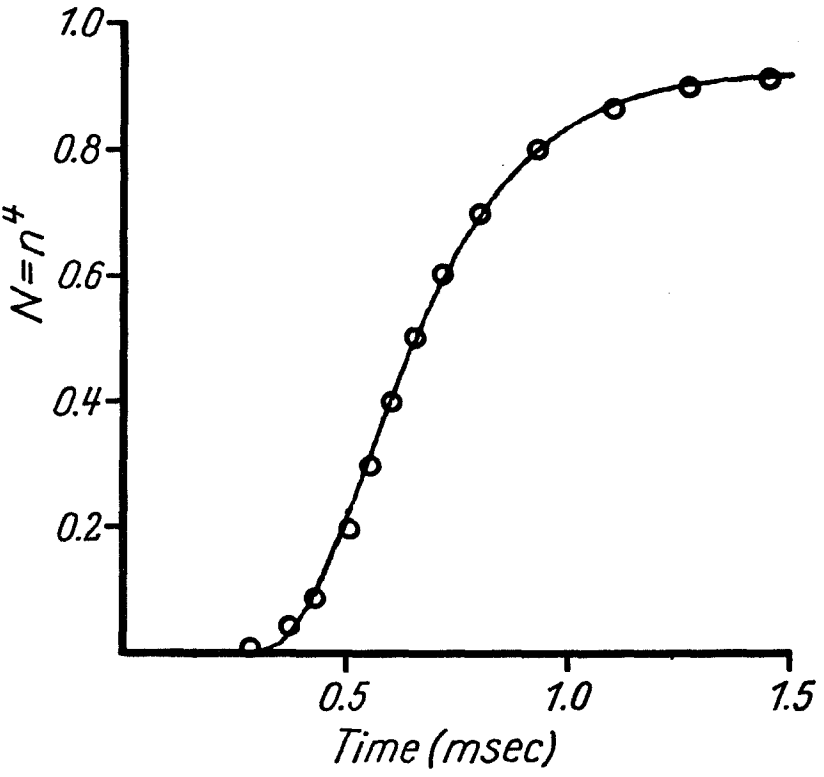

Fig. 6. Simulation of the delay in the increase in potassium conductance following a hyperpolarizing prepulse. The conductance data points are derived from Fig. 5*b* of Cole and Moore (1960) assuming $\bar{g}_K = 55$ mmho/cm^2. The points are fitted by the ($\delta = 4$, $\gamma = 4$) model of potassium conductance. $N = n^4 = g_K/\bar{g}_K$

cannot be explained in terms of the Hodgkin-Huxley ($\delta = 4$) model nor in terms of a ($\delta = 6$) model even if $n_0 = 0$. A ($\delta = 25$) model will accommodate the data but in terms of the membrane subunit model it is difficult to imagine a pore being dependent upon the same conformation state in 25 surrounding subunits. However, an analogous delay is inherent in the kinetics of the interactive models presented above.

Tille (1965) showed that his model could accurately fit the data of Cole and Moore (1960), and a similar result is shown for the present ($\delta = 4$, $\gamma = 4$) model for the square array (Fig. 6). Here $(\alpha_n + \beta_n)$ was 0.44 when n_0 was set at 0.002 and n_∞ at 0.98.

The importance of the value of n_0 in these interactive models cannot be overstressed. It is capable of a far greater range of effect on the delay before n increases than is possible for the Hodgkin-Huxley 3, 4, or 6 power models. In the Cole and Moore (1960) experiment it is quite conceivable that hyper-

polarization would decrease the value of n_0, thus effectively reducing the number of "seeding" subunits in state r^* and consequently increasing the delay.

Discussion

A definitive array structure has not been specified for the membrane subunit model, although there is some evidence to suggest that protein molecules in association with lipid bilayers may favor the dense-packed array (Fromherz, 1971). Furthermore, as it is impossible to choose between the various models when they are considered in terms of "best fit" to the conductance data of Hodgkin and Huxley (1952*b*), it behooves us to choose the simplest adequate model: the subunit model without interaction for the dense-packed array ($\delta = 3, f(n) = 1$). As has been demonstrated, this provides an accurate description of potassium conductance in the normal squid axon under voltage clamp or during an action potential. However, problems arise if one attempts to encompass all the available data in such simple models. This is illustrated by their failure to explain the delayed potassium current following conditioning hyperpolarization. On the other hand, models involving 25 (Cole & Moore, 1960) and unlimited numbers of simultaneous events (FitzHugh, 1965) become physically implausible even though the mathematics may describe the appropriate curves. Similarly, Hoyt (1963) notes the difficulty involved in applying her equations to a physical system.

If we ignore the complications of the latest Hill and Chen (1972*b*) models, we are left with the various interactive models of which only the present example has so far been shown to fulfill all requirements. It is inherent in this model that it does not suffer from the unsatisfactory simulation of "superposition" of potassium current curves (Cole & Moore, 1960) seen in the co-operative models of Hill and Chen (1971*a*, *b*). As in the original Hodgkin-Huxley model, superposition is mathematically exact because dn/dt has only one value for any given value of n (α, β, and γ being constant). The other necessary criterion for a satisfactory model as posed by Hill and Chen, that of an adequate initial delay or "induction" in potassium conductance, is also met by the present model. No illustrations of the fall in potassium conductance at the end of a voltage step have been shown for our subunit models. This was considered unnecessary since both Tille (1965) and Hodgkin and Huxley (1952*b*) have demonstrated the fair fit of solutions of both equation systems (with or without interactions, respectively) to the experimental data.

While Tille's interactive pore model may appear as effective as the present interactive subunit model, and indeed is equivalent to a special case

of this model, it is difficult to justify physically in its original form. Seemingly unrealistic conditions are imposed upon the movement of blocking particles in relation to the membrane. These are, that a blocking particle must be able to move from pore to pore within the membrane and that an open pore can influence at a distance the ability of a blocking particle to enter or leave an adjacent open pore. The co-operative pore models due to Adam (Hill & Chen, 1971*a*) are quite unconvincing, because they explain experimental results less satisfactorily than any of the other models that have been mentioned.

We have, however, considered only large arrays, although it is possible that discrete potassium conducting areas are as small as one minimum functional group (e.g. three subunits). If there is no interaction between subunits this is again equivalent to the Hodgkin-Huxley model (*see*, for example, Stevens, 1972). But interaction such that conformation change is prevented unless a neighboring subunit is in the activated state requires that either: (1) there must always be at least one activated subunit in any such group (or else the group becomes permanently inexcitable) or (2) the restriction of conformational change to those subunits adjacent to one in the activated state must not be exclusive but rather preferred. The characteristics of such small arrays of interacting subunits, and those of medium sized arrays, remain to be evaluated.

Finally, it should be noted that although subunit models of the excitable membrane seem to be plausible, attempts to show an association between membrane permeability and conformation change in terms of axon birefringence or light scattering have so far proved disappointing (Cohen, Hille, Keynes, Landowne & Rojas, 1971).

Due to the higher current densities in the node of Ranvier and hence, possibly, a higher concentration of subunits involved in conductance changes it might be worth searching for conductance-linked conformation changes there rather than in unmyelinated nerves.

However, the interactive subunit models could probably best be evaluated by a more exacting experimental study of the characteristics of the potassium conductance: especially with respect to the relationship between resting conductance and the delay of conductance increase following a step hyperpolarization. This kind of information has already eliminated the Hodgkin-Huxley noninteractive models and could distinguish between the Tille model with its inherent higher resting potassium conductance and the other interactive models with their lower resting potassium conductance.

Note Added after Submission: Following submission of this paper we have become aware of a model of membrane conductance mathematically similar to our own: Starzak,

M. E. (1973), *J. Theoret. Biol.* **29**:487 and 505. A criticism of Starzak's model, especially of the physical interpretation that he makes, has been submitted for publication by A. H. Bretag, C. A. Hurst, and D. I. B. Kerr to the *Journal of Theoretical Biology*.

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