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A spike-forming model of the neural membrane

(membrane conductance/gates and channels/sodium pump/gate conversion/action potentials)

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ABSTRACT **A model of the neural membrane is described, based on a set of "convertible gates" on its inner surface. The atomic arrangement of a gate is specified to be subject to modification by a set of chemical reactions, sometimes permitting sodium ions, sometimes potassium ions, sometimes neither, to have access to the transmembrane channel it guards. Reaction rate and current/voltage equations are developed, values assigned to the parameters, and computer solutions obtained. Under pulse or continuous stimulating current the model is found to generate action potential spikes closely similar in height and shape to those of real neurons. Other electrical properties are also relatively neuron-like.**

This paper reports the results of an attempt to find a set of reasonable hypotheses about the physical properties of the membrane that, without further assumption, will lead to the observed characteristics of the action potential spike. While this objective is similar to that of other recent studies (see, for example, ref. 1), the postulated membrane mechanisms are different and the resulting predictions appear to agree with experiment more closely than those obtained from previously described models.

DESIGN OF THE MODEL

The model of the neural membrane that is described here uses a fixed set of "pores" through which ions pass to give the membrane its electrical conductance. Each pore consists of a "channel," an "inner gate," and an "outer gate." The channel is envisioned as a chain of trapping sites that span the 50–100 Å thickness of the membrane. Each site consists of an atomic arrangement to which the ion can attach itself and be lightly held until thermal agitation moves it to one of the two adjacent trapping sites. The gates are atomic configurations on the membrane surfaces into which an ion, approaching from the adjacent fluid or from the transmembrane channel, can enter and be held. When the bound ion is knocked loose, it may go either into the fluid or into the channel.

Once an ion is introduced into the channel, it is relatively difficult for it to get out again. Thus there is time for it to make several complete traversals of the channel in a kind of one-dimensional "random walk" along the chain of trapping sites, before it spends enough time in the sites adjacent to the two gates to have a high probability of escape from the membrane. Nevertheless, these events are so rapid in relation to the observed ionic currents that each pore is empty most of the time.

The potential difference across the membrane, when divided by the number of trapping sites in the channel, is never enough to do more than add a small bias to the back-and-forth movement of the ion. Under the specified conditions, the Maxwell-Boltzmann relation applies to impose a value of $e^{-V\epsilon/kT}$ on the ratio of the times the ion spends in the trapping sites adjacent to the gates on the positive and negative sides of the membrane (ϵ is ionic charge, k is Boltzmann constant, T is absolute temperature). The rate at which ions enter a gate from the high-conductance, and therefore essentially equipotential, fluid is independent of the membrane potential.

It can be shown that the flow of ions of a particular type through pores meeting the above specifications is governed by the following equation:

$$I = I_0[e^v - (\alpha\rho_0/\beta\rho_i)] \div [e^v + \alpha] \qquad [1]$$

In this equation v is an abbreviation for $V\epsilon/kT$ and will be used throughout the paper. Since the value of kT/ϵ is very close to 25 mV at normal temperatures, v is simply the membrane potential divided by 25 mV. For positive ions, v is positive when the potential inside the neuron is positive with respect to the surrounding fluid. ρ_0 and ρ_i are the densities of the ion outside and inside the neuron, respectively. α is the ratio of the average amount of time the ion must spend in the trapping site next to the outer gate in order to escape into the fluid surrounding the neuron to the time it must spend in the site next to the inner gate in order to escape into the interior of the neuron. β is the ratio of the capture cross-section of the inner gate to that of the outer gate, for ions that approach the gate from the adjacent fluid. I_0 is a constant whose value depends on membrane area, number of pores, capture cross-section of the inner gate, and average ion velocity. In the equation, a positive value of I signifies an outward flow of positive ions through the membrane.

If the properties of the two gates are the same, $\alpha = \beta = 1$ and Eq. 1 yields a current/voltage relation close to relations that have been used in the past (2). However, if the two gates have different properties, a variety of current/voltage curve shapes is possible. To be sure, for simple gates we might expect α/β to remain close to unity; atomic configurational differences that make it easier for ions to enter from the fluid side are also apt to make it easier for them to enter from the channel side. However, it is not difficult to conceive of situations in which this condition is not met. Even one-way gates would appear possible, in view of the two-step nature of passage through the gate. For example, entry of the ion into the gate from the channel side could trigger rearrangement of the atoms such as to block subsequent release of the ion into the fluid, whereas an ion entering from the fluid side could go into a different "pocket" in the atomic configuration and therefore not cause a rearrangement that blocks further progress. Eq. 1 for such a gate would have an α value of 0, making I a constant independent of v. This could be the explanation of the so-called "sodium pump," that continually moves sodium ions out of the neuron against both voltage and concentration gradients.

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Apart from whatever pores are responsible for the small and constant sodium pump component, a single system of "convertible pores" accounts for all sodium and potassium ion flow through the membrane in the model. It is the inner gate that changes so as sometimes to permit passage of sodium ions, sometimes to permit passage of potassium ions, and sometimes to block both types. At all times the membrane can be entered through the outer gate and the channel traversed, not only by sodium and potassium ions, but also by a doubly-charged positive ion, which is responsible for some of the reactions that change the atomic configuration of the inner gate from one state to another. This ion is probably calcium, whose presence in the external fluid is known to be essential to spike formation (3).

There are six atomic configurations of the inner gate: three pass either sodium or potassium ions, three do not. The conducting states will be designated by the symbols K_1, K_2, and Na, and the nonconducting states by A, B, and C. Each symbol will be used both to designate a state of the gate and to stand for the fraction of the gates that are in that state. When in a K_1 or K_2 state, the inner gate passes potassium ions only; when in the Na state, it passes sodium ions only; permeability is much lower for the K_1 gate than for K_2 and Na gates.

The K_1 state is characterized by the attachment of two calcium ions to the basic gate configuration; the A state involves a single attached calcium ion; the other four states do not contain calcium. Calcium ions can enter the gate configuration only from the channel side. When such attachment occurs, electrical neutrality of the gate is preserved by the prompt acquisition of anions—probably Cl—from the fluid side of the gate. The Maxwell-Boltzmann relation applies to the calcium ions in the channel just as it does to the sodium and potassium ions, so that the probability that a calcium ion is available for combination with the inner gate is proportional to e^{-2v} (the 2 is of course because of the double charge of the ion).

A K_1 gate, with its two attached calcium ions, changes to an A gate when thermal agitation dislodges one of the two ions. Similarly, an A gate changes to a B gate when thermal agitation dislodges the second of the two ions. The time constants of the reactions among states K_1, A, and B are short compared with those of the other gate-conversion reactions. Of these remaining reactions, conversions from state B to state Na, from Na to C, and from C to K_2, are all voltage-independent, perhaps involving participation by potassium ions or some other ingredient of the neural fluid, but not involving ionic activity on the channel side of the gate. A K_2 gate, finally, is converted to an A gate by attachment of a calcium ion on the channel side; if there have been accretions from the fluid in the reaction sequence leading to the K_2 state, attachment of the calcium ion detaches them. The sequence B → Na → C → K_2 → A is a one-way reaction sequence; transition probabilities in the return direction are considered to be negligibly small. Similarly, other transitions, directly from Na to A, for example, are specified to have very low reaction rates.

Equations governing this set of interactions can be written as follows:

$$d(\mathrm{Na})/dt = -\mathrm{Na}/t_{\mathrm{Na}} + (1/t_{\mathrm{B}})(1 - \mathrm{Na} - \mathrm{C} - \mathrm{K}_2) \div (1 + \gamma_{\mathrm{A}}e^{-2v} + \gamma_{\mathrm{A}}\gamma_{\mathrm{K}_1}e^{-4v}) \quad [2a]$$

$$d\mathrm{C}/dt = -\mathrm{C}/t_c + \mathrm{Na}/t_{\mathrm{Na}} \quad [2b]$$

$$d\mathrm{K}_2/dt = -\mathrm{K}_2/\tau e^{2v} + \mathrm{C}/t_c \quad [2c]$$

$$K_1 = \gamma_{\mathrm{A}}\gamma_{\mathrm{K}_1}e^{-4v}(1 - \mathrm{Na} - \mathrm{C} - \mathrm{K}_2) \div (1 + \gamma_{\mathrm{A}}e^{-2v} + \gamma_{\mathrm{A}}\gamma_{\mathrm{K}_1}e^{-4v}) \quad [2d]$$

Here t_{B}, t_{Na}, and t_{C} are the voltage-independent time constants (reciprocals of the reaction rates) for the B → Na → C → K_2 transitions whereas τe^{2v} is the time constant for the K_2 → A transition. $\gamma_{\mathrm{A}}e^{-2v}$ is the ratio of the fixed A → B time constant to the voltage-dependent B → A time constant; $\gamma_{\mathrm{K}_1}e^{-2v}$ is the corresponding ratio for the K_1 → A and A → K_1 reactions.

An equation for v is needed before solution can be attempted. The basic relation is

$$(25\ \mathrm{mV})dv/dt = (I_{\mathrm{ext}} - I_m)/\mathrm{Cap} \quad [3]$$

where Cap is the membrane capacitance, I_{ext} is any externally supplied current, as by an experimenter through a probe inside the neuron (I_{ext} is positive when in a direction to raise the internal potential), and I_m is the positive ion current out of the membrane. From the earlier discussion,

$$I_m = I_p + I_{\mathrm{OK}_1}\mathrm{K}_1(e^v - \lambda_{\mathrm{K}_1}) \div (e^v + \alpha_{\mathrm{K}_1}) + I_{\mathrm{OK}_2}\mathrm{K}_2(e^v - \lambda_{\mathrm{K}_2}) \div (e^v + \alpha_{\mathrm{K}_2}) + I_{\mathrm{ONa}}\mathrm{Na}(e^v - \lambda_{\mathrm{Na}}) \div (e^v + \alpha_{\mathrm{Na}}) \quad [4]$$

Here I_p is the constant "sodium pump" current. The new symbols λ are abbreviations for the terms $(\alpha\rho_0)/(\beta\rho_i)$. From the earlier discussion, they can be expected to have values close to, but not necessarily identical with, the ratios ρ_0/ρ_i for the ions in question (none of the convertible gate states needs to be of the "one-way" variety).

By inserting the above expression for I_m in Eq. 3, the needed differential equation for v is obtained. When this is associated with Eqs. 2, the values of v and of the numbers of gates in each of the six states are in principle determined for all values of t. And if numbers are assigned to the various parameters, computer programs can be set up to obtain numerical solutions for the equations. There is of course no direct experimental information available for setting the time constants of the gate conversion reactions. Thus the ultimate test of suitability of any set of parameter values is the closeness of the resulting model properties to the properties of real neurons. For such comparisons, I have greatly benefitted from the extensive set of measurements by Hodgkin and Huxley on a single squid giant axon (4). I will refer to this carefully studied neuron as the "reference neuron," in view of its role in the choice of parameter values for the model.

The values finally selected are:

$t_{\mathrm{B}} = 0.5$ msec	$I_p = 0.0027\ \mathrm{mA/cm^2} \times \sigma$†
$t_{\mathrm{Na}} = 0.5$ msec	$I_{\mathrm{OK}_1} = 0.029\ \mathrm{mA/cm^2} \times \sigma$
$t_{\mathrm{C}} = 0.63$ msec	$I_{\mathrm{OK}_2} = 2.76\ \mathrm{mA/cm^2} \times \sigma$
$\tau = 100$ msec	$I_{\mathrm{ONa}} = 2.61\ \mathrm{mA/cm^2} \times \sigma$
$\gamma_{\mathrm{A}} = 0.5$	$\mathrm{Cap} = 1.45\ \mu\mathrm{F/cm^2} \times \sigma$
$\gamma_{\mathrm{K}_1} = 0.13$	
$\alpha_{\mathrm{K}_1} = 0$	
$\alpha_{\mathrm{K}_2} = 2$	
$\alpha_{\mathrm{Na}} = 7$	
$\lambda_{\mathrm{K}_1} = 0.09$	
$\lambda_{\mathrm{K}_2} = 0.05$	
$\lambda_{\mathrm{Na}} = 9$	

† σ, membrane area, cancels out of the equations.

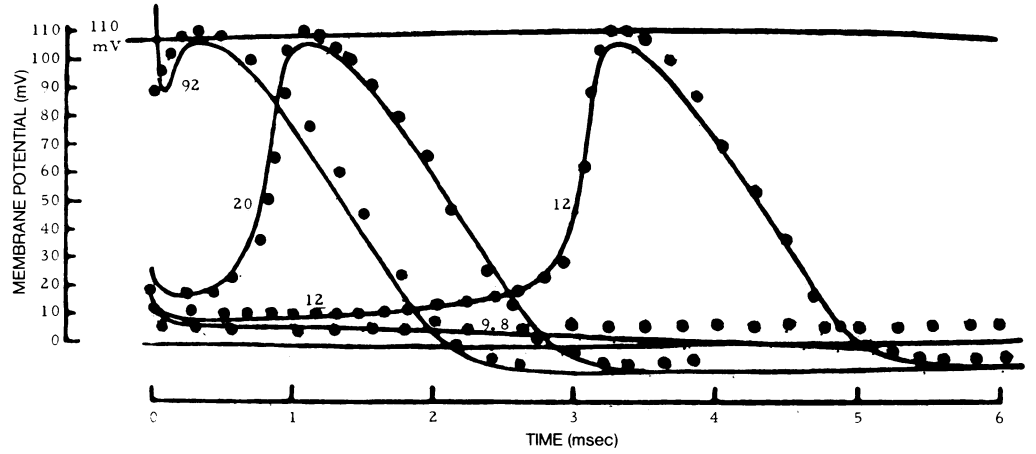

FIG. 1. Action potential spikes resulting from short pulse stimuli. Curves are measurements on reference neuron (ref. 4, p. 65); added points are computer calculations for model. Zero of voltage measurements is the −60 mV resting potential. Amounts of charge in the four stimuli are in ratio 9.8:12:20:92 both for reference neuron and for model.

An immediate consequence of this choice of values is a resting potential slightly below −2.4 (−60 mV) for which both the potassium and sodium currents are zero. −60 mV is as good an estimate of the resting potential of the reference neuron as I could make from the reported data.

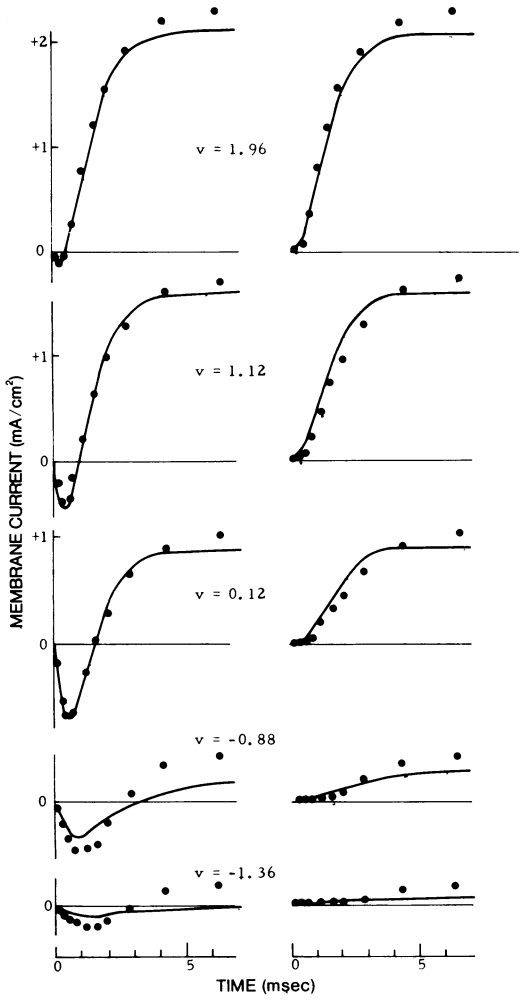

FIG. 2. Membrane current against time after application of voltage clamp. Curves are computed for model; points are measurements on reference neuron (ref. 4, p. 61). Curves and points on left are for neuron immersed in normal seawater; for curves and points on right, sodium content of water is reduced to match that inside neuron.

ELECTRICAL PROPERTIES OF THE MODEL

One of the two major types of experiment performed on the reference neuron consisted of injection of short but relatively strong current pulses and recording of the resulting changes of membrane potential. These experiments were among those simulated for the model by means of a computer program. The results are shown in Fig. 1. Except for the discrete points, which I have added to show the results of the computer simulation, this is a reproduction of a figure on p. 65 of Hodgkin's book (4). In the computer simulation from which the discrete points were plotted, the pulse stimuli had the same 9.8:12:20:92 strength ratios as those used on the reference neuron.

The other extensive set of measurements made on the reference neuron involved use of a voltage clamping technique in which the membrane potential was suddenly raised from its resting value to a new value and held there, while the current through the membrane was measured as a function of time after application of the clamp. This operation was performed twice for each value of clamping voltage—first with the axon immersed in seawater with nearly the same concentration of sodium, potassium, and calcium ions as squid blood, then with the axon immersed in water from which enough sodium had been removed to bring the concentration down to the much lower value characteristic of the interior of the neuron. By this means it was possible to separate the contributions of sodium and potassium ions to total membrane current.

Fig. 2 shows a comparison of the reference neuron results with those obtained for the model by computer simulation. In this case the points are the discrete measurements made on the reference neuron and the continuous curves are the computer data. The curves of Fig. 2 do not closely resemble those of Hodgkin and Huxley (ref. 4, p. 61), because they first converted each experimental measurement to a kind of linearized conductance value, which minimized the variation in height of the plotted curves. However, they provided information making it easy to retrieve the original measurements, which are the ones plotted in Fig. 2.

Other characteristics of the model are neuron-like, in addition to those used for comparison with the reference neu-

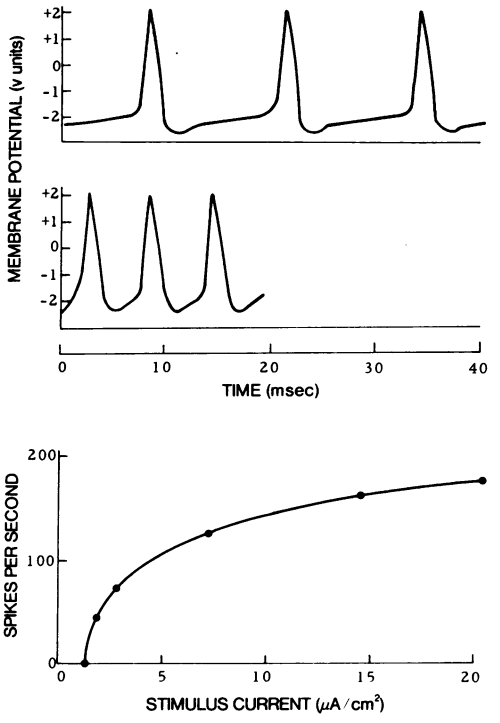

FIG. 3. Continuous spiking in the model. Stimulus current (I_{ext}) is applied at $t = 0$ and held constant. Resulting membrane potential is shown in top two curves, for stimulus values of 2.9 and 14.5 $\mu A/cm^2$, respectively. Bottom curve shows spiking rate as function of stimulus current, plotted from curves of the type shown above.

ron. Thus the model has the important property of generating a continuing series of action potential spikes in response to a sustained stimulus current, with a sharp stimulus threshold followed by a leveling off of spiking rate as the stimulus current increases (Fig. 3). It also exhibits a "refractory period"—an interval after emission of a spike during which it is difficult or impossible to generate a second spike: a second strong stimulus pulse, if applied 2.0 msec after the first peak is reached fails, but if applied 0.3 msec later succeeds, in evoking a second spike. And the plot of high frequency conductance against time during the formation of a spike is similar in shape to the spike but slightly delayed; the conductance at the peak of the spike is 23 times that of the resting neuron model, and 139 times the lowest value reached momentarily during the initial stage of spike formation. These properties are all qualitatively similar and quantitatively in the range of various experimental measurements on real neurons (ref. 5, pp. 136 and 158, and ref. 6).

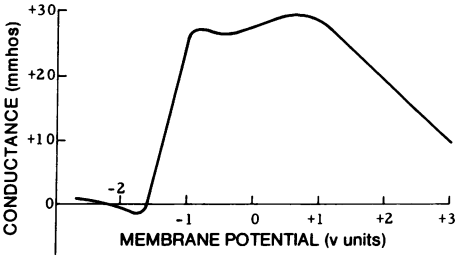

FIG. 4. Low frequency conductance of the model as a function of clamping voltage. Large fractional changes occur near the spiking threshold ($v = -2$).

Particular interest attaches to the low frequency conductance curve for the model, obtained by means of a series of simulated voltage clamping experiments. When the steady-state value of the current finally reached after each clamping operation is plotted against voltage and the slope of that curve is then plotted, the result is the low frequency conductance curve of Fig. 4. This shows that, in the vicinity of the spike-forming threshold (approximately v = −2), the conductance exhibits very large fractional changes. Such changes, in real neurons, have often been commented on (4). Indeed, in the model the low frequency conductance actually goes negative. This is not essential. By relatively small changes in the parameters the conductance can be kept positive (although it does drop to a small fraction of its resting value) without much effect on the height or shape of the action potential spike. Moreover, the changes bring the low voltage clamping curves of the model closer to the experimentally obtained curves in Fig. 2. However, the changes also affect the relation between pulse stimulus strength and time-to-spike, reducing the similarity between model and reference neuron in the comparison of Fig. 1. A preliminary look suggests it may be possible to improve these properties by assigning a small probability to the presently excluded direct transition from state Na to state A. This has not yet been seriously investigated.

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