TRANSIENT POLARIZATION CURRENTS IN THE SQUID GIANT AXON

M. W. P. STRANDBERG, *Department of Physics,*
Massachusetts Institute of Technology, Cambridge, Massachusetts
02139 U.S.A.

ABSTRACT It has been repeatedly noted that the change of conformation of the molecules that serve as the ion-selective channels for sodium and potassium conductance in the nerve membrane will be accompanied by a change in the dipole moment of the molecule. This time-dependent change of dipole moment will produce transient currents in the membrane. The canonical form for these currents is determined with conventional statistical mechanics formalism. It is pointed out that the voltage dependence of the conductance channel conductance determines the free energy of the system to within a factor that is an unknown function of the voltage. Since the dipole currents do not depend on this unknown function, they are completely determined by the observed properties of the conductance system. The predicted properties of these dipole currents, their time constants and strengths, are calculated. By using the observed properties of gating currents, the density of the sodium channels is computed. The predicted properties of the dipole currents are found to compare satisfactorily with the observed properties of gating currents.

INTRODUCTION

A conclusion possible from several different types of considerations—molecular structure analyses, thermodynamics, study of rate equations—is that the putative channels in the nerve axon membrane that selectively conduct sodium or potassium ions possess an electric dipole moment, and that this electric dipole moment varies as the channels change configuration from predominantly conducting states to predominantly nonconducting states (Hodgkin and Huxley, 1952*b*; Chandler and Meves, 1965; Keynes and Rojas, 1973, 1974; Bezanilla and Armstrong, 1974, 1975; Armstrong and Bezanilla, 1973, 1974; Rojas and Keynes, 1975; Urry, 1975; Born and Kitahara, 1975; Strandberg, 1976; Levitan and Palti, 1975). This is the same as saying that the electric dipole moment changes with transmembrane potential, since it is observed that the conductance changes with transmembrane potential.

When the transmembrane potential, V, is changed in magnitude, the accompanying change in the magnitude of the dipole moment, P, will produce a transient current, $n_0 \mathrm{d} P/\mathrm{d}t$, in the membrane when n_0 is the number of dipoles per unit volume. Unusual transient currents in the axon membrane, called "gating charge currents," have been observed and studied quantitatively (Chandler and Meves, 1965; Keynes and Rojas, 1973, 1974; Bezanilla and Armstrong, 1974, 1975; Armstrong and Bezanilla, 1973, 1974; Rojas and Keynes, 1975).

In this paper we develop the canonical form expected for the dipole current transients. This form is compared with the form observed for the gating charge currents. The ultimate question is whether the dipole transients and the gating charge transients are unrelated, related, or identical. The following discussion is a contribution to the ultimate answer to this question.

The structure of the presentation is as follows. First we derive a general expression for the stationary state dipole moment from quantum statistical mechanics, and from classical statistical mechanics. Since the configuration sum that defines the channel dipole moment also defines any other stationary state observable, for example the channel conductance, the observed behavior of the conductance states with change of transmembrane potential is related to the variation of the channel dipole moment with transmembrane potential. If this relationship is exploited, the dipole moment currents are readily predicted. The predicted magnitude, time constant, and *e*-folding potential of the dipole currents produced by the ion-specific sodium and potassium conductance channels in the membrane of the giant axon of the squid are compared with those observed for the gating currents in these membranes.

STATISTICAL DEFINITION OF THE STATIONARY STATE DIPOLE MOMENT

The axon membrane has a layered or lamellar structure, being only perturbed by protein inclusions. In the first approximation the electric field displacement, **D**, is normal to the surface of the membrane. This follows from the observation that it is certainly normal to the surface at a point in the lipid symmetrically remote from the protein inclusions, and it must also be normal to the surface at the center of a protein inclusion. The dielectric constant, κ, however, may vary in this normal direction, s. A transmembrane potential V across the membrane of thickness w will thus give rise to an electric field in the membrane in the direction s of magnitude,

$$\mathcal{E}_s(s) = -\frac{V}{\kappa(s)\int_0^w \mathrm{d}s'/\kappa(s')}. \tag{1}$$

This leads to a mean electric field of

$$\bar{\mathcal{E}}_s = \frac{1}{w}\int_0^w \mathcal{E}_s(s)\,\mathrm{d}s = -\,V/w. \tag{2}$$

In quantum mechanical terms, the electric dipole moment of a molecular system in this mean electric field is the derivative of the Hamiltonian of the system with respect to the electric field. By the Feynman theorem (Feynman, 1939), this derivative is equal to the statistical average over the available states of the system of the derivative of the state energies, E_r, with respect to the s-component of the electric field, $\mathcal{E}_s$. This mean value of the s-component of the dipole moment, P_s, is written

$$P_s = \frac{\sum_r (\partial E_r/\partial \mathcal{E}_s)\, e^{-(E_r/kT)}}{\sum_r e^{-(E_r/kT)}}. \tag{3}$$

Here r is an index of the configuration states of the system.

Standard classical statistical mechanics yields the same result. The Helmholtz free energy, F, is defined by the same configuration sum that appears in the denominator of Eq. 3,

$$e^{-(F/kT)} = \sum_r e^{-(E_r/kT)}. \tag{4}$$

Since the dipole moment per molecule is $P_s = \partial F/\partial \mathcal{E}_s$, one is led again to Eq. 3.

Eq. 3 is a broad, general expression, and of little specific use as it stands. It can be made more useful by using some known properties of the dipole moment of different interesting configurations of large molecules. In particular, we know that a change in conformation can lead to a change in the dipole moment of the molecule (Urry, 1975). The dipole moment will be approximately equal for many configurations referred to as a distinct conformation of the molecule. So it is logical to indicate the sum over these many similar configurations by a single index. To do this, order the configurations so that $\partial E_r/\partial \mathcal{E}_s$ will be P_0 for $0 \le r < k$, and $P_0 + P_i$ for $i \le r < j$, $i \neq 0$. This means that the sum over these subsets of configurations is

$$\sum_{r=i}^{j-1} (\partial E_r/\partial \mathcal{E}_s) e^{-(E_r/kT)} = (P_0 + P_i) e^{-\bar{E}_i/kT}, \tag{5}$$

where

$$e^{-\bar{E}_i/kT} = \sum_{r=i}^{j-1} e^{-(E_r/kT)}.$$

Eq. 3 now will be a sum over these subsets of conformations with index i. Thus,

$$P_s = \frac{\sum_{i=0}^{\infty} (P_0 + P_i) e^{-\bar{E}_i/kT}}{\sum_{i=0}^{\infty} e^{-\bar{E}_i/kT}}, \quad P_i = 0 \text{ if } i = 0. \tag{6a}$$

or

$$P_s = P_0 + \frac{\sum_{i=1}^{\infty} P_i e^{-\bar{E}_i/kT}}{\sum_{i=0}^{\infty} e^{-\bar{E}_i/kT}}. \tag{6b}$$

Divide by $\exp(-\bar{E}_1/kT)$ to obtain

$$P_s = P_0 + \frac{P_1 + \sum_{i=2}^{\infty} P_i e^{-(\bar{E}_i - \bar{E}_1)/kT}}{\sum_{i=0}^{\infty} e^{-(\bar{E}_i - \bar{E}_1)/kT}}. \tag{7}$$

Finally, write the electric field energy explicitly as

$$E_r(V) = E_{r0} + \frac{\partial E_r}{\partial \mathcal{E}} \mathcal{E}, \quad \mathcal{E} \equiv \mathcal{E}_s. \tag{8}$$

Then one has

$$P_s = P_0 + \frac{P_1 + \sum_{i=2}^{\infty} P_i e^{-[(\bar{E}_{i0} - \bar{E}_{10}) + (P_i - P_1)\mathcal{E}]/kT}}{1 + e^{-[(\bar{E}_{00} - \bar{E}_{10}) - P_i \mathcal{E}]/kT} + \sum_{i=2}^{\infty} e^{-[(E_{i0} - E_{10}) + (P_i - P_1)\mathcal{E}]/kT}}. \tag{9}$$

Since Eq. 3 is the canonical form for the statistical average of any observable factor of the system, and in fact since the configuration sum in the denominator of Eq. 3 defines the free energy of the system, the parameters in Eq. 9 can be determined if they are known for any other observable factor. This same analysis has been carried out for the selective ion conductances of the membrane channels. Since it is known that changes in conformation of the molecular channel systems give rise to changes both in molecular dipole moment and ion permeability, the subsets of configuration sums used in Eq. 4 can be taken to be the same for both the dipole moment and the ion conductance.

The experimental data for the selective sodium ion conductance in the squid giant axon yield, for the equilibrium conductance,

$$g_{\mathrm{Na}} = \frac{g_{\mathrm{Na0}}}{1 + e^{-(E' + F')/kT} + e^{-(E'' + F'')/kT}}. \tag{10}$$

The stationary states for a transmembrane potential, $V_r + V$, are defined by, $E' = -72.2$ meV, $F' = -0.52\,V + 70 \tanh(V/20.5)$ meV, $E'' = -207$ meV, $F'' = -1.22\,V + 160 \tanh(V/20.5)$, $V_r = -63$ mV, and $g_{\mathrm{Na0}} = 25$ mmho/cm^2 (Strandberg, 1976).[1]

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[1] These parameter values correct typographical errors that occured in a previous paper (Strandberg, 1976), pp. 42 and 43, after Eq. 13. The states of the system as described in that paper do not have the simple meaning that we have used here, namely the stationary states and the transient states. We have also added a small term in the stationary-state representation so that the equation represents the Hodgkin-Huxley $m_{\infty}^3 h_{\infty}$ precisely at large departure from the resting potential.

After a step change in the transmembrane potential, V, from the resting potential, V_r, the conductance change is found to be represented by Eq. 10, with $F' = 2.58\,V\,[\exp(-t/\tau_2) - \exp(-t/\tau_1)] - [0.58\,V - 70\tanh(V/20.5)][1 - \exp(-t/\tau_2)]$ meV, $F'' = 6\,V\ [\exp(-t/\tau_2) - \exp(-t/\tau_1)] - [1.22\ V - 160\ \tanh\ (V/20.5)][1 - \exp\cdot(-t/\tau_2)]$ meV, with $\tau_1 = 0.25$ ms and $\tau_2/\tau_1 = 20\exp(-V/60)$ at 6°C.

A similar analysis of the experimental data for the potassium conductance in the squid giant axon yields

$$g_K = \frac{g_{K0}}{1 + e^{-(E'+F')/kT} + e^{-(E''+F'')/kT}}. \tag{11}$$

The stationary states are given by $E' = -31$ meV, $F' = 0.686$ V meV, $E'' = -90$ meV, $F'' = 3.60\,V$ meV, with the transmembrane potential given by $V + V_r$, and $V_r = -63$ mV, and $g_{K0} = 24$ mmho/cm^2 (Strandberg, 1976).[2]

After a step change in transmembrane potential, V, from the resting potential, V_r, the potassium conductance varies in time such that $F' = 0.686\,V[1 - \exp(-t/\tau_k)]$ meV, and $F'' = 3.60\,V[1 - \exp(-t/\tau_k)]$, with $\tau_k = 3.5$ ms at 6°C.

The contribution of the dipole moment of the conductance channels to the observed transient current density in the membrane will be $n_0 \partial P_s/\partial t$, with the density of dipoles per unit volume, n_0, taken as the number of channels per unit area, N_c, divided by the thickness of the membrane, w, or $n_0 = N_c/w$. One is going to see most readily the dipole changes with the shortest time constant. For this reason we will discuss the polarization transient currents from the sodium ion channels.

Observe, first, that since any time-dependent measurement of the polarization current will involve the term $\partial P_s/\partial t$, the constant component of the dipole moment, P_0 in Eq. 9, will not be observable.

Second, the form of the observed sodium conductance yields the configuration sum, as the denominator of Eq. 10 times a function of the transmembrane potential. This can be seen by noting that the statistical expression for the conductance is

$$g_{\mathrm{Na}}(V) = \frac{\Sigma\,(g_{\mathrm{Na}})_r\, e^{-E_r/kT}}{\Sigma\, e^{-E_r/kT}}. \tag{12}$$

The numerator, the sum over conducting states, can be written as

$$\Sigma\,(g_{\mathrm{Na}})_r\, e^{-E_r/kT} \equiv g_{\mathrm{Na}0}\, e^{-(E_g + P_g \mathcal{E})/kT}, \tag{13}$$

where the equation itself defines a conductance-weighted mean energy, $(E_g + P_g\mathcal{E})$. The denominator of Eq. 10 is therefore the configuration sum divided by $\exp[-E_g +$

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[2] These parameters differ from those given in a previous paper (Strandberg, 1976). The function is the same. The choice between the two forms is made not on the basis of which represents the Hodgkin-Huxley data better, since they are equivalent in that respect, but on the basis of their serving as a representation for the noise in the membrane. The one we use here can be shown to be preferable in that respect. A discussion of the noise in membranes will be published elsewhere.

$P_g\mathcal{E})/kT]$, or,

$$[\Sigma e^{-E_r/kT}]/e^{-(E_g+P_g\mathcal{E})/kT} = e^{-[F-(E_g+P_g\mathcal{E})]/kT} = g_{\mathrm{Na0}}/g_{\mathrm{Na}}. \tag{14}$$

Since F is the free energy of the conductance system, and since $E_g + P_g\mathcal{E}$ can be regarded as the contribution to the free energy by the high conductance configurations, it is convenient to think of the denominator of Eq. 10 as defining the free energy of the nonconducting states. Of course the contribution to the free energy of the system is not expressible as a sum except when the separate degrees of freedom of the system are independent. This is not the case here, but the form of the definition of the free energy in terms of the configuration sum allows one always to express all the state energies in terms of the mean energy of a particular conformation, and hence display that energy as a singular contribution to the free energy of the total system.

The dipole moment is then found to be,

$$\begin{aligned} P_s &= \partial F/\partial\mathcal{E} \\ &= P_g + (\partial P_g/\partial\mathcal{E})\mathcal{E} + \frac{(\partial F_1/\partial\mathcal{E})e^{-F_1/kT} + (\partial F_2/\partial\mathcal{E})e^{-F_2/kT}}{1 + e^{-F_1/kT} + e^{-F_2/kT}}. \end{aligned} \tag{15}$$

Now, one knows that the induced polarization of molecules, $(\partial P_g/\partial\mathcal{E})\mathcal{E}$, is negligible compared to P_g and the terms in $\partial F_i/\partial\mathcal{E}$, so we can totally neglect the effect of the unknown function, $\exp[(E_g + P_g\mathcal{E})/kT]$, on the observable dipole moment (Golden and Wilson, 1948).

Furthermore, this complicated expression, Eq. 15, is really quite simple. One of the terms in the denominator will dominate the expression if either is greater than one. Hence one finds,

$$P_s - P_g = \partial F_i/\partial\mathcal{E}, \quad e^{-F_i/kT} \gg e^{-F_j/kT} \quad \text{and} \quad 1, \tag{16a}$$

and,

$$P_s - P_g, \quad \text{and} \quad \partial P_s/\partial t \rightarrow 0, \quad \text{as} \quad e^{-F_1/kT} \quad \text{and} \quad e^{-F_2/kT} \ll 1. \tag{16b}$$

TRANSIENT SODIUM AND POTASSIUM CHANNEL DIPOLE MOMENT CURRENTS

The dominant term in the expression for the transient sodium conductance, $F_i = -207 + 6.0\,V[\exp(-t/\tau_2) - \exp(-t/\tau_1)] - [1.22\,V - 160\tanh(V/20.5)][1 - \exp\cdot(-t/\tau_2)]$ meV, determines the transient polarization current after the step change of the transmembrane potential from V_r to $V_r + V$ to be

$$\begin{aligned} \partial P/\partial t \simeq -[&(160/V)\tanh(V/20.5)e^{-t/\tau_2} \\ &- 6(e^{-t/\tau_2} - (\tau_2/\tau_1)e^{-t/\tau_1})](10\,eV/kT)(ew/\tau_2). \end{aligned} \tag{17}$$

The initial behavior of this expression, $t/\tau_i < 1$, defines the effective time constant and initial amplitude as,

$$(\partial P/\partial t)\,|_{t=0} = -[6(\tau_2/\tau_1) + (160/V)\tanh(V/20.5) - 6](10\,eV/kT)\left(\frac{ew}{\tau_2}\right), \tag{18}$$

$$\tau_{\mathrm{eff}}^{-1} \simeq \frac{[6(\tau_2^2/\tau_1^2) + (160/V)\tanh(V/20.5) - 6]}{[6(\tau_2/\tau_1) + (160/V)\tanh(V/20.5) - 6]\tau_2}. \tag{19}$$

This means that near the resting potential $\tau_{\mathrm{eff}} = \tau_1 = 0.25$ ms, and near $V = 90$ mV $\tau_{\mathrm{eff}} = 0.6\,\tau_1 = 0.125$ ms at 6°C.

By a similar procedure, the transient current from the dipole moment of the potassium channels is determined to be,

$$(P_s)_k = (P_{0g})_k + \frac{[-3.6\,e^{-F_1/kT} + 0.686\,e^{-F_2/kT}]ew}{1 + e^{-F_1/kT} + e^{-F_2/kT}}, \tag{20a}$$

$$\partial(P_s)_k/\partial t \simeq -(3.6\,ew/\tau_k)(3.6\,eV/kT)(2 + e^{-F_1/kT})^{-1}e^{t/\tau_k}. \tag{20b}$$

The time constant for potassium, τ_k, is 14 times larger than τ_1 of the sodium channels. The transient is smaller by more than this factor and for comparable channel densities this current will be much more difficult to observe. In a later section we present the evidence that the channel densities of the sodium and potassium channels is of the same order of magnitude.

The integral of the dipole moment transient current is proportional to the difference in the dipole moment in the initial and final states since

$$\int_{t_1}^{t_2} (\partial P/\partial t)\mathrm{d}t = \int_{P_i}^{P_f} \mathrm{d}P = P_f - P_i. \tag{21}$$

This difference is determined from Eq. 15. Since the denominator in this expression is much greater than 1 in any stationary state as $t \rightarrow \infty$, we find that, for the sodium channels,

$$P_f - P_i \simeq \left.\frac{\partial F_1}{\partial \mathcal{E}}\right|_f - \left.\frac{\partial F_1}{\partial \mathcal{E}}\right|_i = -7.95\,ew[\tanh^2(V_f/20.5) - \tanh^2(V_i/20.5)]. \tag{22}$$

This function represents a function which saturates at $V \sim 40$ mV, and which increases as $\exp(V/10)$, that is, it has an e-folding voltage of 10 mV.

Hodgkin and Huxley, in one of their papers reporting the data on the properties of the ion selective conductance channels in the squid axon, included some data on the variation of the maximum time rate of change of the conductance, $\mathrm{d}g/\mathrm{d}t$, for the sodium and potassium systems (Hodgkin and Huxley, 1952*a*). They were fascinated by the fact that, though the maximum conductance, g, saturated for both channels for an offset of the transmembrane potential of more than 30 mV, $\mathrm{d}g/\mathrm{d}t$ increased continuously with no evidence of saturating. They did not make use of the data in their summary paper, however (Hodgkin and Huxley, 1952*b*). The equations given above provide a convenient means with which to study the anatomy of the process involved here, and also to use the data to derive basic parameters of the system.

The expression for the time derivative of the conductance that one derives from either Eq. 10 or 11 is, by simple differentiation,

$$dg/dt = \frac{g_0[(dF_1/dt)e^{-F_1/kT} + (dF_2/dt)e^{-F_2/kT}]}{kT(1 + e^{-F_1/kT} + e^{-F_2/kT})^2}. \quad (23)$$

Algebraic reduction, using the expression for g, allows Eq. 23 to be written as

$$dg/dt = \frac{g(g_0 - g)}{kTg_0}\left[\frac{dF_1}{dt}\left(1 + \frac{e^{-F_2/kT}}{e^{-F_1/kT}}\right)^{-1} + \frac{dF_2}{dt}\left(1 + \frac{e^{-F_1/kT}}{e^{-F_2/kT}}\right)^{-1}\right]. \quad (24)$$

To find the maximum of this function, one notes that the first factor of this expression varies slowly from its maximum of $g_0/4$ at $g = g_0/2$. At $g = g_0/5$ this factor is $4g_0/25$, down only 36% for a variation in g of 60%. On the other hand as g approaches $g_0/2$, the second factor is rapidly decreasing, because the exponential terms are becoming less than 1. A few minutes with a calculator will convince one that the maximum occurs, then, at $g \sim g_0/5$ and dF_i/dt approximately half its initial value. For transmembrane potentials small enough so that g is less then $g_0/5$, the maximum comes at the maximum g with dF_i/dt one-half its initial value.

For transmembrane offset potentials of more than 30 mV, it is therefore the slope of the $(dg/dt)_{\max}$ curve that is most useful. The g-dependent term is then saturated and only the potential dependence of dF_i/dt is determined. This is, by definition, P_{i0}/w where P_{i0} is the initial dipole moment and w is the membrane thickness. Hence we find that,

$$\frac{d}{dV}\frac{dg}{dt}_{\max} \simeq \frac{g_0 P_{i0}/w}{12\,kT\tau}, \quad (25)$$

where τ is the relaxation time.

Fig. 11, page 466 of Hodgkin and Huxley (1952*a*), show the maximum dg/dt vs. V for sodium. The slope is 1.8 mho/cm^2-s-mV, and g_0 is stated to be 16 mmho/cm^2 at 3.5°C. Since P_{i0} for sodium is approximately $6ew$, one concludes that $\tau \sim 0.24$ ms at 3.5°C, or 0.31 ms at 6°C. This is in agreement with 0.25 ms, the value given above for τ_1. The constancy of the slope argues for the relative constancy of τ_1 with change in transmembrane potential which I found from fitting the other transient data.

In Fig. 12, page 466 as above, the potassium data show that, at 6°C, an axon with a g_0 of 20 mmho/cm^2 has a slope of 0.125 mho/cm^2-s-mV, while one at 8.5°C with a g_0 of 31 mmho/cm^2 has a slope of 0.25 mho/cm^2-s-mV. For the potassium channels, P_{i0} is approximately 3.6 ew. These data then give $\tau_k = 2$ ms at 6°C and 1.6 ms at 8.5°C. The latter time constant would be, for a Q_{10} of 3, increased to 2 ms at 6°C. Again the data attest the relative constancy of τ_k. The magnitude of τ_k is smaller than we have determined from the voltage-clamp data, but it may be an error compatible with the errors of the several input data and the approximation of the maximum.

In both figures the decrease of dg/dt proportionally to g for transmembrane potentials less than 30 mV attests that g varies exponentially with V, as we have expressed it.

COMPARISON WITH GATING CHARGE EXPERIMENTAL DATA

We will not give a critical discussion of how the experimental data on gating charge currents are related to the Hodgkin-Huxley model. The papers reporting the data have done this expertly. We merely note a few similarities between the properties of the gating charge currents and the dipole currents that we predict. We do not find exact numerical agreement necessary for the similarity to be established. The numbers that we gave above for the various parameters are obviously typical of one axon, and one must expect to find deviations.

However, using the properties of the dipole moment of the sodium channels, we do predict an e-folding voltage of the sodium conductance to be $kT/6e$, or 4 mV, while the e-folding voltage of the dipole moment change to be 10 mV. The experimental data make the dipole e-folding voltage 20 mV (Rojas and Keynes, 1975; Bezanilla and Armstrong, 1975). The quantitative agreement leaves a bit to be desired, but the analysis shows why one should expect two characteristic e-folding voltages. One is determined by the voltage-independent part of the dipole moment for sodium, and the other measures the variation of the dipole moment with voltage. From Eq. 22 one has 7.95 ew as the total variation in the dipole moment with transmembrane potential. This translates into a saturation charge transport of 7.95e per channel. Using the experimentally determined total charge transport, 1,882$e/\mu m^2$, one determines the surface density of sodium channels therefore to be $240/\mu m^2$ or $2.4 \times 10^{10}/cm^2$ (Bezanilla and Armstrong, 1975; Rojas and Keynes, 1975). This density is in reasonable agreement with the density determined from entropy production, $10^{11}/cm^2$, or 1.3×10^9–$4 \times 10^{10}/cm^2$ as determined for the sodium channels in the squid axon and frog skin by site-specific binding studies. This is also the same order of magnitude as the density of potassium channels, 1.5–$6 \times 10^{10}/cm^2$ (Strandberg, 1976; Bass and Moore, 1973; Cuthbert, 1973).

Finally the time constants that we predict for the gating currents, varying at 6°C from 0.25 ms at the resting potential to 0.1 ms at large transmembrane potentials, agree with the experimental observations (Bezanilla and Armstrong, 1975; Rojas and Keynes, 1975). On decreasing the transmembrane potential to 0, a net transport of gating charge outward is observed. This is the direction predicted by Eq. 22.

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