AN APPROACH TO THE PHYSICAL BASIS OF NEGATIVE CONDUCTANCE IN THE SQUID AXON

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ABSTRACT In considering the problem of steady-state negative conductance in the squid axon from the standpoint of electrodiffusion, the following assumptions produce results which are in reasonable agreement with experimental observations: (1) The major ion distributions are not significantly perturbed by current flows (2) The electric field in the membrane is essentially uniform. (3) The membrane has certain properties appropriate to solids, particularly with respect to chemical potentials. (4) Na^+ and K^+ move according to a single-file interstitialcy migration mechanism and independently of each other. (5) The interaction energy of Na^+ with membrane sites is about 1.4 times that for K^+. Assumptions 1 and 2 are sufficient for the appearance of a negative conductance. Experimental test of the theory is possible and is specifically suggested.

INTRODUCTION

Of the many properties of the squid axon which have been revealed by voltage clamp experiments, perhaps the most important is its negative differential conductance (1, 2). The purpose of this report is to suggest a physical basis for this property. A preliminary paper has already appeared (3) and is here both modified and extended.

There are a number of nonbiological systems which exhibit a negative conductance or *N*-shaped current-voltage characteristic and in some cases, such as the Esaki tunnel diode (4), the system is understood well enough so that the mechanism responsible for this behavior is apparent. In addition to the Esaki diode, this is essentially also true for the positive thermistor (5), the dynatron (6, 7), and the hydraulic fixed charge oscillator (8, 16, 17). In other cases, however, the relevant mechanisms are either unknown or only poorly clarified.

It can be shown analytically (9–11) that if a system which exhibits a negative differential conductance in some region of the current-voltage plane is associated with appropriate reactances a number of physiologically significant phenomena such as excitation threshold, repetitive activity, etc., become possible. It is therefore important to attempt some understanding of the possible physical bases for negative conductance in certain biological membranes, particularly in systems such as the squid axon which have yielded to quantitative experiment.

The fundamental problem, well-known to those who have concerned themselves with this question, is that most of classical electrodiffusion theory by itself seems useless to explain the behavior of the squid axon (2, 12). Both the theory of simple electrolytes (13, 14) and the theory of fixed-charge membranes (15) fail to yield the negative conductance and high rectification produced by the axon membrane. The hydraulic fixed-charge oscillator (8, 16, 17) displays a negative conductance, but pressure is a significant variable in this system and a comparable importance of pressure in the squid axon has yet to be demonstrated. There has been recent interest in the possibility that semiconductor theory might prove fruitful (18), but in those cases where negative conductance appears in a semiconductor system whose behavior is understood, the phenomenon has been related to properties essentially unique to electrons (e.g., quantum mechanical tunneling or deep trapping) (19). Negative conductance in other semiconductor systems (20) remains unexplained. It is not always a simple matter to distinguish between electronic and ionic conduction (21), but the available evidence indicates that in the squid axon ions are the predominant charge carriers (1) and an approximate calculation shows that ion tunneling in this system is very improbable (12).

The negative conductance which appears in the squid axon is ordinarily transient. Whether this is a result of first order processes for several ions or a single ion higher order process has not yet been decisively resolved (2, 22). The evidence suggests, however, that a single ion process, commonly involving Na^+, is operating, and the Hodgkin-Huxley empirical model (1), which has been so successful in describing laboratory results, makes this assumption. The approach taken here is consistent with this premise but not dependent upon it.

Perhaps one of the most significant experimental observations is that under certain conditions the squid axon can show a steady-state negative conductance (23). Because of this, as Cole (2, 24) has suggested, it seems reasonable to first attack this problem rather than the more complicated transient phenomena. The aim, therefore, has been to isolate assumptions which produce a steady-state negative conductance in agreement with both experimental observations and a hypothetical axon without "inactivation". The latter involves a solution to the Hodgkin-Huxley voltage clamp equations (1) after the inactivation variable has been removed, giving a hypothetical steady-state Na^+ I–V curve. Three essential demands must be satisfied: (1) the system must be able to produce a steady-state negative conductance; (2) there must be a possibility for very substantial rectification; (3) the I–V curves for large membrane depolarizations must be linear.

THEORY

The axon membrane is not a geometrically well-defined physical system and the actual physiological barrier to the movement of charged particles may involve something more extensive than the structure revealed by electron microscopy. Enduring macromolecular regions are undoubtedly present on either side of the lipid layer and these should presumably play some role in the partition and movement of ions. It will be assumed here, however, that the major barrier is a 50 A insulating layer, and this will be termed the axon "membrane."

The two fundamental equations which are presumably appropriate are the continuity equation and the Poisson equation:

$$\frac{\partial I}{\partial x}(x, t) = -\frac{\partial \rho}{\partial t}(x, t) \tag{1}$$

$$\frac{\partial \mathrm{E}}{\partial x}(x, t) = \frac{\rho}{\epsilon}(x, t) \tag{2}$$

where I (coul/cm^2·sec) is the current density associated with moving charges; ρ (coul/cm^3) is the charge density; E (v/cm) is the electric field intensity; ϵ (coul/v·cm) is the absolute dielectric constant which is assumed to be invariant; x (cm) is the distance; t (sec) is time; and a one dimensional simplification is used.

If equation 2 is differentiated with respect to time and used with equation 1, then:

$$\frac{\partial I}{\partial x} = -\epsilon \frac{\partial}{\partial t}\left(\frac{\partial \mathrm{E}}{\partial x}\right) = -\epsilon \frac{\partial}{\partial x}\left(\frac{\partial E}{\partial t}\right) \tag{3}$$

and an integration yields the Maxwell current equation:

$$\underset{\text{TOTAL}}{I(t)} = I(x, t) + \epsilon \frac{\partial}{\partial t} E(x, t). \tag{4}$$

The total current density through the membrane is thus the sum of a displacement current $\epsilon \partial E/\partial t$ and a convection current $I(x, t)$. Although an applied potential difference across the membrane may be established with a time constant (determined by the external series resistance) of microseconds, the interior electric field reaches its final profile with a time constant of $\epsilon/\bar{\sigma}$, where $\bar{\sigma}$ is a mean specific conductivity. In the squid axon membrane this latter time constant should be of the order of milliseconds (12).

It is convenient to reduce the Poisson equation to dimensionless form by the following transformations:

$$E \equiv \frac{RT}{F\delta} E^* \tag{5}$$

$$x \equiv \delta y \tag{6}$$

$$\rho \equiv |\bar{\rho}| \rho^* \tag{7}$$

$$\lambda \equiv \sqrt{\frac{RT\epsilon}{F|\bar{\rho}|}} \tag{8}$$

where δ (cm) is the thickness of the membrane, λ (cm) is a Debye length, R (joule/mole deg) is the gas constant, F (coul/mole) is the Faraday constant, T (deg) is the Kelvin temperature, and $\bar{\rho}$ is the mean charge density. Equation 2 now becomes

$$\frac{\partial E^*}{\partial y} = \frac{\delta^2}{\lambda^2} \rho^* \tag{9}$$

suggesting that if $\lambda \gg \delta$ it is reasonable to assume

$$\frac{\partial E^*}{\partial y} \approx 0 \tag{10}$$

without any restriction on ρ^* other than that it is reasonably small. Equation 9 can also be written as

$$\rho^* = \frac{\lambda^2}{\delta^2} \frac{\partial E^*}{\partial y} \tag{11}$$

so that if $\lambda \ll \delta$, $\rho^* \approx 0$ is a sensible approximation.

Consideration of the mean specific conductivity of the axon membrane suggests that it is unlikely that the Debye length is much smaller than the membrane thickness. The assumption $\rho^* \approx 0$, i.e. microscopic electroneutrality, is therefore probably not realistic. An assumption that $\lambda \gg \delta$, i.e. essentially uniform electric field, may be appropriate, and this assumption results in a considerable simplification of the mathematical analysis.

Equation 4 provides an immediate distinction between the charging process associated with the establishment of the interior electric field and the redistribution process associated with the convection current, a distinction discussed by Planck (13) and more recently by Cole (2). An important point revealed by equation 3 however, and one which should be emphasized, is that when the charging process is completed, i.e. when $\partial E/\partial t = 0$ the following must be true:

$$\frac{\partial I}{\partial x} = 0 \quad \text{when} \quad \frac{\partial E}{\partial t} = 0 \tag{12}$$

Therefore, if a redistribution process occurs following the charging process, the total convection current will be time dependent only. The individual ionic currents, however, may depend on both time and position, viz.:

$$\frac{\partial I}{\partial x} = \frac{\partial}{\partial x} \sum I_i = 0 \quad \text{when} \quad \frac{\partial E}{\partial x} = 0. \tag{13}$$

Equation 13 may be said to describe a quasi-steady state, while $\partial I_i/\partial x = 0$ would imply a true steady state (assuming an already terminated charging process). In addition, in a true steady state

$$\frac{\partial I_i}{\partial x} = -Z_i F \frac{\partial c_i}{\partial t} = 0 \tag{14}$$

where C_i(mols/cm^3) is the concentration of the ith species and Z_iF its charge/mole.

With these comments we simplify the analytical problem by assuming that the membrane Debye length is much greater than the membrane thickness and that a true steady state exists, i.e.:

$$\frac{\partial E}{\partial x} = 0$$

$$\frac{\partial E}{\partial t} = 0$$

$$\frac{\partial I_i}{\partial t} = 0 \tag{15}$$

$$\frac{\partial I_i}{\partial x} = -Z_i F \frac{\partial c_i}{\partial t} = 0. \tag{16}$$

Consider now the membrane as a semi-insulating barrier separating two electrolyte solutions. The partial ionic current carried by any species can be expressed as the product of a charge density and a velocity:

$$I_i = \rho_i v_i \tag{17}$$

As a first approximation the velocity, v_i, can be considered to be simply proportional to a driving force or energy density gradient. The proportionality factor will be a parameter dependent upon the type of ion and the medium through which it moves. A complication arises, however, if more than one type of energy density gradient is involved, e.g., both thermal (osmotic) and electrical. In this case it is possible that more than one migration mechanism may be involved, and if this is so a different proportionality factor must be assigned to each driving force, since presumably different ion and medium properties would be relevant for different migration mechanisms. The velocity can therefore be thought of as consisting of a number of components:

$$I_i = -\rho_i \sum_m u_i^m \frac{\partial U_i^m}{\partial x} \tag{18}$$

where u^m(cm$^2\cdot$mol/sec$\cdot$J) is a mobility and U^m(J/mol) is an energy density.

If the relevant driving forces are thermal and electrical, the condition $u^m \neq u^n$ is not trivial, since the immediate implication is that the Nernst-Einstein relation is not obeyed and the equilibrium ion distribution is not described by simple Boltzmann statistics.

If a steady state exists, equation 18 gives:

$$I_i = \frac{-\sum\limits_m u_i^m (U_i^{m''} - U_i^{m'})}{\int_{'}^{''} \frac{dx}{\rho_i}} \tag{19}$$

where the primes refer to the membrane boundaries.

The central problem, then, is the determination of the integral in equation 19. One approach to this is the subject of this paper. Other approaches are possible, some preferable, and will be considered in subsequent reports.

The driving forces of most interest to biologists are gradients of chemical potental and electric potential. The usual assumption is that the chemical potential of ions in a biological membrane is given by

$$\mu_i = \mu_i^0 + RT \ln a_i \tag{20}$$

where μ_i^0 is a reference energy/mol which depends on the interaction energy with the solvent, and a_i is an activity or mole fraction.

As has been noted previously (3), equation 20 is appropriate for dilute solutions, but for other systems the expression for the chemical potential of the species may take another form, and in each case an attempt should be made to relate the chemical potential to the variables of statistical mechanics, at least until experimental evidence indicates which form is most convenient. Such experimental evidence does not yet exist for the axon membrane. If ions in the membrane behave as a lattice gas, then the appropriate expression for the chemical potential was shown (3) to be:

$$\mu_i = \mu_i^0 + RT \ln \left[\frac{c_i}{w_i - c_i} \right] \tag{21}$$

where w_i is the total density of available sites for the ions. An expression such as equation 21 is not unreasonable for condensed fixed charge systems, but although it leads to what appears to be a useful result (linear I–V curve with large depolarizations) it may be totally wrong for the axon membrane.

In reference 3 equation 21 was used to derive a modified electrodiffusion equation which, assuming a uniform electric field and true steady state, takes the form:

$$I_i = -RTu_i^a \frac{w_i}{w_i - c_i} \frac{dc_i}{dx} + \frac{Fu_i^b c_i v}{\delta} \qquad (Z_i = 1) \tag{22}$$

where V (volts) is the potential difference of the axoplasm boundary relative to the sea water boundary; u_i^a (cm²/sec·volt) the diffusion mobility; u_i^b (cm²/sec·volt) the electric mobility. Rearranging and integrating across the membrane:

$$I_i = \frac{(V - V_i^0)Fu_i^b}{\int_{\prime}^{\prime\prime} \frac{dx}{c_i}} \tag{23}$$

$$V_i^0 = \frac{RT}{\alpha_i F} \ln\left[\frac{c_i''(w_i - c_i')}{c_i'(w_i - c_i'')}\right] \tag{24}$$

$$\alpha^i \equiv u_i^b/u_i^a \tag{25}$$

where the double prime refers to the outside boundary; V_i^0 (volts) is the potential difference at which the current is zero; and α_i, which varies according to migration mechanism (25), may be called the *electrodiffusion constant*. It will be assumed that both Na^+ and K^+ move by a collinear (i.e. single-file) interstitial migration mechanism, so that $\alpha_i = 3$. It might be noted that equation 24 can be written as:

$$V_i^0 = \frac{RT}{\alpha_i F} \ln \frac{c_i''}{c_i'} - \frac{RT}{\alpha_i F} \ln \frac{b_i''}{b_i'} \tag{26}$$

where b_i (mol/cm^3) is the density of unoccupied sites. The relation between boundary concentrations and solution concentrations is not specified, but for what follows it is enough that V_i^0 exists and that it can be determined experimentally. Any interfacial potentials presumably are not significant for the phenomena under discussion.

The principal assumption now made is that the electric current produces only a minor perturbation of the equilibrium ion distribution. From equation 22 the equilibrium distribution is given by

$$c_i = \frac{w_i}{\exp\left[\frac{F}{RT}\left(\phi_i - \frac{\alpha_i V x}{\delta}\right)\right] + 1} \tag{27}$$

where $F\phi_i$ (J/mol) is the interaction energy of ions with sites in the absence of a total electric field.

Combining equations 23 and 27:

$$I_i = \frac{-\tilde{I}_i \alpha_i \xi(\xi - \xi_i^0)}{e^{\Phi_i}(e^{-\alpha_i \xi} - 1) - \alpha_i \xi} \tag{28}$$

$$\xi \equiv FV/RT \tag{29}$$

$$\xi_i^0 \equiv FV^0/RT \tag{30}$$

$$\Phi \equiv F\phi_i/RT \tag{31}$$

$$\tilde{I}_i \equiv \frac{RTu_i^b w_i}{\delta} \tag{32}$$

Equation 28 is the principal equation of the steady-state theory. In order to compare theoretical and experimental current-voltage curves, it is convenient to note that when $\xi = 0$ the current is given by

$$I_i^0 = \frac{-\tilde{I}_i \xi_i^0}{\epsilon^{\Phi_i} + 1} \tag{33}$$

and using this in equation 7:

$$\frac{I_i}{I_i^0} = \frac{(\epsilon^{\Phi_i} + 1)\alpha_i \xi(\xi - \xi_i^0)}{\epsilon^{\Phi_i}(\epsilon^{-\alpha_i \xi} - 1) - \alpha_i \xi} \cdot \frac{1}{\xi_i^0}. \tag{34}$$

This procedure reduces any ambiguity due to experimental differences in axons surface area.

There is no a priori basis for estimating Φ_i, but the values $\Phi_K = -0.7$ and $\Phi_{Na} = -1$ have been found to give satisfactory results.

In Fig. 1 experimental data from Cole and Moore (26) are compared with the current-voltage relations predicted by equation 34. The agreement is reasonably good. The discrepancies near the resting potential are difficult to evaluate because of uncertainty concerning the experimental leakage current.

Equation 34 cannot be used when $\xi_i^0 = 0$ (e.g., high external KCl). In this case it is convenient to note that in equation 28 the limiting slope resistance is given by

$$R_i = RT/F\tilde{I}_i. \tag{35}$$

A typical experimental value for R_i in the squid axon is 15 ohm·cm², yielding 1.67 ma/cm² for $\tilde{I}_i$. Using this in equation 28 and varying ξ_i^0, generates the family of

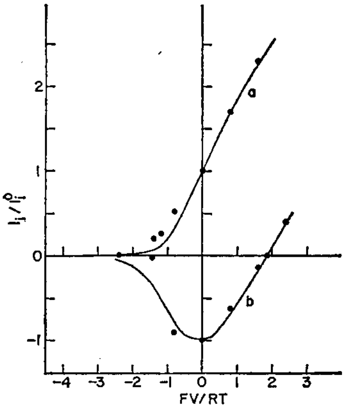

FIGURE 1

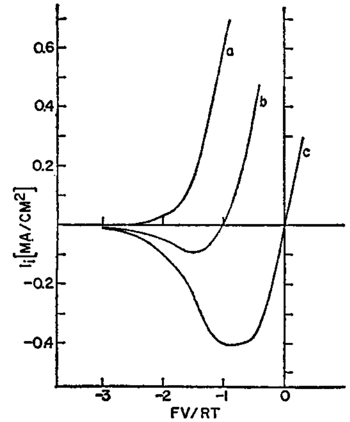

FIGURE 2

FIGURE 1 Comparison of theoretical *I-V* curve (equation 34) with experimental data (reference 26, Fig. 15). The experimental points for curve *b* were taken at 0.2 msec. The experimental points for curve *a* are steady-state values. For the continuous curve *a*, $\Phi_K = -0.7$, $\alpha_K = 3$, $\xi_K^0 = -2.4$. For the continuous curve *b*, $\Phi_{Na} = -1$, $\alpha_{Na} = 3$, $\xi_{Na}^0 = 1.85$.

FIGURE 2 Theoretical *I-V* curves from equation 28 with $\tilde{I}_i = 1.67$ ma/cm². curve *a*, $\xi_K^0 = -2.5$; curve *b*, $\xi_K^0 = -1$; curve *c*, $\xi_K^0 = 0$. $\Phi_K = -0.7$. $\alpha_K = 3$.

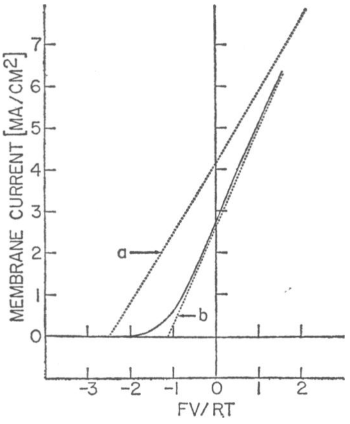

FIGURE 3

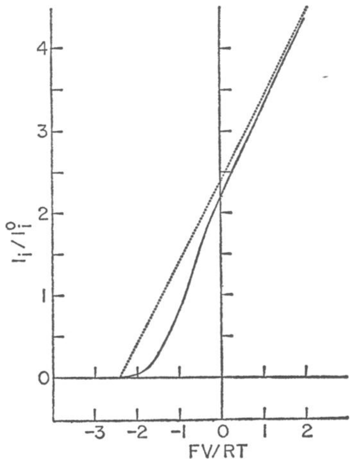

FIGURE 4

FIGURE 3 Theoretical curve from equation 28 with I_i = 1.67 ma/cm². $\xi_K^0 = -2.5$, $\alpha_K = 3$, $\Phi_K = -0.7$. *a* is the true mathematical limiting slope. *b* is the apparent limiting slope.
FIGURE 4 Theoretical curve from equation 34 with $\Phi_K = -2.3$, $\alpha_K = 3$, $\xi_K^0 = -2.4$. The dashed line is the mathematical limiting slope.

curves shown in Fig. 2. This is in reasonable quantitative agreement with experimental observations (23, 27) showing a developing region of negative conductance as ξ_K^0 is reduced.

From equation 28, for two different equilibrium potentials for the same ion, and assuming a constant limiting slope resistance, the following can be deduced.

$$\frac{I_1}{I_2} = \frac{\xi - \xi_1^0}{\xi - \xi_2^0}. \qquad (36)$$

Hoyt (28) has shown that the type of "ohmic" relation described by equation 36 can account for a wide range of experimental squid data. The implication of this relation is that the steady-state ion conductance is independent of boundary concentrations (if it is assumed that these determine the equilibrium potential).

An interesting feature of the theory is that it produces both a true and an "apparent" limiting conductance, as illustrated in Fig. 3, suggesting a reason for the apparent failure of the limiting conductance of experimental K^+ I–V curves to extrapolate to the resting potential (2). In Fig. 3 line *a* is the true limiting slope given by $\tilde{I}_i F/RT$ while line *b* is only an apparent limiting slope. The true limiting slope extrapolates to the equilibrium potential.

Another aspect concerns Φ_K, the reduced zero-field interaction energy of K^+ with the membrane. As shown in Fig. 4, a change in this parameter, producing a marked inflection in the I–V curve, can account for certain anomalous steady-state I–V curves which have been observed in the laboratory (24).

A consideration of equations 2 and 6 shows that the theory predicts that when $V =$

0 the current is given by

$$I^0 = -\frac{Fu^b w V^0}{\delta(\rho^\Phi + 1)} \qquad (37)$$

i.e., a linear relation between I^0 and V^0. This provides an experimental test for an important part of the theory, and since some other theoretical formulations predict a highly nonlinear relation the test is of some significance.

DISCUSSION

The theory which has been presented is based on assumptions involving the following physical picture of the axon membrane:

(1) The electric field in the membrane is essentially uniform.

(2) The membrane has certain properties appropriate to solids, particularly with respect to chemical potentials.

(3) The major ion distributions are not significantly perturbed by current flow.

(4) Na^+ and K^+ move according to a single-file interstitialcy migration mechanism and independently of each other.

(5) The interaction energy of Na^+ with membrane sites is about 1.4 times greater than that for K^+.

These are the major assumptions which have been shown to produce theoretical steady state–current voltage relations in agreement with experimental observation.

The essential physical phenomenon responsible for negative conductance in the theory is a depletion of mobile charges in the membrane over a particular range of membrane potential.

The problem of the electric field has been discussed above. The assumption of a membrane Debye length much greater than the membrane thickness is both useful and reasonable. It has apparently not been previously pointed out that this leads to an intriguing possibility concerning time-dependent processes. It can be shown (2) that

$$\frac{\tau_C}{\tau_D} \approx \frac{\lambda^2}{\delta^2} \qquad (38)$$

where τ_C and τ_D are the charging and redistribution time constants respectively, and λ is a Debye length. If the charging time in a system is much greater than the redistribution time, the existence of space-charge transients is possible and in certain liquid-crystal systems such transients have been experimentally observed and attributed to this cause (29).

The idea that a solid-state approach to the axon membrane might be useful was apparently first suggested by Cole (24). However, if a significant series resistance, r , is assumed it can be shown that equation 23 becomes:

$$I_i = \frac{V - V_i^0}{\dfrac{1}{F}\displaystyle\int_{'}^{''} \frac{dx}{c_i u_i} + r_i} \qquad (39)$$

and an assumption of a Boltzmann distribution for c_i produces results essentially the same as the excluded volume treatment which has been used. The latter was chosen primarily because it involves one less parameter and allows a more stringent comparison with experiment, but the physical model may eventually turn out to be unnecessarily complicated. A theoretical analysis involving equation 39 is in preparation (39). It might also be noted that equation 27 can be obtained from a Stern layer adsorption model (30).

In the preliminary report (3) certain assumptions were made concerning boundary-solution partition functions and the results were used to estimate ion mobilities. These turned out to be appropriate for solids, being in the range 10^{-9} cm²/sec·volt. The basic assumptions, however, are arbitrary and lead to difficulties, and have therefore been abandoned. The best estimate of ion mobilities is still that given by Cole (2) (also appropriate for solids).

It might be noted that if the density, b_i, of unoccupied sites is taken into account, equation 22 transforms to:

$$I_i = -RTu_i^a\left[1 + \frac{c_i}{b_i}\right]\frac{dc_i}{dx} + \frac{Fu_i^b c_i V}{\delta}. \qquad (40)$$

This equation, describing forced diffusion with a concentration dependent diffusion coefficient (31), illustrates more clearly the modification of the classical dilute solution electrodiffusion theory.

Perhaps the most critical assumption in the present theory is that the major ion distributions are not significantly perturbed by current flow, an idea which has been essentially anticipated by others who have noted that the Hodgkin-Huxley axon has ion conductances dependent on membrane potential but not on membrane current. It is this assumption which is responsible for the appearance of a negative conductance, but there is presently no justification for it except its result, at least in terms of the approach considered here.

A necessary assumption in this approach is that the simple Nernst-Einstein relation (32, 33) is not obeyed by either Na^+ or K^+ ions. This relation between electric and diffusion mobilities should be applicable to any system of charged particles distributed according to Boltzmann statistics, provided that electric conductivity and diffusion involve the same migration mechanism. If the system is non-Boltzmann or more than one migration mechanism is present significant deviation from the classical Nernst-Einstein relation can be expected (25, 34). Such deviations have been observed experimentally in several different kinds of systems, including ion-exchange membranes (35). Theoretical explanations of these deviations are somewhat satisfactory for crystalline systems (25), but as yet incomplete for most other cases (36). It has also been proposed that even in a Boltzmann system with a single migration mechanism, if ions are moving in a polarizable medium, considerable deviation from the Nernst-Einstein relation may occur (37). In terms of the parameter α which has been used here, the range of experimental and theoretical deviation can be expressed as $0.5 \leqq \alpha \leqq 3$. A simple physical explanation for the fact that $\alpha = 3$ seems necessary for the theory is that the ions in the membrane move according to a single-file interstitialcy mechanism (25). Other possibilities, however, should not be excluded. It is interesting that Hodgkin and Keynes (38) suggested a "single-file" mechanism to account for isotope flux measurements in the squid axon.

Concerning the interaction energy of ions with membrane sites, a $Na^+:K^+$ interaction energy ratio of about 1.4 has been found necessary. The interaction energy should presumably be inversely related to the ionic radii, and it is interesting that the $K^+:Na^+$ crystal radii ratio is 1.36. Although the agreement may be fortuitous, the value which has been used in the theory is apparently reasonable.

Perhaps the most general conclusion of this report is that the mere appearance of a negative conductance (and the associated possibilities for excitation phenomena) in a biological membrane need not depend upon interaction of divalent ions, conformational changes of macromolecules, micelle transformations of lipid systems enzyme reactions, ion-specific carriers, redistributions of pores, chemical gates, etc. Any of these may be involved, but there is at present apparently no theoretical necessity to include them as effective causes.

In summary, the theory which has been outlined, and which is applicable only to the steady state and a hypothetical axon without inactivation, may provide a means for describing the current-voltage behavior of the squid axon in terms of molecular processes. The assumptions upon which the theory is based are not unreasonable, and the physical parameters involved may be useful in interpreting experimental results.

The author wishes to thank K. S. Cole, T. Teorell, R. Schlogl, D. Goldman, and J. Sandblom for their helpful comments.

This work was supported by grants from the Shell Companies Foundation and the William C. and Clara A. Abbott Memorial Fund of the University of Chicago.

Received for publication 15 August 1968.

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