KINETIC THEORY MODEL FOR ION MOVEMENT THROUGH BIOLOGICAL MEMBRANES

I. FIELD-DEPENDENT CONDUCTANCES IN THE PRESENCE OF SOLUTION SYMMETRY

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ABSTRACT A model for ion movement through specialized sites in the plasma membrane is presented and analyzed using techniques from nonequilibrium kinetic theory. It is assumed that ions traversing these specialized regions interact with membrane molecules through central conservative forces. The membrane molecules are approximated as massive spherical scattering centers so that ionic fractional energy losses per collision are much less than one. Equations for steady-state membrane ionic currents and conductances as functions of externally applied electric field strength are derived and numerically analyzed, under the restriction of identical solutions on each size of the membrane and constant electric fields within the membrane. The analysis is carried through for a number of idealized ion-membrane molecule central force interactions. For any interaction leading to a velocity-dependent ion-membrane molecule collision frequency, the membrane chord conductance is a function of the externally applied electric field. Interactions leading to a collision frequency that is an increasing (decreasing) function of ionic velocity are characterized by chord conductances that are decreasing (increasing) functions of field strength. For ion-neutral molecule interactions, the conductance is such a rapidly decreasing function of field strength that the slope conductance becomes negative for all field strengths above a certain value.

INTRODUCTION

Attempts to develop a satisfactory theory of ion transport through cell membranes have been largely based on the Nernst-Planck equations (Nernst, 1898, 1899; Planck, 1890 *a*, *b*) describing ion transport in electrolyte solutions. Many aspects of ion penetration through membranes are satisfactorily described by the constant-field solutions of the Nernst-Planck equations (Goldman, 1943; Hodgkin and Katz, 1949). Cole (1968) has extensively studied and reviewed this electrodiffusion approach and concludes that it cannot account for a number of phenomena characteristic of early and late ionic current pathways in a squid axon membrane.

It is not known whether such failures are due to fundamental defects in the assumpions underlying the equations, or to approximations in their development which are inappropriate for membrane ion transport, or both. Derivations of the Nernst-Planck equations are based on the following explicit assumptions: (a) the average directed velocity of an ion in an electric field is directly proportional to the field strength (mobility independent of field strength); (*b*) Fick's first law holds; (*c*) the diffusion coefficient and mobility are related through the Einstein relation. These assumptions imply that the only possible source of nonlinear behavior in a homogeneous, one-phase membrane model system is concentration asymmetry.

In this paper, I specifically deal with the assumption of constant ionic mobility in the membrane. A model, definable on a molecular basis, is analyzed to determine the relation between ionic current flow and membrane potential in the absence of concentration gradients. The motivation to study this particular problem is twofold. First, the electrical properties of a number of laboratory-produced and naturally occurring membrane systems with concentration symmetry have been determined and reported in the literature. In many cases, the relation between ionic current density and membrane potential is highly nonlinear. Secondly, in terms of furthering our concepts about important forces within membranes, it is of interest to examine the consequences of specific molecular mechanisms for membrane electrical properties.

The generalized relation between current density and membrane potential derived here takes account of effects introduced by high electric field strengths when the energy of an ion due to the electric field is of the order of, or greater than, its thermal energy. Under such conditions ion currents are nonlinear functions of the electric field strength. This behavior is expressed by giving mobility coefficients as implicit functions of electric field strength and ion-membrane molecule interaction parameters.

The second paper of this series (Mackey, 1971) considers the ion-selective properties of the model as functions of ion-membrane molecule interaction parameters and electric field strength for steady-state situations in the absence of concentration gradients.

THE MODEL

Assumptions

There is much experimental evidence that ion penetration through excitable cell plasma membranes occurs only at rare specific sites (Hille, 1970). The following assumptions are made about the properties of these sites only, not those of the ion impermeable regions. Some of these assumptions are justifiable from experimental data or order-of-magnitude calculations. Others, however, are not easily justified (or rejected), but are necessary to make the calculations feasible. These assumptions result in calculated ionic conductances that agree well with experimental data.

It is assumed that the passage of an ion through an ion permeable region is impeded by interactions (collisions) between the ion and membrane molecules, the latter having no directed motion but possessing random thermal motion. These interactions are assumed to be the only ones of importance, implying that ionic densities in the membrane are low and that the independence principle is valid. The ion-membrane molecule interactions are assumed to be determined by the following characteristics:

(*a*) Spherical membrane molecules. The membrane molecules may be represented by spherical particles of finite mass.

(*b*) Central interactions. The force between an ion and a membrane molecule during a collision is central, conservative, and either attractive or repulsive. This is related to characteristic *a*, but carries an added restriction: there are only binary collisions between ions and membrane molecules, i.e., the scatterer centers (collision sites) are widely spaced in comparison to ion diameter.

(*c*) Small collisional energy loss. During a collision, the fractional energy loss (ξ) by an ion is much less than one. This is equivalent to the assumption that the mass of a scatterer, compared to the mass of an ion, is large but not infinite (i.e., $\xi \neq 0$). The assumption that $\xi \ll 1$ greatly simplifies an expansion used in the analysis. Relaxation of this assumption requires the inclusion of more expansion terms, and increases the mathematical complexity of the analysis. The restriction of collisions to situations where $\xi \ll 1$ specifically excludes considerations of the potentially important mechanisms of ion fixation or binding, or excitation of rotational and/or vibrational modes in membrane-bound macromolecules. This omission is not one based on desire, but necessity. The analysis techniques employed in this paper are inappropriate for the treatment of such highly inelastic collision processes. To quantitatively deal with transport in the face of violently inealstic collisions, a quantum mechanical formulation must be employed.

(*d*) Negligible role of water. This assumption must be made to avoid the complex difficulties of liquid transport theory. Several arguments help justify this assumption. Models of ion penetration regions (channels) may be constructed where water would seem to play a negligible role; e.g., the wall of a channel having a diameter on the order of a hydrated ion might bind water. However, single water molecules would be moving through the channel, so that collisions between hydrated ions and single water molecules in the channel would result in little energy loss by the ion because of its much greater mass. Thus, in this situation, water would have little effect on ionic current. Alternately the effects of water, if present, could be considered to be lumped with the scattering molecules. A final justification is that the kinetic equations derived here are qualitatively identical with those derived by Rice and Gray (1965; equations 5.3.69–5.3.71) for ion transport in liquids.

(e) External forces. All external forces acting on the ion are independent of ionic velocity (e.g., are not due to magnetic fields) and are much smaller than the ion-membrane molecule forces acting during a collision.

(f) The ionic number density in the membrane is small—so small in fact that $\lambda_D \gg \delta$ (where λ_D is the Debye length in the membrane, and δ is the thickness of the membrane). Therefore, the electric field strength, E, is a constant throughout the membrane.

Relation between Ionic Current Density and Electric Field Strength

To avoid the excessive use of formulae in the text, I have confined the details of the model analysis to an Appendix. Readers interested in the details of the analysis should refer to that section.

In the Appendix it is demonstrated that, with the above assumptions for the model, the steady-state dimensionless ionic current density ($\bar{I}$) established in response to a dimensionless applied electric field ($\bar{a}$) is given by

$$\bar{I} = \left(\frac{3-p}{3}\right)\bar{a}\left[\int_0^\infty du u^2 \exp(-W)\right]^{-1}\int_0^\infty du u^{2-p}\exp(-W). \qquad (1)$$

If the force between ion- and membrane-scattering molecule (separation r) during a collision goes as $(1/r^\alpha)$, then $p = (\alpha - 5)/(\alpha - 1)$. W is given by equation A 6.

The physical significance of equation 1 is the following. Consider an ion (charge q, mass m) moving under the influence of an electric field (E) with velocity between v and $v + dv$. As it moves, it collides with scattering centers at a frequency ν (collisions per second). Let the number of ions with velocities between v and $v + dv$ be $f(v)$. In a steady-state situation the forces due to the field $[qEf(v)\,dv/m]$ and due to collisions ($\nu\,dv$) will exactly balance. Thus we have $(qE/m)f(v)\,dv = \nu\,dv$. The average velocity of ions will be given by $\bar{v} = (qE/m)\int_0^\infty f(v)\,dv/\nu(v)$; and the current, I, carried by them will be $I = nq\bar{v}$ where n is the ionic number density. In the Appendix it is shown that $\nu(v) \sim v^p$ and $[f(v) \sim v^2 \exp(-W)] \Big/ \left[\int_0^\infty v^2 \exp(-W)\,dv\right]$. Substitution of these in the above expression for the average velocity, and using the dimensionless variables of the Appendix, yields equation 1.

If a dimensionless chord conductance, analogous to the conductances $\bar{g}_{Na}(V)$ and $\bar{g}_K(V)$ determined by a voltage clamp procedure (Hodgkin and Huxley, 1952), is defined by $\bar{I} = \bar{a}G_c$, from equation 1

$$G_c = \left(\frac{3-p}{3}\right)\left[\int_0^\infty du u^2 \exp(-W)\right]^{-1}\int_0^\infty du u^{2-p}\exp(-W). \qquad (2)$$

Thus it is seen that G_c is dependent on the dimensionless acceleration (electric field strength). G_c has some interesting general properties. From equation A 6 for W, G_c is an even function of $\bar{a}$. Further, for $p = 0$, corresponding to a velocity-independent collision frequency $G_c = 1$ for all $\bar{a}$; for $p > 0$ (<0), G_c is a decreasing (increasing) function of $\bar{a}$.

These characteristics of the G_c variation with $\bar{a}$ are not unreasonable. The model contains no inherent asymmetry, and therefore no asymmetry in G_c with respect to the direction of $\bar{a}$ is expected. On a simple basis G_c should be inversely proportional to the collision frequency ν—the more collisions an ion makes in going through a region the higher the resistance of that region (the lower its conductance). The effect of an external electric field is to increase the velocity of an ion. For $p > 0$ (ν an increasing function of v) an increase in the field increases the collision frequency and thus decreases the conductance. Conversely, for $p < 0$ (ν a decreasing function of v) an increase in the field decreases the collision frequency. For a velocity-independent collision frequency ($p = 0$) the electric field strength has no effect on ν, and thus none on the conductance.

RESULTS AND DISCUSSION

The complexity of the equations for $\bar{I}(\bar{a})$ and $G_c(\bar{a})$ precludes a complete analytical study of the characteristics of ion movement despite the simplicity of the model; a numerical study was therefore necessary. All computations were done on Raytheon PB-440 digital computer (Raytheon Computer Operation, Santa Ana, Calif.) using a system (Digital Analog Simulator) which effectively transforms the computer into an analog computer with a large number of components. All integrations were carried out with step increments (Δu) of 10^{-4} and the integration was terminated when the quantity being computed at a given electric field strength did not change more than one part in 10^5 between two successive increments. The computed results and their discussion are presented in two sections, the first for $p < 0$ and the second for $p > 0$. The $p = 0$ case, with ohmic conductance characteristics, provides a natural dividing line. The dimensionless quantities $\tilde{I} = \bar{I}/\sqrt{\xi}$ and $E = \bar{a}/\sqrt{\xi}$ are used so $\tilde{I} = EG_c(E)$. Since it is helpful to have some definite numbers (current densities, etc.) to relate to the dimensionless quantities, the first part of the Results section is devoted to obtaining estimates of these values for "reasonable" assumptions about the membrane.

Estimation of Some Membrane Related Quantities

The following hypothetical membrane is postulated to permit comparison of the calculated $\tilde{I}$ vs. E and G_c vs. E relationships with experimental ones.

The model membrane is a planar sheet of nonconducting lipid and protein 100 A in thickness, with ion-permeable sites whose molecular characteristics are one of those employed herein for calculation, e.g. fixed charges, or polarizable particles. Assume that the scatterers in these conducting regions are components of the surrounding lipid-protein matrix, that these regions may be approximated by cylinders 5 A in diameter extending through the membrane, and that there are 10 of these regions per square micron of membrane surface. The estimate of 100 A for the membrane thickness is consistent with many measured thicknesses, and the density of pores is based on work with tetrodotoxin (Moore, Narashi, and Shaw, 1967).

Another quantity that must be estimated is the number density of ions within the membrane. If the hypothetical membrane has a maximum current density of 1 ma/cm^2 carried by monovalent cations, then this corresponds to 6.25×10^6 ions/sec through each pore. For a membrane bathed in 0.1 M electrolyte, elementary kinetic theory indicates that the cross-sectional area of one pore would suffer 6.4×10^9 collisions/sec. Thus only about one ion in 10^3 goes through the pore, and it will therefore be assumed that the number density of ions interacting with the scatterers is 10^{-3} that of the external solution.

Another necessary quantity is the number density of scattering centers. This is taken as 6×10^{20}/cm^3, or about one per pore. Molecular weights of 44 and 1000 were taken as estimates of the effective mass of the scattering center. The value of 44 is the molecular weight of a carboxyl group. Using the parameters of the sodium ion the energy loss factor, ξ_{Na}, has the value of about 0.5 for this effective scattering mass which is large for the approximations made earlier. Thus a second effective molecular weight of 1000 (making $\xi_{Na} = 0.044$) was also used. This effective mass is not unreasonable if the molecule to which the scattering center belongs is quite rigid.

The various interactions require estimates of the charge of the scattering center, its polarizability, etc. For ion-fixed charge collisions, it was assumed that the scatterer carries a net charge of -1, while for ion-fixed permanent dipole interactions, a dipole moment of 5 D was assumed. The assumed properties for ion-induced dipole interactions, London dispersion force interactions, and ion-neutral scatterer interactions between the sodium ion and scatterer (carboxyl oxygen) are given in Table I.

In Table II are presented, for various interactions, the membrane potential, φ_m, (assuming a constant electric field) corresponding to $E_{Na} = 1$; the current density per square centimeter of membrane, I_m, corresponding to $I_{Na} = 1$, and the conductance per square centimeter of membrane, G_m. The first entry in each bin of the table was calculated for an effective scatterer molecular weight of 44, the second for a molecular weight of 1000. The values given may be changed significantly by different assumptions about the several factors. An increase in the scatterer number density will increase the φ_m values by a similar amount. An increase in the ionic number density from its value of 10^{-4} M increases both the current and conductance

TABLE I

MOLECULAR PROPERTIES ASSUMED FOR VARIOUS COMPUTATIONS

Particle	Molecular weight	Polarizability $\times 10^{24}$	Second ionization potential	Crystal radius
		cm^3	*ev*	*A*
Na^+	22.997	0.21*	47.07‡	0.98§
Scatterer (carboxyl oxygen)		0.84§	2.12‖	1.45§

* Moelwyn-Hughes, 1949.

‡ Handbook of Chemistry and Physics, 1957.

§ Ketelaar, 1953.

‖ Latimer, 1952.

TABLE II

MODEL SPECIFIC CONDUCTANCES, CURRENTS, AND MEMBRANE POTENTIALS FOR DIFFERENT INTERMOLECULAR INTERACTIONS AND SPARSELY DISTRIBUTED PORES

For each interaction the membrane potential (φ_m), current density per square centimeter of membrane (I_m), and conductance per square centimeter of membrane (G_m) corresponding to unit values of the dimensionless variables E, I, and G_c are given. For example, with ion-neutral particle scattering and a scatterer mol. wt. of 1000, an $E = 1$ corresponds to a $\varphi_m = 11$ mv, and $I = 1$ corresponds to a $I_m = 2.2$ ma/cm^2, and a $G_c = 1$ corresponds to a $G_m = 0.2$ mmho/cm^2.

Interaction type	p	$\varphi_m(E_{Na} = 1)$	$I_m(I_{Na} = 1)$	$G_m(G_c = 1)$
		mv	*ma/cm*^{2}	*mmho/cm*^{2}
Ion-fixed charge	-3	1.5×10^7 (mol. wt. = 44)	8.6	5.7×10^{-7}
		1.7×10^6 (mol. wt. = 1000)	2.2	1.3×10^{-6}
Ion-permanent dipole	-1	6.8×10^4	As above	1.3×10^{-4}
		1.2×10^4	As above	1.8×10^{-4}
Ion-induced dipole	0	5.5×10^2	As above	1.6×10^{-2}
		1.2×10^2	As above	1.8×10^{-2}
London dispersion force	1/3	99	As above	8.7×10^{-2}
		23	As above	9.6×10^{-2}
Hard sphere–hard sphere	1	44	As above	0.196
		11	As above	0.20

values by like amounts. An increase in collision frequency increases φ_m and decreases the conductances. For example, with ion-fixed charge interactions an increase in the fixed charge valence from -1 to -2 increases the collision frequency and φ_m by a factor of 4 and decreases the conductances by a like amount.

From Table II it is clear that there are enormous differences in the results for various molecular interactions, e.g., in G_m. As a means of comparison, Table III presents the values of G_c for various interactions with $E = 0$. Also shown are the corresponding chord conductances for a square centimeter of membrane, and a mean collision frequency, $\nu_p = \beta_p \nu_{T\,Na}^{\,p}$, for each type of interaction. This reveals the sources of variation in the membrane-related values. For those molecular interactions where the collision frequency decreases with increasing velocity (e.g., coulombic and ion-fixed permanent dipole interactions) the mean collision frequency is several orders of magnitude larger than the collision frequencies for the other interactions where $p > 0$. This is due to the long-range nature of coulombic and dipole forces.

Of course, these estimates depend dramatically on the area of the membrane assumed available for ion penetration. For example, taking the cases of fixed charge and fixed permanent dipole scatterers, assume that there are 10 scatterers per square micron, and that 0.1 of the membrane surface area is available for ion penetration. This leads to a scatterer number density of 10^{16}/cm^3, and the values for the membrane potential in Table II would be correspondingly multiplied by 1.67×10^{-5}. Also taking into account the altered current densities,

TABLE III

THE CONNECTION BETWEEN THE VARIATION IN SPECIFIC MEMBRANE CONDUCTANCES AT $\varphi_m = 0$, AND VARIATIONS IN MEAN IONIC COLLISION FREQUENCY FOR DIFFERENT INTERACTIONS

Interaction type	p	$G_c(E = 0)$	$G_m(E = 0)$	ν_p
			mmho/cm²	*(numbers/sec)*
Ion-fixed charge	-3	2.44	1.4×10^{-6}	9.94×10^{13}
			(mol. wt. = 44)	(mol. wt. = 44 and 1000)
			3.2×10^{-6}	
			(mol. wt. = 1000)	
Ion-permanent dipole	-1	1.23	1.6×10^{-4}	10^{13}
			2.2×10^{-4}	6.83×10^{12}
Ion-induced dipole	0	1.0	1.6×10^{-2}	8.1×10^{10}
			1.8×10^{-2}	6.67×10^{10}
London dispersion force	1/3	0.96	8.4×10^{-2}	6.74×10^{10}
			9.2×10^{-2}	5.66×10^{10}
Hard sphere–hard sphere	1	0.92	1.81×10^{-1}	6.52×10^{9}
			1.85×10^{-1}	6.52×10^{9}

TABLE IV

MODEL SPECIFIC MEMBRANE POTENTIALS, CURRENTS, AND CONDUCTANCES FOR A MEMBRANE WITH MANY PORES AND $p < 0$

Interaction type	p	$\varphi_m(E_{Na} = 1)$	$I_m(I_{Na} = 1)$	$G_m(G_c = 1)$
		mv	*ma/cm²*	*mmho/cm²*
Ion-fixed charge	-3	250	0.044	0.176
		(mol. wt. = 44)		
		28.4	0.0111	0.391
		(mol. wt. = 1000)		
Ion-permanent dipole	-1	1.13	0.044	38.9
		(mol. wt. = 44)		
		0.2	0.0111	55.5
		(mol. wt. = 1000)		

6.25×10^{15} ions would go through this 0.1 cm² every second. For an external ionic concentration of 0.1 M a bombardment rate of 3.25×10^{23} collisions/sec on this area of membrane is expected and the number density of ions interacting with scatterers is approximately 10^{-8} that of the external solution. In Table IV recomputed values of φ_m, I_m, and G_m based on the preceding are presented. It is obvious that for these two types of interactions much more "biological" values of membrane potentials and conductances result.

Result and Discussion for Interactions such that $p < 0$

Computations of the conductance and current-electric field curves were carried out for a range of p values between -0.5 and -3.0. The computed G_c vs. E curves are shown in Fig. 1 and the $\tilde{I}$ vs. E curves in Fig. 2. Two values correspond to actual ion scattering interactions, $p = -3$ and $p = -1$. In terms of ideal interactions these would correspond to ion-fixed charge ($\alpha = 2$) and ion-permanent dipole ($\alpha = 3$) interactions respectively.

As expected from the general considerations of the previous section, and as illustrated in Fig. 1, G_c is an increasing function of E for these ion-scattering interactions in which the collision frequency decreases with increasing ionic velocity. The nonlinear field dependent behavior of G_c for these types of interactions becomes much less pronounced at high field strengths, the conductance varies slowly with E, and the I vs. E curves become nearly linear. For $p = -3$ the increase in conductance with an increase in field strength is rapid, leveling off at high fields at a value (125) about one and one-half orders of magnitude greater than its value at zero field strength (2.44).

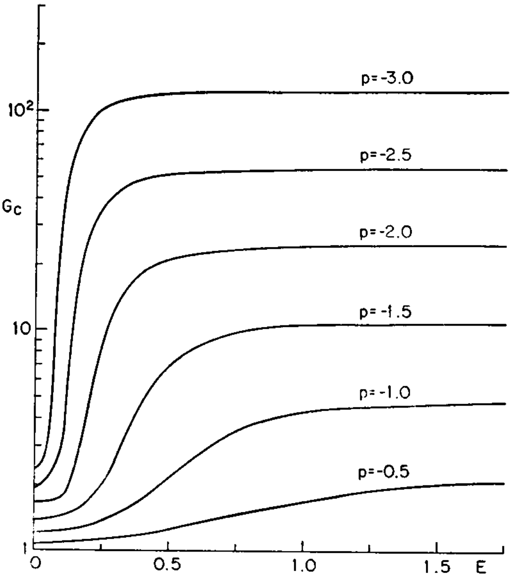

FIGURE 1

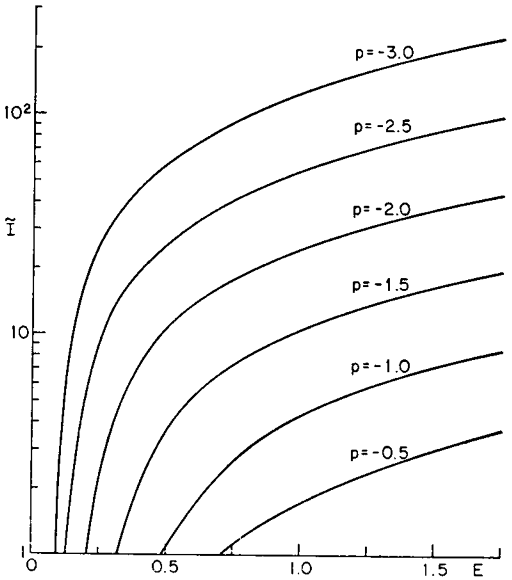

FIGURE 2

FIGURE 1 Dimensionless conductance (G_c) as a function of dimensionless field strength (E) for a number of ion-scatterer interactions characterized by $p < 0$. The curves $p = -1$ and $p = -3$ correspond to ion-fixed dipole and ion-fixed charge interactions, respectively. Note that G_c is an increasing function of E in all cases.

FIGURE 2 Dimensionless current ($\tilde{I}$) as a function of dimensionless field strength (E) for six ion-scatterer interactions with $p < 0$. The computed curves are presented semilogarithmically for clarity.

There are similarities in the observed electrical properties of alamethicin-treated lipid bilayer membranes (Mueller and Rudin, 1968) and the theoretical properties displayed for the membrane model with $p < 0$. The antibiotic alamethicin, a cyclic polypeptide (Meyer and Reusser, 1967), is capable of causing large increases in the conductance of laboratory-produced membranes composed of a variety of substances. The antibiotic, which contains an ionizable carboxyl group at physiological pH, is effective when present in the aqueous solution surrounding the membrane, or in the membrane-forming solution. When placed between identical electrolyte solutions, these antibiotic-modified membranes exhibit a conductance vs. potential curve that is low at 0 mv and rises some four orders of magnitude above this value at 50 mv. The curves are symmetric about zero membrane potential. Thus, in a situation where ion-fixed charge scattering could be quite important there are qualitative similarities between experimentally determined conductances and those predicted for $p < 0$. However, there are also differences. The experimentally observed increase in the chord conductance with increasing membrane potential is at least four orders of magnitude. Theoretically for the fixed charge model ($p = -3$) a rapid continuous increase of slightly less than two orders of magnitude in the conductance is expected. The figures quoted by Mueller and Rudin could be obtained from a model for some $p > -3$, which would require very long-range scattering forces varying more slowly than $1/r^2$. No mention is made by the authors about the existence, if any, of a leveling off of the conductance-membrane potential curve at sufficiently high potentials. If the observed electrical properties are actually due to long-range ion-scatterer interactions such as those being considered here, such behavior should occur.

Results and Discussion for Interactions such that $p > 0$.

As discussed above when $p = 0$ (corresponding, ideally, to ion-induced dipole interactions), $G_c = 1$, and the dimensionless $\tilde{I}$ vs. E curve is a straight line. This is intuitively reasonable. When the collision frequency is independent of ionic velocity, and thus also of electric field strength, the conductance is constant.

Two cases were examined numerically for $p > 0$, $p = \frac{1}{3}$, and $p = 1$. A p of $\frac{1}{3}$ corresponds ideally to a London dispersion force ($\alpha = 7$) interaction. A $p = 1$ results if a classical hard sphere–hard sphere collision process is assumed, e.g. collision of an ion with a nonpolarizable, noncharged scatterer.

In Fig. 3 the dimensionless conductance G_c for $p = \frac{1}{3}$ and $p = 1$ is plotted vs. E. In both cases, G_c is a decreasing function of E. For $p = 1$ the conductance is a much more rapidly decreasing function of E than it is for $p = \frac{1}{3}$. The consequence of this difference for the dimensionless current vs. electric field curves is most interesting, and illustrated in Fig. 4. For $p = \frac{1}{3}$ the decrease in G_c as E increases produces a slight concave downward shape in the $\tilde{I}$ vs. E curve. However, for $p = 1$, G_c decreases so rapidly that the corresponding current vs. electric field relation displays a

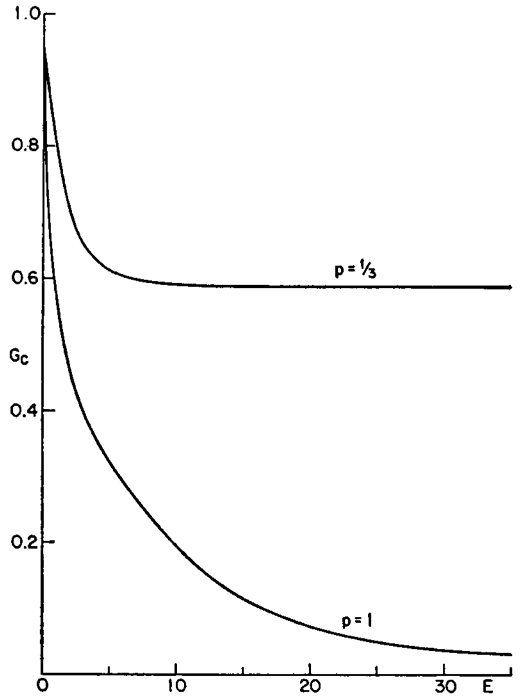

FIGURE 3

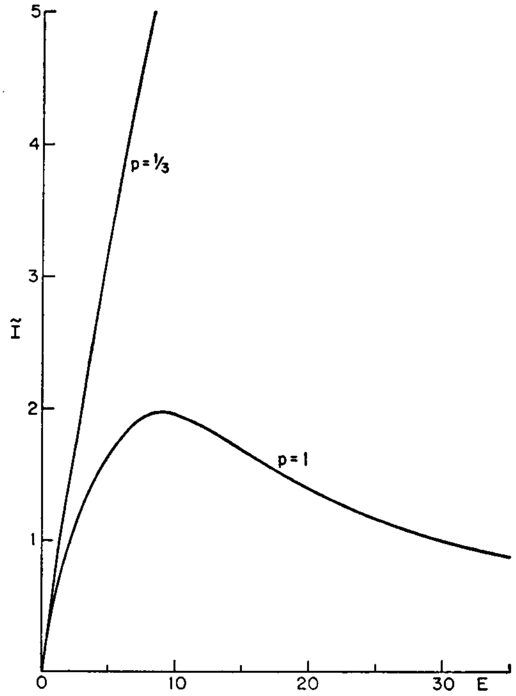

FIGURE 4

FIGURE 3 Dimensionless conductance (G_c) as a function of dimensionless electric field strength (E) for classical ion-induced dipole and ion-neutral scattering interactions, characterized by $p = 1/3$ and $p = 1$, respectively.

FIGURE 4 Dimensionless current ($\tilde{I}$) vs. dimensionless field strength (E) for $p = 1/3$ and $p = 1$. Note that for ion-neutral interactions G_c decreases faster than E^{-1}, yielding a negative slope conductance region in the $\tilde{I}$ vs. E curve for all $E > 9$.

negative slope conductance region. In fact, the current decreases continuously and approaches zero as $E \rightarrow \infty$.

Moore (1959) discovered that if the squid giant axon is placed in isosmotic potassium chloride, the steady-state current voltage relationship for the membrane exhibits a negative slope conductance region when the membrane is hyperpolarized. Under such experimental conditions, the sodium system is largely inactivated, and the observed steady-state behavior is attributed to the potassium channel. Similar phenomenon have been noted in the frog node (Frankenhaeuser, 1962) and lobster axon (Julian, Moore, and Goldman, 1962). The Hodgkin-Huxley equations duplicate the results fairly well as found by Moore and also by Tasaki (1959) (see George and Johnson, 1961). Ehrenstein and Gilbert (1966) have also found a steady-state negative slope conductance region in the depolarizing direction under these same conditions.

Lecar, Ehrenstein, Binstock, and Taylor (1967) also working with squid axons in high potassium solutions were able to separate their current voltage curves into a linear component and a nonlinear time-varying component. The linear component, identified as the leakage current, is increased by the removal of the external divalent cations. The nonlinear conductance component, which gives rise to the negative slope conductance regions in the steady state, has the kinetics of the potassium process and is decreased by the removal of divalent cations.

These experiments led to the conclusion that the steady-state negative slope conductance regions seen in high potassium are characteristic of the potassium system. Further, if the separation of leakage and potassium currents is correct, the steady-state potassium current vs. membrane potential curve has the remarkable property of being approximately "N" shaped; i.e., sufficient elevation of the membrane potential in either a depolarizing or hyperpolarizing direction will cause the current to approach zero.

The nonlinear electrical component of the squid axon membrane in high potassium is grossly similar to the current-field curve of Fig. 4 for $p = 1$. One of the major differences between the theoretically predicted current field curves for $p = 1$ and similarly observed potassium current behavior in squid that is the theoretical rate of decline of the current in the negative slope conductance region is appreciably smaller than experimentally observed. This is a reflection of the decrease in dG_c/dE as E increases, illustrated in Fig. 3. Thus, based on comparisons with theoretical predictions of current-field behavior when ions interact primarily with neutral scattering centers it appears that this, or a similar interaction yielding a p sufficinetly greater than zero, might be a primary interaction for ions traversing the potassium channel in the squid membrane.

APPENDIX

If $\mathbf{x}$ and $\mathbf{v}$ (a boldface quantity denotes a vector), respectively, denote vector position and velocity of a particle of the ith ionic species, then the Distribution Function $f(\mathbf{x}, \mathbf{v}, t)$ for this species is defined as the number of ions of the ith species which, at a time t, are in a spatial volume element ($d^3\mathbf{x}$, cm^3) about $\mathbf{x}$(cm) and a velocity volume element ($d^3\mathbf{v}$, cm^3/sec^3) about $\mathbf{v}$(cm/sec). In this section the relation of macroscopic observables (e.g. ionic current) to f is discussed. An integrodifferential equation in f is presented, without derivation, but the terms of the equation are related to underlying physical processes. Finally, solution of this equation by an expansion of f is considered. This expansion procedure results in two coupled partial differential equations that must be solved.

The distribution function is useful because of its direct relation to measurable macroscopic variables. For example, the number density [$n(\mathbf{x}, t)$, number/cm^3] of particles at a particular $(\mathbf{x}, t)$ may be obtained by summing (integrating) the number of particles in each velocity range:

$$n(\mathbf{x}, t) = \int d^3\mathbf{v} f(\mathbf{x}, \mathbf{v}, t).$$

In a similar manner, the number flux [$\mathbf{N}(\mathbf{x}, t)$, number/cm^2-sec] of particles crossing a unit surface area is

$$\mathbf{N}(\mathbf{x}, t) = \int d^3\mathbf{v}\mathbf{v} f(\mathbf{x}, \mathbf{v}, t).$$

If the particles have a charge $q = z_i e$, then the current density, **I**(amp/cm^2), carried by this flux is $\mathbf{I} = q\mathbf{N}(\mathbf{x}, t)$. In general the distriubtion function is a function of various external driving forces, e.g. gradients of concentration, temperature, or electrical potential.

The distribution function must be expressed as an explicit function of velocity so the above integrations may be carried out. With all of the assumptions listed in the main body of the text, except for assumptions *c* and *f*, the following equation of change for f, commonly known as the Boltzmann transport equation, results (Green, 1952):

$$(\partial f/\partial t) + \mathbf{v}\cdot\nabla_{\mathbf{x}} f + (\mathbf{F}/m)\cdot\nabla_{\mathbf{v}} f = \iint d^3\mathbf{v}_s \, d\Omega(f'f_s' - ff_s)g_{is}I_{is} . \quad \text{(A 1)}$$

In equation A 1 m is the mass (g/particle) of a particle of the ith ionic species, $\mathbf{F}$ is the external force (dynes/particle) acting on the ith species, f_s is the distribution function for the scatterer molecules, and $g_{is} = |\mathbf{v}_i - \mathbf{v}_s|$ is the speed (cm/sec) of an ion relative to a scattering particle. I_{is} is a differential scattering cross-section (cm^2), $d\Omega = 2\pi \sin\chi \, d\chi$ is a solid angle (steradians), and χ is the angle (radians) through which the ion is deflected during a collision. (See Goldstein, 1950, for a discussion of the mechanics of binary collisions.) Primed distribution functions refer to a postcollisional state while unprimed ones are precollisional.

Equation A 1 is a conservation equation for $f(\mathbf{x}, \mathbf{v}, t)$ and some insight into the origin of the various terms is desirable. Typical conservation equations relate the time rate of change of a quantity to the divergence of its flux. The present case requires a relation between the time rate of change of $f(\mathbf{x}, \mathbf{v}, t)$ and the divergence of its flux in $\mathbf{x}$ space, $\nabla_{\mathbf{x}}\cdot[f(d\mathbf{x}/dt)]$, the divergence of its flux in $\mathbf{v}$ space, $\nabla_{\mathbf{v}}\cdot[f(d\mathbf{v}/dt)]$, and the rate of change of $f(\mathbf{x}, \mathbf{v}, t)$ due to collisions. The integral expression on the right-hand side of equation 1 gives the rate of change of $f(\mathbf{x}, \mathbf{v}, t)$ due to collisions, $\mathbf{v}\cdot\nabla_{\mathbf{x}} f$ is due to flow in position space, and $\mathbf{a}\cdot\nabla_{\mathbf{v}} f$ arises because of flow in velocity space in the presence of a velocity-independent acceleration $\mathbf{a} = \mathbf{F}/m$.

Solutions to equation A 1 are usually based on an expansion of $f(\mathbf{x}, \mathbf{v}, t)$ in terms of some suitably small parameter. The form of the expansion used here is suggested by expressing the ion velocity $\mathbf{v}$ in spherical coordinates (v, θ, ϕ), where θ and ϕ are now the variables during a collision, and expressing the distribution function as $f(\mathbf{x}, \mathbf{v}, t) = f(\mathbf{x}; v, \theta, \phi; t)$. This may be expanded in spherical harmonics. Such an expansion is equivalent (Johnston, 1960, 1966) to a tensor expansion

$$f = f_0(\mathbf{x}, \mathbf{v}, t) + (\mathbf{v}/v)\cdot\mathbf{f}_1 + (\mathbf{v}\mathbf{v}/v^2)\underset{\sim}{\mathbf{f}}_2 + \cdots . \quad \text{(A 2)}$$

Morrone (1968) has shown that terms f_j in the expansion of equation A 2 are proportional to $(\xi)^{j/2}$, where ξ is the ion fractional energy loss during an ion-scatterer collision. Thus with assumption *c* that $\xi \ll 1$, terms f_j for $j > 1$ may be neglected in equation A 2. Therefore, the expansion is written as $f = f_0(\mathbf{x}, \mathbf{v}, t) + (\mathbf{v}/v)\cdot\mathbf{f}_1(\mathbf{x}, \mathbf{v}, t)$.

In terms of f_0 and f_1, integral expressions for the number density and current density become

$$n(\mathbf{x}, t) = 4\pi \int_0^\infty dv v^2 f_0 \quad \text{(A 3)}$$

and

$$\mathbf{I}(\mathbf{x}, t) = (4\pi q/3) \int_0^\infty dv v^3 \mathbf{f}_1 \quad \text{(A 4)}$$

This communication is limited to an examination of the steady-state electrical properties of a membrane bounded by symmetrical electrolyte solutions. Thus from the continuity equation and the expressions for $n(\mathbf{x}, t)$ and $\mathbf{I}(\mathbf{x}, t)$ we conclude that $(\partial f_0/\partial t) = 0$, $\nabla_{\mathbf{x}} \cdot f_1 = 0$, and $f = f(v)$.

With the above remarks in mind, and assuming the acceleration a of the ions due to external forces is in the z direction (perpendicular to the membrane surface), substitution of the expansion $f(v) = f_0(v) + (\mathbf{v}/v) \cdot \mathbf{f}_1$ into the transport equation yields the equations (Ginsburg and Gurevich, 1960)

$$(a/3v^2)\, d(v^2 f_1)/dv = (\tfrac{1}{2}v^2)\, d\{\xi \nu v^3 [f_0 + (kT/m\mathrm{v})\, f d_0/dv]\}/dv \qquad (\mathrm{A}\ 5)$$

and

$$a(df_0/dv) = -\nu f_1. \qquad (\mathrm{A}\ 6)$$

The fractional energy loss $\xi = 2m/(m + m_s)$, where m_s is the scatterer mass, k and T are, respectively, Boltzmann's constant (erg/°K) and the absolute temperature (°K) of the system. The frequency of collisions of an ion of the ith species with the membrane scatterers, $\nu(v)$ (collisions/sec), is given by

$$\nu(v) = n_s v \int_0^{\pi} d\Omega (1 - \cos \chi) I_{is},$$

where n_s is the number density of scatterers. ν is, in general, a function of the ionic velocity v.

In order to obtain a solution to equations A 5 and A 6 for f_0 and f_1, and thus enable a calculation of current flow through the membrane model as a function of external driving forces, ν must be expressed as an explicit function of v. The form of this velocity dependence is determined by the nature of the intermolecular forces between ion and membrane molecule. For central conservative forces there is a simple power law relation between ν and v.

If, as assumption b requires, the force F_{is} between ion and membrane scatterer is given by $F_{is} = -K_{is}/r_{is}^{\alpha}$ where r_{is} is the separation between ion and scatterer, and α is a constant, then (Chapman and Cowling, 1958) the collision frequency is given by

$$\nu(v) = \beta_i v^p, \qquad (\mathrm{A}\ 7)$$

where $p = (\alpha - 5)/(\alpha - 1)$ and

$$\beta_i = 2\pi n_s A(\alpha) [2K_{is}/m_s \xi]^{2/(\alpha - 1)} \qquad (\mathrm{A}\ 8)$$

is a constant involving ionic and scatterer parameters. $A(\alpha)$ is a pure number depending only on α.

Equations A 5–A 7 are the complete set needed for a calculation of f_0 and f_1.

It is convenient to rewrite the equations for f_0 and f_1 in dimensionless form. Define a dimensionless variable u by $u = v/v_T$ where $v_T = (3\,kT/m)^{1/2}$ is the thermal velocity. Further, define a dimensionless acceleration $\bar{a}$ by $\bar{a} = a/\beta v_T^{p+1}$, where β is defined from $\nu = \beta v^p = \beta v_T{}^p u^p$.

With these new variables, equations A 5 and A 6 become

$$(\bar{a}/3u^2)\, d(u^2 f_1)/du = (\xi/2u^2)\, d\{u^{p+3}[f_0 + (df_0/du)/3u]\}/du \qquad (\mathrm{A}\ 9)$$

and

$$\bar{a}(df_0/du) = -u^p f_1, \qquad (\mathrm{A}\ 10)$$

which are easily combined to given an equation for f_0 alone:

$$[1 + (2\bar{a}^2/\xi u^{2p})](df_0/du) = -3uf_0. \qquad \text{(A 11)}$$

Equation A 11 has the solution

$$f_0 = A \exp(-W), \qquad \text{(A 12)}$$

where

$$W = 3 \int_0^u ds s^{2p+1}/[s^{2p} + (2\bar{a}^2/\xi)]. \qquad \text{(A 13)}$$

It should be noted that f_0 will be maxwellian (have the form $\exp[-mv^2/2kT]$) if $\bar{a} \sim 0$, or $p = 0$, corresponding to an ideal ion-scatterer force law with $\alpha = 5$.

Thus from equation A 6

$$f_1 = (\bar{a}A/u^p)(\partial W/\partial u) \exp(-W). \qquad \text{(A 14)}$$

In equation A 14, A is determined from equation A 3 so

$$A = n\left[4\pi v_T^3 \int_0^\infty du u^2 \exp(-W)\right]^{-1}. \qquad \text{(A 15)}$$

With the expressions for f_0 and f_1 given above, and using integration by parts, the current for $p < 3$ is

$$I = \left(\frac{3-p}{3}\right)\bar{a}qv_T n\left[\int_0^\infty du u^2 \exp(-W)\right]^{-1} \int_0^\infty du u^{2-p} \exp(-W). \qquad \text{(A 16)}$$

Defining a dimensionless current, $\bar{I}$, by

$$\bar{I} = I/qv_T n, \qquad \text{(A 17)}$$

equation A 16 may be written as

$$\bar{I} = \left(\frac{3-p}{3}\right)\bar{a}\left[\int_0^\infty du u^2 \exp(-W)\right]^{-1} \int_0^\infty du u^{2-p} \exp(-W). \qquad \text{(A 18)}$$

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