DETERMINANTS OF TIME-DEPENDENT MEMBRANE CONDUCTANCE

THE NONROLE OF CLASSICAL ION-MEMBRANE MOLECULE INTERACTIONS

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ABSTRACT We have examined the steady-state and time-dependent electrical properties of a model membrane system. The model assumes that the directed velocity and energy of ions moving through the membrane are determined by the applied electric field, ionic diffusion forces, and central elastic collisions between ions and membrane molecules. A simple analysis of the steady-state electrical properties of the model yields results identical with ones obtained previously using a more complex analysis procedure. The time-dependent conductance changes of the model in response to a step change in electric field strength when there is solution symmetry display three qualitative patterns dependent on the nature of the ion-membrane molecule interaction. One of the patterns of conductance change is quite similar to that observed in the sodium conductance system of a number of excitable tissues: an initial conductance rise to a maximum (activation) followed by a decay to a final steady-state value (inactivation). However, the correspondence between the time-dependent model behavior and known experimental behavior of excitable systems is only qualitative. We conclude that the classical ion-membrane molecule interactions we consider are not involved in determining time-dependent conductance processes in the excitable systems for which comparison is possible.

INTRODUCTION

In the short period of time that excitable membrane biophysics has been a well-defined field of inquiry, many data have accumulated about the time-dependent and steady-state electrical properties of a number of systems. In parallel with this experimental effort there has been a concerted effort on the part of theoretically inclined individuals to explain the data at varying levels of sophistication. Cole (1968) has given a thorough review of these data and modeling efforts.

One of the most widely used approaches in the modeling of excitable membrane

behavior has earned the title "electrodiffusion theory" because of its dual consideration of electric field and concentration gradient-induced ion movement through the membrane. This approach, based on the Nernst (1888, 1889), Planck (1890 *a*, *b*) equations for ion transport, was particularly successful in treating data on total membrane ionic currents. As information accumulated about membrane currents carried by specific ions through individual pathways, electrodiffusion theory was noticeably deficient in several respects (Cole, 1965, 1968).

The failure of the electrodiffusion approach may be one of basic concept or formulation. Recently, a series of theoretical inquiries has raised the possibility that it is the latter. Mackey (1971 *a*, *b*) analyzed a steady-state electrodiffusion model for membrane transport using a kinetic theory approach. The model includes the effects of high electric field strengths on ionic energy, and the effects of various types of ion-membrane molecule interactions. In the absence of ionic concentration gradients across the membrane, the model membrane chord conductance is a nonlinear function of electric field strength. For one type of ion-membrane molecule interaction, the membrane slope conductance is negative for certain values of the field strength. Further, the ionic selectivity of the model is large and is a function of electric field strength. Mackey and McNeel (1971 *a*, *b*) extended this model to situations where ionic concentration gradients exist across the membrane. The model predicts rectification ratios in excess of those expected from traditional electrodiffusion theory, and in accord with those found experimentally. Also, the "nonindependent" behavior exhibited by one-way ionic currents through the potassium channel of the squid giant axon membrane (Hodgkin and Keynes, 1955) could be accommodated by this treatment, which considers the influence of applied and equilibrium fields on ionic mobility and the ionic diffusion coefficient in the membrane.

These results seemed sufficiently encouraging to warrant examining the nonsteady-state properties of the model. However, the model analysis used in the above communications was statistical in nature and required large expenditures of computer time. The extension of the analysis to cover time-dependent situations promised to be even more time consuming, therefore in this paper we present a simplified analysis of the same model.

Steady-state calculations for the model based on the two analyses are in satisfactory agreement. We examine the time response of the model membrane conductance after the application of an electric field across the membrane. This response is dependent on the applied electric field strength, and the nature of the ion-membrane molecule interaction.

THE MODEL

Assumptions

Hille (1970) has reviewed the extensive experimental evidence that ion penetration in the excitable plasma membrane occurs at specific widely spaced locations. It is

only transport through these sites that we deal with. All assumptions relate to these ion-permeable regions.

We assume that the movement of an ion through one of these ion-permeable regions is modulated only by interactions (collisions) with the membrane molecules lining the transport site. Ion-ion interactions are assumed to be unimportant. The way in which ion-membrane molecule interactions influence transport coefficients, and consequently the model membrane electrical properties, is determined by two factors. The first is the frequency of collisions between ion and membrane molecule, and the second is the ionic energy loss during a collision. In general, both factors are complicated functions of ionic and molecular parameters and the force between ion and membrane molecule during an interaction.

Knowledge about the molecules adjacent to ion-permeable regions is almost nonexistent, and we postulate that they may be replaced by an effective membrane molecule. To characterize these membrane molecules we assume that the force between ion and molecule during a collision is central. This assumption gives a simple expression for the ion-membrane molecule collision frequency. The ionic energy loss per collision is determined by ion and membrane molecule masses.

Development

Consider an ion of charge q (coulombs), mass m (g), energy u (dynes), and number density n (number per cubic centimeter) moving through an ion-permeable region of a membrane with directed velocity v_d (centimeters per second) under the influence of an externally applied electric field E (volts per centimeter) and a concentration gradient. The ion is under the influence of a force due to the electric field (qE) a force due to the concentration gradient, $[-\mathrm{d}(nu)/\mathrm{d}x)/n$, and a rapidly fluctuating force ($\mathfrak{F}$) due to its interaction with membrane molecules. The force balance equation for the ion is

$$\frac{1}{n}\frac{\partial(mnv_d)}{\partial t} = qE + \mathfrak{F} - \frac{1}{n}\frac{\partial(nu)}{\partial x}. \tag{1}$$

The microscopic nature of the fluctuating force is unknown, but must be characterized in order to proceed. This is done by making plausible assumptions about the average properties of the fluctuating force. If the frequency of collisions between ions of total velocity v and membrane molecules is $\nu(v)$ (collisions per second), then the deceleration experienced by an ion due to a collision is assumed to be $-\nu(v)\bar{v}_d$, where $\bar{v}_d$ is the directed ionic velocity averaged over many collisions but over a time much less than ν^{-1}. So we take

$$\bar{\mathfrak{F}} = -m\nu(v)\bar{v}_d. \tag{2}$$

If Eq. 1 is averaged over many collisions, the result combines with Eq. 2 to give

$$\frac{1}{n}\frac{\partial(mn\bar{v}_d)}{\partial t} = qE - m\nu(v)\bar{v}_d - \frac{1}{n}\frac{\partial(nu)}{\partial x}. \tag{3}$$

The total ionic velocity (directed plus thermal) appearing in Eq. 3 must not be confused with the directed ionic velocity. Even in the face of strong forces, $v_d \ll v$, so we will alternately consider v to be a function of ionic energy u, $v = v(u)$.

We also need to know how u varies with various parameters, e.g., time and electric field strength. The rate of change of the ionic energy $\dot{u}$ is the difference between the rate at which the ion gains energy from the external electric field qv_dE and from the concentration gradient $-v_d[\mathrm{d}(nu)/\mathrm{d}x]/n$, and the rate at which it loses energy through the rapidly fluctuating force operating during collisions $v_d\mathfrak{F}$. Thus, an energy balance equation

$$\frac{1}{n}\frac{\partial(nu)}{\partial t} = qv_dE + v_d\mathfrak{F} - \frac{v_d}{n}\cdot\frac{\partial(nu)}{\partial x} \tag{4}$$

may be written. Knowledge of the behavior of $\mathfrak{F}$ is needed in order to proceed.

We assume, under the same averaging procedures, that the rate of loss of ionic energy is proportional to the difference between ion energy and scatterer thermal energy u_s times the fractional ion energy loss per collision ξ and the collision frequency:

$$\overline{v_d\mathfrak{F}} = -\xi(u - u_s)\nu(u). \tag{5}$$

Averaging Eq. 4 and substituting Eq. 5 in the result yields

$$\frac{1}{n}\frac{\partial(nu)}{\partial t} = qv_dE - \xi(u - u_s)\nu(u) - \frac{v_d}{n}\frac{\partial(nu)}{\partial x}. \tag{6}$$

We have not yet considered the specific energy dependence of the collision frequency and energy loss per collision. It is through ξ and ν that the unique nature of the different collision processes is introduced.

For elastic collisions, if two particles interact centrally then the collision frequency may be written as a simple function of the magnitude of the relative velocity between scatterer and incident particle. If the force between ion and the fixed effective membrane molecule is given by $F_{is} = -K_{is}/r_{is}^{\alpha}$, where r_{is} is the ion-scatterer separation and α and K_{is} are constants, then (Chapman and Cowling, 1958) the collision frequency is given by $\nu(u) = \beta u^{p/2}$, where $p = (\alpha - 5)/(\alpha - 1)$ and

$$\beta = 2\pi n_s A(\alpha)[K_{is}(m + m_s)/mm_s]^{2/\alpha-1}$$

is a constant involving the scatterer mass m_s, number density n_s, and $A(\alpha)$ is a pure number. The average fractional ionic energy loss per collision is independent of ionic energy for elastic interactions and is given by $\xi = 2m/(m + m_s)$.

Thus, for dominant elastic collision processes we may write Eq. 3 as

$$\frac{1}{n}\frac{\partial(mnv_d)}{\partial t} = qE - m\beta v_d u^{p/2} - \frac{1}{n}\frac{\partial(nu)}{\partial x}, \tag{7}$$

Eq. 5 becomes

$$\overline{v_d \mathfrak{F}} = -\xi\beta(u - u_s)u^{p/2},$$

and Eq. 6 therefore takes the form

$$\frac{1}{n}\frac{\partial(nu)}{\partial t} = qv_d E - \xi\beta(u - u_s)u^{p/2} - \frac{v_d}{n}\frac{\partial(nu)}{\partial x}. \tag{8}$$

To write an equation for current density through the membrane we must solve Eq. 7 and 8 for the velocity v_d. Once v_d has been obtained, the constitutive relation

$$j = qnv_d \tag{9}$$

will give the connection between v_d and ionic current density j (amperes per square centimeter).

To deal with Eq. 7 and 8 it will be convenient to use the following dimensionless variables:

$$\begin{aligned} V &= v_d/v_T \qquad N = n/n_0 \\ I &= j/qv_T n_0 \qquad E = qE/mv_0 v_T \\ U &= u/u_s \qquad t = v_0 t \\ L &= xv_0/v_T \qquad v_0 = \beta u_s^{p/2} \\ u_s &= mv_T^2/2 = kT. \end{aligned} \tag{10}$$

With the definitions of Eq. 10, Eqs. 7 and 8 become

$$\frac{1}{N}\frac{\partial(NV)}{\partial t} = E - VU^{p/2} - \frac{1}{2N}\cdot\frac{\partial(NU)}{\partial L}, \tag{11}$$

and

$$\frac{1}{N}\frac{\partial(NU)}{\partial t} = 2V\left[E - \frac{1}{2N}\cdot\frac{\partial(NU)}{\partial L}\right] + \xi(1 - U)U^{p/2}, \tag{12}$$

respectively, and Eq. 9 becomes

$$I = NV. \tag{13}$$

Steady-State Behavior

If in the steady state, a concentration gradient exists across the membrane, Eqs. 11–13 become

$$I = (NE/U^{p/2}) - (1/2U^{p/2})[\mathrm{d}(NU)/\mathrm{d}L], \tag{14}$$

and

$$0 = 2IE - (I/N)[\mathrm{d}(NU)/\mathrm{d}L] + \xi N(1 - U)U^{p/2}. \tag{15}$$

We assume $\bar{E}$ and U to be independent of L, which implies that ν is also independent of L. In the statistical analysis of this model, Mackey and McNeel (1971 *a*) have shown that U independent of L is a logical consequence of the constant field assumption. If the membrane is of thickness $\bar{\delta}$, and if at $L = 0$ ($\bar{\delta}$) the conditions $N = N_1$ (1) and $\varphi = \varphi_1(\varphi_2)$ hold, then $\varphi(L) = \varphi_1 + (\varphi_2 - \varphi_1)L/\bar{\delta}$ and $\bar{E} = -\mathrm{d}\varphi/\mathrm{d}L = -\varphi_m/\bar{\delta}$, where $\varphi_m = \varphi_1 - \varphi_2$ is the membrane potential.

With the above assumptions and boundary conditions, Eq. 14 is easily integrated to give

$$I = \frac{\bar{E}}{U^{p/2}} \cdot \frac{1 - N_1 \exp(2\bar{\delta}\bar{E}/U)}{1 - \exp(2\bar{\delta}\bar{E}/U)}. \tag{16}$$

The expression for the current density requires knowledge of how U depends on $\bar{E}$ and N_1. We obtain this by integrating Eq. 15, again obtaining an expression for I, and equating the result with Eq. 16. The result is the transcendental equation

$$\frac{\xi U^p(U - 1)}{\bar{E}^2} = \frac{2}{N_1}\left[\frac{1 - N_1 \exp(2\bar{\delta}\bar{E}/U)}{1 - \exp(2\bar{\delta}\bar{E}/U)}\right] \tag{17}$$

which implicitly gives $U = U(\bar{E}, N_1)$.

From Eq. 16 as $(\bar{E}/U) \to -(2\bar{\delta})^{-1}\ln N_1$, $I \to 0$. We define the value of $\bar{E}$ such that $I \equiv 0$ as the equilibrium field $\bar{E}_e$ and the corresponding membrane potential, the equilibrium potential φ_e. From Eq. 17, as $I \to 0$, $U \to 1$, and the equilibrium field is given by

$$\bar{E}_e = -(2\bar{\delta})^{-1}\ln N_1. \tag{18}$$

Use of the equilibrium field defined by Eq. 18 allows us to write Eqs. 16 and 17 in a more symmetric form; namely

$$I = \frac{\bar{E}(N_1)^{1/2}}{U^{p/2}} \cdot \frac{\sinh[\bar{\delta}(\bar{E} - U\bar{E}_e)/U]}{\sinh[\bar{\delta}\bar{E}/U]}, \tag{19}$$

and

$$\xi U^p(U - 1) = 2\bar{E}^2 \frac{\sinh^2[\bar{\delta}(\bar{E} - U\bar{E}_e)/U]}{\sinh^2[\bar{\delta}\bar{E}/U]}, \tag{20}$$

respectively.

The generalized Goldman equation derived above, Eq. 19, in conjunction with Eq. 20 has behavior virtually identical with that described by Mackey and McNeel (1971 *a*, *b*) for the same model analyzed in a more complex manner. Comparison between the two analyses indicates that $U^{-p/2}$ plays the role of a dimensionless

mobility $\bar{\mu}$ while $2^{-1}U^{(2-p)/2}$ is a dimensionless diffusion coefficient $\bar{D}$. The advantage of the present model analysis is that U may be obtained as the solution of a transcendental equation. Previously, the numerical computation of three integrals was required to determine $\bar{\mu}(\bar{E}, \bar{E}_e)$ and $\bar{D}(\bar{E}, \bar{E}_e)$.

Because of the similarity of the results obtained with the two methods of analysis, we reproduce none of the steady-state calculations for the analysis used here. This model predicts rectification ratios close to those observed experimentally (Mackey and McNeel, 1971 *a*). One-way fluxes and flux ratios qualitatively similar to those found biologically (Hodgkin and Keynes, 1955) are predicted by this model. The Goldman (1943) formulation of electrodiffusion theory is deficient in these respects.

It should be noted that in a steady-state situation with no concentration gradient across the membrane, Eqs. 14 and 19 become

$$I = \bar{E}U^{-p/2}, \tag{21}$$

and

$$\xi U^p(U - 1) = 2\bar{E}^2. \tag{22}$$

For small field strengths, $(2\bar{E}^2/\xi) \ll 1$, $U \simeq 1$ (the ionic energy has not been increased significantly over its thermal energy) and the chord conductance $G_c = U^{-p/2}$ is approximately constant. For large field strengths, $(2\bar{E}^2/\xi) \gg 1$, $U \gg 1$ so Eq. 22 may be solved approximately to give $U \simeq (2\bar{E}^2/\xi)^{1/(p+1)}$. Thus for high field conditions the conductance is given by $G_c \sim (2\bar{E}^2/\xi)^{-p/2(p+1)}$ and G_c is a decreasing (increasing) function of electric field strength for $p > 0 (-1 < p < 0.)$ This is the same conclusion reached in Mackey (1971 *a*) using a more complicated kinetic theory analysis for the same model.

For $p < -1$ the situation is not as simple, for U is an increasing function of $\bar{E}$ only to a certain value of $\bar{E}$. To determine for what values of $\bar{E}$ the dimensionless energy is defined, we must examine the behavior of the equation $(2\bar{E}^2/\xi) = (U - 1)/U^m$, where $m = -p > 1$.

If we let $f(U) = (U - 1)/U^m$, it is a simple matter to show that $(df/dU) > 0$ for $1 \leq U < m/(m - 1)$. At $U = m/(m - 1)$, $(df/dU) = 0$ and $f = m^{-1}[(m - 1)/m]^{m-1}$. For any given m value our formulae are applicable for

$$0 \leq |\bar{E}| < \left[\frac{\xi}{2m}\left(\frac{m - 1}{m}\right)^{m-1}\right]^{1/2}, \qquad m > 1.$$

For $p = -1 (m = 1)$ the formulae are applicable for $\bar{E} < (\xi/2)^{1/2}$.

Two classes of classical interactions are characterized by $p < 0$: for ion-permanent dipole collisions $p = -1 (m = 1)$, and for ion-fixed charge (coulombic) collisions $p = -3 (m = 3)$. For these two classes of interactions, the normalizing constants relating dimensionless $\bar{E}$ values to actual membrane potentials may be calculated from first principles. When this is done the E_{max} values for which our

formulae apply, i.e. $[\bar{E}_{max}/(\xi)^{1/2}] = 0.707$ for $p = -1$, $[\bar{E}_{max}/(\xi)^{1/2}] = 0.273$ for $p = -3$, correspond to membrane potentials much greater than those likely to be encountered in biological situations (cf. Table II, Mackey, 1971 *a*).

Time-Dependent Behavior

In this section we examine the time-course of the model conductance changes in response to an "instantaneously" applied electric field. Valuable insight into the mechanisms of these changes is provided by examining the response of the system in the absence of concentration gradients, so we confine our attention to this situation.

In the absence of a concentration gradient, the model equations become

$$dV/d\bar{t} = \bar{E} - VU^{p/2}, \tag{23}$$

and

$$dU/d\bar{t} = 2V\bar{E} + \xi(1 - U)U^{p/2}, \tag{24}$$

respectively. This system has no simple closed solution except for $p = 0$, but we may obtain numerical solutions, and approximate solutions to a simplified system.

If a field $\bar{E}$ is suddenly applied across the membrane, the initial effect will be to accelerate the ions so $\dot{V} \neq 0$. For short times ($t \ll \nu_0^{-1}$ or $\bar{t} \ll 1$) there will be little change in ionic energy, as this is accomplished through collisional energy losses. Hence, for $\bar{t} \ll 1$ we expect $\dot{U} \sim 0$. If there is no field across the membrane before $\bar{E}$ is applied, $U \simeq 1$ and the early time behavior will be approximately described by $\dot{V} + V = \bar{E}$. Thus

$$\bar{G}(\bar{t}) = (I/\bar{E}) = 1 - \exp(-\bar{t}). \tag{25}$$

In Fig. 1 the full behavior of $\bar{G}(\bar{t})$, computed from Eqs. 23 and 24, is shown for a range of $\bar{E}$ and $p = \frac{1}{3}, \frac{1}{2}, 1$, and 4. ($p = \frac{1}{3}$ corresponds to a classical induced-dipole collision; $p = 1$ characterizes an ion-neutral particle interaction, cf. Mackey, 1971 *a*.) At early times ($\bar{t} \ll 1$), when accelerative effects are expected to dominate, $\bar{G}(\bar{t})$ is indeed closely approximated by Eq. 25 which is shown as a dashed line for each value of p. The deviation from the behavior predicted by Eq. 25 will arise as collision-induced ionic energy losses become appreciable. The behavior in Fig. 1 illustrates that increases in p and/or $\bar{E}$ enhance the early appearance of these phenomena, as would be expected.

The numerical solutions of Eqs. 23 and 24 shown in Fig. 1 indicate that $\bar{G}(\bar{t})$ reaches a maximum, then declines to a final steady-state value. If we denote the maximum value of $\bar{G}(\bar{t})$ reached at time $\bar{t}_m$ as $\bar{G}_m$, then both $\bar{G}_m$ and $\bar{t}_m$ are decreasing functions of p and $\bar{E}$ as indicated in Figs. 2 and 3, respectively.

Within the context of the model presented here, the maximum in the $\bar{G}(\bar{t})$ vs. $\bar{t}$ relation simply implies that a point ($\dot{V} = 0$) has been reached where the accelerating

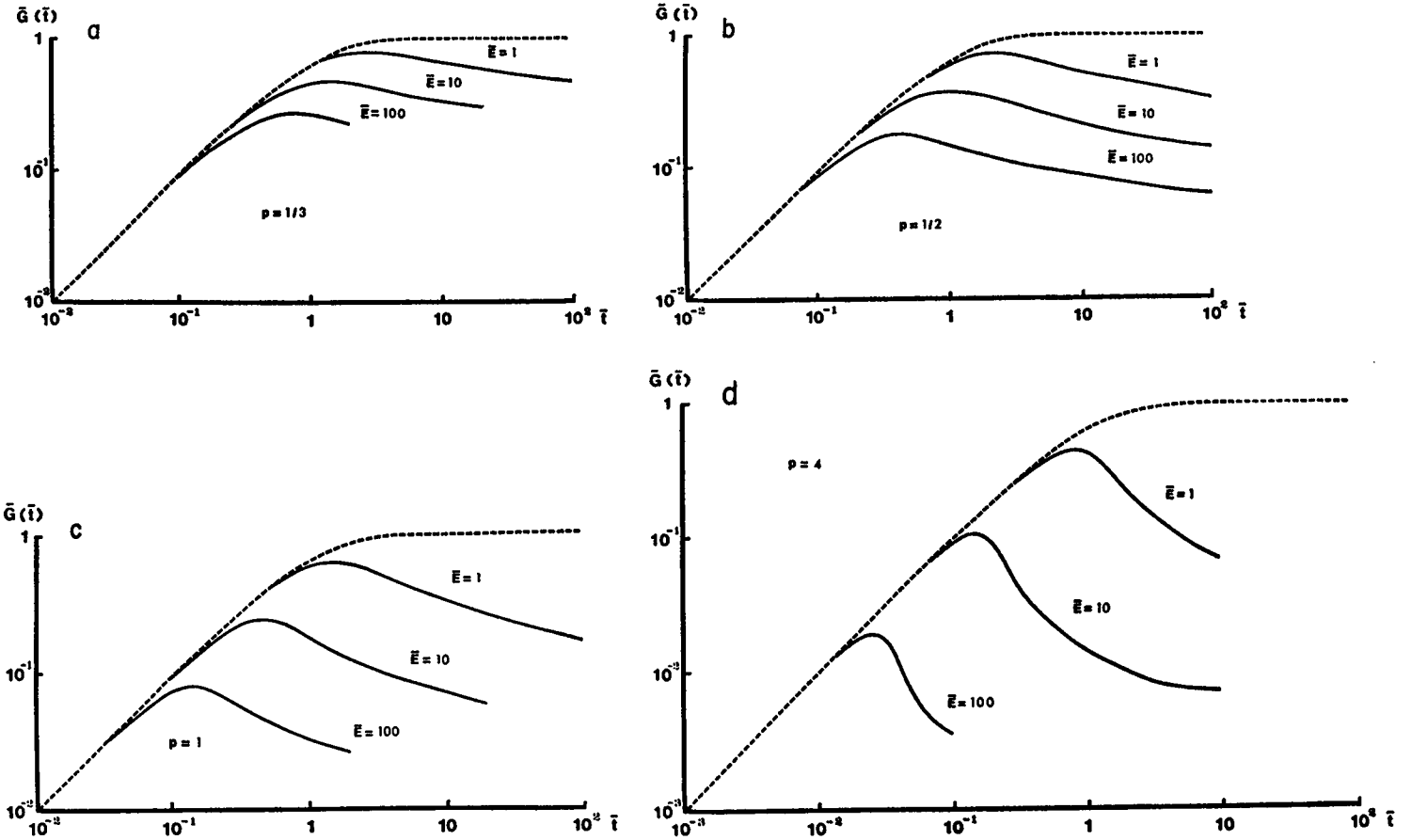

FIGURE 1 Full logarithmic plots of $\bar{G}(\bar{t})$ vs. $\bar{t}$ in response to a change in $\bar{E}$ from zero to the indicated value at $\bar{t} = 0$, as obtained from the numerical solutions of Eqs. 23 and 24. The computations were carried out for $p = (\frac{1}{3}), (\frac{1}{2}), 1$, and 4 with $\xi = 10^{-3}$ in every case. The broken line gives the response for $p = 0$, $\bar{G}(\bar{t}) = 1 - \exp(-\bar{t})$, which is also the approximate behavior for early times according to Eq. 25.

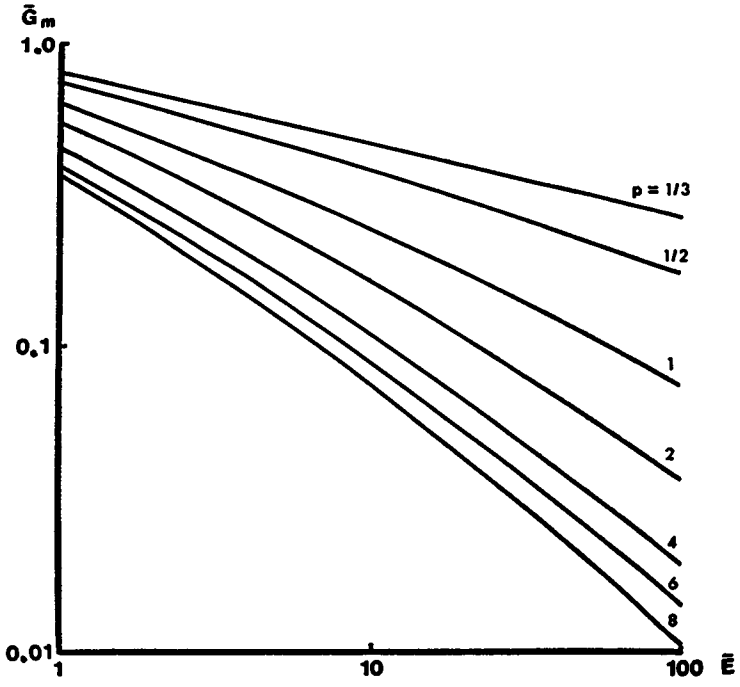

FIGURE 2 The variation in the maximum conductance of the model ($\bar{G}_m$) with respect to the applied electric field ($\bar{E}$) for a range of $p > 0$. $\xi = 10^{-3}$.

effect of the electric field on the ion is exactly balanced by the collision-induced deceleration. Thus, at the maximum, the net force on the ion is zero even though the ionic energy is still changing. As the exchange between electric field and collision-induced energy changes continues, the ion exhibits net deceleration ($\dot{V} < 0$) characterized by $\dot{U} > 0$ until a steady-state with $\dot{V} = \dot{U} = 0$ is obtained. The dependence of this steady state on the electric field strength is given by the solutions of Eqs. 21 and 22 above.

In real (as opposed to dimensionless) time the ionic acceleration due to the applied electric field has a characteristic time of ν_0^{-1}, while the ionic deceleration due to collisions has a characteristic time of $(\xi\nu_0)^{-1}$. In Figs. 1–3 we used $\xi = 10^{-3}$ in our numerical computations, assuring the separation of these two characteristic times by a factor of 10^3 and the resultant appearance of the maximum in $\bar{G}(\bar{t})$ with respect to time.

To obtain an approximate quantitative picture of the above events we may proceed as follows. For $\bar{t} \gg 1$ ($t \gg \nu_0^{-1}$) we expect that the primary source of time variation arises from energy changes. Therefore we approximate the model with $\dot{V} \sim 0$ and $\dot{U} \neq 0$, so

$$V \simeq \bar{E}U^{-p/2}, \tag{26}$$

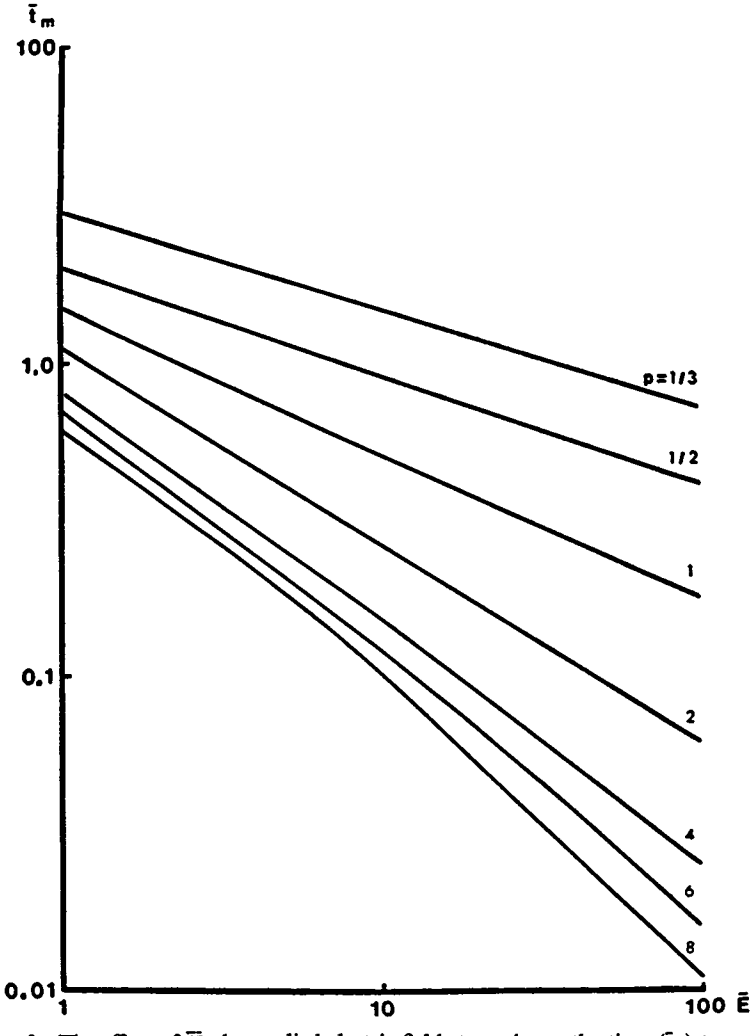

FIGURE 3 The effect of $\bar{E}$, the applied electric field strength, on the time ($\bar{t}_m$) to maximum conductance in the model when $p > 0$. $\xi = 10^{-3}$ throughout.

and

$$dU/dt = 2V\bar{E} + \xi(1 - U)U^{p/2}. \tag{27}$$

If we combine Eqs. 26 and 27 the result is

$$U^{p/2}(dU/dt) = 2\bar{E}^2 + \xi(1 - U)U^{p/2}. \tag{28}$$

If in Eq. 28 we set $U^{p/2} = R$ and take R to be approximately independent of $\bar{t}$, we obtain $U(\bar{t}) \simeq 1 + (2\bar{E}^2/\xi R)[1 - \exp(-\xi R\bar{t})]$. Now R will range from 1 to $U(\bar{t} \rightarrow$

$\infty)^{p/2}$, so we can get an approximate idea of the extremes of behavior exhibited by the system.

For small values of $\bar{E}$, $R \simeq 1$, $U(\bar{t}) \simeq 1\ (2\bar{E}^2/\xi)[1 - \exp(-\xi\bar{t})]$, and the chord conductance is approximately

$$\bar{G}(\bar{t}) \simeq \{1 + (2\bar{E}^2/\xi)[1 - \exp(-\xi\bar{t})]\}^{-p/2}. \tag{29}$$

For large $\bar{E}$, R is approximated by $(2\bar{E}^2/\xi)^{p/2(p+1)}$, so $U(\bar{t}) \simeq (2\bar{E}^2/\xi R^2)[1 - \exp(-\xi R\bar{t})]$ and the chord conductance varies

$$\bar{G}(\bar{t}) \simeq (2\bar{E}^2/\xi)^{-p/2(p+1)}[1 - \exp(-\xi R\bar{t})]^{-p/2}. \tag{30}$$

In Eq. 29, as $\bar{t} \to \infty$, $\bar{G}(\bar{t}) \to 1$ for small $\bar{E}$ as described in the section on steady-state behavior. For large field strengths, $\bar{G}(\bar{t})$ as given by Eq. 30 approaches the limiting approximate value given in the steady-state section. The characteristic time for changes in $\bar{G}(\bar{t})$ is also seen to differ from that of Eq. 25 by a factor of ξ as discussed above.

As in the steady state, interactions characterized by $p = 0$ provide a natural dividing line for the time-dependent behavior. When $p = 0$ we have, from Eq. 23. $\bar{G} = 1 - \exp(-\bar{t})$. Thus $\bar{G}$ rises exponentially and maintains a constant steady-state level. From Eqs. 29 and 30 we see that $\bar{G}$ will be a decreasing (increasing) function of $\bar{t}$ for $p > 0$ $(-1 < p < 0)$, which is intuitively reasonable. For $p < 0$, as $\bar{t}$ increases the ionic energy increases. But the frequency of collisions is decreasing at the same time, therefore the conductance goes up. Eventually a balance is reached between collisional energy losses and field-induced energy gains. Qualitatively the same behavior is exhibited for $p < -1$, but with the above noted restrictions on $\bar{E}$. Exactly the converse argument serves to explain the behavior when $p > 0$, for in this case the collision frequency increases as ionic energy increases. Thus, the conductance decreases until a balance is again attained.

All of the computed solutions for Eqs. 23 and 24 presented here have been for $p > 0$. When $p = -1$, -2, or -3, and $\xi = 10^{-3}$, the solutions are well described by Eq. 25 for $\bar{t} \leq 10$. With this value of ξ there is a very wide separation in time between electric field and collision-related phenomena, and it is more pronounced than with $p > 0$. In any case, the behavior of $\bar{G}(\bar{t})$ in response to a step change in $\bar{E}$ will initially follow the dashed curve as shown in Fig. 1, remain at a constant value $(=1)$ for some time, then rise to a second steady-state value.

DISCUSSION

The time-dependent behavior exhibited by the conductance of this model when $p > 0$ is strikingly similar to the known behavior of the sodium conductance in a number of excitable systems (cf. Cole, 1968), In response to a step change in the applied electric field, the conductance rises to a maximum and then decays to a

lower steady-state value. Both the maximum conductance and the time to maximum vary with respect to the membrane potential, and this variation is at least qualitatively similar to that found experimentally.

Many interpretations of sodium conductance data have started with the assumption that the activation-inactivation sequence is the result of two separate mechanisms operating independently (Hodgkin and Huxley, 1952). The activation-inactivation pattern displayed by the conductance in this model is not a result of the action of two completely separate mechanisms. Rather, it is due to the subtle interplay of two interdependent physical processes, and inactivation of the conductance is a process intimately tied to activation. Indeed, Hoyt (1963, 1968) and Hoyt and Adelman (1970) have been able to fit voltage clamp data on g_{Na} using a model in which activation-inactivation is a coupled process, and explain the results of certain inactivation experiments not resolved by the Hodgkin-Huxley formulation of the process.

The conceptual similarity between the Hoyt model and the one we are considering in conjunction with the results of the two models might seem to imply that the molecular mechanisms we consider play a significant role in the determination of time-dependent transport processes in excitable membranes. However, this interpretation fails on at least three points.

First, we must note that the characteristic time (ν_0^{-1}) of this model differs from that found experimentally by at least three orders of magnitude (cf. Mackey, 1971 *a*). Second, the effect of temperature on the time parameters of this model may be shown to be quite small ($Q_{10} \sim 1.1$) with respect to those found experimentally ($Q_{10} \sim 2$–3). The temperature dependence of the steady-state model conductances is more in accord with those found in excitable systems. Finally, this model would predict a sensitivity of the time parameters to ionic properties almost as great as those observed in the steady-state conductance. Experimental data (Binstock and Lecar, 1969; Chandler and Meves, 1965; Meves and Chandler, 1965; Moore et al., 1966), indicate no change in the time constants of sodium conductance activation and inactivation when current through the sodium channel is carried by a number of monovalent sodium ion substitutes.

It is for the above reasons that we feel we must reject classical elastic, central ion-membrane molecule interactions as the source of time-dependent conductance changes observed in most excitable membrane systems, even though they may serve to explain steady-state behaviors.

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