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Single-Ion Electrodiffusion Models of the Late Sodium and Potassium Currents in the Giant Axon of the Squid

Jarl V. Hägglund

Institute of Physiology and Medical Biophysics,
Biomedical Center, Uppsala University, Uppsala, Sweden

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Summary. Single-ion electrodiffusion has been studied theoretically as a possible mechanism responsible for potassium activation and sodium inactivation; i.e., the processes constituting the late current following a voltage-clamp potential step in the Hodgkin-Huxley axon. Nonsteady-state conductance changes under voltage clamp have been computed in the nonlinear range, assuming a constant electric field. The results show a general agreement with the Hodgkin-Huxley equations. The shapes, sigmoidal or exponential, of the conductance transients are well reproduced in the electrodiffusion models. The behavior of the time constant is also compatible with squid axon data. Some discrepancies are present and possible theoretical explanations of them are discussed.

The detailed mechanisms behind the conductance changes during excitation of the nerve axon are still unknown. Theoretical models are complicated by the facts (i) that nerve-membrane behavior is highly nonlinear and (ii) that the electro-physiological excitation phenomena are of a transient nature.

Many models of the nerve membrane have been based on electrodiffusion theory. The well-known Hodgkin-Huxley model of the squid axon membrane was also partly based on electrodiffusion phenomena [16]. Several-ion and single-ion electrodiffusion models of the squid axon have been extensively reviewed and discussed by Cole [7].

The kinetics and nonlinearities of electrodiffusion regimes are only partly known, mainly because of the mathematical difficulties involved in a complete solution. A general approach to the problem should include the use of the Nernst-Planck equations, combined with the continuity and Poisson equations. The transient response of such a system to stepwise current change has been studied by Cohen and Cooley [6]. Another kinetic

approach was made by Sandblom [19], who calculated the frequency response of an electrodiffusion regime in the linear range. However, computations for the case of potential steps corresponding to voltage-clamp experiments have not been made. Voltage-clamp calculations are of special interest, as regards the theoretical explanation of Hodgkin and Huxley's equations. The Hodgkin-Huxley theory adequately describes a number of experiments beyond the voltage-clamp measurements on which the theory was initially based. Thus, a theoretical explanation of axon membrane behavior must be compatible with the Hodgkin-Huxley equations [8].

The aim of the present investigation is to study the voltage-clamp kinetics of single-ion electrodiffusion models on the assumption of a constant electric field. Such a model was studied by Cole in the linear range [7], but the analysis in the present paper is extended to the nonlinear case. The constant-field assumption is an uncertain approximation [1, 7] but simplifies the mathematical treatment considerably and is a reasonable attempt at a general nonlinear solution.

The single-ion regimes are applied as models of the two processes associated with the activation of the potassium conductance and the inactivation of the sodium conductance, which together are responsible for the late current following voltage-clamp potential steps in the Hodgkin-Huxley axon. The results conform in many respects with the squid axon behavior.

Model

Two different single-ion electrodiffusion regimes, selective for sodium and potassium, respectively, are adopted as models of the sodium and potassium channels of the Hodgkin-Huxley axon (Fig. 1). At the outside, the sodium concentration is high and the potassium concentration low, as compared with the inside concentrations. The outside and inside concentrations are called c_1 and c_2, respectively. The membrane extends from 0 to δ in the x-direction perpendicularly to the membrane surface. Across the membrane a potential difference E is applied, measured as the intracellular potential minus the extracellular. The membrane potential causes an electric field, $-\partial E/\partial x$, directed in the positive x-direction.

At the resting potential, E is negative, which causes an upward convex sodium-concentration profile under the influence of the electric field, but an upward concave potassium profile (continuous lines in Fig. 1). The concentration profiles reflect the ion content in the channels. Thus, the sodium conductance is high and the potassium conductance is low at the resting potential.

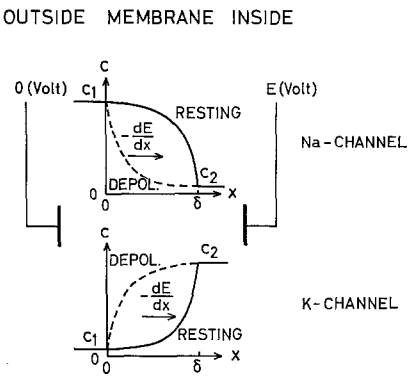

Fig. 1. Single-ion electrodiffusion models of the sodium inactivation (Na-channel) and potassium activation (K-channel). The concentration profile is influenced by diffusion and by the electric field ($-dE/dx$). At rest, the membrane potential E is negative, which causes a high sodium conductance and a low potassium conductance (continuous concentration profiles). Depolarizing the membrane corresponds to the dashed profiles and the subsequent changes in the conductances

Depolarizing the membrane by increasing the potential difference E stepwise causes a relaxational change in the concentration profiles and thus also in the conductances of the ionic channels. The sodium conductance will decrease and the potassium conductance will increase (dashed profile curves in Fig. 1). This behavior means that the present model describes, at least qualitatively, the processes of sodium inactivation and potassium activation, which together constitute the conductance changes associated with the late current under voltage clamp, as given by the Hodgkin-Huxley model. The sodium activation determines the early current, which is fast, as compared with the late current. Thus, for the present analysis, the process of sodium activation is considered to have decayed at times when sodium inactivation and potassium activation have developed appreciably.

Theory

The Electrodiffusion Model

The Nernst-Planck flux equation is applied to the sodium channel in Fig. 1, taking into consideration the osmotic and electric driving forces acting on the ions in the membrane.

$$J = -D\frac{\partial c}{\partial x} - u\,cF\frac{\partial E}{\partial x} \tag{1}$$

where J (mole/cm^2 sec) is the total sodium flux (positive in the positive x-direction), D is the diffusion coefficient (cm^2/sec), u is the molar mobility (cm^2 mole per joule sec), $c=c(x, t)$ is the ion concentration (mole/cm^3), E is the electric potential (volts), and F is the Faraday constant (coul/mole). Eq. (1) is valid for single monovalent-ion electrodiffusion in one dimension.

The rate of change of the concentration with respect to time t is given by the continuity equation

$$\frac{\partial c}{\partial t}=-\frac{\partial J}{\partial x}. \tag{2}$$

It is now assumed that the electric field $-\partial E/\partial x$ is constant with respect to x. Combining Eqs. (1) and (2) then leads to

$$\frac{\partial C}{\partial T}=\frac{\partial^2 C}{\partial X^2}+\bar{E}\frac{\partial C}{\partial X} \tag{3}$$

where the following normalizations have been introduced:

$$X=x/\delta,$$

$$C=C(X, T)=c/c_1,$$

$$T=tD/\delta^2,$$

$$\bar{E}=\frac{\partial E}{\partial x}\delta F u/D=EFu/D.$$

$\bar{E}$ stands for the normalized electric field (with reversed sign) or normalized membrane potential. If D obeys the Einstein equation, $D=RTu$ (R is the gas constant and T is now the absolute temperature), then the potential normalization factor is $RT/F=24.0$ mV, when the temperature is 6.3 °C, as in the Hodgkin-Huxley axon [16].

An analytical solution of Eq. (3) in response to a voltage step from $\bar{E}_1$ to $\bar{E}_2$ has been given in its fundamental form by Cole [7]. Eq. (3) is analogous to a convection-diffusion system, studied previously by the present author [12, 13]. A Fourier-series solution was found [12], using a transformation given by Fürth [10], which transferred the problem to an equation analogous to the problem of heat conduction [4]. The detailed solution was given in Ref. [12] and has been applied to the single-ion electrodiffusion problem in the present paper. The details of the numerical procedure were also given in Ref. [12]. The convection-diffusion solution is applicable to the sodium channel in Fig. 1 if the normalized convection velocities V_1 and V_2 are exchanged for $-\bar{E}_1$ and $-\bar{E}_2$. For calculations on the potassium channel, V_1, V_2 and $C_2=c_2/c_1$ in the convection-diffusion model are replaced by $\bar{E}_1$, $\bar{E}_2$ and $C_1=c_1/c_2$ (*cf.* Fig. 1).

When the concentration C has been calculated, the corresponding conductance changes are given by [17]

$$G(T)=1\Big/\int_0^1 \frac{dX}{C(X,T)} \tag{4}$$

where the normalized conductance $G(T)$ is related to the membrane conductance $g(t)$ by $G=g\delta/F^2uc_1$ for the sodium channel and by $G=g\delta/F^2uc_2$ for the potassium channel. The conductance is related to the ionic currents by

$$I=G(T)(E-E_e) \tag{5}$$

where I is the potassium or sodium current density and E_e is the corresponding equilibrium potential. Eq. (5) is obtained by integration of the Nernst-Planck equations.

The Hodgkin-Huxley Model

According to the Hodgkin-Huxley theory, the axon membrane current density I under voltage clamp is divided into three ionic components [16]

$$I=\bar{g}_{\mathrm{Na}}\, m^3 h\,(E-E_{\mathrm{Na}})+\bar{g}_{\mathrm{K}}\, n^4(E-E_{\mathrm{K}})+\bar{g}_L(E-E_L) \tag{6}$$

representing the sodium, potassium and leakage current densities. $\bar{g}_{\mathrm{Na}}$, $\bar{g}_{\mathrm{K}}$ and $\bar{g}_L$ are the maximum steady-state conductances. The kinetic parameters m, h and n affect the sodium and the potassium currents and are associated with the activation (m) and inactivation (h) of the sodium conductance and with the activation of the potassium conductance (n). E_{Na}, E_{K} and E_L represent the equilibrium potentials in the three channels. The capacity component $C\partial E/\partial t$ (C is the membrane capacity per unit area) of the membrane current density has been omitted in Eq. (6), since it is zero in voltage-clamp experiments, except for the fast charging of the capacity following the voltage step. m, h and n were given by first-order differential equations with respect to time. For step changes in the membrane potential, the differential equations were satisfied by solutions of the following type [16]:

$$n=n_\infty-(n_\infty-n_0)\exp(-t/\tau_n) \tag{7}$$

and similar equations for m and h. The parameters m_∞, τ_m, h_∞, τ_h, n_∞ and τ_n in these equations were given quantitative mathematical expressions as functions of the membrane potential E by fitting the theory to the experimental results.

The mechanisms behind the nonlinear kinetics of m, n and h are still unknown, despite a number of theoretical suggestions. The single-ion

electrodiffusion models proposed in the present paper are an attempt to describe the n and h parameters. The sodium activation m is not considered and is assumed to be constant in the calculations presented below.

Computations

Conductance

The conductance response for the ED[1] models under voltage clamp was calculated from Eq. (4) with the solution of $C(X, T)$ derived from Eq. (3) and given in Ref. [12]. For comparison, the corresponding conductance changes of the HH potassium and sodium channels were computed from $\bar{g}_K n^4$ and $\bar{g}_{Na} m_\infty^3 h$ in Eq. (6).

Four different types of voltage steps, classified and designated in Fig. 2, were applied to the models. Depolarization from the resting potential and repolarization back to the resting potential were used both in the case of potassium and sodium. In addition, hyperpolarization from the resting potential and return from the hyperpolarized state to the resting value were used for sodium. The reason for studying sodium hyperpolarization is that the sodium-activated conductance assumes a medium value at the resting potential in contrast to the potassium conductance, which is near zero at rest.

To conform with the voltage-clamp experiments on the giant axon, actual values of the ionic concentrations of axoplasm and seawater, as well as of the resting potential were used in the ED models. The squid axon data were obtained from Hodgkin [15]: for potassium $C_1 = 10\,\text{mM}/400\,\text{mM} = 0.025$, and for sodium $C_2 = 50\,\text{mM}/460\,\text{mM} = 0.11$. The resting potential was taken as -60 mV, which corresponds to $\bar{E} = -2.5$ [*see* definition under Eq. (3)].

In the HH model, the following parameter values were chosen: $\bar{g}_{Na} = 0.120\,\text{mho/cm}^2$, $\bar{g}_K = 0.036\,\text{mho/cm}^2$ (Table 3, Ref. [16]) and $m = m_\infty = 1$. n_∞, h_∞, τ_n and τ_h were calculated from Eqs. (9), (10), and (18) in Ref. [16]. The value of the resting potential E_r used in HH calculations was -65 mV.

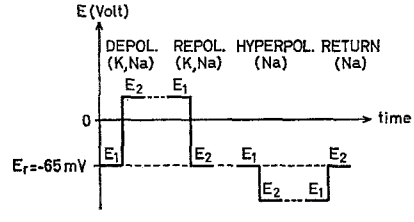

Fig. 2. Classification and designation of the different kinds of potential steps used in calculating the conductance transients

1 In the following pages, "HH" and "ED" will be used as abbreviations of "Hodgkin-Huxley" and "electrodiffusion", respectively.

Curve-Fitting

To compare in more detail the time constants and steady-state conductances of the ED models with those of the HH theory, the HH equations were fitted to the ED conductance transients by using a method previously described [13].

The following approximations of the ED model conductances are introduced; they are equivalent to the HH formulation of the potassium conductance and the sodium conductance inactivation under a voltage-clamp step:

$$G_K = [N_\infty - (N_\infty - N_0)\exp(-T/\tau_N)]^4 \tag{8}$$

and

$$G_{Na} = H_\infty - (H_\infty - H_0)\exp(-T/\tau_H) \tag{9}$$

where G_K and G_{Na} are the fitted potassium and sodium conductances, τ_N and τ_H are the corresponding time constants, and N_0, N_∞, H_0 and H_∞ are the initial and final steady-state parameters of the sodium and potassium ED channels. The steady-state parameters are defined by the actual steady-state values of the ED conductance G_∞.

$$N_\infty = \sqrt[4]{G_\infty} \tag{10}$$

and

$$H_\infty = G_\infty \tag{11}$$

for the potassium and sodium ED channels, respectively.

Eqs. (8) and (9), together with Eqs. (10) and (11), were fitted by a least-squares method to the transient conductances computed from the ED models. The details of the curve-fitting procedure were the same as those presented before [13]. By this method, the equivalent time constants, τ_N and τ_H, of the ED models were calculated as functions of the membrane potential. The potential behavior of the ED parameters τ_N, τ_H, N_∞ and H_∞ could thus be compared with that of the corresponding parameters τ_n, τ_h, n_∞ and h_∞, fundamental to the HH axon.

Results

Potassium Channel

Conductance Behavior. The computed potassium-conductance variation with time is shown in Fig. 3. (*a*) and (*b*) are the results of the HH theory, and in (*c*) and (*d*), the corresponding curves for the ED model are given. It will be seen that the behavior of the HH and ED models show considerable similarities. The conductance increase under a depolarizing potential

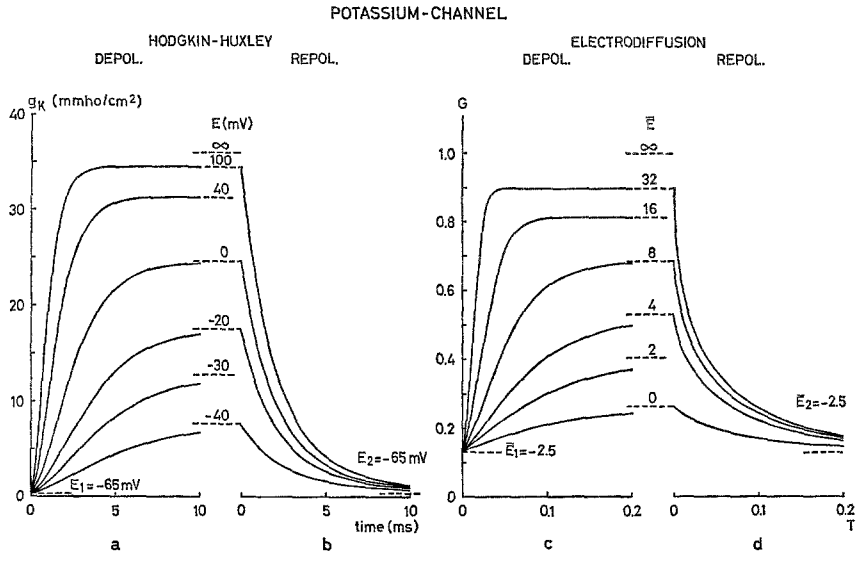

Fig. 3. Conductance changes of the potassium ED model (*c* and *d*), compared with the HH model (*a* and *b*) for depolarizing (*a* and *c*) and repolarizing (*b* and *d*) potential steps. The potential steps are defined by changing E_1 to E (*a*) and E to E_2 (*b*) at $t=0$, and $\bar{E}_1$ to $\bar{E}$ (*c*) and $\bar{E}$ to $\bar{E}_2$ (*d*) at $T=0$. The following values were used: $E_r=-65$ mV, $\bar{E}_r=-2.5$ (resting potentials) and $C_1=0.025$. Note the sigmoidal conductance increase and exponential decrease in both models

step from the resting potential is of *sigmoidal* shape in both models, though in the ED model it is less pronounced (Fig. 3*a* and *c*). In the ED model, the sigmoidal shape is more pronounced when the value of $\bar{E}_1$ is decreased [13].

During repolarization back to the resting potential the conductance fall is approximately exponential in both models (Fig. 3*b* and *d*). The relations between the time scales for the depolarization and repolarization cases are approximately correct, when the two models are compared.

In both models, the time constant of the conductance transient varies with the final potential when the membrane is depolarized (Fig. 3*a* and *c*) but is approximately constant during repolarization (Fig. 3*b* and *d*). Depolarization gives a decreasing time constant when the potential step is increased.

The steady-state properties are similar in both models but differ in that the conductance at the resting potential is higher in the ED model than in the HH theory. The maximum steady-state conductance is also approached rather slowly in the ED model, when the potential is increased, as compared with the situation in the HH model.

An important discrepancy is that the potential scales are quite different in the two cases. Since the values of E and $\bar{E}$ are related to each other by a

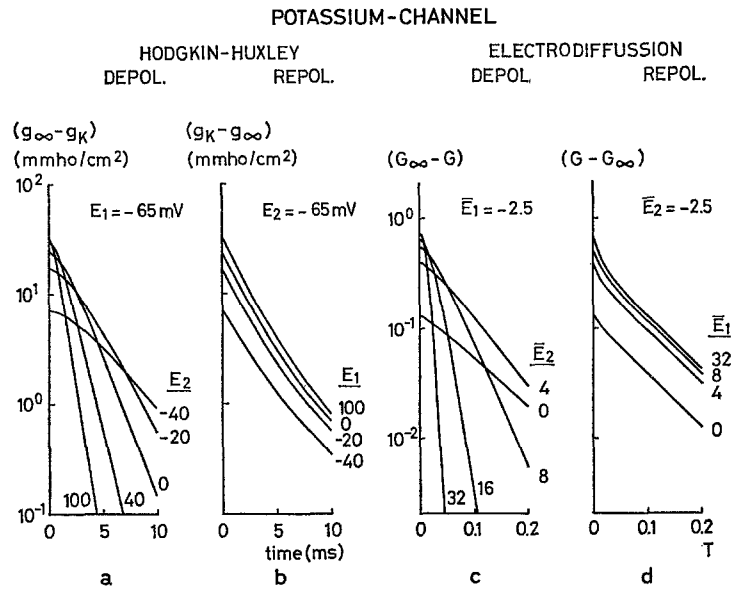

Fig. 4. The transient potassium-conductance deviation from the final value of the conductance on a logarithmic scale as a function of time. The same cases are shown as in Fig. 3. Note that the time constants (corresponding to the slopes of the curves) vary with the final potentials E_2 and $\bar{E}_2$ (*a* and *c*) and that the time constants are approximately independent of the initial potentials E_1 and $\bar{E}_1$ (*b* and *d*)

factor of $RT/F=24$ mV [*see under* Eq. (3)], $E=100$ mV corresponds to $\bar{E}\approx 4$. However, a possible explanation of this discrepancy will be given in the Discussion.

The kinetic properties of the two models are easily compared in Fig. 4, showing the conductance on a logarithmic scale for the same cases as in Fig. 3. The convex appearance of the depolarization curves (Fig. 4*a* and *c*) corresponds to the sigmoidal conductance increase in Fig. 3(*a*) and (*c*). It will be seen, by comparing the slopes of the curves in Fig. 4(*a*) and (*c*), that during depolarization the time constant is decreased when the potential step is increased, as discussed above. In both the HH and ED models repolarization means an approximately exponential decrease with the same time constant, independently of the initial potential (approximately linear and parallel slopes in Fig. 4*b* and *d*). A slight difference between the models is that the early conductance decrease during repolarization is faster in the ED model as compared with the more purely exponential fall in the HH conductance (Fig. 4*b* and *d*; *cf. also* Fig. 3*b* and *d*).

Model Parameters. A summary of many of the essential kinetic and steady-state properties of the HH and ED models is given in Fig. 5. Fig. 5(*a*) shows

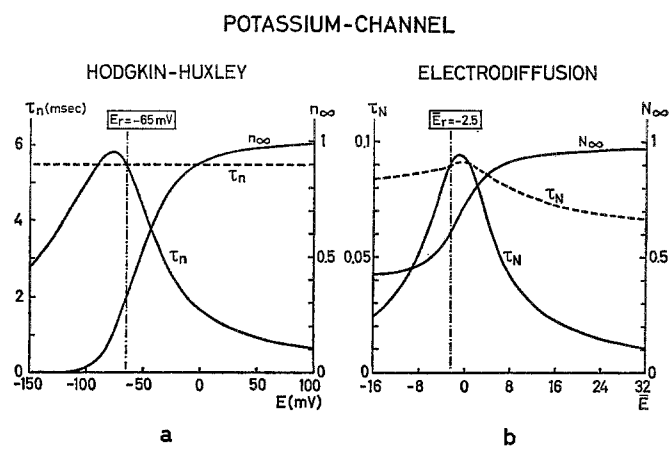

Fig. 5. Time constants (τ_n and τ_N) and steady-state parameters (n_∞ and N_∞) as a function of the membrane potential in the HH theory (*a*) and for the ED potassium model (*b*). The time constants are given for positive and negative potential steps to E or $\bar{E}$, respectively, from the resting potential E_r or $\bar{E}_r$ (continuous curves) and also for the case of restoration of the resting potential from E or $\bar{E}$ (dashed curves). Fig. (*b*) was calculated for $C_1 = 0.025$. N_∞ approaches $\sqrt[4]{C_1} = 0.40$, when E approaches $-\infty$

the HH parameters n_∞, corresponding to the steady-state conductance, and the time constant τ_n, which is an instantaneous function of the membrane potential. In Fig. 5(*b*), the corresponding parameters N_∞ and τ_N of the ED model are shown, as obtained by the curve-fitting procedure described above. The continuous time-constant curve in Fig. 5(*b*) was calculated for steps from the resting potential, and the dashed curve for restoration of the resting potential. These curves correspond to the continuous and dashed time-constant curves, respectively, in Fig. 5(*a*).

The qualitative similarities between Fig. 5(*a*) and (*b*) are obvious. The behaviors of the time constant and the steady-state conductance as functions of the membrane potential show in more detail the important features already discussed. As regards the kinetic properties, two important discrepancies can be seen in Fig. 5. First, the relative potential scales of the two models do not correspond to each other, as mentioned above. Second, the absolute potential scales are displaced with respect to the maximum of the continuous time-constant curves. The maximum of the ED model is centered around zero membrane potential, in contrast to the situation in the HH model, where the maximum is near, but below, the resting potential. These differences will be further commented upon in the Discussion.

The steady-state conductance parameter N_∞ (Fig. 5*b*) has a less steep variation than n_∞ (Fig. 5*a*). At negative potentials, N_∞ approaches the value

$\sqrt[4]{C_1} = 0.40$ (from Eqs. (10) and (4), in contrast to n_∞, which falls to zero. This means a low rectification ratio of the potassium ED regime, as compared with the squid axon data, a fact which Cole has pointed out [8].

Sodium Channel

Conductance Behavior. Fig. 6 shows the voltage-clamp conductance variation of the sodium inactivation in the HH model (*a* and *b*) and in the ED model (*c* and *d*). The upper halves of the figures show the results of hyperpolarizing steps away from and back to the resting potential, and the lower halves show the effects of depolarization and repolarization (*cf.* Fig. 2).

For all the different kinds of steps in Fig. 6, the conductance transients are approximately exponential for both models, except in the case of repolarizing the ED sodium channel, which at high potential steps produces a sigmoid conductance change.

In both models, the time constants corresponding to the conductance changes are high at small potential steps from the resting potential but decrease at higher values of the final potential (Fig. 6*a* and *c*). The rate at which the conductance decays, when the voltage-clamp potential is

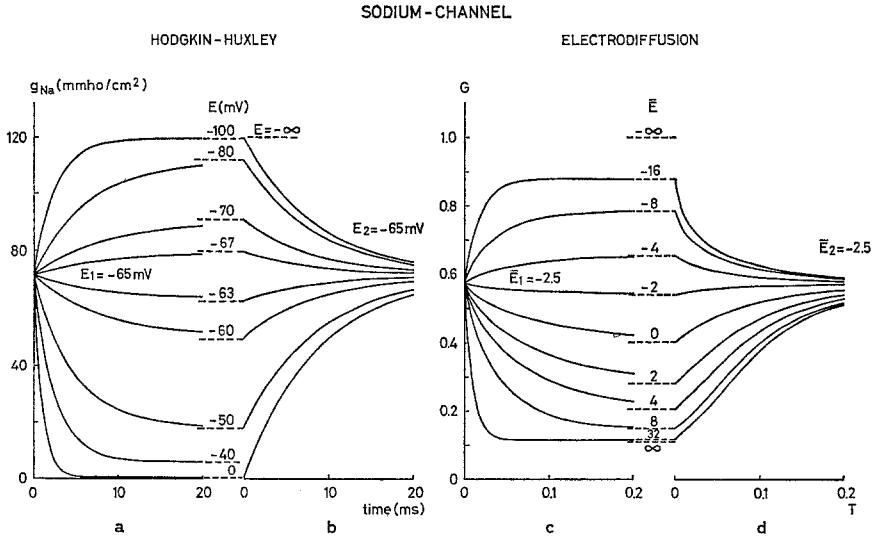

Fig. 6 Conductance response associated with sodium inactivation as a function of time under voltage clamp. Results from the HH model in (*a*) and (*b*) and from the ED model in (*c*) and (*d*). The potential steps were applied at $t=0$ from E_1 to E (*a*), from E to E_2 (*b*) and at $T=0$ from $\bar{E}_1$ to $\bar{E}$ (*c*) and from $\bar{E}$ to $\bar{E}_2$ (*d*). The upper halves of the figures correspond to a hyperpolarized state and the lower halves to depolarization (*a* and *c*) and repolarization (*b* and *d*). The following values were used: $E_r = -65$ mV, $\bar{E}_r = -2.5$ (resting potential), and $C_2 = 0.11$

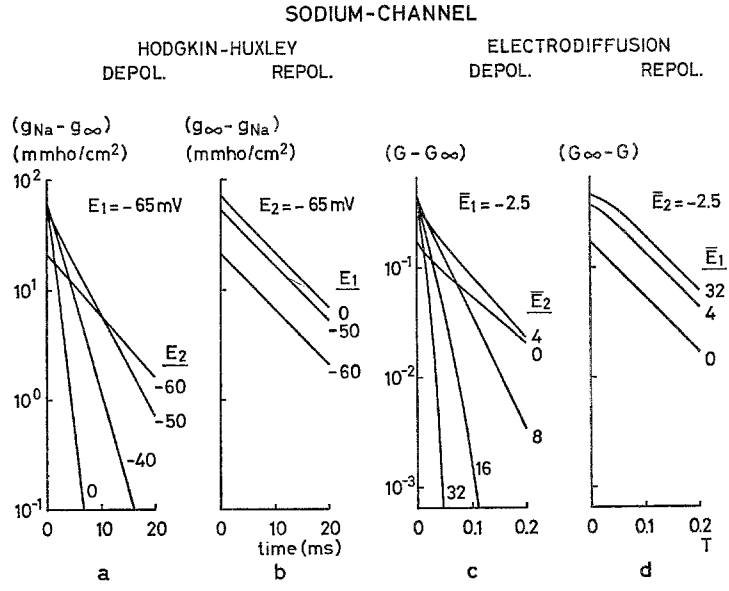

Fig. 7. Logarithmic conductance variation with time for the sodium inactivation. The same cases as in Fig. 6 are shown, but only for depolarization and repolarization, corresponding to the lower halves of Fig. 6. The conductance changes are mostly exponential (approximately straight lines). The time constant is approximately an instantaneous function of the final potential (*cf.* the slopes)

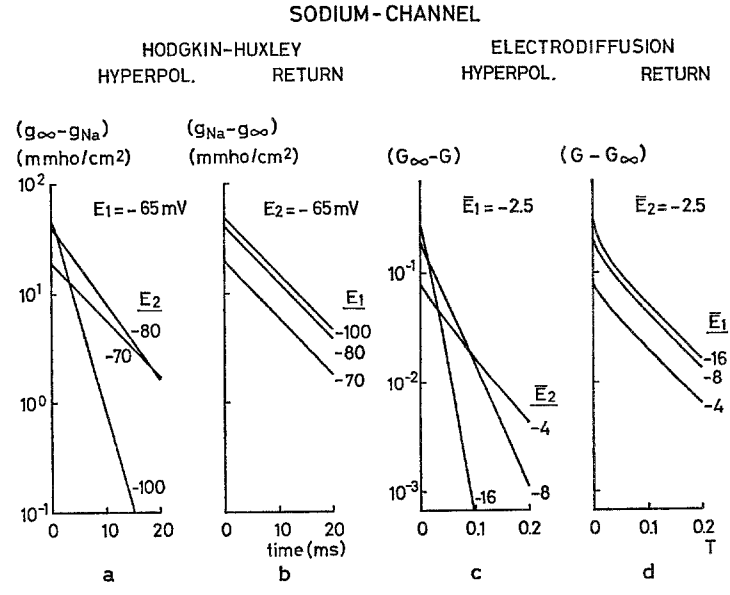

Fig. 8. Same as Fig. 7, but for the case of hyperpolarization from and back to the resting potential. Note the shape of the conductance response and time-constant behavior (*see* comment under Fig. 7)

restored, in the ED model is dependent on the height of the potential step (Fig. 6*d*). This is in contrast to the HH model, where the time constant is determined by the instantaneous potential (Fig. 6*b*).

This behavior of the time constant is more clearly seen on a logarithmic scale in Figs. 7 and 8 for the depolarizing and hyperpolarizing steps, respectively, as well as for restoring steps. In these figures, it is also possible to compare the curve form of the conductance changes. At high potential steps back to the resting potential, the ED model shows deviations from the exponential time course (Figs. 7*d* and 8*d*).

Model Parameters. Many of the fundamental properties of the ED and HH models are summarized in Fig. 9, which shows the equivalent ED parameters τ_H and H_∞ (*b*), compared with the corresponding HH parameters τ_h and h_∞ (*a*). The time constants are given for positive and negative potential steps from the resting potential (continuous lines τ_h and τ_H) and also for restoration to the resting potential (dashed lines).

Qualitatively, the ED model (Fig. 9*b*) shows many features in common with the HH theory (Fig. 9*a*). However, some discrepancies will be seen in Fig. 9. Most of these discrepancies were also phenomenologically present in the potassium case. The *maximum* of the continuous τ_H curve (*b*) is situated about $\bar{E}=0$, in contrast to the continuous τ_h curve (*a*), which is centered at a potential value slightly below the resting potential. Also, the potential scales ($\bar{E}$ and E) are different in the two models (*see* Discussion).

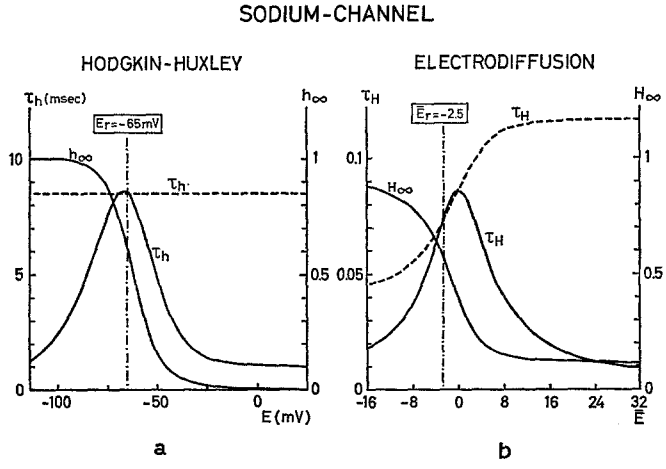

Fig. 9. Steady-state parameters, h_∞ and H_∞, and time constants, τ_h and τ_H, for the sodium inactivation as a function of the membrane potentials E and $\bar{E}$. The HH parameters are shown in (*a*) and the corresponding ED parameters in (*b*). The continuous time-constant curves are for potential steps from the resting potential (E_r or $\bar{E}_r$) and the dashed curves are for potential steps restoring the membrane potential. H_∞ approaches $C_1=0.11$ at high values of $\bar{E}$

In contrast to the behavior in the HH model, the restoration time constant τ_H of the ED model is fairly highly dependent on the initial potential (Fig. 9*b*). In the potassium ED channel, on the other hand, the restoration τ_N was approximately a function of the instantaneous potential (Fig. 5*b*), as in the HH model (Fig. 5*a*).

The steady-state parameter H_∞ approaches $C_2 = 0.11$ at high values of $\bar{E}$ in contrast to h_∞, which falls asymptotically to zero at high E values (Fig. 9). At large negative values of the potential, H_∞ approaches its final value 1 much more slowly than the h_∞ parameter. The values of h_∞ and H_∞ at the resting potential (E_r and $\bar{E}_r$, respectively) are, however, in excellent agreement with each other. This property will also be seen in Fig. 6, if the resting conductances are compared with the maximum conductances.

Discussion

Late Current

The properties of the ED models of the potassium activation and sodium inactivation, compared with the HH axon, are summarized in Table 1. The ED models have some inherent *similarities* with the HH equations. These similarities concern especially the kinetics:

(i) The shape of the conductance transients is well reproduced by the ED models.
(ii) The time constant is approximately a bell-shaped function of the instantaneous membrane potential.

The most important *discrepancies* are as follows:

(i) The time constant varies with the membrane potential much more slowly in the ED models than in the HH axon, and the maxima of the time constant curves are displaced relative to each other with respect to the membrane potential.
(ii) The rectification ratio in the ED models is too low.

The above similarities between the models have not been shown before, but the stated discrepancies have essentially been discussed by Cole [7, 8]. Possible explanations of the discrepancies will now be discussed.

The major uncertainty in the present theory is the constant-field assumption [11, 21] (*see* Agin [1] and Cole [7, 8] for discussions). In general, the constant-field approximation is, according to Cole, reasonably good for some steady-state situations, particularly at low ionic strengths, but open to question in the nonsteady-state [8].

Table 1. Summary of the approximate voltage-clamp properties of the ED model, as compared with the HH model

Properties	Potassium channel		Sodium channel	
	Similarities	Discrepancies	Similarities	Discrepancies
Kinetic properties				
Conductance time variation	Depolarization: sigmoidal increase Repolarization: exponential decrease		Exponential	*See text*
Time constant as a function of membrane potential				
Potential steps from $\bar{E}_r$	Bell-shaped	Maximum dislocated Different potential scales	Bell-shaped	Maximum dislocated Different potential scales
Restoring of $\bar{E}_r$	Constant			Not constant
Steady-state properties				
Resting conductance		Higher in the ED model	Good agreement	
Steady-state conductance parameter as a function of membrane potential	Sigmoidal increase	$\bar{E} \gg 0$: ED conductance too low $\bar{E} \to -\infty$: ED conductance too high	Sigmoidal decrease	$\bar{E} \to \infty$: ED conductance too high $\bar{E} \ll 0$: ED conductance too low

The introduction of Poisson's equation is needed to enable us to drop the assumption of a constant electric field. The mathematical difficulties then increase considerably. However, the single-ion problem can be solved by linearization. It has been shown [14] that for this case the bell-shaped time-constant curve is still obtained but with the following modifications: (i) the maximum is lowered and shifted towards the equilibrium potential at high concentrations and (ii) there is a reduced discrepancy between the E and $\bar{E}$ scales. These conclusions are in favor of the single-ion ED models.

A possible way to account for the differences in the absolute membrane potential scales may follow from the introduction of different mobilities

for diffusion and electric migration. The latter assumption was used by Agin and Schauf [2, 3], who introduced $\alpha = RTu/D$ as the ratio of the electric mobility and the diffusion mobility. According to Agin and Schauf, α varies with the migration mechanism. They suggested $\alpha = 3$ for potassium and sodium. This value may be compared with the values obtained if the present ED models are to fit the HH axon on the assumption of different mobilities. The two kinds of mobility will enter into the diffusional and electrical flux terms in Eq. (1) to give $\bar{E} = E\alpha F/RT$ [*see* Eq. (3)]. When the widths at half the maximum value of the time constants are compared in Figs. 5 and 9, $\alpha_K = 3.4$ and $\alpha_{Na} = 9.4$ are obtained for potassium and sodium, respectively. These α-values are somewhat reduced, when the constant-field assumption is dropped [14].

The difference in the relative membrane-potential scales may be connected with the limitations of the constant-field assumption [14], as mentioned above, but may also be a surface charge effect. In the presence of fixed surface charges on the axon membrane, the potential across the ED regimes is different from the potential measured between the aqueous phases. A layer of fixed negative charges on the inside of the squid axon membrane has been proposed to account for the shift of the sodium inactivation caused by changes in the internal ionic strength [5]. It has also been shown that the conductance of phospholipid bilayer membranes is strongly dependent on the surface potential emanating from the net charge of the polar head groups of the lipid [18].

The discrepancies (ii) in the rectification ratios may be explained by assuming differences in the internal and the external concentrations in the models, as compared with the concentrations in the solutions surrounding the axon membrane (*cf.* the conception of partition coefficient). A lower value of C_1 in the potassium channel and of C_2 in the sodium channel, as compared with the concentration ratios used in the present calculations, would give a better agreement between the steady-state properties of the ED models and the HH axon (*see* Figs. 5 and 9). As regards the potassium channel, a lower value of C_1 will also correspond to a more pronounced sigmoidal shape of the conductance increase during depolarization [13].

A quantitative comparison of the maximum values of the time constants of the ED and HH models yields an estimation of the sodium and potassium diffusion mobilities u_{Na} and u_K. From Figs. 5 and 9, $u_K = 0.35 \times 10^{-14}$ and $u_{Na} = 0.21 \times 10^{-14}$ (cm^2 mole per joule sec) are calculated, using the time-normalization relation in Eq. (3), together with $\delta = 70$ Å. These values may be compared with the ionic mobilities in free solution, u_K^{free} and u_{Na}^{free},

resulting in $u_K/u_K^{free} \approx u_{Na}/u_{Na}^{free} = 0.5 \times 10^{-5}$. These kinds of estimations have also been made and discussed for potassium by Cole [7]. An interesting fact is that the mobility ratio $u_K/u_{Na} = 1.65$, obtained with ED models, compares well with the corresponding ratio for free diffusion $u_K^{free}/u_{Na}^{free} = 1.50$.

Recently, Stark, Ketterer, Benz, and Läuger [20] have performed electrical relaxation experiments with phosphatidylinositol bilayer membranes in the presence of valinomycin and potassium. The measured time constant shows a dependence on the potential jump which is qualitatively similar to the results in the present paper (Figs. 5 and 9), though the experimental results were obtained with equal concentrations in the outer solutions. This agreement further emphasizes the fact that electrodiffusion theory can account for experimental properties of lipid bilayer membranes containing neutral molecular carriers of ions [9].

Early Current

The distribution of sodium and potassium across the axon membrane has made it possible to identify the potassium activation and sodium inactivation with single-ion electrodiffusion processes. It is difficult, however, to explain the sodium activation with the same approach without making further assumptions. That the mechanism for the sodium activation is of a different nature from the other processes is supported by the facts (i) that the resting sodium conductance is much lower than the potassium conductance and (ii) that the process of sodium activation is more than 10 times faster than the sodium inactivation and the potassium activation.

A convection-diffusion (CD) model has been proposed in an earlier publication [13] as being responsible for the early current. If this model is to be combined with the ED models in the present paper, modifications of the theories must be introduced to explain the great difference in the time constants between the early and late currents. An important modification is to drop the constant-field assumption. It has been shown that, for this case, the time constant of a single-ion electrodiffusion model is highly dependent on the ionic concentration [14].

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