A Physical Model for the Passage of Ions through an Ion-specific Channel—
I. The Sodium-like Channel

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ABSTRACT

The sodium-like channel is idealized as a pore containing one electrostatic binding site through which ions pass one at a time by executing a thermally driven random walk under the influence of an electric field. Both exact formal solutions and simple approximate solutions are obtained for the model's current-voltage behavior. The relationship of these forms to that predicted by Goldman is discussed.

INTRODUCTION

The equation most commonly used to describe the current carried by an ionic species across a unit area of membrane is that given by Goldman [2], which may be written

$$J^{(j)} = 1000\mathfrak{F} z^{(j)} P^{(j)} \left[\frac{\frac{1}{2}\kappa_m^{(j)}}{\sinh \frac{1}{2}\kappa_m^{(j)}} \right] \left[a_o^{(j)} e^{-\frac{1}{2}\kappa_m{}^{(j)}} - a_i^{(j)} e^{\frac{1}{2}\kappa_m{}^{(j)}} \right], \tag{1}$$

where $\kappa_m^{(j)} = \mathrm{e} z^{(j)} V_m / kT$, e being the charge on the proton ($\doteq 1.602 \times 10^{-19}$ C); k is Boltzmann's constant ($\doteq 1.381 \times 10^{-23}$ J/°K); T (°K) is the absolute temperature; $z^{(j)}$ is the valence of the species; $P^{(j)}$ (ms^{-1}) is the

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permeability of the membrane to that speices; $\mathcal{F}$ is the Faraday ($\doteq 9.649 \times 10^4$ C mol^{-1}), V_m (V) is the electric scalar potential of the bulk solution inside a volume bounded by the membrane with respect to that outside the volume; and $a_o^{(j)}$ and $a_i^{(j)}$ (mol/l) are, respectively, the activities in the bulk solutions outside and inside that volume.

This equation was originally derived [2] under the somewhat restrictive assumptions of constant-field theory, and since its introduction has been given more general derivations by a number of workers. One of these was that of Pickard [10], who showed that Eq. (1) would hold if certain conditions of mathematical regularity were met and if:

(i) The net flux of species j varied linearly with both $a_o^{(j)}$ and $a_i^{(j)}$ and did not depend upon the activities of other ions. This embodies the ideas of both linearity and a sort of independence.

(ii) In the special case $a_o^{(j)} = a_i^{(j)}$ the net flux reverses exactly whenever V_m is reversed. This is a symmetry condition.

(iii) The net flux is zero whenever the membrane voltage equals the so-called Nernst potential for the ion,

$$V_N^{(j)} = \frac{kI}{ez^{(j)}} \ln \frac{a_o^{(j)}}{a_i^{(j)}}. \tag{2}$$

(iv) Whenever $a_o^{(j)} = a_i^{(j)}$, the net flux is linearly proportional to V_m for all V_m. This is a condition of global ohmicity.

This derivation possesses the advantage of assuming nothing about the specific processes by which an ion moves passively through a membrane. But it leaves unanswered the question of why a membrane should, with respect to a given ionic species, admit of a flux which is either linear, independent, symmetric, Nernstian, or globally ohmic. In order to see why such conditions might obtain for a given flux, it is necessary first to establish a physical model of the permeation process, and second to show that these conditions are consequences of it.

The objects of this paper are (i) to construct an easily visualized physical model for the passage of an ion from one bulk solution to the other by way of channels with properties somewhat akin to those of the sodium channel described by Bertil Hille [3–5], (ii) to quantify this model, and (iii) to determine to what extent it implies (or assumes) independent, linear, symmetric, Nernstian, and globally ohmic behavior for this ion flux.

THE PHYSICAL MODEL

Consider first an ion in bulk solution on one side of the membrane. Unless it is quite close to the membrane, its motion will be largely indifferent to the presence of the membrane, since it will undergo no collisions significantly influenced by the mechanical properties of the membrane, and since the membrane's electrostatic properties will largely be hidden by Debye shielding; at best the ion will undergo a slow drift in the electric field associated with current flow through the membrane. Eventually, however, the ion may approach one end of a channel, pass through the Debye shield, and enter what will be termed that channel's "zone of influence". This "zone of influence" will be loosely defined as a neighborhood about the end of the channel within which the ion either is influenced by the electrostatic properties of the channel and/or has no other ions between it and the mouth of the channel. Once within a zone of influence, either the ion will pass through the channel and into bulk solution on the other side of the membrane or it will return to the bulk solution on the side from which it first approached; the chance of its successfully passing through will be called the transition probability. If the solutions bathing the membrane are so dilute that the interaction of a particular ion with a channel will not be interfered with by other ions interacting with the same channel, then $J^{(j,k)}$, the current per unit area (A m^{-2}) carried by ions of type j through channels of type k will be given by[1]

$$J^{(j,k)} = \mathrm{e}z^{(j)}\gamma^{(k)}\left[\rho_o^{(j,k)}\tau_{oi}^{(j,k)} - \rho_i^{(j,k)}\tau_{io}^{(j,k)}\right], \tag{3}$$

where $\gamma^{(k)}$ (channels/m^2) is the channel density, $\rho_o^{(j,k)}$ (ions/s) is the arrival rate of ions of type j in the zone of influence at the outer end of a channel of type k, $\tau_{oi}^{(j,k)}$ (dimensionless) is the probability of transition which obtains immediately after arrival at the outer end, and $\rho_i^{(j,k)}$ and $\tau_{io}^{(j,k)}$ are analogously defined. Equations (1) and (3) are at least superficially consistent.

To effect a calculation of arrival rate is by no means simple, since, as Hille [3] has pointed out, the cage effect of the solvent favors an ion's migrating but slowly from its present general location. However, this rate should at least be linearly proportional to the activity of the ion near the zone of influence. And, in the mean, this presumable depends upon both the bulk concentration of the ion and the distribution of electric scalar potential about the mouth of the channel. Since [3] these channels, if uniformly spaced, will be at least 50 nm apart, measurements of gross membrane surface potential will reveal little or nothing about the potential near a channel's mouth: neither its general level, nor its decay normal to the membrane surface, nor its angular variation. Therefore, in the absence of

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[1] The term "channel" is here used in the sense of a geometrically defined transmembrane pathway of specifed properties. If the molecules delimiting such a pathway can rearrange to yield pathways of other properties, then each such state has a separate superscript.

compelling evidence to the contrary, it will be assumed that arrival rates can be satisfactorily approximated by

$$\rho_o^{(j,k)} = \beta a_o^{(j)} \tag{4a}$$

and

$$\rho_i^{(j,k)} = \beta a_i^{(j)} \tag{4b}$$

where β ((ions/s)/(mol/1)) is a constant. That is, it will be assumed that the arrival rate of ions of species j is proportional to that species's concentration in bulk solution as modified by an activity coefficient.

It was pointed out by Hille [3] that the data for normally polarized squid axons suggest that almost every sodium ion which arrives at an open sodium channel passes through. This suggests that the process of transit is so rapid that, within such a channel, there is little interaction between transiting charges. It will therefore be assumed for this paper that the interaction of an ion with a channel is completed without direct influence from other ions. That is, it will be assumed that the transition probability of an interacting ion can be computed by considering only the properties of that ion and of the channel. This assumption is, of course, an independence principle.

FORMAL SOLUTION: CONTINUUM MODEL

To obtain an approximate value of a transition probability it is convenient to proceed as follows. Consider the computation of $\tau_{oi}^{(j,k)}$. The interaction will begin somewhere between $x = -d - \delta_o^{(k)}$ and $x = -d$, where $\pm d$ (m) are the coordinates of the outer surfaces of the membrane and $\delta_o^{(k)}$ (m) is a distance beyond which the existence of the outer mouth of the channel has been effectively masked by Debye shielding; presumably, in solutions of reasonable ionic concentration, it will be of the order of 10 to 20 nm or less. The interaction will have ended by the time that the particle has crossed either $x = -d - \delta_o^{(k)}$ or $x = d + \delta_i^{(k)}$, where $\delta_i^{(k)}$ (m) is defined analogously to $\delta_o^{(k)}$. The value of x at which the interaction begins will have a probability distribution $\eta_o^{(j,k)}(x)$, where $\eta_o^{(j,k)}(x)$ is zero outside the range $(-d - \delta_o^{(k)}, -d)$ and $\int_{-d-\delta_o^{(k)}}^{-d} \eta_o^{(j,k)}(x)\,dx = 1$. The expected transition probability $\tau_{oi}^{(j,k)}$ will then be just the probability that a particle with an initial distribution of location $\eta_o^{(j,k)}(x)$ will eventually random-walk across the absorbing boundary $x = d + \delta_i^{(k)}$ before it walks across the absorbing boundary $x = -d - \delta_o^{(k)}$. This is formally analogous to the problem of the diffusion in a potential field of a substance whose initial distribution is $\eta_o^{(j,k)}(x)$; computing the transition probability corresponds to calculating the fraction of the substance eventually absorbed by the boundary at $x = d + \delta_i^{(k)}$.

The relevant set of equations is then (cf. Ref. 7)

$$\frac{\partial \xi(x;t)}{\partial t} = \frac{\partial}{\partial x}\left\{ \frac{1}{\mu^{(j,k)}(x)}\left[kT\frac{\partial \xi}{\partial x} + z^{(j)}\mathrm{e}\xi\frac{\partial \psi^{(j,k)}}{\partial x}\right]\right\}, \tag{5}$$

$$\xi(-d-\delta_o^{(k)};t)=\xi(d+\delta_i^{(k)};t)=0, \tag{6a,6b}$$

$$\xi(x;0)=\eta_o^{(j,k)}(x), \tag{6c}$$

where $\xi(x;t)$ (ions/m) is the one-dimensional density of the fictitious diffusing species, where $\mu^{(j,k)}(x)$ (kg/s) is the effective frictional coefficient of the species in the channel, and where $\psi^{(j,k)}(x)$ (V) is the electric scalar potential perceived by a type-j ion at a position x in a type-k channel. Equations (5) and (6) may appear to be equivalent to a standard electrodiffusion treatment of ion flow, but they are not. First, the philosophy underlying them is different: they are for use in describing what, on the average, happens to a single ion rather than temporal shifts in the distribution of a large number of ions. Second, the potential $\psi^{(j,k)}(x)$ is due entirely to ions in the bulk solutions and to the electromagnetic properties of the channel: it is independent of supposed intrachannel densities of moving charges.

The fraction of ions exiting at $x=d+\delta_i^{(k)}$ will be just

$$-\int_0^\infty dt\left\{ \frac{1}{\mu^{(j,k)}(x)}\left[kT\frac{\partial \xi}{\partial x} + z^{(j)}\mathrm{e}\xi\frac{\partial \psi^{(j,k)}}{\partial x}\right]\right\}_{x=d+\delta_i^{(k)}}. \tag{7}$$

If $\mu^{(j)}$ is the effective frictional coefficient in free solution, then

$$\tau_{oi}^{(j,k)} = -\frac{kT}{\mu^{(j)}}\int_0^\infty\left[\frac{\partial \xi}{\partial x}\right]_{x=d+\delta_i^{(k)}} dt, \tag{8}$$

since $\xi(d+\delta_i^{(k)};t)=0$ by Eq. (6b), and since the total fraction exciting from both ends is unity by the assumptions on $\eta_o^{(j,k)}(x)$.

To evaluate Eq. (8) it is convenient to take the Laplace transforms of Eqs. (5) and (6) to obtain

$$-\eta_o^{(j,k)}(x)+s\Xi = \frac{d}{dx}\left\{ \frac{1}{\mu^{(j,k)}(x)}\left[kT\frac{d\Xi}{dx} + z^{(j)}\mathrm{e}\Xi\frac{d\psi^{(j,k)}}{dx}\right]\right\}, \tag{9}$$

$$\Xi(-d-\delta_o^{(k)};s)=\Xi(d+\delta_i^{(k)};s)=0, \tag{10a, 10b}$$

where $\Xi(x;s)=\int_0^\infty \xi(x;t)e^{-st}dt$. Letting $s\to 0$ and setting $\Xi(x;0)=\tilde{\Xi}(x)$

yields

$$\tau_{oi}^{(j,k)} = -\frac{kT}{\mu^{(j)}}\left[\frac{d\tilde{\Xi}}{dx}\right]_{x=d+\delta_i^{(k)}}, \tag{11}$$

$$-\eta_o^{(j,k)} = \frac{d}{dx}\left\{\frac{1}{\mu^{(j,k)}}\left[kT\frac{d\tilde{\Xi}}{dx} + z^{(j)}e\tilde{\Xi}\frac{d\psi^{(j,k)}}{dx}\right]\right., \tag{12}$$

$$\tilde{\Xi}(-d-\delta_o^{(k)}) = \tilde{\Xi}(d+\delta_i^{(k)}) = 0. \tag{13a, 13b}$$

Thus, finding the transition probability reduces to effecting a solution of Eqs. (12) and (13) for a special case: namely, $d\tilde{\Xi}/dx$ evaluated at $x=d+\delta_i^{(k)}$.

To evaluate Eq. (11), it is convenient to set

$$H_o^{(j,k)}(x) = \int_{-d-\delta_o^{(k)}}^{x} \eta_o^{(j,k)}(x')\,dx' \tag{14}$$

and reduce Eq. (12) to

$$-\frac{\mu^{(j,k)}(x)}{kT}\left[H_o^{(j,k)}(x) + \mathcal{K}_1\right] = \frac{d\tilde{\Xi}}{dx} + \left[\frac{z^{(j)}e}{kT}\frac{d\psi^{(j,k)}}{dx}\right]\Xi, \tag{15}$$

where $\mathcal{K}_1$ is a constant. Equation (15) is linear and of first order; its solution can be written down at once as

$$\Xi(x) = e^{-\kappa^{(j,k)}}\left[-\int_{-d-\delta_o^{(k)}}^{x}\frac{\mu^{(j,k)}(x')}{kT}\left[H_o^{(j,k)}(x') + \mathcal{K}_1\right]e^{\kappa^{(j,k)}}\,dx' + \mathcal{K}_2\right], \tag{16}$$

where $\kappa^{(j,k)}(x) = (z^{(j)}e/kT)\psi^{(j,k)}(x)$. Equations (13), (14), and (15) can then be applied to Eqs. (11) and (16) to obtain $\mathcal{K}_2 = 0$ and

$$\tau_{oi}^{(j,k)} = 1 + \mathcal{K}_1, \tag{17}$$

where $\mathcal{K}_1$ is given by

$$0 = \int_{-d-\delta_o^{(k)}}^{d+\delta_i^{(k)}} \mu^{(j,k)}(x)\left[H_o^{(j,k)}(x) + \mathcal{K}_1\right]e^{\kappa^{(j,k)}(x)}\,dx. \tag{18}$$

Hence,

$$\tau_{oi}^{(j,k)} = 1 - \frac{\displaystyle\int_{-d-\delta_o^{(k)}}^{d+\delta_i^{(k)}} \mu^{(j,k)}(x)H_o^{(j,k)}(x)e^{\kappa^{(j,k)}(x)}\,dx}{\displaystyle\int_{-d-\delta_o^{(k)}}^{d+\delta_i^{(k)}} \mu^{(j,k)}(x)e^{\kappa^{(j,k)}(x)}\,dx}. \tag{19}$$

Since $H_o^{(j,k)}(x)=1$ over $(-d, d+\delta_i^{(k)})$, Eq. (19) reduces to

$$\tau_{oi}^{(j,k)}=\frac{\displaystyle\int_{-d-\delta_o^{(k)}}^{-d}\mu^{(j,k)}(x)\left[1-H_o^{(j,k)}(x)\right]e^{\kappa^{(j,k)}(x)}\,dx}{\displaystyle\int_{-d-\delta_o^{(k)}}^{d+\delta^{(k)}}\mu^{(j,k)}(x)e^{\kappa^{(jk)}(x)}\,dx}. \tag{20}$$

Similarly,

$$\tau_{io}^{(j,k)}=\frac{\displaystyle\int_{d}^{d+d_i^{(k)}}\mu^{(j,k)}(x)\left[1+H_i^{(j,k)}(x)\right]e^{\kappa^{(j,k)}(x)}\,dx}{\displaystyle\int_{-d-\delta_o^{(k)}}^{d+\delta_i^{(k)}}\mu^{(j,k)}(x)e^{\kappa^{(j,k)}(x)}\,dx}, \tag{21}$$

where

$$H_i^{(j,k)}(x)=-\int_x^{d+\delta_i^{(k)}}\eta_i^{(j,k)}(x')\,dx' \tag{22}$$

and $\eta_i^{(j,k)}(x)$ is defined in analogy to $\eta_o^{(j,k)}(x)$.

This completes the description of the model and its formal solution. What remains is to evaluate, for suitable special cases, the integrals occurring in Eqs. (14), (20), (21), and (22) to obtain useful expressions for the current $J^{(j,k)}$.

APPLICATIONS OF THE CONTINUUM SOLUTION

The combination of Eqs. (3), (4), (20), and (21) yields

$$J^{(j,k)}=\mathrm{e}z^{(j)}\gamma^{(k)}\beta\,\frac{\displaystyle a_o^{(j)}\int_{-d-\delta_o^{(k)}}^{-d}\mu^{(j,k)}\left[1-H_o^{(j,k)}\right]e^{\kappa^{(j,k)}}\,dx-a^{(j)}\int_{d}^{d+\delta_i^{(k)}}\mu^{(j,k)}\left[1+H_i^{(j,k)}\right]e^{\kappa^{(j,k)}}\,dx}{\displaystyle\int_{-d-\delta_o^{(k)}}^{d+\delta_i^{(k)}}\mu^{(j,k)}e^{\kappa^{(j,k)}}\,dx}. \tag{23}$$

Although Eq. (23) is too general to be of numerical utility, it nevertheless does reveal a number of interesting properties. First, it is clearly of the form $[a_o^{(j)}F_1(V_m)-a_i^{(j)}F_2(V_m)]/F_3(V_m)$; that is, the current is at least of a general form which includes the Goldman expression as a special case, and the expression for the voltage at which $J^{(j,k)}$ is zero includes the Nernst expression as a special case. Second, while F_1 and F_2 are independent of the variation of $\mu^{(j,k)}(x)$ within the channel, F_3 is not; and, in particular, steric hindrance within the channel will markedly increase $\mu^{(j,k)}(x)$ and $F_3(V_m)$ with a consequent decrease in $J^{(j,k)}$. Third, for the important case of cation influx at large negative V_m, $J^{(j,k)}$ will be maximal for $\kappa^{(j,k)}(x)$ which fall off rapidly before $1-H_o^{(j,k)}(x)$ has decayed to zero; for example, if a sodium channel contains a single negative site, as is suggested by the experiments of Hille [5], then, both from these considerations and from considerations of ionic selectivity, that site's most advantageous location would be near the outer surface of the membrane, and this is precisely where the data on tetrodotoxin blockage [8] suggest that it may be.

To obtain numerically useful expressions it is convenient to make a number of simplifying assumptions: (i) $\delta_o^{(k)}=\delta_i^{(k)}=\delta^{(k)}$; (ii) $\mu^{(j,k)}(x)=\mu^{(j)}$ over $(-d-\delta^{(k)}, -d)$ and $(d, d+\delta^{(k)})$; (iii) $\eta_o^{(j)}=\delta(x+d+\delta^{(k)}/2)$ and $\eta_i^{(j)}=\delta(x-d-\delta^{(k)}/2)$. Equation (23) then assumes the simpler form[2]

$$J^{(j,k)}=\mathrm{e}z^{(j)}\gamma^{(k)}\beta\mu^{(j)}\frac{a_o^{(j)}\displaystyle\int_{-d-\delta^{(k)}}^{-d-\delta^{(k)}/2}e^{\kappa^{(j,k)}}\,dx-a_i^{(j)}\int_{d+\delta^{(k)}/2}^{d+\delta^{(k)}}e^{\kappa^{(j,k)}}\,dx}{\displaystyle\int_{-d-\delta^{(k)}}^{d+\delta^{(k)}}\mu^{(j,k)}e^{\kappa^{(j,k)}}\,dx}. \tag{24}$$

Let it be assumed further that

$$\begin{aligned}\kappa^{(j,k)}(x) &= \frac{z^{(j)}\mathrm{e}}{kT}\left[-\tfrac{1}{2}V_m+\psi_c^{(k)}(x)\right] && \\ &= -\tfrac{1}{2}\kappa_m^{(j)}+\kappa_c^{(j,k)}(x), && x<-d, \quad (25\text{a})\\ &= \tfrac{1}{2}\kappa_m^{(j)}\frac{x}{d}+\kappa_c^{(j,k)}(x), && -d<x<d, \quad (25\text{b})\\ &= \tfrac{1}{2}\kappa_m^{(j)}+\kappa_c^{(j,k)}(x), && x>d, \quad (25\text{c})\end{aligned}$$

where $\kappa_c^{(j,k)}(x)$ is a "correction" term which is negligible outside $(-d-\delta^{(k)}, d+\delta^{(k)})$ and which takes into account the effects of surface potentials, charged sites along the channel, and other deviations from what one would expect on the basis of the most elementary constant-field approach to the

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[2] Except for restricted forms of $\kappa^{(j,k)}(x)$, Eq. (24) will be non-Nernstian. This appears to be a consequence of the fact that an ion can be subjected to quite dissimilar electric fields at the two ends of a channel. Equivalently, the electromagnetic properties of a channel can be said to modify the effective ion activities at the mouths of the channel.

problem of determining $\kappa^{(j,k)}(x)$, This then reduces Eq. (24) to

$$J^{(j,k)}=ez^{(j)}\beta\gamma^{(k)}\,\frac{a_o^{(j)}e^{-\kappa_m^{(j)}/2}\int_{-d-\delta^{(k)}}^{-d-\delta^{(k)}/2}e^{\kappa_c^{(j,k)}}\,dx-a_i^{(j)}e^{\kappa_m^{(j)}/2}\int_{d+\delta^{(k)}/2}^{d+\delta^{(k)}}e^{\kappa_c^{(j,k)}}\,dx}{e^{-\kappa_m^{(j)}/2}\int_{-d-\delta^{(k)}}^{-d}e^{\kappa_c^{(j,k)}}\,dx+\int_{-d}^{d}\dfrac{\mu^{(j,k)}(x)}{\mu^{(j)}}\times e^{(\kappa_m^{(j)}/2)x/d+\kappa_c^{(j,k)}}\,dx+e^{\kappa_m^{(j)}/2}\int_{d}^{d+\delta^{(k)}}e^{\kappa_c^{(j,k)}}\,dx}. \tag{26}$$

But even this is too complicated, and still more simplifying assumptions must be made to achieve results of practical utility.

Consider, therefore, what may be termed a "Goldman limit":

$$\mu^{(j,k)}(x)=\mu^{(j)},\qquad -d<x<d, \tag{27}$$

$$\kappa_c^{(j,k)}=\kappa_o^{(j,k)}\,\frac{x+(d+\delta^{(k)})}{\delta^{(k)}},\qquad -(d+\delta^{(k)})<x<-d, \tag{28a}$$

$$=\left(\kappa_i^{(j,k)}-\kappa_o^{(j,k)}\right)\frac{x}{2d}+\tfrac{1}{2}\left(\kappa_i^{(j,k)}+\kappa_o^{(j,k)}\right),\qquad -d<x<d, \tag{28b}$$

$$=\kappa_i^{(j,k)}\,\frac{(d+\delta^{(k)})-x}{\delta^{(k)}},\qquad d<x<(d+\delta^{(k)}), \tag{28c}$$

where $\kappa_o^{(j,k)}$ and $\kappa_i^{(j,k)}$ are dimensionless constant surface potentials defined in analogy with Eq. (25). With this constant-field-type assumption, the equation for current finally assumes a tractable form:

$$\begin{aligned}J^{(j,k)}={}&ez^{(j)}\gamma^{(k)}\beta\frac{\delta^{(k)}}{2d}\left\{a_o^{(j)}e^{-\frac{1}{2}\kappa_m^{(j)}}\left[\frac{e^{\frac{1}{2}\kappa_o^{(j,k)}}-1}{\kappa_o^{(j,k)}}\right]-a_i^{(j)}e^{\frac{1}{2}\kappa_m^{(j)}}\left[\frac{e^{\frac{1}{2}\kappa_i^{(j,k)}}-1}{\kappa_i^{(j,k)}}\right]\right\}\\&\times\left\{\frac{\delta^{(k)}}{2d}e^{-\frac{1}{2}\kappa_m^{(j)}}\left[\frac{e^{\frac{1}{2}\kappa_o^{(j,k)}}-1}{\kappa_o^{(j,k)}}\right]+\frac{\delta^{(k)}}{2d}e^{\frac{1}{2}\kappa_m^{(j)}}\left[\frac{e^{\frac{1}{2}\kappa_i^{(j,k)}}-1}{\kappa_i^{(j,k)}}\right]\right.\\&\left.+e^{\frac{1}{2}\kappa_i^{(j,k)}+\frac{1}{2}\kappa_o^{(j,k)}}\frac{\sinh\frac{1}{2}\left(\kappa_m^{(j)}+\kappa_i^{(j,k)}-\kappa_o^{(j,k)}\right)}{\frac{1}{2}\left(\kappa_m^{(j)}+\kappa_i^{(j,k)}-\kappa_o^{(j,k)}\right)}\right\}^{-1}.\end{aligned} \tag{29}$$

when $\kappa_i^{(j,k)}$ and $\kappa_o^{(j,k)}$ are negligible and $\delta^{(k)}/2d\ll 1$, this reduces to Eq. (1), the classical Goldman expression.

Eq. (29) also predicts inward-going rectification: when $\kappa_o^{(j,k)}=0$ and $\delta^{(k)}/2d \ll 1$,

$$J^{(j,k)} \propto \left(\kappa_m^{(j)}+\kappa_i^{(j,k)}\right)\frac{\frac{1}{2}a_o^{(j)}-a_i^{(j)}e^{\kappa_m^{(j)}}\left(e^{\frac{1}{2}\kappa_i^{(j,k)}}-1\right)/\kappa_i}{e^{\kappa_m^{(j)}+\kappa_i^{(j,k)}}-1}. \tag{30}$$

As $\kappa_m^{(j)} \to -\infty$, $J^{(j,k)} \propto -\frac{1}{2}(\kappa_m^{(j)}+\kappa_i^{(j,k)})a_o^{(j)}$. As $\kappa_m^{(j)} \to +\infty$, $J^{(j,k)} \propto -(\kappa_m^{(j)}+\kappa_i^{(j,k)})a_i^{(j)}(e^{\frac{1}{2}\kappa_i^{(j,k)}}-1)/(\kappa_i^{(j,k)}e^{\kappa_i^{(j,k)}})$. This, although it is inward-going rectification, is not of the form predicted classically (cf. Ref. 1): the classical result has a limiting form for $\kappa_m^{(j)} \to +\infty$ in which the coefficient of $a_i^{(j)}$ is $e^{-\kappa_i^{(j,k)}}(\kappa_m^{(j)}+\kappa_i^{(j,k)})$ rather than that given above.

Beginning with Eq. (26), it is also possible to gain a clearer understanding of dynamics of a normal sodium channel. $J^{(j,k)}$ will seemingly be maximized by locating a negative charge site near the outer end of the channel, since the second term of the denominator will thereby be minimized with respect to the first term. This feeling can be quantified for the limiting case of a single negative site located at $x=-d$ by examining Eq. (29). For the sake of simplicity it is desirable to set $\kappa_i^{(j,k)}=0$, to consider inward (associated with $a_o^{(j)}$) and outward (associated with $a_i^{(j)}$) currents separately, and to examine only the ratios $\mathcal{R}_{\text{in}}$ and $\mathcal{R}_{\text{out}}$, where $\mathcal{R}_{\text{in}}$ is the ratio of the inward current with $\kappa_o^{(j,k)} \neq 0$ to the inward current with $\kappa_o^{(j,k)}=0$, and where $\mathcal{R}_{\text{out}}$ is analogously defined. Thus,

$$\mathcal{R}_{\text{in}}=\frac{e^{\frac{1}{2}\kappa_o^{(j,k)}}-1}{\frac{1}{2}\kappa_o^{(j,k)}}\,\frac{\dfrac{\delta^{(k)}}{2d}\left[\frac{1}{2}+\frac{1}{2}e^{\kappa_m^{(j)}}\right]+\dfrac{e^{\kappa_m^{(j)}}-1}{\kappa_m^{(j)}}}{\dfrac{\delta^{(k)}}{2d}\left[\dfrac{e^{\frac{1}{2}\kappa_o^{(j,k)}}-1}{\kappa_o^{(j,k)}}+\frac{1}{2}e^{\kappa_m^{(j)}}\right]+\dfrac{e^{\kappa_m^{(j)}}-e^{\kappa_o^{(j,k)}}}{\kappa_m^{(j)}-\kappa_o^{(j,k)}}}. \tag{32}$$

Similarly,

$$\mathcal{R}_{\text{out}}=\frac{\dfrac{\delta^{(k)}}{2d}\left[\frac{1}{2}+\frac{1}{2}e^{\kappa_m^{(j)}}\right]+\dfrac{e^{\kappa_m^{(j)}}-1}{\kappa_m^{(j)}}}{\dfrac{\delta^{(k)}}{2d}\left[\dfrac{e^{\frac{1}{2}\kappa_o^{(j,k)}}-1}{\kappa_o^{(j,k)}}+\frac{1}{2}e^{\kappa_m^{(j)}}\right]+\dfrac{e^{\kappa_m^{(j)}}-e^{\kappa_o^{(j,k)}}}{\kappa_m^{(j)}-\kappa_o^{(j,k)}}}. \tag{33}$$

The variation of $\mathcal{R}_{\text{in}}$ with $\kappa_o^{(j,k)}$ and $\kappa_m^{(j)}$ is illustrated in Fig. 1. For these calculations, it was assumed (i) that $\delta^{(k)}$ was equal approximately to the mean distance between cations in a 125 mM solution, or 1.3 nm, (ii) that $2d$ was roughly 7.0–8.0 nm [6], and (iii) that $\delta^{(k)}/2d$ was about $\frac{1}{6}$. Clearly, the effect of the potential well is to increase inward current near the resting potential and to decrease it near the peak of the action potential. It should however be noted that

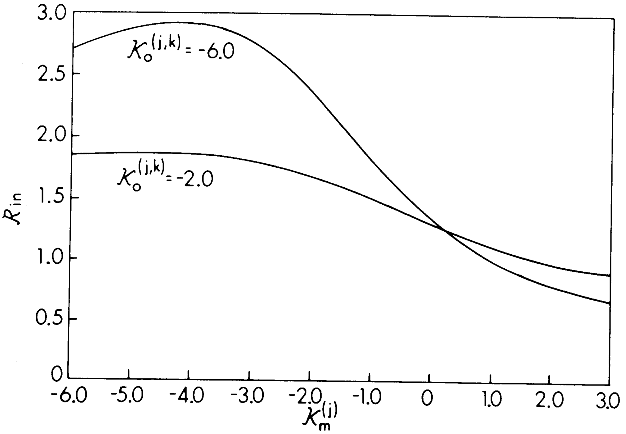

FIG. 1. $\mathcal{R}_{\rm in}$ vs. $\kappa_m^{(j)}$. The calculation was made from Eq. (32) using $\delta^{(k)}/2d = \frac{1}{6}$. The variation of $\mathcal{R}_{\rm out}$ will, by Eq. (34), be proportional.

$$\mathcal{R}_{\rm in} = \left[\frac{e^{\frac{1}{2}\kappa_o^{(j,k)}} - 1}{\frac{1}{2}\kappa_o^{(j,k)}} \right] \mathcal{R}_{\rm out}, \tag{34}$$

and that the net benefits of a negative charge site at the outer end of a sodium channel will therefore peak and eventually decrease as $\kappa_o^{(j,k)}$ becomes increasingly negative.

FORMAL SOLUTION: DISCRETE MODEL

Given that an ion has come within the zone of influence of a channel, it can be imagined that, instead of proceeding in the smooth diffusive fashion described above, it proceeds by a series of finite steps: that is, the ion's motion is modeled not as a continuous electrodiffusive process but as a classical "drunkard's walk" on a biased ramp or a "gambler's ruin" in an unfair game. This, in some sense, is a jump-diffusion model, although the physical visualization and the formal techniques employed are somewhat different from those commonly used (cf. Ref. 12).

Assume therefore that a type-k channel including its zones of influence is $N^{(k)}$ steps long, and let the outer solution be denoted as step-0 and the inner solution as step-$(N^{(k)}+1)$. The probability of jumping inward from step-n to step-$(n+1)$ can be called p_n, while that of jumping outward to step-$(n-1)$ can be called q_n $(=1-p_n)$. Computing the transition probabilities $\tau_{oi}^{(j,k)}$ and $\tau_{io}^{(j,k)}$ reduces then to a calculation on a Markov chain, a computation which can not reasonably be carried out unless the problem is simplified by assuming $p_n = p$ $(n = 0, 1, \ldots, N^{(k)} + 1)$. The relevant formulae are (cf. [9, pp. 229 ff.] or [11])

$$\tau_{oi}^{(j,k)} = \frac{1-(q/p)}{1-(q/p)^{N^{(k)}+1}}, \tag{35a}$$

$$\tau_{io}^{(j,k)} = \frac{1-(p/q)}{1-(p/q)^{N^{(k)}+1}} \tag{35b}$$

The simplest assumption regarding q/p is that it is a function of $\kappa_m^{(j)}$ which is unity when the membrane voltage is zero and which approaches unity as the number of steps increases. An obvious choice is

$$q/p = e^{\kappa_m^{(j)}/(N^{(k)}+1)}\ ; \tag{36}$$

and, in point of fact, this form can be simply derived from the considerations of Maxwell-Boltzmann statistics presented in the following paper [11].

It then follows from Eqs. (3), (4), (35), and (36) that

$$J^{(j,k)} = \mathrm{e}z^{(j)}\gamma^{(k)}\beta \frac{\sinh\left[\frac{1}{2}\kappa_m^{(j)}/(N^{(k)}+1)\right]}{\sinh\frac{1}{2}\kappa_m^{(j)}} \times\left[a_c^{(j)}e^{-\frac{1}{2}\kappa_m^{(j)}N^{(k)}/(N^{(k)}+1)} - a_i^{(j)}e^{\frac{1}{2}\kappa_m^{(j)}N^{(k)}/(N^{(k)}+1)}\right]. \tag{37}$$

Clearly, as $N^{(k)}$ becomes large, Eq. (37) reduces to Eq. (1), the standard Goldman form.

A difficulty with this approach is that it does not take into account any possible voltage dependence of the passage from bulk solution to zone of influence while, by assuming equal p_n, effectively attributing such a voltage dependence to the passage back. Picturesquely, the problem of the drunkard's getting out of the saloon to begin his walk or of the gambler's raising an initial stake has not been treated. Thus, for small $N^{(k)}$, Eq. (37) fails to yield a Nerstian equilibrium potential. This can be remedied by the *ad hoc* procedure of supposing that the concentrations used in computing the arrival rates in the zones of influence should be modified by Boltzmann distribution factors of the form $e^{-\frac{1}{2}\kappa_m^{(j)}/(N^{(k)}+1)}$ at the outer zone and $e^{\frac{1}{2}\kappa_m^{(j)}/(N^{(k)}+1)}$ at the inner zone; that is, in crossing from bulk solution to zone of influence the electric potential is assumed to shift by one-half a step. With this correction, the current becomes

$$J^{(j,k)} = ez^{(j)}\gamma^{(k)}\beta\frac{\sinh\left[\frac{1}{2}\kappa_m^{(j)}/(N^{(k)}+1)\right]}{\sinh\frac{1}{2}\kappa_m^{(j)}}\left[a_o^{(j)}e^{-\frac{1}{2}\kappa_m^{(j)}} - a_i^{(j)}e^{\frac{1}{2}\kappa_m^{(j)}}\right], \quad (38)$$

a form which displays the anticipated Nernstian behavior. When $|\frac{1}{2}\kappa_m^{(j)}/(N^{(k)}+1)| \ll 1$ it reduces to the classical Goldman form.

DISCUSSION

With respect to the basic question initially raised as to why a flux should be linear, independent, symmetric, Nernstian, or globally ohmic, the model revealed the following: (A) Linearity was an input to the model; but it is certainly intuitively reasonable on the basis of kinetic theory. (B) Independence can also be regarded as an input; or it can be viewed as a consequence of the hypothesis of one ion at a time in the channel. (C) In the continuum case, $J^{(j,k)}$ will satisfy the symmetry and Nernst-like properties only if $\kappa_o^{(j,k)} = \kappa_i^{(j,k)}$; and it will meet the global ohmicity condition only if $\delta^{(k)}/2d \to 0$ as well.

What we have shown therefore is that the thermally driven random walk of a lone ion in an electric field can—under certain circumstances—yield a Goldman-like channel current. The question of the behavior of $J^{(j,k)}$ when more than one ion is permitted into a channel has of course been left open; and actually, as is shown in the following paper [11], such currents need not be Goldman-like.

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