AN ION DISPLACEMENT MEMBRANE MODEL

STEPHEN B. HLADKY *and* JOSEPH D. HARRIS

From the Departments of Physics and Biochemistry, Dartmouth College, Hanover, New Hampshire 03755

ABSTRACT The usual assumption in treating the diffusion of ions in an electric field has been that the movement of each ion is independent of the movement of the others. The resulting equation for diffusion by a succession of spontaneous jumps has been well stated by Parlin and Eyring. This paper will consider one simple case in which a different assumption is reasonable. Diffusion of monovalent positive ions is considered as a series of jumps from one fixed negative site to another. The sites are assumed to be full (electrical neutrality). Interaction occurs by the displacement of one ion by another. An ion leaves a site if and only if another ion, not necessarily of the same species, attempts to occupy the same site. Flux ratios and net fluxes are given as functions of the electrical potential, concentration ratios, and number of sites encountered in crossing the membrane. Quantitative comparisons with observations of Hodgkin and Keynes are presented.

INTRODUCTION

This paper will construct and portray a theoretical model for the diffusion of *monovalent cations* across a membrane. The model meets five criteria: (*a*) accord with equilibrium thermodynamics, (*b*) reasonable agreement with possible membrane structure, (*c*) interaction of ions with each other, (*d*) diffusion as a sequence of steps rather than continuous movement, and (*e*) electrical neutrality.

Interaction of ions was indicated experimentally by the data on the unidirectional fluxes of potassium through the membrane of the cuttlefish, *Sepia officinalis* (Hodgkin and Keynes, 1955). Hodgkin and Keynes proposed the single-file model to explain their data. That model has subsequently been developed by several authors (Heckmann, 1963; Hladky, 1965; Macey and Oliver, 1966). The all or nothing character of the model, however, seems somewhat objectionable. A general treatment of diffusion of holes through the chains is possible by Monte Carlo techniques, but leaves entirely open questions such as the nature of the sites and the shape of the electrical potential.

We have chosen instead to start working from the notion of a lattice of fixed sites, each defined by a unit negative charge. We assume that all of the sites are occupied by one or another of the various (in general) species of monovalent cations present, and that a cation is displaced from its site when and only when another ion attempts to occupy the same site. Thus, within the membrane, cations can only exchange

sites, and at the boundaries, can exchange with external or internal ions. We call the model ion displacement rather than ion exchange since the latter has already been given to a quite different model in which ions can move only to vacant sites (Conti and Eisenman, 1965).

FORMULATION OF THE MODEL

Suppose that sites are restricted to channels penetrating the membrane so that once an ion enters a particular channel it must remain in that channel until it emerges again. The diffusion process is then effectively one-dimensional. All channels are assumed to be alike. Let the sites in an arbitrary channel be indexed by the layer integer i, which runs from 1 to n, the total number of sites per channel. A cation of a particular species bound at the ith site can be displaced from its site either by a cation of any species striking it from the $i - 1$st site, or by a cation of any species striking it from the $i + 1$st site. In the former case, when it is struck from the left, let the probability that it jumps to the right be d. The probability that it jumps to the left will then be $1 - d$. In the latter case, when the cation at the ith site is struck from the right, let the probability that it jumps to the left be l and the probability that it jumps to the right be $1 - l$. For simplicity, and in the absence of any better information, we suppose that the jump probabilities d and l are the same at each site.

Introduce the following symbols: M_{ji}, flux of the jth species to the right out of the ith site; M'_{ji}, flux of the jth species to the left out of the ith site; X_{ji}, fraction of sites occupied at site i by cations of species j. Then our model is described by the following equations:

$$M_{ji} = X_{ji}[dM_{i-1} + (1 - l)M'_{i+1}], \tag{1}$$

$$M'_{ji} = X_{ji}[(1 - d)M_{i-1} + M'_{i+1}], \tag{2}$$

where we have used the convention of dropping the subscript labeling the species to indicate that all species have been summed over. Thus, if there are m species present, $M_i = \sum_{j=1}^{m} M_{ji}$, etc.

So far we have 2 mn equations for the 3 mn unknowns M_{ji}, M'_{ji}, and X_{ji} ($1 \leq i \leq n$, $1 \leq j \leq m$). The other mn equations are, of course, the conservation laws (we consider only the steady state).

$$M_{j,i-1} + M'_{j,i+1} - M_{j,i} - M'_{j,i} = 0. \tag{3}$$

Adding equations (1) and (2), taking account of (3), and summing over j, one easily sees that the basic equations (1)–(3) imply that

$$\sum_{j=1}^{m} X_{ji} = 1, \tag{4}$$

i.e., all sites are filled.

For the purpose of solving these equations, it is convenient to replace them by the equivalent set of 3 *mn* equations

$$M_i = dM_{i-1} + (1 - l)M'_{i+1}, \tag{5}$$

$$M'_i = M_{i-1} + M'_{i+1} - M_i, \tag{6}$$

$$X_{ji} = M_{ji}/M_i = M'_{ji}/M'_i, \tag{7}$$

$$M'_{i+1}(X_{j,i+1} - X_{ji}) = M_{i-1}(X_{ji} - X_{j,i-1}). \tag{8}$$

The n equations (5) are obtained simply by summing equation (1) over all species j, and the n equations (6) by the same procedure applied to equation (3). On account of equation (4), equation (7) contains only $2(m - 1)n$ equations. They follow immediately from equations (1) resp. (2) and (4) on summing equation (1) resp. (2), using (4), and dividing the result into equation (1) resp. (2). Finally, the *mn* equations (8) obtain immediately on substituting in equation (3) from equation (7).

The difference equations (5) and (6) with constant coefficients may be solved by standard procedures. In terms of the boundary fluxes M_0 and M'_{n+1}, the easily verified result is

$$M_i = M_0 + \frac{[1 - (d/l)^i][(1 - l)M'_{n+1} - (1 - d)M_0]}{1 - d - (1 - l)(d/l)^n} \tag{9}$$

$$M'_i = M'_{n+1} + \frac{[(d/l)^n - (d/l)^{i-1}][(1 - l)M'_{n+1} - (1 - d)M_0]}{1 - d - (1 - l)(d/l)^n}. \tag{10}$$

In terms of these quantities, the solutions of equation (8), again tedious to obtain but easy to verify, are

$$X_{ji} = X_{j,n+1} + \frac{[(M_0 \cdots M_n)/(M'_1 \cdots M'_n)] - [(M_0 \cdots M_{i-1})/(M'_1 \cdots M'_i)]M'_{n+1}}{M'_{n+1} - (M_0 \cdots M_n)/(M'_1 \cdots M'_n)} \cdot (X_{j,n+1} - X_{j0}). \tag{11}$$

The remaining quantities, the fluxes, are given by equation (7) simply as

$$M_{ji} = M_i X_{ji} \tag{12}$$

$$M'_{ji} = M'_i X_{ji}. \tag{13}$$

NET FLUXES, UNIDIRECTIONAL FLUXES, AND FLUX RATIOS

The net flux $M'_{j,i+1} - M_{ji}$ is of course independent of i in the steady state, by equation (3). Denote it by J_j. Our solutions (9)–(13) yield

$$J_1 = \frac{l - d}{l^n(1 - d) - d^n(1 - l)} \cdot \frac{M'_1 \cdots M'_n M'_{j,n+1} - M_{j0} M_1 \cdots M_n}{M'_1 \cdots M'_{n+1} - M_0 \cdots M_n} (M'_{n+1} l^n - M_0 d^n). \quad (14)$$

Hence the total net flux J of all cationic species is

$$J = \frac{l - d}{l^n(1 - d) - d^n(1 - l)} (M'_{n+1} l^n - M_0 d^n). \quad (15)$$

The inward and outward unidirectional fluxes obtain on putting M_{j0} resp. $M'_{j,n+1}$ equal to zero in equation (14).

The flux ratio J rat$_j$ of the inward to outward fluxes is then given from equation (14) by

$$J \text{ rat}_j = M'_1 \cdots M'_n M'_{j,n+1} / M_{j0} M_1 \cdots M_n . \quad (16)$$

THE CASE OF NO NET CATION FLUX

From equation (15) we immediately deduce the following statement: The net cation flux J vanishes if and only if $M'_{n+1}/M_0 = (d/l)^n$. Under these conditions equations (9) and (10) yield

$$M_i/M'_i = d/l, \quad (17)$$

so that, from equation (16), the flux ratio reduces in this case to

$$J \text{ rat}_j = M'_{j,n+1} M_0 / M'_{n+1} M_{j0} . \quad (18)$$

THE KNOCK-LOOSE CASE

Suppose that the ion at site i is simply knocked loose by the impact of an ion from either the $i -$ 1st or $i +$ 1st sites, retaining no memory of the direction. Then, since the probability that it moves to the right on impact from the left was defined as d while the probability that it moves to the right on impact from the right was defined as $1 - l$, we have $d = 1 - l$. Similarly, arguing on movement to the left, we have, consistently, $l = 1 - d$. Thus, in the knock-loose case,

$$d + l = 1. \quad (19)$$

Substituting relation (19) into equations (9) and (10), we find for this case again that

$$M_i/M'_i = d/l,$$

so that again J rat is given by formula (18). But, in addition, for this case only,

equation (14) for the net flux becomes simply

$$J_j = \frac{1 - (d/l)}{1 - (d/l)^n} [M'_{j,n+1} - (d/l)^n M_{j0}]. \tag{20}$$

THE KNOCK-ON CASE

The opposite extreme to the knock-loose case occurs when the ion at site i moves in the direction of the ion striking it when that is energetically possible. If the electrical potential is increasing to the right ($\Delta\varphi > 0$, where $\Delta\varphi$ is the membrane potential difference between outside minus inside, multiplied by F/RT to render it dimensionless), the ion at site i will move to the left with probability 1 when struck from the left, i.e. $l = 1$. Similarly, when $\Delta\varphi < 0$, $d = 1$. For these cases equations (9) and (10) easily yield

$$M_i/M'_i = M_0\, d/[M'_{n+1} + M_0(1 - d^{n-i+1})] \qquad (\Delta\varphi > 0), \tag{21}$$

and

$$M_i/M'_i = [(1 - l^i)M'_{n+1} + M_0 l^{i-n}]/lM'_{n+1} \qquad (\Delta\varphi < 0). \tag{22}$$

It is worth noting that in the knock-on case the total cation flux (equation 15) takes a particularly simple form,

$$J = M'_{n+1} - d^n M_0 \qquad (\Delta\varphi > 0), \tag{23 a}$$

$$J = l^n M'_{n+1} - M_0 \qquad (\Delta\varphi < 0). \tag{23 b}$$

PHYSIOLOGICAL APPLICATIONS

Further progress requires an assumption for the transition probabilities. We make the simplest, namely, that since there are n sites and hence $n - 1$ potential maxima in the membrane, the ratio d/l is given simply by the Boltzmann factor

$$d/l = \exp [-\Delta\varphi/(n + 1)] \tag{24}$$

and we assume that the ratio of the boundary fluxes is given by

$$M'_{j,n+1}/M_{j0} = (C_{j\,\mathrm{out}}/C_{j\,\mathrm{in}}) \exp [\Delta\varphi/(n + 1)]. \tag{25}$$

Substituting these relations in equation (18), we find that for the membrane potential $\Delta\varphi_0$, which obtains *when the net cation flux vanishes*, the flux ratio is given by

$$J\,\mathrm{rat}_j = (C_{j\,\mathrm{out}}/C_{j\,\mathrm{in}}) \exp (\Delta\varphi_0). \tag{26}$$

This last result is of course the same as that for independent ion movement, assuming no ion interaction. We therefore find that for membranes permeable pri-

marily to cations, for which the resting potential is determined by the zero net cation flux condition, measurements of the flux ratio under normal resting conditions will not show the presence of ion interactions. The experiments of Sjodin (1965), which show that relation (26) does obtain under normal resting conditions, are not suffi-

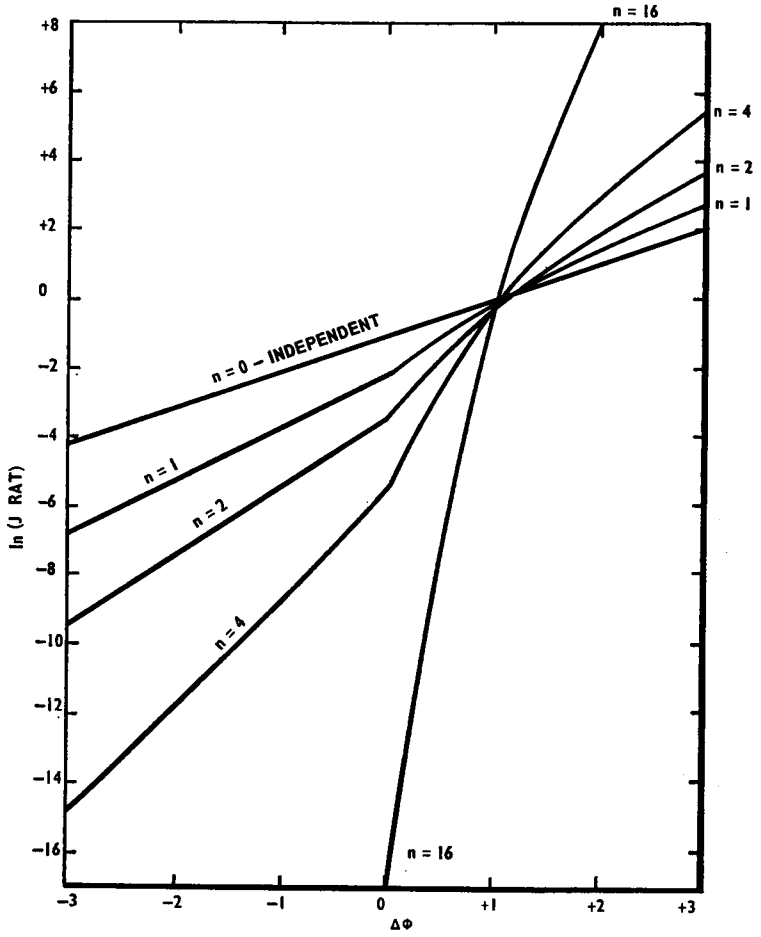

FIGURE 1 Flux ratio J rat as a function of membrane potential $\Delta\varphi$ for the case of a single cationic species, calculated from equations (32) and (33). The equilibrium potential $\Delta\varphi_{eq}$ was chosen to be 1.10. Note the discontinuity in slope at zero membrane potential.

cient evidence that ion movements in skeletal muscle are independent. Further experiments in which flux ratios are measured under abnormal conditions in which the net cation flux is not zero would be necessary to establish independence.

Consider now the knock-loose case. If we assume that the boundary fluxes for this case only are given by

$$M'_{j,n+1} = (n + 1)P_jC_{j\ \text{out}} \exp\left[\Delta\varphi/2(n + 1)\right] \tag{27}$$

and

$$M_{j0} = (n + 1)P_jC_{j\,\text{in}} \exp [-\Delta\varphi/2(n + 1)], \tag{28}$$

where P_j is the permeability coefficient for ionic species j, then equation (20) for the net flux becomes

$$J_j = P_j \frac{\sinh [\Delta\varphi/2(n + 1)]}{\Delta\varphi/2(n + 1)} \frac{\Delta\varphi}{\exp (\Delta\varphi) - 1} [C_{j\,\text{out}} \exp (\Delta\varphi) - C_{j\,\text{in}}]. \tag{29}$$

This result is *identical* with the flux equation for the purely independent case derived by Parlin and Eyring (1954), with no consideration of ion interaction. We write it in

TABLE I

OBSERVED AND CALCULATED POTASSIUM FLUX RATIOS

E (est.)*	$E - E_K$ (est.)*	J rat (obs.)*	J rat (calc. $n = 6$)
mv	*mv*		
37	−45	0.016	0.00472
52	−30	0.030	0.0371
55	−27	0.063	0.0533
62	−20	0.12	0.119
72	−10	0.98	0.353
81	−1	2.3	0.902
58	−7	0.46	0.427
72	7	2.7	2.28
43	1	1.05	1.16
59	17	3.3	11.3
65	23	6.2	25.4
69	27	39	43.1
27	3	1.30	1.76
12	5	1.90	3.22

* Data from Hodgkin and Keynes (1955), Table 8 on page 74.

the particular form (29) to make easily manifest the fact that when the number n of sites becomes large ($n \lesssim 10$, say, in the physiological range of $\Delta\varphi$), the formula reduces to the well known "constant field" result.

Finally, let us consider the more complicated knock-on case. Here our assumptions (equation 24) for d/l lead to

$$d = \exp [-\Delta\varphi/(n + 1)], \qquad l = 1 \qquad (\Delta\varphi > 0) \tag{30}$$

and

$$d = 1, \qquad l = \exp [\Delta\varphi/(n + 1)] \qquad (\Delta\varphi < 0). \tag{31}$$

Substituting these values for d and l into equations (21) and (22), then into the gen-

eral flux ratio formula (16), we find after some manipulation that

$$J \text{ rat} = \exp(\Delta\varphi - \Delta\varphi_{eq}) \prod_{i=1}^{n} \{1 + [\exp(\Delta\varphi - \Delta\varphi_{eq}) - 1] \exp[-i\Delta\varphi/(n+1)]\} \quad (\Delta\varphi > 0), \quad (32)$$

$$J \text{ rat} = \exp(\Delta\varphi - \Delta\varphi_{eq}) \prod_{i=1}^{n} \{1 + [\exp(\Delta\varphi_{eq} - \Delta\varphi) - 1] \exp[i\Delta\varphi/(n+1)]\}^{-1} \quad (\Delta\varphi < 0). \quad (33)$$

Here we have assumed purely for simplicity that only a *single ionic species* is diffusing in a given type of channel, so that the subscript j has been dropped. Furthermore, we have introduced the obvious notation

$$\Delta\varphi_{eq} = \ln(C_{in}/C_{out}). \quad (34)$$

Note that our results imply a discontinuity in slope of J rat as a function of $\Delta\varphi$, for fixed $\Delta\varphi_{eq}$, at the point $\Delta\varphi = 0$. The functional form of these relations is shown in Fig. 1

The data obtained by Hodgkin and Keynes (1955) may be compared with the predicted flux ratios for the knock-on case. Unfortunately, all membrane potentials are positive in their experiments so that we cannot check the predicted discontinuity. But we can make the quantitative comparisons shown in Table I. The values of E and $E - E_K$ are those estimated by Hodgkin and Keynes; the calculated values of the flux ratio are obtained from equation (32) by putting $\Delta\varphi = E/25$ mv, $\Delta\varphi - \Delta\varphi_{eq} = (E - E_K)/25$ mv, and choosing $n = 6$ for the best over-all fit. The number of sites, n, is the *only* adjusted parameter. Taking into account the considerable uncertainties of measurement and estimation discussed by Hodgkin and Keynes in their paper, it would seem that the agreement with the knock-on predictions is as good as one has a right to expect. Further experiments deliberately designed to test the knock-on model would certainly be desirable. One could then look also for evidence of different ions moving in the same channel, which would result in slightly more complicated predictions than equations (32) and (33).

The work on which this paper was based was supported in part by the undergraduate research participation programs of the National Science Foundation and the National Institutes of Health. The use of the Dartmouth Time Sharing Computer System and the assistance of the graphic arts department of American Cyanamid Company in Stamford, Conn., are gratefully acknowledged. We would also like to thank the referee of an earlier version of this manuscript for a number of very helpful suggestions.

Received for publication 31 January 1967.

REFERENCES

CONTI, F., and G. EISENMAN. 1965. *Biophys. J.* **5**:511.

HECKMANN, K. 1963. *In* Funktionelle und morphologische Organization der Zelle. P. Karlson, editor. Springer Verlag, Berlin. 241.

HLADKY, S. B. 1965. *Bull. Math. Biophys.* **88**:79.
HODGKIN, A., and R. KEYNES. 1955. *J. Physiol., (London).* **128**:61.
MACEY, R., and R. OLIVER. 1966. Abstracts of the Biophysical Society Meeting, Boston.
PARLIN, R., and H. EYRING. 1954. *In* Ion Transport Across Membranes. H. T. Clarke, editor. Academic Press, Inc., New York. 103.
SJODIN, R. A. 1965. *J. Gen. Physiol.* **48**:777.