KINETIC THEORY MODEL FOR ION MOVEMENT THROUGH BIOLOGICAL MEMBRANES

II. INTERIONIC SELECTIVITY

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ABSTRACT The equation presented in the previous paper for steady-state membrane ionic current as a function of externally applied electric field strength is numerically analyzed to determine the influence of ionic and membrane molecule parameters on current densities. The model displays selectivity between different ions. A selectivity coefficient S_i, defined as the ratio of current carried by an ionic species i at a given field strength to the current carried by a reference species at the same field strength, has the following properties: (*a*) S_i is a function of electric field strength except for ion-membrane molecule interactions yielding velocity independent collision frequencies; (*b*) for ion-membrane molecule interactions characterized by a collision frequency that is a decreasing (increasing) function of increasing ionic velocity, ions whose $S_i > 1$ (<1) at zero field strength will show maxima (minima) (minima[maxima]) in their S_i vs. electric field strength curves.

INTRODUCTION

Hille (1970) has summarized the current electrical and chemical evidence indicating the existence of physically separate pathways for early, late, and leakage ionic currents in excitable tissue, e.g., squid giant axons and frog myelinated nerve.

Particularly intriguing is the ability of various monovalent cations to substitute for normal ionic carriers of early (Na^+) and late (K^+) currents. Chandler and Meves (1965) and Binstock and Lecar (1969) measured the steady-state conductance of the early current pathway in squid axons to various monovalent cations, relative to its conductance to sodium, and found that

$$g_{Li} : g_{Na} : g_{NH_4} : g_K : g_{Rb} : g_{Cs} = 1.1 : 1.0 : 0.27 : 0.083 : 0.025 : 0.016.$$

Ionic parameters are clearly involved in determining the steady-state conductance of pathway to any given ion. A further most interesting observation is that, within

experimental error, the *kinetic* behavior of these pathways is independent of ionic species.

The previous paper (Mackey, 1971; herafter referred to as paper I) outlined an approach to membrane transport based on the kinetic theory of interacting particles.

In paper I the quantitative nature of the electric field-dependent conductances of a membrane in the presence of solution symmetry was examined. Computed currents and chord conductances, as functions of electric field strength, were presented as dimensionless quantities for ease of computation. Included in the normalizing constants for these dimensionless quantities were ionic and membrane molecular parameters and temperature.

Since any complete model for the electrical properties of ionic pathways in an excitable membrane must exhibit selectivity between various ions, this paper examines the influence of these molecular and ionic parameters on the ability of a given electric field strength to induce current flow. It is shown that the model system does display interionic selectivity. Further, this selectivity is dependent on electric field strength. The qualitative form of this dependence is a function of the force law assumed to be acting between the ion and the membrane molecules.

All symbols not defined here will be found in paper I. Equations from paper I will be prefixed with I, e.g., I A 5.

ANALYSIS OF INTERIONIC SELECTIVITY

In paper I an expression was derived relating dimensionless electric field strength to a dimensionless ionic current density, (equation I A 18). If a selectivity coefficient, S_i, for the ith ionic species is defined as the ratio of *actual* current carried by the ith species relative to the *actual* current carried by a reference species, j, at constant field strength, then $S_i = I_i/I_j$. From the definitions of I, S_i may be written explicitly as

$$S_i = \frac{z_i}{z_j}\left(\frac{m_s + m_j}{m_s + m_i}\right)^{1/2} \eta_{ij} \frac{G_{ci}(\eta_{ij}E_j)}{G_{ci}(E_j)}, \tag{1}$$

$$\eta_{ij} = \frac{z_i}{z_j}\left(\frac{K_{js}}{K_{is}}\right)^{(1-p)/2}\left(\frac{m_j}{m_i}\right)^{1/2}\left(\frac{m_s + m_i}{m_s + m_j}\right)^{p/2}, \tag{2}$$

and $E_j = q_jE/m_j\beta_jV_{Tj}^{p+1}\sqrt{\xi_j}$. Table I shows the ratio of the force constants, K_{js}/K_{is} for the interactions considered, and all other symbols have been previously defined.

In general S_i is a function of the electric field strength unless $G_{ci}(\eta_{ij}E_j) = G_{ci}(E_j)$ for all E_j, and this is true only for ideal ion-induced dipole interactions ($p = 0$). From equation 1 it follows that the selectivity coefficient at zero field strength is

$$S_i(E_j = 0) = \eta_{ij}\left(\frac{m_s + m_j}{m_s + m_i}\right)^{1/2}\frac{z_i}{z_j}.$$

Also,

$$\lim_{E_j \to \infty} G_{ci}(\eta_{ij} E_j) = \lim_{E_j \to \infty} G_{ci}(E_j),$$

so that

$$\lim_{E_j \to 0} S_i(E_j) = \lim_{E_j \to \infty} S_i(E_j).$$

Thus, no matter what the variation of selectivity with field strength, the selectivity for very high fields will always approach the value it had at zero field strength.

In the numerical evaluation of S_i, sodium is taken as the standard species,

TABLE I

RATIOS OF FORCE CONSTANTS FOR DIFFERENT IDEALIZED INTERACTIONS

Type of interaction	p	K_{js}/K_{is}
Ion-fixed charge	-3	(q_j/q_i)
Ion-fixed dipole	-1	(q_j/q_i)
Ion-induced dipole	0	(q_j/q_i)
London dispersion	1/3	$\frac{\alpha_j I_j}{\alpha_i I_i} - \frac{I_i + I_s}{I_j + I_s}$
Hard sphere–hard sphere	1	$\frac{r_j + r_s}{r_i + r_s}$

TABLE II

MOLECULAR PROPERTIES OF UNHYDRATED CATIONS NEEDED FOR VARIOUS COMPUTATIONS

Ion	Ionic constants			
	Molecular weight	Polarizability (α) $\times 10^{24}$	Second ionization potential (I)	Crystal radius
		cm^3	ev	A
Li^+	6.940	0.075	75.28	0.68
Na^+	22.997	0.21	47.07	0.98
NH_4^+	18.040	1.65	31.70	1.45
K^+	39.100	0.87	31.70	1.33
Rb^+	85.480	1.81	27.30	1.48
Cs^+	132.91	2.79	23.40	1.67
Scatterer (carboxyl oxygen)		0.84	2.12	1.45

References: Conway (1952); Handbook of Chemistry and Physics (1957); Ketelaar (1953); Latimer (1952); Moelwyn-Hughes (1949); Mulliken (1933).

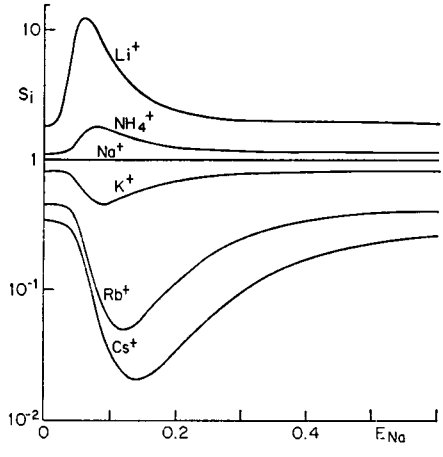

FIGURE 1

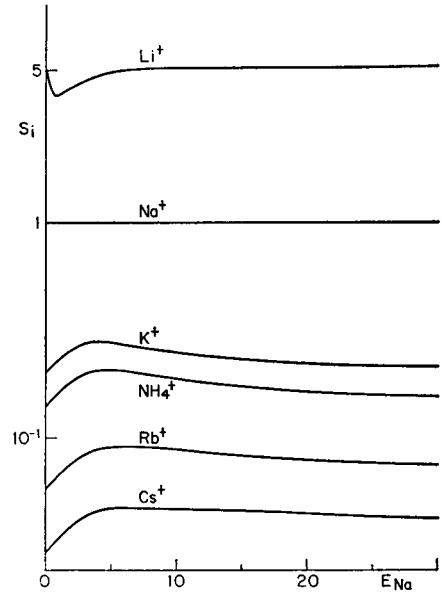

FIGURE 2

FIGURE 1. Selectivity (S_i) vs. electric field strength (E_{Na}) for Li^+, Na^+, NH_4^+, K^+, Rb^+, and Cs^+ and ion-fixed charge interactions ($p = -3$). Effective scatterer molecular weight = 1000. Note that ions with $S_i > 1$ (<1) have maxima (minima) in their S_i vs. E_{Na} curves. For any interaction such that $p < 0$, qualitatively identical results are found.

FIGURE 2. Selectivity (S_i) as a function of electric field strength (E_{Na}) for six different cations experiencing London dispersion force ($p = 1/3$) interactions, scatterer molecular weight = 1000. Note that ions whose $S_i > 1$ (<1) exhibit minima (maxima) in their S_i vs. E_{Na} curves.

($S_i = S_{Na} = 1$). For every interaction, I have calculated the selectivity coefficients for Li^+, NH_4^+, K^+, Rb^+, and Cs^+, since these are the most commonly studied ions in selectivity studies on excitable membranes. The parameters needed for the computation (e.g., ionic mass, radius, and polarizability) are given in Table II. These values, it must be stressed, are for unhydrated ions. Much has been written speculating about the hydration state of ions crossing membranes, but as of this time there is little evidence either supporting or rejecting the hypothesis that ions go through membranes in hydrated form.

Fig. 1 is a graph of the selectivity S_i vs. field strength E_{Na} for the six monovalent cations listed above for ion-fixed change interactions ($p = -3$) and a scatterer molecular weight of 1000. S_i vs. E_{Na} for $p = -1$ (ion-fixed dipole interaction) with a scatterer molecular weight of 1000 is not shown here because it is qualitatively identical with the curves of Fig. 1. Quantitatively the selectivity displayed for $p = -1$ is not as great as for $p = -3$; the differences are quite large for some ions.

S_i vs. E_{Na}, for a collision dominated by London dispersion forces ($p = 1/3$) and a scatterer molecular weight of 1000, is shown in Fig. 2. Fig. 3 shows the same plot

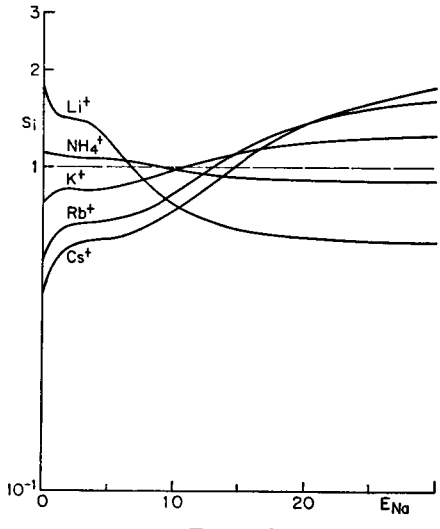

FIGURE 3

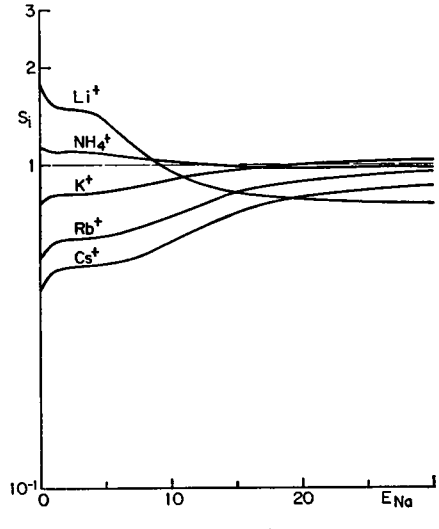

FIGURE 4

FIGURE 3. Ionic selectivity (S_i) vs. electric field strength (E_{Na}) for six cations, ion-neutral scatterer ($p = 1$) interactions, and a scatterer molecular weight of 1000. Note that there exist 11 different selectivity sequences, depending on the value of E_{Na}. Extension of the curves for larger values of E_{Na} would demonstrate the characteristic maxima and minima.
FIGURE 4. S_i as a function of E_{Na}, as in Fig. 3, but with a scatterer molecular weight = 44 to illustrate the effect of this parameter. The 11 different selectivity sequences of Fig. 3 have been reduced in number to six.

for hard sphere collisions ($p = 1$). If these curves were extended over a sufficiently large range of field strengths, maxima and minima would be evident.

Another characteristic of the selectivity is illustrated in Fig. 3. Previously (e.g., for $p = -3$) it was found that the relative selectivity *ratios* could change quite dramatically with the field strength, even though the relative position of an ion in the selectivity sequence remained constant. However, for $p = 1$ the selectivity *sequence* may change with the magnitude of the external electric field. Whether or not this happens is dependent on the molecular weight chosen for the scattering center as illustrated in Fig. 4, calculated for $p = 1$ and a scatterer molecular weight of 44.

DISCUSSION AND SUMMARY

Experimentally, consideration is not usually given to variation in selectivity with membrane potential. Experimental determinations of selectivity in membranes are often based on the effects of ion substitution on the equilibrium potential of a particular pathway. From the observed shift in the equilibrium potential a permeability ratio is obtained from the Goldman equation. This is a different measure of the selectivity of a system than is S_i.

Appropriate experimental data might be obtained from measurements of current as a function of membrane potential taken, for example, on a squid giant axon per-

fused with high equal potassium concentrations both inside and out, and then the same experiment repeated with a number of different cations replacing potassium. Unfortunately, such explicit data do not exist in the published literature. However, there are some data indicating that S_i may indeed be a function of membrane potential; Chandler and Meves (1965) and Adelman and Senft (1966) obtained data indicating that S_{Rb} and S_{Cs} may vary with membrane potential. Both measured the effect of replacing internal potassium by rubidium or cesium on the delayed outward currents through the potassium channel. Both S_{Rb} and S_{Cs} are less than one for zero membrane potential, and show minima at some membrane potential.

The mechanism of interionic selectivity in this model of membrane ion transport has one basic feature: selectivity is determined by the same process that gives rise to nonlinear electric field dependent conductances, i.e., ion-membrane molecule interactions. Two aspects of this interaction important for selectivity are (*a*) the dependence of the (classical) ion-scatterer interaction on particle separation and (b) the ionic and molecular masses and parameters entering the (classical) force constant, K_{is}. The coupling of a selectivity mechanism to a nonlinear conductance seems to be novel, although many previous selectivity theories have been based on variations of ionic and/or molecular parameters. However, the highly nonlinear way in which the electric field might determine selectivity has not previously been considered.

Ling (1962) has put forth a most complete attempt to account for the ion-selective properties of biological membranes. By carefully taking into account a number of forces probably existing between ions and membrane-bound molecules, as well as dielectric saturation, he has been able to quite satisfactorily explain the numerous selectivity ratios found experimentally. In addition to the forces considered here, Ling included permanent dipole-permanent dipole, permanent dipole-induced dipole, induced dipole-induced dipole, and Born repulsion forces.

Ling's method was not the kinetic approach used here, but rather an equilibrium approach. This and the previous paper thus differ from Ling's in that I examine the expected effects of a single type of ion-membrane molecule interaction force on ion transport, a nonequilibrium phenomenon.

An interesting extension of the model presented here would be to adopt Ling's approach. Thus the ion-scatter interaction force would be the sum of all the likely interaction forces and the nonlinear conductance and selectivity behavior of the system could be examined. This would, however, pose severe computational problems. An explicit relation between collision frequency and ionic velocity would no longer be available. A numerical determination would be necessary to carry out the integrations needed for a calculation of $\tilde{I}$. Qualitatively, however, it seems clear that electric fields within membranes may play a potent role in modulating the selectivity mechanisms considered by Ling.

The three qualitative generalizations that may be made about the selectivity of the model system are: (*a*) the selectivity coefficient is a function of the electric field

strength except for $p = 0$; (*b*) as a consequence of the dependence of chord conductance on field strength for $p < 0$, ions whose $S_i > 1$ (<1) at zero field strength will show maxima (minima) in their S_i vs. E_j curves; conversely, for $p > 0$ ions with $S_i > 1$ (<1) at zero field strength will have minima (maxima) in their S_i vs. E_j curves; (*c*) for $p > 0$, the *sequence* of selectivities may be altered by changes in field strength.

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REFERENCES

ADELMAN, W. J., and J. P. SENFT. 1966. *J. Gen. Physiol.* **50**:279.
BINSTOCK, L., and H. LECAR. 1969. *J. Gen. Physiol.* **53**:342.
CHANDLER, W. K., and H. MEVES. 1965. *J. Physiol. (London).* **180**:788.
CONWAY, B. E. 1952. Electrochemical Data. Elsevier, Amsterdam.
Handbook of Chemistry and Physics. 1957. The Chemical Rubber Co., Cleveland, 39th edition.
HILLE, B. 1970. Progr. Biophys. Mol. Biol. **21**:1.
KETELAAR, J. A. 1953. Chemical Constitution: An Introduction to the Theory of the Chemical Bond. Elsevier, Amsterdam.
LATIMER, W. M. 1952. The Oxidation States of the Elements and their Potentials in Aqueous Solutions. Prentice-Hall Inc., Englewood Cliffs, N. J.
LING, G. H. 1962. A Physical Theory of the Living State: The Association-Induction Hypothesis. Blaisdell Publishing Co., Waltham, Mass.
MACKEY, M. C. 1971. *Biophys. J.* **11**:75.
MOELWYN-HUGHES, E. A. 1949. *Proc. Cambridge Phil. Soc.* **45**:477.
MULLIKEN, R. S. 1933. *J. Chem. Phys.* **1**:492.