MASS TRANSFER IN THE CORNEA

I. INTERACTING ION FLOWS IN AN ARBITRARILY CHARGED MEMBRANE

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ABSTRACT The formalisms of irreversible thermodynamics are used to describe multi-ionic nonconvective flow through an arbitrarily charged membrane. Interactions between oppositely charged ions are included and are measured by a single phenomenological coefficient. The consequent generalized Nernst-Planck flux equations are integrated to yield a relation between the species fluxes and the composition of the solutions bounding the membrane. It is assumed in the derivation that activity coefficient gradients within the membrane and direct interactions between ions of like charge are negligible. Some special cases are examined. To illustrate the use of the final equations, a single membrane separating solutions of differing composition is modeled, and the effect of ion-ion interactions on the membrane potential and the ion fluxes is demonstrated for several values of diffusion current density and membrane charge density.

INTRODUCTION

The functioning of essentially all biological structures is intimately tied to transport processes occurring within them. Among these processes, membrane transport is surely among the most important. The formalisms of irreversible thermodynamics are an ideal vehicle for constructing a comprehensive, self-consistent description of membrane transport in the absence of a detailed understanding of this phenomenon at the molecular level. In the work to follow, the generalized Nernst-Planck equations derived from a frictional description of transmembrane flow will be integrated, retaining a measure of direct coupling between the fluxes of oppositely charged ions, and the importance and influence of this coupling will be examined.

This work was initiated as the first step towards a comprehensive model of electrolyte transport in the cornea; the application to the cornea of the general theory presented here is deferred to a later submission. Nonetheless, it is appropriate, at least for the sake of perspective, to discuss briefly the nature of the problem to which the results of the present paper will be directed.

The mechanism by which the thickness of the mammalian cornea is maintained in vivo is still unclear. One plausible explanation, deduced from the temperature reversal effect (for instance, Harris, 1967; Mishima and Kudo, 1967) and the known promotion of swelling by ouabain (for instance, Harris, 1967; Trenberth and Mishima, 1968), is that an ATPase-activated pump in either the epithelium (Green, 1966; Ehlers and Ehlers, 1968) or endothelium (Mishima and Kudo, 1967) may be involved.

The influence of active transport on the swelling tendency of the cornea is usually thought of in terms of the effect of the pump-induced changes in the stromal concentration of the actively transported ion or ions. Thus, Green (1969) discusses the effect of epithelial pumping of sodium in the rabbit in terms of the cation-binding properties of the stromal acid mucopolysaccharides and it has been argued on osmotic grounds (Langham, 1965) that active ion transport out of the cornea is more consistent with deturgescence than is inward pumping.

Even when a series membrane system such as the cornea is short circuited, the influence of a metabolic pump is not seen only in the concentration of the pumped species. The condition of microscopic electroneutrality must still be satisfied, and there is phenomenological coupling between the flux of the transported ion and the other species and solvent. In many studies on the cornea, the tissue is isolated and open circuited; the requirement that the observable current be zero provides yet another influence of active transport on the fluxes and concentration profiles of the other species.

One approach towards understanding the implications of active and passive transport through a series membrane system is computer simulation. The principal element in such a simulation is the single membrane, and this paper is limited in scope to that entity in the steady state. The treatment of electrolyte transport given here is based on a frictional interpretation of the equations of irreversible thermodynamics. Because physiological solutions are rather concentrated, ion-ion interactions are included. The electrolyte phase is multi-ionic, comprised of only monovalent ions. For generality, the membrane is assumed to be charged, but not ideally permselective, and plane parallel, so that all flows are one-dimensional, normal to the membrane surfaces. The problem to be solved is the following. Given the compositions $\{c_j^a\}$ and $\{c_j^b\}$ just inside the membrane surfaces, the observable current density and the parameters of any assumed metabolic pumps, what is the membrane potential and what are the net fluxes of each of the mobile ions? This problem cannot be solved explicitly as a two-point boundary value problem; instead, a set of equations giving $\{c_j^b\}$ as a function of $\{c_j^a\}$ and the passive fluxes $\{J_j\}$ will be constructed. The roots of these equations are the values of J_j which, with the known values of c_j^a, give the correct values of c_j^b and diffusion current.

In relation to earlier studies of membrane transport, this work is closest to that of Behn (1897). The solution given here differs from Behn's in that ion-ion interactions are included. These interactions are naturally present in any irreversible thermodynamic formulation of the transport problem and have been included in descriptions of the transport properties of electrolytes in free solution (Katchalsky and Curran, 1965; Miller, 1967). The principal problem associated with the introduction of solute-solute interactions is not the statement of the flux equations, but is that they are coupled not only through the electrostatic potential, but through the interaction terms as well.

DEVELOPMENT OF THE FLUX EQUATIONS

We start with Kedem and Katchalsky's (1961) force balance

$$-\frac{d\tilde{\mu}_j}{dx} = \sum_{k\neq j} f_{jk}(v_j - v_k), \tag{1}$$

where $\tilde{\mu}_j$ is the electrochemical potential of the jth species, x is distance through the membrane, f_{jk} is a frictional coefficient measuring the drag on a mole of j caused by a flow of the kth species relative to the jth, and v is species velocity. The index j includes all n ions to which the membrane is permeable, and water; k includes these $n + 1$ species, and the membrane, whose velocity is set equal to zero. The velocity v is related to the transmembrane flux J by

$$v_j = J_j/C_j, \tag{2}$$

where C_j is the concentration of the jth species at x, per unit volume membrane.

The phenomenological equation for the jth species is

$$-\frac{d\tilde{\mu}_j}{dx} = \sum_i R_{ji}J_i = \sum_{i\neq j} R_{ji}J_i + R_{jj}J_j \qquad (j, i = 1, \cdots, n + 1), \tag{3}$$

where the phenomenological coefficient R_{ji} is a generalized resistance which obeys the Onsager reciprocal relation. Equations 1 and 2 also give a linear relation between the electrochemical potential gradient and the fluxes. Equating the coefficients of J_i $(i \neq j)$,

$$R_{ji} = -f_{ji}/C_i = R_{ij} = -f_{ij}/C_j. \tag{4}$$

The integration of the generalized Nernst-Planck flux equations which follow from the phenomenological description of membrane transport is facilitated considerably if bulk solvent flow can be neglected. There are several lines of evidence to show that, insofar as solute transport is concerned, convection in the isolated cornea, at least, is small relative to diffusion and migration under near physiological conditions. Green has found (private communication) that the equilibrium sodium content and hydration of clamped rabbit corneas bathed on both surfaces with isotonic solutions are insensitive to the magnitude of the simulated intraocular pressure (IOP), so long as the corneal membranes are undamaged. Edelhauser, Hoffert, and Fromm (1968) and Donn, Miller, and Mallett (1963) measured the unidirectional fluxes of HTO in isolated corneas and found no measurable bulk flow in the steady state under zero (presumably) and 5–35 cm H_2O IOP, respectively. Accordingly, in the analysis to follow, the flow of water relative to the membrane will be set equal to zero. Consequently, the equations to be derived below should be applied to data on real systems only in conjunction with a demonstration that convective effects are minor.

The result of substituting equation 2 into equation 1 is solved for J_j. The influence of pressure variations on the chemical potential of the ions is small and will be ignored; at constant temperature,

$$J_j = \frac{C_j}{\sum_{k\neq j} f_{jk}}\left(-RT\frac{d\ln a_j}{dx} - z_j F\frac{d\psi}{dx} + \sum_{i\neq j}\frac{f_{ji}}{C_i}J_i\right) \qquad (j, i = 1, \cdots, n), \qquad (5)$$

where the notation is standard. Equations analogous to equation 5 have been obtained by Coster and George (1968) and Albrecht-Bühler (1968). It is useful to cast equation 5 in a form whereby comparisons with the Nernst-Planck flux equation may be made. To do this, it is necessary to replace C_j by c_j, which is the concentration of the jth ion in the solution through which diffusion actually takes place. In coarse membranes (such as the corneal stroma) or membranes through which transport is by pore diffusion (such as the corneal endothelium [Maurice, 1961]), the concentrations may be related by $C_j = \varphi c_j$ (Kedem and Katchalsky, 1961), where φ is the volume fraction of the membrane available to the solution. The coefficient of the right-hand side of equation 5 is then $c_j/\sum_{k\neq j}(f_{jk}/\varphi)$. In the absence of membrane drag and ion-ion interactions, the coefficient becomes $c_j/(f_{jw}/\varphi)$, where f_{jw} measures solvent drag. Comparing equation 5 with the Nernst-Planck equation in free solution ($\varphi = 1$), f_{jw} is inversely proportional to the mobility of the jth ion. Since the mobility is insensitive to changes in concentration (Katchalsky and Curran, 1965; Mackie and Meares, 1955), f_{jw}, and by inference the membrane drag f_{jm}, will be regarded as constants. Since the membrane is assumed to be uniformly porous, it follows from equation 4 that R_{jw} and R_{jm} vary with concentration to the same extent as do f_{jw} and f_{jm}.

The ion-ion interaction coefficients R_{ji} and f_{ji} do not vary similarly through the membrane. To discuss these variations with the object of deciding which of the two variables leads to a more convenient representation of solute-solute flow coupling, we use "total concentration" to refer to the total ionic content of the solution, measured by $N = \sum_j c_j$, and "composition" to measure the relative amounts of each species. The principal variations across membranes of biological interest are in composition rather than in total concentration. To examine the implications of assuming either R_{ji} or f_{ji} to be independent of composition, consider a series of experiments which differ from one another only in that the total amount of a minor species i' is less in each succeeding one. Thus, the total concentration is nearly the same in each experiment. In successive runs, $J_{i'}$ and $C_{i'}$ tend towards zero, and $J_{i'}/C_{i'}$ approaches some limiting velocity, $v_{oi'}$. Multiplying equation 5 by $\sum_{k\neq j} f_{jk}$, a term $J_j f_{ji'}$ remains on the left-hand side of the equation and $C_j f_{ji'} v_{oi'}$ remains on the right in the limit. The terms cannot cancel for all j except in the special case that all the v_j are the same; that is, when there is no ion drag. If $f_{ji'}$ is replaced (equation 4) by $-C_{i'} R_{ji'}$ and $R_{ji'}$ is assumed to be constant, the residual terms vanish from equation 5 when $C_{i'}$ vanishes. Accordingly, R_{ij} will be used as a constant, composition-insensitive measure of ion drag.[1]

It will be seen later that the flux equations 5 can, after some manipulation, be integrated in terms of tabulated functions if the substitution $d \ln c_j = d \ln a_j$ is made; that is, if activity coefficient gradients within the membrane are neglected. This assumption is not needed yet; for now, the activity term will be split into a concentration term and an activity coefficient term, and the activity coefficient will be carried in a simple form into the final differential equations for species concentration and potential. Then, the activity coefficient term will be dropped. The question of the proper treatment of activity coefficient gradients may be moot; the activity coefficient as a thermodynamic concept may not be appropriate to nonequilibrium systems (Meares and Ussing, 1959).

In treating the activity coefficients, γ_j, it is assumed, first, that these quantities are defined. Then, since for a mixture of $1-1$ electrolytes at concentrations near those of physiological interest, the mean activity coefficients are nearly the same for each electrolyte and depend on only N (Davies, 1968), it follows that the activity coefficients of all ions of like charge are the same. The term $d \ln \gamma_j/dx$ can be replaced by $(d \ln \gamma_j/dN)(dN/dx)$. We now assume that $d \ln \gamma_j/dN$ is the same for both cations and anions, and replace it by γ', a function of N. Multiplying both sides of equation 5 by $\sum_{k\neq j} f_{jk}/\varphi$ and subtracting $J_j c_j R_{jj}$ from both sides,

$$J_j \frac{f_{jT}}{\varphi} - J_j \sum_i c_i R_{ji} = -c_j RT\gamma' \frac{dN}{dx} - RT\frac{dc_j}{dx} - z_j F c_j \frac{d\psi}{dx} - c_j \sum_i R_{ji} J_i, \qquad (6)$$

where $f_{jT} = f_{jw} + f_{jm}$.

Assume that the n fluxes $\{J_j\}$ and the conditions at one side of the membrane $(x = a)$ are known. The dependence of the $n + 2$ variables $\{c_j\}$, ψ, and N on x is sought. Two relations among the unknowns are needed in addition to the n equations

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[1] The dependence on concentration and composition of coefficients analogous to R_{ij} has been considered by earlier workers. Newman (1967) has proposed the use of a generalized "diffusion coefficient," $\mathfrak{D}_{ij}$, as a composition-insensitive (Smyrl and Newman, 1968) measure of species interactions. This coefficient is inversely proportional to $R_{ij} c_T$, where $c_T = N + c_w$. Since c_w, the concentration of the solvent, is effectively constant and is much larger than N, the constancy of $\mathfrak{D}_{ij}$ implies that of R_{ij}. In fact, R_{ij} more correctly is proportional to $N^{-1/2}$ (see Fig. 2 for experimental evidence; also Onsager and Kim, 1957; Schonert, 1969), but since N does not vary much across biological membranes, the influence of this dependence is generally small.

6. The first of these is the definition of N. The second is an electroneutrality condition:

$$\sum_i c_i z_i + z_x X = 0, \tag{7}$$

where X is the uniform concentration of unit charge fixed to the membrane and z_x is ± 1. These two additional equations will be used to simplify two summations of equation 6. Summing over j, $\sum_j f_{jT} J_j/\varphi - \sum_j \sum_i J_j c_i R_{ji} = -NRT\gamma' \, dN/dx - RT \, dN/dx + z_x XF \, d\psi/dx - \sum_j \sum_i c_j R_{ji} J_i$. Interchanging the indices in either of the double sums changes the subscripts of J and c, but R_{ij} obeys the Onsager reciprocal relation $R_{ij} = R_{ji}$. The double sums thus cancel to give

$$\frac{1}{\varphi} \sum_j f_{jT} J_j = -NRT\gamma' \frac{dN}{dx} - RT \frac{dN}{dx} + z_x XF \frac{d\psi}{dx}. \tag{8}$$

When the membrane is uncharged, equation 8 can be integrated directly to give an implicit solution for N, which, if the fluxes are fixed, is independent of the extent of ion-ion interactions. Multiplying equation 6 by z_j and summing over j, $\sum_j J_j z_j f_{jT}/\varphi - \sum_j \sum_i J_j z_j c_i R_{ji} = z_x XRT\gamma' \, dN/dx - FN \, d\psi/dx - \sum_j \sum_i c_j z_j R_{ji} J_i$. The indices are interchanged in the double sum on the left-hand side to give $\sum_j \sum_i J_i z_i c_j R_{ji}$; then the sum over i is broken into two sums—one over those ions for which $z_i = z_j$, and one over those for which $z_i = -z_j$. The double sum on the right-hand side is split similarly, to give

$$\frac{1}{\varphi} \sum_j J_j z_j f_{jT} = z_x XRT\gamma' \frac{dN}{dx} - FN \frac{d\psi}{dx} - 2 \sum_j \sum_{\substack{i \\ z_i = -z_j}} c_j z_j R_{ji} J_i. \tag{9}$$

Equations 6, 8, and 9 are quite general and are sufficient to solve the problem posed in the preceding paragraph. Their solution is complicated by their being coupled and also by the presence of nonlinear terms arising from the activity coefficient gradient. The equations can be integrated numerically, permitting if desired the drag terms f_{jT} and R_{ij} to vary through the membrane. However, such a solution would not be as instructive as an analytic one; furthermore, recalling that these equations must be solved for each trial set of fluxes, the computational effort required could be massive.

The $n + 2$ equations 6, 8, and 9 can be collapsed to n uncoupled equations when two further departures from rigor are made. They are the following.

(*a*) It is assumed with Meares (1959) and with Kedem and Katchalsky (1961) that direct interactions between ions of like charge ($z_i = z_j$) are negligible, and further that $R_{ij}(z_i = -z_j)$ is the same for all such ion pairs. This assumption decouples the flux equations while preserving the essential features of ion drag.

(*b*) It is assumed that activity coefficient gradients *within* a membrane phase are small. This assumption is justified for physiological systems since the ionic strength of body fluids varies little. When multiple membrane systems are treated, activity coefficients will be retained in the description of the interface conditions.

The sum in the left-hand side of equation 6 can then be written as

$$J_j \bar{R} \sum_{\substack{i \\ z_i = -z_j}} c_i ,$$

where $\bar{R}$ is the value of R_{ij} for oppositely charged ions. The sums over concentration in the definition of N and in the electroneutrality condition of equation 7 are split into sums over $i(z_i = z_j)$ and $i(z_i = -z_j)$. These equations are then solved to give

$$\sum_{\substack{i \\ z_i = -z_j}} c_i = [(z_x X / z_j) + N]/2.$$

Equation 6 becomes

$$J_j \frac{f_{jT}}{\varphi} - \frac{J_j \bar{R}}{2}\left(\frac{z_x X}{z_j} + N\right) = -RT \frac{dc_j}{dx} - z_j F c_j \frac{d\psi}{dx} - c_j \bar{R}(\mathrm{J}_{+j} - z_j I), \qquad (10)$$

where J_{+j} is the total net flux of ions charged similarly to j and $I = \sum_j z_j J_j$ is the net diffusion current density. In the double sum in the right-hand side of equation 9, R_{ij} is replaced by $\bar{R}$, z_j is replaced by $-z_i$, and the sums over c_j are evaluated using the earlier equation for

$$\sum_{\substack{i \\ z_i = -z_j}} c_i ,$$

for $z_j = \pm 1$.

Equation 9 is then rearranged to give

$$F \frac{d\psi}{dx} = \frac{\bar{R}}{N}(NI + z_x X \mathrm{J}) - \frac{1}{N\varphi} \sum_j J_j z_j f_{jT}, \qquad (11)$$

where $\mathrm{J} = \sum_j J_j$ is the total net flux. Substituting equation 11 into equation 8,

$$RT \frac{dN}{dx} = z_x X \bar{R} I - \frac{1}{\varphi} \sum_j f_{jT} J_j + \frac{1}{N}\left(X^2 \bar{R} \mathrm{J} - \frac{z_x X}{\varphi} \sum_j J_j z_j f_{jT}\right). \qquad (12)$$

Equation 12 can be integrated from $N(a) = N_a$ to $N(x) = N$ to give

$$\frac{x - a}{RT} = \frac{N_a - N}{\pi_1} + \frac{\pi_2}{\pi_1^2} \ln \frac{\pi_2 + \pi_1 N}{\pi_2 + \pi_1 N_a}, \qquad (13)$$

where $\pi_1 = \sum_j f_{jT} J_j / \varphi - \bar{R} z_x X I$ and $\pi_2 = z_x X \sum_j J_j z_j f_{jT} / \varphi - \bar{R} X^2 \mathrm{J}$.

Since dN/dx is a function of only N, it follows that if $dN/dx = 0$ anywhere, then

$dN/dx = 0$ everywhere. Furthermore, if $dN/dx \neq 0$ anywhere, then $dN/dx = 0$ nowhere. That is, N either varies monotonically with x or N is constant. If N is constant, $d\psi/dx$ is constant[2] (equation 11) and equation 10 can be solved directly for $c_j(x)$.[3] If N is not constant, $d\psi/dx$ varies with x according to equation 11. Then by Poisson's equation, there is a distribution of net charge within the membrane, and the electroneutrality condition of equation 7 is no longer exact. In practice, the net charge required to produce the curvature given by equation 11 is generally trivial compared to N (Planck, 1890; MacGillivray, 1968, gives a criterion), so that equation 7 can still be employed, as it is here, for mass balance purposes. That this is so in any particular case can be established by differentiating equation 11, with equation 12 for dN/dx. The influence of space charge on the utility of equation 7 may possibly be of importance in thin lipid interfaces, where N is small and the potential gradient is steep. Any estimate of space charge effects in the low dielectric regions of biological membranes is subject to uncertainties in the pertinent dielectric constants, partition coefficients, and fixed charge densities (MacGillivray and Hare, 1969). If the electrolyte passes through aqueous pores, space charge effects are small if the membrane thickness exceeds several Debye lengths, a condition easily met when dealing with solutions of physiological strength.

The monotonicity of N allows equation 12 to be used to replace the independent variable x in equation 10 by N. Using equation 11 for $d\psi/dx$, the final flux equations are uncoupled and linear in c_j:

$$J_j \frac{f_{jT}}{\varphi} - \frac{J_j \bar{R}}{2}\left(\frac{z_x X}{z_j} + N\right) = \left(\pi_1 + \frac{\pi_2}{N}\right)\frac{dc_j}{dN} - z_j c_j\left[\bar{R}\left(z_j \mathrm{J}_{+j} + \frac{\mathrm{J} z_x X}{N}\right) - \frac{1}{N\varphi}\sum_i J_i z_i f_{iT}\right]. \quad (14)$$

SOLUTION OF THE FLUX EQUATIONS

Equation 14 is linear in c_j, of the form $dc_j/dN + P_j(N)c_j = Q_j(N)$; its solution is

$$c_j = \frac{1}{I_j(N)}\left[\int_{N_a}^{N} I_j(N')Q_j(N')\,dN' + I_j(N_a)c_j^a\right],$$

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[2] A sufficient condition for the constancy of N in the steady state, when the drag terms f_{jT} and $\bar{R}$ are independent of x, is that the solutions just inside the membrane have the same total concentration $[N(a) = N(b)]$. Since physiological structures cannot withstand considerable osmotic pressures, most biological membranes are bounded by near isotonic solutions. This may explain the empirical success of the constant field equation (Goldman, 1943; see Geduldig, 1968) in describing the membrane potential of such systems. The constant-field equation is not generally consistent with the Nernst-Planck equations; its limitations have been explored elsewhere (Zelman, 1968; Friedman, 1969).

[3] In general, N will be different on each side of the membrane. So that the same computational technique can be used when $dN/dx \equiv 0$, the fluxes and species concentration profiles when N is constant can be found by setting $N(b) = N_b = N_a(1 \pm \epsilon)$, $\epsilon << 1$, and averaging the results.

where $I_j(N) = \exp\,[\int P_j(N)\,dN]$. To simplify the final answer, N is replaced by the nondimensional total concentration $u = -\bar{R}J_{+j}(\pi_2 + N\pi_1)/\pi_1^2$.[4] Then

$$I_j(u) = \left(-\frac{\pi_1^2}{\bar{R}J_{+j}}\right)^{\pi_3} u^{\pi_3} \exp\left(u + \frac{\pi_2 \bar{R}J_{+j}}{\pi_1^2}\right), \tag{15 a}$$

$$\begin{aligned}\int I_j Q_j\,du = \frac{1}{\pi_1^2}\,[\exp\,(\bar{R}J_{+j}\,\pi_2/\pi_1^2)]\left(-\frac{\pi_1^2}{\bar{R}J_{+j}}\right)^{\pi_3} \\ \times \int e^u\left[\pi_2\left(-\frac{\bar{R}J_j\,\pi_2}{2\pi_1} - \pi_{4j}\right)\right. \\ \left. - \frac{u\pi_1}{J_{+j}}\left(\frac{\pi_{4j}\,\pi_1}{\bar{R}} + J_j\,\pi_2\right) + u^2\left(-\frac{J_j\,\pi_1^3}{2\bar{R}J_{+j}^2}\right)\right] u^{\pi_3-1}\,du,\end{aligned} \tag{15 b}$$

where $\pi_3 = \pi_2[\bar{R}J_{+j} + \pi_1 z_j/(z_x X)]/\pi_1^2$ (footnote 4) and $\pi_{4j} = J_j f_{jT}/\varphi - \bar{R}J_j z_x z_j X/2$. The integral in equation 15 *b* consists of terms of the form $\int_{u_a}^{u} e^{u'}(u')^{\zeta}\,du'$, with $u_a = u(N_a)$, which can be expressed as the difference of incomplete gamma functions, $\gamma^*(a, x)$:

$$\int_0^u e^{u'}(u')^{\zeta}\,du' = u^{\zeta+1}\Gamma(\zeta + 1)\gamma^*(\zeta + 1, -u).$$

The integral then becomes

$$\begin{aligned}\int_0^u e^{u'}[\alpha_{0j} + \alpha_{1j}u' + \alpha_{2j}(u')^2](u')^{\pi_3-1}\,du' \\ = u^{\pi_3}\{\Gamma(\pi_3)\gamma^*(\pi_3, -u)[\alpha_{0j} - \alpha_{1j}\pi_3 + \alpha_{2j}\pi_3(\pi_3 + 1)] \\ + e^u[\alpha_{1j} - \alpha_{2j}(\pi_3 + 1 - u)]\} \\ \equiv U_j(u),\end{aligned}$$

where the recurrence formulas for Γ and γ^* have been used and α_{nj} denotes the coefficient of u^n in the brackets in the integrand of equation 15 *b*.

The solution of equation 14, in terms of u, is

$$c_j = e^{-u}u^{-\pi_3}\left\{\frac{1}{\pi_1^2}\,[U_j(u) - U_j(u_a)] + e^{u_a}u_a^{\pi_3}c_j^a\right\}. \tag{16}$$

Once the steady fluxes are known, equation 11 can be integrated, using equation 12, to give the membrane potential

$$F(\psi - \psi_a) = \bar{R}J(x - a) + \frac{RT\pi_2}{\pi_1 z_x X}\ln\frac{u}{u_a}, \tag{17}$$

where $\psi_a = \psi(\mathrm{a})$.

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[4] The variables u and π_3 are not subscripted here but they do depend on j through J_{+j}; thus u (and π_3) are the same for all ions of like charge.

SPECIAL CASES

It was noted earlier that when N does not vary through the membrane, the solution is considerably simplified, but is not given by equation 14. This is most importantly the case for highly permselective membranes containing a large concentration of uniformly distributed charge. For these,

$$N \approx \sum_{\substack{i \\ z_i = -z_x}} c_i \approx X.$$

We now examine some other special cases, which can be described by equation 14.

No Ion-Ion Interactions

When $\bar{R} = 0$, the solution for c_j given by equation 16 cannot be used directly because $u \equiv 0$. In real electrolytic solutions, $\bar{R}$ is never zero. Nonetheless, limiting solutions of the flux equations are useful for assessing the importance of ion drag; these can be found numerically by setting $-\bar{R} < < f_{iT}/(\varphi N)$. In the limit $\bar{R} \rightarrow 0$, equation 16 becomes identical to the Behn (1897) solution.

Exchange Diffusion

A second case in which $u \equiv 0$ is that of exchange diffusion. When the net diffusion current and the net flux of each (for instance) anion are zero, $\pi_3 = 1$ and $J_{+j} = 0$ for the exchanging cations. In the limit $J_{+j} \rightarrow 0$, $U_j(u) \rightarrow u(\alpha_{0j} + u\alpha_{1j}/2 + u^2\alpha_{2j}/3)$, where the parenthesized terms are $\Theta(J^0_{+j})$. When $u^{-\pi_3} = u^{-1}$ is multiplied into the brackets in equation 16, a solution for c_j is obtained which is neither singular nor trivial.

Diffusion Potential, Single Electrolyte, Zero Current

In general, the diffusion potential in a multi-ionic system cannot be directly related to the boundary conditions because the fluxes are unknown. However, when only a single salt is present and $I = 0$, an explicit solution can be found. To facilitate comparisons with similar solutions, the friction coefficients are replaced by mobilities $v_i = F\varphi/f_{iT}$. Then equation 17 becomes

$$F(\psi_b - \psi_a) = \frac{RT}{v_- + v_+}\left(v_- - v_+ - \frac{2\bar{R}z_x X v_+ v_-}{F}\right) \times \ln \frac{z_x XF(v_- - v_+) - 2\bar{R}X^2 v_+ v_- + N_b F(v_- + v_+)}{z_x XF(v_- - v_+) - 2\bar{R}X^2 v_+ v_- + N_a F(v_- + v_+)}.$$

By definition, $N = c_+ + c_-$, and by electroneutrality, $z_x X = c_- - c_+$, where $c_+ (c_-)$ is the concentration of cation (anion). In terms of concentrations, the argument of the logarithm is $(c^b_- v_- + c^b_+ v_+ - \bar{R}X^2 v_+ v_-/F)/(c^a_- v_- + c^a_+ v_+ - \bar{R}X^2 v_+ v_-/F)$. It is interesting to note that ion-ion interactions affect the diffusion potential only if the membrane is charged. When $R = 0$, the equation for diffusion potential given by Harris (1956) is recovered.

AN EXAMPLE

To illustrate the application of equation 16 and the influence of solute-solute interactions, consider the membrane or junction in Fig. 1. The membrane is bounded by well-mixed isotonic solutions at 25°C and, for simplicity, is conveniently very loose ($\varphi \approx 1$). Its effective thickness, corrected for tortuosity, is 1 cm. R^+ is a difficultly permeating cation whose mobility is one-tenth that of sodium. The frictional coefficients used are those for pure solutions; f_{jT}/φ is replaced by f_{jw}.

The values of the frictional coefficients and the interaction coefficient R are based on the computations for NaCl solutions given by Katchalsky and Curran (1965). Their data are used to find $f_{\mathrm{Na},w}$ and the frictional coefficients for the other ions are computed by assuming that f_{jw} is inversely proportional to u_j^0, the infinite dilution mobility at 25°C; $f_{jw} = f_{\mathrm{Na},w} u_{\mathrm{Na}}^0 / u_j^0$. The interaction coefficient was equated to that between sodium and chloride in the ternary system. Fig. 2 shows the variation of $f_{\mathrm{Na},w}$, $R_{\mathrm{Na,Cl}}$, and $R_{\mathrm{Na,Cl}} c_s^{1/2}$ with c_s, where c_s is the concentration of the common salt

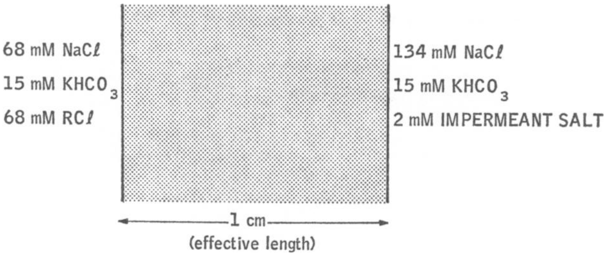

FIGURE 1 Example membrane.

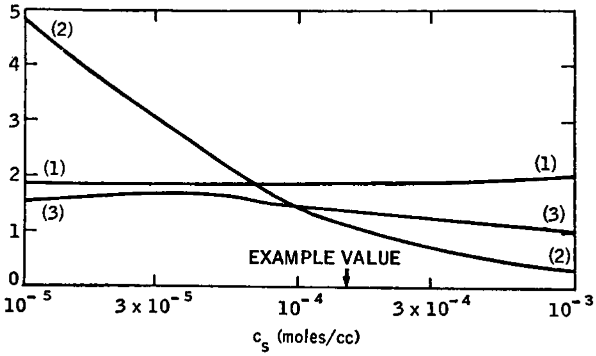

FIGURE 2 Solute-solvent and solute-solute interaction parameters as a function of NaCl concentration, c_s. (1) $f_{\mathrm{Na},w} \times 10^{-8}$, j-sec/mole-cm^2; (2) $-R_{\mathrm{Na,Cl}} \times 10^{-11}$, j-sec-cm/mole^2; (3) $-R_{\mathrm{Na,Cl}} c_s^{1/2} \times 10^{-9}$, j-sec/mole$^{3/2}$-cm$^{1/2}$.

solution. As indicated in Fig. 2, the value of c_s taken to describe the system in Fig. 1 was $c_s = 0.15$ M. R was equated to $R_{Na,Cl}$ at this concentration. The translation of Katchalsky and Curran's variables into those used here is summarized in the Appendix. The symbol v_j again means species velocity, as given by equation 2.

Figs. 3-5 illustrate the effect of ion-ion interactions on the diffusion fluxes (J_j) and the membrane potential (ψ) at various membrane charge (X) and current (I) densities. Since the current density refers to diffusion current only, the results in the figures describe as well the behavior of an open-circuited membrane possessing an electrogenic pump. In the discussion to follow, all trends in J_j and ψ will be described algebraically; values obtained when ion-ion interactions are included will be denoted by the superscript i. Flux towards the right is positive.

When the membrane is uncharged, the major flux across it is that of Na^+ diffusing down its concentration gradient. The diffusion potential at zero current is negative (right side of membrane relative to left side), so that the net anion flux equals the net cation flux. As I becomes more negative, ψ becomes more positive and the magnitudes of the K^+, Cl^-, and HCO_3^- migrations diminish (J_{Cl} is not shown in Fig. 3 for the sake of clarity; its behavior is similar to that of J_{HCO_3}). The flux of R^+ is much less than $-J_{Na}$ because of the low mobility of the former.

When ion-ion interactions are included, the chloride still migrates towards the left when I is near zero, but $|v^i_{Cl}| < |v^i_{Na}|$, so the sodium flux towards the left is retarded

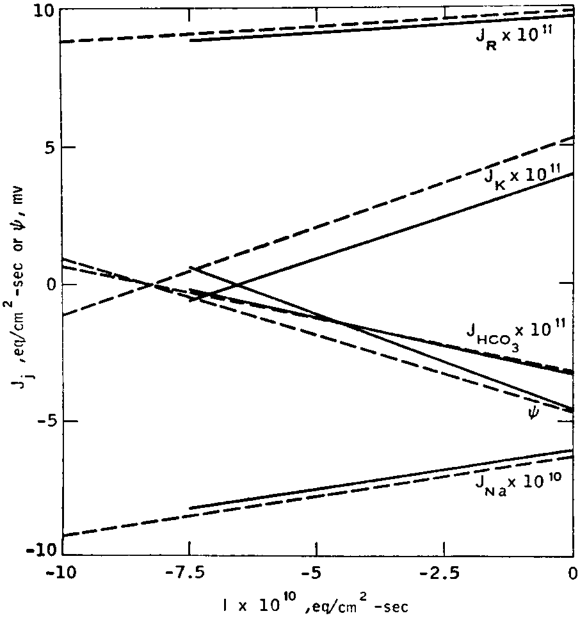

FIGURE 3 Species fluxes (J_j) and membrane potential (ψ) across uncharged example membrane vs. diffusion current density: --- ion-ion interactions omitted; —— ion-ion interactions included. J_{Cl} is omitted for the sake of clarity.

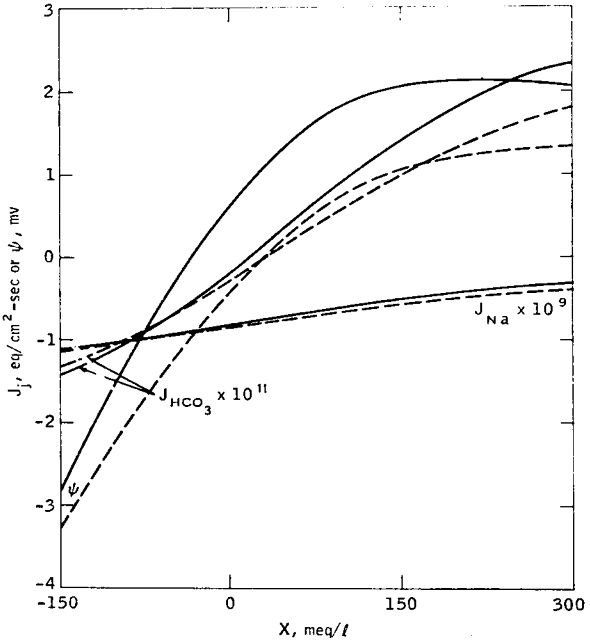

FIGURE 4 Species fluxes (J_j, j = Na$^+$, HCO$_3^-$) and membrane potential (ψ) across charged example membrane with diffusion current density $I = -7.5 \times 10^{-10}$ eq/cm^2-sec vs. membrane charge density: – – – ion-ion interactions omitted; —— ion-ion interactions included.

and the diffusion potential is less negative. The difference between ψ^i and ψ increases as I becomes more negative and $v^i_{Cl} - v^i_{Na}$ rises. The flux of R^+ is also retarded by the oppositely directed chloride flux, but the drag effect is less pronounced for R^+ than for Na$^+$, since the resistance of the membrane to flow of the former is large. The effect of the increase in ψ which results when ion drag is included is to retard both the potassium flux to the right and the bicarbonate flux to the left. The potassium flux is further retarded by the oppositely directed chloride flux, and J^i_K is much less than J_K. On the other hand, the leftward bicarbonate flux is augmented by the considerable flux of sodium to the left; the effects of $(\psi^i - \psi)$ and J^i_{Na} nearly cancel, and $J^i_{HCO_3}$ is very close to J_{HCO_3}.

The open circuit value of ψ is not greatly affected by the inclusion of ion drag; when $I = 0$, $\psi = -4.65$ mv, and $\psi^i = -4.58$ mv. However, the short-circuit current (SCC) changes from SCC $= -8.2 \times 10^{-10}$ eq/cm^2-sec to SCC$^i = -6.5 \times 10^{-10}$ eq/cm^2-sec. Thus, if this membrane possessed an active ion transport system, neglect of ion-ion interactions could lead to a considerable error (1.7×10^{-10} eq/cm^2-sec) in pump rate (P) as calculated from P = observed SCC − SCC calculated in the absence of pumping.

The influence of membrane charge density on J_j and ψ (exclusive of Donnan potentials at the membrane interfaces) at a fixed current $I = -7.5 \times 10^{-10}$ eq/cm^2-sec,

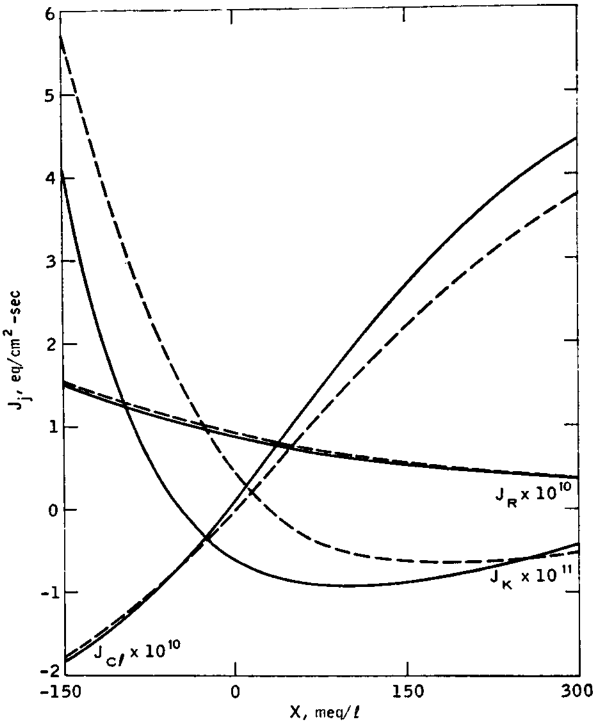

FIGURE 5 Species fluxes (J_j, j = Cl$^-$, K$^+$, R^+) across charged example membrane with diffusion current density $I = -7.5 \times 10^{-10}$ eq/cm^2-sec vs. membrane charge density: – – – ion-ion interactions omitted; —— ion-ion interactions included.

is shown in Figs. 4 and 5. In positively charged membranes, an increasing proportion of the current is carried by the chloride (Fig. 5). Since there is only a small chloride concentration gradient across the membrane, this flux is essentially a migration, driven by the larger values of ψ across cationic membranes (Fig. 4). In negatively charged membranes, ψ is negative to retard the more facile flux of the sodium ions under their concentration gradient. The value of ψ^i is larger than ψ for all values of X. When X is positive, ψ^i is larger to compensate for the interaction between the oppositely directed major ion (Na$^+$ and Cl$^-$) fluxes; when X is negative, ψ^i need not be as negative as ψ because some retardation of the sodium flux is provided by the slower coions. At large $|X|$, ψ^i approaches ψ because coions are excluded in the limit and there is no opportunity for direct interactions between oppositely charged species. Thus $\psi^i - \psi$ exhibits a maximum, and this is reflected in the maximum value of ψ^i when $X \approx 200$ meq/liter.

In general, the magnitudes of the counterion fluxes increase as $|X|$ increases, and those of the coions approach zero. Stated in another way, for the jth ion, J_j approaches zero as z_jX increases. This trend, though necessarily true for highly charged membranes, is perturbed somewhat in less charged membranes by the variation of

ψ with X. Thus the negative value of ψ when X is negative causes J_{HCO_3} and J_{Cl} to go negative, and the positive value of ψ when X is positive causes J_K to go negative. As a consequence, the fluxes of these species exhibit minima; this can be seen for K^+ in Fig. 5 and occurs for HCO_3^- and Cl^- at membrane charge densities more negative than those used here.

The inclusion of ion-ion interactions does not introduce any qualitative change in the dependence of species flux on membrane charge. The influence of ion drag on the fluxes of counterions can generally be interpreted in terms of the change in membrane potential when ion drag is included. Thus $J^i_{Cl} > J_{Cl}$ and $J^i_{HCO_3} > J_{HCO_3}$ in positively charged membranes and $J^i_K < J_K$ when $X < 0$. When j is a coion, J^i_j approaches J_j as $|X|$ increases, since both fluxes tend to zero. Coions are particularly influenced by direct interactions, since they are dilute and in the presence of much counterion; these interactions are sufficient to offset the effect of $\psi^i - \psi$, and the curves of J^i_{Cl} and J_{Cl}, $J^i_{HCO_3}$ and J_{HCO_3}, and J^i_K and J_K cross when the membrane charge is large and of the same sign as the ion. Again, the membrane itself provides the major resistance to the flow of R^+; J^i_R is always close to J_R.

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APPENDIX

Frictional and Interaction Coefficients in NaCl Solutions

The phenomenological equations for which the coefficients are given by Katchalsky and Curran (1965) are $J_1 = -L_{11}\, d\tilde{\mu}_1/dx - L_{12}\, d\tilde{\mu}_2/dx$ and similarly for J_2, where the subscripts 1 and 2 denote sodium and chloride, respectively. For this system, it is easy to show, using equation 3, that $R_{12} = -R_{11}L_{12}/L_{22}$. Equating the coefficient of J_j in equation 3 with that from equations 1 and 2, $R_{jj} = \sum_{k\neq j} f_{jk}/C_j$. For sodium in the absence of a membrane, this becomes $R_{11} = (f_{1w} + f_{12})/c_s$, where c_s is the concentration of the salt solution. But $f_{12} = -c_s R_{12}$ by equation 4, so

$$R_{12} = -\frac{L_{12}}{L_{22}\, c_s}(f_{1w} - c_s R_{12}). \qquad \text{(A 1)}$$

R_{12} can thus be found once f_{1w} is known.

To find f_{1w}, consider a NaCl solution of uniform composition in an electric field $E = -d\psi/dx$. Equation 10 simplifies in this case to

$$J_1(f_{1w} - R_{12}c_s) = c_s(FE - R_{12}J_2). \qquad \text{(A 2)}$$

Katchalsky and Curran (1965) describe the migration of the ions in such a system by $J_j = z_j c_s u_j E$, where u_j is the practical mobility and is tabulated as a function of c_s for NaCl solutions. This equation for J_j is substituted into equation A 2, which is solved with equation A 1 for f_{1w} :

$$f_{1w} = \frac{F}{u_1 - \mathrm{L}_1(u_1 + u_2)}, \tag{A 3}$$

where $\mathrm{L}_1 = -L_{12}/(L_{22} - L_{12})$.

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