THE ELECTRICAL CONDUCTANCE OF SEMIPERMEABLE MEMBRANES

III. BIPOLAR FLOW-SYMMETRIC ELECTROLYTES

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ABSTRACT The first paper of this series presented a general formulation of the problem of stationary ion flow through membranes. The second treated in detail the special case of unipolar flow across membranes separating symmetric electrolytes. In this, the third paper of the series, we deal with another special case, that of bipolar flow between symmetric electrolytes. Here it is assumed that the total current is carried by both positive and negative permeant ions. The restriction to symmetric electrolytes implies that all ions present in the membrane and surrounding solutions have valences of identical absolute magnitude. After extracting from the general development a set of equations appropriate to the special case being considered, we outline a procedure for the numerical solution of the conductance problem for this case. Numerical results, presented as part of a discussion of approximate analytic methods of solution, establish the utility of these methods. A discussion of the significance of this work for membrane studies is presented in conclusion.

INTRODUCTION

The objective of this paper is the evaluation of conductance relationships appropriate for the characterization of a stationary bipolar flow of ions across a semipermeable membrane separating symmetric electrolytes. The approach is based upon a general formulation developed in the first paper of this series, that of Bruner (1965). All assumptions and restrictions set forth therein will apply here. The application of the general formulation to a special case follows a pattern established by our second paper which is included in the citation given above. The latter dealt with the case of unipolar ion flow between symmetric electrolytes. We now undertake an evaluation of membrane conductance under conditions specified by the following criteria:

(*a*) The ion current is bipolar, being comprised of contributions from the flow of both positive and negative permeant ions.

(*b*) Our restriction to symmetric electrolytes implies that the valence states of all ions present are of equal absolute magnitude.

It will be assumed that the reader is completely familiar with the first and second papers of this series. These will be referred to here simply as I and II respectively, with citation of numbered equations therein taking the form I(*n*) or II(*n*) as appropriate. Notation previously introduced will be used here without restatement of its meaning.

THE FORMAL DEVELOPMENT

To adapt the general formalism of I to the special case defined above we note from equation II(1) that

$$q^+ = q^- = \tfrac{1}{2} \tag{1}$$

establishes the symmetry of the electrolytes. The assumption of bipolar flow is stated in a negative sense by means of the inequality

$$a^+ \neq \pm a^- \tag{2}$$

which asserts that the flow is not unipolar. The inequality (2, *u*) becomes, upon reduction to equality, equation II(2) which is appropriate to a description of unipolar flow of positive ions. Similar reduction of the inequality (2, *l*) yields an equation describing a unipolar flow of negative ions.

Having specified the case of bipolar flow between symmetric electrolytes we continue by setting forth, for each of the three regions which comprise the membrane-solution system, the differential equations which describe the spatial variation of the electric displacement. Apply equation (1) to equation I(52) to obtain

$$\left(\frac{dy}{d\xi}\right)^2 = \alpha^2 y^4 + \alpha y^2 \tag{3}$$

which is the differential equation appropriate to region I. This result is identical with equation II(5) as may be expected since, because of our assumption that the phases external to the membrane are perfectly conducting, equation I(52) does not involve the current parameters, a^+, and a^-. Its reduction to equation (3) is a consequence solely of the assumed symmetry of the electrolytes.

For region II apply equation (1) to equation I(53) to obtain

$$\frac{d^2y}{d\xi^2} = 2y\,[y^2 - a^-\xi + B^2] - a^+ \tag{4}$$

where the constant, B^2, is given by

$$y(0)^2 + B^2 = \frac{c^+_{\text{per}}(0) + c^-_{\text{per}}(0)}{4c_1} \tag{5}$$

Observe that, if $a^- = a^+$, equation (4) would be identical in form with equation II(7) and a first integral corresponding to equation II(8) could be obtained. This can also be done if $a^- = -a^+$, but is not possible under the condition for bipolar flow given by equation (2). This important formal distinction between the cases of unipolar and of bipolar flow has its counterpart in significant physical differences to be described below.

An explicit expression for B^2 in terms of $y(0)$ and equilibrium parameters of the system is obtained by use of equations (1), (4), and I(74). Equation (3) is used to eliminate $(dy(0)/d\xi)_{\mathrm{I}}$, with selection of roots being made in accordance with criteria set forth in II. The expression for B^2 is

$$\begin{aligned} y(0)^2 + B^2 = {} & \frac{1}{4(1+\gamma^+)} [(2\alpha y(0)^2 + 1) \pm \{(2\alpha y(0)^2 + 1)^2 - 1\}^{1/2}] \\ & + \frac{1}{4(1+\gamma^-)} [(2\alpha y(0)^2 + 1) \mp \{(2\alpha y(0)^2 + 1)^2 - 1\}^{1/2}] \end{aligned} \tag{6}$$

where equation (6, *u*) is used when $y(0)$ is positive and equation (6, *l*) applies when $y(0)$ is negative.

For region III equations (1) and I(58) yield

$$\left(\frac{dy}{d\xi}\right)^2 = \alpha^2 y^4 + \alpha R y^2 \tag{7}$$

which, for reasons noted above in the discussion of equation (3), is identical to equation II(13).

We conclude this section by specifying the initial and terminal slopes of y within region II. Apply equation (1) to equations I(69) and I(73) using appropriate roots of equations (3) and (7) to obtain

$$\begin{aligned} \left(\frac{dy(0)}{d\xi}\right)_{\mathrm{II}} = {} & \frac{1}{4(1+\gamma^+)} [(2\alpha y(0)^2 + 1) \pm \{(2\alpha y(0)^2 + 1)^2 - 1\}^{1/2}] \\ & - \frac{1}{4(1+\gamma^-)} [(2\alpha y(0)^2 + 1) \mp \{(2\alpha y(0)^2 + 1)^2 - 1\}^{1/2}] \end{aligned} \tag{8}$$

and

$$\begin{aligned} \left(\frac{dy(\xi_1)}{d\xi}\right)_{\mathrm{II}} = {} & \frac{\exp(-\rho_0)}{4R(1+\gamma^+)} [(2\alpha y(\xi_1)^2 + R) \mp \{(2\alpha y(\xi_1)^2 + R)^2 - R^2\}^{1/2}] \\ & - \frac{\exp(\rho_0)}{4R(1+\gamma^-)} [(2\alpha y(\xi_1)^2 + R) \pm \{(2\alpha y(\xi_1)^2 + R)^2 - R^2\}^{1/2}] \end{aligned} \tag{9}$$

where equations (8, *u*) or (9, *u*) are used when $y(0)$ or $y(\xi_1)$ respectively are positive, and equations (8, *l*) or (9, *l*) are appropriate otherwise.

NUMERICAL ANALYSIS

The search for solutions of equation (4) which satisfy the specified boundary conditions in region II is facilitated, as noted in section 7 of I, by use of an auxiliary condition derivable from equation I(25). We specialize the latter to the case of symmetric electrolytes, then write it in dimensionless form as

$$\frac{\overset{+}{c}_{\text{per}} + \overset{-}{c}_{\text{per}}}{4c_1} = y^2 - a^{-}\xi + B^2 \tag{10}$$

using equation (5). This result holds throughout region II. Its evaluation at $\xi = \xi_1$, and evaluation of equations I(72, *u* and *l*) at the same point, lead to

$$\begin{aligned} y(\xi_1)^2 - a^{-}\xi_1 + B^2 & \\ = \frac{\exp(-\rho_0)}{4R(1+\gamma^{+})} & [(2\alpha y(\xi_1)^2 + R) \mp \{(2\alpha y(\xi_1)^2 + R)^2 - R^2\}^{1/2}] \\ + \frac{\exp(\rho_0)}{4R(1+\gamma^{-})} & [(2\alpha y(\xi_1)^2 + R) \pm \{(2\alpha y(\xi_1)^2 + R)^2 - R^2\}^{1/2}] \end{aligned} \tag{11}$$

where equation (11, *u*) applies when $y(\xi_1)$ is positive and equation (11, *l*) is used for negative values of $y(\xi_1)$.

One could begin the numerical solution of the problem by arbitrarily assigning a value to either $y(0)$ or $y(\xi_1)$, thereby fixing upon a particular stationary state of the system. In obtaining numerical solutions we proceed as follows:

(*a*) Fix a value for $y(\xi_1)$ and retain it throughout the ensuing procedure.

(*b*) Pick a value for $y(0)$. Use these end point values, together with the equilibrium parameters of the system which must be specified at the outset, in equations (6) and (11) to determine B^2 and a^{-}.

(*c*) Now determine $(dy(0)/d\xi)_{\text{II}}$ using equation (8), then integrate equation (4) numerically using an arbitrarily chosen value of a^{+}. The solution thus obtained will in general yield a terminal value of y which is not equal to the value, $y(\xi_1)$, chosen initially. Inspection of equation (4) reveals that the parameter, a^{+}, contributes directly to the curvature of the solution and thus it is possible to change a^{+} systematically, retaining the same initial value and slope of y and the same value of a^{-}, until a numerical solution of equation (4) is achieved which has a terminal value of y as close to the initially chosen value of $y(\xi_1)$ as may be desired. This procedure yields an "end point matched" or EPM solution which will in general satisfy all of the boundary conditions except one; namely, the terminal slope of the EPM solution obtained numerically will not agree with that required by equation (9).

(*d*) One then returns to (*b*), selects a new value of $y(0)$ and generates a new EPM solution, repeating this process until a solution is achieved which satisfies all boundary conditions within desired accuracy. Since, for EPM solutions, the terminal slope proves to be a monotonic function of the initial value of y, this procedure may readily be systematized also.

(*e*) This technique produces unique solutions with completely specified values of a^+, a^-, and $y(0)$, corresponding to the value of $y(\xi_1)$ initially chosen. All that remains is the determination of the corresponding value of P, the transmembrane potential, defined as $(\rho(-\infty) - \rho(\infty))$. A convenient expression for this quantity is

$$P = \ln\left[\left\{\frac{(2\alpha y(0)^2 + 1) + 2\left(\dfrac{dy(0)}{d\xi}\right)_{\mathrm{I}}}{(2\alpha y(\xi_1)^2 + R) + 2\left(\dfrac{dy(\xi_1)}{d\xi}\right)_{\mathrm{III}}}\right\} R\right] + 2\int_0^{\xi_1} y \, d\xi \qquad (12)$$

and is obtained from equations I(78) and I(76), with use being made of the constancy of the electrochemical potentials in the phases exterior to the membrane. The integral is computed numerically and the logarithmic term is evaluated with the aid of appropriately selected roots of equations (3) and (7).

A computer program has been written to perform the sequence of operations described above. Presentation of numerical results will complement the discussion of approximate analytic methods of solution given below.

ANALYTIC APPROXIMATIONS

1. *The Case*, $(\alpha = 0)$

We will treat separately the case in which the media exterior to the membrane are infinitely polarizable, $(\alpha = 0)$, and the case in which the polarization of these media is finite in finite electric field, $(\alpha > 0)$. In the former case electric fields present in the membrane are completely screened from the exterior by induced charge at the interfaces; in the latter case this screening is not complete. These cases represent quite different situations in the high current limit as was seen in II and as will be demonstrated again here. Approximations valid when $\alpha = 0$, though strictly speaking this case cannot be realized in practice, may nonetheless provide useful results at intermediate current levels for which $\alpha y^2 \ll 1$. This point will be illustrated by a numerical example given below. We proceed with an abbreviated treatment of the case, $(\alpha = 0)$.

Equations (8) and (9) show that, when $\alpha = 0$, the initial and terminal slopes of y in region II become constants, expressible in terms of γ^+, γ^- and ρ_0, which we label S_1 and S_2, respectively. The slope at each boundary is related, through Poisson's equation, to the difference between the positive and negative permeant ion concentrations at that boundary. These concentrations are also constants for $\alpha = 0$, as indicated by equations I(68) and I(72). Thus it follows that the left side of equation (10), evaluated at $\xi = 0$, and at $\xi = \xi_1$, may be similarly equated to constants which we label G_1, and G_2, respectively. These constants, which fix the sums of the positive and negative permeant ion concentrations at each boundary, may also be expressed in terms of γ^+, γ^- and ρ_0.

The constancy of the slopes of y at the boundaries implies that the variation of y in region II will not be large. We make this assumption and linearize equation (4) by introducing an incremental displacement function, $\Delta(\xi)$, defined by

$$y(\xi) = y(0) + \Delta(\xi) \tag{13}$$

Assume that $\Delta(\xi) \ll y(0)$, and substitute equation (13) into equation (4). Equate the right side of equation (5) to G_1, and thereby eliminate B^2, to obtain the linear second order equation

$$\frac{d^2\Delta}{d\xi^2} = 4y(0)^2\Delta - 2a^-y(0)\xi + [2G_1 y(0) - a^+] \tag{14}$$

Here terms in Δ^2 and Δ^3 have been dropped, as well as terms in G_1, and Δ, where the latter occur in additive combination with $y(0)^2$, and $y(0)$, respectively. The solution of equation (14) for which $\Delta(0) = 0$, and $(d\Delta(0)/d\xi)_{\text{II}} = S_1$, is

$$\begin{aligned}\Delta(\xi) = \frac{1}{4y(0)^2} [\{2S_1 y(0) - a^+\} \sinh (2y(0)\xi) \\ + \{2G_1 y(0) - a^+\} \cosh (2y(0)\xi) \\ + \{2a^-y(0)\xi - (2G_1 y(0) - a^+)\}]\end{aligned} \tag{15}$$

Linearization of equation (11) yields

$$(G_1 - G_2) + 2y(0)\Delta(\xi_1) - a^-\xi_1 = 0 \tag{16}$$

with use of equations (5) and (10), and the definitions of G_1 and G_2 given above. Evaluation of equation (15) at $\xi = \xi_1$, and use of the result in equation (16), provide the first of two linear inhomogeneous equations which we will solve for a^+ and a^-. The second is provided by differentiating equation (15) and requiring that the result, when evaluated at $\xi = \xi_1$, be consistent with the relation, $(d\Delta(\xi_1)/d\xi)_{\text{II}} = S_2$. The resulting expressions for the current parameters will incorporate the factor, $2y(0)\xi_1$, so we note from equation (12) that, with $\alpha = 0$, and with $\Delta \ll y(0)$, that factor may be equated to P, the transmembrane potential. Thus we obtain the conductance relations

$$a^+ \cong \left(\frac{G_1 + G_2}{2\xi_1}\right) P \left[1 + \Upsilon\left\{\frac{1 + \cosh (P)}{\sinh (P)}\right\}\right] \tag{17}$$

and

$$a^- \cong \left(\frac{S_1 + S_2}{2\xi_1}\right) P \left[1 + \Upsilon\left\{\frac{1 + \cosh (P)}{\sinh (P)}\right\}\right] \tag{18}$$

where it may be shown that

$$\Upsilon = \frac{\sinh(\rho_0)}{1 + \cosh(\rho_0)} \tag{19}$$

independent of γ^+ and γ^-. Note that a^+ and a^- will both vanish when $P = -\rho_C$, i.e., in the equilibrium state.

In Table I we present a comparison of numerical results, obtained for $\alpha = 0$, with results of the analytic approximation. The other equilibrium parameters are as shown in the table and are the same for both calculations. In the first column the value of $y(\xi_1)$ used as the starting point for the numerical analysis is listed. Corresponding values of a^+, a^-, and P, are shown in the next three columns. The numerical value of P is then used in equations (17) and (18) to obtain the approximate values for a^+ and a^- shown in the last two columns. Thus the numerical and analytic values for the current parameters correspond to the same transmembrane potential.

TABLE I

EQUILIBRIUM PARAMETERS

$\rho_0 = 2.0, \quad \gamma^+ = 0.0, \quad \gamma^- = 25.0$

$R = 1.0, \quad \xi_1 = 1.0$

Numerical results ($\alpha = 0.0$)				Analytic approximation ($\alpha = 0.0$)	
$y(\xi_1)$	a^+	a^-	P	a^+	a^-
2.00	1.2589	0.6847	3.9002	1.2745	0.7104
1.50	0.9689	0.5267	2.9109	0.9811	0.5468
1.00	0.7003	0.3809	1.9229	0.7087	0.3951
0.50	0.4631	0.2522	0.9356	0.4681	0.2609
0.00	0.2658	0.1452	−0.0521	0.2682	0.1495
−0.50	0.1117	0.0612	−1.0412	0.1125	0.0627
−1.00	−0.0032	−0.0018	−2.0325	−0.0033	−0.0018
−1.50	−0.0884	−0.0487	−3.0263	−0.0887	−0.0494
−2.00	−0.1540	−0.0851	−4.0222	−0.1544	−0.0861

Table II provides results for the case where all equilibrium parameters are the same as before except that, for the numerical analysis, we have set $\alpha = 0.05$, which is a reasonable physiological value for this quantity. To demonstrate the utility of the analytic approximation in this case we again list approximate values of a^+ and a^-, computed by using the listed numerical values of P in equations (17) and (18). Agreement is generally good in the interval, $-\rho_0 \leq P \leq 0$.

A graphical presentation is omitted since the total current density is proportional to a linear combination of a^+, and of a^-, which cannot be specified unless the transference number of each permeant ion species is known. This point is discussed in detail in Appendix A.

TABLE II

EQUILIBRIUM PARAMETERS

$\rho_0 = 2.0, \quad \gamma^+ = 0.0, \quad \gamma^- = 25.0$

$R = 1.0, \quad \xi_1 = 1.0$

	Numerical results ($\alpha = 0.05$)			Analytic approximation ($\alpha = 0.0$)	
$y(\xi_1)$	a^+	a^-	P	a^+	a^-
2.00	2.6934	1.3252	5.4605	1.7600	0.9808
1.50	1.7283	0.8694	4.1044	1.3368	0.7451
1.00	1.0362	0.5324	2.7257	0.9281	0.5173
0.75	0.7761	0.4027	2.0284	0.7365	0.4105
0.50	0.5642	0.2955	1.3263	0.5589	0.3115
0.25	0.3934	0.2078	0.6199	0.3994	0.2226
0.00	0.2563	0.1364	−0.0903	0.2613	0.1457
−0.25	0.1456	0.0779	−0.8037	0.1459	0.0813
−0.50	0.0540	0.0291	−1.5194	0.0521	0.0291
−0.75	−0.0251	−0.0136	−2.2366	−0.0229	−0.0128
−1.00	−0.0978	−0.0530	−2.9544	−0.0833	−0.0464
−1.50	−0.2442	−0.1327	−4.3882	−0.1753	−0.0977
−2.00	−0.4179	−0.2271	−5.8144	−0.2478	−0.1381

2. *The Case*, ($\alpha > 0$)

This analysis is confined to the case of high level flow. Consider first forward flow for which both the membrane field, $y(\xi)$, and the transmembrane potential, P, are large and positive. Equation (6, u) then shows the constant of integration, B^2, to be negative provided that $[\alpha/(1 + \gamma^+)] < 1$. This will be the case under conditions of physiological interest. We assume that a^- will be positive; the condition for this will be established below. The other current parameter, a^+, must always be positive for forward conduction.

Now introduce a new independent variable, ζ, defined by

$$\zeta = \frac{1}{3a^+}\left[2a^+\left\{\xi - \frac{B^2}{a^-}\right\}\right]^{3/2} \tag{20}$$

which will always be positive under the conditions set forth above. A new dependent variable,

$$\begin{aligned} v &= \left[2a^+\left\{\xi - \frac{B^2}{a^-}\right\}\right]^{-1/2} y \\ &= (3a^+\zeta)^{-1/3} y \end{aligned} \tag{21}$$

likewise positive, is also introduced. Finally we define

$$g^2 = a^-/2a^+ \tag{22}$$

and rewrite equation (4) in terms of the new variables as

$$\frac{d^2v}{d\zeta^2} = 2v[v^2 - g^2] - \frac{1}{3\zeta} - \frac{1}{\zeta}\left(\frac{dv}{d\zeta}\right) + \frac{v}{9\zeta^2} \tag{23}$$

Appropriate solutions of equation (23) may be developed as ascending power series in $(1/\zeta)$, namely

$$v = k_0 + k_1(1/\zeta) + k_2(1/\zeta)^2 + \cdots \tag{24}$$

Though there is no general recursion relation for the coefficients k_i, we compute as many as desired by inserting equation (24) into equation (23), collecting terms incorporating like powers of $(1/\zeta)$, and equating to zero these collected coefficients of each power of $(1/\zeta)$. The first three solution coefficients are

$$k_0 = g \tag{25}$$

$$k_1 = (1/12g^2) \tag{26}$$

$$k_2 = -(1/12g^2)[(g/3) + (1/8g^3)] \tag{27}$$

where g is the positive square root of equation (22). Thus we have selected that solution of equation (23) which satisfies the requirement of equation (21), namely that $v(\zeta)$ be positive when $y(\xi)$ is positive. Criteria for the convergence of the series solution will be discussed below.

Equation (10), expressed in terms of the new variables, is

$$\frac{\overset{+}{c}_{\text{per}} + \overset{-}{c}_{\text{per}}}{4c_1} = (3a^+\zeta)^{2/3}[v^2 - g^2] \tag{28}$$

Equation I(59), similarly expressed for the symmetric case, is

$$\frac{\overset{+}{c}_{\text{per}} - \overset{-}{c}_{\text{per}}}{4c_1} = (3a^+\zeta)^{2/3}\left[\frac{dv}{d\zeta} + \frac{1}{3}\left(\frac{v}{\zeta}\right)\right] \tag{29}$$

Both expressions apply throughout region II. Now approximate $v(\zeta)$ by terminating the series solution after the second term on the right of equation (24). Then, from equations (28) and (29) we obtain the first order results

$$\frac{\overset{+}{c}_{\text{per}}}{4c_1} = \frac{1}{12}(3a^+)^{2/3}\frac{(1 + 2g^2)}{(g\zeta^{1/3})} \tag{30}$$

and

$$\frac{\overset{-}{c}_{\text{per}}}{4c_1} = \frac{1}{12}(3a^+)^{2/3}\frac{(1 - 2g^2)}{(g\zeta^{1/3})} \tag{31}$$

Now at $\xi = 0$, at which point the corresponding value of ζ will be labeled ζ_0, the positive permeant ion concentration will be much larger than that for negative permeant ions under conditions of high level forward flow. Equations (5), (6, *u*) and (8, *u*) yield

$$\frac{c^{+}_{\text{per}}(0)}{4c_1} \cong \frac{1}{2(1+\gamma^+)}\,(2\alpha y(0)^2 + 1) \tag{32}$$

Replace $y(0)$ by $v(\zeta_0)$, using equation (21); then use the first order approximation for the latter quantity. Equate the result to the right side of equation (30), evaluated at $\zeta = \zeta_0$, to obtain

$$(g\zeta_0^{1/3})^3 + \frac{1}{2\alpha}\,(3a^+)^{-2/3}(g\zeta_0^{1/3}) - \left[\frac{(1+2g^2) - \{2\alpha/(1+\gamma^+)\}}{\{12\alpha/(1+\gamma^+)\}}\right] = 0 \tag{33}$$

On the other boundary, at $\xi = \xi_1$, or $\zeta = \zeta_1$, the negative permeant ion concentration will be dominant for high level forward flow. Now use equations (9, *u*), (10), (11, *u*) and (31), to obtain

$$(g\zeta_1^{1/3})^3 + \frac{R}{2\alpha}\,(3a^+)^{-2/3}(g\zeta_1^{1/3}) - \left[\frac{(1-2g^2) - \{2\alpha\exp(\rho_0)/(R[1-\gamma^-])\}}{\{12\alpha\exp(\rho_0)/(R[1+\gamma^-])\}}\right] = 0 \tag{34}$$

Now from equation (20), evaluated at $\zeta = \zeta_0$, and at $\zeta = \zeta_1$, and from equation (22), we obtain

$$(g\zeta_1^{1/3})^2 - (g\zeta_0^{1/3})^2 = \tfrac{2}{3}(3a^+)^{1/3}g^2\xi_1 \tag{35}$$

We apply equations (33)–(35) by first fixing a^+ at some sufficiently large positive value. Then a trial value of g^2 is placed in the bracketed term on the left of equations (33) and (34). Thus, with the equilibrium parameters known, the quantities, $(g\zeta_0^{1/3})$, and $(g\zeta_1^{1/3})$, are obtained as the single real roots of these equations. These quantities are then used in equation (35) to obtain a corrected value for g^2. The iterative process thus described is repeated until the trial and corrected values of g^2 agree to within desired accuracy. The value of a^- is then established by equation (22).

The corresponding transmembrane potential, using equation (12), is

$$P = -\rho_0 + \ln\left[\frac{(1+\gamma^+)(1+\gamma^-)(3a^+)^{4/3}}{9(g\zeta_0^{1/3})(g\zeta_1^{1/3})}\,\{1 - 4g^4\}\right] + \frac{2}{g^2}\,[(g\zeta_1^{1/3})^3 - (g\zeta_0^{1/3})^3] + \frac{1}{2g^2}\ln\left[\frac{(g\zeta_1^{1/3})}{(g\zeta_0^{1/3})}\right] \tag{36}$$

The third and fourth terms on the right represent that portion of the transmembrane potential contributed by integrating over region II. They are obtained by use of the approximate form for $\nu(\zeta)$ employed above.

In Table III we compare the approximation with precise numerical results for a specified set of equilibrium parameters. Here the value of a^+ obtained numerically is used as the starting point for computation of corresponding approximate values of a^- and P. The table compares results for high level reverse flow as well. Modifications necessary for this case are given below.

We now make several points about the approximation as developed so far. We first assert that g^2 tends to zero in the high current limit, and then demonstrate the internal consistency of this statement. It implies, by reason of equations (33) and (34), that $(g\zeta_0^{1/3})$ and $(g\zeta_1^{1/3})$ go to constant limiting values determined solely by the equilibrium parameters of the system. Then equation (35) establishes that g^2 will vanish as a^+ becomes large. Obviously the quantities $\zeta_0^{1/3}$, and $\zeta_1^{1/3}$, increase in the limit with sufficient rapidity so that their products with g do not vanish even though g itself does so.

TABLE III

EQUILIBRIUM PARAMETERS

$\rho_0 = 2.0, \quad \gamma^+ = 5.0, \quad \gamma^- = 50.0$

$R = 1.0, \quad \xi_1 = 1.0, \quad \alpha = 0.05$

	Numerical results			Analytic approximation	
$y(\xi_1)$	a^+	a^-	P	a^-	P
10.0	33.800	1.9368	26.145	1.9088	26.151
8.0	18.188	1.0820	21.365	1.0651	21.362
6.0	8.4387	0.5214	16.413	0.5127	16.393
4.0	3.1048	0.1993	11.226	0.1955	11.160
2.0	0.7550	0.0503	5.7447	0.0487	5.6994
−2.0	−0.0998	−0.0069	−5.7356	−0.0069	−5.5416
−4.0	−0.4222	−0.0291	−11.227	−0.0291	−11.130
−6.0	−1.1516	−0.0791	−16.428	−0.0789	−16.387
−8.0	−2.4893	−0.1699	−21.400	−0.1696	−21.378
−10.0	−4.6379	−0.3141	−26.206	−0.3141	−26.202

Inspection of equations (25)–(27) suggests that each term in the series of equation (24) will differ from the preceding one by a factor of order $[1/(g\zeta^{1/3})^3]$, and, therefore, if the first order approximation for $\nu(\zeta)$ is to be accurate over the entire range of the independent variable, the quantities $(g\zeta_0^{1/3})$ and $(g\zeta_1^{1/3})$ should both be greater than unity. Thus equations (33) and (34) yield

$$\frac{14\alpha}{1 + \gamma^+} < 1 \tag{37}$$

and

$$\frac{14\alpha \exp(\rho_0)}{R(1+\gamma^-)} < 1 \tag{38}$$

as criteria for rapid convergence of the series solution for $\nu(\zeta)$.

If g^2 approaches zero through positive values, then equation (35) states that we must have $(g\zeta_1^{1/3}) > (g\zeta_0^{1/3})$. This is the condition under which a^- will be positive and, from equations (33) and (34), it is seen to be equivalent to the requirement that

$$\frac{1}{1+\gamma^+} > \frac{\exp(\rho_0)}{R(1+\gamma^-)} \tag{39}$$

We establish the limiting power laws for current flow by observing that the third and fourth terms on the right of equation (36) will dominate the limiting expression for P. Furthermore the left side of equation (35) is a constant in the limit. Thus

$$a^+ \cong \delta_1 \left(\frac{P^3}{\xi_1^3}\right) \tag{40}$$

where the constant, δ_1, is readily obtained in terms of the limiting values of $(g\zeta_0^{1/3})$ and $(g\zeta_1^{1/3})$. These in turn are expressible in terms of equilibrium parameters as we have seen above. The resulting expression for δ_1 is cumbersome and is omitted. By reference to equation (22) we get

$$a^- \cong \delta_2 \left(\frac{P^2}{\xi_1^3}\right) \tag{41}$$

where again we omit the expression of the constant, δ_2, in terms of the equilibrium parameters.

The ion current flowing through the membrane will, as previously observed, be proportional to a linear combination of a^+ and a^-. Equations (40) and (41) indicate the possibility that some linear combination of these quantities would, when plotted as a function of P, show a region of negative slope, i.e., negative dynamic conductance. It will be shown in Appendix A that the possible linear combinations are bounded by $(a^+ + a^-)$, and $(a^+ - a^-)$. For the case discussed above the latter would be most likely to exhibit a region of negative slope. The slope will be negative if

$$\left(\frac{da^+}{dP}\right) \Big/ \left(\frac{da^-}{dP}\right) \cong \frac{3}{2}\left(\frac{\delta_1 P}{\delta_2}\right) < 1 \tag{42}$$

The quantity, a^-, cannot, however, exceed a^+ in magnitude, or

$$\frac{a^+}{a^-} \cong \left(\frac{\delta_1 P}{\delta_2}\right) > 1 \tag{43}$$

must hold. These inequalities cannot be satisfied simultaneously so we conclude that the approximation leading to equations (40) and (41) fails for values of the transmembrane potential, P, which are sufficiently small so that the inequality, (42), could be satisfied. Thus our approximation does not predict the occurrence of negative dynamic conductance for flow between symmetric electrolytes. Furthermore we have found no combination of equilibrium parameters for which numerical analysis reveals such behavior.

We now outline approximate conductance calculations for the case of high level forward flow with a^- negative. Replace ξ by

$$\bar{\xi} = \xi_1 - \xi \tag{44}$$

and B^2 by

$$\overline{B^2} = B^2 - a^-\xi_1 \tag{45}$$

Then introduce

$$\bar{\zeta} = \frac{1}{3a^+}\left[2a^+\left\{\bar{\xi} + \frac{\overline{B^2}}{a^-}\right\}\right]^{3/2} \tag{46}$$

$$\bar{v} = (3a^+\bar{\zeta})^{-1/3}y \tag{47}$$

and

$$\overline{g^2} = -a^-/2a^+ \tag{48}$$

When expressed in terms of these variables equation (4) takes a form identical with that of equation (23), and, in consequence, has a solution of identical form. The expression corresponding to equation (28) is also obtained by replacing v, ζ, and g by $\bar{v}$, $\bar{\zeta}$, and $\bar{g}$, respectively. The result corresponding to equation (29), however, requires not only the exchange of variables noted above, but a minus sign preceding the quantity on the right as well. Now the independent variable, $\bar{\zeta}$, has its minimum value, $\bar{\zeta}_0$, when $\xi = \xi_1$, and thus $\bar{\zeta} = \bar{\zeta}_1$ when $\xi = 0$. The above considerations yield

$$(\bar{g}\overline{\zeta_1^{1/3}})^3 + \frac{1}{2\alpha}(3a^+)^{-2/3}(\bar{g}\overline{\zeta_1^{1/3}}) - \left[\frac{(1 - 2\overline{g^2}) - \{2\alpha/(1 + \gamma^+)\}}{\{12\alpha/(1 + \gamma^+)\}}\right] = 0 \tag{49}$$

and

$$(\bar{g}\overline{\zeta_0^{1/3}})^3 + \frac{R}{2\alpha}(3a^+)^{-2/3}(\bar{g}\overline{\zeta_0^{1/3}}) - \left[\frac{(1 + 2\overline{g^2}) - \{2\alpha \exp(\rho_0)/(R[1 + \gamma^-])\}}{\{12\alpha \exp(\rho_0)/(R[1 + \gamma^-])\}}\right] = 0 \tag{50}$$

corresponding to equations (33) and (34) respectively. It can then be shown that results corresponding to equations (35) and (36) are obtained by the replacement of variables referred to above. Thus it follows that if $\overline{g^2}$ is to be positive, and hence a^- negative, we must require $(\bar{g}\zeta_1^{1/3}) > (\bar{g}\zeta_0^{1/3})$. This will be the case in the high current limit if the sense of inequality (39) is reversed.

Consider now the case of high level reverse flow for which a^- is positive. For reverse flow a^+ will be negative as will $y(\xi)$. Suitable transformed variables, $\bar{\zeta}$, $\bar{v}$ and $\overline{g^2}$, may be obtained from equations (20)–(22) by replacing a^+ by $-a^+$. Thus $\bar{\zeta}$ is positive, but $\bar{v}$, since it carries the same sign as y, is negative. The current parameter ratio, $\overline{g^2}$, is positive since we assume that a^- is positive. The equations corresponding to equations (28) and (29) are of identical form since here the sign of a^+ can produce no ambiguity. For high level reverse flow, however, the negative permeant ion concentration will be dominant at $\xi = 0$, or $\bar{\zeta} = \bar{\zeta}_0$, while positive permeant ions will be in the majority at $\xi = \xi_1$. All this, and reference to equations (5), (6, *I*), (8, *I*), (9, *I*), (10) and (11, *I*), will yield

$$(\bar{g}\bar{\zeta}_0^{1/3})^3 + \frac{1}{2\alpha}(3a^+)^{-2/3}(\bar{g}\bar{\zeta}_0^{1/3}) - \left[\frac{(1+2\overline{g^2}) - \{2\alpha/(1+\gamma^-)\}}{\{12\alpha/(1+\gamma^-)\}}\right] = 0 \qquad (51)$$

and

$$(\bar{g}\bar{\zeta}_1^{1/3})^3 + \frac{R}{2\alpha}(3a^+)^{-2/3}(\bar{g}\bar{\zeta}_1^{1/3}) - \left[\frac{(1-2\overline{g^2}) - \{2\alpha\exp(-\rho_0)/(R[1+\gamma^+])\}}{\{12\alpha\exp(-\rho_0)/(R[1+\gamma^+])\}}\right] = 0 \qquad (52)$$

The result analogous to equation (35) involves the corresponding transformed variables and is identical in all respects except that the current parameter, a^+, is replaced by $-a^+$. Thus, if $\overline{g^2}$ is positive, equations (51) and (52) show that the inequality

$$\frac{1}{1+\gamma^-} > \frac{\exp(-\rho_0)}{R(1+\gamma^+)} \qquad (53)$$

must hold. If it holds, then a^- is positive as assumed. The equation for P is identical in form with equation (36), except that all signs preceding the four terms on the right are minus signs.

In the case of high level reverse flow with a^- negative, we obtain appropriate transformed variables by substitution of $-a^+$ for a^+ in equations (46)–(48). Interchange of $(\bar{g}\bar{\zeta}_0^{1/3})$ and $(\bar{g}\bar{\zeta}_1^{1/3})$, and substitution of $-\overline{g^2}$ for $\overline{g^2}$, in equations (51) and (52) yields the corresponding equations for this case. The condition which establishes that a^- will be negative is obtained by reversing the sense of the inequality, (53). The form of the expression for P is identical with that stated for the previous case.

This concludes our enumeration of the cases to be considered in a complete description of high level flow. In all of these the limiting power laws are given by equations (40) and (41), but the constants δ_1, and δ_2, must be determined for each case separately.

We now return to the first case considered, that of high level forward flow for which a^- is positive, and present a qualitative evaluation of the physical significance of the results which applies, with obvious modifications, to the other cases as well. Typical profiles of positive and negative permeant ion concentrations, as determined by numerical analysis, are illustrated by the solid line curves of Fig. 1. The heavy dashed line curve exhibits the variation of space charge across the membrane. Equations (30) and (31), do not in general predict the regions of high concentration gradient in region II which are features of the numerical analysis. The deviations which they imply are indicated by the dotted lines of Fig. 1. Our illustration is for a situation in which the difference between $(g\zeta_0^{1/3})$ and $(g\zeta_1^{1/3})$ is small.

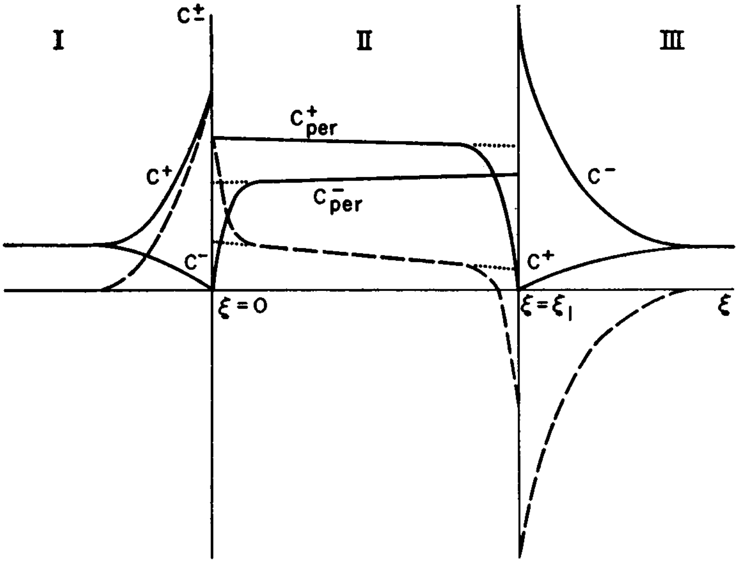

FIGURE 1 Concentration and space charge profiles appropriate to a stationary state of high level forward flow are illustrated qualitatively. The solid lines depict total concentrations of cations, or of anions, as labeled. Thus both permeant and impermeant ions contribute to the profiles illustrated in regions I and III, whereas only the permeant ions contribute in region II. This accounts for the discontinuities exhibited by the concentration profiles at the membrane boundaries. The dashed line curves depict the distribution of space charge. The significance of the dotted line segments in region II is discussed in the text.

The validity of the approximation is, however, dependent only upon the congruence of the predicted and computed concentration profiles in the regions of low concentration gradient. Thus, from the standpoint of the approximation, we may consider the magnitude of the principal current parameter, a^+, to be determined primarily by the electric field within the membrane. The concentration of the dominant charge carriers, positive permeant ions near $\xi = 0$, and negative permeant ions near $\xi = \xi_1$, is proportional to the square of the electric fields at these points. The current density within the membrane is proportional to the product of the concentration and the field; thus the variation of a^+ with $(P/\xi_1)^3$ follows. The uniform flow of minority ions near each boundary is, however, sustained by a steadily increasing gradient as their concentration decreases.

Equations (30) and (31) will also yield the expression

$$\frac{\overset{+}{c}_{\text{per}}(\xi) - \overset{-}{c}_{\text{per}}(\xi)}{\overset{+}{c}_{\text{per}}(\xi) + \overset{-}{c}_{\text{per}}(\xi)} = 2g^2 \tag{54}$$

which, though it does not apply near the boundaries, is valid in the interior of region II. To equate the interior space charge to zero is thus seen to be equivalent to setting the current difference parameter, a^-, equal to zero. This quantity does become negligible when compared to a^+ in the high current limit, but will generally, except for special choices of the equilibrium parameters, be of the same order as a^+ at moderate flow levels.

These points are emphasized by presentation of approximate equations for the current parameters which incorporate suitable averaged quantities. We note equation II(50), and the fact that

$$\left\langle \frac{d\overset{-}{\theta}_{\text{per}}}{d\xi} \right\rangle_{\text{II}} \cong \frac{P}{\xi_1} \tag{55}$$

also holds at high flow levels. Angular brackets are used here, as they were in II, to indicate averaged quantities. Manipulation of equations I(80, *u* and *l*) will now yield

$$a^{\pm} \cong 2\left\langle \frac{\overset{+}{c}_{\text{per}} \pm \overset{-}{c}_{\text{per}}}{4c_1} \right\rangle_{\text{II}} \frac{P}{\xi_1} \tag{56}$$

which indicates that the coefficient relating a^+ to the electric field is proportional to the averaged energy density of the field and is always positive; the magnitude and sign of the coefficient relating a^- to the field is, however, determined by the average space charge in region II.

The significant points of difference between the case of bipolar flow discussed here, and the previously treated problem of the unipolar flow of positive permeant ions, should now be noted. It is to be emphasized that the latter cannot be regarded as a limiting case of bipolar flow in which the flow of permeant cations makes the major contribution to the total current density. An obvious point of difference is in the limiting form of the voltage-current relationship, being a square law in the unipolar case and a cube law for bipolar flow. Another clear point of difference is in the description of the equilibrium state. In the bipolar case permeant ions of both signs are to be found in the membrane phase, and, in thermodynamic equilibrium, their concentration profiles will be independent of the relative mobilities of the permeant species. In the unipolar case discussed in II, on the other hand, negative ions are, by hypothesis, excluded from the membrane phase under all conditions, including that of thermodynamic equilibrium.

DISCUSSION

The essential features of our development are most effectively elucidated by comparing it with previous analyses of the Nernst-Planck system in the steady state, such as that of Cohen and Cooley, (1965). Though primarily concerned with the time-dependent problem, they present, as an appendix, a succinct résumé of their steady-state analysis. They adopt a widely accepted view of the Nernst-Planck system as one in which all gradients of electric potential and of permeant ion concentration are confined to the membrane phase. It follows that, for steady nonequilibrium states, the electrochemical potential gradients of permeant ion species are similarly confined. We retain the latter view, but remove the more restrictive condition on both the electric field and the permeant ion concentration gradient.

Cohen and Cooley construct solutions of the differential equation for the membrane electric field which satisfy the Planck condition on the field gradient, namely that the gradient vanish at the interior membrane boundaries. This condition, also employed by Bass (1964), follows from Poisson's equation and the assumption of charge neutrality just inside the membrane boundaries. The latter follows in turn from the presumption of charge neutrality throughout the exterior phases. These treatments show, however, that the electric fields at the interior boundaries of the membrane phase will generally not be zero, and will in fact change in magnitude as the system is carried from one steady state to another. The exterior electric fields are, as previously noted, taken to be zero. The resultant discontinuities in field imply, for exterior media of finite polarizability, corresponding discontinuities in electric displacement and hence the presence of geometric surface charge layers on the boundaries which do not arise from dielectric polarization. Though this condition might be approximated in real systems by assuming the presence of adsorbed charge layers, it is not clear that the requisite variation in surface charge density needed to accommodate changes in the steady state of the system, could reasonably be postulated.

In our development the screening of the membrane electric field is accomplished in extended boundary layers in the exterior phases. The requisite extended charge distribution, in which the field gradually terminates, arises by a segregation of mobile ions of opposite sign which in turn is induced by the electric field. This relaxation process, as it proceeds into either solution phase, yields a progressively closer approach to the usual exterior boundary conditions of zero electric field and zero field gradient, with the latter implying charge neutrality. The characteristic length for this relaxation process is the solution Debye length.

The development of concentration polarization, i.e. space charge, implies the presence of ion concentration gradients in the exterior boundary layers. These gradients, developed by both permeant and impermeant ionic species in the exterior layers, form in response to the relaxing electric field therein so as to insure that the electrochemical potential gradients of all ionic species present will be zero. It follows that the concentrations of permeant ions at the membrane boundaries will depend upon the magnitude of the electric fields at the exterior boundaries; the concentrations will differ from their bulk solution values when these fields differ from zero. This point is crucial to our description of membrane conductance, in that it provides the basis of our prediction that the asymptotic form of the voltage-current relation should be a square law for the case of unipolar flow and a cube law for the case of bipolar flow. This contrasts with prior analyses, such as that of Cohen and Cooley, which yield linear asymptotic conductance relations. Linear asymptotic relations have been obtained for the case of fixed charge membranes by Conti and Eisenman (1965), as well. Our own development of the hypothetical case, ($\alpha = 0$), for which the electric field at each interior membrane boundary is fully screened from the exterior phases by infinitely polarizable media in these phases, yields similar results. All of the treatments mentioned which yield linear asymptotic conductance relations make the assumption that the concentrations of permeant ion species at the interior membrane boundaries are constant, i.e. are unaffected by variations in the boundary values of the electric field which accompany transitions from one steady state to another.

The existence of exterior boundary layers has been previously recognized, particularly by workers dealing with fixed charge membranes. These include Mauro (1962), Coster (1965), and George and Simon (1966). George and Simon, in their numerical analysis of a special case, not only treat the boundary layers, but also take account of the fact that the exterior phases will not be perfectly conducting. The ohmic character of the current density-field relationship in the exterior phases at large distances from the membrane boundaries is noted explicitly.

Though a complete quantitative comparison of our treatment with experiment must rely upon numerical analysis, we may nonetheless offer two significant qualitative predictions. The first is that membrane conductance relations should display a more rapid than linear increase of current with applied potential difference at high flow levels. The second is our observation that membrane impedance should decrease if the dielectric constant of the exterior phases is decreased by substitution of solvents. Here we have assumed that the dielectric constants of both solvent phases exceed that of the membrane phase, and have further assumed full dissociation of all electrolytes in both solvents. Both predictions are direct consequences of our treatment of the boundary conditions.

We emphasize, however, that our development shows these effects to become significant only when $\alpha y^2 \geq 1$. Equations I(44) and I(47) permit a reexpression of this statement as $E \geq (2kT\lambda K_1^{1/2}/ezK_2)$ in terms of previously defined dimensioned variables. Thus we see that the membrane electric field must be of the order of the equivalent thermal potential, (kT/e), divided by the characteristic Debye length, $(1/\lambda)$, for the nonlinear effects considered here to be appreciable. Under physiological conditions this criterion indicates that $E \geq 10^6$ volt/cm would be required. For potentials in the physiological range ($\sim$0.1 volt) this corresponds to membrane thicknesses of the order of 10^{-6} cm. This thickness range typifies not only biological membranes, but a particularly interesting synthetic structure as well. Conductance relationships in this structure, the biomolecular lipid membrane, were first studied by Mueller and Rudin (1963). It is difficult, however, to assess the extent of applicability of our continuum theory to such systems. Experiments based upon the use of dilute solutions should permit the above criterion to be achieved at lower fields and for thicker membranes. Membranes fabricated from amphoteric ion exchange resins may prove appropriate to investigations of this type.

The cases studied here and in II bear a significant formal resemblance to the problems of single carrier injection (unipolar flow) and double injection (bipolar flow) in insulators. The case of single carrier injection in insulator diodes has been studied by Sinharay and Meltzer (1964), who have developed a numerical treatment based upon universal carrier concentration and electric field curves. Their treatment, in its most general form, permits the specification of any cathode and anode carrier concentrations without regard for the physical mechanisms by which these concentrations are established. Our development in II of the case of unipolar flow resembles their presentation for the case of one ohmic contact and one blocking contact. They obtain an asymptotic square law for the voltage-current relationship in that case as do we for the case of unipolar flow. Sinharay and Meltzer specifically exclude from their considerations any effects due to trapping of carriers.

The case of double injection has been treated by Lampert (1962), and extended by Baron (1965), to take account of carrier diffusion. Lampert has analyzed the problem in terms of three different "regimes" which are determined by the carrier injection level. In the high injection or insulator regime his treatment, including the effects of space charge, yields an asymptotic cube law for the current-voltage characteristic as does our development for the case of bipolar flow. Experimental verification of the asymptotic cube law for high level double injection in silicon p-i-n structures has been provided by Baron, Mayer, and Marsh (1964). Mechanisms considered by Lampert to be operative at lower injection levels, in particular that relating to the dependence upon injection level of the effectiveness of recombination centers as barriers to hole transit, have no analogue in our model as presently formulated.

APPENDIX A

The relationship between the total ion current density, j, and the dimensionless parameters a^+, and a^-, is established in this appendix. We begin by writing equation I(12, u) explicitly for any two positive permeant ion species, the concentrations of which are labeled c_i^+, and

c_k^+, respectively. This gives

$$\frac{j_i^+}{\mu_i^+} = -kT\frac{dc_i^+}{dx} + ez^+c_i^+ E \tag{57}$$

and

$$\frac{j_k^+}{\mu_k^+} = -kT\frac{dc_k^+}{dx} + ez^+c_k^+E \tag{58}$$

where we have set $z_i^+ = z_k^+ = z^+$, in conformity with the general restrictions on valence multiplicity set forth in I. The subscript "per" will be omitted throughout this discussion to avoid confusion with subscripts designating different species. All references will be to permeant ion concentrations. Now differentiate equations (57) and (58), then divide the first by c_i^+, and the second by c_k^+. Subtract the second from the first and rearrange terms to obtain

$$ez^+E\frac{d}{dx}\left\{\ln\left(\frac{c_i^+}{c_k^+}\right)\right\} - kT\frac{d^2}{dx^2}\left\{\ln\left(\frac{c_i^+}{c_k^+}\right)\right\} - kT\left[\frac{d}{dx}\left\{\ln\left(\frac{c_i^+}{c_k^+}\right)\right\}\right]\left[\frac{d}{dx}\{\ln(c_i^+c_k^+)\}\right] = 0 \tag{59}$$

which holds both in equilibrium and for stationary flow. It is valid in each of the three regions of the membrane-solution system and holds for any pair of positive permeant ion species chosen from those present. These stringent requirements are met only if

$$\frac{d}{dx}\left\{\ln\left(\frac{c_i^+}{c_k^+}\right)\right\} = 0 \tag{60}$$

Hence the ratio, (c_i^+/c_k^+), is constant throughout each region.

Now return to equations (57) and (58); divide the first by c_i^+, and the second by c_k^+. Then subtract the second from the first and use equation (60) to obtain the relation

$$\frac{j_i^+}{\mu_i^+c_i^+} = \frac{j_k^+}{\mu_k^+c_k^+} \tag{61}$$

which is valid for any pair of permeant cation species in region II. Next define the partial fraction

$$x_i^+ = \frac{c_i^+}{\sum_k^{(+)} c_k^+} \tag{62}$$

The summation is, as implied by the superscript, (+), over permeant positive ion species only. Obviously

$$\sum_i^{(+)} x_i^+ = 1 \tag{63}$$

Equation (61) may now be given as

$$\frac{j_i^+}{\mu_i^+ \, x_i^+} = \frac{j_k^+}{\mu_k^+ \, x_k^+} \tag{64}$$

It is to be emphasized that the partial fractions are constants within a given region in spite of the fact that the concentrations in terms of which they are defined may vary with position. The partial fraction for each species is, subject to the validity of our assumption that permeant ion concentrations are continuous functions of position at the membrane boundaries, the same in all three regions of the membrane-solution system as well.

Now add equations I(14, *u*) and I(14, *l*). Then sum over positive permeant species, using equations (63) and (64) to obtain

$$\Gamma^+ + \Gamma^- = \frac{j_i^+}{\mu_i^+ \, x_i^+} \tag{65}$$

which holds for any one of the permeant cation species present.

The entire sequence presented above, beginning with equation (57), may be repeated to yield

$$\Gamma^+ - \Gamma^- = \frac{j_i^-}{\mu_i^- \, x_i^-} \tag{66}$$

for each permeant negative ion species present.

Equations (65), (66), and I(46) may now be used to obtain

$$j = \Big(\sum_k{}^{(+)} \mu_k^+ \, x_k^+ + \sum_k{}^{(-)} \mu_k^- \, x_k^-\Big)\Gamma_0 \cdot \Big[a^+ + \Big\{\sum_k{}^{(+)} t_k^+ - \sum_k{}^{(-)} t_k^-\Big\} \, a^-\Big] \tag{67}$$

where we have introduced the parameter

$$\Gamma_0 = \frac{1}{2\pi}\left(\frac{kT\lambda}{ez}\right)^2 \frac{\lambda}{K_2^{1/2}} \tag{68}$$

and the transference numbers

$$t_i^\pm = \frac{\mu_i^\pm \, x_i^\pm}{\sum_k{}^{(+)} \mu_k^+ \, x_k^+ + \sum_k{}^{(-)} \mu_k^- \, x_k^-} \tag{69}$$

which are always positive. This, plus the fact that

$$\sum_k{}^{(+)} t_k^+ + \sum_k{}^{(-)} t_k^- = 1 \tag{70}$$

is sufficient to show that the quantity in curly brackets which precedes the parameter, a^-, in equation (67) must have a numerical value lying between the limits, +1, and −1. The positive limit will be approached if the flow of permeant cations makes the principal contribution to the current density, and the negative limit will be approached if the flow of permeant anions predominates.

APPENDIX B

A recent publication in this journal by Dr. Alexander Mauro (1966), presents a critical examination of two assumptions which were made in the two earlier papers of this series. We offer here our own evaluation of these assumptions.

The first of these was our assertion that the concentrations of permeant ions could be taken to be a continuous function of position across the membrane-solution interfaces. It was stated in I that this assumption would be valid only if the concentration of a permeant ion species in each phase could be equated to its absolute activity therein. It will now be shown that the removal of this requirement, and the attendant assumption of continuity of permeant ion concentrations at the membrane-solution interfaces, are readily accomplished within the framework of the analysis presented in I. The demonstration will depend, however, upon a simplified view of the formidable problem of ion-solvent interaction. Account will be taken only of the interaction of isolated ions with each solvent phase. The complexities of the associative interaction between ions will be ignored.

We will follow the usage of Guggenheim (1957), in that the absolute activity of an ionic species in a homogeneous solvent will be equated to a product of three factors, i.e.

$$\lambda_i^{\pm} = l_i^{\pm} c_i^{\pm} \tau_i^{\pm} \tag{71}$$

where, with all dependences upon temperature ignored, the constant of proportionality, $l_i^{\pm}$, depends only upon the solvent phase. The concentration is $c_i^{\pm}$, and the activity coefficient, $\tau_i^{\pm}$, is so defined that it goes to unity in the limit of high dilution of all solute ion species present. The activity coefficient, which also depends upon the solvent phase, will generally vary with total solute concentration as well. Equation (71) thus illustrates the decomposition of the total ion-solvent interaction into two parts. The first, characterized by the constants, $l_i^{\pm}$, is the interaction of isolated ions with the solvent phase. The second part, the associative interaction between ions, is described by the activity coefficients, $\tau_i^{\pm}$, and becomes insignificant only in the limit of high dilution of all ionic species present. Both interactions are electrostatic in character. Both depend—to the extent that a continuum theory may be applied—upon the macroscopic dielectric constant of the solvent. The solvation of isolated ions is discussed in an illuminating paper by Buckingham (1957). The well-known theory of Debye and Hückel (1923) treats the associative interaction using the linearized Poisson-Boltzmann equation.

Equation (71) permits the expression of the chemical potential of a solute ion species in such a way that its standard state need not appear as a separate additive term. Differences in the standard state of such a species in two different solvents are indicated by deviations from unity of the ratio of the constants, $l_i^{\pm}$, appropriate to each phase. Such deviations can generally be expected for dissimilar phases as indicated above. Partition of permeant ion species between dissimilar phases can therefore be expected, even when the activity coefficients of these species are equated to unity. Partition occurring subject to this restriction will, however, be constant; i.e., the ratio of permeant ion concentrations on the two sides of a phase boundary will be independent of the concentrations on either side. Under these conditions a straightforward generalization of our development is possible.

To demonstrate this we introduce a set of constant partition coefficients, $K_i^{\pm}$, defined by

$$c_i^{\pm}(0)_{\mathrm{I}} = K_i^{\pm}\{c_i^{\pm}(0)_{\mathrm{II}}\} \tag{72}$$

where, though the reference is to permeant ions, the subscript "per" will again be omitted in the interest of clarity. We also introduce a set of constants, $\gamma_i^{\pm}$, defined by

$$c_{\mathrm{imp}}^{\pm}(0)_{\mathrm{I}} = \gamma_i^{\pm}\{c_i^{\pm}(0)_{\mathrm{I}}\} \tag{73}$$

The results of Appendix A are readily extended to show that this equation holds not only at the membrane boundary in region I, but at any other point throughout this region. Thus from equation I(28) we see that the quantities, $\gamma^{\pm}$, previously introduced, are related to the newly defined constants by

$$\frac{1}{\gamma^{\pm}} = \sum_k^{(\pm)} \left(\frac{1}{\gamma_k^{\pm}}\right) \tag{74}$$

Now form the ratios

$$\chi^{\pm} = \frac{\sum_k^{(\pm)} c_k^{\pm}(0)_{\mathrm{II}}}{c_{\mathrm{imp}}^{\pm}(0)_{\mathrm{I}} + \sum_k^{(\pm)} c_k^{\pm}(0)_{\mathrm{I}}} \tag{75}$$

These ratios measure the discontinuity in the total concentration of cations, and of anions, existing at the interface between regions I and II; they are sufficient to establish the effects of partition upon the discontinuity in the electric displacement gradient occurring at that interface. Equations (72)–(75) now yield

$$\chi^{\pm} = 1/(1 + \overline{\gamma^{\pm}}) \tag{76}$$

where

$$\overline{\gamma^{\pm}} = \left(1 + \frac{1}{\gamma^{\pm}}\right)\left[\sum_k^{(\pm)} \left(\frac{1}{K_k^{\pm}\gamma_k^{\pm}}\right)\right]^{-1} - 1 \tag{77}$$

is a constant independent of the concentrations at the interface. With all ionic partition coefficients equated to unity, the right side of equation (77) reduces to $\gamma^{\pm}$, as would be expected. The same set of coefficients, $K_i^{\pm}$, will suffice to describe partition at the interface between regions II and III since the solvents in regions I and III are the same in our model. It is readily determined that the substitution of $\overline{\gamma^{\pm}}$, as given by equation (77), for $\gamma^{\pm}$ is sufficient to account for partition at this interface as well.

It should also be noted that the partial fractions defined by equation (62), and its analogue for permeant anions, will be

$$(x_i^{\pm})_{\mathrm{I,\,III}} = \gamma^{\pm}/\gamma_i^{\pm} \tag{78}$$

in regions I and III, but, with partition, will be

$$(x_i^{\pm})_{\mathrm{II}} = \frac{(1/K_i^{\pm}\gamma_i^{\pm})}{\sum_k^{(\pm)}(1/K_k^{\pm}\gamma_k^{\pm})} \tag{79}$$

in region II. They are identical when all the coefficients, $K_i^{\pm}$, are equated to unity, but the partial fractions given by equation (79) would be used in equations (67) and (69) when partition is considered.

The substitution of $\overline{\gamma^{\pm}}$ for $\gamma^{\pm}$ would be made generally throughout the development, being omitted only where the quantities $\gamma^{\pm}$ appear in specific applications to regions I and III.

An exhaustive list of these includes equations I(28), I(38)–(39), I(66)–(68), and I(71)–(72). All statements of conductance relations and all expressions pertaining to quantities determined in region II, including in particular those obtained by application of equations I(68) and I(72) to the determination of permeant ion concentrations at the interior boundaries of the membrane phase, would require the substitution of $\overline{\gamma^{\pm}}$ for $\gamma^{\pm}$ wherever the latter quantities appear. In the case of unipolar flow considered in II we need only substitute $\overline{\gamma^{+}}$ for γ^{+}. The ease with which constant partition coefficients may be incorporated into the development is attributable to the fact that, in regions I and III, the classification of an ion as permeant or impermeant is essentially a matter of convenience. The classification will not affect the contribution of that ion to the charge and field distribution. Estimates of the ionic partition coefficients could, in principle, be made on the basis of determinations, for each phase, of ionic solvation energies such as those presented by Buckingham for monovalent ions in aqueous solution. We expect, however, that the quantities $\overline{\gamma^{\pm}}$ would generally have to be regarded as adjustable parameters.

The simple generalizations of the definitions of the quantities $\gamma^{\pm}$ and $x_i^{\pm}$ will not be entirely adequate to describe the effects of partition in real systems since the partition coefficients $K_i^{\pm}$ will generally depend upon the concentrations of the partitioned species. This is traceable to the fact that the activity coefficients $\tau_i^{\pm}$ will, by reason of the associative interactions between ions which is always appreciable at nonvanishing solute concentration, depend upon the total concentration of solute in each phase. Though the evaluation of this problem would appear to be possible in very dilute solutions where the Debye-Hückel limiting law could be applied, it is not likely that an analysis of general validity could be extended to the concentration ranges appropriate to biological systems. We observe, however, that our failure to take account of the concentration dependence of activity coefficients involves more than the matter of boundary conditions. The substitution of concentration gradients for activity gradients in the Nernst-Planck equations of flow, as applied within a homogeneous phase, would presumably be a deficiency of comparable severity. Our model calculation does not take this complication into account, nor, to the best of our knowledge, does any other which utilizes the kinetic approach and yields a quantitative determination of membrane conductance.

The second point raised by Dr. Mauro relates to the special case of unipolar flow for which we assume that permeant ions of only one valence state are present. His discussion indicates that an essential condition of electroneutrality is violated if it is hypothesized that permeant ions carrying only one sign of charge are to be found within the membrane phase. Such a condition must be met, but we submit that it should, with use of Poisson's equation, I(59), properly take the form

$$\int_{-\infty}^{\infty} \left(\frac{dy}{d\xi}\right) d\xi = 0 \qquad (80)$$

for any one-dimensional model. This requirement of over-all electroneutrality is always met in our treatment, as reference to the boundary conditions expressed by equations I(49) and I(54) will indicate. A more restrictive specification of the range of integration, as, for example, to the membrane phase only, or to thin electric double layers at the interfaces which delimit a comparatively thick membrane, may indeed be appropriate for the space charge distributions characteristic of some models. Such a specification cannot, however, be said to have general validity. For the special case discussed in II the positive space charge which is always present in the membrane phase is balanced by a net negative charge distributed near the interfaces, over distances of the order of the appropriate Debye length, in regions I and III. This charge will not generally be distributed symmetrically between the exterior phases. It may in fact be positive in one and negative in the other. The over-all charge neutrality required by equation (80) will, nevertheless, always be maintained.

We have sought to apply a simple continuum theory under the stringent conditions represented by situations in which the membrane thickness is comparable to the Debye lengths characteristic of the exterior phases. As such we have carefully avoided any a priori assumption of microscopic electroneutrality. This condition will, however, always be approached in the interior of thick homogeneous membranes. To illustrate this point for the case of unipolar flow, we combine equations II(10) and II(59), correcting the typographical error noted below in the latter, and obtain

$$\left\langle \frac{\overset{+}{c}_{\text{per}}}{4c_1} \right\rangle_{\text{II}} \cong \delta_1(P/\xi_1^2) \tag{81}$$

This result shows that, for fixed transmembrane potential P, the average positive permeant ion concentration, or space charge, in the membrane phase will vary inversely with the square of the membrane thickness. Equation (81) follows from an analysis of the case of high level steady-state flow. Dimensional considerations utilizing Poisson's equation suggest, however, that the conclusion presented will be generally valid.

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Errata: Equations I(43) and II(59) should have read

$$\xi = \frac{\lambda}{(K_2)^{1/2}}\,x \tag*{I(43)}$$

and

$$\left\langle \frac{dy}{d\xi} \right\rangle_{\text{II}} \cong \delta_1(P/\xi_1^2) \tag*{II(59)}$$

respectively. We overlooked these typographical errors in the galley proof.

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