

SOLUTIONS OF THE FIELD EQUATIONS IN THE FIXED-CHARGE MODEL OF CELL MEMBRANES

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Summary

A general method is given for the numerical solution of the equations governing the diffusion of charged ions through layers containing specified concentrations of fixed charge. Using this method, the properties of a membrane model 50 Å thick in which the first half is positively and the second half negatively charged are investigated. Results presented are: the required ionic mobility to give resistance values similar to those observed, the voltage-current relation in such a model, the profiles of ionic concentration. The ionic concentrations found were compared with those given by the Boltzmann distribution. It is found that there is good agreement with the Boltzmann values for zero current, but that for finite membrane currents there is a significant disagreement.

The amount of disagreement for finite current was investigated theoretically, and a criterion established which specifies the distance from a reference point over which the Boltzmann distribution is a sufficient approximation.

I. INTRODUCTION

At present there is no quantitative theory which accounts satisfactorily for membrane excitability. Two models which have received much attention are the "activation" type of model of Davson and Danielli (1952) and Goldmann (1964) on the one hand, and the "fixed-charge" model of Meyer and Sievers (1936) and Teorell (1953) on the other.

The fixed-charge theory attempts to explain the diffusion kinetics of ions diffusing perpendicularly to the plane of a thin membrane separating two electrolytes which may have different compositions. In the membrane the existence of one or more layers of fixed charges which may be of either sign is assumed. Recently, Mauro (1962) has shown that the fixed-charge theory can provide an understanding of membrane capacity, and Coster (1965) has discussed the membrane voltage-current relation from the viewpoint of the fixed-charge theory and, in particular, has presented a model accounting for ionic "punch through" observed at large hyperpolarizing voltages.

In all of the above discussions of biological membranes from the fixed-charge point of view, simplifying assumptions have been made in order to arrive at an approximate solution.

We are currently engaged in obtaining computer solutions for various fixed-charge configurations, and in this report we give results obtained up to the present time.

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II. THEORY

The model is shown in Figure 1, and consists of two regions of fixed space charge, a region of fixed positive charge extending from $x = a$ to $x = b$ and a region of fixed negative charge extending from $x = c$ to $x = d$. These regions are assumed permeable to mobile ions of charge $\pm q$.

This system is assumed immersed in an electrolyte in which the concentrations of positive and negative ions are P and N . A steady current flows, taken as positive if flowing from left to right.

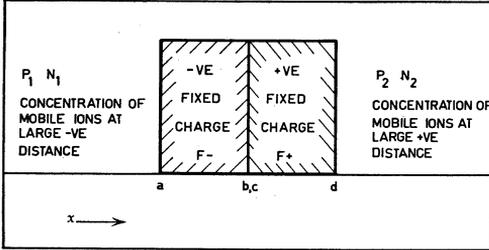


Fig. 1.—The general membrane model. In the particular problem considered in this paper, $P_1 = N_1 = P_2 = N_2 = 6 \times 10^{23}/\text{m}^3$, $F^- = F^+ = 6 \times 10^{25}/\text{m}^3$, and $ab = cd = 25 \text{ \AA}$.

Let I_p (I_n) = current carried by positive (negative) ions, and let μ_p (μ_n) = mobility of positive (negative) ions. F is the fixed charge concentration. In the steady state

$$I_p = \text{const.} = -kT\mu_p \frac{dP}{dx} + Pq\mu_p E, \quad (1)$$

$$I_n = \text{const.} = kT\mu_n \frac{dN}{dx} + Nq\mu_n E, \quad (2)$$

where E = electric field intensity. Therefore

$$\frac{dP}{dx} = (-I_p + Pq\mu_p E)/kT\mu_p, \quad (3)$$

$$\frac{dN}{dx} = (I_n - Nq\mu_n E)/kT\mu_n, \quad (4)$$

$$d\phi/dx = -E, \quad (5)$$

and

$$dE/dx = q[F + P - N]/\epsilon_r \epsilon_0, \quad (6)$$

where ϵ_r = relative permittivity of the membrane,

ϵ_0 = permittivity of free space, and

ϕ = electric potential.

In order to integrate these equations by numerical methods, the difficulty presents itself that the boundary conditions are only specified for $x \rightarrow \pm \infty$, namely, as $x \rightarrow \infty$, $dP/dx \rightarrow 0$, and, from (3) and (4),

$$\left. \begin{aligned} I_p &= P_1 q \mu_p E_1 \\ I_n &= N_1 q \mu_n E_1 \end{aligned} \right\}, \quad (7)$$

and as $x \rightarrow +\infty$

$$\left. \begin{aligned} I_p &= P_2 q \mu_p E_2 \\ I_n &= N_2 q \mu_n E_2 \end{aligned} \right\}, \quad (8)$$

where E_1 and E_2 are constant field strengths. It is shown in the Appendix that for distances large compared with the Debye length, L_D , where

$$L_D = (\epsilon_r \epsilon_0 kT / 2q^2 P_1)^{1/2},$$

i.e. at

$$x = -L \quad (L \gg L_D)$$

then

$$\left. \begin{aligned} E &= E_1 + e_1 \exp(\alpha x) \\ P &= P_1 + p_1 \exp(\alpha x) \\ N &= N_1 + n_1 \exp(\alpha x) \end{aligned} \right\} \quad (9)$$

where each of the second terms on the right-hand side of equation (9) is small in comparison with its corresponding first term. The attenuation constant α is given by

$$\alpha = [(2q^2 P_1 / \epsilon_r \epsilon_0 kT) + (qE_1 / kT)^2]^{1/2}. \quad (10)$$

Of the three constants n_1 , p_1 , e_1 , only one (say n_1) is independent, the remaining two being given by [see Appendix, equations (A9)–(A11)]:

$$e_1 = -n_1 [(qE_1 + \alpha kT) / qP_1], \quad (11)$$

$$p_1 = -n_1 [(qE_1 + \alpha kT) / (qE_1 - \alpha kT)]. \quad (12)$$

III. COMPUTER PROCEDURE

We begin by assuming the current density I is specified. Since

$$I = I_p + I_n = P_1 q E_1 (\mu_p + \mu_n), \quad (13)$$

this determines E_1 and hence I_p , I_n separately from (7) and α from equation (10).

An arbitrary value is chosen for n_1 . Equations (11) and (12) give e_1 , p_1 , and hence we may now integrate equations (3)–(6) starting at $x = -L$ and using as initial conditions [from (9)]

$$\left. \begin{aligned} E(-L) &= E_1 + e_1 \exp(-\alpha L) \\ P(-L) &= P_1 + p_1 \exp(-\alpha L) \\ N(-L) &= N_1 + n_1 \exp(-\alpha L) \end{aligned} \right\} \quad (14)$$

So far, the value of n_1 is arbitrary. The various solutions obtained for different values of n_1 are all possible solutions of the set of equations (3)–(6). In order to determine the value of n_1 for our specific problem, some further criterion needs to be specified. Then that solution which satisfies this additional criterion is accepted as the solution to the specified problem.

The nature of the additional criterion will depend on the particular problem to be solved. The problem considered in this report is that illustrated in Figure 1, with $P_1 = N_1 = P_2 = N_2 = 6 \times 10^{23} / \text{m}^3$. Two adjacent equal and opposite layers of fixed charge, 25 Å thick, are surrounded by electrolyte of equal concentration on each side. For simplicity we also assumed $\mu_p = \mu_n$. From symmetry it follows that at $x = 0$ (the junction of the two fixed-charge layers), the concentrations of the negative and positive mobile ions should be equal, i.e.

$$P(0) = N(0). \quad (15)$$

We found $x = L = 500 \text{ \AA}$ to be a convenient starting point. We therefore integrated equations (3)–(6) from this point using the Runga Kutta routine on the KDF9 Computer in the Basser Computing Department, University of Sydney. Initial conditions were obtained from equations (14) and the integration continued as far as $x = 0$ using integration steps of 0.1 \AA . At $x = 0$ the difference $P(0) - N(0)$ was examined. If this difference was greater than $P(0)/1000$, then n_1 was modified and the computation repeated until

$$|P(0) - N(0)|/P(0) < 10^{-3}. \quad (16)$$

This was taken as satisfying equation (15) to sufficient accuracy. In our experience, some 20–30 runs were required before (16) was satisfied, though with some experience it should be possible to reduce this number.

IV. RESULTS

(a) Internal Ionic Mobility, μ_I

The ionic mobility in the surrounding electrolyte is well known, and for this we took the value for potassium ions, namely $\mu_0 = 7.6 \times 10^{-8} \text{ m}^2 \text{ sec}^{-1} \text{ V}^{-1}$. However, μ_I , the mobility in the membrane substance is not so well known, and we therefore explored possible values for μ_I .

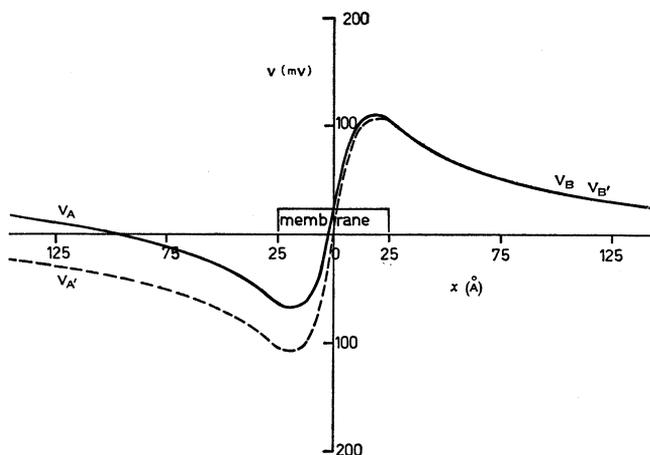


Fig. 2.—Potential profiles for $I = 0$ (---) and for $I = 1.17 \text{ mA/cm}^2$ (—).

In Figure 2 is shown a plot of potential against distance for zero current (broken line) and for a current of 1.17 mA/cm^2 (full line). At sufficient distance from the membrane the potential on each side, A and B , is seen to be the same for $I = 0$ (i.e. $V_A' = V_B'$). Namely the membrane potential $V_{AB} = 0$. However, for $I = 1.17 \text{ mA/cm}^2$, the asymptotic potential values V_A and V_B on each side of the membrane differ, and this difference we have taken as the membrane potential, V :

$$V = V_A - V_B. \quad (17)$$

Next we obtained curves of V [eqn. (17)] against I for various values of μ_I and the

results are shown in Figure 3. It is seen that only for $\mu_I = 10^{-3}$ – $10^{-4}\mu_0$ do we obtain membrane resistances of order 100–1000 $\Omega \text{ cm}^2$ as found in practice. For all further investigations we therefore took $\mu_I = 10^{-3}\mu_0$, i.e.

$$\mu_I = 7.6 \times 10^{-11} \text{ m}^2 \text{ sec}^{-1} \text{ V}^{-1}. \quad (18)$$

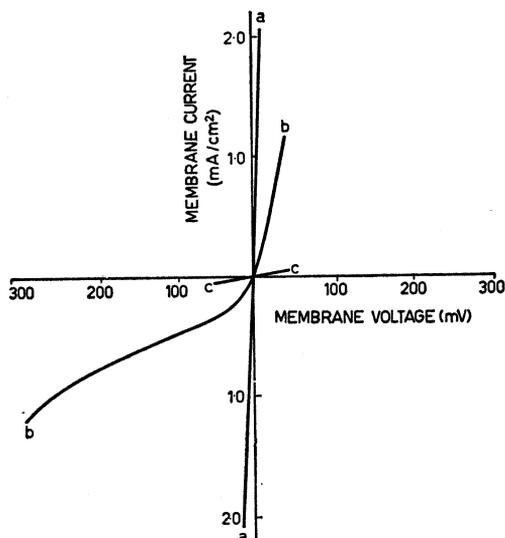


Fig. 3.—Current–voltage relations for fixed-charge membrane model for various values of the internal mobility: *a*, 7.6×10^{-10} ; *b*, 7.6×10^{-11} ; *c*, 7.6×10^{-12} MKS units. μ_0 , mobility in external solution = 7.6×10^{-8} MKS units. For $\mu_I = 7.6 \times 10^{-9}$ the curve is indistinguishable from the vertical axis, and for $\mu_I = 7.6 \times 10^{-13}$, from the horizontal axis.

(b) Rectification

For the μ_I value given in equation (18) a more extended V *v.* I curve is shown in Figure 3, curve *b*. This is seen to show a mild degree of rectification, the resistance in the forward direction being about one-fifth of that in the backward direction.

(c) Ionic Concentrations

These are shown in Figure 4 for zero current. The positive ion concentration, P , shows the expected maximum in the negative fixed-charge region and minimum in the positive fixed-charge region. These maximum and minimum values are: $P_{\max} = 3.4 \times 10^{25}/\text{m}^3$, $P_{\min} = 1.0 \times 10^{22}/\text{m}^3$. The profile of the negative ion concentration is the mirror image of that for the positive ions for the problem in hand. For the thickness of the fixed-charge region chosen, 50 Å, the mobile ion concentrations never settle down to steady values inside the membrane. Over the range of currents so far investigated (0–2.0 mA/cm²) the change in the concentration profiles is not very great, being less than 30%. It was found that the changes in the minority ion concentrations were greater than the changes in the majority ion concentrations by a factor of 2–3, depending on the current density.

(d) Space Charge

The space charge concentration is given by

$$\rho = q(F + P - N), \quad (19)$$

and the values given by equation (19) are plotted in Figure 5 for $I = 0$. The dotted lines indicate the values of F . The distributions for the other currents investigated are very similar. The space charge is seen to be large throughout the entire "membrane" thickness and to extend into the ionic solution, with a change of sign at the membrane boundary.

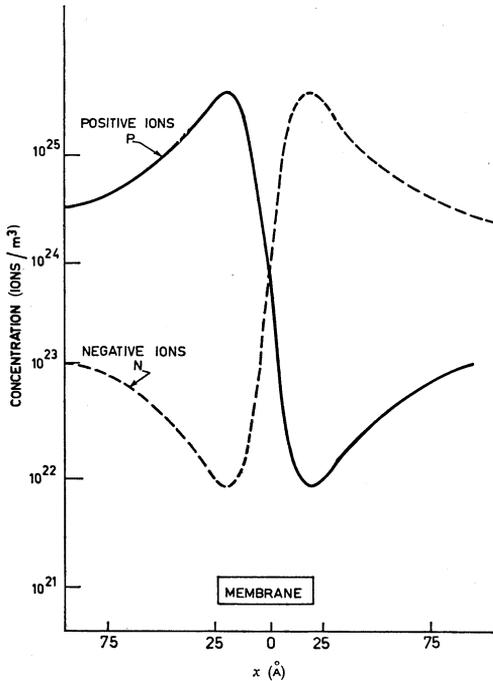


Fig. 4.—Concentration profiles of positive and negative ions for zero membrane current.

(e) The Boltzmann Distribution

In the absence of net current, the charge distributions satisfy the Boltzmann distribution:

$$\left. \begin{aligned} P(x) &= P(x_0)\exp(-q\phi/kT) \\ N(x) &= N(x_0)\exp(q\phi/kT) \end{aligned} \right\}, \quad (20)$$

where x_0 is some reference point and ϕ is the electrical potential with respect to this point.

It is frequently assumed (e.g. Teorell 1953; Mauro 1962; Coster 1965) that the Boltzmann distribution is still satisfied in the presence of current. This is obviously not so in the case of a metallic conductor, and it seemed worth investigating to what extent this assumption was valid for the present problem.

We therefore in all cases computed the values of $P(x)$ and $N(x)$ from equation (20) and compared them with the values obtained by integration.

The zero of potential was taken at the point where the integration was started, namely $x_0 = L = 500 \text{ \AA}$. Such a comparison is presented in Table 1 for currents $I = 0$ and $I = 0.6 \text{ mA/cm}^2$. For $I = 0$, of course, there should be complete agreement. The small discrepancies observed ($\approx 1\%$) can be attributed to the cumulative errors in the computation. For a current of 0.6 mA/cm^2 , however, it is seen that the discrepancies are significantly greater, and become progressively so as one proceeds through the membrane.

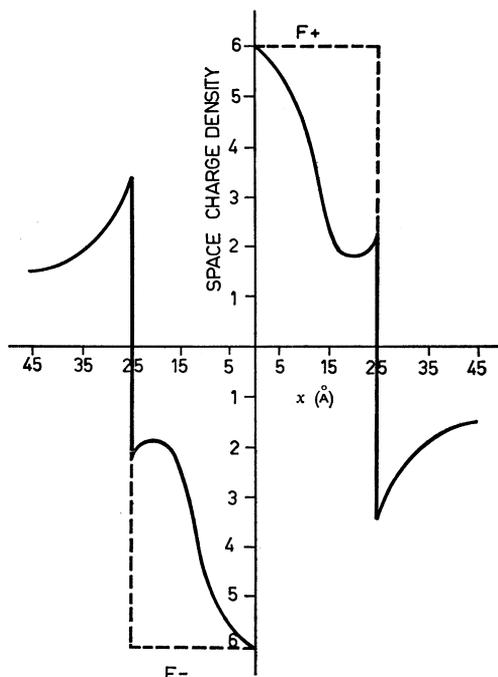


Fig. 5.—Space-charge density (in units of 10^{25} electronic charges/ m^3) in the membrane model for zero current.

V. DISCUSSION

(a) Ionic Mobility

The results in Figure 3 show that the resistance of the fixed-charge membrane model can only be brought into line with that observed by assuming the ionic diffusion coefficient to be much lower, by a factor of order 10^{-3} in the membrane compared with that in aqueous solution. This may be compared with the rates of diffusion through monolayers of fatty acids measured for a variety of gases by Hawke and Alexander (1962) and for monolayers of alcohols by Blank (1962). In both cases the diffusion rates are in many cases similar to those found for the aqueous phase.

A way out of this difficulty would be to suppose that the ions can only diffuse through pores which present a total area equal approximately to 10^{-3} of the membrane

TABLE 1

COMPARISON OF CONCENTRATIONS OF POSITIVE AND NEGATIVE IONS IN A "MEMBRANE" 50 Å THICK WITH THOSE GIVEN BY THE BOLTZMANN DISTRIBUTION

The values in the last four columns should be multiplied by 10^{23} to give actual concentrations per cubic metre. The "membrane" extends from $x = -25$ Å to $x = +25$ Å

x (Å)	ϕ (mV)	Negative Ion Concentration, N		Positive Ion Concentration, P	
		Boltzmann Distribution	Present Results	Boltzmann Distribution	Present Results
$I = 0$					
-100	38.55	26.62	26.61	1.351	1.352
-75	51.45	43.83	43.82	0.821	0.821
-50	70.7	92.3	92.3	0.389	0.390
-25	104.7	343.8	343.7	0.1047	0.1047
-20	109.7	416.3	416.3	0.08643	0.08645
-15	105.85	358.8	358.7	0.1002	0.1003
-10	90.69	199.65	199.62	0.1801	0.1802
-5	57.48	55.32	55.31	0.651	0.651
-2	26.14	16.48	16.48	2.184	2.184
-1	13.61	10.15	10.15	3.55	3.55
0	0	6.0	6.0	6.0	6.0
1	-13.71	3.53	3.53	10.19	10.19
2	-26.36	2.17	2.17	16.61	16.61
5	-58.02	0.637	0.637	56.47	56.48
10	-91.86	0.172	0.172	208.7	208.8
15	-108.1	0.0919	0.0919	391.5	391.6
20	-114.7	0.0713	0.0714	504.0	504.5
25	-109.6	0.0865	0.0865	416.2	416.3
$I = 6.0 \text{ A/m}^2$					
-100	37.5	25.6	25.6	1.407	1.404
-75	50.01	41.5	41.5	0.867	0.866
-50	68.5	84.7	84.8	0.425	0.423
-25	100.35	290.1	290.4	0.124	0.124
-20	103.0	320.8	321.2	0.112	0.0661
-15	92.41	213.4	213.7	0.169	0.0393
-10	64.26	71.91	72.04	0.50	0.0271
-5	12.59	9.76	9.798	3.69	0.0397
-2	-31.06	1.807	1.826	20.0	0.140
-1	-47.76	0.947	0.964	38.0	0.254
0	-65.56	0.476	0.491	75.7	0.491
1	-83.40	0.238	0.253	151.2	0.966
2	-100.2	0.125	0.139	288	1.834
5	-144.0	0.023	0.0394	1,592	9.901
10	-195.9	0.00309	0.0269	11,650	73.56
15	-224.4	0.00103	0.0389	34,950	221.4
20	-235.7	0.00066	0.0645	54,550	342.6
25	-234.9	0.00068	0.115	53,000	311.0

area. Within these pores, diffusion is limited by fixed charges on the walls of the pores. Such a model has been suggested by Sollner (1945). This model then comes rather close to the alternative, activation, type of picture.

(b) *Ionic Concentration Profiles*

For fixed-charge regions considerably thicker than those considered here, the concentrations of mobile ions assume constant values except at the boundaries (Mauro 1962). For this to occur the fixed-charge regions would need to be several hundred microns in thickness. It would seem to follow that discussions of the fixed-charge model which assume constant values of the mobile ion concentrations in the fixed-charge regions for zero membrane current, and small linear departures from these for finite current must be assumed as applying only to membranes much thicker than those found in practice (Coster 1965).

(c) *Space Charge*

Space charge has either been assumed to be non-existent (Teorell 1953) or confined to a narrow "depletion layer" at the boundary of the fixed-charge region (Mauro 1962; Coster 1965). It is seen that neither of those assumptions can be made for membranes whose thickness is of the order of that observed in practice. For a membrane in which the thickness of the fixed-charge region is 50 Å, it is seen (Fig. 5) that the space charge extends through the entire membrane, in disagreement with the treatment presented by Mauro (1962). Mauro has shown that an applied potential so modifies the thickness of the depletion layer as to give rise to an effective membrane capacitance. Where the depletion layer extends right through the membrane, and beyond, it is still possible for the capacitance to be explained along the lines suggested by Mauro, but the numerical value of the capacitance will doubtless be different from that so far estimated.

(d) *Boltzmann Distribution*

The results in Table 1 indicate that the Boltzmann distribution [equation (20)] may not be a good predictor of ionic concentration in the presence of current. Setting $I = 0$ in equations (3) and (4) leads immediately to the Boltzmann distribution. Thus, if I is small we may expect only small departures from the Boltzmann distribution, which increase progressively as the current I is increased. It would be convenient to have a criterion indicating the region of approximate validity of Boltzmann's distribution for a given current. This may be obtained as follows.

In equation (3), for example, set

$$P = P_0 \exp(-q\phi/kT) + p(x), \quad (21)$$

in which

$$\left. \begin{array}{l} \phi = 0 \\ P = P_0 \end{array} \right\} \text{ at } x = L \text{ and } p/P \ll 1.$$

L is an arbitrary reference point and is also the point at which the integration of

equations (3)–(6) was commenced. Substituting (21) in (3):

$$dp/dx - pqE/kT = -I_p/kT\mu_p \quad (22)$$

as a first approximation. The numerical results obtained show that the second term is small compared with the third, thus

$$p \simeq I_p(L-x)/kT\mu_p. \quad (23)$$

Thus $p/P \ll 1$ if $I_p(L-x)/kTP\mu_p \ll 1$, or

$$(L-x) \ll kT\mu_I/E_0q\mu_0 \quad (24)$$

where

μ_I = membrane ionic mobility,

μ_0 = ionic mobility in open solution,

E_0 = field strength at large distance.

In our particular case, equation (24) leads to the numerical value:

$$L-x < 100 \text{ \AA} \quad (25)$$

for a current of 1.5 A/m^2 . The more exact solution of equation (22) leads to $p/P \ll 1$ if

$$\frac{I_p}{P_0 kT\mu_p} \int_L^x \exp(q\phi/kT) dx \ll 1. \quad (26)$$

Clearly $p = 0$ if $I_p = 0$. In our case an average value of $\exp(q\phi/kT)$ is e^2 approximately and equation (26) leads to a similar value [equation (25)] for the range over which the Boltzmann distribution may be taken as a guide to the ionic concentration. This prediction is seen to be consistent with the results in Table 1. It thus appears inadvisable to assume the Boltzmann distribution for the ionic concentrations unless the inequality (26) is satisfied.

VI. CONCLUSIONS

From the results obtained the following conclusions may be drawn concerning the electrical properties of the fixed-charge membrane model discussed in this paper:

- (1) The observed values for membrane resistance are only obtained if the ionic mobility inside the membrane is 10^{-3} – 10^{-4} of that observed in ionic solution. This could be explained in terms of normal mobility in pores which occupy only 10^{-3} – 10^{-4} of the total membrane area.
- (2) Under the conditions investigated the model shows a mild degree of rectification.
- (3) The characteristic length over which changes in ionic concentration occur is comparable with the "membrane" thickness studied, namely 50 \AA . Consequently, in fixed-charge membranes of realistic thickness, the ionic concentrations never achieve the steady values they would approach asymptotically for membranes of greater thickness.

- (4) From the previous conclusion, it follows that the region of space charge occupies the entire thickness of the membrane.
- (5) For membrane currents in the range of practical interest, passage of current produces a significant departure of the ionic concentrations from those given by the Boltzmann distribution.

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APPENDIX

In equations (3)–(6) substitute the following approximations, valid for distances large compared with the Debye length L_D , bearing in mind that e , p , and n are small perturbations:

$$E = E_1 + e(x),$$

$$P = P_1 + p(x),$$

$$N = N_1 + n(x).$$

We then obtain

$$dp/dx = (1/kT\mu_p)[-I_p + q\mu_p(P_1 + p)(E_1 + e)], \quad (\text{A1})$$

$$dn/dx = (1/kT\mu_n)[I_n - q\mu_n(N_1 + n)(E_1 + e)], \quad (\text{A2})$$

$$de/dx = (q/\epsilon_r \epsilon_0)[p - n]. \quad (\text{A3})$$

In (A1)–(A3) equate terms of various orders:

$$I_p = q\mu_p P_1 E_1; \quad I_n = q\mu_n N_1 E_1, \quad (\text{A4})$$

$$dp/dx = (q/kT)[E_1 p + P_1 e], \quad (\text{A5})$$

$$dn/dx = (-q/kT)[E_1 n + N_1 e], \quad (\text{A6})$$

and ignore terms in second order of smallness. Substituting

$$\left. \begin{aligned} p(x) &= p_1 \exp(\alpha x) \\ n(x) &= n_1 \exp(\alpha x) \\ e(x) &= e_1 \exp(\alpha x) \end{aligned} \right\}, \quad (\text{A7})$$

where e_1 , p_1 , and n_1 are small constants, in (A3), (A5), and (A7) gives

$$(qE_1 - \alpha kT)p_1 + qP_1 e_1 = 0 \quad (\text{A8})$$

$$(qE_1 + \alpha kT)n_1 + qP_1 e_1 = 0 \quad (\text{A9})$$

$$-qp_1/\epsilon_r \epsilon_0 + qn_1/\epsilon_r \epsilon_0 + \alpha e_1 = 0 \quad (\text{A10})$$

The determinant of the equations (A8)–(A10) must be zero, and this gives

$$\alpha = [(2q^2 P_1 / \epsilon_r \epsilon_0 kT) + (qE_1 / kT)^2]^{\frac{1}{2}}, \quad (\text{A11})$$

α being known, equations (A8)–(A11) give expressions for any two of the constants p_1 , n_1 , e_1 in terms of the third.