

EQUIVALENT CIRCUITS AS RELATED TO IONIC SYSTEMS

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ABSTRACT The purpose of this paper is to clarify the relationship between certain "equivalent circuits" and the fundamental flux equations of Nernst and Planck. It is shown that as a direct algebraic consequence of these equations one may construct two types of equivalent circuits for a homogeneous (charged or uncharged) membrane. The one, which we term the "pure electrical equivalent circuit," correctly predicts all of the electrical properties of the membrane for both steady and transient states. The other, which we call the "mixed equivalent circuit," predicts the *steady state* I, Ψ characteristics of the membrane and the *steady state* ionic fluxes; it is not applicable to non-steady state properties or measurements. We emphasize that with regard to the portrayal of the physical basis of the properties of a homogeneous membrane, the mixed equivalent circuit can be misleading. This is particularly significant because this same circuit can also be used to depict a mosaic membrane, in which case the circuit gives a realistic pictorialization of the physical origin of the membrane properties. It is hoped that our analysis will be of aid to workers in electrophysiology who make use of equivalent circuit terminology in discussing the behavior of the plasma membrane.

INTRODUCTION

In recent years, the concept of an "equivalent circuit" to represent the electrical behavior of excitable membranes has found increasing prominence in the electrophysiological literature. The use of this construct by Hodgkin and Huxley (1) to describe the properties of the squid axon is particularly well known to workers in the field. Despite, however, the interest and frequent use of equivalent circuits, there does not seem to be in the literature a discussion of the physical implications inherent in such a formalism. Because of this, we have been motivated to examine this question in some detail, in particular with regard to ionic diffusion through a "homogeneous" membrane. We shall see that such a physical system may be *formally* represented by two different types of equivalent circuits, each representation describing certain features of the actual system while failing to depict other properties. It is hoped that

from this analysis, we shall gain more insight into the meaning of equivalent circuits as a device for treating ionic systems.¹

ANALYSIS

General. Let us consider a convection-free, homogeneous,² uncharged membrane separating two infinitely large aqueous solutions of univalent ions, both solutions being continuously stirred to maintain uniform composition (Fig. 1). We further

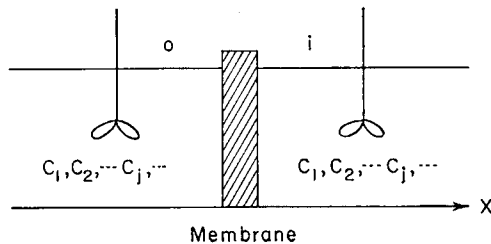


FIGURE 1 Homogeneous membrane separating two solutions of univalent ions. The solutions are essentially "infinite" and well stirred so that the boundary conditions are maintained.

assume that the membrane is freely permeable to all ions and water, that water flow can be neglected, and that the mobilities of the ions are constant; i.e., not a function of concentration. In short, we are considering the diffusion of ions across a membrane subject to constrained boundary conditions. Our discussion will be restricted to the *steady state*, which is characterized by a constant flux, ϕ_j , of the j 'th ion at any point in the membrane. We may now write down the fundamental flux equations of Nernst and Planck (2, 3) for an arbitrary cation and anion subject to gradients of concentration and electric potential:

$$\phi_j^+ = -u_j c_j^+ \left(RT \frac{1}{c_j^+} \frac{dc_j^+}{dx} + F \frac{d\psi}{dx} \right) \quad (1a)$$

$$\phi_k^- = -v_k c_k^- \left(RT \frac{1}{c_k^-} \frac{dc_k^-}{dx} - F \frac{d\psi}{dx} \right) \quad (1b)$$

where, u_j = the "molar" mobility of the j 'th cation

v_k = the "molar" mobility of the k 'th anion

(Note these quantities are the conventional mobilities divided by F .)

¹ The present paper will serve to extend and correct the cursory treatment of "equivalent circuits" which arose in the discussion section of a recent review paper on anomalous impedance by one of the authors (Mauro, 5; cf. p. 370).

² By a homogeneous membrane, we mean one whose properties do not show any macroscopic variation within any plane parallel to the membrane surface. Thus, there are no regions showing special permeabilities to certain ions; this is in contrast to the mosaic membrane which we shall discuss later.

c_j^+ , c_k^- = the concentration of the j 'th and k 'th ions, respectively, at any point x in the membrane.

ψ = the electrical potential at any point in the membrane (with a value of 0 in the outside solution and a value of $-\Psi$ in the inside solution).

R = the gas constant

T = the absolute temperature

F = the Faraday constant

Subject to the boundary conditions and the condition of electroneutrality ($\sum_i c_i^+ = \sum_k c_k^-$), these equations can be solved for c_i and ψ as a function of x and hence for the flux ϕ_i of each ion (see Planck, 3; and Teorell, 4).³ Thus, the complete description of the system can be carried out. It is not our purpose, however, to proceed in this way. Instead, we shall rewrite these equations in a form which will enable us to relate them formally to certain electrical circuits. We wish to emphasize that we are doing this, not because such a procedure is superior to the classical Planck analysis (in fact, as we shall see, it is less satisfactory), but because we wish to demonstrate how equivalent circuit terminology evolves from the basic flux equations.

Rewriting (1a) we have:

$$\phi_i^+ = -u_i c_i^+ F \left(\frac{RT}{F} \frac{d \ln c_i^+}{dx} + \frac{d\psi}{dx} \right) \quad (1)$$

Recalling that ϕ_i^+ is a constant throughout the membrane as a consequence of the *steady state*, integration from the outside (o) to the inside (i) gives:

$$\phi_i^+ \int_o^i \frac{dx}{F u_i c_i^+} = -\frac{RT}{F} \ln \frac{(c_i^+)_i}{(c_i^+)_o} - (-\Psi) \quad (2)$$

Although it is only the algebraic sum of all ion flows across an element of surface that is an electric current, we may formally consider the ion flux $F\phi_i^+$ as an electric current I_i^+ and define

$$E_i^+ \equiv \frac{RT}{F} \ln \frac{(c_i^+)_i}{(c_i^+)_o}$$

as the "Nernst EMF" of the j 'th ion. Then noting that

$$\int_o^i \frac{dx}{F^2 u_i c_i^+}$$

is the integral resistance R_i of the j 'th ion,⁴ or

$$1 / \int_o^i \frac{dx}{F^2 u_i c_i^+}$$

³ The solution of these equations by the method of Planck for the case of zero current flow is given in the appendix of the book, *The Principles of Electrochemistry*, by Duncan A. MacInnes (New York, Dover Publications, Inc.).

⁴ The integral resistance is a consequence of integrating the specific resistivity $1/F^2 u_i c_i$ of the j 'th ion as a function of x .

the integral conductance g_i of the ion, expression (2) can be rewritten in electrical language as:

$$I_i^+ = g_i(\Psi - E_i^+) \quad (3)$$

An identical expression can be derived from (1b) for anions, taking note of the fact that $I_k^- = -F\phi_k^-$, i.e. a flux of negative ions in the positive direction constitutes a negative electric current. In this case E_k^- will be given by:

$$E_k^- \equiv -\frac{RT}{F} \ln \frac{(c_k^-)_i}{(c_k^-)_o}$$

Equation (3) is the relation describing the type of equivalent circuit popular in membrane physiology (Fig. 2). (Again we emphasize that the expression for the ionic flux

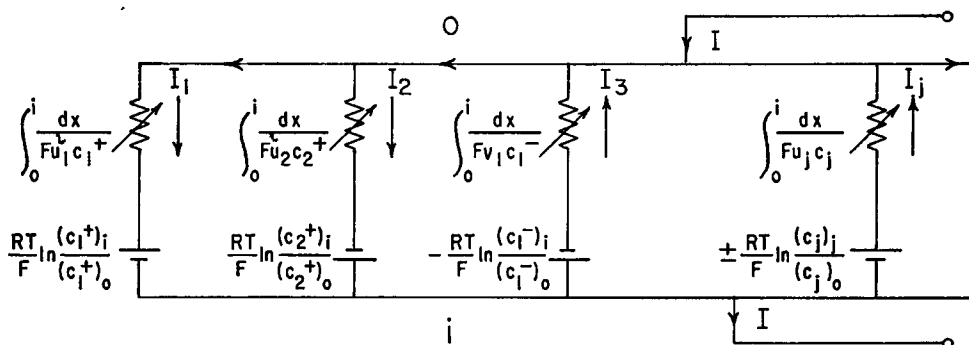


FIGURE 2 The "mixed equivalent circuit" for the system shown in Fig. 1. The j 'th resistance element is the integral resistance of the j 'th ion, while the j 'th EMF is the "Nernst EMF" of the j 'th ion. Note that the resistances may be voltage-dependent, but the EMF's are constant. $I = \sum_j I_j$. (Note: The Faraday constant must be squared in the expressions for resistance appearing in this and succeeding figures. The units of resistance are then consistent with those of the text.)

can be kept in the language of the flux equations without resorting to the electrical circuit language. This has been done very comprehensively by Teorell (4); see his equation (7).) We note that the only restriction we have placed on our derivation of (3) is that the system has attained a *steady state*; thus, the equivalent circuit of Fig. 2 holds equally well for the free diffusion case where no current is passed through the membrane as for the case where a constant I (established by means of a pair of electrodes) is flowing across the membrane. This can be stated alternatively as follows: if a constant current I is passed across the membrane, the ionic profiles within the membrane will, *in general*, shift but will finally attain steady-state values. These concentration profiles can be found by solving the system of equations (1) together with that for electroneutrality—generally a rather tedious procedure but, nevertheless, possible (see Teorell, 4)—and then, by integrating, the corresponding g 's are determined. If these g 's, along with the "Nernst EMF's," which are invariant to current

flow, since they are only functions of the ion concentrations on the two sides of the membrane, are inserted in the equivalent circuit of Fig. 2, we obtain I_i for each ion and the total membrane potential Ψ , with, of course, Kirchhoff's law of current

$$\sum_i I_i^+ + \sum_k I_k^- = I$$

always being satisfied. It should also be understood that I_i is physically determinable, being the net amount of the j 'th ion that crosses the membrane in unit time. (A double tracer experiment, if carried out with proper precautions, is a convenient way of getting I_i . In the squid axon, because of the rapidity of events, Hodgkin and Huxley (6) had to identify " I_{Na} " and " I_K " by somewhat indirect means, but *in principle*, these could be identified by the same means as for the artificial membrane we are considering). Thus, the equivalent circuit of Fig. 2, where the g 's are integral conductances of each ion species, will give for any value of current I the correct membrane potential and the correct flux of each ion. (Of course, if the independent variable is the membrane potential Ψ , *i.e.*, if we "voltage clamp" the membrane, the equivalent circuit gives us the correct fluxes of each ion and the total current I crossing the membrane.) It should be noted that we have, as yet, said nothing concerning the total resistance of the membrane as compared to the total resistance of the equivalent circuit; this aspect of the problem will be considered a little later below.

We can treat the flux equations (1a and 1b) in an alternative manner to obtain another equivalent circuit. Summing these equations for all ion species, we obtain:

$$I \equiv \sum_i I_i^+ + \sum_k I_k^- = FRT \left(\frac{dV}{dx} - \frac{dU}{dx} \right) - F^2 \frac{d\psi}{dx} (U + V)$$

where

$$U = \sum_i u_i c_i^+ \quad V = \sum_k v_k c_k^-$$

Dividing through by $F^2(U + V)$ and integrating across the total membrane thickness gives:

$$\Psi = I \int_0^l \frac{dx}{F^2(U + V)} + \frac{RT}{F} \int_0^l \frac{d(U - V)}{(U + V)} \quad (4)$$

a fundamental relationship originally derived by Planck.⁵ Now,

$$\int_0^l \frac{dx}{F^2(U + V)}$$

is the *total* integral resistance of the membrane (again, as in the case of the single species given above, this is a consequence of integrating the specific resistivity of the entire region as a function of x) and, hence, the first term on the right in (4) represents the IR drop across the membrane. Equation (4) then states that the total mem-

⁵ Note that, unlike equation (3), equation (4) is valid for all states of the system, and is not restricted to the steady state condition.

brane potential is made up of an IR drop plus another term which we may call the diffusion EMF (Ψ_D) contribution to the total potential (when $I = 0$, this is the only term). That is:

$$\Psi = IR_{\text{total}} + \Psi_D \quad (4a)$$

where,

$$R_{\text{total}} = \int_0^i \frac{dx}{F^2(U+V)}; \quad \Psi_D = \frac{RT}{F} \int_0^i \frac{d(U-V)}{(U+V)}$$

Equation (4a) represents the type of equivalent circuit shown in Fig. 3. This circuit

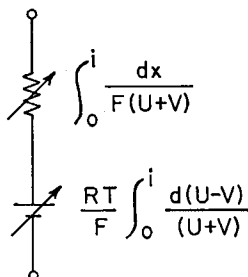


FIGURE 3 The "pure electrical equivalent circuit" for the system shown in Fig. 1. The resistance element is the total integral resistance of the membrane, and the EMF is the diffusion EMF of the membrane. Note that both the resistive element and the EMF may be voltage-dependent. (Although not shown in the figure, it is understood that an external current I can be flowing through the circuit as in Fig. 2).

describes all of the electrical properties of the homogeneous membrane; *i.e.*, membrane potential, resistance, and diffusion EMF as a function of the current crossing the membrane; it gives no information, however, concerning ion fluxes.

We thus see in Figs. 2 and 3 two circuits which one may choose to draw to represent certain properties of the steady state behavior of a homogeneous membrane across which ion movement is occurring.⁵ For convenience, we shall henceforth refer to the equivalent circuit in Fig. 3 as the "pure electrical equivalent circuit," since it pertains exclusively to all of the electrical properties of the membrane, while we shall call the equivalent circuit of Fig. 2 the "mixed equivalent circuit," as it gives some information both about the electrical properties of the membrane and about the ion fluxes across the membrane. With the general treatment of the flux equations taken as far as is necessary for our immediate purposes, we now turn to two specific cases in order to illustrate the meaning of the two circuits and to point out some paradoxes inherent in using the mixed circuit for describing a homogeneous membrane.

Case I. The Single Salt Case. In the case being considered, the solutions on the two sides of the membrane consist of a single salt (for example NaCl) at concentrations c_i and c_o . The two equivalent circuits relating to this system are shown in Figs. 4a and 4b. Let us first consider the mixed circuit. In order to establish g

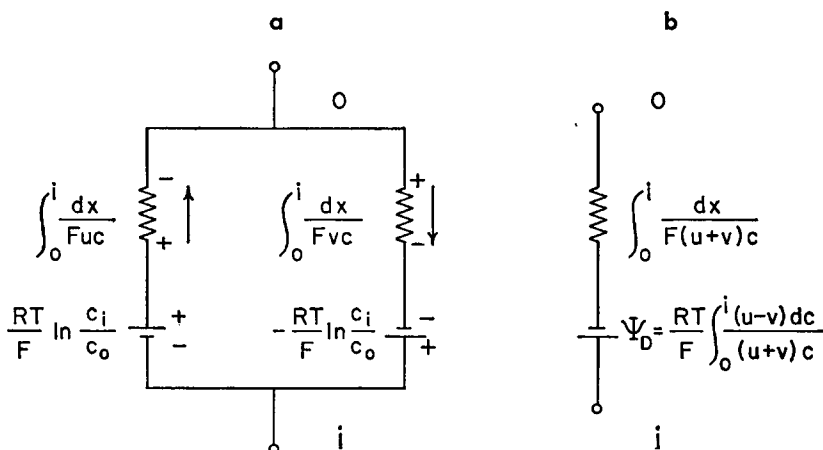


FIGURE 4 (a) Mixed equivalent circuit for the single salt case. Note that the resistances are voltage-independent. (b) Pure electrical equivalent circuit for the single salt case. Note that both the resistance and EMF are voltage-independent.

for the anion and cation, we must turn to the flux equations and, remembering that the condition of electroneutrality holds at any point in the membrane (namely, $c^+ = c^- = c$) we have following Planck (3):

$$-A \equiv \frac{I^+}{u} = -RT \frac{dc}{dx} - Fc \frac{d\psi}{dx}$$

$$B \equiv \frac{I^-}{v} = RT \frac{dc}{dx} - Fc \frac{d\psi}{dx}$$

and subtracting:

$$(A + B) = 2RT \frac{dc}{dx} \quad (5)$$

Taking the membrane thickness as δ , integration of (5) gives:

$$(A + B) = \frac{2RT}{\delta} (c_i - c_o)$$

and substituting this back into (5) and integrating between 0 and x , we get:

$$c = \frac{(c_i - c_o)}{\delta} x + c_o \quad (6)$$

Then, accordingly we have for the integral conductances of the respective ions:

$$g^+ = 1 / \int_0^i \frac{dx}{F^2 uc} = \frac{(F^2 u / \delta)(c_i - c_o)}{\ln c_i / c_o} \quad (7a)$$

$$g^- = 1 / \int_0^i \frac{dx}{F^2 vc} = \frac{(F^2 v / \delta)(c_i - c_o)}{\ln c_i / c_o} \quad (7b)$$

We note that these conductances are not functions of I . (This is the well known result that, for the single salt case, the ionic profiles will not be disturbed by the passage of current.)

If we calculate from the mixed equivalent circuit the free diffusion potential ($\Psi_{I=0}$), by noting that

$$I^+ = g^+(\Psi - E^+) = \frac{(F^2 u / \delta)(c_i - c_o)}{\ln c_i / c_o} \left(\Psi - \frac{RT}{F} \ln \frac{c_i}{c_o} \right)$$

$$I^- = g^-(\Psi - E^-) = \frac{(F^2 v / \delta)(c_i - c_o)}{\ln c_i / c_o} \left(\Psi + \frac{RT}{F} \ln \frac{c_i}{c_o} \right)$$

we have, since $I = 0$,

$$I^+ + I^- \equiv I = 0 = \frac{(F^2 / \delta)(c_i - c_o)}{\ln c_i / c_o} \left(u \Psi_{I=0} + v \Psi_{I=0} - \frac{RT}{F} u \ln \frac{c_i}{c_o} + \frac{RT}{F} v \ln \frac{c_i}{c_o} \right)$$

and finally,

$$\Psi_{I=0} = \frac{RT}{F} \frac{u - v}{u + v} \ln \frac{c_i}{c_o} \quad (8)$$

which is the familiar result obtained by solving the flux equations by the conventional methods, namely, equating (1a) and (1b) and solving for $\Psi_{I=0}$.

What is now of interest is an examination of the manner in which the free diffusion potential, $\Psi_{I=0}$, arises in the mixed equivalent circuit as compared to its actual physical origin in the diffusion regime. In the latter instance, due to the difference in mobilities of the cation and anion, an electric field is set up within the membrane which acts on all ions, so that, at any point in the membrane, the ions diffuse as a consequence of the gradient of their chemical potential

$$\left(RT \frac{1}{c} \frac{dc}{dx} \right)$$

and of the gradient of electrical potential

$$\left(F \frac{d\Psi}{dx} \right)$$

Furthermore, at any point in the membrane the cation and anion fluxes are equal and *no electric current flows* in the membrane. In the mixed equivalent circuit, on the other hand, the ionic diffusion fluxes are interpreted as real currents, the cation being driven by $\Psi - E^+$ acting across its integral resistance and the anion being driven by $\Psi - E^-$ acting across its integral resistance. Within the circuit, local currents flow with IR drops appearing across the two resistance elements. Certainly, the physical situation depicted by the mixed equivalent circuit is quite different from the one actually existing. To really emphasize this point, consider the case where the cation and anion mobilities are identical (KCl is a good approximation for this situation). In this case, both the direct consideration of the diffusion regime in the membrane

and the mixed equivalent circuit give $\Psi_{I=0} = 0$. But in the former case, no state of electrification exists anywhere in the system, while in the latter, despite the fact that $\Psi_{I=0} = 0$, there exist internally local currents, two IR drops, and two EMF's, the EMF's being equal to the IR drops (see Fig. 5). Thus, despite the fact that the mixed equivalent circuit predicts the correct fluxes and membrane potential, the physical conditions implicit in the circuit are far from those existing within the membrane.

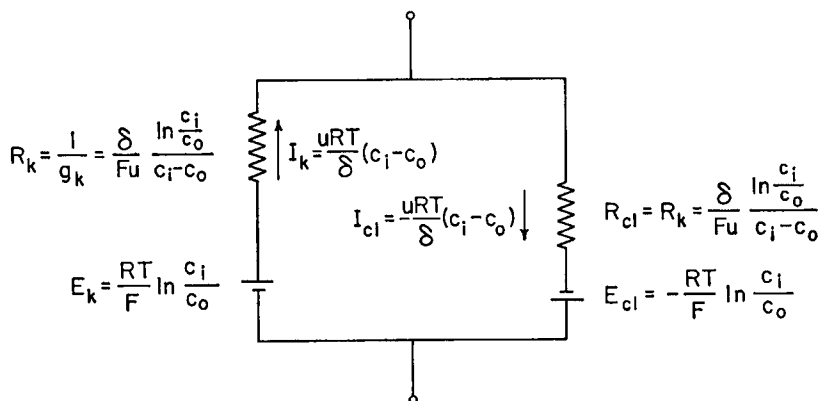


FIGURE 5 The mixed equivalent circuit, with no external current flowing through the system, for the single salt case where the cation and anion have equal mobilities (approximated by KCl). Note that although the potential across the membrane is 0, there are internal currents, EMF's, and IR drops.

Of course, being an "equivalent" circuit, it makes no pretense of necessarily saying anything about the physics of the membrane process; it is just this point which must be continually kept in mind. Note, however, that if instead of a homogeneous membrane we were dealing with a mosaic membrane consisting of some regions *exclusively* permeable to cations and other regions *exclusively* permeable to anions, the same equivalent circuit (Fig. 4a) would be used as for the homogeneous membrane, but in this case the "equivalent" circuit would, in fact, accurately represent the actual physical process by which ions crossed the membrane, namely, through local currents, as indicated, flowing in each branch pertaining to the region for a given ionic species.

Turning to the pure electrical equivalent circuit for the single salt case (Fig. 4b), we find for free diffusion no fictitious currents as arose above in the mixed circuit; indeed, in this "pure" representation, the current in the circuit is zero for free diffusion; i.e., $I = 0$. We simply have a diffusion EMF

$$\Psi_D \equiv \frac{RT}{F} \int_0^i \frac{d(U - V)}{(U + V)} = \frac{RT}{F} \int_0^i \frac{(u - v)dc}{(u + v)c} = \frac{RT}{F} \frac{u - v}{u + v} \ln \frac{c_i}{c_o} \quad (9)$$

in series with the total membrane integral resistance (which may be evaluated with the help of (6)):

$$R_{\text{total}} \equiv \int_0^\delta \frac{dx}{F^2(U+V)} = \frac{1}{F^2(u+v)} \int_0^\delta \frac{dx}{c} = \frac{1}{F^2(u+v)} \int_0^\delta \frac{dx}{(c_i - c_o)(x/\delta) + c_o}$$

$$R_{\text{total}} = \frac{\delta}{F^2(u+v)(c_i - c_o)} \ln \frac{c_i}{c_o} \quad (10)$$

(We may note that Ψ_D and R_{total} are not functions of I , which we knew *a priori* from the fact that the concentration profiles do not change. We shall see shortly that, in general, the situation is not so simple). For the case in which the anion and cation mobilities are identical, we see from (9) that $\Psi_D = 0$, and the equivalent circuit is just an ohmic resistance with no internal state of electrification, which is precisely the situation within the diffusion regime of ions. Clearly, as far as the electrical state of the membrane is concerned, the pure electrical equivalent circuit is a more accurate representation than the mixed circuit.

Case II. Equal Total Concentrations of Ions on the Two Sides of the Membrane.

In this case (and for any more general situation) the ionic profiles within the membrane will be, unlike the single salt case, voltage-dependent, so that *a priori* we should expect the individual ionic integral conductances (g 's), the total integral conductance ($1/R_{\text{total}}$), and the diffusion EMF (Ψ_D) to be altered by the passage of current through the membrane. We have chosen to consider the special case of equal total concentrations on the two sides of the membrane rather than the general case only because, for the former situation, it can be proved that the potential varies linearly through the membrane; that is, there is a "constant field" within the membrane (Appendix I). Because of this, the solution of the flux equations (1a) and (1b) is considerably facilitated, and, hence, also the calculation of g_i , R_{total} , and Ψ_D . This has been done in Appendix II so that the reader may have some idea of the nature of these functions. Even for this simple case, the expressions become rather awkward. For our purposes, however, it is necessary only to note that these quantities are, in general, functions of the current passed across the membrane.⁶

Now our remarks for *Case I* concerning the erroneous physical impression that the mixed equivalent circuit conveys apply equally well to the present case and need not be repeated. There is, however, as a consequence, of the voltage dependence of the ionic profiles, a further discrepancy that arises. This has to do with the method of depicting the non-linearity in the voltage-current relationship that must result from the shift of the ionic profiles. In the mixed-equivalent circuit, the membrane potential is artificially represented only by IR terms and constant EMF's. Thus, the non-linear properties of the membrane are depicted as due *solely* to the non-linear nature of the g 's (Fig. 2). But consideration of equation (4a), in view of our remarks

⁶ In those cases where the total concentration of ions is the same on the two sides of the membrane, but there is *only one* anion (or cation) involved in the system, it can be shown that Ψ_D , the diffusion EMF, will be invariant to current flow; the special case in this class occurs where three species are present, one ion being common, and is usually referred to as the "bi-ionic" case.

of the preceding paragraph, reveals that the non-linearity of the membrane potential actually will be due, in general, not only to the non-linearity of the membrane conductance ($1/R_{\text{total}}$), but also to a change in the basic EMF of the membrane (Ψ_D). In other words, both the resistance and the EMF, Ψ_D , depend on the concentration profiles, and in the relaxation of the system from one state to another they will be time variant. The pure electrical equivalent circuit faithfully depicts this (Fig. 3), but the mixed equivalent circuit fictitiously lumps both of these phenomena together as time-variant conductances. On the other hand, if we were dealing with a mosaic membrane consisting of regions of complete selectivity for individual ions, the mixed equivalent circuit not only would give the correct values for Ψ and the ionic fluxes (which it, of course, does for the homogeneous membrane), but would also convey an accurate physical description of the system. (In fact, the branches in the mixed circuit would refer to local homogeneous regions.) Thus, any non-linear properties of the mosaic membrane would be entirely due to non-linear behavior of the separate conductances.⁷

Anomalous Impedance. The AC impedance characteristics associated with a diffusion regime of ions provides an opportunity to elaborate on certain other consequences which arise from the currents flowing in the branches of the mixed circuit. We shall first restrict ourselves to the relaxation of the system to the steady state at $I = 0$. In the mosaic membrane if the resistances have time variant properties, a non-ohmic response will result when a small direct current is removed suddenly; *i.e.*, the voltage across the system will not drop to the steady-state value instantaneously. This, as has been explained previously (5), is due to the modulating effects on the local resting current flowing through the branches of the "capacitive" and "inductive" time-variant resistance elements. In this instance, the AC impedance characteristic is strictly anomalous since the EMF's in the system are time-invariant and, thus, no mechanism is available for storage of electrical energy as a consequence of current flow; *i.e.* the system is purely dissipative. In a homogeneous regime, the mixed equivalent circuit, because of the (formal) local currents flowing through the time-variant resistances, predicts a similar response to a small step of current and, accordingly, an anomalous impedance just as in the mosaic membrane. But this prediction is physically inadmissible, since the diffusion regime is in the state of zero current ("free diffusion") and, thus, there is no resting current to be modulated *via* the time-variant resistance—which is the essential condition for the anomalous impedance effect. In the homogeneous membrane, the non-ohmic response and, thus, the reactive component of the impedance is due exclusively to a time-variant EMF which is related to the relaxing of ionic profiles back to the previous steady state

⁷ In a mosaic membrane consisting of permselective regions for individual ions, the voltage dependence of the individual conductances would not be due to the shifting of ionic profiles, since in each region there is only one permeant ion. The conductances, however, could change as the result of an increase or decrease in the number of regions, or through various other effects. Independent of the mechanism, the branched circuit would be appropriate.

condition. (This is correctly portrayed in the pure electrical circuit by the fact that Ψ_D is, indeed, a time variant EMF.) Note here that the concomitant effect of relaxation of ionic profiles on the integral resistance, which is also present, will not be revealed in this observation, since the current has been brought to zero. As stated above and repeated here for emphasis, the mixed equivalent circuit, as applied to the homogeneous regime, conceals the time-variant EMF. Finally, if a bias current were established in the regime, a small signal sinusoidal perturbation would reveal an impedance characteristic that would consist of two components, namely, an anomalous component due to the time-variant resistance of the regime and the ordinary (or bona fide) component due to the time-variant EMF.⁸

Fixed-Charge Membrane. As a final example of the distinction between the mixed equivalent circuit and the pure electrical circuit, we shall show that both of these may be used to represent a homogeneous fixed-charge membrane. The properties of such a membrane have been extensively discussed by Teorell (4); we shall merely recall that at the membrane interfaces exist two Donnan EMF's π_1 and π_2 , which are assumed to be invariant to current flow, i.e. the Donnan conditions are invariant to current flow, while within the membrane there is a Planck-diffusion EMF (Ψ_{internal}). The total membrane potential (Ψ_{total}) is the algebraic sum of these three EMF's. Now our derivations of equations (3) and (4) would apply equally well to the fixed-charge membrane provided we neglect the Donnan "jumps" and were just concerned with the situation existing within the membrane. Thus, we can rewrite (3) for an arbitrary cation as:

$$I_i^+ = g_i \left(\Psi_{\text{internal}} - \frac{RT}{F} \ln \frac{(c_i^+)_{im}}{(c_i^+)_{om}} \right) \quad (11)$$

where the added subscript m means that the concentrations involved are those within the membrane occurring immediately after the Donnan jumps. Being careful to maintain our original sign convention, we can then write:

$$(c_i^+)_{im} = r_i (c_i^+)_{ie} \quad (12a)$$

$$(c_i^+)_{om} = r_o (c_i^+)_{oe} \quad (12b)$$

$$\pi_1 + \pi_2 = -\frac{RT}{F} \ln \frac{r_i}{r_o} \quad (12c)$$

where the subscript e refers to the concentrations in the bulk solutions and the r 's are the Donnan ratios. Substituting (12a) and (12b) into (11), we get:

$$I_i^+ = g_i \left(\Psi_{\text{internal}} - \frac{RT}{F} \ln \frac{r_i}{r_o} - \frac{RT}{F} \ln \frac{(c_i^+)_{ie}}{(c_i^+)_{oe}} \right)$$

⁸ Unfortunately, the explicit analytical solution of the non-steady state for the general case (or even for the simplest homogeneous regime of interest, i.e. the bi-ionic case), is not available as yet, and at this time we can only proceed by approximate and heuristic considerations.

and from (12c) and the fact that $\Psi_{\text{total}} = \Psi_{\text{internal}} + (\pi_1 + \pi_2)$, we have:

$$I_i^+ = g_i(\Psi_{\text{total}} - E_i) \tag{13}$$

where the E_i is the "Nernst EMF" calculated from the concentrations of the j 'th ion in the external solutions. A similar relation can be derived for an arbitrary anion, thus demonstrating that the mixed equivalent circuit, where g_i is the integral conductance of the j 'th ion, will give the correct membrane potential and correct ion fluxes for a fixed-charge membrane. We note that all of the subtlety of the total potential being composed of three physically separate EMF's is completely hidden by this equivalent circuit representation. On the other hand, the pure electrical circuit will display this feature, being in this case a resistance in series with three EMF's— Ψ_{internal} , π_1 , and π_2 (Fig. 6).

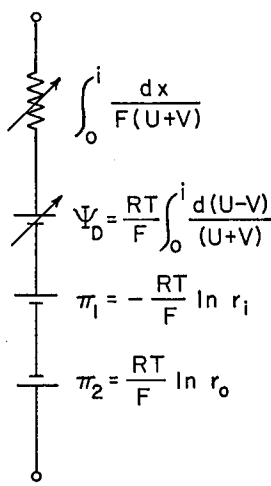


FIGURE 6 Pure electrical equivalent circuit for the fixed-charge membrane. The resistance and Planck diffusion EMF (Ψ_D) are voltage-dependent, but the Donnan EMF's (π_1 and π_2) are constant.

DISCUSSION

As was pointed out in the previous pages, the pure electrical equivalent circuit presents all of the electrical characteristics of a homogeneous membrane, charged or uncharged; *i.e.*, if current is chosen as the independent variable, it predicts the membrane potential, the integral resistance of the membrane, and the inherent diffusion EMF of the system. On the other hand, it contains no information at all concerning ionic fluxes. It is, perhaps, for this reason that the mixed equivalent circuit has received virtually exclusive use in the electrophysiological literature. In view of this fact and of the physical inconsistencies of this circuit to which we have drawn atten-

tion, we feel it may be fruitful to discuss this circuit in somewhat more detail, and it is to this that we now turn.

We have already demonstrated that both a homogeneous membrane and a mosaic membrane can be represented by the mixed equivalent circuit to give the correct ion fluxes and the correct membrane potential for all values of I . The question that immediately arises is how can one distinguish between these two physically different kinds of membranes. The first, and perhaps most obvious, way is by measuring the magnetic field that will arise only from the mosaic membrane, as a consequence of the local currents. While in principle this is a valid method, in practice such a measurement will be impossible if the mosaic regions are built up on a small enough scale, for the fields will tend to cancel each other out in terms of a macroscopic measurement. There do exist, however, other electrical measurements that in practice will distinguish between the two membranes (the possibility of using these for the case of the plasma membrane will be commented upon at the close of this discussion), and such measurements we now wish to consider.

Conductance. Hitherto we have refrained from any remarks concerning the relationship between the total membrane and the total mixed equivalent circuit conductances. In dealing with ionic systems in which the ionic profiles can be shifted as a consequence of current flow, one must be careful to specify what is meant when speaking about the membrane conductance. Fig. 7 represents a hypothetical I versus Ψ

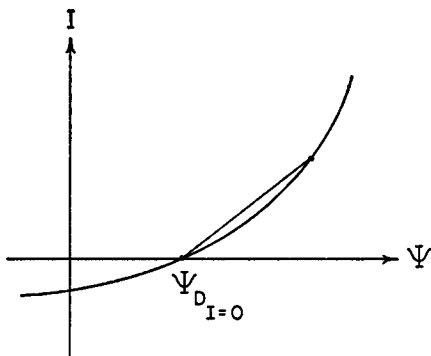


FIGURE 7 Hypothetical *steady state* I , Ψ plot for a membrane. If Ψ_D is voltage-independent; i.e., $\Psi_D = \Psi_{D, I=0}$, then the slope of the chord shown in the figure is the integral conductance of the membrane when the membrane potential is Ψ .

plot for a membrane, where we must remember that the Ψ and I being plotted are *steady state* values. The most unambiguous conductance is the *slope* conductance defined as $dI/d\Psi$ at any value of Ψ . Experimentally this can be found either by determining the entire I versus Ψ plot of the membrane and taking the slope at the desired Ψ , or, if the membrane is already at the desired Ψ , by applying a small step $\Delta\Psi$ of voltage and measuring the *steady state* ΔI to which this gives rise, the slope conductance then being given by $(\Delta I/\Delta\Psi)_{\Psi}$. Since we have shown that the mixed

equivalent circuit gives the correct Ψ and correct I_i 's (hence, the correct total I) for the membrane it is representing, it is clear that $dI/d\Psi$ will be the same for both the membrane measurement and the circuit calculation.

There exists, however, another physically significant conductance, namely, the chord or integral conductance (G_{integral}). (This, in fact, arose already in our discussion of the pure electrical equivalent circuit; *i.e.* $G_{\text{integral}} = 1/R_{\text{total}}$). If we assume that Ψ_D is independent of I , G_{integral} is given by the slope of the line drawn between $(\Psi_{I=0}, 0)$ and (Ψ, I) (Fig. 7). In other words, I times the integral resistance ($1/G_{\text{integral}}$) gives the IR contribution to the total membrane potential. On the other hand if Ψ_D is a function of I , one cannot draw the line whose slope is the chord conductance unless the functional relationship between Ψ_D and I is known. However, in all circumstances, G_{integral} , at a given Ψ , is determinable by a high frequency measurement, *i.e.*, by applying a high frequency voltage $\Delta\Psi$ and measuring the resulting current ΔI or by applying a small step $\Delta\Psi$ of voltage and measuring the "instantaneous"⁹ ΔI . Then, by either method, $G_{\text{integral}} = (\Delta I/\Delta\Psi)_{t=0}$. It is clear that in ionic terms for a homogeneous membrane:

$$G_{\text{int}} = 1 / \int_0^I \frac{dx}{F^2(U + V)} = 1 / \int_0^I \frac{dx}{F^2(\sum_i u_i c_i^+ + \sum_k v_k c_k^-)} \quad (14)$$

while for the mixed equivalent circuit, it will be given by:

$$(G_{\text{int}})_{\text{mixed}} = \sum_i g_i \quad (15)$$

which, from our definition of the g 's, may be written as:

$$(G_{\text{int}})_{\text{mixed}} = \sum_i 1 / \int_0^I \frac{dx}{F^2 u_i c_i^+} + \sum_k 1 / \int_0^I \frac{dx}{F^2 v_k c_k^-} \quad (16)$$

As can be seen by inspection, in general the expression in (16) will not equal that in (14); *i.e.*, the integral resistance of the mixed equivalent circuit will not equal that of the homogeneous membrane it is representing.¹⁰ Thus, we could distinguish between the homogeneous and mosaic membrane which had the identical I, Ψ plots and the identical g 's at all values of Ψ , by determining the integral conductance of the membrane (by the high frequency measurement described above). If we are dealing with a mosaic membrane, we should find that $G_{\text{integral}} = \sum_i g_i$ while if the membrane is homogeneous, we should find $G_{\text{integral}} \neq \sum_i g_i$.

It may appear paradoxical that since the g 's of the mixed equivalent circuit are

⁹ By instantaneous we mean a measurement in so short a period of time that the ion profiles have not had time to undergo any rearrangement to their new steady state values.

¹⁰ An exceptional case is the single salt case where the two will be equal. This is easily shown mathematically but is even more obviously seen physically, since this is the one case where ionic profiles do not shift with current. Hence, the steady state values of I and Ψ are the same as the "instantaneous" values. The I, Ψ plot in this case is a straight line and, hence, integral and slope conductances are the same constant value for all Ψ .

the individual ionic integral conductances of the membrane, their sum does not in general give the integral conductance of the same (homogeneous) membrane. The basis for this discrepancy may be indicated by the following: In order for the individual integral conductances to sum to the total integral conductance, they must exist as simple parallel elements (Fig. 8a). In fact, however, the correct way of representing them is that shown in (Fig. 8b). What this representation is meant to convey

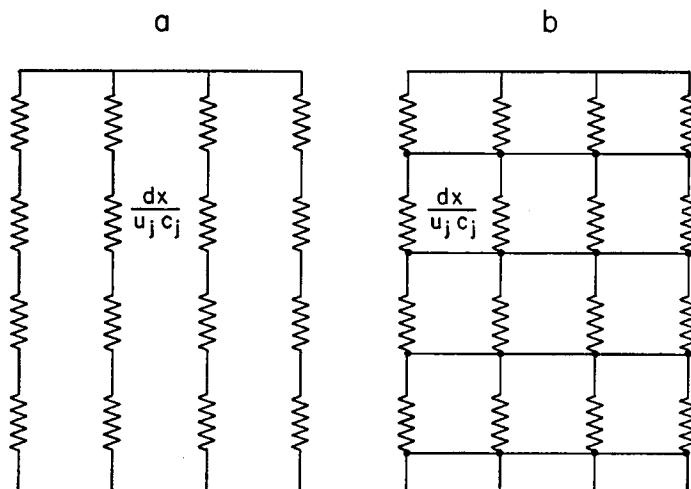


FIGURE 8 (a) Relationship of the individual ionic integral resistances in the mixed equivalent circuit. This corresponds to equation (16) of the text. (b) Relationship of the individual ionic integral resistances in the homogeneous membrane. This corresponds to equation (14) of the text.

is that at any given point in the membrane, all the ions are tied to the same potential (ψ) existing at that point. When this is realized, then it is clear why the individual conductances do not, in general, sum to the total conductance, since, in general, the conductance of the network in (Fig. 8a) does not equal the conductance of the network in (Fig. 8b).

Potential. As a second means of distinguishing between the homogeneous and mosaic membrane, let us turn to the potential instead of the conductance and consider the following type of experiment. The diffusion potential across the membrane is measured at $I = 0$. Then, a finite current is passed across the membrane until a steady state is reached. At this time, the current is turned off and the potential “instantaneously” appearing across the membrane is measured. *In general* (excluding, of course, the single salt case), the value obtained from the mixed equivalent circuit will be different from that derived from a direct treatment of the homogeneous diffusion regime, as can be seen from the following specific example. Consider the situation shown in Fig. 9, in which we have equal total concentrations and only one

anion A^- . If we assume that A^- has a very small mobility and, therefore, a negligible integral conductance (and, of course, its Nernst EMF is zero), the mixed equivalent circuit will be given by (Fig. 9b). At $I = 0$, there is, of course, zero membrane potential ($u_{NH_4} \approx u_K$), and the mixed equivalent circuit correctly predicts this in that $g_{NH_4} = g_K$ and $E_{NH_4} = -E_K$. Now if high enough current is passed from left to right, in the limit K^+ will have a concentration of 0.1 N in the membrane and NH_4^+

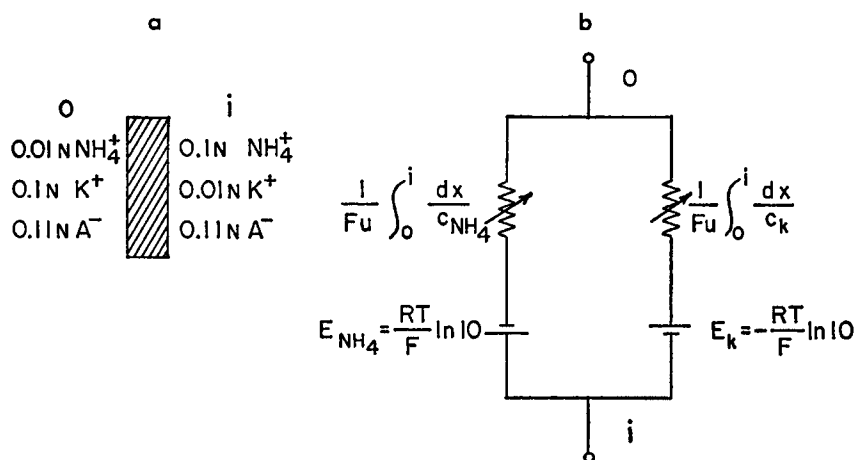


FIGURE 9 (a) Homogeneous membrane separating the two solutions indicated. The mobility of the anion A^- is assumed to be approximately 0. (b) The mixed equivalent circuit for the system depicted in Fig. 9a.

a concentration of 0.01. If the circuit is now opened, what is the situation? Across the actual membrane, there will still be zero potential difference since, as pointed out in footnote 6 for this case, although profiles will change with current flow the EMF (diffusion potential) remains constant, namely zero. But from the mixed equivalent circuit we should predict a value of:

$$\Psi = \frac{0.1E_K - 0.01E_K}{0.1 + 0.01} = \frac{0.09}{0.11} \frac{RT}{F} \ln \frac{0.1}{0.01} \approx 50 \text{ mV (room temperature)}$$

This is a somewhat extreme example, but it illustrates the point, which is the following: if the g 's are known at a steady state value of I , and the circuit is now opened, the "instantaneous" value of the membrane potential predicted by the mixed equivalent circuit will not, in general, be that seen across the membrane if this is homogeneous. It will, of course, predict the correct value for the mosaic-type membrane. A corollary is that the mixed equivalent circuit cannot be used to predict correctly non-steady state electrical properties of a homogeneous regime.

We can summarize our remarks in the previous pages with the following obser-

vation. Summing (3) over all species, we have:

$$\Psi = I \frac{1}{\sum_i g_i} + \frac{\sum_i g_i E_i}{\sum_i g_i} \quad (\text{Mixed equivalent circuit}) \quad (17)$$

On the other hand:

$$\Psi = IR_{\text{total}} + \Psi_D \quad (\text{Pure electrical equivalent circuit}) \quad (4a)$$

Now while both (17) and (4a) give the same steady state Ψ , I characteristic for the homogeneous membrane they are representing, there is *not* (with the exception of the single salt case) a term for term correspondence between these two equations. That is, the resistance of the mixed equivalent circuit is not the integral resistance (R_{total}) of the homogeneous membrane it is representing, nor is the second term in (17) the diffusion EMF (Ψ_D) of the membrane. As a matter of fact, the two terms in (17) have no relevance to any directly measurable electrical property of the homogeneous membrane; they are two *formal* quantities that add together to give for any value of current, I , the correct *steady state* membrane potential, Ψ .

The Plasma Membrane. We shall conclude this paper with a few remarks concerning the "equivalent circuit" of the plasma membrane. As has been alluded to previously, the circuit shown in Fig. 2 is of the type generally used to represent the cell membrane, in particular the excitable cell membrane of nerve and muscle. (Actually, this circuit is not quite complete, for in order to apply to the plasma membrane, Fig. 2 should include a capacitance in parallel with the other branches (1).) Since, as we have shown, this circuit is applicable in some respects both to a homogeneous and mosaic membrane, we should like to know if the measurements in the Discussion section can be used to decide in which category the cell membrane belongs. The answer is that in principle they can, but that there are several technical problems which make these measurements quite difficult.

Assuming that g_{Na} , g_K , etc. have been accurately determined (which in itself poses theoretical problems because of the indirect means by which these must be obtained in the biological system (6)) there is the difficulty of obtaining G_{integral} . (If we could determine this last quantity, then we could decide between the homogeneous and mosaic membrane depending on whether $G_{\text{integral}} \neq \sum_i g_i$ or $G_{\text{integral}} = \sum_i g_i$ (see page 229).) We recall that G_{integral} is given by the "instantaneous" value of $\Delta I / \Delta \Psi$. But, because of the thinness of the plasma membrane, the relaxation of the ionic profiles is so rapid that in practice this quantity is difficult to obtain. Thus, for example, the "instantaneous" measurement of conductance performed by Hodgkin and Huxley (7) is, in reality, a steady state measurement as far as ionic profiles are concerned. We think it worthwhile, however, to alert investigators to the fact that the determination of G_{integral} could prove to be a significant datum. Finally, we may note that, because of the capacitance associated with the plasma membrane, the potential measurement discussed on page 230 will not be useful, since the potential

appearing "instantaneously" across the membrane when the current is abruptly brought to zero will always be the same value as just prior to the removal of the current.

APPENDIX I

We shall prove that for a homogeneous fixed-charge membrane separating two solutions of equal total concentration of univalent electrolytes, the potential within the membrane in the *steady state* will be a linear function of x ("constant field").

Since the concentrations on the two sides are equal, the Donnan potentials cancel each other, and we are only concerned with the concentrations and potential following the Donnan "jumps." Our notation will be essentially that used by Teorell (4). (The same notation is followed as in the text.) Writing the flux equations (1a) and (1b) in slightly different form, we have:

$$\phi_i^+ = -u_i \left(RT \frac{dc_i^+}{dx} + Fc_i^+ \frac{d\psi}{dx} \right) = -u_i A_i$$

$$\phi_k^- = -v_k \left(RT \frac{dc_k^-}{dx} - Fc_k^- \frac{d\psi}{dx} \right) = -v_k B_k$$

and letting $A = \sum_i A_i$ and $B = \sum_k B_k$ we obtain:

$$A = RT \frac{dc^+}{dx} + Fc^+ \frac{d\psi}{dx} \quad (1a)$$

$$B = RT \frac{dc^-}{dx} - Fc^- \frac{d\psi}{dx} \quad (1b)$$

where $c^+ = \sum_i c_i^+$ and $c^- = \sum_k c_k^-$ at any point x .

Introducing the condition of electric neutrality:

$$c^+ + \omega \bar{X} = c^-$$

where $\omega \bar{X}$ is the concentration of fixed-charge, and adding (1a) and (1b), we obtain:

$$(A + B) = RT \frac{d}{dx} (2c^+ + \omega \bar{X}) - F\omega \bar{X} \frac{d\psi}{dx} \quad (2)$$

Integrating from $x = 0$ ($\psi = 0$) to $x = \delta$ ($\psi = \Psi$) and remembering that $c_o^+ = c_s^+$, we get:

$$(A + B)\delta = -F\omega \bar{X} \Psi \quad (3)$$

Integrating (2) from $x = 0$ ($\psi = 0$) to $x = x$ ($\psi = \psi$), we find:

$$c^+ = \frac{F\omega \bar{X}}{2RT} \left(\psi - \frac{x}{\delta} \Psi \right) + c_o^+ \quad (4)$$

Subtracting (1b) from (1a) we have:

$$(A - B) = RT \frac{d(c^+ - c^-)}{dx} + F(c^+ + c^-) \frac{d\psi}{dx} = F(2c^+ + \omega \bar{X}) \frac{d\psi}{dx} \quad (5)$$

and substituting (4) into (5) and rearranging we have:

$$(A - B) \frac{dx}{d\psi} = \frac{F^2 \omega \bar{X}}{RT} \psi - \frac{F^2 \omega \bar{X} \Psi}{RT \delta} x + F(2c_o^+ + \omega \bar{X}) \quad (6)$$

We wish to solve (6) for $(A - B)$. For notational convenience let:

$$\begin{aligned}\alpha &= \frac{F^2 \omega \bar{X}}{RT} \\ \beta &= -\frac{F^2 \omega \bar{X} \Psi}{RT \delta} \\ \gamma &= F(2c_o^+ + \omega \bar{X})\end{aligned}$$

Changing variables by writing:

$$v = \alpha \psi + \beta x + \gamma \quad (7)$$

differentiation leads to:

$$\frac{dv}{d\psi} = \alpha + \beta \frac{dx}{d\psi} \quad (8)$$

and comparing (7) and (8) with (6) we can write:

$$\frac{dx}{d\psi} = \frac{v}{A - B} = \frac{1}{\beta} \left(\frac{dv}{d\psi} - \alpha \right)$$

and rearranging we have finally:

$$\frac{dv}{\alpha + \beta v / (A - B)} = d\psi \quad (9)$$

The integration of (9) will be between $v = \gamma$ and $v = \alpha \Psi + \beta \delta + \gamma$. In order to perform this integration, we must exclude for the time being the particular value:

$$(A - B) = -\frac{\beta \gamma}{\alpha} \quad (10)$$

since for this value of $(A - B)$, $\alpha + \beta v / (A - B)$ becomes infinite at $v = \gamma$. Remembering this restriction, integration of (9) gives:

$$\ln \frac{\alpha(A - B) + \alpha \beta \Psi + \beta^2 \delta + \beta \gamma}{\alpha(A - B) + \beta \gamma} = \frac{\beta}{A - B} \Psi$$

and since $\alpha \beta \Psi + \beta^2 \delta = 0$, we obtain:

$$\beta \Psi = 0 \quad (11)$$

Since, however, β and Ψ can assume any finite value we choose, relation (11) is absurd. But equation (11) results from any value of $(A - B)$, except that which is given in (10). This must mean that the value of $(A - B)$ which we excluded, (10), was the correct value; *i.e.*:

$$(A - B) = -\frac{\beta \gamma}{\alpha} = \frac{F \Psi}{\delta} (2c_o^+ + \omega \bar{X})$$

Introducing this into (6) and rearranging we get:

$$\left[\frac{F \omega \bar{X}}{RT} \left(\psi - \frac{x \Psi}{\delta} \right) + 2c_o^+ + \omega \bar{X} \right] \frac{d\psi}{dx} = \frac{\Psi}{\delta} (2c_o^+ + \omega \bar{X}) \quad (12)$$

By inspection, the solution of (12) is:

$$\psi = \frac{x}{\delta} \Psi \quad (13)$$

i.e., the potential is a linear function of x . We may note that the only restriction in our derivation was that a *steady state* exists. Thus, the result is valid with finite current flowing across the membrane.

APPENDIX II

We wish to determine the *steady state* values of g_i , R_{total} , and Ψ_D for the case of a homogeneous uncharged membrane separating two solutions of equal total concentration of univalent electrolytes. In order to do this, we must calculate the ionic profiles within the membrane; *i.e.*, we must obtain an expression for the concentration of each ion as a function of x . Once this is accomplished, the evaluation of the desired quantities is merely a matter of integration.

We start with the flux equation for an arbitrary cation:

$$\phi_i^+ = -u_i \left(RT \frac{dc_i^+}{dx} + Fc_i^+ \frac{d\psi}{dx} \right) \quad (1)$$

Since the concentrations on the two sides of the membrane are equal, $d\psi/dx$ is a constant (Appendix I). If we take the membrane thickness as δ and let $\psi = 0$ at $x = 0$ and $\psi = -\Psi$ at $x = \delta$, then $d\psi/dx = -\Psi/\delta$ and (1) becomes:

$$\phi_i^+ = -RTu_i \frac{dc_i^+}{dx} + Fu_i c_i^+ \frac{\Psi}{\delta} \quad (2)$$

Integrating (2) from $x = 0$ [$c_i^+ = (c_i^+)_o$] to $x = \delta$ [$c_i^+ = (c_i^+)_i$] we get:¹¹

$$\phi_i^+ = \frac{F\Psi}{\delta} u_i \frac{(c_i^+)_o - (c_i^+)_i e^{-F\Psi/RT}}{1 - e^{-F\Psi/RT}} \quad (3)$$

Integrating (2) from $x = 0$ to $x = x$ we obtain:

$$c_i^+ = \frac{F\Psi u_i (c_i^+)_o - \delta \phi_i^+ (1 - e^{-(F\Psi/RT)(x/\delta)})}{F\Psi u_i e^{-(F\Psi/RT)(x/\delta)}} \quad (4)$$

Substituting (3) into (4) gives:

$$c_i^+ = \frac{(c_i^+)_o - (c_i^+)_i e^{-F\Psi/RT}}{1 - e^{-(F\Psi/RT)}} (1 - e^{-(F\Psi/RT)(x/\delta)}) \quad (5)$$

Letting,

$$\xi_x \equiv e^{F\psi/RT} \equiv e^{-(F\Psi/RT)(x/\delta)}$$

$$\xi \equiv e^{-F\Psi/RT}$$

¹¹ The approach we have taken to solve the flux equations is essentially the same as that followed by Hodgkin and Katz (8). We wish to emphasize, however, that this method is valid *only* for the case when the total concentration on both sides of the membrane is the same. It is only then that a "constant field" exists within the membrane. In the Hodgkin and Katz paper, the electric field was *assumed* constant; this will in general *not* be correct. For the general (and always correct) method of solving the flux equations, see Planck (3) and Teorell (9).

equation (5) can be written in a more condensed form:

$$c_i^+ = \frac{[(c_i^+)_i \xi - (c_i^+)_o](\xi_x - 1)}{\xi_x(\xi - 1)} + \frac{(c_i^+)_o}{\xi_x} \quad (6a)$$

An analogous treatment starting with the flux equation for an anion gives:

$$c_k^- = \frac{[(c_k^-)_i - \xi(c_k^-)_o](1 - \xi_x)}{(1 - \xi)} + \xi_x(c_k^-)_o \quad (6b)$$

With (6a) and (6b) we can now directly calculate all of the relevant quantities of the two types of equivalent circuits:

$$g_i^+ \equiv \frac{1}{\int_0^{\delta} dx / F^2 u_i c_i^+} = \frac{u_i F^3 \Psi}{RT \delta} \frac{(c_i^+)_i \xi - (c_i^+)_o}{(1 - \xi) \ln [(c_i^+)_i \xi / (c_i^+)_o]} \quad (7a)$$

$$g_k^- \equiv \frac{1}{\int_0^{\delta} dx / F^2 v_k c_k^-} = \frac{v_k F^3 \Psi}{RT \delta} \frac{(c_k^-)_o \xi - (c_k^-)_i}{(1 - \xi) \ln [(c_k^-)_o \xi / (c_k^-)_i]} \quad (7b)$$

$$R_{total} \equiv \int_0^{\delta} \frac{dx}{F^2(U + V)} = \frac{RT \delta}{F^3 \Psi} \frac{(1 - \xi)}{\sqrt{b^2 - 4ac}} \cdot \ln \frac{\xi(U_i + V_o) + (U_o + V_i) - \sqrt{b^2 - 4ac}}{\xi(U_i + V_o) + (U_o + V_i) + \sqrt{b^2 - 4ac}} \quad (8)$$

$$\Psi_D \equiv \frac{RT}{F} \int_0^{\delta} \frac{d(U - V)}{(U + V)} = \Psi + \frac{RT}{F} \frac{b}{\sqrt{b^2 - 4ac}} \cdot \ln \frac{\xi(U_i + V_o) + (U_o + V_i) - \sqrt{b^2 - 4ac}}{\xi(U_i + V_o) + (U_o + V_i) + \sqrt{b^2 - 4ac}} \quad (9)$$

where,

$$U_o = \sum_i u_i (c_i^+)_o; \quad U_i = \sum_i u_i (c_i^+)_i; \quad V_o = \sum_k v_k (c_k^-)_o; \quad V_i = \sum_k v_k (c_k^-)_i$$

$$a = (V_o - V_i); \quad b = (U_o + V_i) - \xi(U_i + V_o); \quad c = \xi(U_i - U_o)$$

We note from these expressions that, in general, g_i , R_{total} , and Ψ_D are voltage dependent. It is interesting, however, that for the special case where there is only one anion (or cation) in the system, then, since $V_i = V_o = V$, equation (9) becomes:

$$\Psi_D = \frac{RT}{F} \ln \frac{U_i + V}{U_o + V}$$

for all Ψ . That is, Ψ_D is independent of voltage, which we asserted in footnote 6.

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