STEADY-STATE ELECTRODIFFUSION

SCALING, EXACT SOLUTION FOR IONS OF ONE CHARGE, AND THE PHASE PLANE

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ABSTRACT This is the first of two papers dealing with electrodiffusion theory (the Nernst-Planck equation coupled with Gauss's law) and its application to the current-voltage behavior of squid axon. New developments in the exact analysis of the steady-state electrodiffusion problem presented here include (*a*) a scale transformation that connects a given solution to an infinity of other solutions, suggesting the possibility of direct comparison of electrical data for membranes with different thicknesses and other properties; (*b*) a first-integral relation between the electric field and ion densities more general than analogous relations previously reported, and (*c*) an exact solution for the homovalent system, i.e., a membrane system permeated by various ion species of the same charge. The latter is a generalization of the known one-ion solution. The properties of the homovalent solution are investigated analytically and graphically. In particular we study the phase-plane curves, which reduce to the parabolas discussed by K. S. Cole in the special case in which the current-density parameter (a linear combination of the ionic current densities) is zero.

INTRODUCTION

Electrodiffusion, the oldest and simplest model of the electrical behavior of the unmyelinated nerve membrane, was adapted by Bernstein (1) from the work of Nernst (2) and Planck (3) on electrolytes. The analysis of this model has been approached by several methods, including the simplifying assumptions of electrical neutrality (4–6) and constant (uniform) electric field (7, 8), and direct numerical integration (9, 10). Difficulties such as the apparent inability of the theory to account for the measured rectification ratios and negative-resistance regions led K. S. Cole to conclude in a 1965 review (11) that "... such simple models and such elementary analyses are not adequate." We hope here to shed some light on whether these difficulties arise because the model is too simple, the analyses too elementary, or both. Because the validity of the approximations used often depends on the smallness of parameters that can only be estimated, we drop these a priori approximations and study certain problems in exact electrodiffusion theory.

In this paper, the first of two, we formulate the general steady-state electrodiffusion

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equations and derive their scaling properties and their first integral. We derive the exact solution for what we call the homovalent case, in which all the ions permeating the membrane are of one charge. We then discuss and illustrate graphically the properties of the various forms of this solution and analyze the relations in the field-concentration phase plane. In the second of this pair of papers, we will apply the membrane (two-point) boundary-value conditions to these solutions, restricted to the one-ion case. We will also report on the comparison of digital computations based on these results with published voltage-clamp data from two squid-axon experiments. While our emphasis is on biological, and in particular squid-axon, membranes, the present analysis is sufficiently general to be applicable to artificial membranes (10, 12–14) and, to an extent, semiconductor and insulator diodes (15–18).

The exact steady-state electrodiffusion problem for a single species of charged particles was solved for the zero-current case by von Laue (19) in 1918 and for the general case by Borgnis (20) in 1936. The latter, as well as Skinner (15) and Adirovich (16), expressed this solution in terms of Bessel functions. The simpler Airy function form we use below was applied by Fan (18) and Sinharay and Meltzer (17); the latter work (as well as Skinner's) was cited in Cole's *Membranes, Ions and Impulses* (21), p. 199. Further studies of the Bessel function solutions in a biomembrane context by de Levie et al. (12–14) included the computation of one-ion membrane profiles of potential, field, and concentration. Some results have also been reported on the electrodiffusion problem in membranes with two ion species of different charges (22, 23). The present work is based on the Ph.D. thesis (24) of one of us (H.R.L.); some of the results given here and in the other paper have been presented in preliminary reports (25, 26).

RELATION TO CHANNEL THEORIES

The channel theories, recently reviewed by Ehrenstein and Lecar (27), define and locate macromolecular structures within the membrane (known as "gates") that embody the mathematical statements of the Hodgkin-Huxley description of the axon membrane current. How does the macroscopic, continuum approach of electrodiffusion theory relate to this microscopic channel approach?

After Hodgkin and Katz (28), anticipated in 1902 by Overton (27, pp. 3, 268), removed a serious shortcoming of Bernstein's membrane hypothesis by pointing out the key role of the sodium ion, Hodgkin and Huxley (29) developed a set of equations that, when solved numerically, accurately (but not perfectly) duplicated the action potential. The major components of this theory are the cable theory, the independence principle (that the flow of ions of one type is unaffected by the presence of ions of other types and hence can be thought of as traversing separate noninteracting channels), and the formally linear relations between the membrane potential V_m, and the individual ion current densities, $J_{\text{channel}} = g_{\text{channel}}(V_m - \mathcal{E}_{\text{channel}})$, channel = Na, K, l, where l refers to a leakage channel, the g's are conductances, and the $\mathcal{E}$'s, the Nernst emf's for the given ions. The hypothesis of channel specificity is based on the results of substitution experiments, although a recent review of these indicates that this specificity is not absolute (30).

Because of these assumptions, the resulting mathematical system would be entirely linear (and its solution elementary) if the channel conductances were constants. Actually, because Hodgkin and Huxley (29) assumed these to be functions of membrane potential and time (as well as calcium-ion concentration), the above "linear" relations turn out to be highly nonlinear. The potassium conductance is the fourth power and the sodium conductance the product of first and third powers of first-order kinetic functions.

Both in their original papers and in subsequent work by many investigators, this description by Hodgkin and Huxley was used as a guide in searching for hypothetical structures in the membrane with properties consistent with these functions (27, 30). A number of these researchers have postulated the existence of charged or dipolar gates within the membrane, viewed as moving in response to the electric field to control the flow of ions through their respective channels.

This theory is widely accepted, and currents interpreted as being due to displacement currents caused by the opening and closing of sodium gates have been measured (31). It has, however, been pointed out that the forms for the conductances are not unique in their ability to describe the data accurately, and alternative forms have been proposed (32). In addition to the action potential, the formalism has also been shown to predict subthreshold propagated waves (33), in a search for which only strongly attenuated waves were found (34).

When the mathematical expressions developed by Hodgkin and Huxley for the conductances are considered in the steady state (consistent with the scope of this paper), g_K and g_{Na} are functions of the membrane potential V_m and g_l is a constant. These equations are not entirely unrelated to electrodiffusion: The α's and β's that entered into them were of empirical form chosen to be as close as possible to the J-V_m relation derived by Goldman from the electrodiffusion equations under the constant-field approximation (29). The forms have been applied to recent experiments, but with the empirical constants changed (35). The Hodgkin-Huxley relation between net current density and membrane voltage results when these conductances are substituted into the above relations for the ionic current densities and summed.

Here our goal also is to develop a J-V_m relation, but on the basis of electrodiffusion theory, which treats the membrane as a continuum. As in other macroscopic theories, e.g. Jackson (36), p. 109 ff, the constants and variables in electrodiffusion are averages smoothing out molecular details. In the approach of the element of transverse distance, dX, to zero, it is implicitly assumed to remain large compared to interatomic distances. Averaging is also implicit over area—and in a typical experiment the membrane area between electrodes is of the order of tens of square millimeters. This averaging process can be assumed to yield the ion concentrations, electric field, and potential as continuous functions of the coordinate X normal to the membrane and independent of position in the plane of the membrane.

In relating this continuum approach to the microscopic membrane structure, the constants of the membrane, dielectric constant and ion mobilities, can be considered as representing a distribution of rigid channels of various kinds, including those with properties that depend on ionic species.

THE GENERAL STEADY-STATE PROBLEM

We begin by considering a membrane with no limitations on the number and charge (or valence) of the ion species permeating it. The membrane is considered to be planar, of fixed thickness L, isothermal, and subject to no pressure differences, convective flows, magnetic forces, or quantum effects. (As Agin [37] has pointed out, the membrane is several orders of magnitude too thick for ion tunneling.) Ions are also assumed not to bind chemically to one another or the membrane. We assume that the entire potential difference is across the membrane.

The ion density of the jth ion species of charge q_i is designated N_{ij} with a corresponding mechanical mobility (velocity per unit force) u_{ij} and a diffusion coefficient D_{ij}. The latter two parameters are connected by Einstein's relation, $D_{ij} = u_{ij}\theta$, where θ is the product of Boltzmann's constant k_B and the Kelvin temperature T. The electric field is E. We use electrostatic cgs units.

The Nernst-Planck equation (3, 21, 38) states that the flux of ions is composed of a contribution due to diffusion and one due to migration. In terms of the ionic current density (flux times charge),

$$J_{ij} = -q_i D_{ij}\left(\frac{dN_{ij}}{dX} - \frac{q_i}{\theta} E N_{ij}\right). \tag{1}$$

In the steady state with no ion sources or sinks, continuity implies that J_{ij} is constant with respect to X. If there are k_i species of ions of charge q_i and m different charges present, the total number of species is $k = \sum_{i=1}^{m} k_i$; thus there are k equations of type 1.

The system of equations is completed by Gauss's law (36):

$$\frac{dE}{dX} = \frac{4\pi}{\epsilon}\sum_{i=1}^{m} q_i \sum_{j=1}^{k_i} N_{ij}, \tag{2}$$

where ϵ is the dielectric constant of the membrane considered, like the mobilities, to be uniform across its thickness. As always, the field is derivable from the potential V,

$$E = -\frac{dV}{dX}. \tag{3}$$

Since E and the N_{ij} represent $k + 1$ dependent variables, 1 and 2 constitute the required number of equations for a well-posed problem. E, V, and N_{ij} will be assumed to be finite and continuous, and N_{ij} nonnegative, over the membrane.

Only the boundary conditions remain to be specified. These will be given in terms of the boundary ion concentrations $N_{ij}(0)$ and $N_{ij}(L)$, designated N_{I}^{ij} and N_{II}^{ij}, respectively. Since the membrane constitutes an entirely different environment for ions from the aqueous phases it separates, it would not be correct to equate these to the measured intra- and extraaxonal concentrations. Instead, we follow Hodgkin and Katz (28) in assuming that the effect of the transition from water to membrane is describable in terms of a constant partition coefficient β_{ij}. In terms of the corresponding inner and outer solution concentrations,

$$N_{\text{I}}^{ij} = \beta_{ij} N_{\text{in}}^{ij} \quad \text{and} \quad N_{\text{II}}^{ij} = \beta_{ij} N_{\text{out}}^{ij}. \tag{4}$$

Fig. 1 illustrates the geometry of the model and the boundary conditions in the general

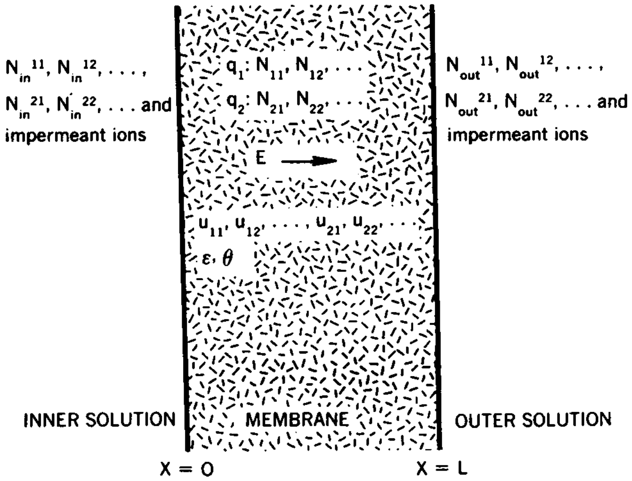

FIGURE 1 Cross-section of membrane, indicating boundary conditions and symbols used for the general case with ions of arbitrary charges.

case. While the electric field is essentially zero in the body of an electrolyte, we cannot assume that $E = 0$ at the membrane boundaries, because of the existence of charged boundary layers.

The Scaling Property

The second, migration, term on the right-hand side of Eq. 1 is, together with Eq. 2, responsible for the nonlinearity of the system. (Replacing the right-hand side of Eq. 2 by zero—the constant-field approximation—linearizes Eq. 1 and decouples the N_{ij}'s.) Because of this nonlinearity, the principle of superposition, so useful for linear systems, will not be obeyed by solutions of the electrodiffusion equations. The coupling of all the equations shows that solutions of these equations will not obey the independence principle mentioned above. Despite these complications, the electrodiffusion equations have the simplifying property that, if one solution of them is known, an infinity of other solutions may be derived from it, as follows:

Given any nonzero real constant α, if a solution to the system of Eqs. 1 and 2 is characterized by variables E, X, N_{ij}, J_{ij}, and V, the equations are also satisfied by the corresponding set of variables E', X', N'_{ij}, J'_{ij}, and V' given by the scale transformation

$$E' = \alpha E, \quad X' = X/\alpha, \quad N'_{ij} = \alpha^2 N_{ij}, \quad J'_{ij} = \alpha^3 J_{ij}, \quad \text{and} \quad V' = V. \qquad (5)$$

This statement can be derived directly; its validity can also be easily verified by substituting the relations 5 into Eqs. 1, 2, and 3. As relation 5 shows, the potential V is an invariant under the transformation. Invariant combinations, such as JX^3 and J^2/N^3, can also be formed. These invariants of exact electrodiffusion theory may well find a role analogous to those played, for example, by the Reynolds number in hydrodynamics and the Fourier number in heat conduction theory (39).

The scaling relations should be helpful in resolving the differences observed from one membrane experiment to another. For example, since L transforms like X, it should be possible to use the scaling property to compare the electrical behavior of membranes of the same composition but different thicknesses. In that case, a plot of $J'L'^3$ versus V' should be identical to one of JL^3 versus V, if the solutions have been adjusted so that, at the boundaries, $N_{ij}'L'^2 = N_{ij}L^2$. A possible way to test this prediction might be to use artificial bimolecular phospholipid membranes that have molecules of different chain lengths but are similar in their dielectric constants and mobilities. An extension to membranes of unlike composition is given below, in the paragraph under Eq. 19.

The usefulness of scaling property 5 in the search for parameters to match known experimental data will be indicated in the second of these two papers. The scaling property has also been generalized to the time-dependent case (24).

The First Integral

The Nernst-Planck and Gauss equations may be manipulated to yield an exactly integrable expression. Dividing both sides of Eq. 1 by $-q_i u_{ij}$, summing over i and j, substituting Eq. 2, and integrating from 0 to X results in a first-integral relationship between E, N, and X,

$$\theta N - \frac{\epsilon}{8\pi} E^2 + \theta \Gamma X = \theta N_{\mathrm{I}} - \frac{\epsilon}{8\pi} E_{\mathrm{I}}^2, \qquad (6)$$

where $N = \sum_{i,j} N_{ij}$, $N_{\mathrm{I}} = N(0)$, $E_{\mathrm{I}} = E(0)$, and $\Gamma = \sum_{i,j} J_{ij}/q_i D_{ij}$. The first term is, by van't Hoff's law, the osmotic pressure of a dilute solution (38) and the second is the electrical energy density (36). One-ion (13, 16, 18, 20) and two-ion (22) versions of this relation have been reported earlier.

For fixed values of X such as at the boundaries, or for the case $\Gamma = 0$, Eq. 6 expresses a relationship between the phase-plane variables E and N alone (see "The Phase Plane," below). This relation, as Cole (21), p. 197f has pointed out in the one-ion zero-current case, is parabolic: When $\Gamma = 0$, the point (E, N) describes a segment of a parabola as X goes from 0 to L. This is one of a family of parabolas determined by the constant on the right-hand side of Eq. 6. We will refer to the case in which this constant is positive as the *osmodominant* case, that in which it is negative as the *electrodominant* case, and that in which it is zero as the *balanced* case.[1] We note for $\Gamma = 0$ that, in the osmodominant case, the vertex of the parabola, located at $N = N_{\mathrm{I}} - E_{\mathrm{I}}^2/8\pi\theta$, is in the upper half of the phase plane, while in the electrodominant case it is in the lower, forbidden, half-plane $N < 0$. Since E rises with increasing X, this

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[1] The electrodominant (osmodominant) case was referred to as that of a thin (thick) membrane by Cole (11) and the less (more) symmetrical case by de Levie and Moreira (12). As the sign of this integration constant does not generally bear such a simple relation to the membrane thickness and as the concentration, field, and potential profiles are generally unsymmetrical, we propose the present terminology, which we believe to be more descriptive.

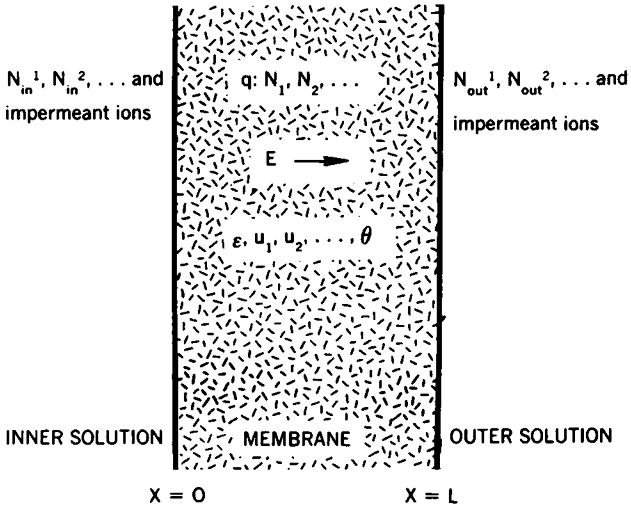

FIGURE 2 Cross-section of membrane as in Fig. 1, but for the homovalent case; all ions permeating the membrane have charge q.

implies that for $\Gamma = 0$ an osmodominant ion profile may have a minimum but an electrodominant one may not. We shall see this borne out by the exact solutions below.

The Homovalent Equations

At this point we restrict the discussion to the homovalent case: that of a membrane permeated by an arbitrary number of ion species, all, however, of the same valence (in magnitude and sign). We shall show that the well-known solution for the one-ion case applies with some modification to this case.

The homovalent case is an important one for squid axon membrane, because experimental evidence indicates that the primary current carriers are Na^+ and K^+ (29), while anions are virtually excluded from the membrane (40,41), and divalent cations do not carry appreciable current (42) although they significantly affect the properties of the membrane. In perfusion experiments, the monovalent cations Li^+, NH_3^+, Cs^+, and Rb^+ act as satisfactory substitutes for K^+ and Na^+ (21, pp. 452f, 470).

In the homovalent case, that is, when $m = 1$, $N_{ij} = N_j$, $J_{ij} = J_i$, $D_{ij} = D_j$, and $q_i = q$ (see Fig. 2), Eqs. 1 and 2 become

$$\frac{dN_j}{dX} - \frac{q}{\theta} E N_j = -\Gamma_j, \tag{8}$$

where $\Gamma_j = J_j/q\,D_j$, and

$$\frac{dE}{dX} = \left(\frac{4\pi q}{\epsilon}\right)\sum_{j=1}^{k} N_j. \tag{9}$$

Boundary conditions 4 become

$$N_j(0) = N^j{}_{\mathrm{I}} = \beta_j N^j_{\mathrm{in}} \quad \text{and} \quad N_j(L) = N^j{}_{\mathrm{II}} = \beta_j N^j_{\mathrm{out}}. \tag{10}$$

This second-order nonlinear system of $k + 1$ differential equations in $k + 1$ dependent variables may be reduced to a similar system in two variables by summing Eq. 8 over j:

$$\frac{dN}{dX} - \frac{q}{\theta} E N = -\Gamma, \tag{11}$$

$$\frac{dE}{dX} = \left(\frac{4\pi q}{\epsilon}\right) N. \tag{12}$$

In these equations, the ion densities N_j and reduced current densities Γ_j no longer appear individually but are replaced by their sums, $N = \Sigma N_j$ and $\Gamma = \Sigma \Gamma_j$. Thus, after Eqs. 11 and 12 have been solved for E and N, and V obtained by integrating E, there would still remain the problem of recovering the individual ion concentrations N_j. However, this problem was solved (in the context of, but not requiring, the electroneutrality assumption) in 1954 by Schlögl (5). We will rederive this expression, in our notation and with minor changes, for $\Gamma \neq 0$.

Using Eqs. 8 and 3, with differentiation by X denoted by a prime, we may write

$$[N_j \exp(qV/\theta)]' = (qV' N_j/\theta + N_j') \exp(qV/\theta) = -\Gamma_j \exp(qV/\theta);$$

and, from Eq. 11, a similar equation without the subscripts.

Thus, for $\Gamma \neq 0$,

$$[N_j \exp(qV/\theta)]' = (\Gamma_j/\Gamma)[N \exp(qV/\theta)]';$$

integration from 0 to X and rearrangement yield the result.

Schlögl's formula is

$$N_j = \Gamma_j N/\Gamma + (N^j_{\mathrm{I}} - \Gamma_j N_{\mathrm{I}}/\Gamma) \exp[-q(V - V_{\mathrm{I}})/\theta]. \tag{13}$$

This relation gives, for known N and V, the desired function N_j in terms of the boundary conditions and the ratio of the current-density parameters Γ_j/Γ.

It is convenient to simplify the notation by transforming to dimensionless variables. Let N_0 be an arbitrary unit of ion density (16), and λ the corresponding membrane Debye length $\lambda = (\epsilon \theta / 4\pi q^2 N_0)^{1/2}$. We define the new variables as follows:

$$\begin{aligned} s &= X/2^{1/2}\lambda & l &= L/2^{1/2}\lambda \\ v &= qV/2\theta & e &= \lambda q E/2^{1/2}\theta \\ n_j &= N_j/N_0 & \gamma_j &= 2^{1/2}\lambda \Gamma_j/N_0 \end{aligned} \tag{14}$$

Note that v has the same sign as V (and e as E) only for cations.

In these variables, Eqs. 9 (and 12), 11, and 3 read, respectively,

$$\frac{de}{ds} = \Sigma n_j = n \tag{15}$$

$$\frac{dn}{ds} = 2en - \gamma \tag{16}$$

$$\frac{dv}{ds} = -e. \tag{17}$$

The boundary conditions 10 become

$$\begin{aligned} n(0) &= n_{\mathrm{I}} \\ n(l) &= n_{\mathrm{II}} \end{aligned} \tag{18}$$

and the first integral 6 becomes

$$e^2 - n - \gamma s = e_{\mathrm{I}}^2 - n_{\mathrm{I}}, \tag{19}$$

where e_{I} is the value of e at $s = 0$.

Eqs. 15, 16, and 17 clearly satisfy the scaling relations 5 with e, s, n_j, γ_j, and v playing the roles of E, X, N_{ij}, J_{ij}, and V. Expressing the scaling property in these dimensionless quantities broadens their applicability, as this form permits comparison of membranes not only of different thicknesses but of different dielectric constants and mobilities as well.

The Quasiequilibrium Solutions

The case in which the current-density parameter γ is zero is a relatively simple one, which, however, must be treated separately from the finite-γ case. After substituting Eq. 17 into Eq. 16 (without the second term on the right), we may integrate immediately to obtain the Nernst-Boltzmann equation

$$n = n_{\mathrm{I}} \exp[-2(v - v_{\mathrm{I}})]. \tag{20}$$

This equation characterizes the one-ion equilibrium case. The relation between net ion density and potential distribution thus corresponds to electrical equilibrium, but the individual ion densities are not necessarily in equilibrium. We will therefore refer to the $\gamma = 0$ case as that of quasiequilibrium.

From Eq. 19 with $\gamma = 0$ and Eq. 15 we obtain the differential equation

$$\frac{de}{ds} = e^2 - g, \tag{21}$$

where $g = e_{\mathrm{I}}^2 - n_{\mathrm{I}}$.

Only the results are stated in the text; the derivations are given in the Appendix. Since the quantity on the right-hand side of Eq. 6 is equal to $-\theta N_0 g$, the terms (osmodominant, etc.) defined in the paragraph below it may be applied, with the sign change, to g.

The form of the solution depends on the sign of g. In the osmodominant case,

$g < 0$, in which the vertex of the Cole parabola is above the origin, the solution is:

$$e = a \tan [a(s - s_0)] \tag{22a}$$

$$n = a^2 \sec^2 [a(s - s_0)] \tag{22b}$$

$$v - v_{\mathrm{I}} = \ln | [(e_{\mathrm{I}}/a)^2 + 1]^{1/2} \cos [a(s - s_0)] | , \tag{22c}$$

where $a = (-g)^{1/2}$ and $s_0 = -(1/a) \tan^{-1} (e_{\mathrm{I}}/a)$.

In the balanced case, $g = 0$, the vertex of the Cole parabola is at the origin of the (e, n) plane, and the solution is:

$$e = e_{\mathrm{I}}/(1 - e_{\mathrm{I}}s) \tag{23a}$$

$$n = e_{\mathrm{I}}^2/(1 - e_{\mathrm{I}}s)^2 \tag{23b}$$

$$v - v_{\mathrm{I}} = \ln | 1 - e_{\mathrm{I}}s | \tag{23c}$$

In the electrodominant case, $g > 0$, the solution to the system of differential equations, when $n \neq 0$, is

$$e = -b \coth [b(s - s_0')] \tag{24a}$$

$$n = b^2 \operatorname{csch}^2 [b(s - s_0')] \tag{24b}$$

$$v - v_{\mathrm{I}} = \ln | [(e_{\mathrm{I}}/b)^2 - 1]^{1/2} \sinh [b(s - s_0')] | , \tag{24c}$$

where $b = (g)^{1/2}$ and $s_0' = (1/b) \coth^{-1}(e_{\mathrm{I}}/b) = (1/2b) \ln | (e_{\mathrm{I}} + b)/(e_l - b) |$. In the zero-$n$ case, however, we have simply

$$e = e_{\mathrm{I}}, \quad n = 0, \quad v - v_{\mathrm{I}} = -e_{\mathrm{I}}s. \tag{25abc}$$

With no ions, the field becomes uniform and the potential distribution, linear; the constant-field approximation is, in this extreme case, exact.

Equations equivalent to 22–24 (but not 25) were given for the one-ion case by von Laue (19) and more recently by Skinner (15), Cole (11), and de Levie and Moreira (12). To convert our results to the forms given by de Levie and Moreira, the addition formulas for trigonometric and hyperbolic functions may be used, although the differences in notation should be observed.

THE GENERAL SOLUTION

As derived in the Appendix, the general solution to Eqs. 15 and 16, valid for all values of γ except zero, is

$$e = -\gamma^{1/3} \frac{\mathrm{Ai}'(x) + R\,\mathrm{Bi}'(x)}{\mathrm{Ai}(x) + R\,\mathrm{Bi}(x)} \tag{26a}$$

$$n = \gamma^{2/3} \left\{ \left[\frac{\mathrm{Ai}'(x) + R\,\mathrm{Bi}'(x)}{\mathrm{Ai}(x) + R\,\mathrm{Bi}(x)}\right]^2 - x \right\} \tag{26b}$$

$$v = \ln | \mathrm{Ai}(x) + R\,\mathrm{Bi}(x) | + \text{const}, \tag{26c}$$

where $x_l = \gamma^{-2/3} g$, $x = \gamma^{1/3} s + x_l$, and R is an arbitrary constant; x_l (or e_l) and R must be evaluated from the boundary conditions. Ai, Bi, Ai′, and Bi′ are the two Airy functions and their first derivatives (43); we have made use of a Fortran subroutine developed by R. G. Gordon (44) for computing these. Eqs. 26*a*,*b*,*c* may be converted into corresponding Bessel-function forms by means of well-known identities (43).

The new independent variable x is an invariant to scale transformation 5. The additive quantity x_l is a scale-invariant constant closely related to the right-hand side of Eq. 19. The arguments of the exponential, logarithmic, trigonometric and hyperbolic functions in the quasiequilibrium solutions are likewise invariants.

A STUDY OF THE SOLUTIONS

We have seen that the homovalent electrodiffusion solutions assume five different forms, four for $\gamma = 0$ and one for $\gamma \neq 0$. To apply these to the experimental situation in the membrane requires the imposition of the two-point boundary conditions 10. However, as the properties of these functions and the relations between them are not well understood, we make here a brief computational study of them, leaving the application of the membrane boundary conditions to the other paper. This discussion is partly based on the work of Sinharay and Meltzer (17), who discussed these functions in the case $e_l = 0$. The study of v, e, and n as functions of s reveals their general behavior and interrelations, as well as yielding valuable information about the useful extent of these solutions, i.e., the extent over which n remains positive, finite, and continuous. After choosing parameters n_l and e_l, we can generate solutions for an arbitrary distance along s. Since the choice of reference potential is arbitrary, we choose for convenience to set $v = 0$ at $s = 0$ (we will, however, choose the outside of the membrane as our reference for the membrane calculations in our second paper). The constants are evaluated as follows:

With $v(x_l) = 0$, Eq. 26*c* becomes

$$v = \ln \left| \frac{\mathrm{Ai}(x) + R\,\mathrm{Bi}(x)}{\mathrm{Ai}(x_l) + R\,\mathrm{Bi}(x_l)} \right| .$$

To find R, it is sufficient to evaluate Eq. 26*a* at $s = 0$ $(x = x_l)$, and solve for R to obtain

$$R = -\frac{e_l\,\mathrm{Ai}(x_l) + \gamma^{1/3}\,\mathrm{Ai}'(x_l)}{e_l\,\mathrm{Bi}(x_l) + \gamma^{1/3}\,\mathrm{Bi}'(x_l)} .$$

The curves in Figs. 3–14 were generated and plotted with a CDC 6600 computer (Control Data Corp., Minneapolis, Minn.) and Calcomp plotter (California Computer Products, Anaheim, Calif.) by a Fortran program, LOLIGO, developed for this purpose.

A set of typical curves of v, e, and n versus s has been generated from the solutions 22–26 and plotted in Figs. 3–11. The values of the parameters used are γ: $-1, 0, 1$; g: $-2, 0, 2$; and e_1: $-2, 2$. The coordinate s ranges from 0 to 4. This set of graphs suffices to illustrate the major features of each case and the relations between them. In examining these curves it is helpful to keep in mind that: (*a*) e is the derivative of $-v$ and n is the derivative of e; (*b*) n may also be obtained from e and s algebraically, by the relation $n = e^2 - \gamma s - g$; and (*c*) when $\gamma = 0$, as in Figs. 6–8, n bears the simple exponential relationship 20 to v.

Positivity of n. In the biophysical problem under consideration, n must clearly be a positive number. Is this positivity automatically satisfied by the mathematical solutions or must it be specified as an additional constraint? In the quasi-equilibrium solutions with $g \leq 0$, the positivity of n already follows from the first-integral relation, $n = e^2 - g$, and the forms of Eqs. 22*b* and 23*b* reflect this. However, in the electrodominant case, $g > 0$, it was necessary to *assume* that $n > 0$ in deriving Eqs. 24. Thus the positive definite form 24*b* is not the only possible mathematical form for n; an unphysical negative-n solution also exists, as indicated in the Appendix. Negative values of n also occur in the general case; Figs. 3, 4, and 5 show

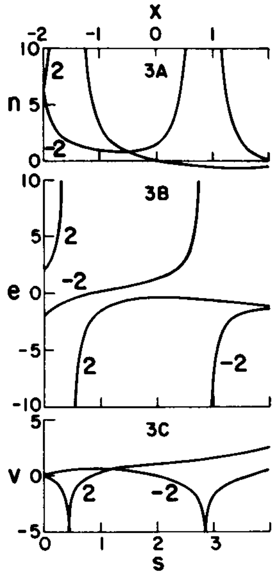

FIGURE 3

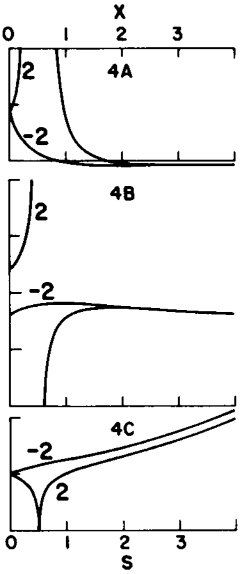

FIGURE 4

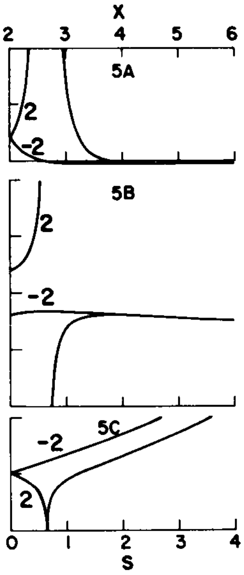

FIGURE 5

FIGURE 3 This and the following eight figures are graphs of (A) dimensionless net ion concentration n, (B) field e, and (C) potential v as functions of s (and, when $\gamma \neq 0$, x). The parameter e_1 takes the values 2.0 and -2.0, as indicated by labeling on the first branch of each curve. In this figure $g = -2$ and $\gamma = 1$.

FIGURE 4 As in Fig. 3, with $g = 0$ and $\gamma = 1$.

FIGURE 5 As in Fig. 3, with $g = 2$, $\gamma = 1$.

regions of negative n. These values occur when x exceeds the first term in the curly bracket of Eq. 26b, hence only for positive values of x.

Since it therefore does not follow from the mathematical form of the solution, the condition that n be positive must be imposed when calculations are made. When satisfied, this condition implies that (a) e must rise monotonically within the membrane (by Eq. 15), and (b) the potential profile must be concave downward (by Eq. 17).

Infinities and Branches. The most conspicuous features of these solutions are their infinities; these are physically unrealizable and must be excluded from the region of the solution that is to represent the situation in the membrane. (It will be shown in the second paper that this is possible in experimentally relevant cases.) As s approaches one of these points from the left, $e \rightarrow +\infty$, while from the right, $e \rightarrow -\infty$. The variables n and v go to $+\infty$ from both sides, but the infinity in the potential is logarithmically weaker. As pointed out by Sinharay and Meltzer (17), these infinities divide the solutions into distinct branches.

For the osmodominant quasiequilibrium solutions (Eqs. 22), the infinities occur at

$$s_\infty = s_0 + \pi/2a, s_0 + 3\pi/2a, s_0 + 5\pi/2a, \ldots$$

The branch containing $s = 0$ must be chosen to satisfy the required boundary conditions, and $s = l$ must be on the same branch. In Fig. 6, e.g., the first infinity for $e_l = 2$ is at $2^{-1/2} \cdot (\pi/2 - \tan^{-1} 2^{1/2}) = 0.435$ and for $e_l = -2$, at $2^{-1/2}(\pi/2 + \tan^{-1} 2^{1/2}) = 1.79$.

In the balanced case, Eqs. 23, there is a single infinity, located at $s = 1/e_l$; since we are

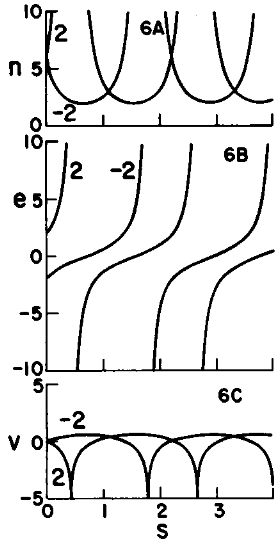

FIGURE 6

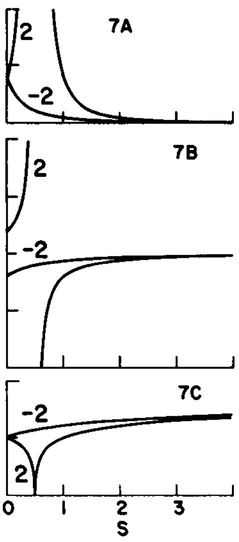

FIGURE 7

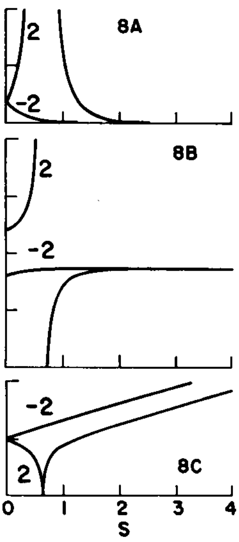

FIGURE 8

FIGURE 6 As in Fig. 3, with $g = -2, \gamma = 0$.
FIGURE 7 As in Fig. 3, with $g = 0, \gamma = 0$.
FIGURE 8 As in Fig. 3, with $g = 2, \gamma = 0$.

only interested in positive s, the continuous solution has an upper bound only for positive e_I's; see Fig. 7, where for $e_I = 2$ an infinity appears at $s = \frac{1}{2}$.

In the case of the electrodominant quasiequilibrium solutions 24, there is again only one infinity, this time at

$$s_\infty = s_0' = \tfrac{1}{2}g^{-1/2}[\ln \mid e_I + g^{1/2} \mid - \ln \mid e_I - g^{1/2} \mid].$$

If $e_I > 0$, this value is positive; see Fig. 8, with an infinity at $2^{-3/2}[\ln(2 + 2^{1/2}) - \ln(2 - 2^{1/2})] = 0.623$ for $e_I = 2$.

Only the extreme case of Eq. 25, which describes an ion-free membrane, is without infinities for all values of e_I.

The determination of the locations of the infinities is not as simple for the general equations as in the quasiequilibrium cases, as we now have the additional complication of the parameter γ. Any one of the three Eqs. 26*a*, *b*, and *c* shows that the infinities of x occur when $\mathrm{Ai}(x) + R\,\mathrm{Bi}(x) = 0$, but before these points can be determined quantitatively, R must be obtained from the boundary conditions. Nevertheless, an examination of the Airy functions (43) allows one to make some general remarks:

Since Ai and Bi oscillate with interlacing zeros over the negative x-axis, their linear combination likewise oscillates there. Thus Eqs. 26*a*, *b*, and *c* have an infinite number of infinities in this region, which corresponds to $\gamma s < -g$. Here e also has an infinity of zeros (corresponding to potential maxima), and n has an infinity of minima. The solutions in the region $\gamma s < -g$ therefore break up into discrete branches, with e crossing the axis once in each branch. These branches, called Type I by Sinharay and Meltzer (17), are qualitatively similar to those of the tangent solution 22*a*. They differ from it, however, in that they are now no longer spaced uniformly: they have a period that decreases as the argument of the Airy functions becomes more negative.

On the positive x-axis e has, owing to the monotonicity of the Airy functions there, only zero or two roots; these are branches of type III and II, respectively (17). The reason for this is that the rightmost field branch rises to a maximum (when $n = 0$) and then drops again, thus crossing the axis either twice or not at all (or, in the bounding case, touching the axis at its maximum). This branch thus has only a slight resemblance to the negative hyperbolic cotangent of 24*a*.

As we stated in the assumptions above, realistic solutions require finite ion concentrations; it follows that the two membrane boundaries, I and II, must lie within the first branch of the solution. This continuity requirement and the monotonicity of e imply that e_I must be less than e_{II} in an actual membrane problem. The equivalent relation in physical quantities is, from 12, $qE_I < qE_{II}$.

Minima of n. In some cases the ion concentration goes through a minimum. Among the quasiequilibrium solutions only the osmodominant case can have this property (see Fig. 6). Since in this case $dn/ds = 2en = 0$, the (nonzero) minima of n occur at the zeros of e; they are evenly spaced, at $s = s_0,\ s_0 \pm \pi/a,\ s_0 \pm 2\pi/a, \ldots,$ with ordinates in each case equal to $n = -g = n_I - e_I^2$. These points are also, by 20, potential maxima (when $n \neq 0$).

The general condition for an ion-concentration minimum is, from Eq. 16, $2\,en = \gamma$. Note that the diffusion flux vanishes at these points. As Fig. 9 A shows, the minima of the general solutions do not have uniform spacing but move closer as the branches narrow with decreasing x. Furthermore, they are no longer of the same height, as Figs.

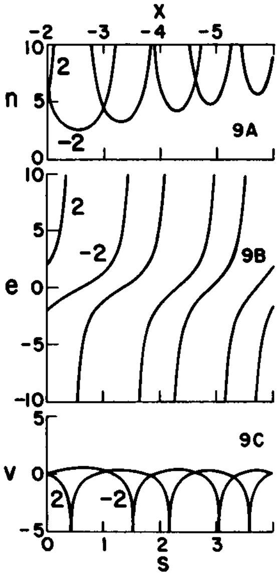

FIGURE 9

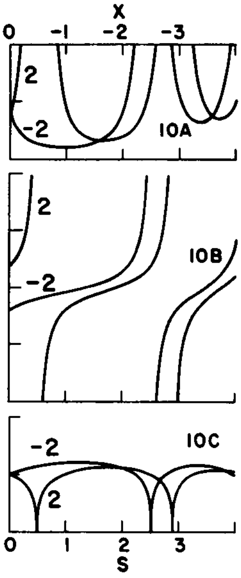

FIGURE 10

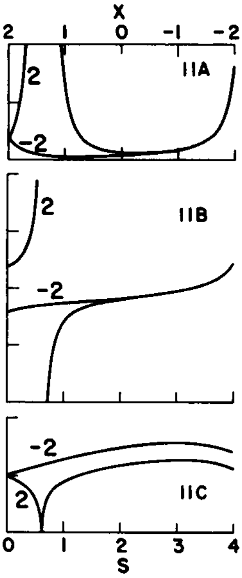

FIGURE 11

FIGURE 9 As in Fig. 3, with $g = -2, \gamma = -1$.
FIGURE 10 As in Fig. 3, with $g = 0, \gamma = -1$.
FIGURE 11 As in Fig. 3, with $g = 2, \gamma = -1$.

9 A and 10 A show clearly. These figures also demonstrate that the potential maxima are not generally at the same points as the concentration minima; this is to be expected, as Eq. 20 does not hold in general.

The Phase Plane

An approach pioneered by Cole is that of the (e, n) or phase plane. (See ref. 11, p. 353ff; note that a plot of dI/dt vs. I for the action potential is an entirely different phase plane.) To eliminate the independent variable s, we rewrite Eqs. 15 and 16 as follows:

$$\frac{de}{n} = \frac{dn}{2en - \gamma} (= ds); \tag{27}$$

the two variables that remain are e and its first derivative n. From this equation follows the relation

$$dn/de = 2e - \gamma/n, \tag{28}$$

which defines the slope at each point of the (e, n) plane (ref. 21, p. 198). Eq. 19 shows that, when $e = \pm\infty$, n goes to $+\infty$ for finite $\gamma s + g$. This is consistent with the behavior seen in computed phase trajectories, Figs. 12, 13, and 14. In all these plots s increases counterclockwise with respect to a point above the curve, as the arrows indicate.

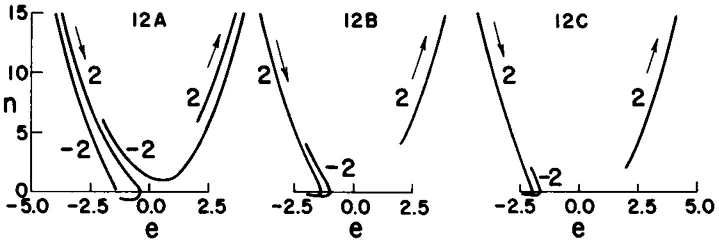

FIGURE 12 The phase plane for $\gamma = 1$. Graphs of n vs. e for (A) $g = -2$ and $e_I = -2$ and 2 as labeled (compare with Fig. 3); (B) $g = 0$ (cf. Fig. 4); (C) $g = 2$ (cf. Fig. 5). The arrows alongside the graphs indicate the direction of increasing s.

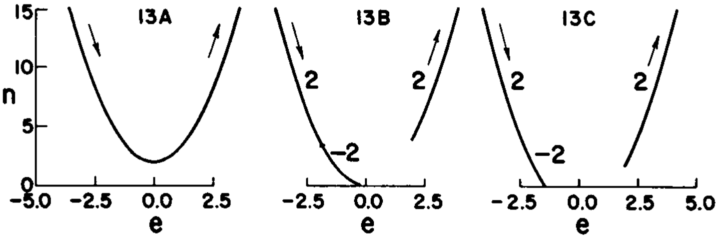

FIGURE 13 The phase plane as in Fig. 12, but for $\gamma = 0$. (A) $g = -2$ (cf. Fig. 6); (B) $g = 0$ (cf. Fig. 7); (c) $g = -2$ (cf. Fig. 8). Note that the n-axis is here an axis of symmetry, with all minima at $e = 0$.

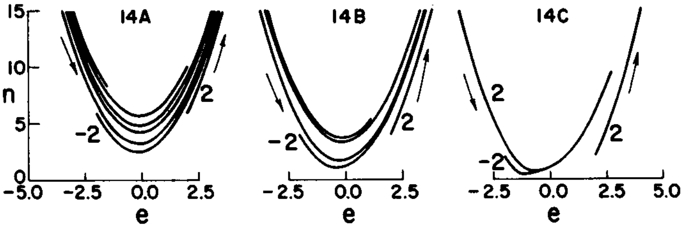

FIGURE 14 The phase plane as in Fig. 12, but for $\gamma = -1$. (A) $g = -2$ (cf. Fig. 9); (B) $g = 0$ (cf. Fig. 10); (C) $g = 2$ (cf. Fig. 11).

We have already seen (in the discussion below Eq. 6) that, when $\gamma = 0$, the phase-plane relation is the parabola $n = e^2 - g$, the vertex of which is located at $(0, -g)$. This relationship is shown in Fig. 13 for $g = -2, 0$, and 2. Here each trajectory represents two distinct solutions, $e_I = -2$ and 2.

For nonzero current-density parameter the picture of course becomes more complex, but graphs 12 and 14 help give an idea of the phase-plane behavior. The vertex point is no longer on the n-axis but lies, as can be seen by setting the left-hand side of Eq. 28 to zero, on the hyperbola $2en = \gamma$, on which the diffusional component of current density is zero. At several points in Fig. 12, $n = 0$; as Eq. 28 indicates for positive γ, the slope of the trajectory becomes $-\infty$ at these points.

SUMMARY

Although the argument is not completed, we shall pause here to summarize the ground covered so far.

The macroscopic approach is the method of examining a system on the scale of its own dimensions; in this case, those of membrane thickness and electrode area. We use the electrodiffusion theory, a formulation marked by economy and generality of hypothesis, and explore it without first simplifying the nonlinear differential equations that result. Our aim is to obtain the current-voltage behavior of the axon from the membrane parameters (thickness, dielectric constant, mobilities) and the boundary ion concentrations.

In this discussion we have been concerned with the analysis of the steady-state electrodiffusion problem. We have shown that all exact solutions of this problem must conform to a scaling property, which in turn leads to certain interesting predictions regarding the comparative behavior of different membranes. We have derived a first integral, which relates the electric field, net ion concentration, and transverse coordinate. When the sum of the reduced current densities is zero (quasiequilibrium case), this integral reduces to the parabola that K. S. Cole has already described for the one-ion case.

Specializing to systems of ions all of the same charge (a class of cases important in axon and other cell membranes), we have demonstrated that the mathematical problem posed by these homovalent systems in the steady state is only slightly more complicated than the one-ion problem. Solutions are given for the quasiequilibrium (further broken down into electrodominant, balanced, and osmodominant cases) and nonequilibrium cases.

We have seen that, for the steady-state homovalent electrodiffusion problem, the electric-field function e has the following properties as a function of the distance: When the current-density parameter γ is zero (quasiequilibrium), it is a tangent, a hyperbola, or a negative hyperbolic cotangent (or a constant), depending on whether g is negative, zero, or positive (the osmodominant, balanced, and electrodominant cases). In the general case, $\gamma \neq 0$, the more complicated function 26*a* adopts features of the quasiequilibrium solutions, with "tan-like" branches to the left, and "minus-coth-like" branches to the right of the point $x = x_1$.

Once the electric field is known, the ion density is readily obtainable from it by the first-integral relation. The continuity (or finiteness) and positivity of n must be specified for realistic solutions. As a result, e increases monotonically and v, its negative integral, is concave downward.

The phase-plane curve, which Cole showed to be a parabola in the one-ion zero-current case, is a parabola for the net ion density in quasiequilibrium. The general e-n curve is more complicated, but can be investigated graphically.

We have compiled the basic analytical tools for calculating the properties of a homovalent electrodiffusion system. There remains the problem of evaluating the arbitrary constants so as to satisfy the membrane boundary conditions with continuous, positive-n segments of the solutions discussed in this paper, and thereby generating current-voltage curves that can be compared with experimental data. This we do in our second paper for a membrane permeated by a single ion species (potassium for the squid-axon membrane in physiological fluids).

We are greatly indebted to R. G. Gordon of Harvard University for subroutine AIRY (part of his program, "Coupled Channel Scattering Matrices"), to John Wills of Indiana University for calling Gordon's work to our attention, and to the Quantum Chemistry Program Exchange (Indiana University) for supplying the program. Our special thanks go to Erika Epstein of the Courant Institute, New York University, for assistance with the writing of program LOLIGO. We gratefully acknowledge the use of the computing and graphics facilities at the ERDA computing laboratory, Courant Institute, and at Indiana University.

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APPENDIX: DERIVATIONS OF THE SOLUTIONS

Quasiequilibrium ($\gamma = 0$)

Osmodominant Case. Since $g < 0$, we define $a = (-g)^{1/2}$ and separate the variables in Eq. 21 to write

$$\frac{de}{e^2 + a^2} = ds \tag{29}$$

This form (a standard one in tables) is easily integrated. If we define $s_0 = -(1/a)\tan^{-1}(e_1/a)$ we obtain Eq. 22*a*, $e = a\tan a(s - s_0)$. This, substituted into $n = e^2 + a^2$, gives with a trigonometric identity

$$n = a^2\sec^2[a(s - s_0)]. \tag{30}$$

We then solve Eq. 20 for v and substitute Eq. 30:

$$v - v_\mathrm{I} = \frac{1}{2} \ln\left|\frac{n_\mathrm{I}}{n}\right| = \ln\left\{\left(\frac{e_\mathrm{I}^2 + a^2}{a^2}\right)^{1/2} |\cos[a(s - s_0)]|\right\}. \tag{31}$$

Balanced Case. Eq. 23 is easily obtained by integrating $de/e^2 = ds$ and substituting into the relations for n and v.

Electrodominant Case. Here Eq. 21 becomes

$$\frac{de}{e^2 - b^2} = ds, \tag{32}$$

where $b = g^{1/2}$, except when $|e| = b$. The physically meaningful case, corresponding to $n > 0$, is the one in which $e^2 > b^2$. In that case we may substitute $e = b \coth \theta$ to obtain Eq. 24*a*. Substitution into the relations for n and v and some manipulation yield 24*b* and *c*. When $e = b$, $e^2 = g$ and Eq. 21 becomes simply $de/ds = 0$, from which 25*abc* follow trivially. A negative-n solution can be derived by taking $e^2 < b^2$ in 32, but it has no biophysical significance.

General ($\gamma \neq 0$)

When Eq. 19 is substituted into 15, the nonlinear first-order differential equation

$$(de/ds) = e^2 - \gamma s - g \tag{33}$$

results. The change of independent variable $s = y - g/\gamma$ turns this into

$$(de/dy) - e^2 + \gamma y = 0, \tag{34}$$

a form of Riccati's equation. The standard transformation

$$w^2 = \exp(-2 \int^y e dy),$$

the first derivative of which is $dw/dy = -ew$, converts 34 into the linear second-order equation $d^2w/dy^2 = \gamma y w$. Another change of independent variable, $y = \gamma^{-1/3}x$, yields Airy's equation,

$$d^2w/dx^2 = xw, \tag{35}$$

of which the Airy functions $\mathrm{Ai}(x)$ and $\mathrm{Bi}(x)$ are linearly independent solutions. The solution for the dimensionless field is therefore

$$e = -\frac{d}{dy}(\ln w) = -\gamma^{1/3}\frac{d}{dx}(\ln w) = -\gamma^{1/3}\frac{A\,\mathrm{Ai}'(x) + B\,\mathrm{Bi}'(x)}{A\,\mathrm{Ai}(x) + B\,\mathrm{Bi}(x)} \tag{36}$$

One of the two constants, A or B, is immaterial here, and the equation may be written in the form 26*a*, with $R = B/A$.

When the first integral 19 is written in terms of independent variable x,

$$n = e^2 - \gamma^{2/3}x, \tag{37}$$

26*b* follows from substituting 26*a* into 37 or, alternatively, by differentiating 26*a*, since $n = \gamma^{1/3} de/dx$, and using 35 for the Airy functions. The potential is

$$v = -\int^s e ds = -\int^y e dy = \ln|w| + \text{const},$$

from which we obtain 26*c*.