KINETIC THEORY MODEL FOR ION MOVEMENT THROUGH BIOLOGICAL MEMBRANES

III. STEADY-STATE ELECTRICAL PROPERTIES WITH SOLUTION ASYMMETRY

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ABSTRACT An electrodiffusion model for plasma membrane ion transport, which takes into account the influence of high electric field strengths and ion-membrane molecule interactions, is presented and analyzed. A generalized Nernst-Planck equation for steady-state situations is derived which has electric field–dependent mobility and diffusion coefficients. Under the assumption of a constant electric field within the membrane, this equation is integrated to give a more general form of the Goldman equation. Based on this equation numerical computations of ionic chord conductance as a function of applied electric field strength were carried out for several permeant ion concentration ratios. The model is capable of yielding significantly larger rectification ratios than is the Goldman equation. Further, high field asymptotes to the current vs. electric field strength curve do not generally intersect at the origin.

INTRODUCTION

A number of studies have been conducted in the past 10 years on naturally occurring excitable membranes with ionic concentration symmetry. Data from these studies implicate mechanisms possibly involved in membrane ion transport, and have stimulated much theoretical work. The observation most fully explored and modeled is the appearance of negative slope conductance characteristics in the slow (potassium) channel of squid (Lecar et al., 1967).

Traditional electrodiffusion theory has been extensively used to interpret data taken on excitable membrane systems separating one or more ionic species at different concentrations. The fact that the Goldman (1943) equation fails to predict the nonlinear electrical behavior observed in symmetrical systems raises serious doubts about the applicability of the electrodiffusion concept. Cole (1965, 1968) has discussed these and other objections.

However, the question concerning the usefulness of the electrodiffusion concept seems to be largely unanswered. Mackey (1971 *a*) explored a more detailed electrodiffusion model for steady-state ion transport under conditions of ionic concentration symmetry and showed that the model had a variety of nonlinear electrical properties. These included negative slope conductance regions and electric field–dependent ion selectivity. The model considered several possible ion-membrane molecule interactions, and situations far from equilibrium. These results reopen the possibility that electrodiffusion mechanisms may be of importance in determining membrane electrical properties.

In this paper we extend the model analyzed by Mackey to the situation where ionic concentration gradients exist across the membrane. A Goldman-like equation is derived, and we show that it reduces to its familiar form when the electric field strength is not too large. We examine computed model chord conductance and rectification ratios with respect to the Goldman formulation.

THE MODEL

Assumptions

Hille (1970) has reviewed the extensive experimental evidence that ion penetration in excitable cell plasma membranes occurs at widely spaced and specific sites. It is steady-state transport through these restricted regions that this model deals with, and the following assumptions relate only to these ion-permeable regions. The assumptions result in generalized Nernst-Planck and Goldman equations. Both equations reduce to their customary forms for situations close to equilibrium; therefore, any objections to these assumptions are applicable to the customary forms of these equations.

It is assumed that the movement of an ion through ion-permeable regions is modulated by elastic interactions (collisions) between the ion and the membrane molecules lining the transport site. Ion-ion interactions are considered negligible. Knowledge about the molecules adjacent to the ion-permeable region is nonexistent, so we postulate that they may be represented by effective membrane molecules. The effective membrane molecules are taken to be spherical mass centers with random thermal motion. The spacing of the effective molecules is such that there are only binary collisions between them and the permeant ion. Thus, the force between ion and membrane molecule is taken to be central and conservative. Finally, it assumed that the effective membrane molecules are massive with respect to the permeating ions. This is equivalent to assuming that during a collision the fractional energy loss (ξ) by an ion is much smaller than 1.

Relation Between Ionic Current Density, Electric Field Strength, and Concentration Differences

To avoid the extensive use of formulae in the text we have confined the mathematical details of our analysis to appendixes. Equations from the appendixes are referred to in the manner (A 5).

In Appendix I we have shown that under the above assumptions a generalized Nernst-Planck equation

$$\bar{I} = N\bar{E}\bar{\mu} - \partial(N\bar{D})/\partial L \qquad \text{(A 11)}$$

may be derived where $\bar{I}$, $\bar{E}$, N, and L are the (dimensionless) steady-state current density, electric field strength, ionic number density, and spatial coordinate through the membrane respectively. The (dimensionless) mobility ($\bar{\mu}$) and diffusion coefficient ($\bar{D}$), both functions of L and $\bar{E}$, are defined by equations A 12–A 14.

Under the additional assumption of a constant (spatially independent) electric field in the membrane we have integrated equations A 11–A 14 (Appendix II). A generalized Goldman equation,

$$\bar{I} = \bar{E}\bar{\mu}[\exp{(\bar{\delta}\bar{E}\bar{\mu}/\bar{D})} - 1]^{-1}[N_1 \exp{(\bar{\delta}\bar{E}\bar{\mu}/\bar{D})} - N_2], \qquad \text{(A 15)}$$

results where $\bar{\delta}$ is the dimensionless membrane thickness. This equation describes the ionic current flow through our model membrane system when it separates two solutions of ionic number densities N_1 and N_2 respectively. With the constant field assumption, we have derived expressions for $\bar{\mu}$ and $\bar{D}$ (equations A 16 and A 17) which are functions of $\bar{E}$ and the equilibrium field strength $\bar{E}_e$. For situations close to equilibrium, equation A 15 reduces to the Goldman equation which, in our notation, is

$$\bar{I}_G = \bar{E}[\exp{(3\bar{\delta}\bar{E})} - 1]^{-1}[N_1 \exp{(3\bar{\delta}\bar{E})} - N_2].$$

The subscript G on $\bar{I}_G$ will serve to identify this current as derived from the Goldman equation. The two important differences between equation A 15 and the customary Goldman equation are that the ionic mobility and energy ($\bar{D}/\bar{\mu}$) are no longer constant. They are functions of the applied and equilibrium electric field strengths.

COMPUTED RESULTS FROM THE MODEL; DISCUSSION

The expressions for $\bar{\mu}$ and $\bar{D}$ derived in Appendix II are too complicated to be evaluated analytically except in special cases. Thus, a numerical procedure was used to examine the model membrane electrical properties expressed implicitly in equation A 16. In examining the model we used three types of ion-membrane molecule interactions, characterized by $p = 0$ and $p = \pm 3/4$. (See Appendix I for a discussion of the collision frequency dependence on ionic velocity.) This was done to reveal any general characteristic that might emerge for ion-membrane molecule collision frequencies that are increasing ($p > 0$) or decreasing ($p < 0$) functions of ionic velocity.

The results of our computations are presented in terms of dimensionless variables. It is of interest to have definite numbers appropriate to biological situations to

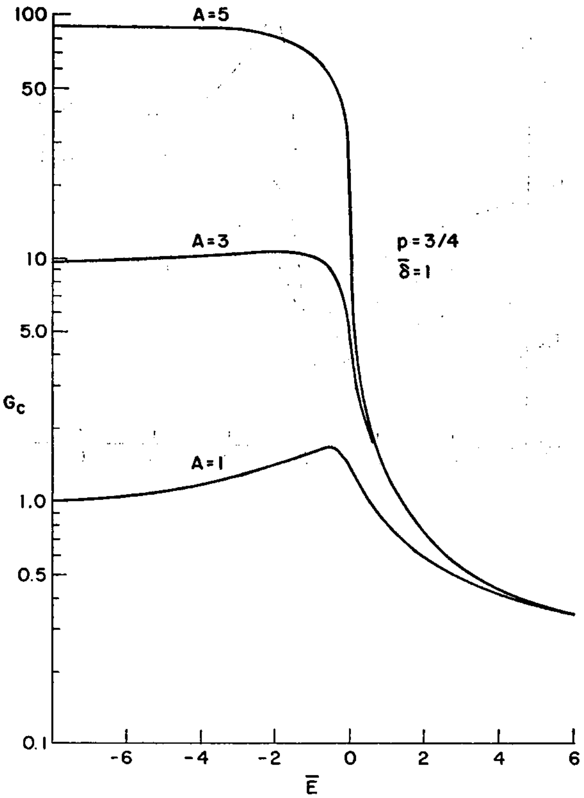

FIGURE 1 Some typical chord conductance $[G_c = \bar{I}/(\bar{E} - \bar{E}_c)]$ vs. applied electric field strength ($\bar{E}$) curves for $p = +\frac{3}{4}$, $\bar{\delta} = 1$, and three different concentration ratios.

relate to these dimensionless quantities. Mackey (1971 *a*) has presented such considerations in detail, and reference should be made to that paper for order of magnitude estimates of membrane-related quantities.

In Fig. 1 we show the chord conductance $G_c = \bar{I}/(\bar{E} - \bar{E}_e)$ of the model as a function of $\bar{E}$ for various values of the concentration ratio across the membrane $\bar{\delta} = 1$, and $p = +\frac{3}{4}$. The figure illustrates that concentration ratios within the physiologically encountered range are capable of producing chord conductance vs. electric field strength plots similar in form to those observed experimentally, e.g., in squid (Hodgkin and Huxley, 1952).

Even though the curves of Fig. 1 are similar to known data, computations from the Goldman equation yield qualitatively equivalent results. To compare quantitatively the results of the Goldman formulation of electrodiffusion with ours, we define the ratio $R(\bar{E}, A) = \bar{I}_G/\bar{I}$. R as a function of $\bar{E}$ is shown in Fig. 2 for $p = +\frac{3}{4}$. In every case the Goldman equation predicts significantly larger currents at large positive and negative values of field strength than does our model. R for $A > 0$

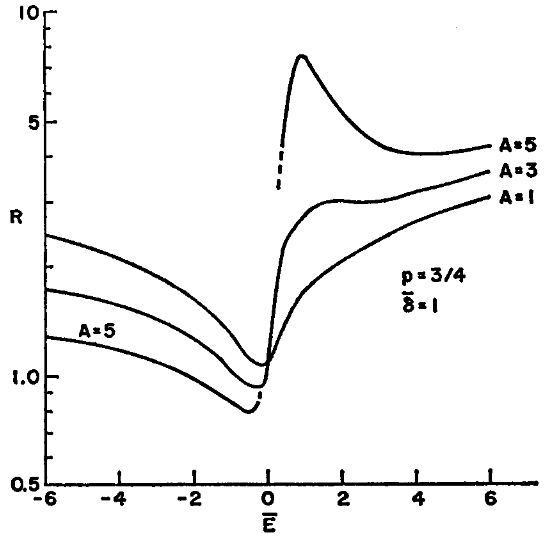

Figure 2 A comparison of the current-carrying capacities of the Goldman and present formulations of an electrodiffusion membrane model. Here we show $R = \bar{I}_G/\bar{I}$ as a function of applied electric field strength ($\bar{E}$), when $p = \frac{3}{4}$ and $\bar{\delta} = 1$, with three different concentration ratios.

at large positive E values is greater than R at an equally large but negative E, and the discrepancy is more pronounced as A becomes larger.

Computations of R as a function of $\bar{E}$ for $p = -\frac{3}{4}$ and $p = 0$ give results qualitatively identical with those for $p = +\frac{3}{4}$. These are illustrated in Fig. 3 for positive $\bar{E}$.

Mackey (1971 *a*, *b*) demonstrated that the sign of p gives very distinctive features to the general electrical properties of this model in the presence of solution symmetry. For example, with $p > 0$ (< 0) the chord conductance is a strictly decreasing (increasing) function of electric field strength. When an equilibrium field is present in the membrane model those highly distinctive features are no longer observed. We take this as a strong argument for studying membrane transport in the absence of concentration gradients. Experimental support for this conclusion is given by the studies on several systems under isoosmotic potassium conditions.

Measured current rectification ratios in squid giant axon membrane (Cole and Curtis, 1941; Cole and Moore, 1960) are always larger than predicted by the Goldman formulation of the electrodiffusion model. The rectification ratio R_R for a membrane system is defined as

$$R_R = \lim_{\bar{E}\to-\infty} G_c / \lim_{\bar{E}\to+\infty} G_c \, .$$

In Table I, for $p = +\frac{3}{4}$ and $\bar{\delta} = 1$, the rectification ratios expected for the Goldman equation (equal to N_2/N_1) are compared with the values found from our for-

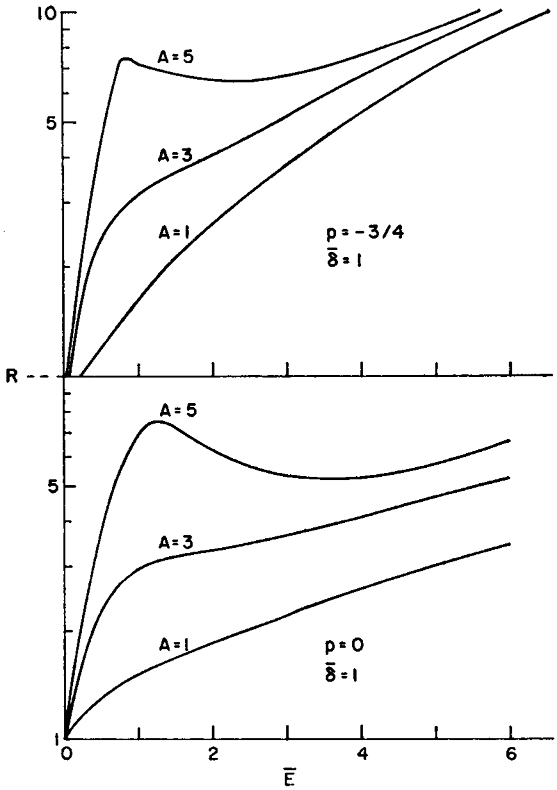

FIGURE 3 As in Fig. 2, but for $p = -\frac{3}{4}$ and $p = 0$. Note the qualitative similarity in the behavior of $R(\bar{E}, A)$ for all values of p.

mulation. In every case we obtain ratios greater than those expected using the traditional approach and closer to those measured experimentally.

Another point of contention between experimental data and the traditional electrodiffusion development has been the predicted zero-field intersection of high field asymptotes to the current vs. electric field strength curve. Experimentally, a nonzero intersection is found (Cole and Curtis, 1941; Cole and Moore, 1960). The asymptote to the current vs. electric field curve will intersect the origin only if the curve has become linear with a slope of $\bar{I}/\bar{E}$ at high field strengths. Figs. 2 and 3 illustrate that this does not occur in our formulation.

In summary, a high field strength analysis of a model membrane system incorporating electrodiffusion mechanisms removes many of the discrepancies previously noted between experimental data and the Nernst-Planck-Goldman electrodiffusion formulation. The basic difference between the two approaches resides in our treatment of electric field–induced alterations of the Einstein relation and specific ion-membrane molecule interactions. Some of the discrepancies resolved are the existence of field-dependent conductances (including negative slope conductance characteristics) in the presence of solution symmetry (Mackey, 1971 *a*), order of magni-

TABLE I

A COMPARISON OF THE THEORETICAL RECTIFICATION RATIOS EXPECTED FROM THE GOLDMAN EQUATION AND OUR ANALYSIS FOR $p = \frac{3}{4}$ AND $\bar{\delta} = 1$

A	R_R	
	Goldman	This study
1	2.72	3.02
2	7.39	8.95
3	20.09	29.41
4	54.60	90.04
5	148.41	273.02

Note the increased rectification efficiency of the present model as compared with the Goldman version.

tude variations in cation selectivity (Mackey, 1971 *b*), and anomalously large rectification ratios (this paper). In addition, the high field version of electrodiffusion theory raises the possibility of field-dependent selectivity (Mackey, 1971 *b*) and field-dependent chord conductance temperature coefficients (Mackey, 1968). The above considerations lead us to conclude that electrodiffusion mechanisms may be important in determining excitable membrane electrical properties.

APPENDIX I

Derivation of a Generalized Nernst-Planck Equation

In Mackey (1971 *a*) it was shown that the kinetic theory approach utilized there, under our stated assumptions, leads to the expression

$$n(z) = 4n \int_0^{\infty} dv v^2 f_0(z, v) \tag{A 1}$$

for the number density n of ions, when a particular ion has velocity v. (We assume that all spatial variations are in one direction z perpendicular to the membrane surface.) Further, the membrane current density I carried by ions (charge $q = eZ$, mass m) due to externally applied forces is

$$I = (4\pi q/3) \int_0^{\infty} dv v^3 f_1(v). \tag{A 2}$$

The functions $f_0(z, v)$ and $f_1(z, v)$ appearing in equations A 1 and A 2 are given (Ginsberg and Gurevich, 1970) as solutions of the coupled equations

$$(a/3v^2)[\partial(v^2 f_1)/\partial v] = (2v^2)^{-1}\,\partial\{v^3 \nu(v)\xi[f_0 + (kT/mv)(\partial f_0/\partial v)]\}/\partial v \tag{A 3}$$

and

$$-\nu(v) f_1 = v(\partial f_0/\partial z) + a(\partial f_0/\partial v). \tag{A 4}$$

In equations A 3 and A 4, ν is the frequency of elastic collisions between ions with velocity v and membrane scattering centers, $a = qE/m$ is the force on an ion due to an external field, and k and T are the Boltzmann constant and absolute temperature respectively.

It is well-known from classical scattering theory (see Goldstein, 1950) that if two particles interact centrally, then the collision frequency may be written as a simple function of v. Thus, if the force between ion and the effective membrane molecule is given by $F = -K/r^{\alpha}$, where r is the separation between particles and K and α are constants, then (Chapman and Cowling, 1958) the collision frequency is given by

$$\nu(v) = \beta v^{p}. \tag{A 5}$$

In equation A 5, $p = (\alpha - 5)/(\alpha - 1)$ and

$$\beta = 2\pi n_s A(\alpha)[K(m + m_s)/mm_s]^{2/(\alpha-1)}$$

is a constant involving the effective membrane molecule mass m_s, number density n_s, and a pure number $A(\alpha)$.

By use of equation A 4 in equation A 2 we may immediately write a generalized Nernst-Planck equation

$$I = q^2 nE\mu - q\partial(nD)/\partial z \tag{A 6}$$

wherein the mobility μ and diffusion coefficient D are given by

$$\mu = \left[3m \int_0^{\infty} dv v^2 f_0\right]^{-1} \int_0^{\infty} dv v^3 (- \partial f_0/\partial v)/\nu(v), \tag{A 7}$$

and

$$D = \left[3 \int_0^{\infty} dv v^2 f_0\right]^{-1} \int_0^{\infty} dv v^4 f_0(v)/\nu(v), \tag{A 8}$$

where f_0 is the solution of

$$[1 + (2ma^2/3\xi kT\nu^2)](\partial f_0/\partial v) + mvf_0(v)/kT + (2mav/3\xi kT\nu^2)(\partial f_0/\partial z) = 0. \tag{A 9}$$

The above equations describe ion transport for the model membrane. We must solve equation A 9 in conjunction with equation A 5 to obtain $f_0(v, z, E)$. This is used to compute $\mu(z, E)$ and $D(z, E)$ from equations A 7 and A 8 respectively. These values for μ and D are then used in equation A 6 which yields the relation between current flow, membrane potential, and concentration gradients.

In dealing with the equations describing the model properties it will be convenient to express them in terms of dimensionless variables. We define

$$\begin{aligned} v_T^2 &= 3kT/m, & \hat{E} &= qE/m\nu_0 v_T\sqrt{\xi}, \\ \nu_0 &= \beta v_T^{p}, & \bar{I} &= I/qv_T n_0\sqrt{\xi}, \\ u &= v/v_T, & N &= n/n_0. \\ L &= \sqrt{\xi} z\nu_0/v_T, \end{aligned} \tag{A 10}$$

With the definitions of equation A 10, equation A 6 takes the form

$$\bar{I} = N\bar{E}\bar{\mu} - \partial(N\bar{D})/\partial L, \tag{A 11}$$

wherein $\bar{\mu} = mv_0\mu$ is given by

$$\bar{\mu}(L, \bar{E}) = \left[3\int_0^\infty duu^2 f_0\right]^{-1}\int_0^\infty duu^{3-p}(-\partial f_0/\partial u) \tag{A 12}$$

and $\bar{D} = (v_0/v_T^2)D$ is

$$\bar{D}(L, \bar{E}) = \left[3\int_0^\infty duu^2 f_0\right]^{-1}\int_0^\infty duu^{4-p} f_0\,. \tag{A 13}$$

Finally, equation A 9 becomes

$$[1 + (2\bar{E}^2/u^{2p})](\partial f_0/\partial u) + 3uf_0 + (2\bar{E}u/u^{2p})(\partial f_0/\partial L) = 0. \tag{A 14}$$

APPENDIX II

A General Form for the Goldman Equation

As in Goldman (1943) and Mackey (1971 *a*, *b*), we assume that the electric field within the membrane due to an externally applied membrane poetntial is constant. With this assumption, the solution to equation A 14 for $f_0(v, L, \bar{E})$ may be written as $f_0(v, L, \bar{E}) = f_{0u}(u, \bar{E})f_{0L}(u, \bar{E})$. Thus, $\bar{\mu}$ and $\bar{D}$, given by equations A 12 and A 13 respectively, are independent of L.

If the membrane is of thickness $\bar{\delta}$ and the conditions $N = N_1(N_2)$ and $\varphi = \varphi_1(\varphi_2)$ at $L = 0(\bar{\delta})$ hold at the boundaries, then $\varphi(L) = \varphi_1 + [(\varphi_2 - \varphi_1)/\bar{\delta}]L$ across the membrane and $\bar{E} = -\partial\varphi/\partial L = -\varphi_m/\bar{\delta}$, where $\varphi_m = \varphi_1 - \varphi_2$ is the membrane potential.

With the assumptions concerning $\bar{E}$ and the boundary values of N, the solution of equation A 11 is

$$\bar{I} = \bar{E}\bar{\mu}[\exp(\bar{\delta}\bar{E}\bar{\mu}/\bar{D}) - 1]^{-1}[N_1\exp(\bar{\delta}\bar{E}\bar{\mu}/\bar{D}) - N_2], \tag{A 15}$$

which is the general form of the Goldman equation.

To calculate $\bar{\mu}$ and $\bar{D}$ for use in equation A 15, we must solve equation A 14 for $f_0(v, L, \bar{E})$. With the constant field assumption, the spatially dependent portion of f_0 is given by $f_{0L} = \exp(AL)$, where A is given from the boundary conditions as $A = \bar{\delta}^{-1}\ln(N_2/N_1)$. The equation

$$[1 + (2\bar{E}^2/u^{2p})](df_{0u}/du) + [3u + (2\bar{E}Au/u^{2p})]f_{0u} = 0$$

defines the velocity-dependent portion of f_0, given by

$$f_{0u}(u, \bar{E}, A) = \exp(-W_0 - W_1),$$

wherein

$$W_0 = 3\int_0^u dss^{2p+1}/[s^{2p} + 2\bar{E}^2],$$

and

$$W_1 = (2EA) \int_0^u dss/[s^{2p} + 2E^2].$$

In the absence of a concentration gradient, $N_1 = N_2$, $A = 0$, $W_1 = 0$, $f_{0L} = 1$, and $f_0 = f_{0u}(\bar{E}, u)$ is as given in Mackey (1971 *a*).

The foregoing expression for f_{0u} enables us to write

$$\bar{D}(\bar{E}, A) = \left[3 \int_0^\infty duu^2 \exp(-W_0 - W_1)\right]^{-1} \int_0^\infty duu^{4-p} \exp(-W_0 - W_1) \quad (\text{A } 16)$$

and

$$\bar{\mu}(\bar{E}, A) = (3 - p)\left[3 \int_0^\infty duu^2 \exp(-W_0 - W_1)\right]^{-1} \int_0^\infty duu^{2-p} \exp(-W_0 - W_1), \quad (\text{A } 17)$$

where integration by parts was used in the expression for $\bar{\mu}(\bar{E}, A)$. Although $\bar{\mu}$ and $\bar{D}$ are independent of L, they are functions of $\bar{E}$ and A. A is a driving force for ionic movement, as is $\bar{E}$.

The generalized Goldman equation reduces to its familiar form when $p = 0$ and $\bar{E}$ is small. That is, when the energy of the ion due to $\bar{E}$ is much smaller than its thermal energy. Under this condition, $W_0 \sim 3u^2/2$, $W_1 \sim 0$, the integrals in equations A 16 and A 17 give $(\bar{D}/\bar{\mu}) = (1/3)$ (or $D = \mu kT$, the Einstein relation) and equation A 15 reduces to the form given earlier for the Goldman equation.

The field strength at which $\bar{I} = 0$ for a given value of A (the equilibrium field $[\bar{E}_e]$) is given as the solution of the equation

$$\bar{E}_e\bar{\mu} - A\bar{D} = 0. \quad (\text{A } 18)$$

Substituting the expressions given in equation A 16 and A 17 for $\bar{D}$ and $\bar{\mu}$ respectively, we conclude that equation A 18 will be satisfied for all u if and only if

$$(\partial W_0/\partial u) + (\partial W_1/\partial u) = 9uA/\bar{E}_e. \quad (\text{A } 19)$$

Substitution of the explicit forms for $(\partial W_0/\partial u)$ and $(\partial W_1/\partial u)$ in equation A 19 gives $\bar{E}_e = A/3$. If this relation is put into standard (as opposed to dimensionless) notation the Nernst equation results. Therefore, at any point in the previous expressions where A is encountered, it may be immediately related to $\bar{E}_e$.

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