# Permeation in Ionic Channels: A Statistical Rate Theory Approach

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ABSTRACT A novel way to model permeation through ionic channels is formulated. Our method does not require that equilibrium exists in the channel or at the channel interfaces. In addition, the potential profile does not need to be specified and the assumption of constant field across the membrane does not need to be made. Our formulation relies on statistical rate theory for its development and uses a form of the electrochemical potential which assumes that the ions are in solution.

We show that the conductance and the degree of nonlinearity are dependent on the relative equilibrium exchange rates in the channel and at the interfaces. Nonlinear current-voltage plots can be obtained in symmetric solutions as well as a nonunity exponent for the Ussing flux ratio. Due to the dependence of the partition coefficient on solubility, it is highly unlikely that the intracellular and extracellular partition coefficients are the same. A manifestation of unequal partition coefficients is a current reversal at a membrane voltage that is different from the Nernst potential of the current-carrying ionic species.

## INTRODUCTION

Electrical signalling in nerve and muscle relies on the passive movement of ions down their electrochemical gradient. Ionic channels, macromolecular pores in the cell membrane, provide this pathway for ions. The biophysical properties of ionic channels involve permeation, gating, and selectivity. To describe permeation, there are two approaches which are commonly used, electrodiffusion (e.g., Levitt, 1986), and reaction rate theory (e.g., Läuger, 1973). Barrier kinetic models for ionic channels have been used in several situations. For example, Begenisich and Cahalan (1980) used a three-barrier, two-site model for sodium channels, and Hille (1975) used a four-barrier, one-ion model also for sodium channels. However, the basic assumption of this theory which is that the initial reactants are always in equilibrium with the activated complexes (Glasstone et al., 1941), is not generally valid when applied to ionic channels (e.g., see Cooper et al., 1985). In this paper we introduce a novel way to view permeation through ionic channels. This method relies on statistical rate theory (SRT), a nonequilibrium thermodynamic approach.

In modelling ionic channels, equilibrium is often assumed to exist at the channel interfaces between the bulk solution and the channel extremities (e.g., Jakobsson and Chiu, 1987; Levitt, 1987). The assumption of equilibrium has been investigated in physical systems such as the molecular transport across a liquid-gas interface (Ward, 1977; Ward et al., 1982b; Tikuisis and Ward, 1992), and the rate of molecular adsorption at a gas-solid interface (Ward and Elmoselhi, 1986). In both of these cases it was found that if local equilibrium was assumed, the measured and predicted rates did not give consistent results. However, if in the theoretical description of these interfacial transport processes, nonequilibrium was allowed to exist, then consistency was obtained. The characteristic times of these nonequilibrium processes was in the millisecond range. The time constants for ionic channels in biological systems also fall in the millisecond range (Hille, 1992). Therefore, nonequilibrium phenomena are likely to be important considerations here also.

The SRT equations for ion permeation derived in this paper do not rely on equilibrium as a fundamental assumption. Equilibrium is not assumed to exist either at the channel interfaces or within the channel itself. Instead, it relies on quantum mechanics with ion movement occurring via transitions between different molecular distributions. Due to our use of a quantum theory, we do not need to make the assumption of a constant field across the membrane (Goldman, 1943), despite our assumption of steady-state conditions. Our fundamental assumption is in the form used for the electrochemical potential which assumes that the ion is in solution. Ion movement through the pore occurs in solution, and any interactions (e.g., ion-ion, ion-channel) are reflected in the various parameters of this electrochemical potential.

In this paper we describe (i) current-voltage relationships and show how conductance can be related to equilibrium exchange rates, (ii) unidirectional fluxes and their ratios, and (iii) current reversals in terms of unequal partition coefficients. Using our SRT equations, nonlinear current-voltage plots can be obtained when the intracellular and extracellular media are the same, i.e., in symmetric solutions, and the Ussing flux ratio can have a nonunity exponent. The premise of unequal partition coefficients is used to explain the inconsistency between measured reversal potentials and the Nernst potential.

## THEORY

### Statistical rate theory

The statistical rate theory (SRT) approach may be used to derive the expression for the rate of particle (molecule, atom, ion, electron) transport (Ward, 1977; Ward et al., 1982a, 1982b). The transport process considered can be a chemical

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reaction, transport of a particle across the interphase between fluid phases or the transport of a particle within a phase (diffusion). This approach is based on the concept of quantum mechanical transition probabilities. It allows the rate to be expressed in terms of the equilibrium exchange rate of the process and the change in the electrochemical potential experienced when a particle undergoes the process being considered. For example, consider a chemical reaction in which:

$$A + B \rightleftharpoons C + D. \tag{1}$$

Suppose that the reaction takes place in a system which has an equilibrium state (such a system is thermodynamically constrained to have a constant internal energy, volume, and mass). The equilibrium exchange rate, $K_x$, is the rate at which the reaction proceeds in both the forward and reverse directions when the system is in the equilibrium state. When the system is in a nonequilibrium state, the SRT approach uses a first order perturbation analysis of the Schrödinger equation to obtain the expression for the probability of a transition occurring in the system in which the reaction proceeds forward by one step and simultaneously the probability of a transition occurring in which the system moves one step in the reverse direction. The difference between these two transition probabilities is used to formulate the expression for the net rate of the reaction. Under the following conditions: (*a*) adoption of the Boltzmann definition of entropy, (*b*) assumption that the system may be described in terms of the local equilibrium variables, and (*c*) identification of the equilibrium exchange rate as certain quantum mechanical integrals, the net rate of the reaction, $j$, is given by (Ward, 1983):

$$j = K_x(\delta - \delta^{-1}) \tag{2}$$

where

$$\delta = \exp\left(\frac{\mu_A + \mu_B - \mu_C - \mu_D}{RT}\right) \tag{3}$$

and $\mu_\gamma$ is the electrochemical potential of component $\gamma$. It should be noted that the electrochemical potentials in this expression are to be evaluated in the nonequilibrium or instantaneous state of the system, whereas $K_x$ is to be evaluated in the final equilibrium state of the system.

Similarly, if one considers the transport of a particle (ion, atom, or molecule) from phase $a$ to phase $b$, the same approach leads to the following expression for the net flux $j$:

$$j = 2K_x \sinh\left(\frac{\mu^a - \mu^b}{RT}\right) \tag{4}$$

where $\mu^\xi$ is the electrochemical potential for the component in phase $\xi$.

These relations may be applied to a number of different systems. The actual expression for the rate may be different for each of the systems considered, because the expression for the electrochemical potential of a component may be different in each of the systems examined. For example, the electrochemical potential of component $\gamma$ in an ideal gas mixture is given by:

$$\mu_\gamma = \mu_\gamma^0(T, P) + RT \ln(x_\gamma) \tag{5}$$

where $\mu^0(T, P)$ is the electrochemical potential of the pure component $\gamma$ at temperature, $T$, and pressure, $P$, and $x$ is the mole fraction of the component in the gas mixture. If the same gas component is dissolved in a liquid phase and forms a weak solution, then its electrochemical potential is given by:

$$\mu_\gamma = \mu_\gamma^0(T, P) + RT \ln([\gamma]/[\gamma]_S) \tag{6}$$

where $[\gamma]$ is the concentration of component $\gamma$ in the solution, and $[\gamma]_S$ is its solubility in the solution.

Since the basic expression for a rate is in terms of the electrochemical potentials, a means is provided by which these expressions can be examined experimentally, because the rate of processes in different types of systems can be predicted for each by using the expression for the electrochemical potentials that are relevant to that particular system.

For example, suppose that the reaction indicated in Eq. 1 takes place between ionic isotopes in solution as a result of an electron being transferred between species $A$ and $B$,then the electrochemical potential may be expressed as:

$$\mu_\gamma = \mu_\gamma^0(T, P) + RT \ln(a_\gamma) \tag{7}$$

where $a_\gamma$ is the activity of species $\gamma$. If $\alpha_\gamma$ is the activity coefficient of this component, then:

$$a_\gamma = \alpha_\gamma[\gamma]. \tag{8}$$

For the isotopes of an ion, the activity coefficients are equal and after introducing the equilibrium constant, $K_e$, Eqs. 2, 7, and 8 lead to the following expression for the rate (Ward, 1983):

$$j = K_x\left(\frac{K_e[A][B]}{[C][D]} - \frac{[C][D]}{K_e[A][B]}\right). \tag{9}$$

The expression for the rate given in Eq. 9 is based on the concept of transition probabilities as defined in quantum mechanics. As such, it is perhaps difficult to grasp physically. To elucidate the basis for the rate expression more clearly, we show that it can be obtained from a more physical point of view.

If the activity coefficients for the reaction given by Eq. 1 may be approximated as unity, then the equilibrium constant for the reaction, $K_e$, may be written as:

$$K_e = \frac{[C]_e[D]_e}{[A]_e[B]_e} \tag{10}$$

where $[X]_e$ is the equilibrium concentration of $X$. This expression for the equilibrium constant may be interpreted as saying that when the ratio of product concentration to reactant concentration reaches the value $K_e$, the reaction proceeds in the forward and reverse directions at the same rate. Under equilibrium conditions then, the ratio $[C]_e[D]_e/K_e[A]_e[B]_e$ would be unity and if $K_x$ is the equilibrium exchange

rate, then

$$K_x \frac{[C]_e[D]_e}{K_e[A]_e[B]_e} \tag{11}$$

would also be the equilibrium exchange rate. The equilibrium exchange rate is a constant, and its value can be predicted in terms of the properties that are constrained to be constant. If at any instant the value of the ratio $[C][D]/K_e[A][B]$ is greater than unity, then there is an excess of products compared to reactants, and the net reaction proceeds in the reverse direction. The larger this ratio is compared to unity, the further the system is displaced from equilibrium in the direction away from the reactants and therefore, the larger should be the magnitude of the "force" driving the system toward equilibrium, i.e., toward the reactants. Thus one might reasonably take the reverse rate of the reaction to be given by:

$$j_{rev} = K_x \frac{[C][D]}{K_e[A][B]}. \tag{12}$$

If one now considers the circumstance in which there is an overabundance of reactants compared to products, the ratio $K_e[A][B]/[C][D]$ will be greater than unity, the system will be displaced from equilibrium in the direction of the reactants and the force restoring the system to equilibrium would be the latter ratio. Thus the rate at which the system proceeds in the forward direction could be reasonably assumed to be

$$j_{for} = K_x \frac{K_e[A][B]}{[C][D]}, \tag{13}$$

and the net rate of the reaction is:

$$j = K_x\left(\frac{K_e[A][B]}{[C][D]} - \frac{[C][D]}{K_e[A][B]}\right).$$

The latter expression is the same as that obtained from the SRT approach, i.e., Eq. 9.

We note that the experimental support for Eq. 9 is described previously by Ward (1983). The equation has been used to examine three different electron transfer reactions. The predictions were found to agree well with the measurements, and the theory provided an explanation for certain observations that had been attributed to experimental difficulties.

## Application of SRT to ion permeation

Consider the channel and bulk media to be aqueous phases with different properties: one phase for the intracellular medium, one for the channel medium, and one for the extracellular medium. Define the electrochemical potentials of ionic species $X$ in our system as (Everett, 1971):

$$\mu_X^{Ci} = \mu_X^0(T, P) + RT \ln a_X^{Ci} + z_X F\phi^{Ci} \tag{14}$$

$$\mu_X^{Ce} = \mu_X^0(T, P) + RT \ln a_X^{Ce} + z_X F\phi^{Ce} \tag{15}$$

$$\mu_X^{i} = \mu_X^{0,i}(T, P) + RT \ln a_X^{i} + z_X F\phi^{i} \tag{16}$$

$$\mu_X^{e} = \mu_X^{0,e}(T, P) + RT \ln a_X^{e} + z_X F\phi^{e} \tag{17}$$

where $\mu_X^{Ci}$, $\mu_X^{Ce}$, $\mu_X^{i}$, and $\mu_X^{e}$ are the electrochemical potentials of species $X$ on the intracellular side in the channel medium, on the extracellular side in the channel medium, in the intracellular bulk medium, and in the extracellular bulk medium, respectively; $\mu_X^0$, $\mu_X^{0,i}$, and $\mu_X^{0,e}$ are the reference electrochemical potentials of species $X$ in the channel medium, in the intracellular bulk medium, and in the extracellular bulk medium, respectively, which are dependent on temperature ($T$) and pressure ($P$); $a$ is the activity, $\phi$ is the electrical potential, and the superscripts refer to the intracellular side in the channel ($Ci$), the extracellular side in the channel ($Ce$), the intracellular bulk medium ($i$), or the extracellular bulk medium ($e$); $z$ is the valency, $R$ is the gas constant, and $F$ is Faraday's constant.

We obtain the partition coefficient by considering the situation when equilibrium exists between the phases. Define the quantity $\theta_X$ as follows:

$$\theta_X = \frac{z_X F}{RT} \tag{18}$$

where $X$ refers to the particular ionic species. Thermodynamic equilibrium exists in the system when:

$$\mu_X^{i} = \mu_X^{Ci} = \mu_X^{Ce} = \mu_X^{e}. \tag{19}$$

Using Eqs. 14–17, this implies that:

$$\frac{[C_X]_{i,\,equil}\exp(\theta_X\phi_{equil}^{Ci})}{[X]_{i,\,equil}\exp(\theta_X\phi_{equil}^{i})} = \frac{\alpha_X^{i}}{\alpha_X}\exp\left(\frac{\mu_X^{0,i} - \mu_X^0}{RT}\right) \tag{20}$$

and

$$\frac{[C_X]_{e,\,equil}\exp(\theta_X\phi_{equil}^{Ce})}{[X]_{e,\,equil}\exp(\theta_X\phi_{equil}^{e})} = \frac{\alpha_X^{e}}{\alpha_X}\exp\left(\frac{\mu_X^{0,e} - \mu_X^0}{RT}\right) \tag{21}$$

where $\alpha_X^{i}$, $\alpha_X$, $\alpha_X^{Ce}$ are the activity coefficients of species $X$ in the intracellular medium, in the channel medium, and in the extracellular medium, respectively, and the activity coefficients are related to the solubility of species $X$ in the particular medium (Prigogine and Defay, 1969); $[C_X]_{i,\,equil}$, $[X]_{i,\,equil}$, $[C_X]_{e,\,equil}$, $[X]_{e,\,equil}$ are the equilibrium concentrations in the channel on the intracellular side, in the intracellular medium, in the channel on the extracellular side and in the extracellular medium, respectively. Also, the activity coefficient relates the activity and concentration by $a_X = \alpha_X[X]$, as indicated in the previous section. Define the partition coefficient of species $X$, $\beta_X$, as:

$$\beta_X^{i} = \frac{[C_X]_{i,\,equil}\exp(\theta_X\phi_{equil}^{Ci})}{[X]_{i,\,equil}\exp(\theta_X\phi_{equil}^{i})} \tag{22}$$

on the intracellular side, and

$$\beta_X^{e} = \frac{[C_X]_{e,\,equil}\exp(\theta_X\phi_{equil}^{Ce})}{[X]_{e,\,equil}\exp(\theta_X\phi_{equil}^{e})} \tag{23}$$

on the extracellular side. Therefore, the partition coefficients are:

$$\beta_X^{\mathrm{i}} = \frac{\alpha_X^{\mathrm{i}}}{\alpha_X} \exp\left(\frac{\mu_X^{0,\mathrm{i}} - \mu_X^0}{RT}\right) \tag{24}$$

and

$$\beta_X^{\mathrm{e}} = \frac{\alpha_X^{\mathrm{e}}}{\alpha_X} \exp\left(\frac{\mu_X^{0,\mathrm{e}} - \mu_X^0}{RT}\right). \tag{25}$$

It is important to note that the partition coefficient is dependent on the solubility, since the activity coefficient is related to the solubility. Also note that since we have assumed that there is a single phase within the channel, the partition coefficient within the channel is unity.

Now, using Eq. 4 from SRT, the rate of transport of ionic species $X$ across a unit area from phase 1 to phase 2 is given by:

$$j_{1,2} = K_{1,2}(\delta_{1,2} - \delta_{1,2}^{-1}) \tag{26}$$

where $K_{1,2}$ is the equilibrium exchange rate across a unit area of the interface, and

$$\delta_{1,2} = \exp\left(\frac{\mu_X^1 - \mu_X^2}{RT}\right). \tag{27}$$

Applying this to our system, we obtain three fluxes; from the intracellular medium to the channel, $j_{\mathrm{i,Ci}}$, across the channel, $j_{\mathrm{Ci,Ce}}$, and from the channel to the extracellular medium, $j_{\mathrm{Ce,e}}$. These fluxes are:

$$j_{\mathrm{i,Ci}} = K_{\mathrm{i,Ci}}\left[-\frac{u(\mathrm{Ci})}{u(\mathrm{i})\beta_X^{\mathrm{i}}} + \frac{u(\mathrm{i})\beta_X^{\mathrm{i}}}{u(\mathrm{Ci})}\right] \tag{28}$$

$$j_{\mathrm{Ci,Ce}} = K_{\mathrm{Ci,Ce}}\left[\frac{u(\mathrm{Ci})}{u(\mathrm{Ce})} - \frac{u(\mathrm{Ce})}{u(\mathrm{Ci})}\right] \tag{29}$$

$$j_{\mathrm{Ce,e}} = K_{\mathrm{Ce,e}}\left[\frac{u(\mathrm{Ce})}{u(\mathrm{e})\beta_X^{\mathrm{e}}} - \frac{u(\mathrm{e})\beta_X^{\mathrm{e}}}{u(\mathrm{Ce})}\right] \tag{30}$$

where

$$u(\mathrm{Ci}) = [C_X]_{\mathrm{i}}\exp(\theta_X\phi^{\mathrm{Ci}}) \tag{31}$$

$$u(\mathrm{Ce}) = [C_X]_{\mathrm{e}}\exp(\theta_X\phi^{\mathrm{Ce}}) \tag{32}$$

$$u(\mathrm{i}) = [X]_{\mathrm{i}}\exp(\theta_X\phi^{\mathrm{i}}) \tag{33}$$

$$u(\mathrm{e}) = [X]_{\mathrm{e}}\exp(\theta_X\phi^{\mathrm{e}}). \tag{34}$$

If we assume steady-state conditions, the fluxes across the channel are equal:

$$j_{\mathrm{i,Ci}} = j_{\mathrm{Ci,Ce}} = j_{\mathrm{Ce,e}}. \tag{35}$$

Therefore the current density, which we define as $J_{\mathrm{SRT}}$, is given by:

$$J_{\mathrm{SRT}} = z_X F j_{\mathrm{i,Ci}} = z_X F j_{\mathrm{Ci,Ce}} = z_X F j_{\mathrm{Ce,e}}. \tag{36}$$

In the special case where equilibrium exists at the interfaces, i.e., the rates at the interfaces are infinite, we have:

$$u(\mathrm{Ci}) = \beta_X^{\mathrm{i}} u(\mathrm{i}) \tag{37}$$

and

$$u(\mathrm{Ce}) = \beta_X^{\mathrm{e}} u(\mathrm{e}), \tag{38}$$

which then gives the flux across the channel from Eq. 29 as:

$$j_{\mathrm{Ci,Ce}} = K_{\mathrm{Ci,Ce}}\left\{\frac{u(\mathrm{i})\,\beta_X^{\mathrm{i}}}{u(\mathrm{e})\beta_X^{\mathrm{e}}} - \frac{u(\mathrm{e})\beta_X^{\mathrm{e}}}{u(\mathrm{i})\beta_X^{\mathrm{i}}}\right\}. \tag{39}$$

Noting that $\phi^{\mathrm{i}} - \phi^{\mathrm{e}} = V$, where $V$ is the transmembrane voltage, we can rewrite the flux as:

$$j_{\mathrm{Ci,Ce}} = K_{\mathrm{Ci,Ce}}\left\{\frac{\beta_X^{\mathrm{i}}[X]_{\mathrm{i}}}{\beta_X^{\mathrm{e}}[X]_{\mathrm{e}}}\exp(\theta_X V) - \frac{\beta_X^{\mathrm{e}}[X]_{\mathrm{e}}}{\beta_X^{\mathrm{i}}[X]_{\mathrm{i}}}\exp(-\theta_X V)\right\}, \tag{40}$$

and the current density is:

$$J_{\mathrm{SRT}} = z_X F K_{\mathrm{Ci,Ce}}\left\{\frac{\beta_X^{\mathrm{i}}[X]_{\mathrm{i}}}{\beta_X^{\mathrm{e}}[X]_{\mathrm{e}}}\exp(\theta_X V) - \frac{\beta_X^{\mathrm{e}}[X]_{\mathrm{e}}}{\beta_X^{\mathrm{i}}[X]_{\mathrm{i}}}\exp(-\theta_X V)\right\}. \tag{41}$$

For ions in solution, flux must be considered in the context of activity and potential differences. Zero flux occurs when there is no potential gradient and no *activity* difference. Consider Eq. 40 above which gives the flux when equilibrium exists at the channel interfaces. It involves concentrations, voltages (potential differences), and partition coefficients. Note that when the electrochemical potential for $X$ on one side is equal to the electrochemical potential on the other side, the flux is zero. In this case, there is equilibrium since the electrochemical potentials are equal. We have $\mu_X^i = \mu_X^e$, which gives (using Eqs. 16 and 17):

$$\frac{a_X^{\mathrm{i}}}{a_X^{\mathrm{e}}}\exp\left(\frac{\mu_X^{0,\mathrm{i}} - \mu_X^{0,\mathrm{e}}}{RT}\right)\exp(\theta_X(\phi^{\mathrm{i}} - \phi^{\mathrm{e}})) = 1. \tag{42}$$

From Eqs. 24 and 25, we have:

$$\frac{\beta_X^{\mathrm{i}}}{\beta_X^{\mathrm{e}}} = \frac{\alpha_X^{\mathrm{i}}}{\alpha_X^{\mathrm{e}}}\exp\left(\frac{\mu_X^{0,\mathrm{i}} - \mu_X^{0,\mathrm{e}}}{RT}\right), \tag{43}$$

which in Eq. 42 above, implies that:

$$\frac{\beta_X^{\mathrm{i}}[X]_{\mathrm{i}}}{\beta_X^{\mathrm{e}}[X]_{\mathrm{e}}}\exp(\theta_X V) = 1. \tag{44}$$

Plugging Eq. 44 back into Eq. 40, we get zero flux. Therefore, if the electrochemical potentials are equal, then the flux is zero. If the activities and potentials are equal on both sides, then the flux is also zero. In this case we have:

$$\mu_X^{\mathrm{i}} - \mu_X^{\mathrm{e}} = \left(\frac{\mu_X^{0,\mathrm{i}} - \mu_X^{0,\mathrm{e}}}{RT}\right) + \ln\left(\frac{a_X^{\mathrm{i}}}{a_X^{\mathrm{e}}}\right) + \theta_X(\phi^{\mathrm{i}} - \phi^{\mathrm{e}}). \tag{45}$$

If the activities and potentials are the same on both sides (and the temperature and pressure are also the same), then we must also have $\mu_X^{0,i} = \mu_X^{0,e}$ since they are reference electrochemical potentials which only depend on temperature and pressure. This would imply that the electrochemical potentials are equal, and as shown above, if the electrochemical potentials are equal, the flux is zero.

The new expressions for the current density, our SRT equations for ion permeation, Eq. 36, do not assume either that equilibrium exists at the channel interfaces or that there is a constant field across the channel. Since the basis of this derivation does not rely on a continuum theory, but on statistical mechanics, the steady-state assumption of Eq. 36 does not imply that there is a constant field across the membrane. However it does imply that there is no mass storage in the channel.

## Solution of equations

The current density, $J_{SRT}$, is obtained by numerically solving Eqs. 36 using the Newton-Raphson method. Taking the reference electrical potential as that of the extracellular medium, i.e., $\phi^e = 0$, the equations to be solved are:

$$K_{Ci,\,Ce}\left(\frac{u(Ci)}{u(Ce)} - \frac{u(Ce)}{u(Ci)}\right) = K_{i,\,Ci}\left(-\frac{u(Ci)}{\beta_X^i[X]_i\exp(\theta_X V)} + \frac{\beta_X^i[X]_i\exp(\theta_X V)}{u(Ci)}\right) \quad (46)$$

$$K_{Ci,\,Ce}\left(\frac{u(Ci)}{u(Ce)} - \frac{u(Ce)}{u(Ci)}\right) = K_{Ce,\,e}\left(\frac{u(Ce)}{\beta_X^e[X]_e} - \frac{\beta_X^e[X]_e}{u(Ce)}\right) \quad (47)$$

where $\phi^i - \phi^e = V$, and the two independent variables are $u(Ci)$ and $u(Ce)$. By making the above equations dimensionless, we find that the solution depends on three parameters: the ratio of the equilibrium exchange rates,

$$\frac{K_{i,\,Ci}}{K_{Ci,\,Ce}}, \qquad \frac{K_{Ce,\,e}}{K_{Ci,\,Ce}},$$

and a quantity given by

$$\frac{\beta_X^e[X]_e}{\beta_X^i[X]_i\exp(\theta_X V)}.$$

In the next section we examine the special case where the equilibrium exchange rates at the intracellular and extracellular interfaces are the same. However, we do consider a particular case where the equilibrium exchange rates at the intracellular and extracellular interfaces are different. Define the equilibrium exchange rates as:

$$K_{if} = K_{i,\,Ci} = K_{Ce,\,e} \quad (48)$$

$$K_{ch} = K_{Ci,\,Ce}. \quad (49)$$

Therefore, the current density depends on voltage and on the two parameters given by:

$$\text{Parameter 1} = \frac{K_{if}}{K_{ch}} \quad (50)$$

$$\text{Parameter 2} = \frac{\beta_X^e[X]_e}{\beta_X^i[X]_i}. \quad (51)$$

The solution can be obtained analytically for two particular cases. The first case occurs if equilibrium exists at the interfaces. Then $J_{SRT}$ reduces to the single equation given by Eq. 41. The second special case occurs if the equilibrium exchange rates are the same for the three fluxes in Eqs. 28–30, i.e., $K_{Ci,\,Ce} = K_{i,\,Ci} = K_{Ce,\,e} = K_{if} = K_{ch}$. The analytical solution for this case is given by:

$$J_{SRT} = z_X F K_{ch}\left[\left(\frac{\beta_X^i[X]_i\exp(\theta_X V)}{\beta_X^e[X]_e}\right)^{1/3} - \left(\frac{\beta_X^e[X]_e}{\beta_X^i[X]_i\exp(\theta_X V)}\right)^{1/3}\right]. \quad (52)$$

# RESULTS

## Current-voltage relationships

We now demonstrate the current-voltage relationships produced by our SRT equations. The current-voltage relationships are illustrated by varying the two parameters given in Eqs. 50 and 51.

In the first two figures, we vary the equilibrium exchange rate at the interfaces, for a fixed ratio of extracellular to intracellular partition coefficients and concentrations, i.e., Parameter 2 = constant. The plots in Fig. 1 show the current-voltage relationships for four cases. In each case, the equilibrium exchange rate in the channel, $K_{ch}$, is kept constant at $1.036 \times 10^{-5}$ pmol/s, and the ratio of extracellular to intracellular partition coefficients and concentrations, Parameter 2, is kept constant at 1. The four plots correspond to values of the equilibrium exchange rate at the interfaces of $\infty$, $2K_{ch}$, $K_{ch}$, and $0.5\,K_{ch}$, or to Parameter 1 values of $\infty$, 2, 1, and 0.5. It is interesting to note that nonlinear current-voltage plots can be obtained even when the intracellular and extracellular concentrations are the same, assuming that the intracellular and extracellular partition coefficients are also the same. Also, as the ratio of the equilibrium exchange rate at the interfaces to the equilibrium exchange rate in the channel increases, the slope, or the conductance increases. The largest conductance occurs when equilibrium exists at the channel interfaces, i.e., $K_{if} = \infty$. This is shown in the next figure.

In Fig. 2 the conductance is plotted as a function of voltage, using the same conditions as in Fig. 1. This figure shows, in addition to an increase in conductance, there is an increase in the degree of nonlinearity with an increase in the equilibrium exchange rate at the interfaces. For example, if equilibrium exists at the channel interfaces ($K_{if} = \infty$), Parameter 1 = $\infty$, then the conductance changes from 74.8 pS at 0 mV to 80.1 pS at 10 mV, whereas if the equilibrium exchange rate

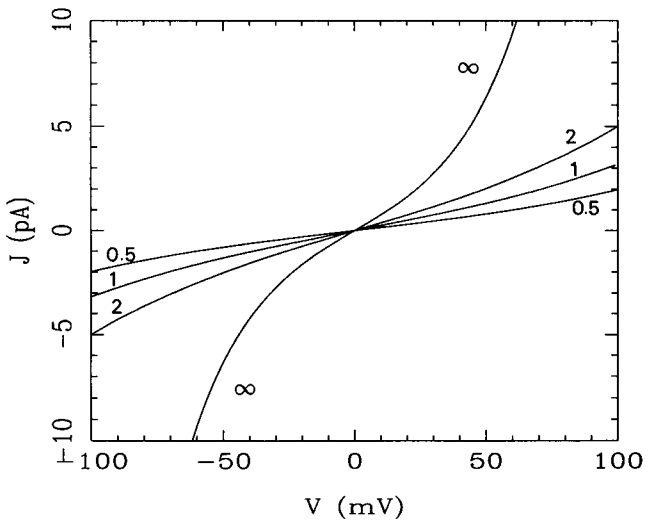


FIGURE 1 Current-voltage relationships for four $K_{if}$ values, using our SRT equations. The $K_{if}$ values shown are $0.5K_{ch}$, $K_{ch}$, $2K_{ch}$, and $\infty$, where $K_{ch} = 1.036 \times 10^{-5}$ pmol/s, and the ratio of extracellular to intracellular partition coefficients is 1. Note that the curves are nonlinear even though the intracellular and extracellular concentrations are the same, and that the slope increases with increasing $K_{if}$ values.

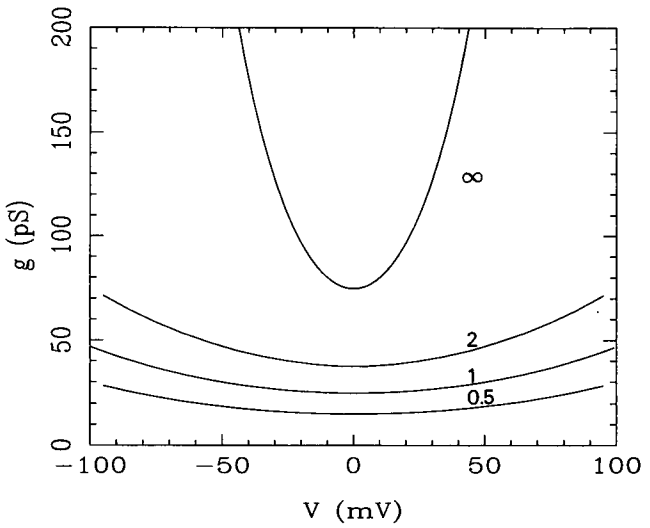


FIGURE 2 Conductance ($g$) versus voltage plots using the same conditions as in Fig. 1. Note that the conductance and the degree of nonlinearity increases as $K_{if}$ increases.

at the interfaces is $1.036 \times 10^{-5}$ pmol/s ($<\infty$), Parameter 1 = 1, then the conductance changes from 24.9 pS at 0 mV to 25.1 pS at 10 mV. Fig. 2 also shows that for certain ranges of voltages, the current-voltage plot is linear. Specifically, in regions around the reversal potential of 0 mV, the conductance remains approximately constant. This region of constant conductance is extended as the equilibrium exchange rate at the interfaces decreases. The above results illustrate that the conductance and the degree of nonlinearity are strongly influenced by the equilibrium exchange rate at the channel interfaces.

If the equilibrium exchange rates at the intracellular and extracellular interfaces are different (not shown), the conductance obtained would be between the conductance values obtained if the equilibrium exchange rates at the interfaces were the same at the two different values. For example, if the equilibrium exchange rate at the intracellular interface is half of the equilibrium exchange rate in the channel, and the equilibrium exchange rate at the extracellular interfaces is twice the equilibrium exchange rate in the channel, then the conductance for this system would be between the conductance value obtained if the equilibrium exchange rate at both interfaces was half the equilibrium exchange rate in the channel, and the conductance value obtained if the equilibrium exchange rate at both interfaces was twice the equilibrium exchange rate in the channel. The same observation holds for a consideration of the degree of nonlinearity.

Fig. 3 shows the current-voltage relationships for five cases in which the ratio of extracellular to intracellular partition coefficients and concentrations, Parameter 2, is varied. Parameter 1, the ratio of the equilibrium exchange rate at the interfaces to the equilibrium exchange rate in the channel, is maintained at a constant value of unity. The equilibrium exchange rate in the channel and at the interfaces is $1.036 \times 10^{-5}$ pmol/s. The five cases correspond to the ratio of extracellular to intracellular concentrations and partition coefficient values of 0.1, 0.5, 1, 5, and 10. The reversal potentials for these cases are −61.5, −18.5, 0, 43.0, and 61.5 mV, respectively. As this ratio increases, the slope or the conductance decreases for positive, outward (for positive ions) currents since there is a decreasing outward concentration gradient. This trend is reversed for negative,

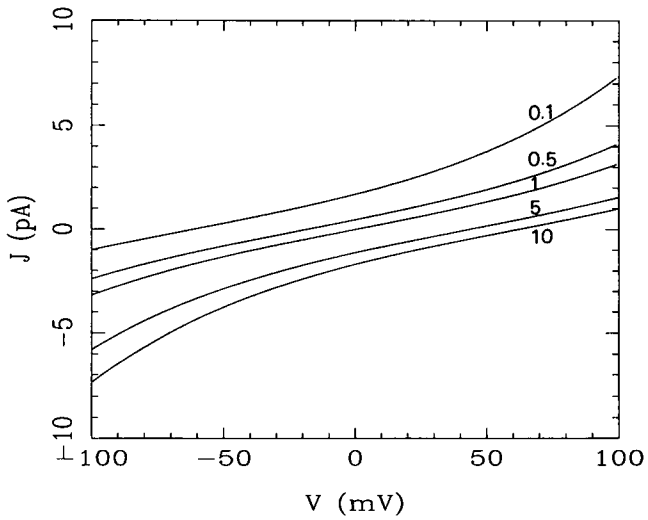


FIGURE 3 Current-voltage relationships for five values of the ratio of extracellular to intracellular partition coefficients and concentrations, using our SRT equations. The ratio values shown are 0.1, 0.5, 1, 5, and 10, and the reversal potentials are −61.5, −18.5, 0, 43.0, and 61.5 mV, respectively. The equilibrium exchange rates in the channel and at the interfaces are equal at $1.036 \times 10^{-5}$ pmol/s. For positive currents, the slope decreases with increasing ratio values, and, for negative currents, the slope increases with increasing ratio values.

inward (for positive ions) currents since there is an increasing inward concentration gradient, i.e., the conductance increases as the ratio of extracellular to intracellular concentrations and partition coefficients increases. It is interesting to note that if the ratio of extracellular to intracellular concentrations and partition coefficients is nonunity, then there is a net current when the voltage is zero. This implies that if two solutions have the same concentrations and there is no voltage difference between them, but they have different solubilities, then there will be a chemical potential difference between the two solutions brought about by their solubility difference, i.e., the solutions are not identical. The solubility is related to the activity coefficient, a parameter in the electrochemical potential. However, if the *activity* gradient between the two solutions is zero, then there is no net current at zero voltage. This is the case for a unity ratio of extracellular to intracellular concentrations and partition coefficients.

From the current-voltage plots in Fig. 3, the conductance versus voltage plots in Fig. 4 are produced. This figure shows that the conductance does decrease as the ratio of extracellular to intracellular concentrations and partition coefficients increases for outward currents. Note that the five cases can be compared only for voltages >61.5 mV since the currents are all outward for voltages >61.5 mV. Similarly, the figure shows that the conductance does increase as the ratio of extracellular to intracellular concentrations and partition coefficients increases for inward currents. This time, the five cases can be compared only for voltages <−61.5 mV.

We can analytically compute the conductance for the two particular cases in which an analytical solution is available. The first case is if equilibrium exists at the channel interfaces.

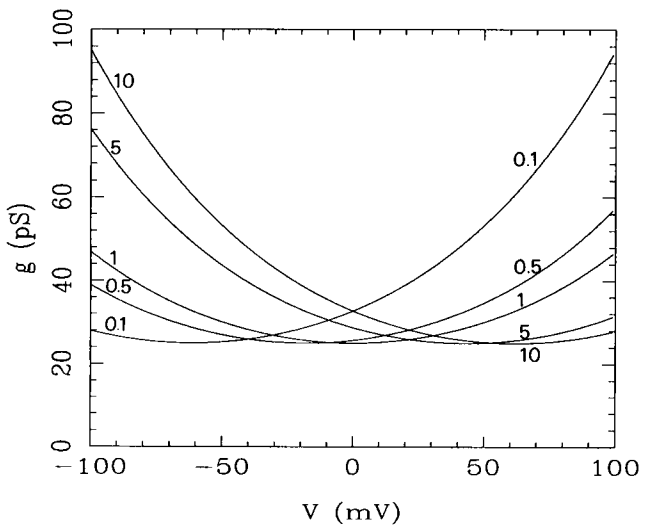


FIGURE 4 Conductance ($g$) versus voltage plots using the same conditions as in Fig. 3. Note that the conductance decreases as the ratio of extracellular to intracellular partition coefficients and concentrations increases for positive currents ($V > 61.5$ mV), and that the conductance increases as this ratio increases for negative currents ($V < -61.5$ mV).

The conductance is given by:

$$\frac{dJ_{SRT}}{dV} = z_X F K_{ch} \theta_X \left\{ \frac{\beta_X^i [X]_i}{\beta_X^e [X]_e} \exp(\theta_X V) + \frac{\beta_X^e [X]_e}{\beta_X^i [X]_i} \exp(-\theta_X V) \right\}. \quad (53)$$

Therefore, at zero voltage, if equilibrium exists at the interfaces and the intracellular and extracellular concentrations and partition coefficients are the same, the conductance is:

$$2 \frac{z_X^2 F^2}{RT} K_{ch}. \quad (54)$$

The second case is if the equilibrium exchange rates in the channel and at the interfaces are the same, i.e., $K_{if} = K_{ch}$. The conductance is given by:

$$\frac{dJ_{SRT}}{dV} = \frac{z_X F K_{ch} \theta_X}{3} \left\{ \left( \frac{\beta_X^i [X]_i}{\beta_X^e [X]_e} \exp(\theta_X V) \right)^{1/3} + \left( \frac{\beta_X^e [X]_e}{\beta_X^i [X]_i} \exp(-\theta_X V) \right)^{1/3} \right\}. \quad (55)$$

Therefore, at zero voltage, if the equilibrium exchange rates are equal, and the intracellular and extracellular concentrations and partition coefficients are the same, the conductance is:

$$\frac{2}{3} \frac{z_X^2 F^2}{RT} K_{ch}. \quad (56)$$

As expected, this conductance is less than the conductance in Eq. 54, where the equilibrium exchange rate at the interfaces is infinite. In this way, we have obtained a relationship between conductance and the equilibrium exchange rate in the channel.

Current-voltage relationships obtained from single channel current data are often linear (Florio et al., 1990; Inoue et al., 1987; Marty and Neher, 1985; Rorsman and Trube, 1986; Singer and Walsh, 1987), but it is not unusual for nonlinearity to be observed (Ascher and Nowak, 1988; Rorsman and Trube, 1986; Sullivan, 1987; Wonderlin and French, 1991). Linear current-voltage curves for a given voltage range do not necessarily imply that nonlinearity is not present outside the observed voltage range. More likely, as pointed out by some authors (e.g., Florio et al., 1990), the linear relationship is only valid for a given range of voltages.

The occurrence of nonlinear current-voltage relationships in the literature suggests that the general use of the equation, $I = g(V - V_{rev})$, to describe single channel current-voltage behavior is inadequate. The current-voltage relationships produced by our SRT equations are nonlinear. However, as discussed above, for certain ranges of voltages the current-voltage curves are approximately linear. Thus, linear current-voltage relations obtained experimentally do not conflict with the results from our SRT equations.

The possible current-voltage relationships using the Goldman-Hodgkin-Katz (GHK) current equation are considered below. The GHK current equation is given by (Goldman, 1943; Hille, 1992, p. 341):

$$J_{GHK} = P_X z_X F \theta_X V \left( \frac{[X]_e - [X]_i \exp(\theta_X V)}{1 - \exp(\theta_X V)} \right) \quad (57)$$

where $P_X$ is the permeability of species $X$, and the other parameters have been defined earlier. One of the assumptions in the derivation of the GHK current equation is that the partition coefficients on the intracellular and extracellular interfaces are the same (Hille, 1992, p. 345). This assumption allows one to define the permeability as:

$$P = \frac{D\beta}{l} \quad (58)$$

where $D$ is the diffusion coefficient, $\beta$ is the partition coefficient, and $l$ is the membrane thickness. Nonlinear current-voltage relationships in the GHK current equation can only occur if there are different concentrations in the intracellular and extracellular media, as demonstrated in Hille (1992, p. 343). For equal concentrations, Eq. 57 reduces to:

$$J_{GHK} = P_X z_X F \theta_X V [X], \quad (59)$$

a linear current-voltage relationship. This is in stark contrast to our SRT equations which can produce nonlinearity even when the intracellular and extracellular concentrations are the same (see Fig. 1).

The GHK current equation can be derived from the Nernst-Planck equation for fluxes in the membrane using the appropriate assumptions (Hille, 1992, p. 345). In the Appendix, we show how the Nernst-Planck equation can be derived as a special case of our SRT equations. In doing this, we obtain a relation between the diffusion coefficient and the equilibrium exchange rate in the channel:

$$D_X = \frac{2K_{ch} l}{[X]}. \quad (60)$$

The GHK current equation does not exhibit nonlinearity in equal intracellular and extracellular concentrations. Since nonlinearity in symmetric solutions does occur for single channel data (e.g., Wonderlin and French (1991)), the GHK current equation cannot be considered to be adequate in describing current-voltage relationships. A strong example of this is the inward rectifying potassium channel (Hille, 1992, p. 129; Sullivan, 1987). This channel shows strong inward rectification in symmetric solutions (Sullivan, 1987), i.e., it is highly nonlinear. The GHK current equation does not and cannot explain the large nonlinearity observed. In contrast, our equations can describe this nonlinearity by assuming that the equilibrium exchange rate at the interfaces is larger than the equilibrium exchange rate in the channel. Therefore, we would predict that, at equilibrium, the rate of exchange of potassium ions is larger across the channel interfaces than across the channel itself for inward rectifying potassium channels.

## Unidirectional flux ratios

An important difference between the GHK current equation and our equations is in the unidirectional fluxes and their ratio. Comparing the GHK current equation, Eq. 57, and our equations, for example when equilibrium exists at the channel interfaces (Eq. 41), it is clear that the unidirectional fluxes depend on absolute concentrations in the GHK current equation, whereas the unidirectional fluxes depend on concentration ratios in our equation. In addition, if we consider the ratio of unidirectional fluxes, we obtain the following: For the GHK current equation, the ratio of unidirectional fluxes is given by the Ussing flux ratio expression:

$$\frac{\text{Efflux}}{\text{Influx}} = \frac{[X]_i}{[X]_e} \exp(\theta_X V). \quad (61)$$

With our approach, the ratio of unidirectional fluxes if equilibrium exists at the interfaces is (using Eq. 41):

$$\frac{\text{Efflux}}{\text{Influx}} = \left\{ \frac{[X]_i}{[X]_e} \exp(\theta_X V) \right\}^2, \quad (62)$$

assuming that the intracellular and extracellular partition coefficients are the same. If equilibrium does not exist at the interfaces, but the equilibrium exchange rates at the interfaces and in the channel are the same, then the ratio of unidirectional fluxes is (using Eq. 52):

$$\frac{\text{Efflux}}{\text{Influx}} = \left\{ \frac{[X]_i}{[X]_e} \exp(\theta_X V) \right\}^{2/3} \quad (63)$$

where the intracellular and extracellular partition coefficients have been assumed to be the same. In our case, it is clear that the exponent of the expression $([X]_i/[X]_e)\exp(\theta_X V)$ depends on the relative equilibrium exchange rates at the interfaces and in the channel.

The Ussing flux ratio criterion states that with passive diffusion and no flux coupling, the exponent of the expression should be 1. Deviations from an exponent of 1 were taken to imply flux coupling, and multi-ion pore models were developed to describe such deviations (e.g., Levitt (1982, 1987); also see Hille (1992), Chap. 14). Here we have shown that a nonunity exponent arises naturally with varying equilibrium exchange rates in the channel and at the interfaces, and without the assumption of flux coupling. Using our SRT equations, a nonunity exponent does not necessarily imply flux coupling. Instead, a nonunity exponent may imply that inherent assumptions in the underlying model are invalid. These assumptions may include equilibrium in the channel and at the channel interfaces or a constant field across the membrane. For example, it is interesting to note that in the best studied model pore, gramicidin A, the highest exponent so far reported is 1.99 (see Hille (1992), Chap. 11). Our SRT equations would suggest that for this case, equilibrium exists

at the channel interfaces (see Eq. 62), and flux coupling is *not* required to obtain this result.

## Unequal partition coefficients

The consideration of partition coefficients is critical in the determination of reversal potentials. The voltage at which the current reverses occurs when the current is zero. Using Eq. 41 or 52, this gives:

$$V_{X,\text{rev}} = \frac{1}{\theta_X} \ln\left(\frac{\beta_X^e [X]_e}{\beta_X^i [X]_i}\right). \tag{64}$$

If the intracellular and extracellular partition coefficients are equal, this reduces to the well-known Nernst potential (see for example, Hille (1992, p. 13)):

$$V_{X,\text{Nernst}} = \frac{1}{\theta_X} \ln\left(\frac{[X]_e}{[X]_i}\right). \tag{65}$$

Therefore, the dependence of the reversal potential on the partition coefficients is given by:

$$V_{X,\text{rev}} = \frac{1}{\theta_X} \ln\left(\frac{\beta_X^e}{\beta_X^i}\right) + V_{X,\text{Nernst}}. \tag{66}$$

From this expression we see that the reversal potential is much more sensitive for $\beta_X^e/\beta_X^i < 1$ than for $\beta_X^e/\beta_X^i > 1$. Thus, errors between measured reversal potentials and Nernst potentials are more pronounced as the intracellular partition coefficient exceeds the extracellular partition coefficient rather than if the extracellular partition coefficient exceeds the intracellular partition coefficient.

The partition coefficient is a function of the activity coefficient (solubility), temperature, and pressure. Since we are dealing with the extracellular and intracellular media which differ in composition, it is possible and even highly likely for the partition coefficients to be different. The solubility of a solute in a given solvent changes as the solvent itself changes for example by the addition of drugs or other ions. For example, consider that the solubility of potassium chloride in water is 26.34 wt% (25°C) and 0.03 wt% (25°C) in ethanol (Stephen and Stephen, 1963).

In the experimental literature, there are many examples of measured reversal potentials being different from their Nernst potentials (Brown et al., 1981; Droogmans and Callewaert, 1986; Florio et al., 1990; Inoue et al., 1987; Schwartz and Kado, 1977; Sims et al. 1988; Vivaudou et al., 1988). There are several reasons for this discrepancy. For example, the channel may have imperfect selectivity or the intracellular and/or extracellular concentrations may not be accurately determined. In addition, we suggest that the discrepancy could result from the the assumption of equal partition coefficients at the intracellular and extracellular interfaces.

Landowne and Scruggs (1981) measured the relationship between the magnitude of the sodium current, membrane potential, and sodium concentrations on both sides of the membrane. Their findings required that the partition coefficients for the two aqueous/membrane interfaces were different by a factor of three. Colatsky (1980) obtained a 10-fold increase in permeability with about an 8-fold decrease in extracellular sodium concentration. Since permeability is a function of the partition coefficient (see Eq. 58), this observation could be due to changes in the partition coefficient. It is important to realize that once permeability is being considered for selective channels, an assumption of equal partition coefficients has already been made. Since Colatsky's calculations assumed equal partition coefficients and equilibrium at the interfaces and intracellular concentration are not given, a direct calculation cannot be done. In an attempt to better model their permeability data, Schwartz and Kado (1977) considered unequal partition coefficients in their studies. However, the difference between intracellular and extracellular partition coefficients was due only to surface voltages.

A detailed example of differences between the Nernst potential and the measured reversal voltage is given for the NMDA channel (Ascher, 1988). In their studies, it was found that the reversal voltage changed from 0 to 30 mV with an increase in extracellular calcium from 1 to 100 mM. This was explained with changes in the outer surface voltage at the mouth of the NMDA channel. They modified the GHK equation to account for internal and external surface voltages. For an extracellular calcium concentration of 100 mM, they obtained the following equation:

$$\frac{P_{Ca}}{P_{Cs}} = 0.385 \exp\left(\frac{\psi_o + 40}{25}\right) \tag{67}$$

where $\psi_o$ is the external surface voltage (in millivolts) and $P_{Ca}$ and $P_{Cs}$ are the permeabilities of calcium and cesium, respectively. They plotted the relation (Eq. 67) and obtained a value of $\psi_o = -16$ mV when $P_{Ca/PCs} = 1$, from which a value of $\psi_o = -56$ mV (40 mV more negative) was deduced when the extracellular calcium concentration was 1 mM. Eq. 67 could be rewritten as:

$$\frac{D_{Ca}\beta_{Ca}^e}{D_{Cs}\beta_{Cs}^i} = 0.385 \exp\left(\frac{\psi_o + 40}{25}\right) \tag{68}$$

where $D_{Ca}$ and $D_{Cs}$ are the diffusion coefficients of calcium and cesium, respectively, and $\beta_{Ca}^e$,$\beta_{Cs}^i$ are the partition coefficients of calcium on the extracellular interface and cesium on the intracellular interface, respectively. Eq. 68 reduces to:

$$\frac{\beta_{Ca}^e}{\beta_{Cs}^i} = 1.004 \exp\left(\frac{\psi_o + 40}{25}\right) \tag{69}$$

using values of $D_{Cs} = 2.06 \times 10^{-5}$ cm$^2$/s and $D_{Ca} = 0.79 \times 10^{-5}$ cm$^2$/s from Hille (1992, p. 268). If there is no difference in the partition coefficient ratio, this would give an approximate $\psi_o$ value of $-40$ mV which in turn would give an approximate $\psi_o$ value of $-80$ mV in 1 mM extracellular calcium. A nonunity ratio of partition coefficients would change the external surface voltage according to Eq. 69. Using our SRT approach to ion permeation this ratio of partition

coefficients is dependent on solubilities and activity coefficients, temperature, and pressure (see Eqs. 24 and 25):

$$\frac{\beta^{e}_{Ca}}{\beta^{i}_{Cs}} = \frac{\alpha^{e}_{Ca}/\alpha_{Ca}}{\alpha^{i}_{Cs}/\alpha_{Cs}} \exp\left(\frac{(\mu^{0,e}_{Ca} - \mu^{0}_{Ca}) - (\mu^{0,i}_{Ca} - \mu^{0}_{Ca})}{RT}\right). \quad (70)$$

By assuming that $\psi_o$ in 1 mM external calcium is 40 mV more negative than $\psi_o$ in 100 mM external calcium, Ascher (1988) has assumed that the internal surface voltage does not change. If the partition coefficients are assumed not to change with different concentrations of calcium, i.e., there is no change in solubilities or activity coefficients, temperature, and pressure with concentration, then a contradiction is obtained: Either, (i) if Eq. 67 is obtained for 1 mM external calcium, $\psi_o$ would be about 90 mV more negative than $\psi_o$ in 100 mM external calcium, and $\psi_i$ would be about 50 mV more negative than $\psi_i$ in 100 mM external calcium, a contradiction in that the internal surface voltage does change, or, (ii) forcing the internal surface voltage not to change does not allow Eq. 67 and the similar equation for 1 mM external calcium to be valid. This contradiction can be resolved by allowing the partition coefficient ratio (Eq. 70) to be different for the different concentrations of external calcium. In particular, the contradiction is resolved if:

$$\left(\frac{\beta^{e}_{Ca}}{\beta^{i}_{Cs}}\right)_{100\ mM} = 0.543 + 0.1102\left(\frac{\beta^{e}_{Ca}}{\beta^{i}_{Cs}}\right)_{1\ mM}. \quad (71)$$

Using Ascher's value of $\psi_o = -16$ mV in 100 mM calcium, consistency would require that the partition coefficient ratios should be 2.62 and 18.85 in 100 and 1 mM calcium, respectively. The imperfect selectivity of the NMDA channel at 1 mM external calcium could account for some of this difference. However, Ascher and Nowak (1988) deduce that in 1 mM calcium, the channel is still 7.5 times more selective for calcium than sodium. The parameters which can account for this difference in the partition coefficient ratio are the solubilities or the activity coefficients. Therefore, there must be a change in the solubilities with changing concentrations, since the solvent is being changed. This example underlines the unacceptability of the assumption that partition coefficients are the same in different concentrations. In turn, this implies that the intracellular and extracellular partition coefficients for a given ionic species can be expected to be different if the intracellular and extracellular media are different.

## DISCUSSION

SRT has been used to develop a new way to view permeation through ionic channels. Our resulting equations do not require that equilibrium exists at the channel interfaces or in the channel. The quantum mechanical basis of the method removes the need for the specification of the potential profile. Only the potential at various locations in the system is required. Therefore, unlike a continuum theory, our steady-state assumption across the membrane does not imply that a constant field exists across the membrane. In addition, since our system involves ions in solution, any interactions are reflected in the parameters of the electrochemical potential. These parameters include the activity, electrical potential, temperature, and pressure. Even though our approach does not suffer from assumptions common in other approaches such as GHK theory, our formulation is straightforward and yields analytical solutions when the equilibrium exchange rates in the channel and at the interfaces rates are the same or when equilibrium exists at the channel interfaces.

With our approach, we have identified three equilibrium exchange rates, which can be considered in an analogous manner to Levitt's channel system (Levitt, 1986). Our rates refer to movement from bulk solutions (intracellular and extracellular) to the channel and within the channel itself. Note that these rates are equilibrium parameters. They depend on physical and chemical attributes of the system (e.g., see Ward and Elmoselhi (1986)). The nonequilibrium behavior is due to the different number of microscopic states in the different molecular distributions. Using Nernst-Planck continuum theory, Levitt (1986) separated the system into three resistances. They are resistance of the channel and diffusion-limited access resistance of the channel (intracellular and extracellular). Diffusion-limited ion flow through pores was considered by Läuger (1976) in a similar way. Here, the pore was described in terms of an intrinsic permeability and left and right convergence permeabilities. Several other authors have considered the effects of access resistance (e.g., Chiu and Jakobsson (1989); Gates et al. (1989); Peskoff and Bers (1988)). In particular, Chiu and Jakobsson (1989) found that the continuum theory was limited in that it was inadequate in describing the interaction between potential gradients and ion distributions in the bath near the channel mouth.

An important advantage of our quantum mechanical approach over electrodiffusion and reaction rate theory is that the potential, but not the potential profile is required. The specification of the potential profile is critical when using an electrodiffusion approach. The most common profile used is a constant field across the membrane (Goldman, 1943). The behavior of diffusion models for one-ion channels using a set of simple potential profiles was investigated by Gates et al. (1989). These potential profiles included constant field, a ramp potential, a step potential, a Z potential and single and double extrema potentials. In reaction rate theory, several energy barriers are often used for the potential profile to attain a fit to experimental data. Besides the issue of a unique correspondence of these barriers with features of the channel profile, the basic assumptions of reaction rate theory are not valid (Dani and Levitt, 1990; Cooper et al., 1985, 1988a, 1988b). For example, the barriers cannot be too low so that they deviate from their near equilibrium assumption. Barrier heights should be greater than about $10RT$, but there is evidence that this is not the case (Cooper et al., 1985).

In several systems, the GHK equations have been unable to describe the experimental results. This suggests that an alternate approach is required. Ascher (1988; Ascher and Nowak, 1988) found that the predictions of the GHK equations were insufficient to describe their current-voltage relation of the NMDA channel in high calcium. Schwartz and

Kado (1977) found that a potassium-selective, chemically excitable channel could not be accurately described by the GHK current equation. They resolved the insufficiency of the GHK current equation by removing the simplifying assumptions of constant field and a homogeneous membrane. Their method was semi-empirical in that the permeability was deduced as a function of voltage. They also included surface voltages in their calculations. For ionic channels at the frog neuromuscular junction, Lewis (1979) found that the GHK equation, with or without the addition of surface voltages, could not adequately predict her conductance values.

We have shown that our approach is necessary to adequately describe current-voltage relationships. The observation of nonlinear current-voltage plots in equal intracellular and extracellular media requires that nonlinear, non-GHK like equations be used. The degree of nonlinearity and the conductance are dependent on the relative equilibrium exchange rates in the channel and at the interfaces. We have obtained a relationship between conductance and the equilibrium exchange rate in the channel. In addition, we have derived the Nernst-Planck equation as a special case of our SRT equations.

One of the consequences of our SRT equations is that the exponent of the Ussing flux ratio is not necessarily unity. The value of the exponent is dependent on the equilibrium exchange rates in the channel and at the interfaces. Therefore, a nonunity exponent in the Ussing flux ratio does not necessarily imply that flux coupling is present.

It is highly unlikely that partition coefficients at the intracellular and extracellular interfaces are the same. The composition of extracellular and intracellular media are different in many cell types, for example, in smooth muscle the external potassium concentration is 5.9 mM and the internal potassium concentration is 164 mM (Casteels, 1981). Different extracellular and intracellular compositions imply different solubilities for the particular species. The different internal and external compositions and conditions imply that the partition coefficients must be different, i.e., the assumption of equal partition coefficients used in the derivation of the GHK current equation cannot be justified. A current reversal can occur at a voltage that is different from the Nernst potential if the intracellular and extracellular partition coefficients are different.

The use of SRT to model ion permeation links the two well-established fields of quantum mechanics and modelling of ionic transport mechanisms. Recently, SRT has been used to model pump and exchanger mechanisms (Skinner et al., 1993). At present, there are some shortcomings to our approach. In particular, our equations do not show saturation since we have not included binding sites in the system. However, our equations have allowed us to obtain other results such as nonlinear current-voltage relationships in symmetric solutions. We feel that our SRT equations for ion permeation present an attractive alternative to the other approaches of electrodiffusion and reaction rate theory.

## APPENDIX

### Derivation of the Nernst-Planck equation from SRT

We examine the expression for the flux in a channel that is obtained from SRT in the near-equilibrium limit. As will be seen below, if one adopts the continuum approximation and assumes that the gradient in concentration and in the potential is sufficiently close to the equilibrium value, then after adopting a particular interpretation of the diffusion coefficient, one obtains the Nernst-Planck expression for the flux. If one then makes the GHK assumptions (i.e., the constant field approximation and the assumption of equilibrium at the entrance to the channel and at its exit), this latter relation may be integrated to obtain the GHK expression for the flux.

Consider an arbitrary point in the channel, say $y_1$, and a second point in the channel, $y_2$ ($y_2 > y_1$) that is a distance $\Delta$ away:

$$y_2 = y_1 + \Delta.$$

According to SRT, the expression for the flux between these two points may be written (see Eq. 29):

$$j = K_{1,2}\left\{\frac{u(y_1)}{u(y_2)} - \frac{u(y_2)}{u(y_1)}\right\} \tag{72}$$

where $K_{1,2}$ is the exchange rate between these two points *under* equilibrium conditions, and $u(y_i)$ is given by:

$$u(y_i) = C_X(y_i)\exp(\theta_X\phi(y_i)). \tag{73}$$

It is particularly important to recall that $K_{1,2}$ is the equilibrium exchange rate. Under equilibrium conditions, the electrochemical potential, $\mu$, is uniform and this requires that $u(y)$ is uniform as well.

As the condition for near-equilibrium to exist in the channel, we assume that the gradient in both the concentration and in the potential to be sufficiently small so that the following two relations are valid:

$$C_X(y_2) = C_X(y_1) + \left(\frac{dC_X(y)}{dy}\right)_1\Delta \tag{74}$$

$$\phi(y_2) = \phi(y_1) + \left(\frac{d\phi(y)}{dy}\right)_1\Delta. \tag{75}$$

After inserting Eqs. 74 and 75 into Eq. 72, and neglecting second order and higher powers in the gradients in the concentration and in the potential, Eq. 72 may be written:

$$j = K_{1,2}\left\{\left[1 \frac{\Delta}{C_X(y_1)}\left(\frac{dC_X}{dy}\right)_1\right]\left[1 - \Delta\theta_X\left(\frac{d\phi}{dy}\right)_1\right] - \left[1 + \frac{\Delta}{C_X(y_1)}\left(\frac{dC_X}{dy}\right)_1\right]\left[1 + \Delta\theta_X\left(\frac{d\phi}{dy}\right)_1\right]\right\}. \tag{76}$$

After performing the indicated multiplications and neglecting second order and higher powers in the differentials of $C_X$ and $\phi$, one finds:

$$j = K_{1,2}\left\{\frac{2\Delta}{C_X(y_1)}\left(\frac{dC_X}{dy}\right)_1 - 2\Delta\theta_X\left(\frac{d\phi}{dy}\right)_1\right\}. \tag{77}$$

If the diffusion coefficient is defined as:

$$D = \frac{2\Delta K_{1,2}}{C_X(y_1)} \tag{78}$$

and it is noted that $y_1$ is an arbitrary point in the channel, then Eq. 77 may be written:

$$j = -D\left(\frac{dC_X}{dy} + C_X\theta_X\frac{d\phi}{dy}\right). \tag{79}$$

This equation is the Nernst-Planck equation and is the starting point in the derivation of the GHK current equation.

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