Ion flow through a membrane: Effect of chemical reaction on time dependence
(Nernst–Planck/electrodiffusion/binding)

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ABSTRACT The membrane model previously described [Hays, T. R., Buckwalter, C. Q., Lin, S. H. & Eyring, H. (1978) Proc. Natl. Acad. Sci. USA 75, 1612–1615] for ion flow through a membrane is expanded to include the effect of binding of the mobile ion at the occupiable sites in the membrane. Two different effects were investigated: alteration of the association-dissociation rates at constant equilibrium constant and alteration of the equilibrium constant at constant dissociation constant. Increasing the rates of association and dissociation initially causes an increased slowing of the relaxation to the final steady state, though ultimately the curves for the faster rates cross those for the slower states. Increasing the equilibrium constant causes a greater delay in the relaxation curve, with the curves for different equilibrium constants not crossing. Overall, the effect of binding is not very great unless the equilibrium constant for binding is quite large.

Attempts to formulate models for ion flow through a membrane often use the Nernst–Planck electrodiffusion equations (1) as a starting point. This enables the modeler to incorporate the effects of potential and concentration gradients on ion flow in a continuous membrane. The method is not free of problems, however. The general equation has so far escaped solution, though the steady-state case has been solved analytically (2) and several simplifications of the time-dependent processes due to various effects have been solved either numerically or analytically (3–5). Also, the equations assume a continuous path through the membrane, an assumption that may not always hold true, especially with membrane thicknesses on the order of nanometers. In such cases, a random walk model based on discrete jumps from one site to the next (6) could prove to be a better starting point.

In a previous paper (7), we considered the effect of a step potential change across a membrane on the concentration profile and current for a singly charged cation, comparing concentration profiles and currents from a continuous membrane model to those for discrete models with different numbers of occupiable sites. In this paper, we expand the model to include the effect of binding at the various sites. Of major concern here are the dependence on the equilibrium constant of binding and the relative rates of association-dissociation compared to the rate of diffusion through the membrane.

The continuous (macroscopic) model

The assumptions used include all of those used in the previous paper (7), i.e., the membrane is treated as one-dimensional (0 \leq z \leq l), the diffusion constant (D), the electric mobility (U), and the electric field (E = -\partial V/\partial x) are assumed independent of the position of the ion within the membrane, the electric potential is a step function (V_0 for t < 0, V for t \geq 0), and the concentration at either side of the membrane is constant (C_0 at the outer surface and C_I at the inner surface). The incorporation of binding requires three additional parameters: the rate constant for the association of the free ion to the binding site (k_a), the rate constant for the dissociation of the bound ion back into the mobile state (k_d), and the concentration of the bound ion at any given position in the membrane (B). With the inclusion of these new terms, the starting equations for the Nernst–Planck analysis become

\[ \frac{\partial C}{\partial t} = \frac{D}{\partial z^2} \frac{\partial^2 C}{\partial x^2} - \frac{ZeF}{RT} \frac{\partial C}{\partial x} + k_d B - k_a C \] 

\[ \frac{\partial B}{\partial t} = k_a C - k_d B \]

\[ I = ZeF \left[ - \frac{\partial C}{\partial x} + \frac{ZeFE}{RT} C \right] \]

in which \(Z\) is the charge on the ion, \(e\) the electron charge, \(F\) the Faraday constant, and \(I\) the current density, the \(U\) term being replaced by \(ZeF/RT\) from the Einstein relationship.

From the boundary conditions and through the use of the Laplace transform, Eqs. 1 and 2 may be solved simultaneously to yield

\[ C_2(t) = C_0 + \frac{(C_I - C_0) \left[ \exp(-AVx/l) - 1 \right]}{\exp(-AV) - 1} \times \sum_{n=1}^{\infty} \frac{2\pi D a V_0 (V - V_0) \sin(n\pi x/l)}{n^2 \pi^2 + A^2 (V_0 - V/2)^2} \times \left[ 1 - (-1)^n \exp\left( \frac{AV}{2} - AV_0 \right) \right] \]

\[ \left( P_n^+ \left[ 1 + \frac{k_a k_d}{(P_n^+ + k_d)^2} \right] + \exp(P_{n+} - t) \right) \]

\[ P_n^- \left[ 1 + \frac{k_a k_d}{(P_n^- + k_d)^2} \right] \]

in which \(A = ZeF/RT\) and

\[ P_{n+} = -\frac{1}{2} \left( k_a + k_d + \frac{DA^2 V^2}{4l^2} + \frac{Dn^2 \pi^2}{l^2} \right) \pm \frac{1}{4} \left( k_a + \frac{DA^2 V^2}{4l^2} + \frac{Dn^2 \pi^2}{l^2} - k_d \right)^{1/2} \]
Eq. 4 can be re-expressed in terms of reduced quantities as
\[ C'(t') = 1 + (C_1 - 1) \left[ \frac{\exp(-V'x'/2)}{\exp(-V') - 1} \right] \]
\[ \times \sum_{n=1}^{\infty} \left\{ \frac{2n\pi V'\delta(V' - V') \sin(n\pi x')}{n^2\pi^2 + (V'_0 - V')^2} \right\} \]
\[ \times \left[ 1 - (-1)^n \exp \left( \frac{V'}{2} - V'_0 \right) \right] \left[ \frac{\exp(P'_{n+}t')}{P'_{n+} \left( 1 + \frac{k'_a k'_d}{(P'_{n+} + k'_d)^2} \right)} \right] + \frac{\exp(P'_{n-t'} \left( 1 + \frac{k'_a k'_d}{(P'_{n-} + k'_d)^2} \right))}{P'_n} \right\} \] [5]
in which \( V' = ZeFV/RT \), \( C' = C/C_0 \), \( x' = x/l \), \( t' = tD/l^2 \), \( k' = kD/D \), and \( P'_{n\pm} = P_{n\pm}D/D \). The current can be found by using Eq. 4 in Eq. 3. For the reduced current, Eq. 3 is modified to
\[ I'(t') = -\frac{\partial C'}{\partial x'} - V'C' \] [6]
in which \( I' = I/IVzeDC_0 \). Eq. 5 is then inserted into Eq. 6 to give the result for the reduced current.

The discrete (microscopic) model

For the discrete model, the earlier concept of the ion hopping from one site to the next is modified to include binding at each of the occupiable sites. If bound at the site, the ion is immobilized. Thus, in order for a bound ion to resume its movement through the membrane, it must first dissociate into the free state. In order to simplify the mathematics, all of the sites are again assumed identical.

The contribution from the transmembrane potential is limited to ion motion through the membrane. Briefly restated, the potential energy due to the transmembrane potential \( \frac{ZeFV}{R} \) for a membrane with \( n = 1 \) equally spaced sites and potential energy maxima midway between the sites alters the forward and reverse rate constants \( k_f \) and \( k_r \), respectively, due to alteration of the activation energy. From the Arrhenius equation it can be shown that
\[ k_f = k_0 \exp \left( -\frac{ZeFV}{2nRT} \right) = k_0Q \] [7]
and
\[ k_r = k_0Q^{-1} \] [8]
in which \( k_0 \) is the rate constant in the absence of a transmembrane potential.

Including all of these factors leads to the rate equation for the time-dependent concentration changes at site \( i \):
\[ \frac{dC_i}{dt} = k_fC_{i-1} + k_rC_{i+1} + k_dB_i - (k_f + k_r + k_d)C_i \]
\[ = k_0 \left[ QC_{i-1} + Q^{-1}C_{i+1} + \frac{k_d}{k_0} B_i \right] - \left( Q + Q^{-1} + \frac{k_d}{k_0} \right) C_i \] [9]
\[
\begin{align*}
\text{(2)} & \quad n = 4 \\
C_1 &= C_0 + \frac{(C_1 - C_0)}{(1 + Q^5)(1 + Q^4)} + \frac{\exp(-tk_0(e1 - e2))}{4e2} \\
&\times \left[ [QC_0 - Q^{-3}C_1] \left[ 1 - \frac{e1 + e2}{Q + Q^{-1}} \right] + [C_1^0 - Q^{-2}C_0^0] \right] \\
&\times [K_a + K_d + e2 - e1] + \frac{\exp(-tk_0(e1 + e2))}{4e2} \\
&\times \left[ [QC_0 - Q^{-3}C_1] \left[ \frac{K_d}{e1 + e2} - 1 \right] \right] + [C_1^0 - Q^{-2}C_0^0] \\
&\times [K_a + K_d + e10 - e9] + \frac{\exp(-tk_0(e9 + e10))}{24e10} \\
&\times \left[ [QC_0 + Q^{-5}C_1] \left[ \frac{K_d}{e9 + e10} - 1 \right] \right] + [C_1^0 + \sqrt{3}(Q^{-1}C_2^0) + Q^{-4}C_0^0] \\
&\quad + [e9 + e10 - K_a - K_d] \tag{16}
\end{align*}
\]

(3) \( n = 3 \)

\[
\begin{align*}
C_1 &= C_0 + \frac{(C_1 - C_0)}{1 + Q^2 + Q^4 + \frac{\exp(-tk_0(e1 - e2))}{4e2}} \\
&\times \left[ [QC_0 - Q^{-2}C_1] \left[ 1 - \frac{e1 + e2}{Q + Q^{-1}} \right] \right] + [C_1^0 - Q^{-1}C_0^0][K_a + K_d + e2 - e1] + \frac{\exp(-tk_0(e1 + e2))}{4e2} \\
&\times \left[ [QC_0 + Q^{-2}C_1] \left[ \frac{K_d}{e1 + e2} - 1 \right] \right] + [C_1^0 - Q^{-1}C_0^0] \\
&\times [K_a + K_d + e4 - e3] + \frac{\exp(-tk_0(e3 + e4))}{4e4} \\
&\times \left[ [QC_0 + Q^{-2}C_1] \left[ \frac{K_d}{e3 + e4} - 1 \right] \right] + [C_1^0 + Q^{-1}C_0^0][e3 + e4 - K_a - K_d] \tag{17}
\end{align*}
\]

in which the values for the \( e \) terms are given in Table 1, \( C_n \) and \( C_i \) are alternative expressions for the inner surface concentration, and \( K_a = k_a/k_0 \) and \( K_d = k_d/k_0 \). Corresponding values for \( C_{n-1} \), i.e., the site next to the inner surface, may be found by replacing \( Q^1 \) by \( Q^{-1} \), replacing \( C_0^0 \) by \( C_n^0 \), and switching \( C_0 \) and \( C_1 \) around. The currents at the inner and outer surface may then be calculated by substituting the appropriate concentration terms into

\[
I_{i+1}(t) = \frac{ZeFk_0Q}{n} \left[ C_t - Q^{-2}C_{t+1} \right] \tag{19}
\]

in which \( I_{i+1} \) represents the current flowing from site \( i \) to site \( i + 1 \). For the surface currents, \( i = 0 \) for the outer surface current and \( i = n - 1 \) for the inner surface current.

The reduced equations use the same substitutions as the continuous equations except that \( D \) is replaced by \( k_d^2n^{-2} \).

Results and discussion

The effect of increasing the rates of association and dissociation without altering the equilibrium constant can be seen in Fig. 1. For short reduced times \( (t' \leq 0.5) \), the relaxation from the initial state to the final state is slower for faster rate constants. Beyond this point, the situation begins to reverse so that, ultimately, the responses for the slower rate constants lag behind those of the faster rate constants. This results because the concentration of bound ion stays closer to equilibrium with the free ion when the rate constants are faster. The bound ions thus act as a buffer against changes in the free ion concentration, the
buffering being more efficient for faster rate constants. Since the total buffering capacity of the bound ion depends only on its concentration relative to the free ion concentration, i.e., the equilibrium constant for binding, and not on the individual rate constants, the buffering capacity is depleted more rapidly at the higher rates. Eventually, the bound ion profile in the faster system approaches the final state closely enough and the buffering capacity for the slower rates is still high enough that the current for the slower rates lags behind.

Because the effect is due to the rate of equilibration between bound and free ions, two limiting cases can be investigated. As the rate constants approach zero, the response approaches that of the membrane without association-dissociation; as they approach infinity, the bound ion approaches instantaneous equilibrium with the free ion at any and all times. One outcome of this instantaneous equilibrium is a simplification of the temporal effect of binding relative to the membrane system without binding. While the intermediate rate constants do not have simple correlations with the shift in the current against time curve, the time scale for the infinite rate curve is simply $(1 + K_{eq})$ times the time scale for the nonbinding system. In other words, the current for the nonbinding system at a reduced time units is the same as that for the infinite limiting case in the binding system at $n(1 + K_{eq})$ reduced time units. The $(1 + K_{eq})$ factor results because the concentration of ions being changed is always $(1 + K_{eq})$ times the free ion concentration while the current is dependent only on the free ion concentration. It thus requires $(1 + K_{eq})$ times as long for the current to change the free ion concentration than it would have if the buffering effect of the bound ions was not a factor.

Unlike the effect of increasing the rate constants at a constant equilibrium constant, increasing the equilibrium constant at a constant dissociation constant has a monotonic effect on the relaxation of current and concentration profiles to the final state. As seen in Fig. 2, increasing the equilibrium constant causes an immediate lag in the membrane current which remains significant until the final state is reached or very nearly so. Such a result is in complete agreement with expectations, since increasing the equilibrium constant increases the buffering capacity so that the change to the final state is slower.
the time shift approaching \((1 + K_{eq})\) times the values for the time shifts in the absence of binding. In between these two cases, however, there is no constant time shift. This is no great surprise since Fig. 1 indicates a more complex situation in the intermediate cases.

It can thus be seen that the addition of association-dissociation to the membrane current model presented earlier (7) can cause noticeable retardation of the relaxation to the final steady state of a membrane current-concentration response to a step potential change. However, there is no great effect on the time scale of the response unless the equilibrium constant for binding is quite large. Too large an equilibrium constant might present problems, though, since one of the assumptions in the original rate equations is that an insignificant fraction of the sites is occupied so that the problem of ions interfering with the motion of other ions is ignored. Association-dissociation processes thus have some quantitative effects on the current and concentration response of the system without a considerable qualitative effect, at least in the model as presented.

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