ABSTRACT We present a far-field analysis of ion diffusion toward a channel embedded in a membrane with a fixed charge density. The Smoluchowski equation, which represents the 3D problem, is approximated by a system of coupled three- and two-dimensional diffusions. The 2D diffusion models the quasi-two-dimensional diffusion of ions in a boundary layer in which the electrical potential interaction with the membrane surface charge is important. The 3D diffusion models ion transport in the bulk region outside the boundary layer. Analytical expressions for concentration and flux are developed that are accurate far from the channel entrance. These provide boundary conditions for a numerical solution of the problem. Our results are used to calculate far-field ion flows corresponding to experiments of Bell and Miller (Biophys. J. 45:279, 1984).

GLOSSARY
Symbols that appear in two or more sections of the text are listed. When uppercase and lowercase symbols are given together, lowercase denotes dimensionless quantities. We follow a common convention and do not distinguish by symbol between functions representing the same physical quantity on the same physical domain but represented in different coordinate systems.

Latin symbols
- \( a \): Radius of channel entrance
- \( b \): Far-field capture radius
- \( C_b, c_b \): Bulk concentration in Boundary Surface Model
- \( C_p, c_p \): Concentration of permeant ion in Boundary Layer Model
- \( C_s, c_s \): Surface concentration in Boundary Surface Model
- \( C_s, \; c_s \): Surface concentration far from channel entrance
- \( C_0 \): Bulk concentration far from channel entrance
- \( D \): Permeant ion diffusion coefficient
- \( \varepsilon_0 \): Elementary electrical charge
- \( F_b, F_s, F_T \): Bulk, surface, and total ion flux toward channel entrance
- \( h \): Lattice spacing
- \( J_b, J_s \): Bulk and surface flux densities
- \( K_{bs}, k_{bs} \): Rate constant from bulk to surface
- \( K_{sb}, k_{sb} \): Rate constant from surface to bulk
- \( K_{se} \): Rate constant for ion entrance into channel

Greek symbols
- \( \epsilon \): Spacing between 0 and \( \epsilon \) rows as a fraction of \( h \)
- \( \xi \): Coordinate normal to membrane in physical surface layer
- \( \xi_0 \): Depth of boundary layer
- \( \theta \): Polar angle in spherical polar coordinates
- \( \kappa \): The membrane association constant \( K_{bs}/K_{sb} \)
- \( \rho, \; \rho \): Radial variable in cylindrical coordinates, dimensionless radial variable
- \( \Delta \tau \): A fixed time step, independent of \( n \)
- \( \Psi, \; \psi \): Macroscopic electrical potential of permeant ion

INTRODUCTION
Understanding the role of surface diffusion is a problem of widespread interest in biophysics, as in the area of chemoreception, for example (Adams and Delbrück, 1968; Berg...
There is experimental evidence that a similar mechanism can also play a very important role in ion transport from solution to an ion channel entrance. Negatively charged lipid bilayers greatly enhance cation channel conductance, especially at low ionic strength (Apell et al., 1979; Bell and Miller, 1984; Aguilleira et al., 1997). A straightforward interpretation is that cations are attracted to a concentrated surface layer close to the membrane surface, where they undergo a quasi-two-dimensional diffusion, and then enter the channel from the concentrated layer. We shall call this quasi-two-dimensional transport mechanism \textit{boundary layer diffusion}.

As information regarding the three-dimensional structure of membrane channels becomes available, it will be desirable to build detailed spatial models of ion conduction toward membrane channels. These would offer further insight into the role of boundary layer diffusion. One approach would be to solve the Smoluchowski equation with appropriate boundary data:

\begin{equation}
D \nabla^2 C_p + D \nabla \cdot (\nabla \psi C_p) = 0, \tag{1}
\end{equation}

where $C_p$ is the permeant ion concentration, $D$ is a diffusion coefficient, and $\psi = \varepsilon_0 \Psi/k_B T$ is the dimensionless electrical potential. Physically, the Smoluchowski equation models ion movement as being due to diffusion under the influence of the electrical field $-\nabla \Psi$ (e.g., Risken, 1989). Concentrations are assumed to be time independent.

This paper presents a far-field analysis of boundary layer diffusion for a simplified system that approximates Eq. 1. A partial solution is obtained that incorporates only the boundary conditions far from the channel entrance. In this region, the flow field does not depend on the details near the entrance, but only on properties of the solution and membrane. The far-field analysis offers direct insight into the role of boundary layer diffusion and yields boundary conditions in solution a finite distance from the channel that are used for a numerical solution.

We now consider two models of an ion channel in a membrane, introduce terminology, and state simplifying assumptions. The Boundary Layer Model solves Eq. 1 for a single channel in a planar membrane, as sketched in Fig. 1 A. The coordinate $\zeta$ is perpendicular to the plane of the membrane. Ions in solution screen a fixed membrane charge density, and the resultant electrical potential decays rapidly as $\zeta$ increases. We choose $\zeta_0$ so that the potential is significant only in the boundary layer region, $0 < \zeta < \zeta_0$. The ion channel entrance structure is also contained in the boundary layer, and may be described by very complicated boundary conditions. The bulk region corresponds to $\zeta > \zeta_0$. Here the electric field associated with the membrane charge density is weak, and the second term in Eq. 1 is unimportant.

The Boundary Surface Model of Fig. 1 B simplifies this geometry, allowing a useful mathematical analysis. The coordinate $Z = \zeta - \zeta_0$, $Z > 0$ models the bulk region above the boundary layer. In this region, the ion concentration is described as a solution of Laplace’s equation:

\begin{equation}
\nabla^2 C_b(\rho, Z) = 0, \tag{2}
\end{equation}

where $C_b$ is the ion concentration and $(\rho, Z)$ are cylindrical coordinates, assuming azimuthal symmetry. Next we integrate the boundary layer over the interval $0 < \zeta < \zeta_0$, reducing it to a 2D boundary surface. Rate constants $K_{bs}$ and $K_{sb}$ are introduced and adjusted to model the unidirectional fluxes of ions between the boundary surface and the bulk, far from the ion channel entrance. The expression for the net flux density out of the boundary surface is

\begin{equation}
-D \frac{\partial C_b}{\partial Z}(\rho, 0) = C_b(\rho, 0)K_{sb} - C_b(\rho, 0)K_{bs}. \tag{3}
\end{equation}

where $C_b(\rho)$ is the concentration on the boundary surface. Diffusion in the boundary surface itself is modeled by a 2D Poisson’s equation, where the right-hand side corresponds to the flux density out of the surface:

\begin{equation}
D \nabla^2 C_b(\rho) = C_b(\rho)K_{sb} - C_b(\rho, 0)K_{bs}. \tag{4}
\end{equation}

Equations 2–4 describe the Boundary Surface Model used for the far-field analysis. In the Methods section we first derive them as the diffusion limit of a random walk, showing that they do consistently represent coupled 2D and
3D diffusions. We next show how $K_{bs}$ and $K_{sb}$ can be chosen to model average properties of transport to and from the boundary layer. A multipole expansion of Laplace’s equation is then used to obtain an asymptotic expression for the solution of the Boundary Surface equations valid in the far field. The asymptotic expressions are used to obtain boundary conditions suitable for a numerical study.

A result of our analysis is that the solution in the far field only depends on the details at the channel entrance through the total current flowing into the channel. Our numerical solution has a simple representation of the channel entrance, which allows the total current to be adjusted. In the entrance region, $\rho < a$ of Fig. 1 B, an additional rate constant $K_{se}$ is introduced on the right-hand side of Poisson’s equation:

$$D \nabla^2 C_\rho (\rho) = C_\rho (\rho) (K_{sb} + K_{se}) - C_\rho (\rho, 0) K_{bs}. \quad (5)$$

$K_{se}$ is adjusted to give the desired value of the total current. In Results the far-field analysis is illustrated by a simple example that admits an exact solution of the Boundary Layer Model. The far-field behavior of this solution is in complete agreement with our conclusions obtained from the Boundary Surface Model. The simple example is then used to illustrate the numerical method, which is finally applied to obtain far-field solutions under the experimental conditions of Bell and Miller (1984).

**METHODS**

**Construction of Boundary Surface Model**

In this section we obtain the Boundary Surface Model from a discrete-time, discrete-state random walk on a cubic lattice. The mathematical theory of random walks converging to diffusion processes is discussed, for example, by Karlin and Taylor (1981). This technique was used by Berg and Purcell (1977) in their treatment of surface diffusion, and more recently by McGill and Schumaker (1996) to construct boundary conditions for single ion diffusion.

Consider the cubic volume $0 \leq X, Y, Z \leq L$, with lattice sites at locations $iLn$, $jLm$, and $kLn$, where indices $i$ and $j$ and $k \in \{0, \ldots, n\}$. We will refer to the square sublattices associated with each fixed $k$ as levels. The level $k = 0$ represents the boundary surface, and each lattice site on that level corresponds to an area $(Ln)^2$. The levels $k \geq 1$ represent the bulk solution, and each lattice site on these levels corresponds to a volume $(Ln)^3$.

Let $P_{i,j,k}(t)$ be the probability that the lattice site $(i, j, k)$ is occupied by a random walker at time $t$. Lattice site probabilities can be related to concentrations of random walkers in the bulk $C_{i,j,k}$ and on the surface $C_{i,j}$ according to

$$P_{i,j,k}(t) = C_{i,j,k}(t)L^2n^{-2}, \quad (6)$$

$$P_{i,j,k}(t) = C_{i,j,k}(t)L^3n^{-3}, \quad (7)$$

for $i, j, k \geq 1$. Alternatively, the concentrations may be expressed using the notation

$$C_{i,j}(t) = C_{i,j,k}(X, Y, t), \quad (8)$$

$$C_{i,j,k}(t) = C_{i,j,k}(X, Y, Z, k), \quad (9)$$

where $X = i/n$, $Y = j/n$, and $Z = kL$.

Random walkers step between nearest-neighbor lattice sites at discrete time intervals $\Delta t$. There will be four different transition probabilities. A walker may take a step between lattice sites in the bulk solution with probability $\gamma_b$. A step may be taken between sites on the boundary surface with probability $\gamma_s$. Steps occur from the bulk (level 1) to the surface with probability $\gamma_{bs}$ and from the surface to bulk with probability $\gamma_{sb}$. These transition probabilities are defined according to

$$\gamma_b = \Delta tDL^{-2}n^2, \quad (10)$$

$$\gamma_s = \Delta tDL^{-2}n^2, \quad (11)$$

$$\gamma_{bs} = \Delta tK_{bs}L^{-n}n. \quad (12)$$

$$\gamma_{sb} = \Delta tK_{sb}. \quad (13)$$

In the diffusion limit that follows, $n \rightarrow \infty$. So that transition probabilities never sum to a value greater than one, the time step must also scale with $n$:

$$\Delta t = \Delta t/n^2. \quad (14)$$

We must now analyze three cases, corresponding to time evolution on levels $k = 0, k = 1$, and $k > 1$.

Consider a lattice site in the interior of the bulk solution, with $k > 1$. A walker on this site may step to one of six adjoining sites with probability $\gamma_b$. On the other hand, the lattice site may receive a walker from one of the six adjoining sites. According to these rules, the time evolution of an interior lattice site is given by

$$P_{i,j,k}(t + \Delta t) - P_{i,j,k}(t) = [P_{i+1,j,k}(t) + P_{i-1,j,k}(t) - 2P_{i,j,k}(t)]\gamma_b + [P_{i,j+1,k}(t) + P_{i,j-1,k}(t) - 2P_{i,j,k}(t)]\gamma_s + [P_{i,j,k+1}(t) + P_{i,j,k-1}(t) - 2P_{i,j,k}(t)]\gamma_{sb}. \quad (15)$$

Now substitute the definition of the bulk concentration, Eq. 7, and transition probability $\gamma_b$, Eq. 10. Divide through by $L^3n^{-3}\Delta t$. On the left-hand side we obtain a familiar difference quotient whose limit as $n \rightarrow \infty$ is a time derivative. The right-hand side is a sum of $3$-second differences. Let $n \rightarrow \infty$, scaling $i, j, k \rightarrow \infty$ in such a way that $X_i \rightarrow X, Y_j \rightarrow Y$, and $Z_k \rightarrow Z$. We then obtain, for example,

$$\lim_{n \rightarrow \infty} L^3n^{-3}[C_{i+1,j,k}(t) + C_{i-1,j,k}(t) - 2C_{i,j,k}(t)] = \frac{\partial^2}{\partial X^2} C_b(X, Y, Z). \quad (16)$$

Evaluating these limits, we obtain the diffusion equation in
the bulk:
\[ \frac{\partial C_b}{\partial t} = D \nabla^2 C. \] (17)

Now consider a lattice site in the interior of the boundary surface, for which \( k = 0 \). A walker on this site may step to four adjoining sites on the boundary surface with probability \( \gamma_s \), or to the adjoining site on level \( k = 1 \) with probability \( \gamma_{bs} \). Walkers may also step in the reverse direction in each case, in particular, from level \( k = 1 \) with probability \( \gamma_{bs} \). The time evolution of such a lattice site on the boundary surface is given by
\[ P_{i,j,k}(t + \Delta t) - P_{i,j,k}(t) = \left[ P_{i+1,j,k}(t) + P_{i-1,j,k}(t) - 2P_{i,j,k}(t) \right] \gamma_s + \left[ P_{i,j+1,k}(t) + P_{i,j-1,k}(t) - 2P_{i,j,k}(t) \right] \gamma_s + P_{i,j,k}(t) \gamma_{bs} - P_{i,j,k-1}(t) \gamma_{bs}. \] (18)

Substitute the definitions of the concentrations and transition probabilities. Divide through by \( L^2 \). Letting \( n \to \infty \), and scaling \( i, j, \) and \( k \) as before, obtain
\[ \frac{\partial C_s}{\partial t} = D \nabla^2 C_s + C_b(X, Y, 0, t)K_{bs} - C_s(X, Y, t)K_{sb}. \] (19)

This is a diffusion equation for concentration on the surface, with an additional inhomogeneous term representing current flowing between the surface and the bulk.

Finally, consider a lattice site on level \( k = 1 \). A walker from this site may step to one of five neighboring sites in the bulk with probability \( \gamma_b \) or to a site on the surface with probability \( \gamma_{bs} \). Walkers may also step in the reverse direction, from the surface with probability \( \gamma_{sb} \). The time evolution is given by
\[ P_{i,j,1}(t + \Delta t) - P_{i,j,1}(t) = \left[ P_{i+1,j,1}(t) + P_{i-1,j,1}(t) - 2P_{i,j,1}(t) \right] \gamma_b + \left[ P_{i,j+1,1}(t) + P_{i,j-1,1}(t) - 2P_{i,j,1}(t) \right] \gamma_b + P_{i,j,1}(t) \gamma_{sb} - P_{i,j,0}(t) \gamma_{sb}. \] (20)

Substitute definitions for the concentrations and transition probabilities. Divide through by \( L^2 \) and let \( n \to \infty \), scaling \( i, j, \) and \( k \) as before. Only the last two terms on the right-hand side make nonzero contributions to this limit. Obtain
\[ \frac{\partial C_b}{\partial t} = D \nabla^2 C_b + C_s(X, Y, 0)K_{bs} - C_b(X, Y)K_{sb}. \] (21)

Equations 17, 19, and 21 form a time-dependent model for coupled bulk and boundary layer diffusion. We are interested only in steady-state currents to the ion channel entrances and set the time derivatives to zero. Transforming to cylindrical coordinates, we finally obtain Eqs. 2–4 in the Introduction.

**Mean dwell time on boundary surface**

The random walk construction also gives us insight into the behavior of trajectories on the surface in the Boundary Surface Model. In the following, we shall calculate the mean dwell time on the surface, ignoring the possibility that the diffuser is absorbed at the entrance region.

Consider a walker that first enters the boundary surface at a time \( t_0 \). The probability that it will leave the surface on the next time step is just \( \gamma_{sb} \). The probability that the walker will remain on the surface for at least \( m \) further time steps is \((1 - \gamma_{sb})^m\). Let \( t = m\Delta t \) be a fixed time interval, and now consider the diffusion limit \( n \to \infty \) or \( \Delta t \to 0 \), according to Eq. 14. The probability that the walker will remain on the surface at least a fixed time \( t \) is given by
\[ \lim_{m \to \infty} (1 - \gamma_{sb})^m = \lim_{\Delta t \to 0} \left(1 - \frac{\Delta t K_{sb}}{t} \right)^{t/\Delta t} = e^{-K_{sb} t}, \] (22)

where the limit can be evaluated by using L’Hôpital’s rule. The mean duration of the trajectory on the surface is simply
\[ \bar{T} = \int_0^\infty t e^{-K_{sb} t} dt = K_{sb}^{-1}. \] (23)

**Choosing \( K_{bs} \) and \( K_{sb} \)**

Far from the channel entrance, concentrations in the boundary layer will be close to equilibrium. In this section, \( K_{bs} \) and \( K_{sb} \) are chosen to give fluxes into and out of the boundary layer at equilibrium.

The ratio \( K_{bs}/K_{sb} \) is specified by considering Eq. 3 at equilibrium:
\[ C_s K_{sb} = C_b K_{bs}, \] (24)

where \( C_0 \) is the limiting ion concentration in the bulk far from the channel entrance, and \( C_s \) is the integral over the equilibrium concentration in the boundary layer:
\[ C_s = \int_0^{z_e} C_i e^{-\kappa z} dz. \] (25)

Introduce the boundary surface association constant \( \kappa = K_{bs}/K_{sb} \), in analogy with a chemical equilibrium constant. The two previous equations may be immediately combined to see that \( \kappa \) is simply given by an integral over the Boltz-
mann factor:

$$\kappa = \int_0^{\Theta_0} e^{-\Phi(\zeta)} d\zeta. \quad (26)$$

The mean dwell time in the 3D boundary layer $\hat{T}$ for an ion with initial coordinate $\zeta$ may be calculated as described in the Appendix. Weigh $\hat{T}$ by the equilibrium probability density in the boundary layer to determine $K_{sh}$:

$$K_{sh}^3 = (C_0)^{-1} \int_0^{\Theta_0} C_0 \exp(-\psi(\zeta)) \hat{T}(\zeta) d\zeta. \quad (27)$$

The calculation of $\hat{T}(\zeta)$ in the Appendix assumes that trajectories reflect off the physical membrane surface without delay, an assumption equivalent to calculating the mean escape time using the even extension of the potential profile, as shown in Fig. 2.

**Far-field analysis**

This section obtains a partial solution of the Boundary Surface Model that is valid in the “far field,” far from the channel entrance. $C_0$ satisfies Eq. 2. Far from the channel entrance, $C_0 \to C_\infty$. We therefore begin by considering the most general form of a solution of Laplace’s equation with azimuthal symmetry satisfying these boundary conditions (see, for example, Jackson, 1975):

$$C_\infty(r, \theta) = C_0 + \sum_{m=0}^{\infty} B_m r^{-(m+1)} L_m(\cos \theta), \quad (28)$$

where $r = (X^2 + Y^2 + Z^2)^{1/2}$ and $\cos \theta = Z/r$. In cylindrical coordinates,

$$C_\infty(\rho, Z) = C_0 + \sum_{m=0}^{\infty} B_m (\rho^2 + Z^2)^{-(m+1)/2} L_m(\xi(\rho, Z)), \quad (29)$$

where $\xi(\rho, Z) = Z(\rho^2 + Z^2)^{-1/2}$. $L_m$ denotes the Legendre polynomial of order $m$.

We must now calculate $(\partial/\partial Z)C_\infty(\rho, 0)$ and $C_\infty(\rho)$ to make use of Eq. 3. To differentiate the Legendre polynomial, use the recurrence relation (Jackson, 1975)

$$\left(\xi^2 - 1\right) \frac{d}{d\xi} L_m(\xi) = m\xi L_m(\xi) - mL_{m-1}(\xi). \quad (30)$$

Then by differentiating, setting $Z = 0$, and finally simplifying, obtain

$$\frac{\partial}{\partial Z} C_\infty(\rho, 0) = \sum_{m=0}^{\infty} B_m \rho^{-(m+2)} mL_{m-1}(0). \quad (31)$$

Legendre polynomials have the property that $L_{2m+1}(0) = 0$. Thus

$$\frac{\partial}{\partial Z} C_\infty(\rho, 0) = \sum_{k=0} B_{2k+1}\rho^{-(2k+3)}(2k+1)L_{2k}(0). \quad (32)$$

Combining Eqs. 3 and 4 and writing $\nabla^2$ in polar coordinates,

$$D - \frac{1}{\rho} \frac{d}{d\rho} \frac{d}{d\rho} C_\infty = -D \frac{\partial}{\partial Z} C_\infty(\rho, 0). \quad (33)$$

Substitute Eq. 32 and integrate twice to obtain

$$C_\infty(\rho) = \sum_{k=0} B_{2k+1} \rho^{-(2k+1)} L_{2k}(0) + K_1 \ln \rho + K_2. \quad (34)$$

Because $C_\infty \to C_\infty^\infty$ as $\rho \to \infty$, we must have $K_1 = 0$ and $K_2 = C_\infty^\infty = C_\infty^0 \kappa$, where the last expression is given by Eq. 24. With the exception of the constant term, $C_\infty$ depends only on odd powers of $\rho^{-1}$.

Substitute into Eq. 3 our results: Eq. 29 with $Z = 0$, and Eqs. 32 and 34. Identify the coefficients of $\rho^{-n}$ on either side of the equation; we have for $n = 1$:

$$B_1 = -\kappa B_0. \quad (35)$$

$\kappa$ has units of length. It is convenient to express $B_0$ and $B_1$ in terms of a new quantity. Let

$$B_0 = -bC_0, \quad (36)$$

where $b > 0$, and $b$ has units of length. If we now make use of this result in Eqs. 28 and 34, and using $L_0(\cos \theta) = 1$ and $L_1(\cos \theta) = \cos \theta$, we finally obtain the following far-field expressions:

$$C_\infty(r, \theta) = C_0 \left[ 1 - \frac{b}{r} + \frac{\kappa b}{r} \cos \theta + \mathcal{O}(r^{-3}) \right]. \quad (37)$$

$$C_\infty(\rho) = C_0 \kappa \left[ 1 - \frac{b}{\rho} + \mathcal{O}(\rho^{-3}) \right]. \quad (38)$$

From the dependence of both $C_\infty$ on $1 - b/r$ and $C_\infty$ on $1 - b/\rho$, we may consider $b$ as the effective capture radius of the
channel in the far field. The surface concentration $C_s$ is proportional to the boundary surface association constant given by Eq. 26. $\kappa$ increases with both the thickness of the boundary layer $\xi_0$ and the depth of the electrical potential $\psi$. A corresponding term proportional to $\kappa$ modulates the bulk concentration field in Eq. 37.

Further insight into the far-field solution can be gained by calculating far-field expressions for ion fluxes in the bulk and on the surface. From Fick’s law,

$$\mathbf{J}_b = -D \nabla C_b$$

$$= -DC_b \left[ \frac{1}{r^2} \frac{2\kappa}{r^3} \cos \theta + O(r^{-4}) \right] \mathbf{e}_r , \quad (39)$$

$$+ DC_b \left[ \frac{\kappa}{r^3} \sin \theta + O(r^{-4}) \right] \mathbf{e}_\theta , \quad (40)$$

$$\mathbf{J}_s = -D \nabla C_s$$

$$= -DC_s b \frac{1}{r^2} \mathbf{e}_r + O(r^{-4}) .$$

where $\mathbf{e}_r$, $\mathbf{e}_\theta$, and $\mathbf{e}_\rho$ are unit vectors in the direction of increasing $r$, $\theta$, and $\rho$, respectively.

An analogy with the electrostatic multipole expansion may be useful in visualizing this result. The second term of Eq. 37 is analogous to the monopole contribution to an electrostatic potential. Its contribution to the flux $\mathbf{J}_b$ corresponds to an electric field directed radially inward, toward the channel entrance. The third term of Eq. 37 is analogous to a dipole contribution of strength $\kappa b$ oriented in the direction of the positive $Z$ axis. The resultant flux density, evaluated at $Z = 0$, is into the plane of the membrane. The surface flux is directed radially inward, toward the channel. Its magnitude increases as $r^{-2}$ as $\rho$ decreases. The global picture is that of an ion flux toward the channel, and from the bulk phase to the boundary surface.

The total flux into the channel may be computed as the total flux directed inward through a hemisphere, centered on the channel, and of radius $r_0$. The integrated flux passing into the hemisphere through the bulk medium, $F_b$, may be computed from the far-field expression for the bulk flux density, Eq. 39:

$$F_b = 2\pi \int_0^{\pi/2} \mathbf{J}_b \cdot \mathbf{e}_r \sin \theta r_0^2 \, d\theta$$

$$= -2\pi DC_b (1 - \kappa r_0^{-1}) + O(r_0^{-2}) . \quad (41)$$

The hemisphere intersects the boundary surface on a circle of radius $r_0$. The integrated flux passing into the hemisphere through this circle may be computed from the far-field expression for the surface flux density,

$$F_s = 2\pi r_0 \mathbf{J}_s \cdot \mathbf{e}_\rho$$

$$= -2\pi DC_s bkr_0^{-1} + O(r_0^{-3}) . \quad (42)$$

The total flux into the hemisphere, including the circle at its base, is the sum of these two components. Note that the terms of order $r_0^{-1}$ shown explicitly in Eqs. 41 and 42 cancel. The random walk construction of the boundary surface model shows that it describes a time-stationary state of coupled two- and three-dimensional diffusions. It follows that the flux into a hemisphere of radius $r_0$ must be independent of $r_0$, and we conclude that the total flux $F_T$ is given by

$$F_T = -2\pi DC_b b , \quad (43)$$

where the minus sign reflects the fact that the flux is directed into the hemisphere. This is exactly the expression for the total flux into a hemispherical sink of radius $b$ in the absence of boundary layer diffusion (see, for example, Hille, 1992).

Finally note that the expression for $F_s$ is obtained from a differentiation and integration of the expression for $C_s(\rho)$. As noted below Eq. 34, the powers series for $C_s(\rho)$ includes only the constant term and odd powers of $\rho^{-1}$. It follows that the series for $F_s$ only includes odd powers of $\rho^{-1} = r_0^{-1}$. So that this series may be added to that for $F_b$ to obtain the result Eq. 43, all even powers of $r_0^{-1}$ of order 2 and higher in the series for $F_b$ must vanish. When the corresponding terms are nonzero in the expression for $J_b$, the integral in Eq. 41 must vanish. We may therefore replace the symbol $O(r_0^{-2})$ in Eq. 41 with $O(r_0^{-3})$.

**Boundary conditions from the far-field solution**

The next section describes numerical integration of the Boundary Surface Model on a rectangular domain in cylindrical coordinates: $0 \leq \rho \leq \rho_{\text{max}}$ and $0 \leq Z \leq Z_{\text{max}}$. The channel entrance is at the origin. One significant problem is the specification of appropriate boundary conditions at $\rho_{\text{max}}$ and $Z_{\text{max}}$. The far-field analysis can provide appropriate boundary conditions.

Truncation of the far-field result, Eqs. 37 and 38, to eliminate the $O(r^{-3})$ and $O(r^{-3})$ terms, yields the *dipole approximation*. Consider first the truncation of Eq. 37, written in cylindrical coordinates:

$$C_b(\rho, Z) = C_d \left[ 1 - b(\rho^2 + Z^2)^{-1/2} + \kappa b Z(\rho^2 + Z^2)^{-3/2} \right] . \quad (44)$$

Assuming that $\kappa$ is specified, only $b$ remains unknown. Eliminating $b$ between this equation and its derivative with respect to $Z$, obtain

$$\frac{\partial}{\partial Z} C_b + f(\rho, Z, \kappa) C_b = f(\rho, Z, \kappa) C_0 , \quad (45)$$

where

$$f(\rho, Z, \kappa) = \frac{(Z + \kappa)(\rho^2 + Z^2) - 3\kappa Z^2}{(\rho^2 + Z^2)(\rho^2 + Z^2 - \kappa Z)} . \quad (46)$$

These equations provide a boundary condition at $Z = Z_{\text{max}}$. 
The unknown \( b \) can also be eliminated between Eq. 44 and its derivative with respect to \( \rho \). This yields

\[
\frac{\partial}{\partial \rho} C_b + g(\rho, Z, \kappa) C_b = g(\rho, Z, \kappa) C_0,
\]

(47)

where

\[
g(\rho, Z, \kappa) = \frac{\rho(\rho^2 + Z^2) - 3\kappa \rho Z}{(\rho^2 + Z^2)(\rho^2 + Z^2 - \kappa Z)}.
\]

(48)

These equations provide a boundary condition at \( \rho = \rho_{\text{max}} \).

Finally, Eq. 38 can be used to obtain a boundary condition on the boundary surface, at \( \rho = \rho_{\text{max}} \). Begin with the truncation obtained by neglecting the \( O(\rho^{-3}) \) terms. Differentiate and eliminate \( b \) to find

\[
\frac{d}{d\rho} C_s + \frac{1}{\rho} C_s = \frac{1}{\rho} C_0 k_c.
\]

(49)

These boundary conditions are exactly satisfied by the dipole approximation, and are useful for numerical integration when \( \rho_{\text{max}} \) and \( Z_{\text{max}} \) are so large that the terms \( O(\rho^{-3}) \) and \( O(\rho^{-3}) \) in Eqs. 37 and 38 may be neglected.

A lower bound for \( \rho_{\text{max}} \) and \( Z_{\text{max}} \) is determined by the zeros of the numerators and denominators of \( f \) and \( g \). These zeros reflect an unphysical extremum of the dipole approximation of Eq. 37 when \( r \) is small. If numerical integration is performed with \( \rho_{\text{max}} = Z_{\text{max}} \), positivity of the numerators and denominators requires \( Z_{\text{max}} > 2\kappa \).

**Numerical solution of the Boundary Surface Model**

This section describes an algorithm for numerically integrating the Boundary Surface Model. Unlike the dipole approximation, the Boundary Surface Model has no singularity at the channel entrance. It provides a better representation of the Boundary Layer Model at intermediate length scales.

Even the full Boundary Surface Model cannot give an accurate representation of the physical flow field close to the channel entrance. The values of \( K_{\text{se}} \) and \( K_{\text{sb}} \), used in Eqs. 3 and 4 are obtained by assuming a Boltzmann distribution of concentrations in the boundary layer. Close to the channel, the actual distribution will depend on the detailed kinetics of ion entrance.

To proceed with the numerical solution, first introduce dimensionless coordinates \( x = x/a \), \( y = y/a \), \( z = Z/a \) and concentrations \( c_b = C_b/C_0 \) and \( c_s = C_s/(aC_0) \). Substituting these definitions into Eqs. 2–4, one obtains

\[
\nabla^2 c_b(\hat{\rho}, z) = 0,
\]

(50)

\[
\nabla^2 c_s(\hat{\rho}) = c_s(\hat{\rho}) k_{\text{sb}} - c_s(\hat{\rho}, 0) k_{\text{bs}},
\]

\[
= -\frac{\partial}{\partial z} c_s(\hat{\rho}, 0),
\]

(51)

where \( \hat{\rho} = (x^2 + y^2)^{1/2} \). These cylindrical coordinates are used by the numerical integration. Dimensionless rate constants have also been introduced:

\[
k_{\text{bs}} = aK_{\text{bs}}/D \quad \text{and} \quad k_{\text{sb}} = a^2 K_{\text{sb}}/D,
\]

(52)

where \( D = 1.96 \times 10^{-9} \text{ m}^2 \text{ s}^{-1} \) is the aqueous diffusion coefficient of \( K^+ \) (Hille, 1992), and \( a = 4 \text{ Å} \) was chosen for numerical convenience.

Equations 50 and 51 are solved numerically, using Gauss-Seidel iteration on a 256 by 256 square lattice with two additional rows, as depicted in Fig. 3. Values of \( c_b \) are computed on the square lattice itself, whereas values of \( c_s \) are computed on the surface row shown below the lattice. In the normalized units described above, the lattice spacing is \( h = 2/3 \). The radius of the entrance region is 1, and therefore only the first two points of the surface row fall within the entrance region.

An accurate representation of the entrance region is not important for our purposes. The dipole approximation of the far-field expansion only depends on the boundary conditions at the entrance region through the parameter \( b \). From Eq. 43, we see that \( b \) is proportional to the total flux into the channel. For the purpose of comparison with experiment, values of \( b \) can therefore by obtained from current measurements. The value of \( K_{\text{se}} \) in Eq. 5 is then adjusted to give the appropriate current.

The far-field boundary conditions, Eqs. 45, 47 and 49, are applied at the boundaries \( \hat{\rho} = \rho_{\text{max}} \) and \( z = z_{\text{max}} \). These equations were obtained by eliminating the far-field capture radius \( b \) in the dipole approximation. However, estimates of \( b \) can be recovered from the values of \( c_b \) at the far bound-
aries. If $\hat{p}_{\text{max}}$ and $\hat{z}_{\text{max}}$ are chosen to be large enough that the dipole approximation is accurate at the far boundaries, then similar estimates of $b$ can be made at all points along these boundaries.

This observation has been incorporated into a consistency check for the numerical integration. Estimates of $b$ are calculated at four uniformly spaced points along the boundary $\hat{\rho} = \hat{p}_{\text{max}}$ and at four uniformly spaced points along the boundary $z = \hat{z}_{\text{max}}$. Additional estimates of $b$ are calculated at the intersection of the $\epsilon$ and surface rows with the boundary $\hat{\rho} = \hat{p}_{\text{max}}$. Empirically, we find that $\rho_{\text{max}} = z_{\text{max}} > 10\kappa$ gives reasonably consistent results.

All finite differences are computed with symmetrized formulas whose accuracy improves as $O(\epsilon^2)$, except on the boundaries $\hat{\rho} = \hat{p}_{\text{max}}$, $z = \hat{z}_{\text{max}}$, and $z = 0$, where first-order formulas are used. A relatively accurate first-order finite-difference approximation to the partial derivative with respect to $z$ appearing in Eq. 51 was computed with the aid of an additional row of points placed on the lattice at $z = \epsilon h$. For the results presented here, $\epsilon = 0.1$.

RESULTS

Far-field expansion for an absorbing hemisphere

In this section we consider the example of a hemispherical absorber of radius $s_0$ centered at the origin in the absence of an electrical potential. Fig. 4 illustrates the geometry. The solution $C_p$ of the Boundary Layer Model, Eq. 1, will be identified with the bulk concentration $C_b$ of the Boundary Surface Model for $Z = \zeta - \zeta_0 > 0$. The integral of $C_p$ over the interval $0 < \zeta < \zeta_0$ will be identified with the surface concentration $C_s$ of the Boundary Surface Model. Complete agreement will be obtained with the form of the far-field expansions, Eqs. 37 and 38.

To begin, setting $\psi = 0$ in Eq. 1 gives Laplace’s equation. The well-known solution

$$C_p = C_0 \left(1 - \frac{s_0}{s}\right)$$

satisfies the boundary conditions $C_p = 0$ for $s = s_0$ and $C_p \to C_0$ as $s \to \infty$. Transform the solution to the spherical coordinates $(r, \theta)$ of the Boundary Surface Model and expand in inverse powers of $r$ to obtain

$$C_p = C_0 \left[1 - \frac{s_0}{r} + \frac{s_0 \zeta_0}{r^2} \cos \theta + O(r^{-3}) \right].$$

For $\psi = 0$ we have, according to Eq. 26, $\kappa = \zeta_0$. Identifying $b = s_0$, this form agrees with the explicit terms in the far-field expansion, Eq. 37.

Now consider the higher order terms of $C_p$ in the bulk region $Z > 0$. Because of azimuthal symmetry, $C_p$ has the form given by the right-hand side of Eq. 28. The bulk flux density $J_b$ is obtained from Eq. 39. The bulk current $F_b$ through a hemisphere of radius $r_0$ and centered at the origin $r = 0$ is given by Eq. 41. For $m > 0$ and even, we have the identity

$$\int_0^{\pi/2} L_m(\cos \theta) \sin \theta \, d\theta = 0.$$

and it follows that all even powers of $r^{-1}$ of order 2 or higher vanish in the series for $F_b$. This conclusion agrees with the discussion after Eq. 43.

$C_s$ may be constructed by transforming Eq. 53 to cylindrical coordinates and integrating over the interval $0 < \zeta < \zeta_0$. Obtain

$$C_s = C_0 \left[\zeta_0 - s_0 \sinh^{-1}(\zeta_0/\rho)\right]$$

$$= C_0 \zeta_0 \left[1 - \frac{s_0}{\rho} + \frac{1}{6} \frac{s_0^2 \rho^2}{\rho^2 + C(\rho^{-5})} \right].$$

Identifying $b = s_0$, this agrees with the form of Eq. 38. Because $\sinh^{-1}$ is an odd function of its argument, the series for $C_s$ only contains the constant term and odd powers of $\rho^{-1}$.

We cannot generally expect perfect agreement between the Boundary Layer Model and the far-field expansion of the Boundary Surface Model when $\psi \neq 0$. The form of the expansion depends on the parameter $\kappa$, which in turn depends on both $\psi$ and the choice of $\zeta_0$. For a given choice of $\zeta_0$, the Boundary Surface Model neglects the electrical potential outside the boundary layer. However, this error can be made small with an appropriate choice for $\zeta_0$.

Boundary Surface Model for an absorbing hemisphere

In this section we discuss the numerical solution of the Boundary Surface Model corresponding to the hemisphere example. Parameters are chosen to match the experimental conditions of Bell and Miller (1984) at 200 mM $[K^+]$ for the purpose of later comparison.

The boundary layer thickness is taken to be $\zeta_0 = 3\lambda_D = 2.06$ nm, where $\lambda_D$ is the Debye length. For the numerical
solution, parameter $K_{se}$ appearing in Eq. 5 was adjusted empirically to give a current matching the experimental value of 12.8 pA at 60 mV applied potential. To represent the hemispherical model, $K_{sb}$ and $K_{se}$ were calculated assuming the membrane potential $\psi = 0$; their values are given in the caption of Fig. 5. Details of the numerical integration are described in the Methods section. The far-field capture radius corresponding to the experimental current is $b = 0.538$ Å, according to Eq. 43. This value was used in representations of the dipole approximation (the far-field expansion truncated after order $r^{-2}$; see Eq. 37).

Fig. 5 shows normalized $K^+$ concentrations at the interface between the boundary layer and the bulk region. The solid curve corresponds to the exact solution of the hemisphere example, and filled circles correspond to the numerical solution of the Boundary Surface Model. These latter are values of concentrations calculated at the nodes of the row $z = 0$ in Fig. 3. Concentration values corresponding to the first nine nodes (calculated at $\hat{r} = 0, \hat{h}, \ldots 8\hat{h}$) are shown in Fig. 5 and then every fourth concentration thereafter. The dashed line gives the dipole approximation.

Fig. 5 A details the concentration field within 20 nm of the channel entrance. The Boundary Surface Model does not follow the hemisphere solution close to the channel entrance. However, boundary surface concentrations agree well with the exact solution for $\rho > 3$ nm. The dipole approximation gives concentrations in good agreement with the exact solution for $\rho > 10$ nm. Fig. 5 B gives an expanded view of the concentration differences over the whole domain of the numerical integration. Both the Boundary Surface Model and the dipole approximation follow the exact solution very closely in the far field.

Fig. 6 A compares curves of constant concentration for the exact solution of the hemispherical absorber with those of the numerical solution and the dipole approximation. Concentrations shown along the line $Z = 0$ correspond to Fig. 5. The flux $\mathbf{J}_b$ is locally orthogonal to the level curves, and is directed radially toward the hemisphere 2 nm below the origin. Level curves given by the dipole approximation of the Boundary Surface Model cannot be distinguished from those of the hemisphere example. Level curves for the numerical results are just inside the others because of a slightly smaller total flux.

Fig. 7 shows the $Z$ component of the bulk flux density $\mathbf{J}_b = -D \nabla C_b$ integrated azimuthally and evaluated at $Z = 0$. This is the distribution of integrated current flow from the bulk to the boundary layer as a function of $\rho$. Flux densities are zero at the origin, reflecting the integration around the radial angle. The area under this distribution, including the tail $\rho > \rho_{\text{max}}$, is equal to the total flux into the channel. Therefore, the same area is found under the curves corresponding to the exact solution of the hemisphere problem and the numerical solution of the corresponding Boundary Surface Model. Close to the channel entrance, the computed flux into the boundary surface of the numerical solution is greater than the corresponding flux into the boundary layer of the hemisphere solution. Compensating this excess, there is a region further from the entrance region where the hemisphere flux density is greater.

In contrast to the differences found close to the channel entrance, for $\rho > 10$ nm the two flux densities are in good agreement. Fig. 7 B gives an expanded view of the solution in the far field. For $22 < \rho < 61$ nm, the amplitudes of the hemisphere and Boundary Surface flux densities agree to within 1%. Close to the boundary of the domain of numerical integration, the numerical flux density begins to exceed that of the hemisphere solution, and is finally greater by 2.5% at $\rho = \rho_{\text{max}}$. A possible source of numerical error is the first-order finite-difference formulas used at the boundaries $\hat{r} = \hat{r}_{\text{max}}$ and $z = z_{\text{max}}$, as described in the Methods section.
Fig. 8 shows the integrated flux \( F_s = 2\pi\rho|J_z| \) in the boundary layer or boundary surface as a function of \( \rho \). The small difference in surface flux between the hemisphere and numerical solution near \( \rho = 0 \) is due to the different flux directly into the entrance region from the bulk. The two solutions agree very closely in the far field. For \( 20 < \rho < 38 \) nm, the relative difference is less than 1%.

**Boundary Surface Model of Bell and Miller experiments**

Bell and Miller (1984) measured \( K^+ \) currents through sarcoplasmic reticulum \( K^+ \) channels reconstituted in neutral and negatively charged lipid bilayers. The negatively charged bilayers were a 70% phosphatidylethanolamine mixture with a measured charge density of 0.9 ± 0.2e₀/nm². We use 1.0e₀/nm². Measurements were taken using symmetrical solutions in which \( K^+ \) was the sole cation and the major anion was gluconate. We consider the experimental conditions at \( C_0 = 200 \) mM \( K^+ \). The conductance estimated from their Fig. 2 A was ~213 ps, corresponding to a current of 12.8 pA at a transmembrane potential of 60 mV.

Following Bell and Miller, we modeled the electrical potential using nonlinear uni-univalent Gouy-Chapman-Stern theory (McLaughlin, 1977). This theory incorporates partial neutralization of the membrane due to association of \( K^+ \) with negative charges on the membrane. The binding is assumed to have a Langmuir form, with the experimentally determined association constant \( K_a = 0.15 \) M⁻¹ (Eisenberg et al., 1979). Electrical potential values in the boundary layer range from \( \Psi = -74 \) mV at \( \zeta = 0 \) to \( \Psi = -3 \) mV at \( \zeta = \zeta_0 = 3\lambda_D = 2.06 \) nm. The electrical potential decays slightly faster than exponentially with length constant \( \lambda_D \).
Boundary Surface rate constants $K_{bs}$ and $K_{ab}$ were calculated from the electrical potential profile as described in the Methods section. Their values are given in the caption of Fig. 5. The boundary surface association constant $\kappa = K_{bs}/K_{ab} = 6.36 \text{ nm} > 3\zeta_0$.

We have solved the Boundary Surface Model numerically using these parameters. The parameter $K_{ac}$ of Eq. 5 was adjusted to give the experimental current at 200 mM K$^+$. This model only contains information about the membrane and the total current under the conditions of Bell and Miller. There is no information about the structure of the sarcoplasmic recticulum K$^+$ channel. However, we shall refer to this as the Bell and Miller example.

Fig. 5 shows calculated concentrations at the interface between the bulk and boundary layer. The hemisphere example was constructed with the same total current $F_T$ and thus, from Eq. 43, the same value of $b$ as we are considering here. From Eq. 37, the dipole approximation is independent of $\kappa$ at the interface, where $\theta = \pi/2$. Therefore, the dashed curve gives the dipole approximation for the present case as well as the hemisphere example. Indeed, the numerical solutions show that the computed Bell and Miller concentrations approach those of the dipole approximation as $\rho \rightarrow \rho_{\text{max}}$.

In Fig. 6 $B$, first consider the difference between the hemisphere example and the dipole approximation. These agree on the abscissa, where $\theta = \pi/2$. For smaller angles, the effect of the term proportional to $\kappa$ in the dipole approximation is to flatten the level curves. The flux $J_b$ is orthogonal to these. The dipole approximation flow field is directed into a broad segment of the boundary layer, instead of being radially directed into the channel entrance.

The level curves of the dipole approximation flatten close to the z axis. For those of the numerical solution of the Bell and Miller example, the flattening is less pronounced. This difference may be principally due to the $O(r^{-3})$ term in the far-field expansion, Eq. 37, which depends upon the boundary conditions at the channel entrance. The angular distribution of the difference seems consistent with the requirement that the angular integral over the correction vanish in Eq. 41.

Fig. 7 shows the bulk flux density into the boundary surface, integrated around a circle of radius $\rho$, as a function of $\rho$. The significant difference between the hemisphere and Bell and Miller results is that, in the latter case, relatively more current enters the boundary surface at large $\rho$. In the far-field analysis, this can be seen in Eq. 39, where $J_s$ is given by the term proportional to $\xi_b$ when evaluated at $\theta = \pi/2$. The ratio of the flux densities in the dipole approximation is proportional to $\kappa$ (Bell and Miller)/$\kappa$ (Hemisphere) $\approx 3.1$. Numerically, the ratio approaches $2.9$.

Finally consider again Fig. 8, showing surface current $F_s$ as a function of $\rho$. The Bell and Miller example surface current has approximately the same intercept with the ordinate as the exact and numerical hemisphere example curves. This reflects the total current, which is nearly the same in the two examples, because $F_s \approx F_T$ for $\rho = a$. The ratio of the Bell and Miller to hemisphere surface currents approaches $3.0$ at $\rho = \rho_{\text{max}}$. This ratio is consistent with Eq. 42, which shows that $F_s$ is proportional to $\kappa$ in the dipole approximation.

DISCUSSION

Relationship between boundary surface and boundary layer models

This paper provides an analysis of diffusive flow fields into an ion channel entrance under conditions in which an electric field attracts ions toward the membrane surface, and boundary layer diffusion may be important. To do this, the Boundary Layer Model of Fig. 1 $A$ and Eq. 1 was reduced to the Boundary Surface Model of Fig. 1 $B$ and Eqs. 2–4. These equations were solved simultaneously through $O(r^{-2})$ and $O(\rho^{-2})$ by applying only the equilibrium boundary conditions attained as $r \rightarrow \infty$ and $\rho \rightarrow \infty$. The single adjustable parameter, $b$, which appears in the solution to this order, was shown to be proportional to the total current, which may be measured experimentally. The resulting truncated dipole approximation was analyzed and compared with the numerical solution of the Boundary Surface Model. The Boundary Surface Model is not mathematically equivalent to the Boundary Layer Model. Our method of reducing a 3D boundary layer to diffusion on a plane depends on modeling diffusive transport from the bulk to the surface by rate constants. The rate constants were adjusted to give the correct mean unidirectional fluxes in equilibrium, at which the distribution of ions in the surface layer is proportional to the Boltzmann factor $\exp(-\psi(\xi))$. Close to the channel entrance, the equilibrium approximation will not be accurate. For given boundary conditions at
the channel entrance, one could discuss ρ-dependent $K_{bs}$ and $K_{sb}$. We have no proof that these would not change the lowest order terms that enter into the dipole approximation.

However, we have demonstrated complete agreement of the solution of the hemisphere example with all of our conclusions concerning the far-field expansion, and, in particular, the terms that enter into the dipole approximation. We also have agreement in the case of one other exact example, that of an absorbing disk in the membrane (Smythe, 1968; Hall, 1975; unpublished results). Furthermore, our conclusions from the equilibrium expressions for $K_{sb}$ and $K_{bs}$ seem to be fully self-consistent and physically reasonable. Exact agreement between the Boundary Layer and Boundary Surface Models will not be obtained for nonzero $\psi_0$, because the latter model neglects fields extending outside the boundary layer. But this source of error is made small by an appropriate choice of the boundary layer thickness $\xi_0$.

**Ion interactions with the membrane surface**

There is experimental evidence that cations can pair directly with negative charges on the membrane surface, partially neutralizing the membrane surface charge density (Eisenberg et al., 1979). For this reason we followed Bell and Miller (1984) and calculated the electrical potential with Gouy-Chapman-Stern theory (McLaughlin, 1977), which provides for a Langmuir binding of ions to the membrane surface. However, we have not attempted to include such an interaction in the calculation of the mean dwell time in the boundary layer. Our analysis in the Appendix assumes specular reflection of ion trajectories at the membrane surface.

Interaction of ions with the membrane surface may also reduce their effective diffusion coefficient for motion parallel to the membrane in the boundary layer (Lifson, 1962). Direct binding of ions to the membrane surface would have this effect. Even without direct binding, discreteness of the membrane surface charge can roughen the effective surface potential if the mobile ions can approach the fixed charges too closely, or if the fixed charges are spaced too far apart (Nelson and McQuarrie, 1975).

The Boundary Surface Model can easily be modified to incorporate a reduced diffusion coefficient on the surface layer. One begins, in the random walk construction, by defining the transition probabilities $\gamma_b$ and $\gamma_s$ with distinct diffusion coefficients $D_b$ and $D_s$. In the resulting boundary surface equations, the diffusion coefficient in the bulk is $D_b$, Eq. 3, and the diffusion coefficient on the surface is $D_s$, Eqs. 4 and 5.

The far-field analysis proceeds parallel to the discussion presented in the Methods section, with the result that the $C(r^{-2})$ term in Eq. 37 is multiplied by an additional factor of $D_b/D_{ba}$ but without any other changes in Eqs. 37 or 38. The bulk flux density is calculated using $J_b = -D_b \nabla C_b$ in Eq. 39, and $J_s = -D_s \nabla C_s$ in Eq. 40. In the expressions for the resulting bulk flux density (Eq. 41), the first term is proportional to $D_b$, whereas the $C(r_0^{-1})$ term is proportional to $D_s$. The $C(r_0^{-1})$ term in the surface flux density (Eq. 42) is also proportional to $D_s$.

The effect of reducing the surface diffusion coefficient in the Boundary Surface Model, when the total current $F_s$ is held constant, is to reduce the contribution of the surface current. This result suggests that direct ion binding to the membrane, discreteness of charge, or other factors that roughen the interaction potential of permeant ions near the membrane surface, will have the effect of reducing the current in the boundary layer.

**Boundary layer diffusion and access resistance**

One approach to modeling the influence of a charged membrane on conductance has been to assume that local concentrations of permeant ion in the vicinity of the channel entrance are enhanced by a Boltzmann factor, $C_p(\xi) = C_0 \exp(-\psi(\xi))$, where $\xi$ gives the height of the channel entrance above the plane of the membrane (Apell et al., 1979; Bell and Miller, 1984). From IV curves measured in neutral membranes, increased conductances are predicted by replacing bulk concentrations by the enhanced local concentrations. Implicit in this local concentration model is the assumption that the geometry of the flux into the channel entrance does not change greatly; concentrations in the region important to the channel are uniformly increased by the Boltzmann factor.

Using this local concentration approach, Bell and Miller constructed curves of predicted conductance as a function of bulk concentration $C_0$ for several different values of $\xi$. They found that measured conductances decreased, as $C_0$ decreased, more quickly than predicted by the local concentration model. See their Fig. 5.

Our results suggest that the geometry of the ion flux toward the channel entrance changes dramatically as $C_0$ decreases. At high bulk concentrations flux is directed into the channel with approximately spherical symmetry from the surrounding solution. At lower $C_0$, ion flux from the bulk is directed into a broad region of the boundary layer surrounding the channel. Within the boundary layer, there is a quasi-two-dimensional flux into the entrance.

The time-independent solution of the diffusion equation for a spherically symmetric flow into an absorbing center is given by Eq. 53. The corresponding 2D problem for a circularly symmetrical flow is given by Eq. 33, with zero on the right-hand side. The solution $C(\rho) = A + B \ln \rho$ does not satisfy the physical boundary conditions as $\rho \to \infty$. The more physical solution of the Boundary Surface Model depends on the flux density of ions into the surface from the bulk, as modeled by the right-hand side of Eq. 33. This flux density decreases as $C_0$ decreases. It is plausible that there is a region of depleted permeant ion concentration surrounding the channel entrance that deepens or widens as $C_0$ decreases. Such a local depletion may possibly explain the quickly decreasing conductances observed by Bell and Miller.

Apell et al. (1979) measured the effects of surface charge on $C_s$ conductance through gramicidin in negatively
charged membranes. They also compared their measurements with a model assuming that local concentrations are enhanced by a Boltzmann factor. Somewhat similar to the results of Bell and Miller, they found that the measured conductance decreased slightly but significantly as bulk $[Cs^{+}]$ decreased. In contrast, over the entire range of their measurements, their model predicted local concentrations at the channel entrance far above the saturation concentration of the channel. It is plausible that their measurements may also be explained by a depleted region of ion concentration in the boundary layer near the channel entrance.

This proposed effect due to geometry is similar to the concept of access resistance, discussed in spherical symmetrical flows (for example, Läuger, 1976; Levitt, 1986; Chiu and Jakobsson, 1989). The Boundary Surface Model does not accurately depict ion flows in the immediate vicinity of the channel. A more detailed numerical study may be required to estimate the importance of any increased access resistance associated with the quasi-two-dimensional geometry of surface diffusion at low $C_i$.

**APPENDIX**

**Mean time to escape the potential well**

In this section we obtain a formula for the mean time to escape the potential energy well associated with the boundary layer. We require this to calculate $K_{bs}$ and $K_{sb}$. The formula is a standard result in the theory of stochastic processes (e.g., Karlin and Taylor, 1981; Risken, 1989). Here we show that it can be obtained in a straightforward way by taking the diffusion limit of an appropriate random walk. This derivation is in the spirit of Berg and Purcell (1977).

We assume that the boundary layer extends over the interval $0 \leq \zeta \leq \zeta_0$. Let $\Psi(\zeta)$ be the even extension of the ion potential energy at coordinate $\zeta$, as pictured in Fig. 2. $\psi(\zeta) = \epsilon_0 \Psi/k_B T$ is the corresponding dimensionless quantity.

First construct a sequence of random walks leading to the Smoluchowski equation for the ion potential energy well. The random walk involves steps between $n$ sites spaced uniformly across the even extension of the boundary layer at $\zeta_i = \zeta_0((-1 + 2i)/n)$, $1 \leq i \leq n$. A walker steps from site $i$ to site $i + 1$ with probability $\delta_i$ and from site $i$ to site $i - 1$ with probability $\delta_i$. These transition probabilities are defined by

$$\delta_i = \Delta t D \xi^{-2}(n^2 - n \xi \psi/2),$$

$$\delta_i = \Delta t D \xi^{-2}(n^2 + n \xi \psi/2),$$

where $\xi = 2\zeta_0$ is the length of the extended potential profile, $\Delta t$ is the time interval between steps, and $\psi'(\zeta) = \psi'(\zeta_0)$, with the prime denoting a derivative with respect to $\zeta$. So that the sum of the transition probabilities never exceeds 1, it is necessary to also scale $\Delta t$ with $n$, as shown by Eq. 14. Let $P_i(t)$ be the probability that a walker occupies site $i$ at time $t$. The change in this probability over one time step is

$$P_i(t + \Delta t) - P_i(t) = P_{i+1}(t)\delta_{i+1} + P_{i-1}(t)\delta_{i-1} - P_i(t)\delta_i.$$

Suppose site $i$ is associated with a boundary layer slice of thickness $\xi/n$ and a surface of area $A$. If $C_i(t)$ is the concentration of random walker associated with site $i$, then

$$P_i(t) = C_i(t)A\xi/n,$$

where $C_i(t) = C(\zeta_i, t)$. Substituting Eqs. 57, 58, and 60 into Eq. 59 and dividing by $\Delta t A\xi/n$, we obtain

$$[C_i(t + \Delta t) - C_i(t)]/\Delta t = D\xi^{-2}n[C_{i+1}(t) + C_{i-1}(t) - 2C_i(t)]$$

$$+ D\xi^{-1}(n/2)[\psi_{i+1}C_{i+1} - \psi_{i-1}C_{i-1}],$$

where we recognize that the first term on the right-hand side is proportional to a second difference, and the second term is proportional to a symmetrical first difference. Let $n \to \infty$ and $i \to \infty$, scaling $i$ so that $\zeta_i \to \zeta$, to obtain the Smoluchowski equation,

$$\frac{\partial C}{\partial t} = D \frac{\partial^2 C}{\partial \zeta^2} + D \frac{\partial}{\partial \zeta} (\psi/C).$$

This equation describes diffusion biased by the interaction $\psi$ with the membrane surface. Equation 1 may be obtained in a similar way, generalizing to three dimensions.

We now consider the problem of calculating the mean time to escape the extended boundary layer, that is, to reach the boundary $\zeta = -\zeta_0$ or $\zeta = \zeta_0$ in the limit $n \to \infty$. Let $\bar{T}_i$ be the mean time before a diffuser, starting at site $i$, reaches one of the end points $\zeta_i = \zeta_0((-1 + 2i)/n)$ or $\zeta_n = \zeta_0$. Suppose this process starts at initial time $t_0$. For some fixed lattice site $i$, $2 \leq i \leq n - 1$, we have

$$P_i(t_0) = 1,$$

$$P_j(t_0) = 0,$$

for $i \neq j$. Let $\bar{T}(t)$ be the mean time before the diffuser reaches an end point, averaged over the distribution of lattice site probabilities at time $t$. Then $\bar{T}(t_0) = \bar{T}_i$. After one time step,

$$\bar{T}(t_0 + \Delta t) = \bar{T}_i - \Delta t$$

and

$$P_i(t_0 + \Delta t) = 1 - \delta_i - \delta_i,$$

$$P_{i-1}(t_0 + \Delta t) = \delta_i,$$

$$P_{i+1}(t_0 + \Delta t) = \delta_i.$$
The mean time before the diffuser escapes is now a weighted average:

\[ \tilde{T}(t_0 + \Delta t) = P_i(t_0 + \Delta t)\tilde{T}_i + P_{i+i}(t_0 + \Delta t)\tilde{T}_{i+1} + P_{i-1}(t_0 + \Delta t)\tilde{T}_{i-1}. \] (66)

Substitute Eqs. 57, 58, 64, and 65 into Eq. 66, subtract \( \tilde{T}_i \) from both sides, and divide by \( \Delta t \) to obtain

\[ -1 = D\frac{\partial^2 \tilde{T}}{\partial z^2} - \psi \frac{\partial \tilde{T}}{\partial z}. \] (68)

The limit \( n \to \infty \), \( i \to \infty \), such that \( i/n \to \zeta \), gives

\[ -1 = D\frac{\partial^2 \tilde{T}}{\partial \zeta^2} - \psi \frac{\partial \tilde{T}}{\partial \zeta}, \] (69)

where \( \tilde{T} = \tilde{T}(\zeta) \). The appropriate boundary conditions are clearly \( \tilde{T}(\zeta_0) = \tilde{T}(\zeta_0) = 0 \).

This equation can be solved by the method of variation of parameters. The general solution has the form

\[ D\tilde{T}(\zeta) = \int_{\zeta_0}^{\zeta} [s(\zeta') - s(\zeta')] e^{-\psi(\zeta')} d\zeta' + K_1 s(\zeta) + K_2, \] (70)

where

\[ s(\zeta) = \int_{\zeta_0}^{\zeta} e^{\psi(\zeta')} d\zeta'. \] (71)

Satisfaction of the boundary conditions and a rearrangement of the integral results in

\[ D\tilde{T}(\zeta) = \left( 1 - \frac{s(\zeta)}{s(\zeta_0)} \right) \int_{\zeta_0}^{\zeta} s(\zeta') e^{-\psi(\zeta')} d\zeta' + \frac{s(\zeta)}{s(\zeta_0)} \int_{\zeta_0}^{\zeta} [s(\zeta') - s(\zeta')] e^{-\psi(\zeta')} d\zeta'. \] (72)

This is the formula for the mean first passage time. It is both symmetrical, \( \tilde{T}(\zeta) = \tilde{T}(\zeta) \), and differentiable. It follows that \( \tilde{T}'(0) = 0 \). Therefore, in the physical region \( \zeta \geq 0 \), our solution is equivalent to the solution of Eq. 68 with boundary conditions \( \tilde{T}'(0) = \tilde{T}(\zeta_0) = 0 \). The solution in the extended interval has the merit of making the assumed behavior of ion trajectories at the membrane surface completely clear.

**Numerical integration**

Evaluating Eq. 71 for the Gouy-Chapman potential sketched in Fig. 5 is an exercise in numerical integration. The formula was evaluated using a dimensionless independent variable \( \eta \) defined by \( \zeta = \zeta_0(2\eta - 1) \), with \( 0 \leq \eta \leq 1 \). We then took a multistep approach. The function \( s(\zeta) \) was evaluated by the NIntegrate function of Mathematica 3.0 (Wolfram, 1996) at 21 uniformly spaced values of \( \eta \) (0, 0.05, etc.). The resultant ordered pairs were used as nodes to define a spline interpolant, which in turn was used provide values of \( s(\zeta') \) in the integrand of Eq. 71. The NIntegrate function was used again to evaluate \( \tilde{T}(\zeta) \) at the same 21 values of \( \eta \) to construct a second spline interpolant for use in the integrand of Eq. 27. As a numerical check, the number of nodes used in both stages of interpolation was reduced to 11, without a significant change in the result.

We thank Kevin Cooper, Peter Jordan, Valipuram Manorajan, and Rod- erick MacKinnon for helpful discussions.

This work was supported by grants MCB 94-04430 and 96-30475 from the National Science Foundation.

**REFERENCES**


