Electrodiffusion model simulation of the potassium channel

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A B S T R A C T
The drift-diffusion (Poisson–Nernst–Planck) model is applied to the potassium channel in a biological membrane plus surrounding solution baths. Two-dimensional cylindrically symmetric simulations of the K channel in KCl solutions are presented which show significant boundary layers at the ends of the channel and display the spreading of charge into the bath regions. The computed current–voltage curve shows excellent agreement with experimental measurements. In addition, the response of the K channel to time-dependent applied voltages is investigated.

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1. Introduction
The drift-diffusion (Poisson–Nernst–Planck) model can be applied in the continuum approximation to ion flow in a K channel in a biological membrane plus surrounding KCl solution baths. We will consider a flow of positive and negative ions in water in a channel plus surrounding baths in an electric field $\mathbf{E}(\mathbf{x}, t)$ against a background of fixed ions on the channel protein. The discrete distribution of charges is described by continuum (Eisenberg et al., 1995; Nonner et al., 1998; Nonner and Eisenberg, 1998) particle densities $n_i(\mathbf{x}, t)$ for the mobile ions ($i = \text{K}^+$, $\text{Cl}^-$) and $N(\mathbf{x})$ for the fixed ions of the protein. The permanent fixed charge density $N$ may include both positive and negative charges, but the protein is predominantly negatively charged.

In the experimental setup, a voltage bias $V$ is applied across the channel plus baths by means of a patch clamp. The channel transit time for an ion is on the order of 10 ns, while experimentally the finest temporal resolution of currents is on the order of 10 μs, so experimental measurements are averaging over thousands of ions.

One-dimensional simulations of the K channel were presented in Gardner et al. (2004), which showed significant boundary layers at the ends of the channel and agreement—using a “geometrical factor” fit—with experimental measurements of the K channel current–voltage curve. However, the baths were modeled by funnels which opened from the channel cross sectional area $A = \pi(1 \text{ nm}/2)^2$ out to $A = \pi(11 \text{ nm}/2)^2$ at 5 nm into the baths to give a current of 22.5 pA at a bias of 100 mV. In the present investigation, the current is calculated from first principles without the geometrical fitting factor.

We present two-dimensional cylindrically symmetric simulations of the K channel in KCl solutions using the TRBDF2 method which also show significant boundary layers at the ends of the channel and display the spreading of charge into the bath regions. The computed current–voltage curve shows excellent agreement with experimental measurements. In addition, the response of the K channel to time-dependent applied voltages is investigated.

2. Drift-diffusion model
The flow of ions can be approximated by the drift-diffusion or Poisson–Nernst–Planck (PNP) model, which consists of partial differential equations for conservation of each ion species and Poisson’s equation for the electrostatic potential $\phi(\mathbf{x}, t)$:

$$\frac{\partial n_i}{\partial t} + \nabla \cdot \mathbf{j}_i = 0$$

$$\mathbf{j}_i = z_i \mu_i n_i \mathbf{E} - D_i \nabla n_i$$

$$\nabla \cdot (\varepsilon \nabla \phi) = e N - \sum_i q_i n_i$$

where $\mathbf{E}$ is the proton charge, $\varepsilon$ is the dielectric coefficient, and $\nabla \cdot (\varepsilon \nabla \phi)$ is the diffusion coefficient $D_i = D_i n_i$. The total electric current density $\mathbf{j}_{\text{elec}}$ is

$$\mathbf{j}_{\text{elec}} = \sum_i q_i \mathbf{j}_i$$

The physical parameters $\varepsilon$, $\mu_i$, and $D_i$ are functions of $\mathbf{x}$. 

$$\frac{\partial n_i}{\partial t}$$

$$\nabla \cdot \mathbf{j}_i$$

$$\nabla \cdot (\varepsilon \nabla \phi)$$

$$\mathbf{j}_{\text{elec}}$$
The drift-diffusion equations form a parabolic/elliptic system of PDEs: the transport equations (1) (with \( \mathbf{j} \) specified by Eq. (2)) are parabolic and Poisson’s equation (3) is elliptic. Thus the boundary conditions for both \( n_i \) and \( \phi \) are Dirichlet and/or Neumann.

We will focus our attention on the physiologically important KcsA channel. (K channels play a central role in electrical signaling in the nervous system, and a typical nerve cell has hundreds of thousands of K channels.) The structure of the KcsA channel is derived from X-ray crystallography, and the distribution of charges is given in Table 1.

The K channel is selective; i.e., it allows \( K^+ \) ions to flow freely between the interior and exterior of the cell, but not \( Na^+ \) or \( Ca^{++} \) ions. \( Cl^- \) ions are prevented from flowing through the K channel by the electrostatic field in the channel. We will model the channel plus regions of the bath illustrated in Fig. 1 out to a distance where the ion densities and the electrostatic potential take on their asymptotic values in the baths:

\[
\begin{align*}
n_i &= N_{bi}, \\
\phi &= V \text{ (interior bath far-field BC)}
\end{align*}
\]

The physically relevant boundary condition (BC) types in Fig. 1 are defined by

\[
\begin{align*}
n_i &= N_{bi}, \quad \phi = V \text{ (interior bath far-field BC)} \\
n_i &= N_{bi}, \quad \phi = 0 \text{ (exterior bath far-field BC)}
\end{align*}
\]

Since boundary layers in ionic charge density and the electrostatic potential develop at the ends of the channel, as illustrated in Figs. 2–5, boundary conditions should not be applied there. The ionic charge densities and the electrostatic potential reach their equilibrium far-field values approximately two Debye lengths into the baths, where the Debye length for the \( K^+ Cl^- \) solution equals 1.3 nm in the baths.

The transport equations (1) and the electric current density (4) can be written as

\[
\begin{align*}
\frac{\partial n_i}{\partial t} + \nabla \cdot (z_i \mu_i \mathbf{E} n_i) &= \nabla \cdot (D_i \nabla n_i) \\
\mathbf{J}_{elec} &= \sum_i z_i \mu_i n_i \mathbf{E} - D_i \nabla n_i
\end{align*}
\]

Table 1

<table>
<thead>
<tr>
<th>Region</th>
<th>( l )</th>
<th>( Q )</th>
<th>( \epsilon )</th>
<th>( \mu )</th>
<th>( D )</th>
<th>( z ) interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interior bath</td>
<td>5</td>
<td>0</td>
<td>80</td>
<td>60</td>
<td>1.5</td>
<td>[–5, 0)</td>
</tr>
<tr>
<td>–4e group</td>
<td>0.2</td>
<td>–4e</td>
<td>80</td>
<td>16</td>
<td>0.4</td>
<td>[0, 0.2]</td>
</tr>
<tr>
<td>Nonpolar</td>
<td>1</td>
<td>0</td>
<td>30</td>
<td>16</td>
<td>0.4</td>
<td>(0.2, 1.3)</td>
</tr>
<tr>
<td>Central cavity</td>
<td>1</td>
<td>–e/2</td>
<td>30</td>
<td>16</td>
<td>0.4</td>
<td>(1.3, 2.3)</td>
</tr>
<tr>
<td>Filter</td>
<td>1.2</td>
<td>–3e/2</td>
<td>30</td>
<td>16</td>
<td>0.4</td>
<td>(2.3, 3.5)</td>
</tr>
<tr>
<td>Exterior bath</td>
<td>5</td>
<td>0</td>
<td>80</td>
<td>60</td>
<td>1.5</td>
<td>(3.5, 8.5)</td>
</tr>
</tbody>
</table>

Fig. 1. Diagram of the computational region for the channel, membrane, and baths. Boundary condition types are labeled in italics.

Fig. 2. Simulation of \( K^+ \) density \( n_k \) (red, dark) and \( Cl^- \) density \( n_{cl} \) (cyan, light) along the \( z \)-axis for \( V = 100 \) mV. The protein permanent charge density \( N \) is the dashed curve. The vertical scale is \( \log_{10} \) of density/(10\(^{21} \) cm\(^{-3} \)). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Fig. 3. Simulation of \( K^+ \) density \( \log_{10}(n_k/(10^{21} \text{ cm}^{-3})) \) for \( V = 100 \) mV.

Fig. 4. Simulation of \( Cl^- \) density \( \log_{10}(n_{cl}/(10^{21} \text{ cm}^{-3})) \) for \( V = 100 \) mV.

Fig. 5. Simulation of electrostatic potential in volts for \( V = 0.1 \) V.

---

\[ n_i = N_{bi}, \quad \frac{\partial \phi}{\partial t} = 0 \text{ (ambient bath BC)} \]

\[ \mathbf{n} \cdot \nabla n_i = 0, \quad \mathbf{n} \cdot \nabla \phi = 0 \text{ (no-flux BC)} \]

where \( \mathbf{n} \) is a unit normal vector to the boundary.

The channel problem has an approximate cylindrical symmetry; in other words, the solution \( n_i, \phi \) depends on an excellent approximation only on \( r \) and \( z \), where cylindrical coordinates are denoted by \((r, \theta, z)\), with the \( z \)-axis along the length of the channel. With cylindrical symmetry, only the upper half of the computational region in Fig. 1 is simulated, and no-flux boundary conditions are imposed along the \( z \)-axis.

3. Numerical methods for electrodiffusion

The variables \( n_i \) and \( \phi \) are defined at gridpoints \( f=0, 1, \ldots, N_z, \)

\( k=0, 1, \ldots, N_r \). Given \( n_{jk}^n \) and \( \phi_{jk}^n \) at timelevel \( n \), a timestep consists of two parts. (i) First we solve the transport equations for \( n_{jk}^{n+1} \) with \( \phi = \phi^n \). (ii) Then we solve Poisson’s equation for \( \phi^{n+1} \) using \( n_{jk}^{n+1} \) on the right-hand side.

Spatial derivatives are discretized with second-order accurate central differences, and a pencil of states of radius \( \Delta r/2 \) is omitted along the \( z \)-axis: in other words, the first gridpoint in the radial direction is at \( r = \Delta r/2 \).

We use the implicit, L-stable TRBDF2 (Bank et al., 1985; Fair et al., 1991) (trapezoidal rule/second-order backward difference formula) method for the time-dependent drift-diffusion transport equations, which allows simulations to use large timesteps. TRBDF2 is a one-step second-order accurate method; the timestep is adjusted dynamically by a divided difference formula (TDTR2) method for the time-dependent drift-diffusion transport equations, which allows simulations to use large timesteps.

With the electric field frozen while updating the transport equations, where \( \phi \) is denoted by \( \phi^n \) and \( n_{jk}^n \) consist of two parts. (i) First we solve the transport equations for \( n_{jk}^{n+1} \) with \( \phi = \phi^n \). (ii) Then we solve Poisson’s equation for \( \phi^{n+1} \) using \( n_{jk}^{n+1} \) on the right-hand side.

Spatial derivatives are discretized with second-order accurate central differences, and a pencil of states of radius \( \Delta r/2 \) is omitted along the \( z \)-axis: in other words, the first gridpoint in the radial direction is at \( r = \Delta r/2 \).

We use the implicit, L-stable TRBDF2 (Bank et al., 1985; Fair et al., 1991) (trapezoidal rule/second-order backward difference formula) method for the time-dependent drift-diffusion transport equations, which allows simulations to use large timesteps. TRBDF2 is a one-step second-order accurate method; the timestep is adjusted dynamically by a divided difference formula estimate of the local error.

After discretizing in space, the transport equations may be written as a system of ordinary differential equations \( du/\partial t \approx f(u) \).

The TRBDF2 method then takes the form (1) TR step of \( \gamma \Delta t \):

\[ u^{n+2} = u^n + \gamma \frac{\Delta t}{2} f^n + \frac{(1-\gamma)^2}{2} f^n \]

and (2) BDF2 step of \( \Delta t \):

\[ u^{n+2} = u^n + \gamma \frac{\Delta t}{2} f^n + \frac{(1-\gamma)^2}{2} f^n \]

With the electric field frozen while updating the transport equations, \( f(u) \) is linear. We take the usual value \( \gamma = 2 - \sqrt{2} \) which minimizes the magnitude of the local error.

For Poisson’s equation we use an SOR iterative solver.

4. Simulation of the K channel

We will consider the flow of K\(^+\) ions (in water) through a channel of diameter 1 nm and length 3.5 nm, with baths on either side of diameter 5 nm and length 5 nm. The channel is modeled as one-dimensional; i.e., in the channel, \( n_i \) and \( \phi \) are functions only of \( z \).

For various sections of the K channel and surrounding KCl baths, the lengths \( l \), background permanent charges \( Q \), on the protein, dielectric constants \( \epsilon \), mobility coefficients \( \mu \), and diffusion coefficients \( D \) are given in Table 1. The mobilities and diffusion coefficients satisfy the Einstein relation \( eD/\mu = k_BT_0 \approx 1/40 \text{ eV} \). Note that the diffusion and mobility coefficients of the mobile ions are typically much smaller in the channel than in the baths.

The bath concentrations for the positive and negative ions are 0.15 molar=9 \times 10^{12} \text{ cm}^{-3}. We also assume that there are equal concentrations of ions inside and outside the cell membrane, so that no current flows when \( V = 0 \). The potential bias \( V \) is applied experimentally in the patch clamp technique over a distance of approximately \( l_{\text{clamp}} = 100 \text{ nm} \). We assume that the electric field goes to a constant value far away (\( \geq 4 \text{ nm} \)) from the channel, and therefore scale the applied bias linearly \( V_{\text{comp}} = (l_{\text{clamp}}/l_{\text{clamp}}) V \) for the computations, where \( l_{\text{clamp}} = l_c + 2l_b = 13.5 \text{ nm} \). This assumption is consistent with the simulation results.

These parameters give a linear current–voltage curve (out to a bias of 350 mV) with a current of 22.5 pA at a bias of 100 mV (Fig. 6). Experimentally the current at 100 mV is on the order of 20–30 pA for this type of channel.

The computed ion densities and the electrostatic potential are shown in Figs. 2–5: \( z \) and \( r \) are in nm, and the channel lies between \( z = 0 \) and \( z = 3.5 \). The baths extend 5 nm on either side of the channel. The ion flow is from the interior (left) to the exterior (right) of the cell membrane. The total charge on the channel is \(-6e\); there are about four K\(^+\) ions on average flowing in the channel, with about two K\(^+\) ions on average in the neighborhood of the \(-4e\) charge group and about one K\(^+\) ion on average in the filter. Note that the ion densities and the electrostatic potential reach their equilibrium far-field values within one or two Debye lengths into the baths, and that the ionic charge densities basically achieve charge neutrality subject to diffusive effects. High potential voltages and rapid variation of the ion densities in the channel are induced by the background charge on the channel protein.

The two-dimensional cylindrically symmetric simulations of charge density and electrostatic potential exhibit narrower “funnel” boundary layers near the openings of the channel than in the one-dimensional simulations (Gardner et al., 2004), as is typical of cylindrically symmetric fluid flow structures vs. 2D Cartesian flows.

Figs. 7 and 8 illustrate the response of the K channel to an applied voltage ramp and to a sinusoidal applied voltage. Note the extremely short transient times (\( \sim 1 \text{ ns} \)), and the slight phase shift in the current response in Fig. 8.
5. Conclusion

Macroscopic properties of the biological channel can be efficiently modeled by the continuum approximation (fluid dynamics) of the drift-diffusion model. To predict current–voltage curves or the response of the channel to time varying applied voltages, it is not necessary to model ions as charged spheres.

Although the precise distribution of charge density in the channel predicted by drift-diffusion should not be taken too seriously, still some microscopic properties of the channel can also be effectively modeled in the continuum fluid approximation, like the spreading of charge into the baths near the openings of the channel, and even the approximate number of ions in the channel on average. Most importantly, the current–voltage curve predicted by the drift-diffusion model simulations from the approximate charge distribution of the channel protein (known from X-ray crystallography) accurately reproduces the experimentally measured current–voltage curve.

References


