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Electrodiffusion Model Simulation of Rectangular Current Pulses in a Biological Channel

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Abstract. Numerical simulations are presented of stochastic-in-time current pulses for an electrodiffusion model of the biological channel, with a fixed applied voltage across the channel. The electrodiffusion model consists of the advection-diffusion equation coupled either to Gauss' law or Poisson's equation, depending on the choice of boundary conditions, plus a model for the protein charge density in the channel.

Keywords: electrodiffusion model, biological channel

1. Introduction

Biological cells exchange chemicals and electric charge with their environments through ionic channels. Signaling in the nervous system, coordination of muscle contraction including the pumping action of the heart, and ionic transport in every cell and organ are carried out through ionic channels.

Ionic current pulses have been observed experimentally in a wide variety of channels in the membranes of many types of cells (see Hille (1992) and references therein). These current pulses are of rectangular wave shape with constant heights and are distributed stochastically in time. In this investigation we simulate stochastic-in-time rectangular current pulses for an electrodiffusion model of the biological channel.

We will consider the flow of K^+ ions (in water) through a channel of diameter 7 Å and length 10 Å. K^+ channels play a central role in electrical signaling in the nervous system.

Our electrodiffusion model is based on the drift-diffusion partial differential equations plus a model (Gardner, Jerome and Eisenberg 2000) for the protein charge density in the channel. The electrodiffusion equations have traveling rectangular wave solutions (Gardner, Jerome and Eisenberg 2000), which serve here as an inflow boundary condition for rectangular wave solutions for the full partial differential equations (PDEs). We will present simulations of a 10 Å long biological channel with a fixed applied voltage across the channel for two different sets of boundary conditions. The traveling wave rectangular current pulses are no longer solutions for the finite length voltage biased

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channel, but the rectangular wave nature of input pulses is preserved by the full PDEs.

The finite channel simulations are important because the traveling wave pulses have a length equal to $v_0 \Delta t_P \gtrsim 3000$ channel lengths, where v_0 is the traveling wave velocity and Δt_P is the average duration of a current pulse. This is consistent with experimental measurements of current pulses if the ionic velocities are on the order of the ionic permeation velocity v_p, since the channel is on for a long time Δt_P compared to an ionic transit time 10 Å/v_p.

It is remarkable that an electrodiffusion model can produce not only rectangular current pulses, but the wide variety of current behavior observed experimentally in channels of biological membranes. It is difficult to get rectangular waves with flat tops from differential equations. The addition of noise to the drift-diffusion equations can excite current pulses with different durations and separations but equal heights, in accord with experimental measurements of channel currents. Our model serves as an example where nature may make use of ubiquitous thermal noise to accomplish a biological task—in this case turning the channel on and off.

2. Electrodiffusion Model

We consider a flow of positive ions (cations) in a one-dimensional channel in an electric field $E(x, t)$ against a background of negatively charged atoms on the channel protein. The discrete distribution of charges is described by continuum particle densities $p(x, t)$ for the mobile cations and N for the negatively charged atoms of the protein. We will allow N to be a function of current density and electric field, but not explicitly of x or t. The flow of cations is modeled mathematically by the drift-diffusion model, that is, by a partial differential equation for conservation of the cations and Gauss' law for the electric field, plus a constitutive law specifying the current density $j(x, t)$:

$$\frac{\partial p}{\partial t} + \frac{1}{e}\frac{\partial j}{\partial x} = 0 \tag{1}$$

$$\frac{\partial}{\partial x}(\epsilon E) = e^2(p - N) + \sigma \tag{2}$$

$$j = \mu p E - eD\frac{\partial p}{\partial x} \tag{3}$$

where e is the proton charge, ϵ is the dielectric coefficient (taken here to be constant), $\sigma \ll 1$ is a noise term, μ is the mobility coefficient, and D is the diffusion coefficient. The usual electric field has been multiplied by e (i.e., E has units of eV/cm in the cgs system). Alternatively, Poisson's equation for the electrostatic potential energy ϕ may be used instead of Gauss' law:

$$\frac{\partial^2}{\partial x^2}(\epsilon\phi) = e^2(N - p) - \sigma, \quad E = -\frac{\partial \phi}{\partial x}. \tag{4}$$

The choice of boundary conditions determines whether we use Gauss' law (E is specified at inflow) or Poisson's equation (ϕ is specified at inflow and outflow).

The random noise term σ represents small charge density fluctuations on the right-hand side of Gauss' law. We set σ equal to $+\bar{\sigma}$, 0, or $-\bar{\sigma}$, where $\bar{\sigma} \ll 1$ is a positive constant. The nonzero values of σ are randomly distributed with uniform probability in time with zero mean, i.e., with equal probability of being positive or negative. Generating noise $\pm\bar{\sigma}$ with zero mean guarantees charge conservation. This model for noise generation mimics thermal fluctuations of charge density (where $\bar{\sigma}$ corresponds to the average of the absolute value of the thermal fluctuations), since it is the existence of small thermal fluctuations of charge density that is important, and not their quantitative magnitude.

We model the total charge distribution by

$$\rho(j, E) = p - N(j, E) = -\frac{c}{v_0}(j - \bar{j})\left|\frac{E}{\bar{E}} - 1\right|, \qquad \bar{j} = e v_0 \bar{p} \tag{5}$$

where $c \ll 1$ is a positive constant, $\bar{p}$ is a reference ion density, $\bar{E}$ is a reference electric field, and $v_0 = \mu\bar{E}/e$. This charge model is derived near thermal equilibrium from a Boltzmann factor in Gardner, Jerome and Eisenberg (2000).

For the K^+ channel, the dielectric constant $\epsilon \approx 20$, the mobility coefficient $\mu \approx 6 \times 10^{-5}$ cm^2/(V s), and the diffusion coefficient $D \approx 1.5 \times 10^{-6}$ cm^2/s.

Only the current $I \sim 1$–10 picoamperes and the average duration of a current pulse $\Delta t_P \sim 0.1$–10 milliseconds are directly measurable experimentally. A physically natural magnitude for $\bar{p}$ would be a unit charge e spread uniformly throughout the channel volume (2.6×10^{21} cm^{-3}). We choose $\bar{p}$ to be one half this value so that the average number of ions in the channel when the channel is on is roughly 3.25. The number of ions in the channel is consistent with the energetics of packing the ions single-file in the channel.

Experimentally the external voltage V is applied over a length $\sim 10 l_c$, where $l_c = 10$ Å is the channel length. We have assumed that the potential drop

is very close to linear in x outside of the channel and have therefore scaled $V \to V/10$ at $x = l_c$. We also assume that there are equal concentrations of ions inside and outside the cell membrane, so that no current flows when $V = 0$. We then set $\bar{E} = -eV/(10l_c)$.

These values for $\bar{p}$ and $\bar{E}$ yield an average pulse duration on the order of 0.1–10 or more milliseconds depending on the frequency of the noise term σ, and a current of 2 picoamperes at $V = 10$ millivolts. Our computed pulse durations and currents match roughly the mean of the experimental values, which vary depending on the K^+ channel type. The traveling wave velocity $v_0 = 0.6$ cm/s at $V = 10$ millivolts is the same order of magnitude as the ion permeation velocity v_p through the channel. For these parameters, the constant $c = 3.4 \times 10^{-5} \ll 1$ in Eq. (5).

A typical traveling wave pulse in p, which is proportional to j for the traveling wave, and the associated electric field E are shown in Fig. 1, with $p_0 = 0.01\bar{p}$, $E_0 = 1.01\bar{E}$, $\bar{c} = \bar{E}^2/\bar{p}$, and $\bar{\sigma} = \pm 10^{-9}\bar{E}^2$. The charge density for this pulse is shown in Fig. 2. $\bar{E}$ has been set to 10^4 eV/cm.

The durations and separations of the current pulses vary over a wide range (see Fig. 3 and Gardner, Jerome and Eisenberg (2000)), as is observed experimentally. This wide variety of current pulse durations and separations is obtained by making the noise term more or less frequent.

Physical values predicted in the model like $v_0 \sim v_p$, $\Delta t_P \sim 0.1$–10 milliseconds, etc., are of the right order of magnitude for biological channels. A conformational change in the protein and the concomitant small charge fluctuations ($c \sim 10^{-6}$) produce gating, rather than a mechanical "flap" or "slider". A small dipolar charge wave (a positive spike followed by a negative spike) turns on the current in the channel, and a similar reversed charge wave (a negative spike followed by a positive spike) turns off the current (see Fig. 2).

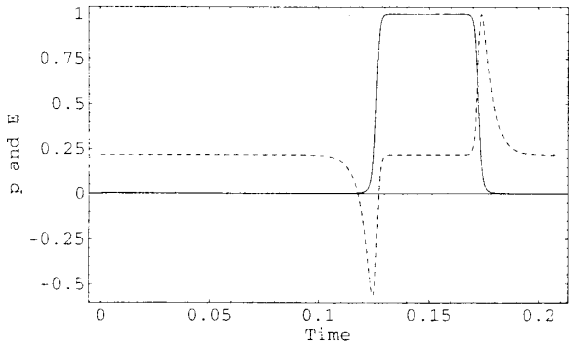

Figure 1. Traveling wave current pulse $j/\max\{j\} = p/\max\{p\}$ and electric field $E/\max\{E\}$ (dotted) vs. time $(x - v_0 t)/v_0$ in millisec.

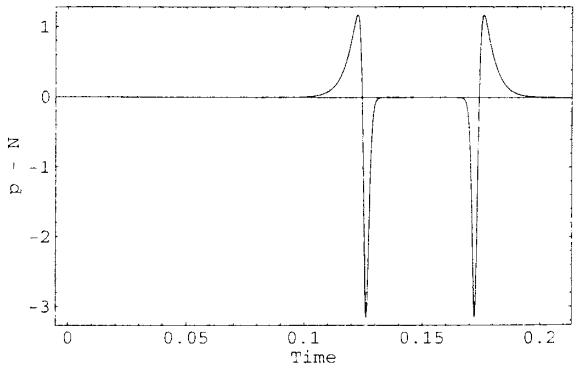

Figure 2. Traveling wave charge density $p - N$ in units of 10^{-5} e/channel vs. time $(x - v_0 t)/v_0$ in millisec.

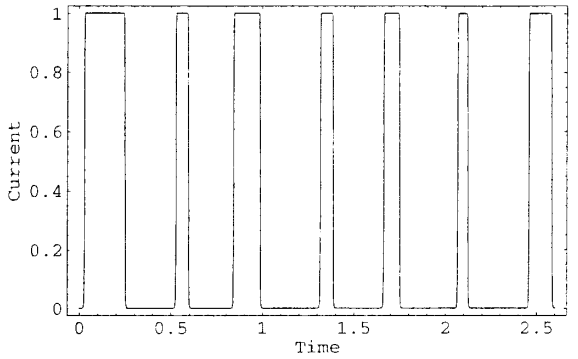

Figure 3. Traveling wave current $j/\max\{j\}$ vs. time $(x - v_0 t)/v_0$ in millisec with random noise added every thousandth timestep on average.

3. Numerical Methods for Electrodiffusion

The drift-diffusion Eqs. (1)–(3) with our charge model (5) take the form

$$\frac{\partial p}{\partial t} + \frac{\mu}{e}\frac{\partial}{\partial x}(Ep) = D\frac{\partial^2 p}{\partial x^2} \tag{6}$$

coupled to either Gauss' law (if E is specified at inflow)

$$\frac{\partial E}{\partial x} = -\frac{ce^2}{v_0 \epsilon}(j - \bar{j})\left|\frac{E}{\bar{E}} - 1\right| + \sigma, \tag{7}$$

or to Poisson's equation (if ϕ is specified at inflow and outflow)

$$\frac{\partial^2\phi}{\partial x^2} = \frac{ce^2}{v_0\epsilon}(j - \bar{j})\left|\frac{E}{\bar{E}} - 1\right| - \sigma, \quad E = -\frac{\partial\phi}{\partial x} \tag{8}$$

where the current density j is given in Eq. (3). The noise term σ is only important at the inflow boundary. Equation (6) is a parabolic PDE. Poisson's equation (8) is elliptic, while Gauss' law (7) is a first-order ordinary differential equation.

Variables p and E are defined at gridpoints $0, 1, \ldots, N$, while ϕ is defined at midpoints of grid cells $-1/2, 1/2, 3/2, \ldots, N + 1/2$.

Given p^n and E^n at timelevel n, a timestep consists of two parts. (i) First we solve the transport equation (6) for p^{n+1} with $E = E^n$. (ii) Then we solve either Gauss' law (7) or Poisson's equation (8) for E^{n+1} using E^n and p^{n+1} on the right-hand side.

For the ion density p, we impose a "pulse" inflow boundary condition $p(0, t)$ from the traveling wave solution with noise at the left boundary of the channel and a through-flow boundary condition $p_{N+1} = p_N$ at the right outflow boundary, where $N + 1$ is a ghost point (we also set $E_{N+1} = E_N$). Gating is controlled by charge movement at the inflow boundary as in Fig. 2. We also either specify $E(0, t)$ from the traveling wave solution and use Gauss' law, or we specify two boundary conditions, $E(0, t)$ from the traveling wave solution (which sets $\phi_{1/2}$) and the voltage bias $\phi_{N+1/2} = \phi(l_c, t) = eV/10$, *plus* the zero of potential energy $\phi_{-1/2} = \phi(0, t) = 0$ and use Poisson's equation. The traveling wave inflow boundary condition for the parabolic PDE (6) is similar in spirit to a characteristic boundary condition for hyperbolic PDEs.

We use the TRBDF2 (trapezoidal rule/second-order backward difference formula) method (Bank *et al.* 1985) for the drift-diffusion transport equation. For Poisson's equation we use a tridiagonal direct solve, while for Gauss' law we integrate forward from $x = 0$ to $x = l_c$ using TRBDF2 now as a spatial integrator.

4. Simulation of Current Pulses in a Finite Channel

We present two sets of simulations which depend on the choice of boundary conditions. Specifying E at inflow (Gauss' law case) from the traveling wave solution yields numerical solutions which are very close to the traveling wave solutions. Specifying $\phi = 0$ at inflow and $\phi = eV/10$ at outflow (Poisson equation case) yields numerical solutions which have rectangular current pulses but greatly diminished electric fields in the channel, so the traveling wave picture is no longer applicable.

Of particular significance is the fact that in both the Gauss' law and Poisson equation cases, the outflow ion density and the current are rectangular waves *with exactly the same on and off durations as the inflow pulse.* Thus the wide variety of stochastic-in-time rectangular current pulses are reproduced in the finite channel by solving the electrodiffusion model PDEs. Only very special charge models like Eq. (5) can preserve the shape of the input rectangular pulses in ion density.

Figure 4 shows the computed outflow current I for both the Gauss' law and Poisson equation cases with the applied voltage $V = -10$ millivolts (time is in milliseconds). The current pulse duration for these simulations with noise every timestep is about 0.5 millisec—however, by decreasing the frequency of the noise term, pulse durations of 10 millisec or more are easily obtained (see Gardner, Jerome and Eisenberg (2000)).

The flat maximum value of the current in the on state vs. voltage is almost exactly linear in both the Gauss' law and Poisson's equation cases (see Fig. 5). The magnitude of the current may be understood from the fact that

$$j = \mu pE - eD\frac{\partial p}{\partial x} \approx \mu p_{\max}E \approx -\mu p_{\max}\frac{V}{10l_c} \tag{9}$$

for the flat tops of the ion density p. ($V > 0$ implies $I < 0$.) This expression produces a linear Ohm's law. Experimental data on channels however indicate that Ohm's law for the biological channel is often nonlinear.

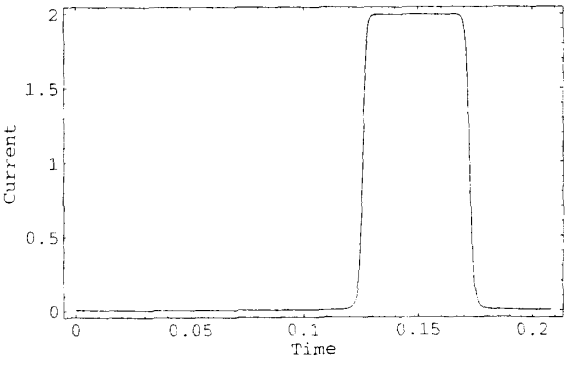

Figure 4. Outflow current in picoamperes for $V = -10$ millivolts. Gauss' law and Poisson's equation cases, vs. time in millisec.

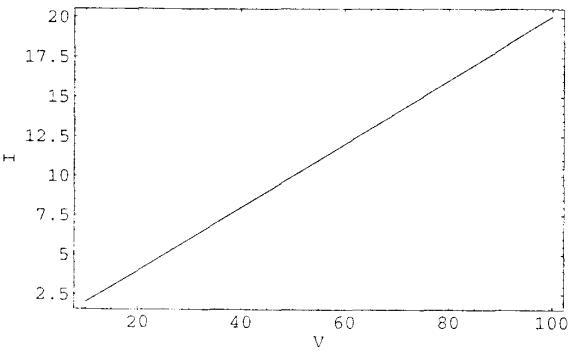

Figure 5. Computed current in picoamperes vs. voltage in millivolts.

e.g. sublinear—see Fig. 6 on p. 328 of Hille (1992). The sublinearity in the experimental IV curve must come from effects neglected in our model (for example, a nonuniform spatial distribution of fixed charge or a significant series resistance arising in the bath or at the interface between the bath and channel (Eisenberg 1998)).

To summarize: In our finite channel model, noise in the pulse boundary condition gives the experimentally observed variation in current pulse durations and separations. A conformational change in the protein and the resultant small charge fluctuations produce gating—in other words, charge movement at the inflow boundary turns the channel on and off.

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