Drift-Diffusion Simulation of the Ephaptic Effect in the Triad Synapse of the Retina

Jeremiah Jones
PhD Thesis Defense, Applied Mathematics

ARIZONA STATE UNIVERSITY
SCHOOL OF MATHEMATICAL AND STATISTICAL SCIENCES

April 5, 2013
Schematic of an Eye [1]
Organization of the Retina [1]
Schematic of an Ion Channel
Schematic of a Triad Synapse [2]
The Ephaptic Hypothesis

- Experimental results show that background illumination causes hyperpolarization in horizontal cells and increased levels of cone interior calcium.
- This is an example of negative feedback from HCs to cones.
- The feedback mechanisms involved are controversial and are not fully understood.
- Our simulations are designed to test the ephaptic hypothesis, first proposed by Byzov et. al. [3] and later expanded on by Kamermans et. al. [2].
- The specialized geometry of the triad synapse can force currents through high-resistance regions into the HC hemichannels, causing a potential drop in the extracellular cleft.
- The cone membrane senses this as a depolarization, which increases the activation of voltage-sensitive calcium channels.
- Calcium current is therefore directly modulated by the electric potential.
**Drift-Diffusion Equations**

- The drift-diffusion model is a parabolic/elliptic system of nonlinear PDEs for the ion densities and electric potential.

- Conservation of charge for each ion:

\[
\frac{\partial n_i}{\partial t} + \nabla \cdot \mathbf{f}_i = 0, \quad \mathbf{f}_i = -z_i \mu_i n_i \nabla \phi - D_i \nabla n_i
\]

\[i \in \{\text{Ca}^{2+}, \text{Cl}^-, \text{Na}^+, \text{K}^+\}\]

- Gauss’s Law for the potential:

\[
\nabla \cdot (\epsilon \nabla \phi) = -\sum_i q_i n_i
\]

- \(n_i(x, t)\) is the particle density
- \(\phi(x, t)\) is the electric potential
- \(\mathbf{f}_i\) is the particle flux
- \(\epsilon\) is the dielectric coefficient of the medium
- \(q_i\) is the ionic charge
- \(\mu_i\) is the mobility coefficient
- \(D_i\) is the diffusion coefficient
- \(z_i = q_i/q_e\)
Computational Region Using Symmetry

- Extracellular space
- Cone interior
- HC interior
- BC interior
- Cone membrane
- HC membrane
- BC membrane
- Open to exterior
Membranes cut through the grid, forming interior boundaries which separate intracellular and extracellular regions.

- All quantities defined on the membrane are double-valued.
- The two sides are labeled by $\pm$.
- The membrane is represented as a “meshed curve”.
Meshing a Curve (a crude example)

- Start with some sample points from the curve (left)
- Move those sample points to the nearest grid points (center)
- Connect pairs of consecutive points through a sequence of horizontal, vertical or diagonal lines that connect neighboring grid points (right)
Membrane Surface Charge

- To obtain boundary conditions along membranes, information about the membrane’s surface charge is required.

- Let \( \sigma_i^{\pm} \) denote the surface charge density carried by ion \( i \) for a point on either side of a membrane.

- Define \( \sigma \equiv \sum_i \sigma_i^{+} \).

- We assume total charge neutrality of the membrane, i.e. \( \sum_i \sigma_i^{+} + \sum_i \sigma_i^{-} = 0 \).

- Surface charge densities are related to spatial charge densities by the 1D approximation:
  \[
  \sigma_i = \int_0^\infty q_i(n_i(x) - n_{b,i})dx
  \]

  - \( x \) is the axis perpendicular to the membrane.
  - \( n_{b,i} \) is the constant asymptotic bath density of ionic species \( i \).
In thermal equilibrium, the densities satisfy

\[ n^\pm_i(x) = n^\pm_{b,i} \exp \left\{ -\frac{q_i\phi^\pm(x)}{k_BT} \right\} \]

In addition, \( \phi^\pm \) satisfies the Poisson-Boltzmann Equation

\[ \phi^\pm_{xx} = -\frac{1}{\epsilon} \sum_i q_i n^\pm_{b,i} \exp \left\{ -\frac{q_i\phi^\pm}{k_BT} \right\} \]

Linearizing and using the charge neutrality condition gives

\[ \phi^\pm_{xx} \approx \frac{1}{\epsilon k_BT} \left[ \sum_i q_i^2 n^\pm_{b,i} \right] \phi^\pm \]

For which the solution is

\[ \phi^\pm(x) = \phi^\pm(0)e^{\mp x/l^\pm_D} \]

\( l^\pm_D \) are the Debye lengths defined by

\[ l^\pm_D = \sqrt{\frac{\epsilon k_BT}{\sum_i q_i^2 n^\pm_{b,i}}} \]
Membrane Surface Charge (cont.)

- Inserting the solution for $\phi^{\pm}(x)$ into the ion density equation and linearizing gives

$$\sigma_{i}^{\pm} = \int_{0}^{\pm\infty} q_{i}(n_{i}^{\pm} - n_{b,i}^{\pm}) \, dx \approx -\frac{n_{b,i}^{\pm} q_{i}^{2} \phi^{\pm}(0) l_{D}^{\pm}}{k_{B}T}.$$  

- Combining this with the relation

$$n_{i}^{\pm}(0) \approx n_{b,i}^{\pm} \left(1 - \frac{q_{i} \phi^{\pm}(0)}{k_{B}T}\right)$$

gives an algebraic relationship between the surface charge densities and the spatial charge densities

$$\sigma_{i}^{\pm} = q_{i} l_{D}^{\pm} (n_{i}^{\pm} - n_{b,i}^{\pm})$$

- $n_{i}^{\pm}(0)$ has been replaced with $n_{i}^{\pm}$, with the understanding that $n_{i}^{\pm}$ is the particle density on the membrane.
Conservation Equations for $\sigma_i^\pm$

- Taking the time derivative of the last equation gives

$$\frac{\partial \sigma_i^\pm}{\partial t} = \frac{\partial}{\partial t} \left[ q_i l_D^\pm (n_i^\pm - n_{b,i}^\pm) \right] = q_i l_D^\pm \frac{\partial n_i^\pm}{\partial t} = -q_i l_D^\pm \nabla \cdot f_i^\pm = -l_D^\pm \nabla \cdot j_i^\pm$$

- This equation assumes there is no transmembrane current through ion channels

- To correct this, we just add in the transmembrane current density $j_{m,i}$

$$\frac{\partial \sigma_i^\pm}{\partial t} = -l_D^\pm \nabla \cdot j_i^\pm + j_{m,i}$$

- We are using the convention that current flowing into a cell is negative

- A separate model is needed for the transmembrane current
Transmembrane Current

- Along the cone membrane, calcium is the only active ion allowed to cross the membrane.

- The transmembrane calcium current along the cone is modeled by Ohm’s law with a voltage-dependent conductance function, motivated by experimental measurements:

  \[ j_{m,Ca} = \frac{g_{Ca}(V_{CP} - V_{Ca})}{N_s A_m[1 + \exp\{(\theta - V_{CP})/\lambda\}]}, \quad V_{CP} = \phi^+_{CP} - \phi^-_{CP} \]

- Along the horizontal cell membrane, we allow any cations to cross the membrane.

- The transmembrane current through the hemichannels along the horizontal cell is modeled by a linear Ohm’s law with constant conductance:

  \[ j_{m,i} = \frac{g_i}{N_s A_m}(V_{HC} - V_i), \quad V_{HC} = \phi^+_{HC} - \phi^-_{HC} \]

- \( g_i \) are channel conductances
- \( V_i \) are the reversal potentials
- \( A_m \) is the surface area of the cone pedicle containing calcium channels
- \( N_s \) is the average number of spine heads in a cone pedicle
- \( \theta \) and \( \lambda \) are curve fitting parameters
- The total current is computed by integrating the density over the area containing channels
Membrane Boundary Conditions

- The first membrane boundary condition for $\phi$ is given by considering the membrane as a capacitor with charge $\sigma$ and capacitance $C_m$

$$[\phi] = \phi^+ - \phi^- = \frac{\sigma}{C_m}$$

- The second boundary condition for $\phi$ enforces total neutrality on membranes

$$[n \cdot \nabla \phi] = n \cdot \nabla \phi^+ - n \cdot \nabla \phi^- = 0$$

- The boundary conditions for $n_i^{\pm}$ are computed by

$$n_i^{\pm} = n_{b,i}^{\pm} + \frac{\sigma_i^{\pm}}{q_i l_D^{\pm}}$$

- The boundary conditions for $n_i$ on each side of the membrane are independent of each other

- The jump conditions on $\phi$ couple the intracellular and extracellular solutions

- Upon discretization, they form a system of linear equations for $\phi^+$ and $\phi^-$
Outer Boundary Conditions

- Along the axis of symmetry, \( x = 0 \), we use homogeneous Neumman boundary conditions for all ionic species

\[ \mathbf{n} \cdot \nabla n_i = 0 \]

- For all other outer boundaries, we use the Dirichlet boundary condition

\[ n_i = n_{b,i} \]

- Outer boundary conditions for \( \phi \) are shown in the figure to the right

- \( U_{CP} \), \( U_{HC} \) and \( U_{BC} \) are constant holding potentials used to mimic a voltage clamp experiment

- \( U_{ref} \) serves as a common reference potential
Implementation

- Implemented in the C language
- Parallelized with OpenMP
- The finite volume box method is used for the spatial discretization
- We use the TRBDF2 method for the temporal discretization
- All discrete equations are solved using the SOR iterative method with Chebyshev acceleration
- Drift-diffusion equations are linearized and decoupled by freezing potential over a time step
State variables are defined at the solid dots
Flux components are defined on the open circles
The main idea is to apply the divergence theorem to each box (dotted lines)
This gives a conservative method that is ideal for handling the double-sided nature of the membranes
Discrete Surface Charge Density Equations

- Recall the conservation equation for $\sigma_\pm^i$:
  \[
  \frac{\partial \sigma_\pm^i}{\partial t} = -l_D^\pm \nabla \cdot j_\pm^i \mp j_{m,i}
  \]

- Let $B^\pm$ denote the portion of the box on the $\pm$ side of the membrane

- Integrating over $B^\pm$ and applying the divergence theorem gives
  \[
  \int_{B^\pm} \frac{\partial \sigma_\pm^i}{\partial t} \, dA = -l_D^\pm \int_{\partial B^\pm} j_\pm^i \cdot n \, ds \mp \int_{B^\pm} j_{m,i} \, dA
  \]

- Simplifying gives
  \[
  A^\pm \frac{\partial \sigma_\pm^i}{\partial t} = -l_D^\pm \sum_{k=1}^{4} j_{i,k}^\pm \cdot n_k s_k^\pm \mp A^\pm j_{m,i}
  \]
  \[
  \Rightarrow \frac{d\sigma_\pm^i}{dt} = -\frac{l_D^\pm}{A^\pm} \sum_{k=1}^{4} j_{i,k}^\pm \cdot n_k s_k^\pm \mp j_{m,i}
  \]

- $k$ indexes the four sides of the box

- $s_k^\pm$ is the length in which the $k$th side of $B$ lies on the $\pm$ side of the membrane
Implementing Jump Conditions on $\phi$

- Recall the second jump condition on $\phi$: $[\mathbf{n} \cdot \nabla \phi] = 0$
- The equivalent charge neutrality condition is: $\rho = 0 = -\epsilon \nabla \cdot \nabla \phi$
- Integrating each side of this equation over the box $B$ gives

$$\int_B \nabla \cdot \nabla \phi \, dA = \int_{B^+} \nabla \cdot \nabla \phi^+ \, dA + \int_{B^-} \nabla \cdot \nabla \phi^- \, dA = 0$$

- Applying the divergence theorem,

$$\int_{\partial B^+} \nabla \phi^+ \cdot \mathbf{n} \, ds + \int_{\partial B^-} \nabla \phi^- \cdot \mathbf{n} \, ds = 0$$

- Simplifying gives

$$\sum_{k=1}^{4} (\nabla \phi^+_k) \cdot \mathbf{n}_k s^+_k + \sum_{k=1}^{4} (\nabla \phi^-_k) \cdot \mathbf{n}_k s^-_k = 0$$

- This leads to an equation of the form

$$L^+ \phi^+ + L^- \phi^- = P^+ + P^-$$

- Combining this with the other jump condition, $\phi^+ - \phi^- = \sigma / C_m$, gives a system of linear equations for $\phi^+$ and $\phi^-$
Given a grid with a meshed curve for the membrane, we must compute the geometric factors $A^\pm$ and $s^\pm_k$

We define $s^\pm_k = 0$ if the $k$th side of the box is not on the $\pm$ side of the membrane.

These factors are determined at each membrane point by the two successive line segments of the meshed curve surrounding the point.

There are 32 possible configurations, taking orientation into account.

There are only four fundamental configurations, the rest being compositions of rotations and/or flips of these.

$A^\pm = \alpha^\pm \Delta x \Delta y$, $\alpha^\pm \in \{\frac{1}{4}, \frac{3}{8}, \frac{1}{2}, \frac{5}{8}, \frac{3}{4}\}$

$s^\pm_k \in \{0, \frac{\Delta x}{2}, \frac{\Delta y}{2}, \Delta x, \Delta y\}$
The TRBDF2 Method

- Consider an autonomous system of $N$ ODEs
  \[ \frac{du}{dt} = f(u), \quad u, f(u) \in \mathbb{R}^N \]

- Use trapezoid rule (TR) to solve for $u^{n+\gamma} = u(t_n + \gamma \Delta t_n), \gamma \in (0, 1)$
  \[ u^{n+\gamma} = u^n + \frac{\gamma \Delta t_n}{2} \left( f(u^n) + f(u^{n+\gamma}) \right) \]

- Use second-order backwards difference formula (BDF2) to solve for $u^{n+1} = u(t_n + \Delta t_n)$
  \[ u^{n+1} = \frac{1}{\gamma(2 - \gamma)} u^{n+\gamma} - \frac{(1 - \gamma)^2}{\gamma(2 - \gamma)} u^n + \frac{1 - \gamma}{2 - \gamma} \Delta t_n f(u^{n+1}) \]

- $\gamma = 2 - \sqrt{2}$ is the optimal value to minimize $\|LTE\|$

- Implicit (composite) one-step method
- L-Stable
- 2nd-order accurate
- Adaptive time step easily implemented
Adaptive Time Step Selection

- The LTE of TRBDF2 at timestep \( n + 1 \) can be approximated as

\[
LTE^{n+1} \approx 2c \Delta t_n \left( \frac{1}{\gamma} f(u_n) - \frac{1}{\gamma(1 - \gamma)} f(u_{n+\gamma}) + \frac{1}{1 - \gamma} f(u_{n+1}) \right)
\]

where

\[
c = \frac{-3\gamma^2 + 4\gamma - 2}{12(2 - \gamma)}
\]

- The typical time step selection algorithm is to set

\[
r_{n+1} = \frac{\|LTE^{n+1}\|}{\epsilon_R \|u_n\| + \epsilon_A}, \quad \Delta t_{n+1} = \Delta t_n r_{n+1}^{-1/(p+1)}
\]

where \( \| \cdot \| \) is the discrete \( L^1 \) norm, \( p \) is the order of the method and \( \epsilon_R \) and \( \epsilon_A \) are the relative and absolute error tolerances.

- If \( r_{n+1} \leq 2 \), the time step is accepted and updated (increased)

- Otherwise, the time step is adjusted (decreased) and the process repeated

- This allows large time steps without loss in accuracy when simulating to steady state
Parallelization with OpenMP

- 70% of the CPU time is spent solving for $\phi$ since the ions remain nearly constant away from the membranes.

- 29% of the CPU time is spent solving for the ions.

- The remaining 1% is spent implementing the boundary conditions.

- We parallelize the Poisson solver by splitting the grid into $N$ subgrids where $N$ is the number of processors available.

- Each subgrid is updated in parallel, keeping $\phi$ in the shared memory space.

- Some points on the subgrid boundaries get updated in the wrong order.

- This leads to a form of chaotic relaxation as the number of subgrids increases.

- The same method is applied to the ion density equations.

- The parallelized code results in a speed-up factor of $N/2$. 
Steady State Potential on a $600 \times 900$ grid
Steady State Charge Density on a $600 \times 900$ grid

![Extracellular Charge Density](image1)

![Intracellular Charge Density](image2)
Steady State IV Curves on a 150 × 225 grid

**Neutral Bipolar Cell**
- HC/BC = −40/−60
- HC/BC = −60/−60

**Depolarized Bipolar Cell**
- HC/BC = −40/−60
- HC/BC = −60/−40

**Hyperpolarized Bipolar Cell**
- HC/BC = −40/−60
- HC/BC = −60/−80

**Shift Curves**
- Neutral
- Depolarized
- Hyperpolarized
Summary of Results

- Potential shows that the “compartment” model, which treats each cell as isopotential, is not a good approach for this problem.

- The charge density is zero away from the membranes with equal and opposite charge layers near the membranes.

- Potential and charge layers are physically consistent.

- The shifting of the IV curves under hyperpolarization of the HC demonstrates the ephaptic effect.

- The magnitude of the shift is dependent on how the BC interior potential changes under illumination.

- The “neutral” case is the most consistent with experimental results.

- This is most likely due to the fact that there are many BCs involved in the experimental recordings, some of which become hyperpolarized and some which become depolarized and the overall effect balances out.
Possible Future Work

- Solve equations in 3D geometry
- Develop a more sophisticated model of the transmembrane current via Hodgkin-Huxley like dynamics
- Demonstrate the importance of hemichannels in modulating feedback
- Include glutamate and glutamate-gated channels in the HC
- Test the GABA and pH hypothesis by including GABA release/binding sites and modeling proton pumps
- Multiscale modeling: “integrate out” short time scales to obtain a model that allows simulations of light flickering
Preliminary Simulation for Entire Cone Pedicle

