SIMULATION OF THE EPHAPTIC EFFECT IN THE CONE–HORIZONTAL CELL SYNAPSE OF THE RETINA*

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Abstract. The drift-diffusion (Poisson–Nernst–Planck) model—including a numerical model for cell membranes that resolves surface-charge boundary layers—is applied to the cone–horizontal cell synapse in the outer plexiform layer of the retina. Numerical simulations reproduce the experimental calcium current-voltage (IV) curves for the goldfish retina in response to a bright spot, with and without an illuminated background. The ephaptic (electrical) effect is demonstrated by computing the shift in the IV curve for background off versus background on for increasingly narrower openings between the sides of the cone and the horizontal cell.

Key words. retina, ephaptic effect, synapse, drift-diffusion model

AMS subject classifications. 92C20, 65M08

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1. Introduction. The nervous system is a complex network of cells which can communicate with each other via electrical and chemical signals. The electric currents in the nervous system are carried by mobile ions dissociated in the solution baths that surround and fill the individual neurons. The retina, which is considered part of the central nervous system, is an ideal area for studying electrical communication between neurons, given its diversity and accessibility.

The outer plexiform layer of the retina consists of four types of interacting neurons: rods, cones, bipolar cells, and horizontal cells. The rods and cones are responsible for visual phototransduction, the process of transforming light into electrical signals that can be interpreted by the brain. The bipolar cells carry visual information to the inner plexiform layer, while the horizontal cells form a network or syncytium that is confined to the outer plexiform layer.

This investigation focuses on the synaptic complex between horizontal cells and cones in the goldfish retina (see Figure 1). When horizontal cells become hyperpolarized (the potential across the cell membrane becomes more negative), cone cells exhibit an increased inward calcium current. There are three major competing hypotheses (see [2] for a review) about what causes this increase in calcium levels: the GABA hypothesis [3], the pH hypothesis [4], and the ephaptic hypothesis [5, 6, 2].

The ephaptic hypothesis states that the specialized geometry of the cone–horizontal cell synapse can create a voltage drop in the intersynaptic space that causes the voltage-sensitive calcium channels of the cone to open. The other two hypotheses involve either a neurotransmitter (GABA) which blocks cone calcium channels or pH-sensitive cone calcium channels. Kamermans and Fahrenfort [2] advocate the ephaptic hypothesis based on their laboratory experiments on the goldfish retina.

Reference [7] discusses the primary importance of the ephaptic effect versus the effect of GABA on *time-dependent* simulations of current responses of the cat retina

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FIG. 1. One micron $\times$ one micron schematic (after [1]) of a horizontal-cell (HC) dendrite contacting a cone pedicle (CP), with a neighboring bipolar cell (BC). The simulation region is suggested by the black rectangle.

FIG. 2. Two-dimensional $400 \text{ nm} \times 40 \text{ nm}$ computational region for the cone-horizontal cell intersynaptic space. The cone-pedicle (horizontal-cell) membrane is 480 nm (370 nm) in length, with a 40-nm gap and $10/20\text{-nm}$ openings at the sides of the horizontal cell. We model only calcium channels in the cone-pedicle membrane, and only hemichannels in the horizontal-cell membrane. Note that ϕ^- and σ_i^- are functions of location on the membranes.

to a flashing spot and an illuminated or unilluminated background, in the context of a multiscale *macroscopic* two-dimensional (2D) model. The model incorporates both GABA and ephaptic mechanisms on the scale of an individual synapse and the scale of the receptive field.

Here we focus on the experimental *steady-state* calcium current-voltage curve [2] for the goldfish retina in response to a bright spot, which exhibits a shift to higher magnitude currents when the background is illuminated (hyperpolarizing the horizontal cells). We simulate this effect numerically at a *microscopic* level through the drift-diffusion (Poisson–Nernst–Planck) model—including a numerical model for cell membranes that resolves surface-charge boundary layers—applied to the cone-horizontal cell synapse in the model 2D geometry shown in Figure 2.

The ephaptic (electrical) effect is demonstrated by computing the shift in the current-voltage (IV) curve for background off versus background on for increasingly narrower openings between the sides of the cone and the horizontal cell.

2. Drift-diffusion model. The drift-diffusion model can be applied in the continuum approximation (see, for example, [8, 9, 10, 11]) to ion flow in the intersynaptic-

space salt bath between the cone membrane and the horizontal-cell membrane. The discrete distribution of ions is described by continuum ion densities $n_i(\mathbf{x}, t)$ for $i = \text{Ca}^{2+}$, Na^+ , K^+ , and Cl^- , and the positive and negative ions flow in water in an electric field $\mathbf{E}(\mathbf{x}, t)$.

In the experimental setup, a voltage bias V is applied between the cone and the horizontal cell by means of a patch clamp.

The drift-diffusion model consists of partial differential equations for conservation of each ionic species and Poisson's equation for the electrostatic potential $\phi(\mathbf{x}, t)$:

$$\begin{aligned} (1) \quad & \frac{\partial n_i}{\partial t} + \nabla \cdot \mathbf{f}_i = 0, \\ (2) \quad & \mathbf{f}_i = z_i \mu_i n_i \mathbf{E} - D_i \nabla n_i, \\ (3) \quad & \nabla \cdot (\epsilon \nabla \phi) = - \sum_i q_i n_i, \quad \mathbf{E} = -\nabla \phi, \end{aligned}$$

where ϵ is the dielectric coefficient of water, and where for each ionic species i , $\mathbf{f}_i$ is the number current density (particle flux), q_i is the ionic charge (for example, $q_{\text{Ca}} = +2e$ with e the proton charge), $z_i = q_i/e$, μ_i is the mobility coefficient, and D_i is the diffusion coefficient. The total electric current density (charge flux) is

$$(4) \quad \mathbf{j} = \sum_i q_i \mathbf{f}_i.$$

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

3. A model of the membrane. We model the membranes (see Figure 3) in a way that is similar to Mori, Jerome, and Peskin [12] and Mori and Peskin [13], but with the crucial difference that we resolve surface-charge boundary layers. (References [12, 13] assume charge neutrality everywhere, including in the salt baths.) The membrane is modeled as a bivalued sheet (in three dimensions) with a capacitance C_m per unit area, with different surface charge densities $\sigma_i^\pm$ and potentials $\phi^\pm$ on the intracellular (+) and extracellular (−) sides. Although the $\sigma_i^\pm$ differ in general, we assume the membrane is overall charge neutral so that $\sigma \equiv \sum_i \sigma_i^+ = -\sum_i \sigma_i^-$. Bath values of the ion densities and potential are denoted with a subscript b : n_{bi} and ϕ_b , respectively.

Our numerical method consists of two steps: (i) given the σ_i^- , we update the interior ion densities and potential through the drift-diffusion equations (1)–(3), using (9), $\sigma_i^\pm \approx q_i l_D (n_i^\pm - n_{bi}^\pm)$, to relate the surface-charge densities to the space-charge densities at the membrane boundary grid points and (10), $[\phi] \equiv \phi^+ - \phi^- = \sigma/C_m$, and (11), $[\hat{\mathbf{n}} \cdot \nabla \phi] = 0$, to relate the total surface-charge densities and intracellular potentials to the extracellular potentials at the membrane boundary grid points; then (ii) we update the surface-charge densities through the membrane-charge-conservation conditions (12)–(14). Note that the superscript $\pm$ always denotes the value of a quantity on the membrane modeled as a sheet; i.e., on the *immediate* intracellular (+) or extracellular (−) side of the membrane.

For the interior solve, the surface-charge densities $\sigma_i^\pm$ are identified with the *excess* (with respect to bath values) membrane boundary layer charges times the layer width $q_i l_D (n_i^\pm - n_{bi}^\pm)$, where the width of the membrane boundary layer is roughly a Debye length (see the derivation of (9) below).

FIG. 3. Computational grid. The membrane is the line denoted by m .

To justify the relationship $\sigma_i^\pm \approx q_i l_D (n_i^\pm - n_{bi}^\pm)$, we make use of thermal equilibrium Poisson–Boltzmann theory. In thermal equilibrium the ion densities are given by

$$(5) \quad n_i = n_{bi} \exp \left\{ -\frac{q_i (\phi - \phi_b)}{kT} \right\}.$$

The Poisson–Boltzmann equation then takes the form

$$(6) \quad \nabla \cdot (\epsilon \nabla \phi) = - \sum_i q_i n_{bi} \exp \left\{ -\frac{q_i (\phi - \phi_b)}{kT} \right\} \approx \left(\sum_i q_i^2 n_{bi} \right) \frac{\phi - \phi_b}{kT}$$

for $|q_i (\phi - \phi_b)| / (kT) \ll 1$.

For z perpendicular to the membrane, $\phi_{zz} \approx (\phi - \phi_b) / l_D^2$, where the Debye length

$$(7) \quad l_D = \sqrt{\frac{\epsilon kT}{\sum_i q_i^2 n_{bi}}} \approx 1 \text{ nm}$$

and

$$(8) \quad \phi \approx \phi_b^\pm + (\phi^\pm - \phi_b^\pm) e^{-|z|/l_D}, \quad n_i \approx n_{bi}^\pm \left(1 - \frac{q_i (\phi^\pm - \phi_b^\pm)}{kT} e^{-|z|/l_D} \right).$$

Equations (8) demonstrate that the potential difference $\phi - \phi_b^\pm$ and the excess charge densities $q_i (n_i^\pm - n_{bi}^\pm)$ decay exponentially away from the membrane on a characteristic

length scale given by the Debye length. Thus on physical grounds, we set

$$(9) \quad \sigma_i^\pm = \int_0^\infty q_i (n_i - n_{bi}^\pm) dz \approx q_i l_D (n_i^\pm - n_{bi}^\pm).$$

This expression differs dramatically from the approach of [12, 13], but agrees numerically with their model for surface charge when $|q_i (\phi - \phi_b)| / (kT) \ll 1$, which is the case here (see Figure 8 with ϕ_b the potential at the center of the intersynaptic space) and for most biological applications. The appendix discusses how to relate the surface-charge densities and equivalent space-charge densities when this inequality is violated.

General jump conditions for Poisson's equation can be written down:

$$(10) \quad [\phi] \equiv \phi^+ - \phi^- \equiv V_m = \frac{\sigma}{C_m},$$

$$(11) \quad [\hat{\mathbf{n}} \cdot \nabla \phi] = 0,$$

where $\hat{\mathbf{n}}$ is a unit normal vector pointing from the + to the - side of the membrane. Here, however, since we are just modeling the intersynaptic space, we use only the first jump condition.

The membrane conditions for the surface-charge densities express conservation of charge, and are identical to those of [12, 13] (j_{mi} is positive for flow out of a cell):

$$(12) \quad \frac{\partial \sigma_i^+}{\partial t} = \hat{\mathbf{n}} \cdot \mathbf{j}_i^+ - j_{mi},$$

$$(13) \quad \frac{\partial \sigma_i^-}{\partial t} = -\hat{\mathbf{n}} \cdot \mathbf{j}_i^- + j_{mi},$$

$$(14) \quad \sigma \equiv \sum_i \sigma_i^+ = - \sum_i \sigma_i^-.$$

4. Simulations and comparison with experiment. The drift-diffusion model with membrane boundary conditions takes the following form (where $i = \text{Ca}^{2+}$, Na^+ , K^+ , and Cl^-). Note that we model only calcium channels in the cone-pedicle membrane, and only hemichannels in the horizontal-cell membrane. (i) Given the σ_i^- , we solve the drift-diffusion equations with membrane and ambient boundary conditions (BCs):

$$(15) \quad \frac{\partial n_i}{\partial t} + \nabla \cdot (z_i \mu_i n_i \mathbf{E}) = D_i \nabla^2 n_i,$$

$$(16) \quad \nabla \cdot (\epsilon \nabla \phi) = - \sum q_i n_i, \quad \mathbf{E} = -\nabla \phi,$$

$$(17) \quad n_i^- = n_{bi}^- + \frac{\sigma_i^-}{q_i l_D}, \quad \phi_{CP,HC}^- = V_{CP,HC}^+ - \frac{\sigma}{C_m} \quad (\text{CP \& HC BCs}),$$

$$(18) \quad n_i = n_{bi}, \quad \hat{\mathbf{n}}_B \cdot \nabla \phi = 0 \quad (\text{ambient BCs at openings}),$$

where $\hat{\mathbf{n}}_B$ is a unit normal vector to the grid boundary, and $V_{CP,HC}^+$ are specified constants along the intracellular cone-pedicle (CP) and horizontal-cell (HC) membranes. V_{HC}^+ is set to -40 mV and then V_{CP}^+ is varied to trace out the IV curves in Figures 10 and 11. (Note that all physical voltages—and thus all voltages in equations—are voltage *differences*, as in $V_{CP,HC}$ below.) Then (ii), we update the surface-charge

TABLE 1
Known biological parameters. Note that $g_i = G_i/(N_s A_m)$.

Parameter	Value	Description
$n_{b,Ca}$	2 mM	bath density of Ca^{2+}
$n_{b,Na}$	140 mM	bath density of Na^+
$n_{b,K}$	2.5 mM	bath density of K^+
$n_{b,Cl}$	146.5 mM	bath density of Cl^-
ϵ	80	dielectric coefficient of water
N_s	20	number of spine heads per CP
A_m	$0.1 \mu m^2$	spine head area
C_m	$1 \mu F/cm^2$	membrane capacitance per unit area
V_{Ca}	50 mV	reversal potential for Ca^{2+}
V_{Na}	50 mV	reversal potential for Na^+
V_K	-60 mV	reversal potential for K^+
G_{Ca}	1.5 nS	Ca^{2+} conductance into HC
G_{Na}	1.5 nS	Na^+ conductance into HC
G_K	2.5 nS	K^+ conductance into HC
G_{hemi}	5.5 nS	hemichannel conductance
D_{Ca}	$0.8 nm^2/ns$	diffusivity of Ca^{2+}
D_{Na}	$1.3 nm^2/ns$	diffusivity of Na^+
D_K	$2 nm^2/ns$	diffusivity of K^+
D_{Cl}	$2 nm^2/ns$	diffusivity of Cl^-
μ_{Ca}	$32 nm^2/(V ns)$	mobility of Ca^{2+}
μ_{Na}	$52 nm^2/(V ns)$	mobility of Na^+
μ_K	$80 nm^2/(V ns)$	mobility of K^+
μ_{Cl}	$80 nm^2/(V ns)$	mobility of Cl^-

TABLE 2
Fitting parameters in the model for the cone calcium transmembrane current density $j_{m,Ca}$ in (20).

Parameter	Value	Description
G_{Ca}	1.5 nS	Ca^{2+} conductance into CP
V_{Ca}	37 mV	reversal potential for Ca^{2+}
θ_-	-33 mV	kinetic parameter, background off
θ_+	-40 mV	kinetic parameter, background on
λ	5 mV	kinetic parameter

densities through the membrane-charge-conservation conditions (12)–(14):

$$(19) \quad \frac{\partial \sigma_i^-}{\partial t} = -\hat{n} \cdot \mathbf{j}_i^- + j_{mi}, \quad \sigma = -\sum \sigma_i^- \quad (\text{CP \& HC}),$$

$$(20) \quad j_{m,Ca} = \frac{g_{Ca}(V_{CP} - V_{Ca})}{1 + \exp\{(\theta_{\pm} - V_{CP})/\lambda\}}, \quad j_{hemi} = 0 \quad (\text{CP}),$$

$$(21) \quad j_{hemi} = \sum_{\text{cations}} g_i(V_{HC} - V_i) = g_{hemi}V_{HC}, \quad j_{m,Ca} = 0 \quad (\text{HC}),$$

where $V_{CP,HC} \equiv V_{CP,HC}^+ - \phi_{CP,HC}^-$. The cone calcium transmembrane current density in (20) is a phenomenological fitting curve due to [14, 15]: a linear current multiplied by a sigmoidal activation curve with θ the half-maximal activation potential. The difference $\theta_+ - \theta_-$ represents the effects of the hyperpolarization of the horizontal cell when the background illumination is turned on. The horizontal cell hemichannel transmembrane current density in (21) is taken to be Ohmic.

Note that Na ions (because of their large density in the intersynaptic space) dominate the electrostatic potential and the Debye length.

The biological parameters in (15)–(21) are given in Tables 1 and 2. Note that 1 mM = $6.022 \times 10^{17} \text{ cm}^{-3}$.

FIG. 4. Drift-diffusion simulation of Ca^{2+} density in mM. FIG. 5. Drift-diffusion simulation of Na^+ density in mM.

We will apply the TRBDF2 (trapezoidal rule/second-order backward difference formula) [16, 10, 11] method for the transport equations (15) and the ODEs (19) to the 2D cone-horizontal cell synapse with the model of the membrane to investigate the importance of ephaptic (electrical) effects. A fast Poisson solver is used to solve Poisson's equation (16). The steady-state solutions in the figures are computed by simulating the time-dependent equations to equilibrium.

Numerical simulations on a 50×500 grid ($\Delta x = \Delta y = l_D = 0.8$ nm) are presented in Figures 4–11. Figures 4–9 are computed at steady-state at $V_{CP} = V_{CP}^+ - \phi_{CP}^- = -15$ mV with background illumination off.

FIG. 6. Drift-diffusion simulation of K^+ density in mM. FIG. 7. Drift-diffusion simulation of Cl^- density in mM.

The buildup of charge layers on the order of a Debye length ($l_D = 0.8$ nm in the intersynaptic region) at the cone-pedicle membrane (left, back, and right sides of the grid) and at the horizontal-cell membrane (front side of the grid) is illustrated in Figures 4–7 and 9. Note the effects of the 10/20 nm openings at the left and right of the horizontal cell on the densities and the potential. The gap scale (y direction) is expanded with respect to the membrane scale (x direction), since most of the variation in the state variables occurs along the y direction. The buildup of positive surface charge along the cone pedicle and negative surface charge along the horizontal cell

FIG. 8. Drift-diffusion simulation of electrostatic potential in mV.

FIG. 9. Drift-diffusion simulation of total charge density in mM.

is consistent with the electrostatic potential plotted in Figure 8. The shape of the potential also explains why Ca^{2+} is flowing *into* the cone ($I_{Ca} < 0$).

The cone calcium transmembrane current is defined by integrating $j_{m,Ca}$ over the cone-pedicle membrane,

$$(22) \quad I_{Ca} = N_s \int_{A_m} j_{m,Ca} da,$$

and is negative since Ca^{2+} is flowing into the cone. The IV curve for the cone calcium

FIG. 10. Computed versus experimental [2] I_{Ca} versus V_{CP} shift turning on background illumination.

FIG. 11. Ephaptic effect: Shift in I_{Ca} versus V_{CP} for varying opening widths.

transmembrane current is displayed in Figure 10. The parameters in Table 2 were adjusted to give the best fit with the experimental curves [2]. The shifts in the experimental and the phenomenological model (20) IV curves when the background illumination is turned on may include secondary effects of other mechanisms, but the ephaptic effect is dominant. Note the increase in the magnitude of the current when the background illumination is turned on. The shift between the background off versus background on IV curves is plotted in Figure 11 for three different side-opening widths. Decreasing the size of the side openings increases the electrical resistance there, diverting more current into the membranes. The dependence of the shift in I_{Ca} with respect to resistance in the side openings demonstrates the ephaptic effect.

5. Conclusion. There is convincing experimental evidence [2] for the dominance of the ephaptic effect in the cone–horizontal cell synapse of the retina. The ephaptic effect demonstrated here by computing the shift in the IV curve for background off

versus background on for increasingly narrower openings between the sides of the cone pedicle and the horizontal cell, in conjunction with the results of [7] that demonstrate the primary importance of the ephaptic effect versus the effect of GABA on simulations of current responses of the cat retina, indicate on the theoretical level that GABA dynamics is of secondary importance.

Our numerical model of the cell membrane that resolves surface-charge boundary layers—involving a transcription between surface-charge densities and space-charge densities—is quite generally applicable in cell biology, and should be useful in many other specific applications.

The model for the cone calcium transmembrane current density $j_{m, Ca}$ in (20) is a phenomenological fitting curve, with $\theta_+ - \theta_-$ representing the *nonlocal* effect of hyperpolarization of the horizontal cell when the background illumination is turned on. The calcium current ought to couple *locally* to only the electric potential, which is modified globally by the horizontal cell's hyperpolarization. Modeling the effects of the hyperpolarization of the horizontal cell on the cone calcium transmembrane current at a microscopic level through the drift-diffusion model is in progress.

Appendix A. Cell membrane surface charges. The ionic surface-charge densities are given by

$$(23) \quad \sigma_i = \int_0^\infty q_i (n_i - n_{bi}) dz.$$

Using the excellent approximation for the potential in (8), the normalized surface-charge densities are

$$(24) \quad \bar{\sigma}_i = \frac{\sigma_i}{q_i n_{bi} l_D} = \int_0^\infty \left(\frac{n_i}{n_{bi}} - 1 \right) dx \approx \int_0^\infty (\exp\{-u_0 e^{-x}\} - 1) dx,$$

where $x = z/l_D$, $u_0 = q_i(\phi_0 - \phi_b)/(kT)$, and the subscript 0 denotes membrane values at $z = 0^+ = x$.

Our physical approximation (A) is based on the fact that charges in an ionic fluid are screened over roughly a Debye length:

$$(25) \quad \bar{\sigma}_i \approx \frac{n_{0i}}{n_{bi}} - 1 = e^{-u_0} - 1 \quad (\text{A})$$

which gives the approximation $\sigma_i \approx q_i l_D (n_{0i} - n_{bi})$.

The approximation (M) of [12] is based on the twice-linearized approximation

$$(26) \quad \bar{\sigma}_i \approx - \int_0^\infty u_0 e^{-x} dx = -u_0 \quad (\text{M})$$

which is also the linearized version of (A).

For higher magnitude potentials $|u_0|$, the integral (24) can be evaluated in terms of the exponential integral

$$(27) \quad \bar{\sigma}_i \approx \int_0^\infty (\exp\{-u_0 e^{-x}\} - 1) dx = -E_1(u_0) - \ln(u_0) - \gamma_E,$$

where $E_1(\eta) = \int_\eta^\infty dt e^{-t}/t$. Numerical values for $\bar{\sigma}_i(u_0)$ can be precomputed, and a table lookup and interpolation can be performed during the drift-diffusion simulations to transcribe the membrane boundary conditions by inverting the monotonically decreasing $\bar{\sigma}_i(u_0)$ to find u_0 and then $n_{0i} = n_{bi} \exp\{-u_0\}$. The approximations (A) and

FIG. 12. Comparison of the nearly exact Poisson–Boltzmann solution for $\bar{\sigma}_i$ versus $u_0 = q_i(\phi_0 - \phi_b)/(kT)$ with the approximations (A) and (M).

(M) are compared with this nearly exact numerical Poisson–Boltzmann solution (27) in Figure 12.

The drift-diffusion simulations of the cone–horizontal cell synapse using the approximation (A) and the nearly exact Poisson–Boltzmann solution (27) produce the same IV curves to within a line width, since for this problem $|u_0| \ll 1$.

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