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

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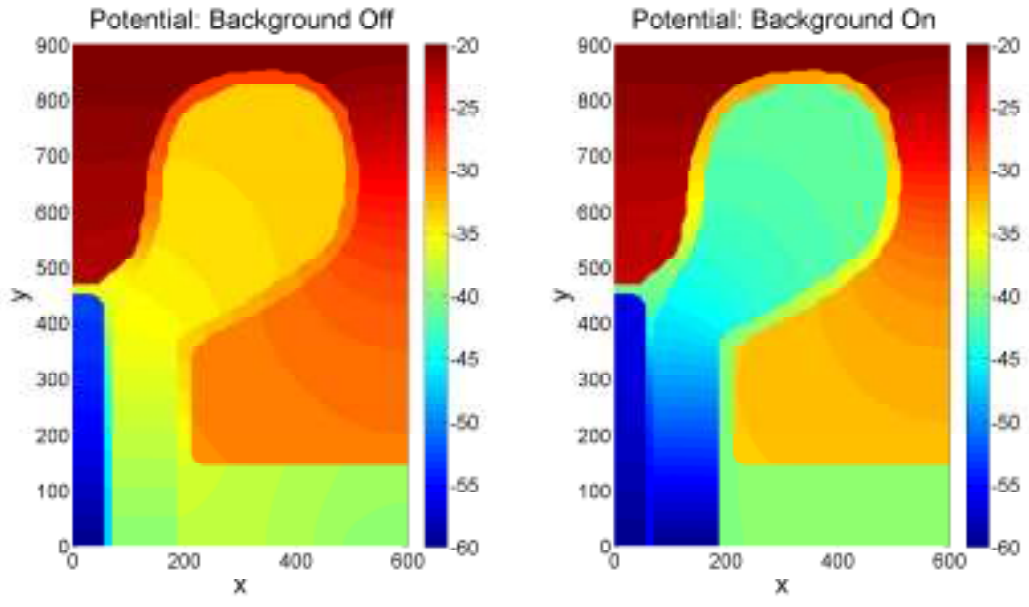


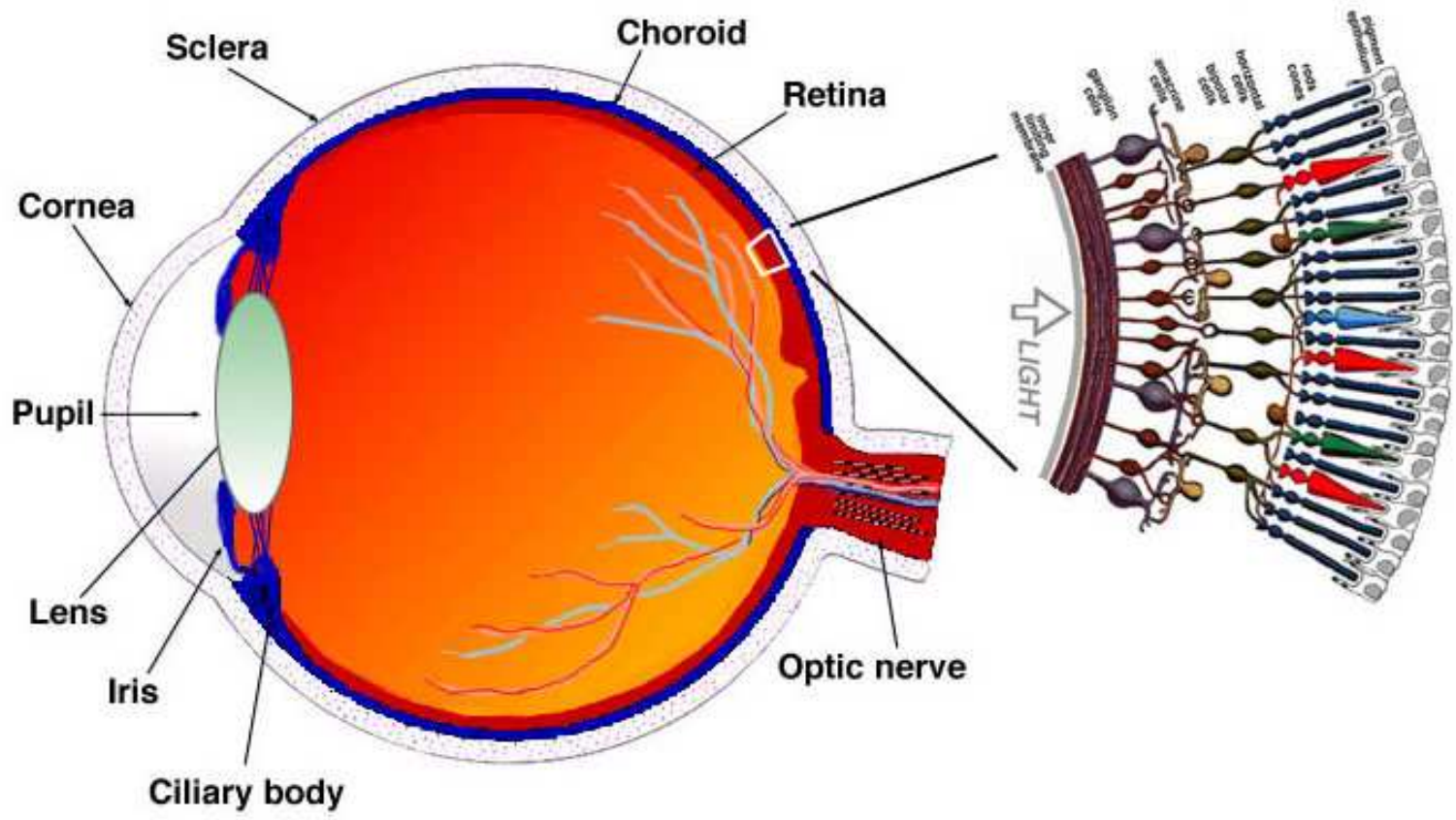


Fig. 1.1. A drawing of a section through the human eye with a schematic enlargement of the retina.

http://webvision.med.utah.edu/

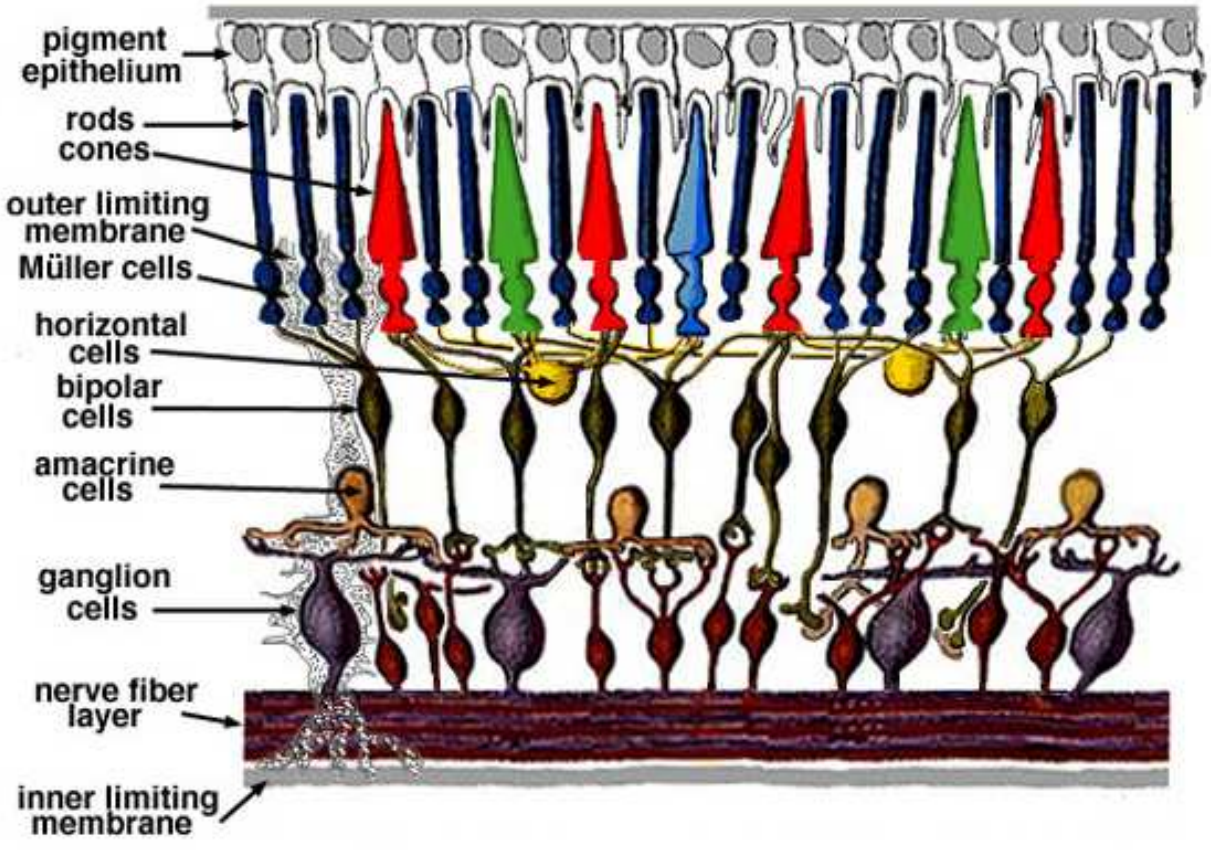
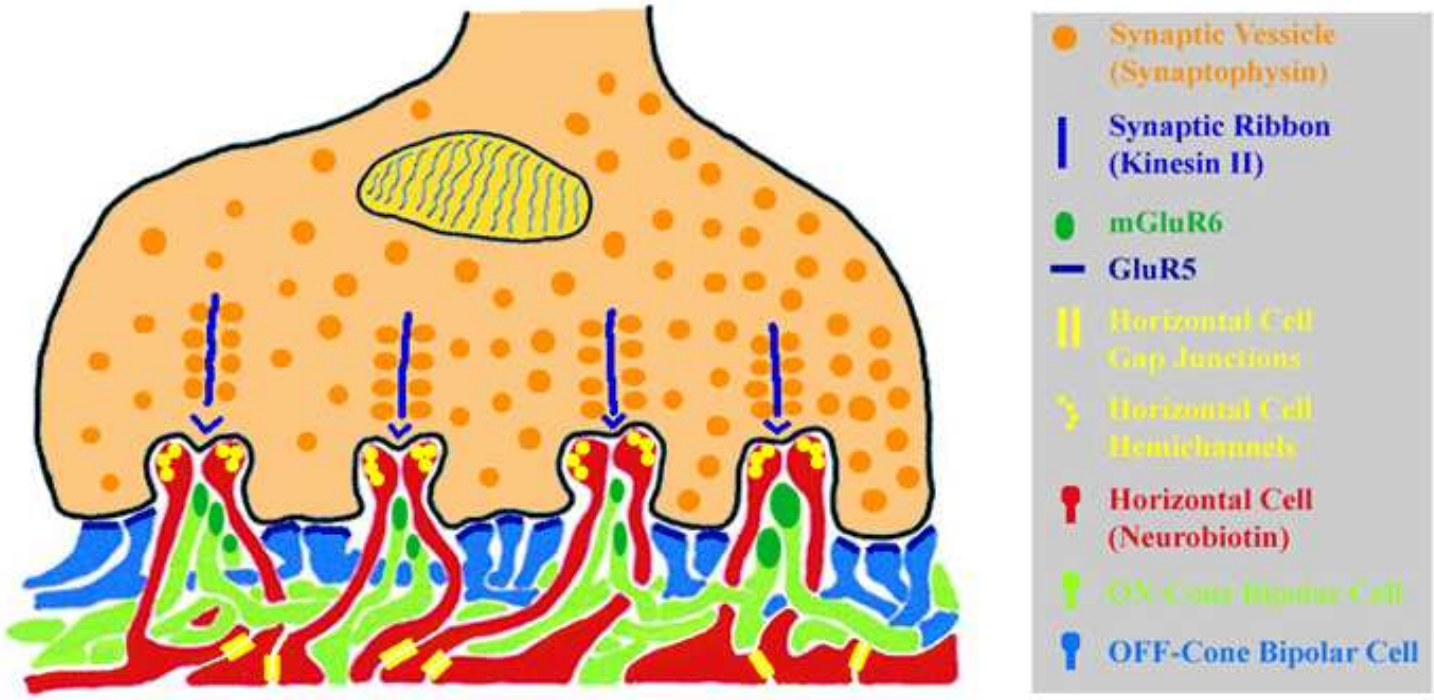
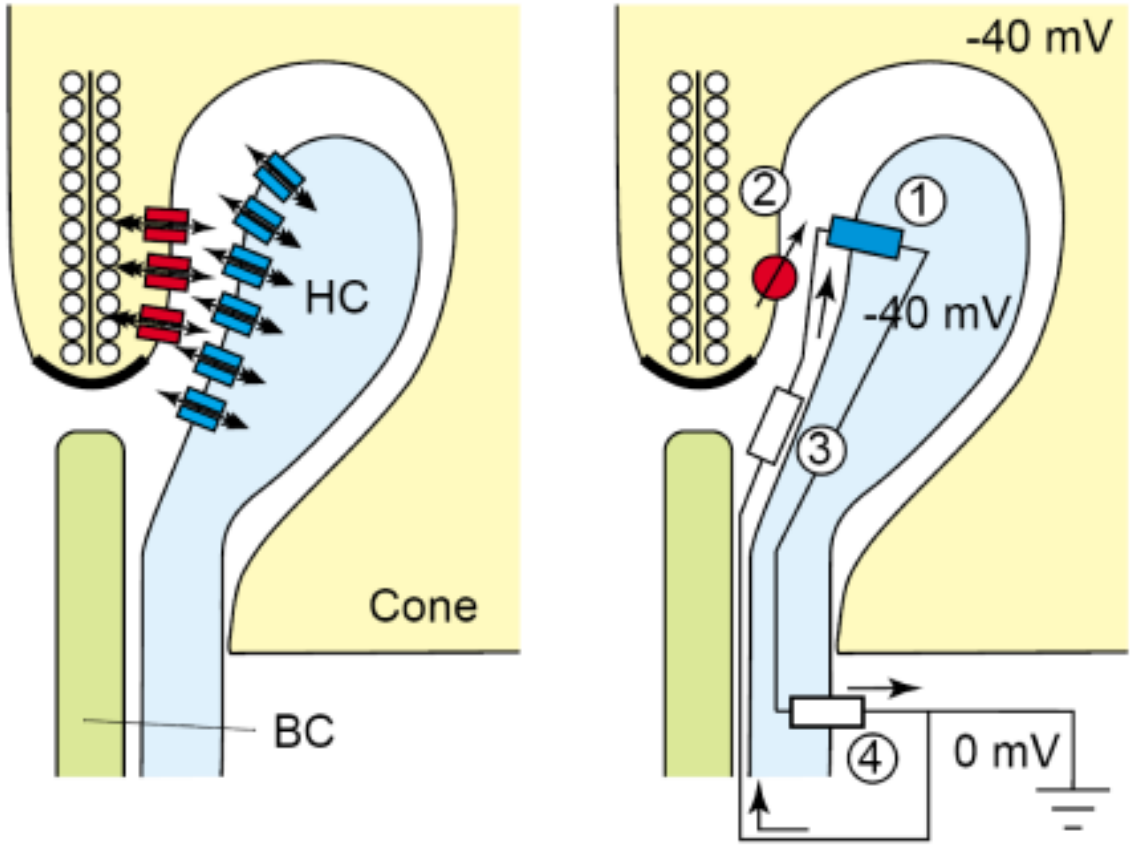


Fig. 2. Simple diagram of the organization of the retina.



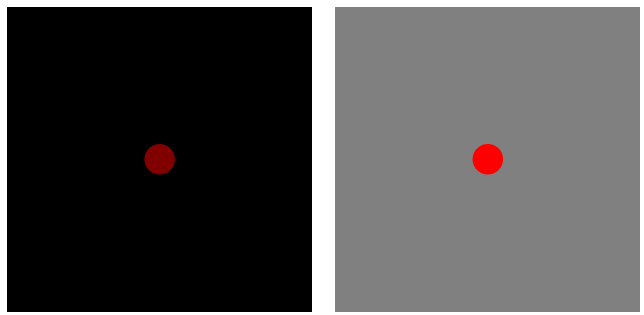
Schematic of cone pedicle showing four triad synapses

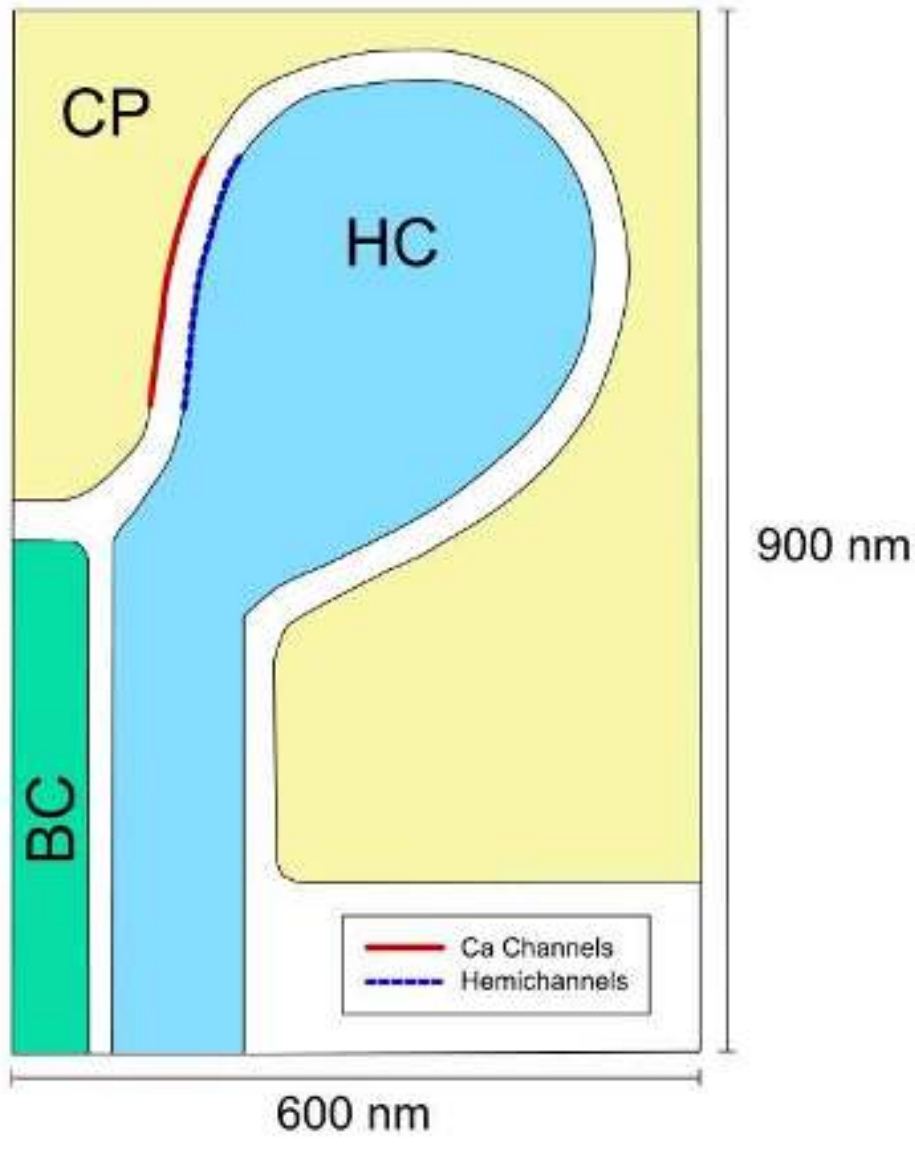


Schematic (Kamermans & Fahrenfort) of horizontal cell dendrite contacting cone pedicle: simulate 600 nm $\times$ 900 nm region

Ephaptic Effect

1. Experiments show illumination of cone causes hyperpolarization of horizontal cells & increased levels of intracellular cone Ca (Ca^{2+} current flows into cone)
2. Ephaptic hypothesis: specialized geometry of synapse can force currents through high-resistance bottlenecks causing potential drop in extracellular cleft
3. Cone membrane senses this as depolarization, which increases activation of voltage-sensitive Ca channels
4. Implies Ca^{2+} current is directly modulated by electric potential




CP
HC
BC
900 nm
600 nm
Ca Channels
Hemichannels

Drift-Diffusion (PNP) Model

$$\frac{\partial n_i}{\partial t} + \nabla \cdot \mathbf{f}_i = 0, \quad i = \mathrm{Ca}^{2+},\ \mathrm{Na}^{+},\ \mathrm{K}^{+},\ \mathrm{Cl}^{-}$$

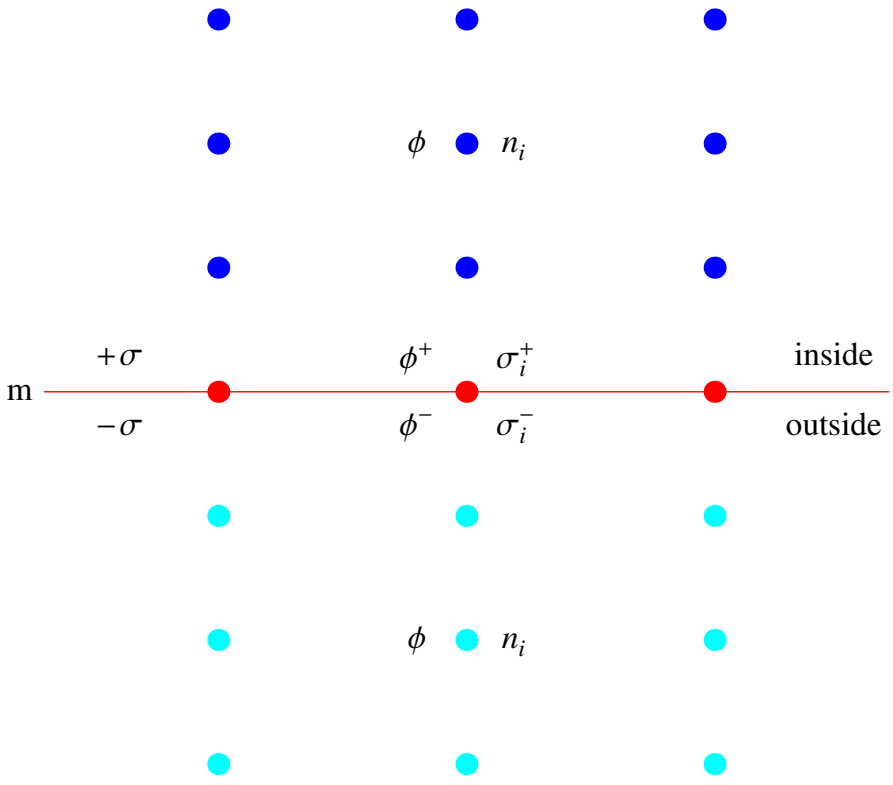
$$\mathbf{f}_i = z_i \mu_i n_i \mathbf{E} - D_i \nabla n_i, \quad z_i = \frac{q_i}{q_e}, \quad \mathbf{j}_i = q_i \mathbf{f}_i, \quad \mathbf{j} = \sum_i \mathbf{j}_i$$

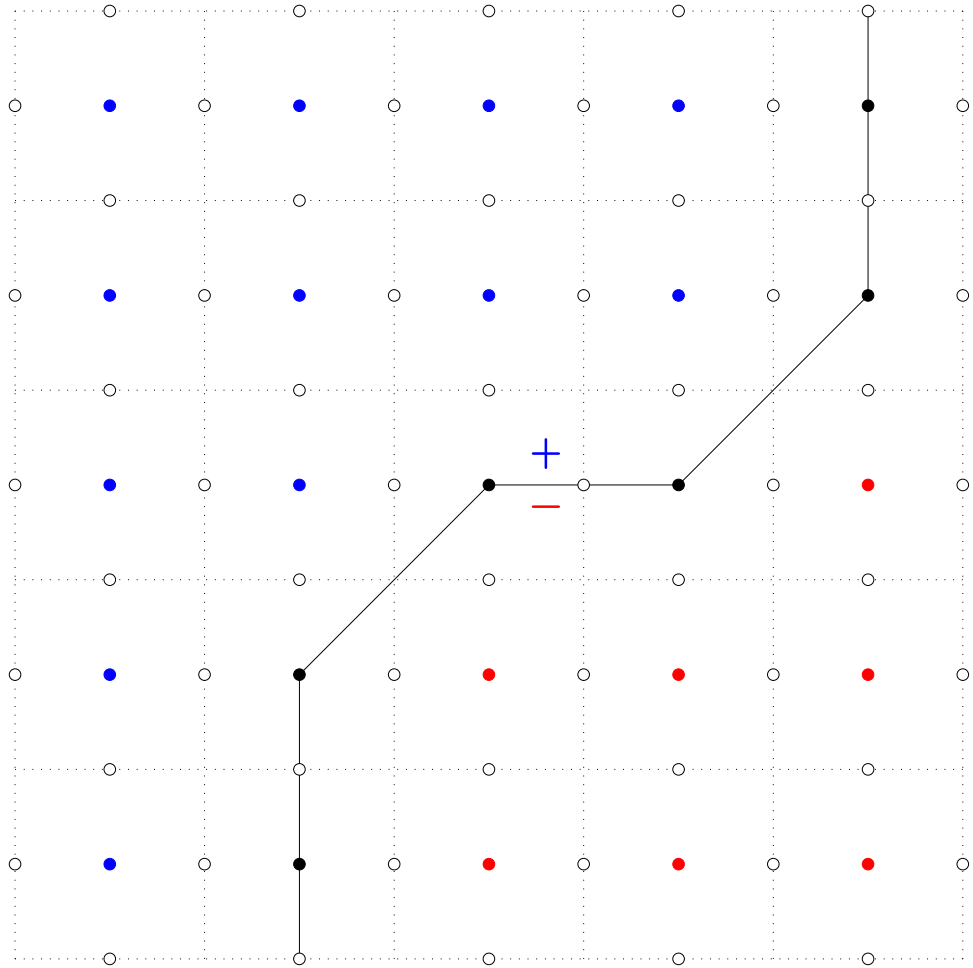
parabolic/elliptic system of PDEs:

$$\frac{\partial n_i}{\partial t} + \nabla \cdot (z_i \mu_i n_i \mathbf{E}) = D_i \nabla^2 n_i, \quad i = \mathrm{Ca}^{2+},\ \mathrm{Na}^{+},\ \mathrm{K}^{+},\ \mathrm{Cl}^{-}$$

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

A Model of the Membrane
(similar to Mori-Jerome-Peskin)





Poisson-Boltzmann Equation

$$n_i = n_{bi} \exp\left\{-\frac{q_i \phi}{kT}\right\}$$

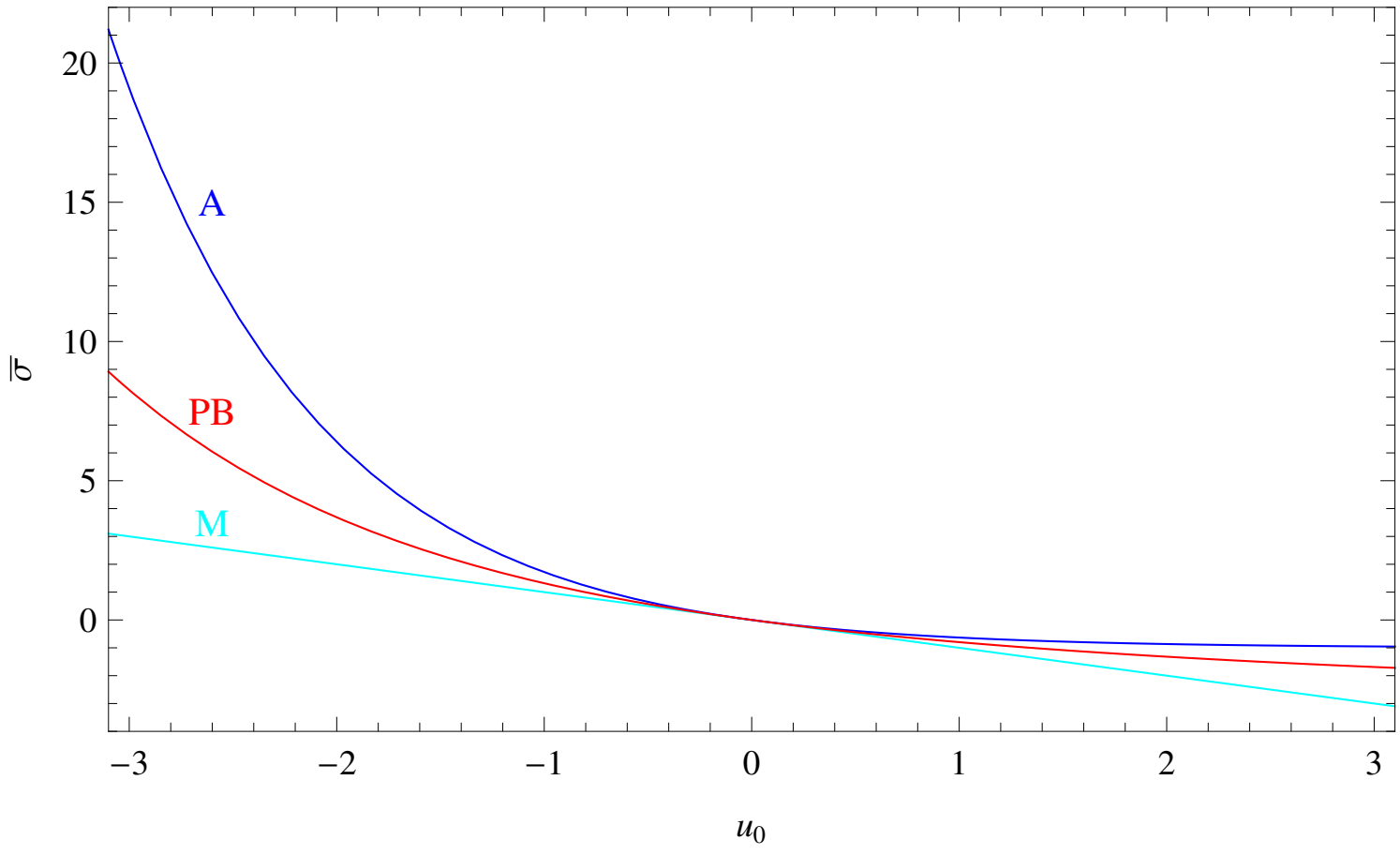
$$\nabla \cdot (\epsilon \nabla \phi) = -\sum_i q_i n_{bi} \exp\left\{-\frac{q_i \phi}{kT}\right\} \approx \left(\sum_i q_i^2 n_{bi}\right) \frac{\phi}{kT}$$

$$\text{Debye length } l_D = \sqrt{\epsilon kT / \left(\textstyle\sum_i q_i^2 n_{bi}\right)} \approx 1 \text{ nm}$$

For $z \perp$ & near membrane $\phi_{zz} \approx \phi / l_D^2$

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

Set $\sigma_i^+ = \int_0^\infty q_i \left(n_i - n_{bi}^+\right) dz \approx q_i l_D \left(n_i^+ - n_{bi}^+\right)$



Comparison of nearly exact Poisson-Boltzmann solution for $\sigma_i/(q_i n_{bi} l_D)$ vs. $u_0 = q_i(\phi_0 - \phi_b)/(kT)$ with approximations

Jump conditions for Poisson's equation

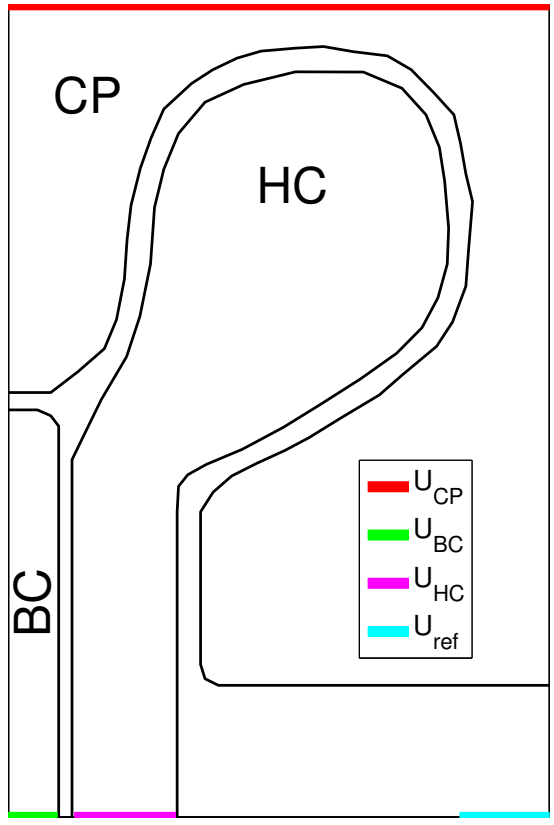
$$[\phi] \equiv \phi^+ - \phi^- = V = \frac{\sigma}{C_m}$$

$$[\hat{\mathbf{n}} \cdot \nabla \phi] = 0$$

BCs for drift-diffusion equation (Mori-Jerome-Peskin), but we use $\sigma_i^{\pm} = q_i l_D^{\pm} \left(n_i^{\pm} - n_{bi}^{\pm} \right)$

$$\frac{\partial \sigma_i^{\pm}}{\partial t} = q_i l_D^{\pm} \frac{\partial n_i^{\pm}}{\partial t} = -l_D^{\pm} \nabla \cdot \mathbf{j}_i^{\pm} \mp j_{mi}$$

$$\sigma \equiv \sum_i \sigma_i^+ = -\sum_i \sigma_i^-$$



Along axis of symmetry, homogeneous Neumann BCs for n_i & ϕ; along other outer boundaries, Dirichlet (bath) BCs for n_i & homogeneous Neumann or Dirichlet (colors) BCs for ϕ: $U_{ref} = -40$ mV, $U_{HC} = -60$ (on) or -40 (off) mV, $U_{BC} = -80$, -60, or -40 mV, $U_{CP} = -80$ to $+10$ mV

Numerical Methods

Simulate time-dependent equations to steady state $\sim$ *few 100,000 timesteps*

Given initial data, for each Δt*:*

(i) Compute ϕ from Poisson's equation with Dirichlet/Neumann BCs using "chaotic relaxation" Chebyshev SOR

(ii) Compute n_i from drift-diffusion equations with Dirichlet/ Neumann BCs using TRBDF2

(iii) *Membrane sweep:* Update $\sigma_i^{\pm}$ from $d\sigma_i^{\pm}/dt$ equations using TRBDF2 & transcribe to $n_i^{\pm}$; update $\phi^{\pm}$ with two jump conditions

Numerical Methods

TRBDF2 for drift-diffusion equations (about 30% of computation time), "chaotic relaxation" Chebyshev SOR for Poisson equation (about 70%), membrane BCs (about 1%)

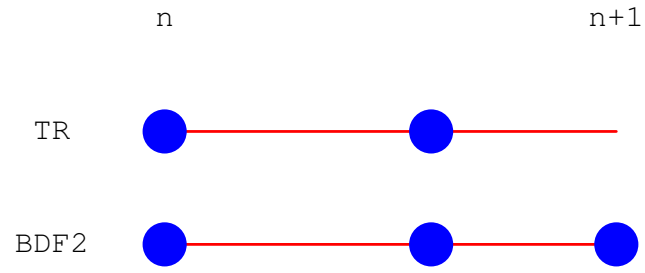
OpenMP gives speedup $\sim N_{cores}/2$

$\Delta t \sim 1$ ps initially $\rightarrow 50$ ps, charge layer relaxation ~ 1 ns

Steady state ~ 1 μs, GABA diffusion ~ 1 ms

Solution computed on 600×900 fine grid on 8 cores ~ 10 hrs

TRBDF2 Method



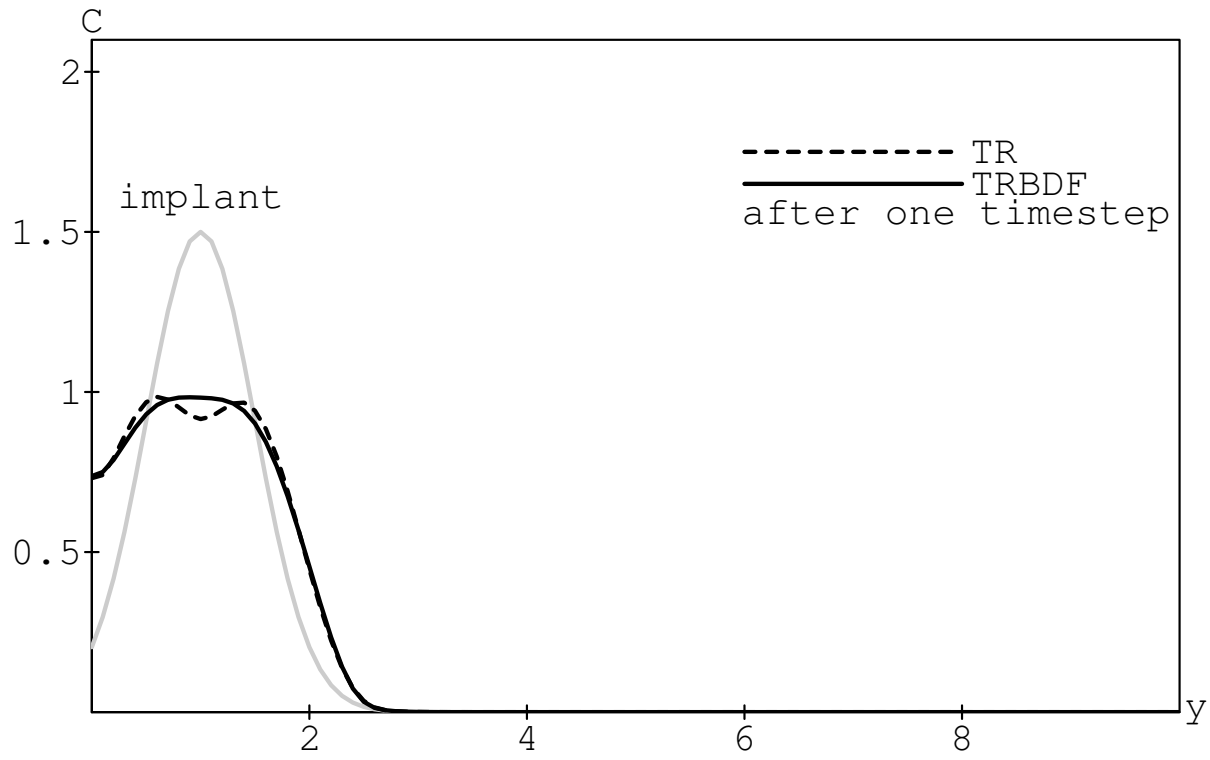
Timelevel $n+\gamma = n+(2-\sqrt{2})$. For $du/dt = f(u)$:

TR step

$$u^{n+\gamma} - \gamma\frac{\Delta t_n}{2}f^{n+\gamma} = u^n + \gamma\frac{\Delta t_n}{2}f^n$$

BDF2 step

$$u^{n+1} - \frac{1-\gamma}{2-\gamma}\Delta t_n f^{n+1} = \frac{1}{\gamma(2-\gamma)}u^{n+\gamma} - \frac{(1-\gamma)^2}{\gamma(2-\gamma)}u^n$$



Bank, Coughran, Fichtner, Grosse, Rose, & Smith (1985): composite one-step method, second-order accurate & L-stable, Δt dynamically adjusted by divided-difference estimate of local error

Known Biological Parameters

Parameter	Value	Description
$n_{b,Ca}$	10^{-4}, 2 mM	intra/extracellular bath density of Ca^{2+}
$n_{b,Na}$	10, 140 mM	intra/extracellular bath density of Na^{+}
$n_{b,K}$	150, 2.5 mM	intra/extracellular bath density of K^{+}
$n_{b,Cl}$	160, 146.5 mM	intra/extracellular bath density of Cl^{-}
ϵ	80	dielectric coefficient of water
N_s	20	number of spine heads per cone pedicle
A_m	0.1 μm^2	spine head area
C_m	1 μF/cm^2	membrane capacitance per 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_{hemi}	5.5 nS	hemichannel conductance

mM $= 6 \times 10^{17}$ ions/cm^3

Known Biological Parameters

Parameter	Value	Description
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^{-}

Einstein relation: $D_i = \mu_i kT/q_e$

Transmembrane Currents

$$j_{hemi} = \sum_{cations} g_i \left(V_{HC} - V_i\right) = g_{hemi} V_{HC}$$

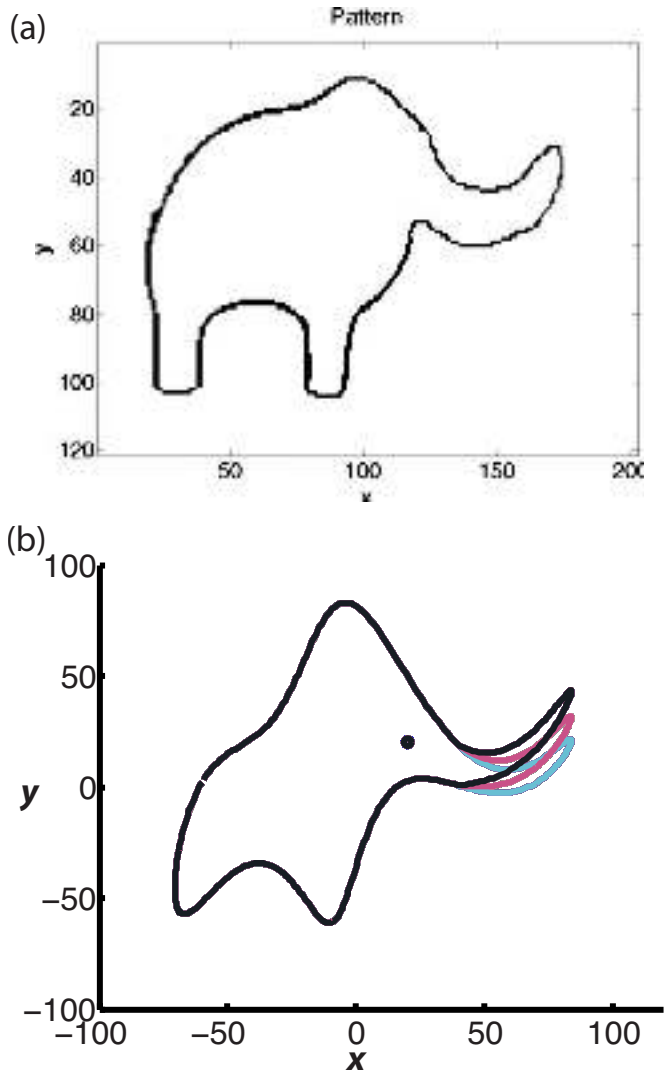
$$j_{m,Ca} = \frac{g_{Ca}\left(V_{CP} - E_{Ca}\right)}{1 + \exp\{\left(\theta - V_{CP}\right)/\lambda\}}$$

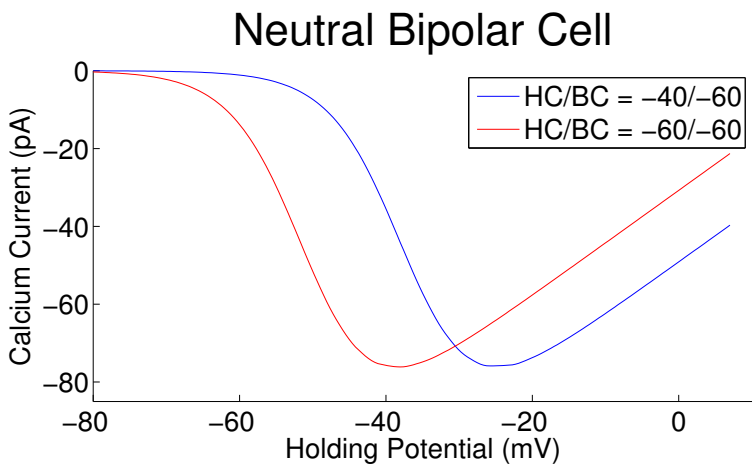
Parameter	Value	Description
E_{Ca}	50 mV	cone reversal potential for Ca^{2+}
G_{Ca}	2.2 nS	Ca conductance
θ	5 mV	kinetic parameter (independent of bg)
λ	3 mV	kinetic parameter

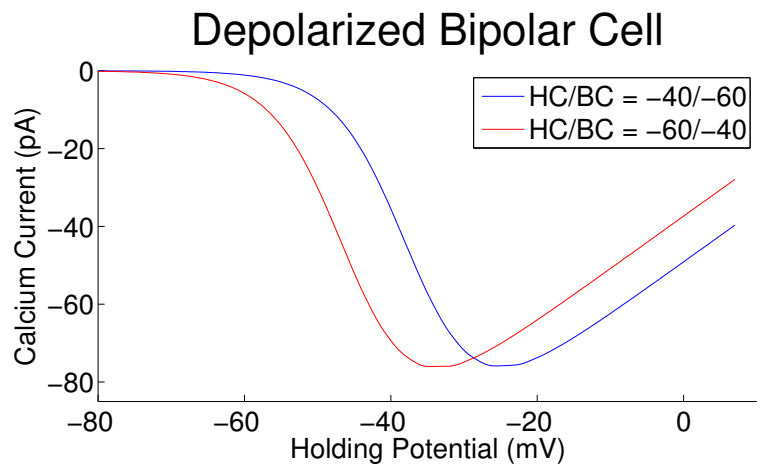
$g_i = G_i/(N_s A_m)$; $I_{Ca} = N_s \int_{A_m} j_{m,Ca}\, da$ flows into cone

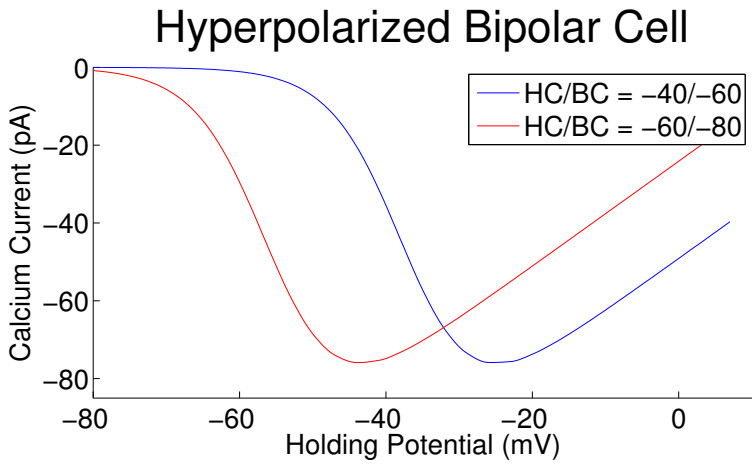
In desperation I asked Fermi whether he was not impressed by the agreement between our calculated numbers & his measured numbers. He replied, "How many arbitrary parameters did you use for your calculations?" I thought for a moment about our cut-off procedures & said, "Four." He said, "I remember my friend Johnny von Neumann used to say, with four parameters I can fit an elephant, & with five I can make him wiggle his trunk." –Freeman Dyson

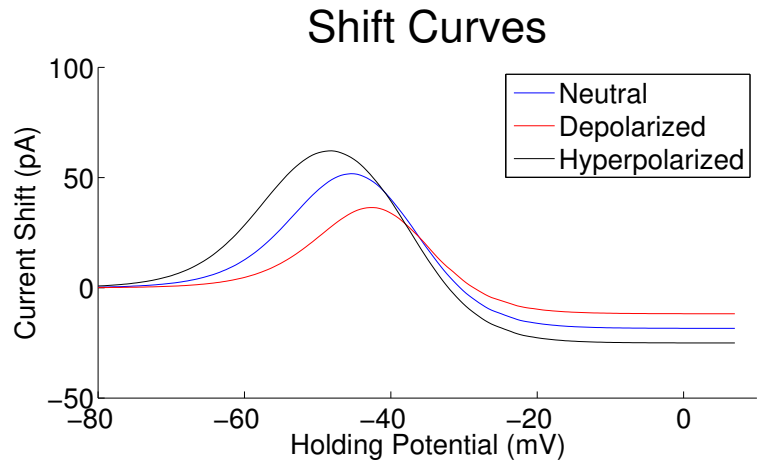
Not a very good elephant though—see next page: Fitting an elephant with (a) 30 (Wei 1975) & (b) 4 parameters, from J. Mayer, K. Khairy, & J. Howard, Am. J. Phys. 78, 648 (2010)


(a)
Pattern
20
40
60
80
100
120
y
50
100
150
200
x
(b)
100
50
0
−50
−100
y
−100
−50
0
50
100
x





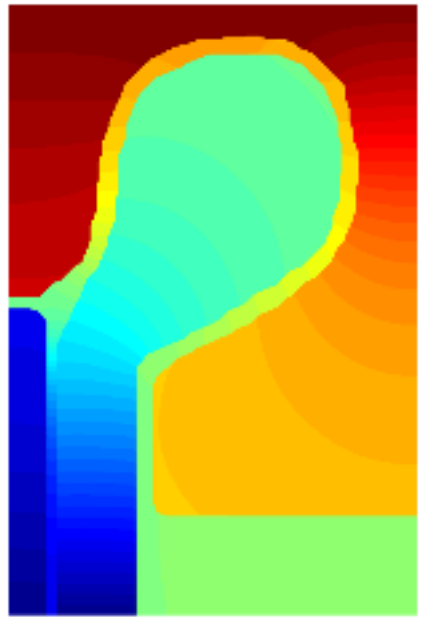


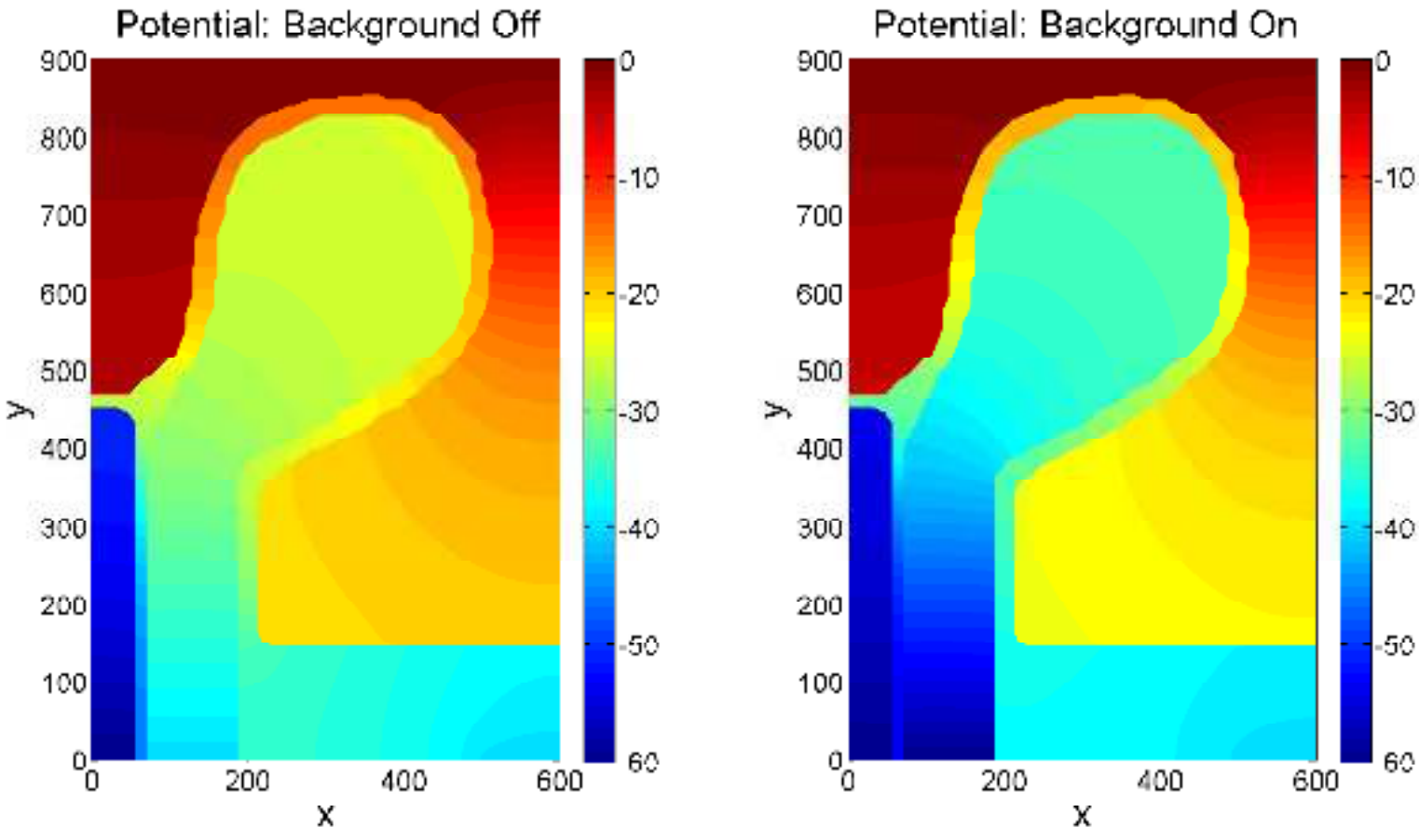


3-parameter fit to background off (blue) curve; then background on (red) curve is a prediction of the model

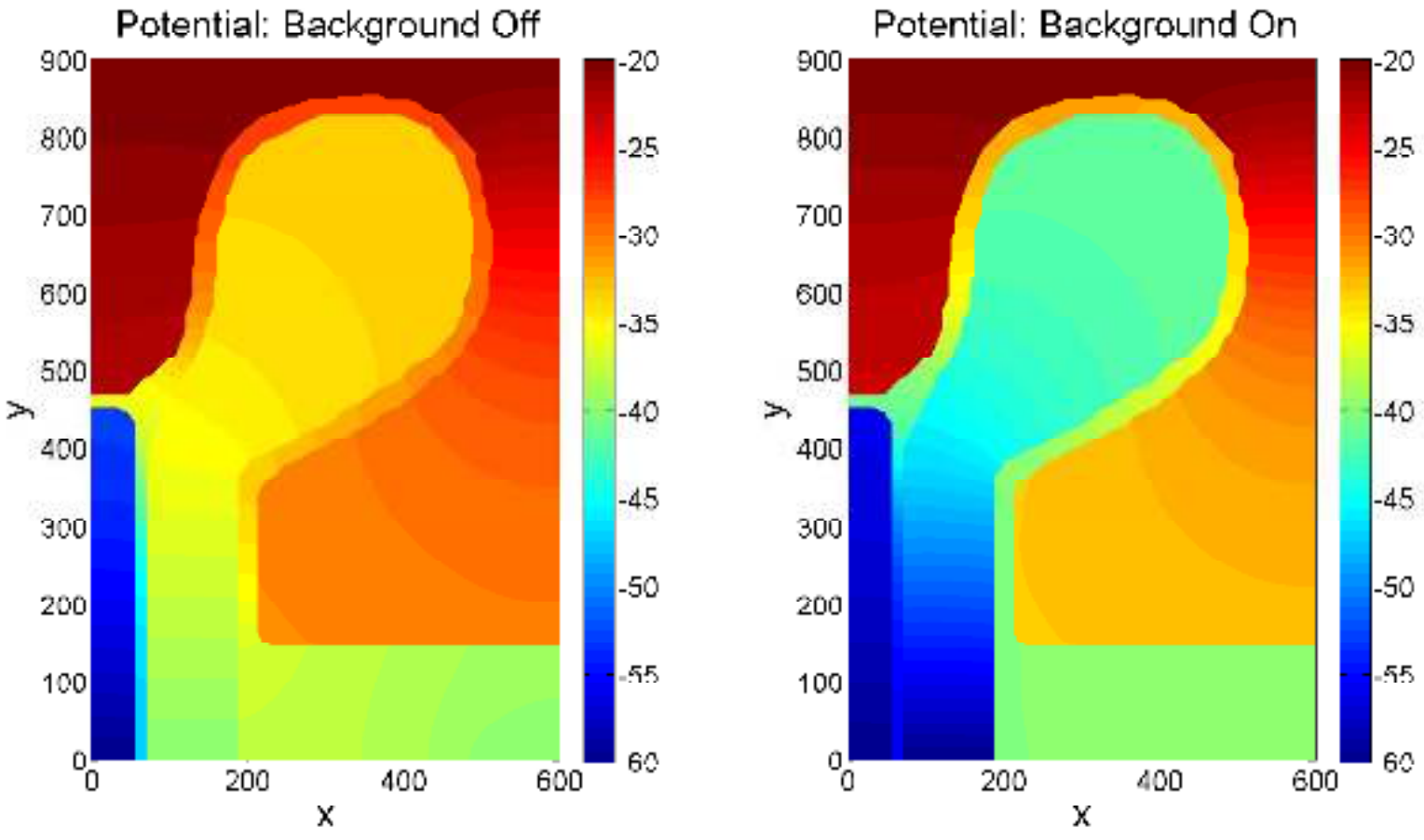
2D Complex Geometry of the Synapse

1. Model effects of complex geometry
2. Specify holding potential U_{CP} as in voltage clamp experiment
3. Apply 2D TRBDF2 drift-diffusion code (with Chebyshev SOR for Poisson equation) inside cells as well as outside, along with membrane boundary conditions
4. Computed potential shows simple compartment model is not adequate for triad synapse

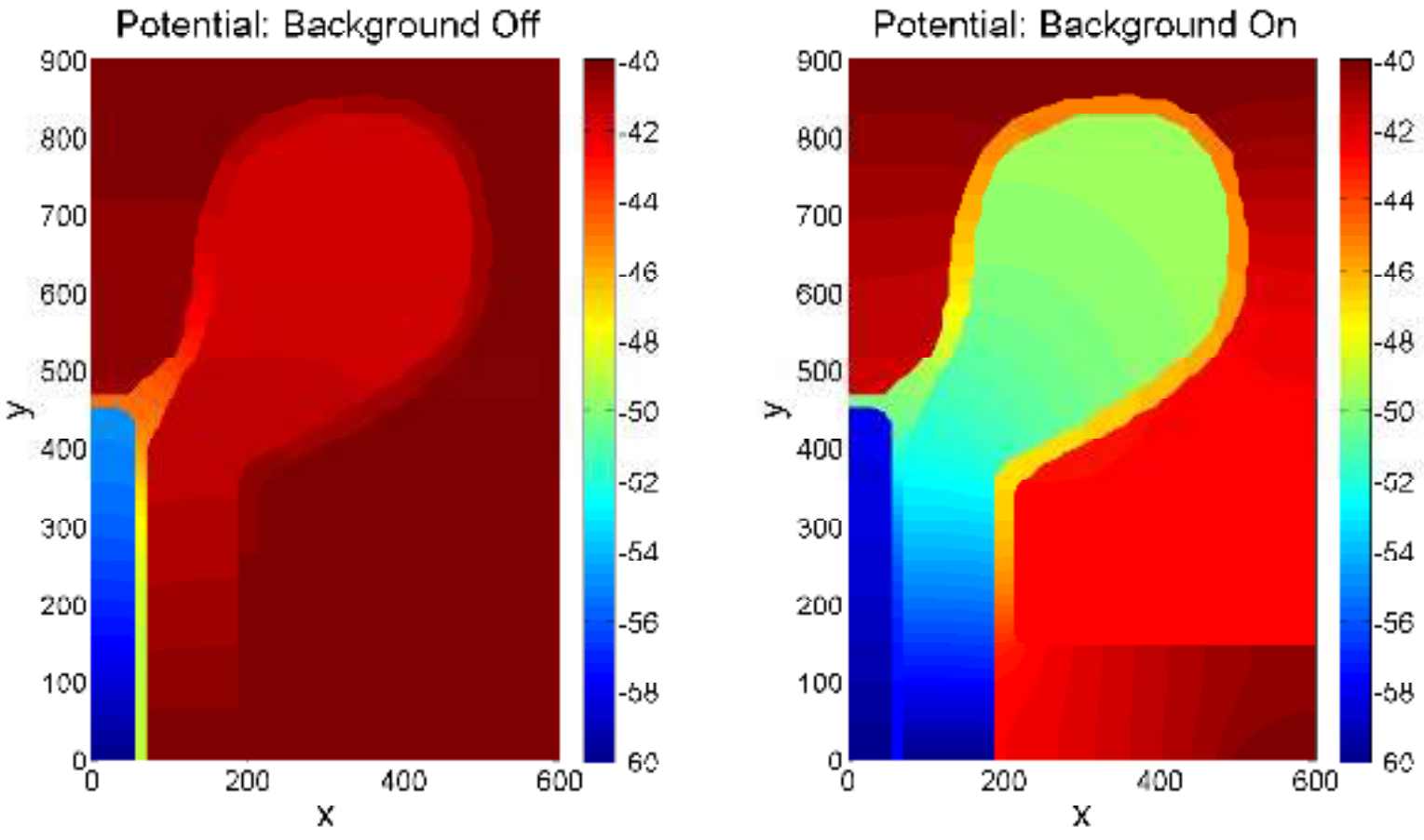




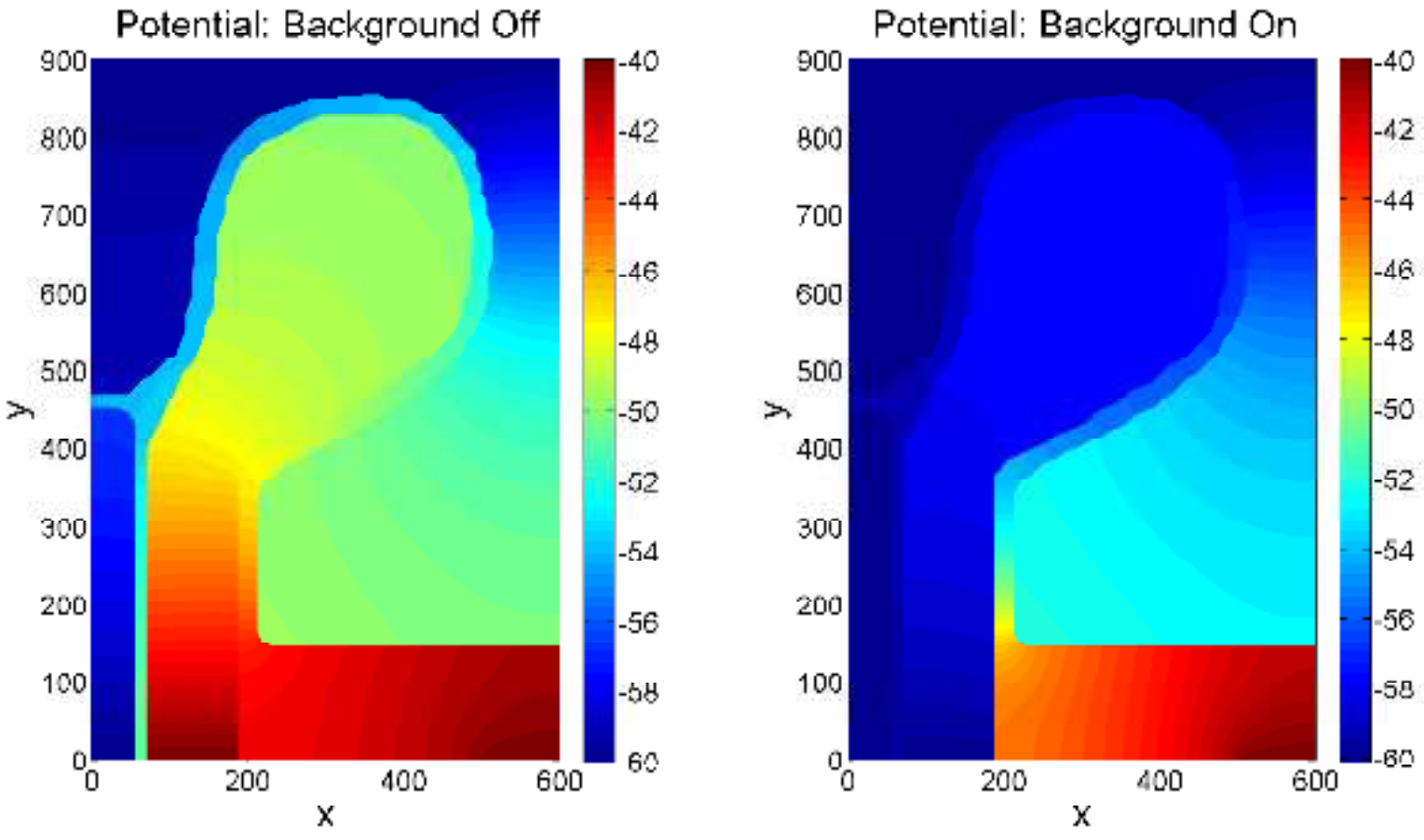
$U_{CP} = 0$ mV, $U_{HC} = -40, -60$ mV, $U_{BC} = -60$ mV



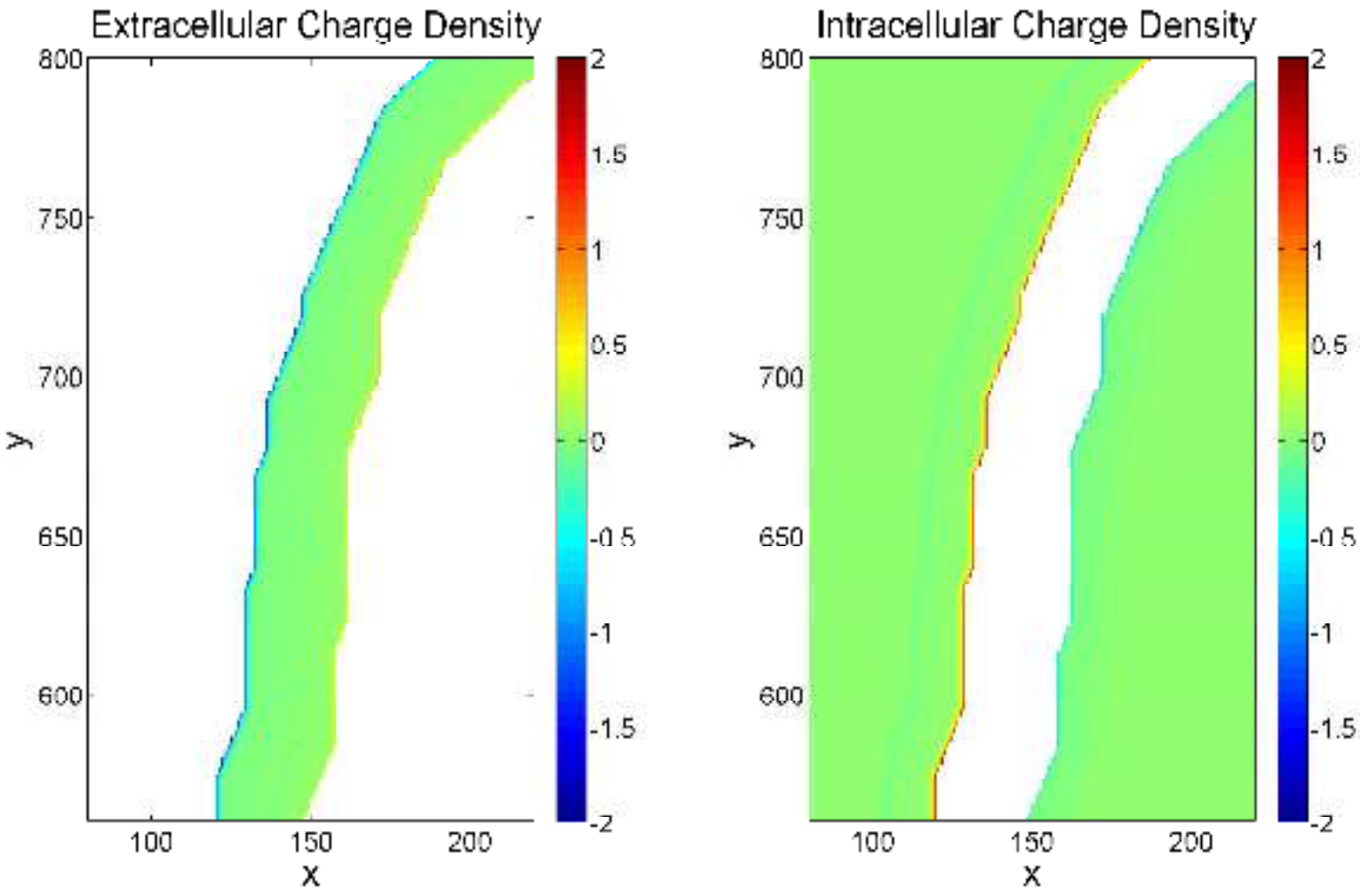
$U_{CP} = -20$ mV, $U_{HC} = -40, -60$ mV, $U_{BC} = -60$ mV



$U_{CP} = -40$ mV, $U_{HC} = -40, -60$ mV, $U_{BC} = -60$ mV

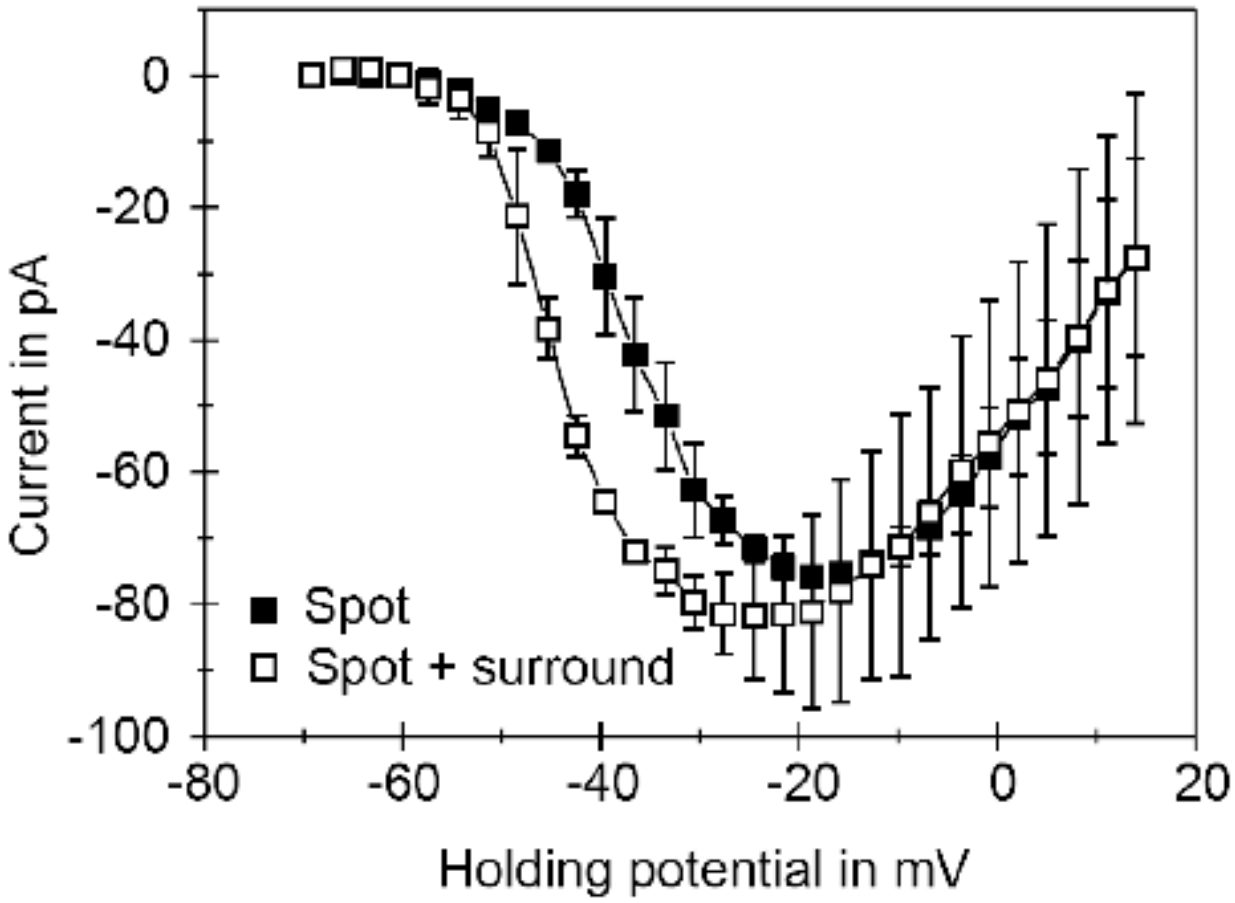


$$U_{CP} = -60 \text{ mV}, U_{HC} = -40, -60 \text{ mV}, U_{BC} = -60 \text{ mV}$$

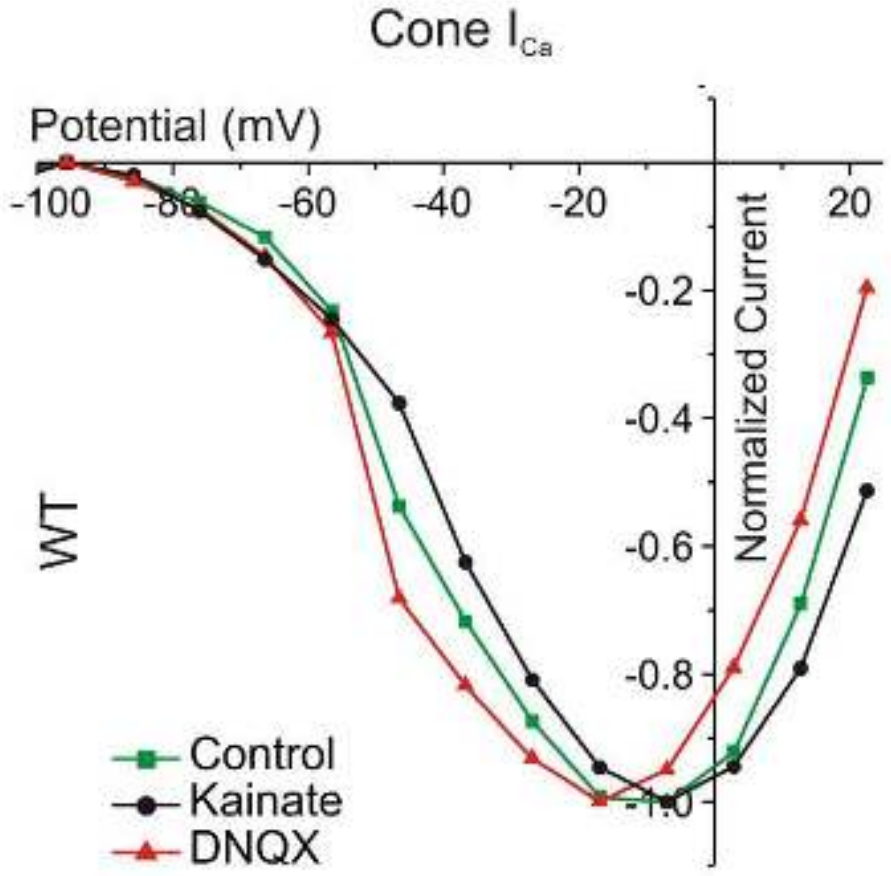


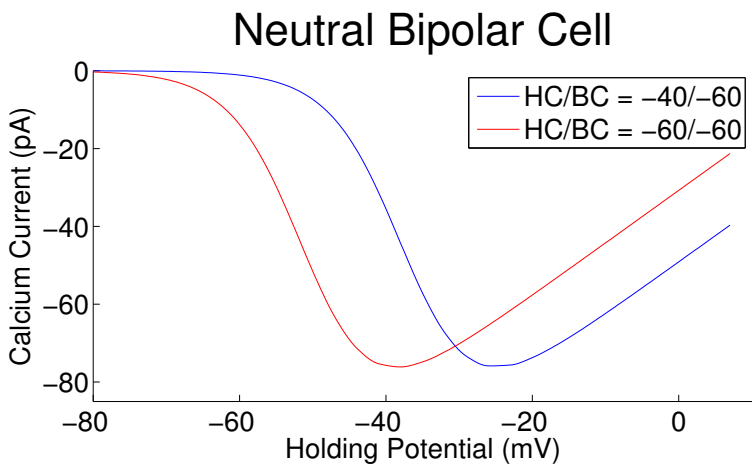
$U_{CP} = -20$ mV, $U_{BC} = -60$ mV, $U_{BC} = -60$ mV

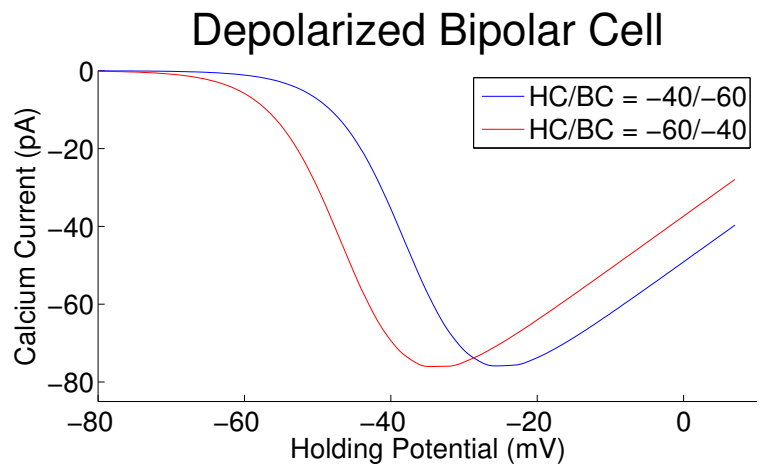
Experimental IV curves (Kamermans & Fahrenfort)

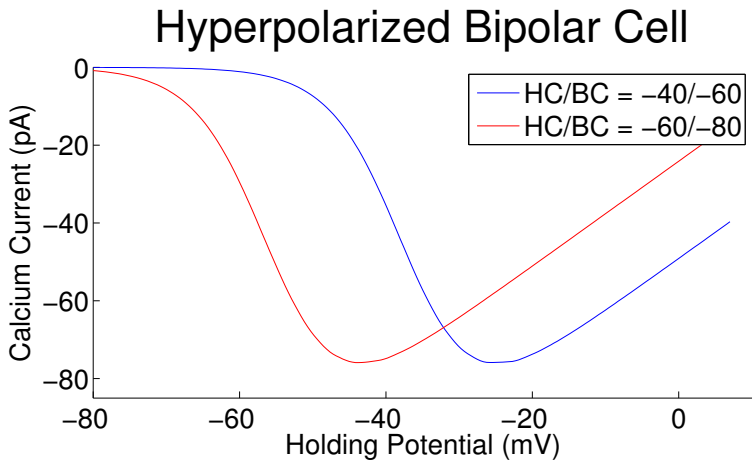


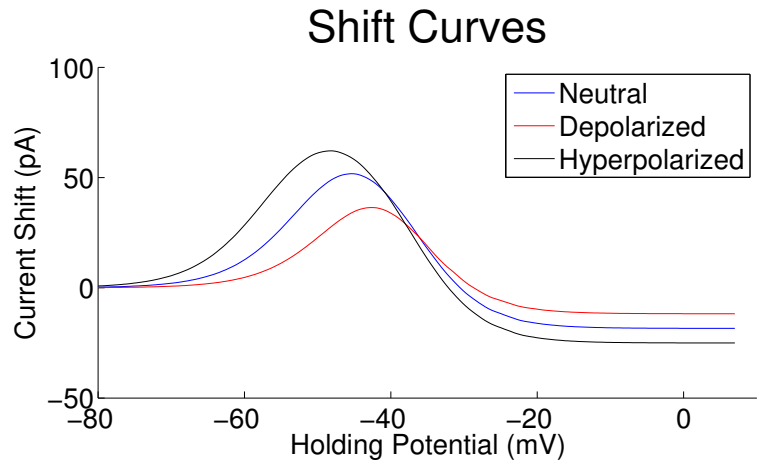
Experimental IV curves (Kamermans et al.)











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Future Work

1. Model nonperiodic arrays of synapses in order to realistically model entire cone pedicle
2. Multiscale modeling: integrate out shortest time scales in drift-diffusion model to obtain intermediate model, so we can treat time-dependent illuminations of retina