Modeling the role of lateral membrane diffusion in AMPA receptor trafficking along a spiny dendrite

Paul C. Bressloff Berton A. Earnshaw

Department of Mathematics, University of Utah
Salt Lake City, Utah 84112

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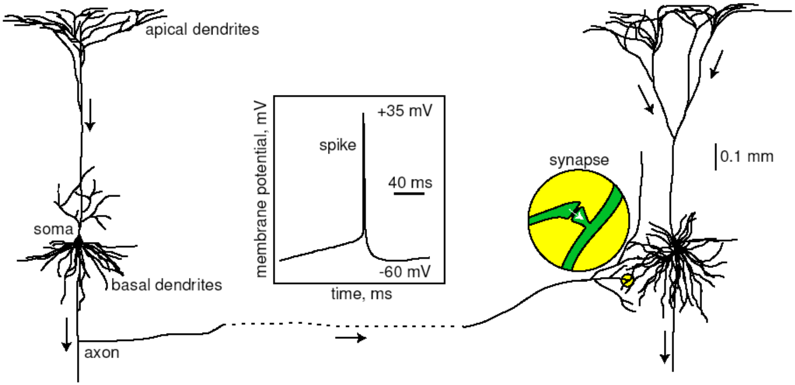
1. Introduction
   - The brain: neurons, synapses and plasticity
2. AMPAR Trafficking
   - Trafficking at a single dendritic spine
   - Long-range receptor trafficking
3. Analysis of Model
   - Steady-state Analysis
4. Results

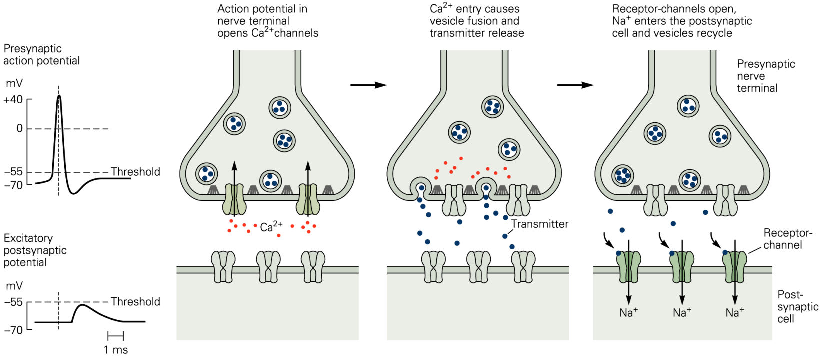
The brain: unparalled parallel computer

- 10^{11} neurons
- 10^{14} synapses
- network of neurons is plastic
- regulates behavior
- can **learn** and **remember**!

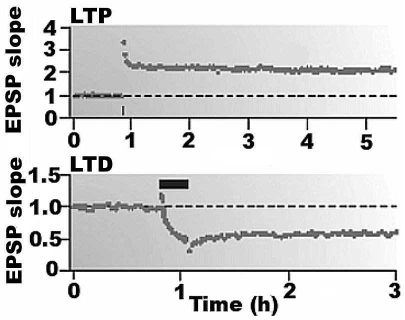
Neurons communicate via synapses

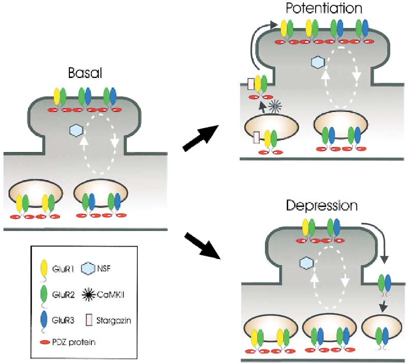


Synaptic transmission

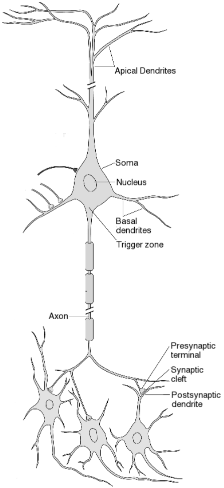


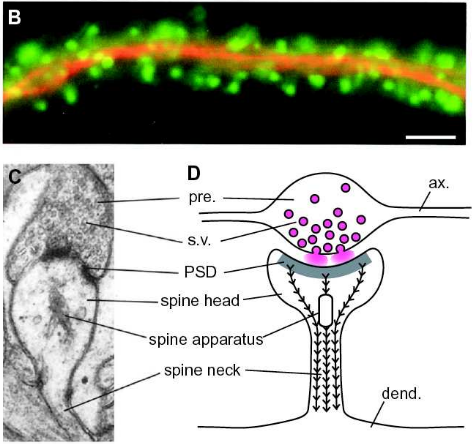
Synaptic plasticity



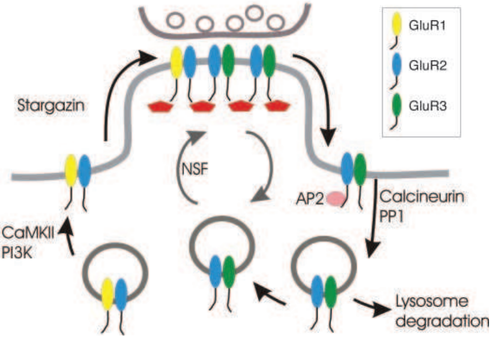


Excitatory synapses on dendritic spines





Local receptor trafficking at spines



- Synaptic receptors recycled with intracellular pools
- Crosslink to scaffolding proteins in PSD
- AMPA receptors laterally diffuse in synaptic membrane

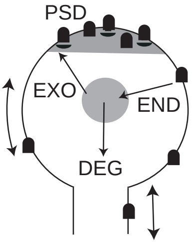
Model of trafficking at a single spine

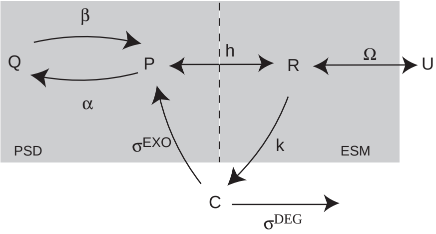
ESM: $$\frac{\mathrm{d}R}{\mathrm{d}t} = \frac{1}{A}\left(\Omega[U-R] - kR - h[R-P]\right)$$

PSD unbound: $$\frac{\mathrm{d}P}{\mathrm{d}t} = \frac{h}{a}[R-P] - \alpha[Z-Q]P + \beta Q + \frac{\sigma^{\mathrm{EXO}}C}{a}$$

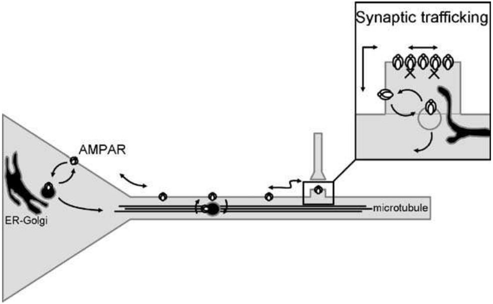
PSD bound: $$\frac{\mathrm{d}Q}{\mathrm{d}t} = \alpha[Z-Q]P - \beta Q$$

Intracellular: $$\frac{\mathrm{d}C}{\mathrm{d}t} = -\sigma^{\mathrm{EXO}}C - \sigma^{\mathrm{DEG}}C + kR + \delta,$$





Long-range receptor trafficking



- Receptors trafficked in vesicles along microtubules
- Receptors diffuse from soma to synapse?

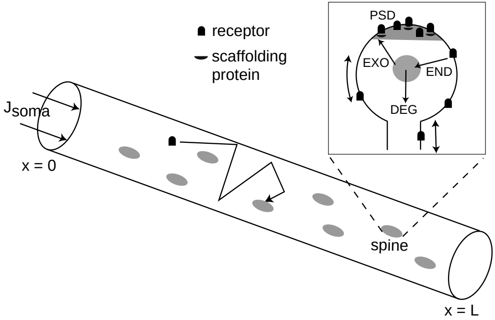
Model of trafficking along a spiny dendrite

$$\frac{\partial U}{\partial t} = D\frac{\partial^2 U}{\partial x^2} - \rho(x)\Omega(x)[U(x,t) - R(x,t)]$$

$$D\left.\frac{\partial U}{\partial x}\right|_{x=0} = -J_{\mathrm{soma}}, \quad D\left.\frac{\partial U}{\partial x}\right|_{x=L} = 0.$$

D = diffusion coefficient, $\rho(x)$ = spine density at x

J_{soma} = surface flux from soma

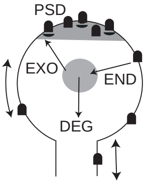


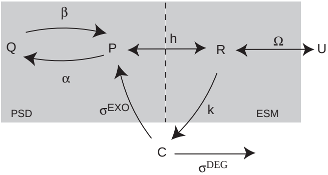
Steady-state at single spine

$$\sigma^{\mathrm{EXO}}(x)C(x) = \lambda(x)[k(x)R(x)+\delta(x)], \quad \lambda(x) = \frac{\sigma^{\mathrm{EXO}}(x)}{\sigma^{\mathrm{EXO}}(x)+\sigma^{\mathrm{DEG}}(x)}$$

$$P(x) = R(x) + \frac{\sigma^{\mathrm{EXO}}(x)C(x)}{h(x)}, \quad Q(x) = \frac{\alpha(x)P(x)Z(x)}{\beta(x)+\alpha(x)P(x)}$$

$$R(x) = \frac{\Omega(x)U(x)+\lambda(x)\delta(x)}{\Omega(x)+k(x)(1-\lambda(x))}.$$





- Everything depends on the steady-state solution $U(x)$!

Steady-state dendritic concentration

$$D\frac{d^2U}{dx^2} - \rho(x)\widehat{\Omega}(x)U(x) = -\rho(x)\widehat{\Omega}(x)r(x)$$

$$\widehat{\Omega}(x) = \frac{\Omega(x)k(x)(1-\lambda(x))}{\Omega(x)+k(x)(1-\lambda(x))}$$

$$r(x) = \frac{\lambda(x)\delta(x)}{k(x)(1-\lambda(x))} = \frac{\sigma^{\mathrm{EXO}}(x)\delta(x)}{\sigma^{\mathrm{DEG}}(x)k(x)}$$

One can view

- $\widehat{\Omega}(x)$ as effective spine–neck hopping rate
- $r(x)$ as effective ESM receptor concentration

Distribution of AMPA receptors along uniform cable

- Assume all parameters are x-independent, then

$$\frac{d^2U}{dx^2} - \Lambda_0^2 U(x) = -\Lambda_0^2 r, \quad \Lambda_0 = \sqrt{\frac{\rho_0 \widehat{\Omega}_0}{D}}$$

- Integrating wrt x over cable give conservation equation

$$lJ_{\text{soma}} = N\widehat{\Omega}\left[\int_0^L U(x)dx/L - r\right]$$

- Implies total number of receptors entering dendrite from soma is equal to mean number of receptors hopping from the dendrite into N spines

Solution of cable-like equation

- Steady-state equation solved using Green's function methods like standard cable equation describing electrical current flow in passive dendrites (Rall, 1962; Tuckwell, 1988; Dayan and Abbott, 2001)

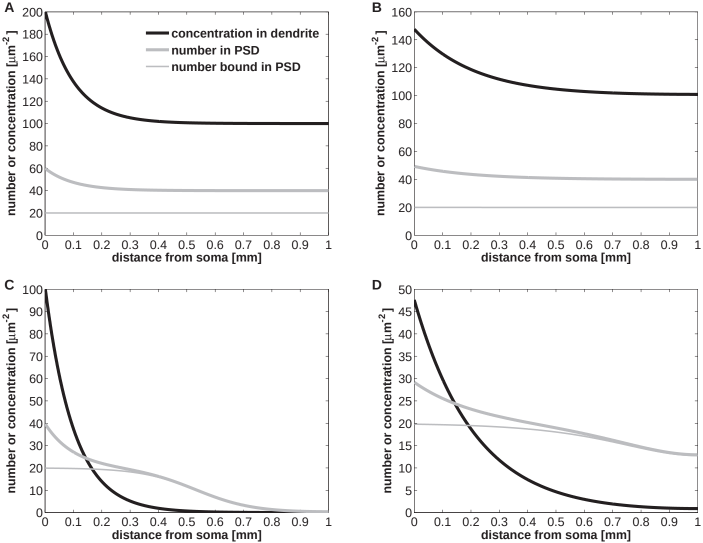
$$U(x) = \frac{J_{\rm soma}}{D} G(x,0) + r$$

- $G(x,x')$ is 1-D Green's function for uniform cable of length L with closed ends at $x = 0, L$

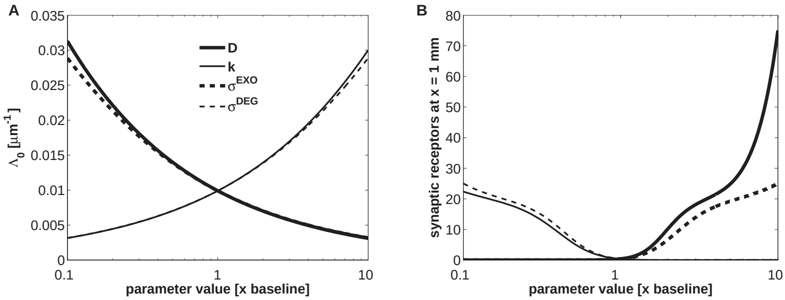
$$G(x,x') = \frac{\cosh(\Lambda_0[|x-x'|-L])}{2\Lambda_0 \sinh(\Lambda_0 L)} + \frac{\cosh(\Lambda_0[x+x'-L])}{2\Lambda_0 \sinh(\Lambda_0 L)}$$

$$=> U(x) = \frac{J_{\rm soma}}{D} \frac{\cosh(\Lambda_0[x-L])}{\Lambda_0 \sinh(\Lambda_0 L)} + r.$$

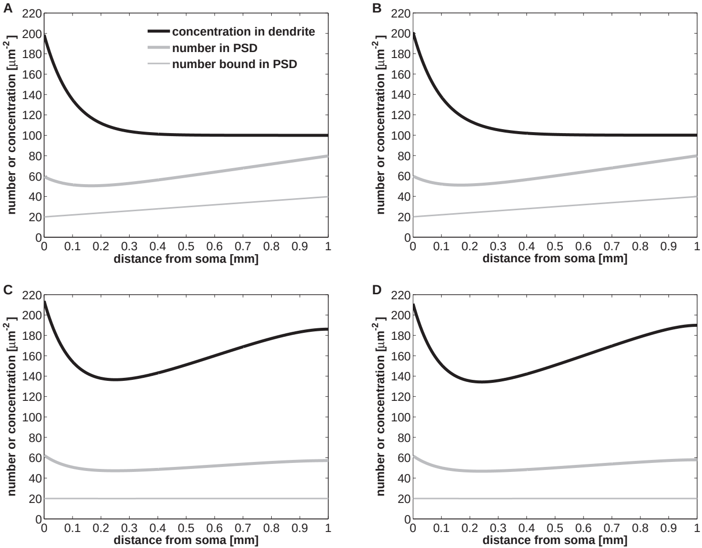
Receptor profiles



Dependence on parameters



Receptor profiles for nonuniform cable



Heterosynaptic dependence on constitutive recycling