Diffusion-trapping models of protein receptor trafficking along spiny dendrites

Paul C. Bressloff\textsuperscript{1}, Berton A. Earnshaw\textsuperscript{1} and Michael J. Ward\textsuperscript{2}

\textsuperscript{1}Department of Mathematics, University of Utah
Salt Lake City, Utah, USA
\textsuperscript{2}Department of Mathematics, University of British Columbia
Vancouver, B.C., Canada

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The amazing brain
Trafficking at synapses

Neurons communicate at synapses

Synapses can “learn”

Synapses “learn” by regulating receptor numbers

Receptor trafficking at synapses

- constitutively recycled with intracellular stores
  - AMPA receptors turned over in 10-30 mins (or 16 hrs?)
- immobilized by scaffolding proteins in synapse
- diffuse laterally within membrane

Sheng & Kim, 2002
Receptors diffuse laterally between synapses

How are receptors transported to synapses?
Synapses located in dendritic spines


Long-range transport of receptors along spiny dendrite

1. somatic exocytosis
2. lateral membrane diffusion
3. surface entry into spine
4. local exo/endocytosis

motor transport along microtubules

**diffusion** within dendritic membrane? (Adesnik et al., 2005)
How should we model diffusion-trapping of receptors?
Treat dendritic membrane as cylinder with holes

- receptor
- scaffolding protein

$J_{soma}$

$x = 0$

$x = L$

spine

PSD

EXO

END

DEL

DEG
Diffusion equation on dendritic membrane

\[
\frac{\partial U}{\partial t} = D \nabla^2 U \quad \text{on } \Omega_\varepsilon
\]

- \(U\) = receptor concentration
- \(\Omega_\varepsilon\) is rectangle \((0, L) \times (-\pi l, \pi l)\) minus the holes

\[
\Omega_j = \{ \mathbf{r} \in \Omega_0 \mid |\mathbf{r} - \mathbf{r}_j| \leq \varepsilon \rho \}, \quad j = 1, \ldots, N
\]
Boundary conditions

- Periodic bcs at $y = \pm \pi l$
- No-flux bc at $x = L$, and at $x = 0$

$$-D \frac{\partial U}{\partial x} = J_{soma} = \frac{\sigma}{2\pi l}$$

- bcs at the holes:

$$-\varepsilon D \frac{\partial U}{\partial n}(\mathbf{r}, t) = \frac{\mu_j}{2\pi \rho} (U(\mathbf{r}, t) - R_j), \quad \mathbf{r} \in \partial \Omega_j$$

- $\mu_j$ = spine neck hopping rate
- $R_j$ = receptor concentration on surface of $j$th spine
Treat each spine as having 3 compartments

- **P, Q:** unbound, bound receptor concentrations in PSD
- **R, U:** free receptor concentrations in spine head, dendrite
- **C:** number of intracellular receptors
- **k, σ^{EXO}:** rates of endocytosis, exocytosis
- **σ^{DEG}, δ:** rates of degradation, intracellular delivery
- **h, μ:** hopping rates across boundary of PSD, spine neck
- **α(Z-Q):** rate of binding to scaffolding (Z = scaffolding concentration)
- **β:** rate of unbinding from scaffolding
All steady-state concentrations at $j$th spine depend on the mean value of $U$ on $\partial \Omega_j$:

$$U_j = \frac{1}{2\pi \varepsilon \rho} \int_{\partial \Omega_j} U(r) dr$$
Steady-state solution

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- $U_j$’s are determined by solving $\nabla^2 U = 0$ in $\Omega_\varepsilon$ with bcs
Steady-state solution

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\[
U_j = \frac{1}{2\pi \varepsilon \rho} \int_{\partial \Omega_j} U(r) \, dr
\]

- \( U_j \)'s are determined by solving \( \nabla^2 U = 0 \) in \( \Omega_\varepsilon \) with bcs
- But this is \textbf{hard} because of bcs at the holes!

\[
-\varepsilon D \frac{\partial U}{\partial n}(r) = \frac{\mu_j}{2\pi \rho} (U(r) - R_j), \quad r \in \partial \Omega_j
\]
Three steps for finding approximate steady-state solution

1. Solve assuming $U = U_j$ on the boundary of $j$th hole
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- **Singular perturbation**: match logarithmic solutions in each inner region

\[ |r - r_j| = \mathcal{O}(\varepsilon) \]

with Green’s function singularities in outer region

\[ |r - r_j| = \mathcal{O}(1) \text{ for all } j \]
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2. Solution has $N + 1$ unknowns: $U_j$’s and integration constant
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     \[ |\mathbf{r} - \mathbf{r}_j| = \mathcal{O}(1) \text{ for all } j \]
   - Solution has $N + 1$ unknowns: $U_j$’s and integration constant

2. Substitute this solution into $N$ simplified bcs at holes
   \[-\varepsilon D \frac{\partial U}{\partial n}(\mathbf{r}) = \frac{\widehat{\mu}_j}{2\pi\rho}(U_j - \widehat{R}_j), \quad \mathbf{r} \in \partial\Omega_j\]
Three steps for finding approximate steady-state solution

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   \]

3. Conservation condition gives $(N + 1)$th equation
   \[
   \sigma = \sum \hat{\mu}_j \left( U_j - \hat{R}_j \right)
   \]
Effect of $\varepsilon$ on solution

- Dendrite 2µm long, circumference 1µm
- One spine at $r = (1, 0.5)$
- Numerical solutions look similar
Comparison of dendritic receptor concentration

- Dendrite 100µm long, circumference 1µm, $\epsilon \rho = 0.1\mu$m
- 100 identical spines spaced 1µm apart, all in a row
- Solutions are almost identical!
- Similar results if spines are not identical, not in a row
Can we make things simpler?
When the aspect ratio $L/l \gg 1$, we can approximate 2D model by the following 1D model

$$\frac{\partial U}{\partial t} = D \frac{\partial^2 U}{\partial x^2} - \sum_{j=1}^{N} \delta(x - x_j) \mu_j (U_j - R_j)$$

$$-D \frac{\partial U}{\partial x} \bigg|_{x=0} = J_{\text{soma}}, \quad \frac{\partial U}{\partial x} \bigg|_{x=L} = 0.$$
Comparison of models

- **2D model as before**
  - Dendrite 100\(\mu\)m long, circumference 1\(\mu\)m, \(\epsilon \rho = 0.1\mu\)m
  - 100 identical spines spaced 1\(\mu\)m apart, all in a row

- **1D model use same parameters when relevant**
- Solutions are almost identical!
Can we make things even simpler?
If spines are sufficiently dense, treat sum of delta functions as a density $\eta$

$$\frac{\partial U}{\partial t} = D \frac{\partial^2 U}{\partial x^2} - \eta(x)\mu(x)(U - R)$$

$$-D \left. \frac{\partial U}{\partial x} \right|_{x=0} = J_{\text{soma}}, \quad \left. \frac{\partial U}{\partial x} \right|_{x=L} = 0.$$
Assume all parameters are $x$-independent, then get “cable” equation for receptor trafficking

$$\frac{d^2 U}{dx^2} - \Lambda^2 U = -\Lambda^2 \hat{R}$$

$$\Lambda = \sqrt{\frac{\eta \hat{\mu}}{D}} \text{ is length-scale of diffusive coupling}$$
Steady-state solution for identical spines: “cable” equation

- Assume all parameters are $x$-independent, then get “cable” equation for receptor trafficking

$$\frac{d^2 U}{dx^2} - \Lambda^2 U = -\Lambda^2 \hat{R}$$

$$\Lambda = \sqrt{\frac{\eta \hat{\mu}}{D}}$$ is length-scale of diffusive coupling

- Solve using Green’s function methods

$$U(x) = \frac{J_{\text{soma}}}{D} \frac{\cosh(\Lambda(x - L))}{\Lambda \sinh(\Lambda L)} + \hat{R}$$
Steady-state receptor concentrations for identical spines

- Dendrite 1 mm long
- 1,000 identical spines spaced 1µm apart
- Two sources of receptors
  - at soma
  - local intracellular delivery
Consequences of diffusive coupling

10-fold reduction in rate of exocytosis in gray region

10-fold increase in rate of endocytosis in gray region
Steady-state is nice...
...but what about time-dependent phenomena?
AMPA receptor recycling via thrombin cleavage

AMPAM receptor recycling via photoinactivation

Adesnik et al., Neuron (2005)
Fast or slow recycling of AMPA receptors?

Passafaro et al., 2001

Adesnik et al., 2005
Simulation of photoinactivation of AMPA receptors

- No intracellular delivery but source at soma
- In steady-state $t < 0$
- At $t = 0$ all surface AMPA receptors instantaneously “inactivated”
Simulation of photoinactivation of AMPA receptors

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Rates of exo/endocytosis are **fast** (10-30 mins)
Rate of recycling depends on distance from soma

- Fast exo/endocytosis consistent with slow recycling
- There are many time scales!
Future directions

- Models with many kinds of receptors (AMPA, NMDA, kainate, etc.)
- Models with receptor function, electrophysiology
- Computational learning rules (e.g., STDP)
- Role of AMPA receptor trafficking in Alzheimer’s disease
- **Stochastic models**
Intrinsic vs. extrinsic noise of synaptic trafficking

- AMPA receptor
- scaffolding protein

- intrinsic noise: e.g., binding/unbinding
- extrinsic noise: e.g., fluctuating gate
Time-course of variance during FRAP

- black: with binding
- gray: no binding
Time-course of variance during Inverse FRAP

- black: with binding
- gray: no binding