Multiple spatial scales of AMPA receptor trafficking
From synapse to spiny dendrite

Paul Bressloff    Berton Earnshaw

Department of Mathematics
University of Utah

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The amazing brain
Neurons communicate at synapses
Communication at a synapse

Action potential in nerve terminal opens Ca²⁺ channels

Ca²⁺ entry causes vesicle fusion and transmitter release

Receptor-channels open, Na⁺ enters the postsynaptic cell and vesicles recycle

Presynaptic action potential

Excitatory postsynaptic potential

Synapses can “learn”

Collingridge et al., Nat Rev Neurosci (2004)
Synapses “learn” by regulating receptor numbers

Depressed → LTD → Naïve → LTP → Potentiated
Synapses located in dendritic spines

Bressloff, Earnshaw (Utah)
Receptor trafficking at a synapse
Receptors diffuse laterally between synapses

Long-range transport of receptors

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

Groc & Choquet, 2006
• Single-spine model (deterministic)
• Single-synapse model (stochastic)
• 2D diffusion model
• 1D diffusion models
• Other diffusion-trapping problems
Model of single-spine AMPAR trafficking

Spine head: \[
\frac{dR}{dt} = \frac{1}{A} \left( \mu[U - R] - kR - h[R - P] \right)
\]

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

PSD bound: \[
\frac{dQ}{dt} = \alpha[Z - Q]P - \beta Q
\]

Intracellular: \[
\frac{dC}{dt} = -\sigma^{EXO} C - \sigma^{DEG} C + kR + \delta
\]
Block exo/endocytosis

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{ampar-trafficking-figure}
\end{figure}

Luscher et al., Neuron (1999)
LTP simulation

- Activation of GluR1/2 intracellular pool
- Rapid insertion of receptors into ESM
- AMPARs transport slot proteins into PSD

O’Connor et al (PNAS 2005)

Graph showing time course of AMPAR trafficking with different trajectories for bound and free GluR1/2 and GluR2/3.
LTD simulation

- Switch from AMPA-GRIP to AMPA-PICK receptor-protein complexes
- Rapid unbinding from PSD and trafficking to ESM followed by endocytosis.
- Unbound scaffolding proteins are degraded.

\[ t \text{ [min]} \]

\[ \text{number of receptors} \]

\[ \text{Total} \quad \text{Scaffolding} \]

\[ \text{Dudek & Bear (1993)} \]
Conclusions

1. Significant fraction of PSD receptors are mobile (Groc et al., 2004; Ashby et al., 2006)
   - Requires PSD-ESM barrier (Choquet & Triller, 2003)

2. Diffusive impedance of spine neck is significant (Ashby et al., 2006)

3. Insertion of GluR1/2 during LTP must combine synaptic targeting
   - Requires increased hopping and binding rate (Schnell et al., 2002) and scaffolding (Shi et al., 2001)

4. Slow exchange of GluR1/2 with GluR2/3 after LTP requires maintenance of additional binding sites (McCormack et al., 2006)

5. LTD requires loss of binding sites (Colledge et al., 2003)
- Single-spine model (deterministic)
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Stochastic model of trafficking at PSD

\[ \frac{dp}{dt} = -\alpha (Z - q)p + \beta q - \mu p + \sigma \]
\[ \frac{dq}{dt} = \alpha (Z - q)p - \beta q \]
Stochastic model of trafficking at PSD

$$\frac{dp}{dt} = -\alpha(Z - q)p + \beta q - \mu p + \sigma$$

$$\frac{dq}{dt} = \alpha(Z - q)p - \beta q$$

$$P_{n,m}(t) = \text{Prob}\{n \text{ unbound, } m \text{ bound at time } t\}$$
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\[ P_{n,m}(t) = \text{Prob}\{n \text{ unbound, } m \text{ bound at time } t\} \]

\[ \frac{dP_{n,m}}{dt} = \sigma P_{n-1,m} + \mu (n + 1) P_{n+1,m} \]

\[ + \alpha (n + 1)[Z - (m - 1)]P_{n+1,m-1} \]

\[ + \beta (m + 1) P_{n-1,m+1} \]

\[ - [\sigma + \mu n + \alpha n(Z - m) + \beta m]P_{n,m} \]
Stochastic model of trafficking at PSD

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\frac{dp}{dt} = -\alpha (Z - q)p + \beta q - \mu p + \sigma \\
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+ \beta (m + 1)P_{n-1,m+1} \\
- [\sigma + \mu n + \alpha n(Z - m) + \beta m]P_{n,m}
\]

stochastic gate : \[
\begin{align*}
\gamma - & : 0 < \mu_{open} & \leftrightarrow \mu_{closed} = 0 \\
\gamma + & : \sigma(t) = C \mu(t) \quad (C \text{ bath conc.})
\end{align*}
\]
Analysis in two regimes: un/saturated binding sites

- Can do math in two regimes:
  - unsaturated binding sites: \( m(t) \ll Z \) for all \( t \) (i.e., \( \alpha n(t) \ll \beta \))
  - saturated binding sites: \( m(t) = Z \) for all \( t \) (i.e., \( \alpha n(t) \gg \beta \))
Analysis in two regimes: un/saturated binding sites

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  - unsaturated binding sites: $m(t) \ll Z$ for all $t$ (i.e., $\alpha n(t) \ll \beta$)
  - saturated binding sites: $m(t) = Z$ for all $t$ (i.e., $\alpha n(t) \gg \beta$)
- Unsaturated regime: master equation is linear in $n, m$
  - Generating function

$$G(u, v, t) = \sum_{n=0}^{\infty} \sum_{m=0}^{\infty} u^n v^m P_{n,m}(t)$$

satisfies first-order linear PDE

$$\frac{\partial G}{\partial t} + [\mu(t)(u - 1) + \alpha Z(u - v)] \frac{\partial G}{\partial u} - \beta(u - v) \frac{\partial G}{\partial v} = \sigma(t)(u - 1)G$$
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\]

- Obtain mean, variance from derivatives of \( G \)

\[
E_\mu(n) = \left. \frac{\partial G}{\partial u} \right|_{u=v=1}, \quad E_\mu(m) = \left. \frac{\partial G}{\partial v} \right|_{u=v=1}
\]
Averaging over realizations of $\mu$

- Can show that

\[
E(n) \equiv \langle E_\mu(n) \rangle = C + (n_0 - C)\langle N_{11} \rangle + (m_0 - C\alpha Z / \beta)\langle N_{21} \rangle \\
E(m) \equiv \langle E_\mu(m) \rangle = C\alpha Z / \beta + (n_0 - C)\langle N_{12} \rangle + (m_0 - C\alpha Z / \beta)\langle N_{22} \rangle
\]

where

\[
N(t) = \exp \left( -\int_0^t M(t')dt' \right), \quad M(t) = \begin{pmatrix} \mu(t) + \alpha Z & -\alpha Z \\ -\beta & \beta \end{pmatrix}
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- Can derive a system of ODEs for the averages of the entries of $N$ using method of Kubo and Zwanzig
Saturated binding sites

- Since $m(t) = Z$ for all $t$, master equation becomes

$$\frac{dP_n}{dt} = \mu(t) [CP_{n-1} + (n + 1)P_{n+1}(t) - (C + n)P_n]$$
Saturated binding sites

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$$\frac{dP_n}{dt} = \mu(t) [CP_{n-1} + (n + 1)P_{n+1}(t) - (C + n)P_n]$$

- Brown et al. (*Biophys J*, 2000) showed that

$$E(n) = (n_0 - C)\langle w \rangle + C$$
$$\text{Var}(n) = E(n) - n_0\langle w^2 \rangle + (n_0 - C)^2 (\langle w^2 \rangle - \langle w \rangle^2)$$

$$\langle w(t)^j \rangle = \begin{pmatrix} 1 \\ 1 \end{pmatrix}^T \exp \left[ -t \begin{pmatrix} j\mu_o + \gamma & -\gamma \\ -\gamma & \gamma \end{pmatrix} \right] \begin{pmatrix} \Pi_o \\ \Pi_c \end{pmatrix}, \quad (j = 1, 2)$$

$$\Pi_o = \frac{\gamma +}{\gamma + \gamma -}, \quad \Pi_c = \frac{\gamma -}{\gamma + \gamma -}$$
FRAP and inverse FRAP experiments

- **FRAP**
  - Initial state: PSD with unbleached receptors
  - Process: FRAP
  - Result: Recovery of bleached receptors

- **Inverse FRAP**
  - Initial state: PSD with bleached receptors
  - Process: Inverse FRAP
  - Result: Recovery of PSD with unbleached receptors

Legend:
- ● unbleached receptor
- ○ bleached receptor
- □ scaffolding protein
Simulations of FRAP and inverse FRAP
• Single-spine model (deterministic)
• Single-synapse model (stochastic)
• 2D diffusion model
• 1D diffusion models
• Other diffusion-trapping problems
Treat dendritic membrane as cylinder with holes

\[ J_{\text{soma}} \]

<table>
<thead>
<tr>
<th>receptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>- scaffolding protein</td>
</tr>
</tbody>
</table>

\[ x = 0 \]

\[ x = L \]

Diffusion equation on dendritic membrane

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

- \( U \) = 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 $x = 0$

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

- bcs at the holes:

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

  - $\mu_j$ = spine neck hopping rate
  - $R_j$ = receptor concentration on surface of $j$th spine

\[\Omega_\varepsilon\]

\[\Omega_j\]

\[x = 0\]

\[y = \pm \pi l\]

\[x = L\]
Treat each spine as before
Steady-state solution

- Assume concentrations in \( j \)th spine see 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

• Assume concentrations in $j$th spine see mean value of $U$ on $\partial \Omega_j$:

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

• $U_j$’s are determined by solving $\nabla^2 U = 0$ in $\Omega_\varepsilon$ with boundary conditions
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- $U_j$'s are determined by solving $\nabla^2 U = 0$ in $\Omega_\varepsilon$ with boundary conditions

- But this is **hard** because of boundary conditions 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
     \[ |\mathbf{r} - \mathbf{r}_j| = \mathcal{O}(\varepsilon) \]
     with Green’s function singularities in outer region
     \[ |\mathbf{r} - \mathbf{r}_j| = \mathcal{O}(1) \text{ for all } j \]
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2. Substitute this solution into $N$ simplified bcs at holes
   \[ -\varepsilon D \frac{\partial U}{\partial n}(r) = \frac{\mu_j}{2\pi \rho} (U_j - \hat{R}_j), \quad r \in \partial \Omega_j \]
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3. Conservation condition gives $(N + 1)$th equation

   \[ \sigma = \sum \mu_j \left( U_j - \hat{R}_j \right) \]
Comparison of dendritic receptor concentration

- Dendrite 100 µm long, circumference 1 µm, $\epsilon \rho = 0.1 \mu m$
- 100 identical spines spaced 1 µm apart, all in a row
- Solutions are almost identical!
- Similar results if spines are not identical, not in a row
• Single-spine model (deterministic)
• Single-synapse model (stochastic)
• 2D diffusion model
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• Other diffusion-trapping problems
2D model well-approximated by 1D model

When the aspect ratio $L/l \gg 1$, we can approximate 2D model by the following 1D model

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

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

Bressloff & BAE, PRE (2007)
Comparison of models

- 2D model as before
  - Dendrite 100µm long, circumference 1µm, $\epsilon \rho = 0.1\mu m$
  - 100 identical spines spaced 1µm apart, all in a row
- 1D model use same parameters when relevant
- Solutions are almost identical!
Can we make things even simpler?
Treat spine population as continuous density

If spines are sufficiently dense, treat sum of delta functions as a density $\eta$

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

$$-D \left. \frac{\partial U}{\partial x} \right|_{x=0} = J_{\text{soma}}, \quad \left. \frac{\partial U}{\partial x} \right|_{x=L} = 0.$$
Steady-state solution for identical spines: “cable” equation

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

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

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

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

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

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

- 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 1 µm apart
- Two sources of receptors
  - at soma
  - local intracellular delivery

Piccini & Malinow, 2002

GluR1/2
GluR2/3
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

AMPA receptor recycling via photoinactivation

(A) Functional Receptor → ANQX → UV → Photoinactivated Receptor

(B) UV, ANQX, ANQX + UV

(C) Pre, Post, Overlay

Glu: Glutamate

+40 mV, -60 mV

80 pA, 50 ms
Fast or slow recycling of AMPA receptors?

Passafaro et al., 2001

Adesnik et al., 2005

Percent of steady state

Time (min)

Sucrose-evoked Current (%)

Time after Inactivation (h)
Simulation of photoinactivation of AMPA receptors

![Graph showing recovery of AMPA receptors over time with two lines representing different distances.]

- **Fast insertion from pool**
- **Depletion of pool**
- **Recovery of pool**
- **Replacement of bound AMPARs**

**Legend:**
- inactive AMPAR
- active AMPAR
- scaffolding protein

**Diagram Labels:**
- PSD
- intracellular pool

---

**Text:**

- AMPA receptor trafficking
- 1D diffusion model with density of spines
- Simulation of photoinactivation of AMPA receptors
- Multiple scales of AMPAR trafficking
• Single-spine model (deterministic)
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CaMKII translocation waves

Rose et al., Neuron (2009)
Diffusion-activation model of CaMKII translocation waves

(a) Schematic diagram showing the priming and activation of CaMKII across a dendritic membrane. The priming process occurs in the soma-dendritic region, and subsequent activation occurs as a translocation wave moves from the soma towards the dendrite.

(b) Representation of CaMKII molecules at different stages of the translocation wave. On the left, unprimed CaMKII molecules are diffusing; on the right, primed CaMKII molecules are translocating into the dendrite.

(c) Graphical representation of the diffusion-activation process, illustrating the transition from unprimed to primed CaMKII and further to activated CaMKII. The primed CaMKII is shown moving towards the dendrite, with a peak indicating activation.

Equation: $x = L$
Equations for diffusion-activation model

\[ \frac{\partial p}{\partial t} = D \frac{\partial^2 p}{\partial x^2} - kap \]

\[ \frac{\partial a}{\partial t} = D \frac{\partial^2 a}{\partial x^2} + kap - ha \]

\[ \frac{\partial s}{\partial t} = ha \]

- \( p \) = concentration of primed CaMKII in shaft
- \( a \) = concentration of activated CaMKII in shaft
- \( s \) = concentration of activated CaMKII in spines
- \( k, h \) = rate of activation, translocation

BAE & Bressloff, *In prep.*
Simulation of diffusion-activation model

![Graph showing the simulation of diffusion-activation model over time.](image)

- **x [µm]**: The horizontal axis represents the distance in micrometers.
- **CaMKII [norm. conc.]**: The vertical axis represents the normalized concentration of CaMKII.
- The graphs show the changes in total CaMKII concentration in spines and dendrites, as well as primed and activated CaMKII in the dendrites over time (10 sec, 65 sec, 140 sec, 348 sec).

These graphs illustrate the dynamics of AMPA receptor trafficking and diffusion-trapping problems.
Calculation of wave speed

- When $h = 0$ (no translocation), recover Fisher’s equation with speed

$$c = 2\sqrt{Dk}$$
Calculation of wave speed

- When $h = 0$ (no translocation), recover Fisher’s equation with speed
  \[ c = 2\sqrt{Dk} \]

- When $h \neq 0$, wave speed is
  \[ c = 2\sqrt{D(k - h)} \]

\[ \begin{align*}
  \text{Activation rate } k &\quad \text{[1/s]} \\
  \text{Wave speed } c &\quad \text{[\(\mu\text{m/s}\)]}
\end{align*} \]
Calculation of wave speed

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\[ c = 2\sqrt{Dk} \]

- When $h \neq 0$, wave speed is

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- Wave propagation failure when $k < h$
Other projects with diffusion-trapping models

- other heterosynaptic molecules, e.g. PSD-95
- changes in spine volume during late-phase LTP
  - mRNA transport/capture/translation
  - F-actin regulation/stabilization by AMPA receptors
- protein transport/capture during synaptogenesis, e.g. NMDA receptors
- AMPA receptor trafficking in more detailed model of PSD
- put all the pieces together!
Thank you!

Thanks to

- Paul Bressloff (Utah)
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