Biophysical models of AMPA receptor trafficking

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1 Synaptic plasticity

2 AMPA receptor trafficking

3 Model of AMPA receptor trafficking at single dendritic spine

4 Model of AMPA receptor trafficking along a spiny dendrite
Most excitatory synapses of CNS occur in protrusions of dendrite called spines
Synaptic Plasticity

AMPAR Trafficking


- Fast synaptic transmission
- Complexes with other proteins $\rightarrow$ trafficking
LTP/LTD expression via AMPAR trafficking

Time-scales of synaptic plasticity

**INDUCTION**
- High [Ca\(^{2+}\)] (LTP)
- Low [Ca\(^{2+}\)] (LTD)

**EXPRESSION**
- Synaptic vesicles
- AMPAR conductance
- Number of AMPARs

**MAINTENANCE**
- Protein synthesis
- Structural changes in spine morphology

**TIME**
- seconds
- minutes/hours
- hours/days...
AMPAR Trafficking

**AMPAR receptor trafficking at spines**

- Surface AMPARs:
  - diffuse laterally within membrane
  - constitutively recycle with intracellular stores
  - crosslink to scaffolding proteins in PSD

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Sheng & Kim, 2002
AMPAR diffusion

AMPAR recycling via thrombin cleavage

AMPAR recycling via photoinactivation

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

Passafaro et al., 2001

Adesnik et al., 2005
**Long-range AMPAR trafficking**

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

Groc & Choquet, 2006

- AMPARs trafficked in vesicles along microtubules?
- AMPARs diffuse from soma to synapse?
Model of single-spine AMPAR trafficking

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

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

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

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

A

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t [min]

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t [min]

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)
More LTP simulations
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.

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)
   - Required for exocytosis blockade and LTD saturation

2. Diffusive impedance of spine neck is significant (Ashby et al., 2006)
   - Required for endocytosis blockade and LTP

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)
Model of trafficking along a spiny dendrite

- receptor
- scaffolding protein

$J_{soma}$

$x = 0$

$x = L$
1D model: Spine population as continuous density

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

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

\[U = \text{AMPAR conc. in dendritic membrane outside of spines}\]
\[R = \text{AMPAR conc. in extrasynaptic membrane of spine head}\]
\[D = \text{diffusion coefficient}\]
\[\rho = \text{spine density}\]
\[\Omega = \text{spine neck hopping rate}\]
\[J_{\text{soma}} = \text{flux of surface AMPAR from soma}\]
Steady-state AMPAR profiles for identical spines

- 1,000 identical spines uniformly spaced in 1 mm dendrite
- Two sources of AMPARs
  - at soma
  - local intracellular delivery
- diffusion coefficient $D = 0.1 \, \mu m^2 s^{-1}$ in dendrite
Nonidentical spines: Synaptic democracy

- PSD surface area
  - or spine density increases linearly

- rate of delivery
  - or exocytosis increases linearly
Identical spines without intracellular delivery

\[ D = 0.1 \, \mu m^2 s^{-1} \]

\[ D = 0.45 \, \mu m^2 s^{-1} \]

- Mean time to reach distance \( X \) from soma > \( \frac{X^2}{2D} \)
- For \( D = 0.45 \, \mu m^2 s^{-1} \)
  - \( X = 100 \, \mu m \Rightarrow \frac{X^2}{2D} \sim 3 \, \text{hr} \)
  - \( X = 1 \, mm \Rightarrow \frac{X^2}{2D} \sim 300 \, \text{hr}! \)
Intensive vs. extensive parameters

- Trafficking parameters categorized into two groups:
  Do local changes in parameter produce nonlocal changes in steady-state synaptic AMPAR numbers?

**Intensive**
(local effect only)

- PSD surface area $a$
- scaffolding concentration $Z$
- binding rate $\alpha$
- unbinding rate $\beta$

**Extensive**
(nonlocal effect)

- rate of exocytosis $\sigma^\text{EXO}$
- rate of endocytosis $k$
- intracellular delivery rate $\delta$
- degradation rate $\sigma^\text{DEG}$

- Spine neck hopping rate $\Omega$ can be extensive, but not in current parameter regime ($\sigma^\text{EXO} \gg \sigma^\text{DEG}$)
Heterosynaptic dependence on constitutive recycling

10-fold reduction in rate of exocytosis in gray region

10-fold increase in rate of endocytosis in gray region
Globally scaling exo/endocytosis does not imply multiplicative scaling of synaptic AMPAR numbers

- True when spine properties vary along dendrite
- E.g., identical spines except scaffolding concentration is

\[
Z(x) = 100[2 + \sin(x/10)] \ \mu m^{-2}
\]
Simulation of photoinactivation

Assume

- no intracellular delivery but source at soma
- in steady-state $t < 0$
- at $t = 0$ all surface AMPARs instantaneously “inactivated”
Rate of recycling depends on distance from soma

- **Fast exo/endocytosis consistent with slow recycling**
- **Rate-limiting steps:**

![Diagram showing synaptic plasticity](image)

- PSD
- Intracellular pool
- Fast insertion from pool
- Depletion of pool
- Recovery of pool
- Replacement of bound AMPARs

**Legend:**
- Inactive AMPAR
- Active AMPAR
- Scaffolding protein
Conclusions

1. Source of AMPARs at soma implies
   - exponential decay for identical spines
   - synaptic democracy for nonidentical spines

2. Need fast lateral diffusion to deliver AMPARs to distal synapses from soma
   - Takes too long?

3. Local changes in recycling produce nonlocal changes in synaptic AMPAR numbers
   - Extensive vs. intensive trafficking parameters

4. Globally scaling exo/endocytosis does not multiplicatively scale synaptic AMPAR numbers in nonidentical spines

5. Constitutive recycling rate is distance-dependent when soma is only source of AMPARs
   - fast recycling at proximal synapses
   - slow recycling at distal synapses
The end
## Baseline parameter values

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<tr>
<th>Parameter</th>
<th>Symbol</th>
<th>Value</th>
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<td>1 mm</td>
<td>Sorra &amp; Harris 2000</td>
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<td>Circumference of dendrite</td>
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<td>Spine neck hopping rate</td>
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<td>O’Brien et al. 1999</td>
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Steady-state at single spine

\[ \sigma^{\text{EXO}} C = \lambda [kR + \delta], \quad \lambda = \frac{\sigma^{\text{EXO}}}{\sigma^{\text{EXO}} + \sigma^{\text{DEG}}} \]

\[ P = \left[ 1 + \frac{\lambda k}{h} \right] R + \frac{\lambda \delta}{h}, \quad Q = \frac{\alpha PZ}{\beta + \alpha P} \]

\[ R = \frac{\Omega U + \lambda \delta}{\Omega + k(1 - \lambda)}. \]
Steady-state dendritic concentration

\[ D \frac{d^2 U}{dx^2} - \rho \hat{\Omega} U = -\rho \hat{\Omega} r \]

\[ \hat{\Omega} = \frac{\Omega k (1 - \lambda)}{\Omega + k(1 - \lambda)}, \quad r = \frac{\sigma^{\text{EXO}} \delta}{\sigma^{\text{DEG}} k} \]

One can view
- \( \hat{\Omega} \) as effective spine neck hopping rate
- \( r \) as effective ESM receptor concentration
Solution for identical spines: “cable” equation

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

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

- Solve using Green’s function methods like standard cable equation for electrical current flow in passive dendrites

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