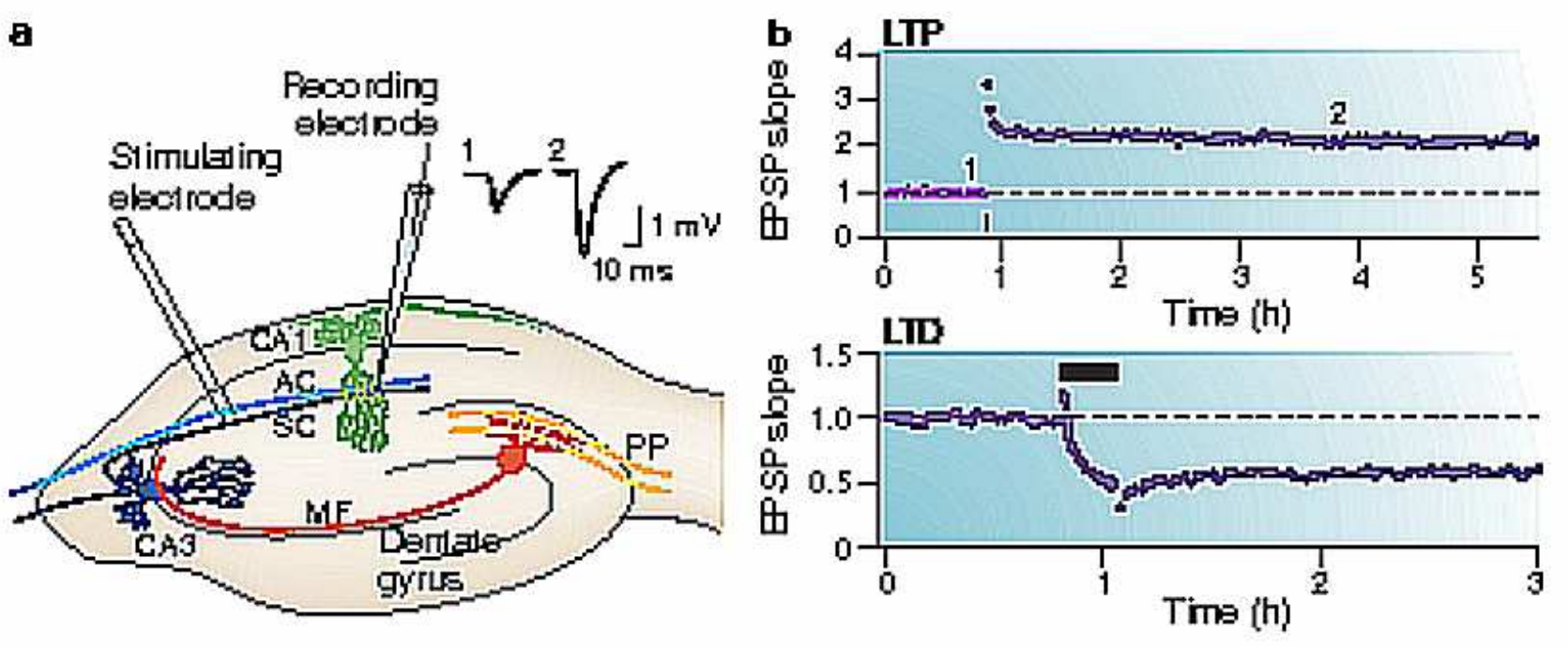
Diffusion-trapping model of AMPA receptor trafficking along a spiny dendrite

Paul C. Bressloff, Berton A. Earnshaw

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

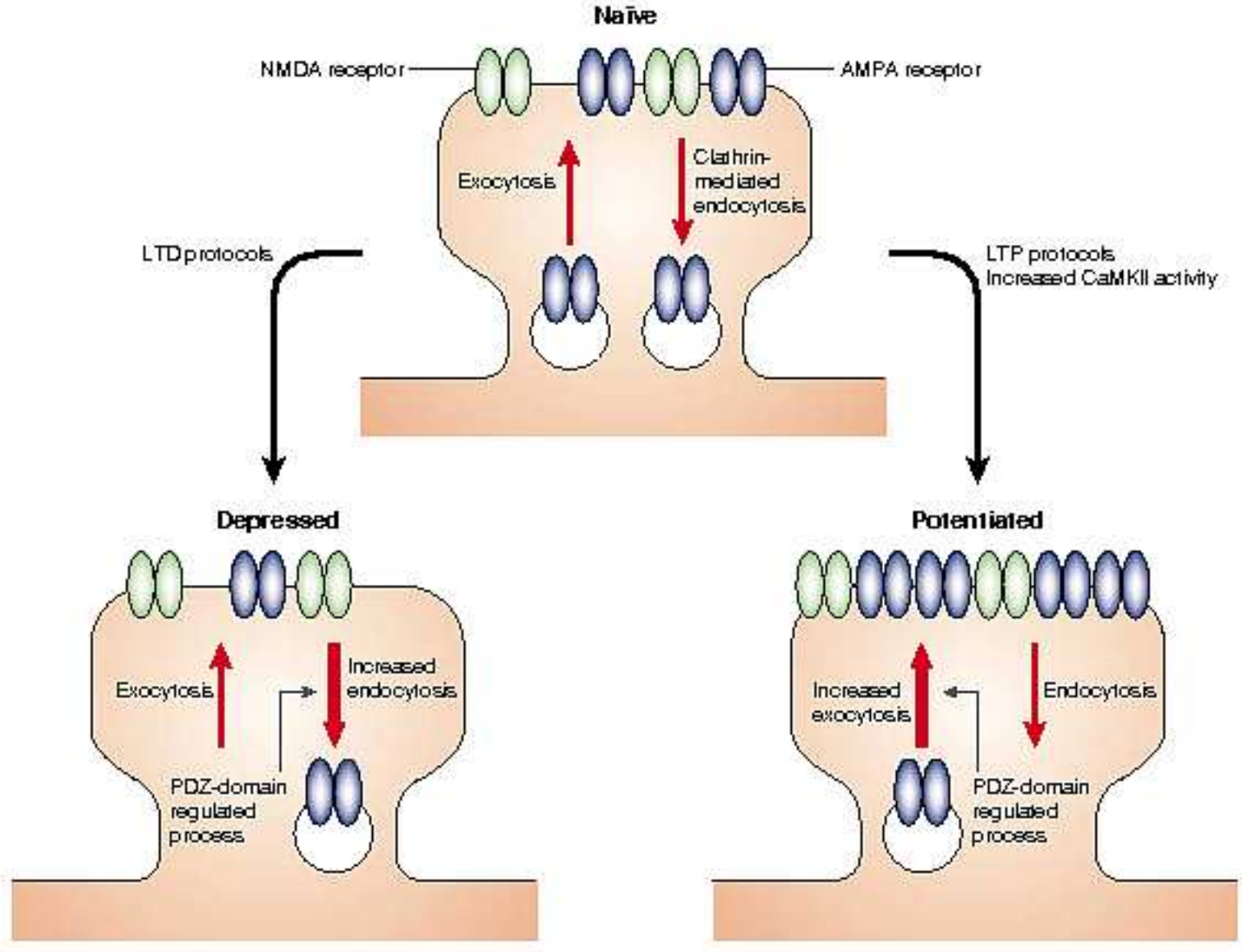
August 4, 2008

Synapses can "learn"



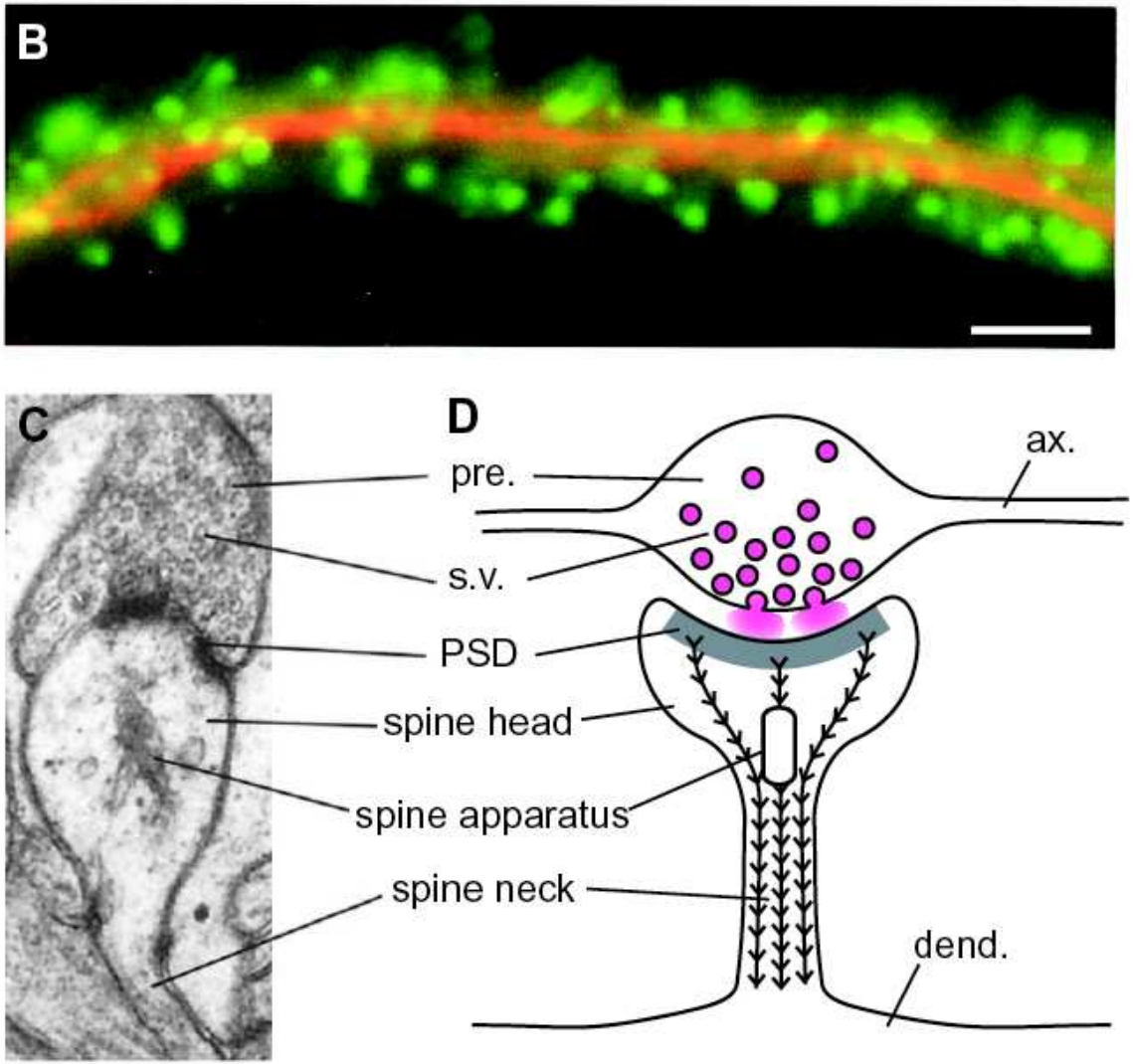
Collingridge et al., *Nat. Rev. Neurosci.* (2004)

Synapses "learn" by regulating AMPA receptor numbers



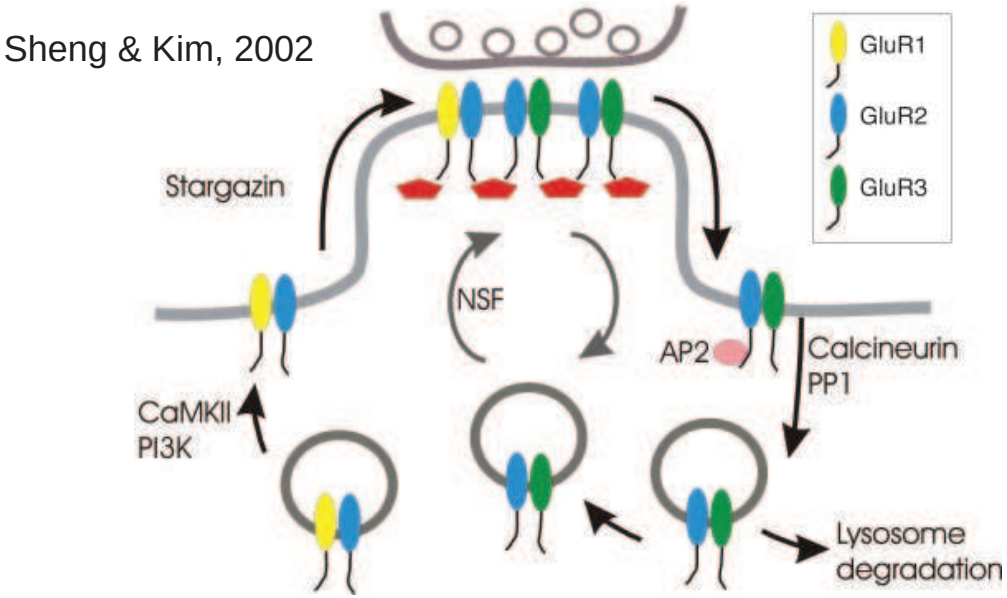
Scannevin & Huganir, *Nat. Rev. Neurosci.* (2000)

Synapses located in dendritic spines



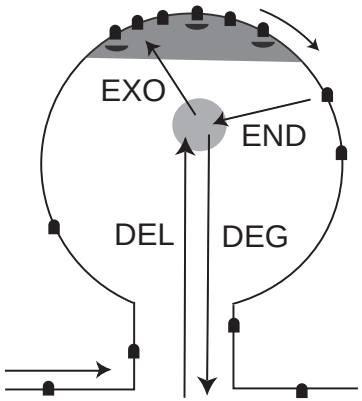
Matus, *Science* (2000)

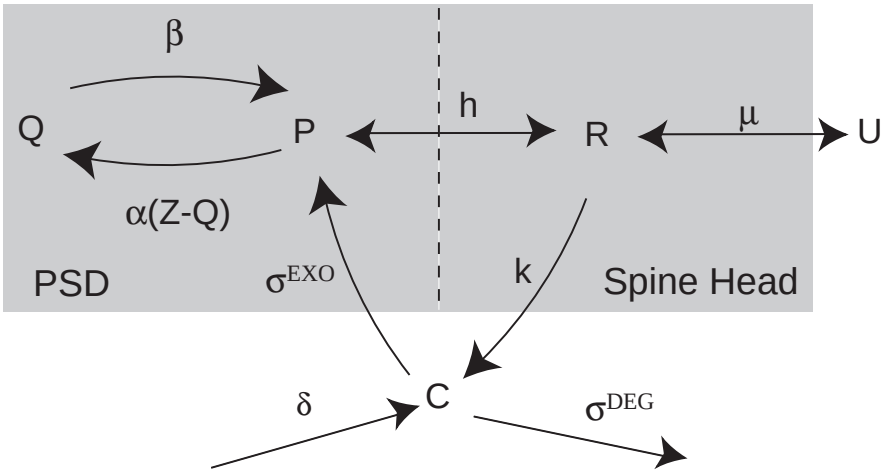
AMPA receptor trafficking at spines



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

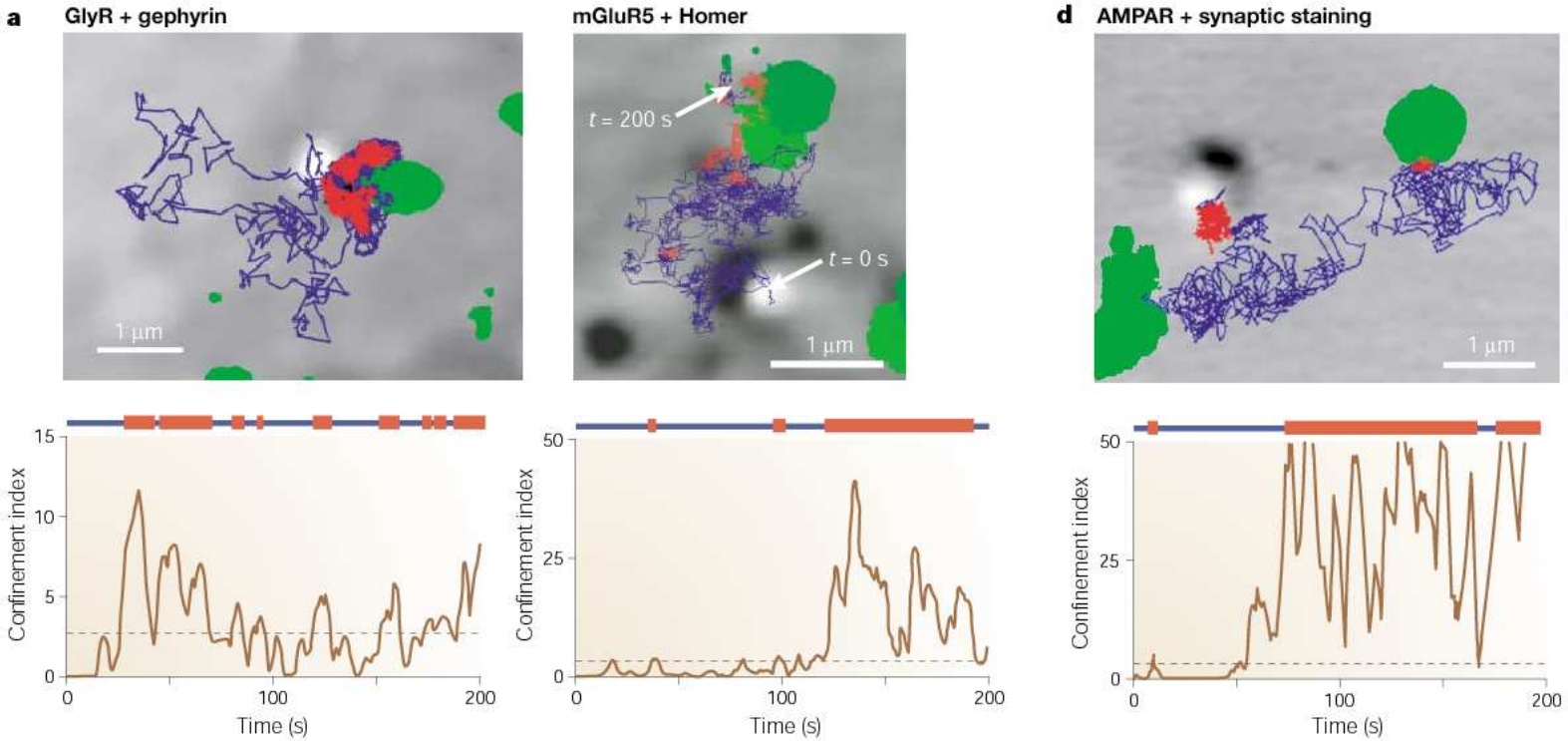
Model of AMPAR trafficking at a single spine





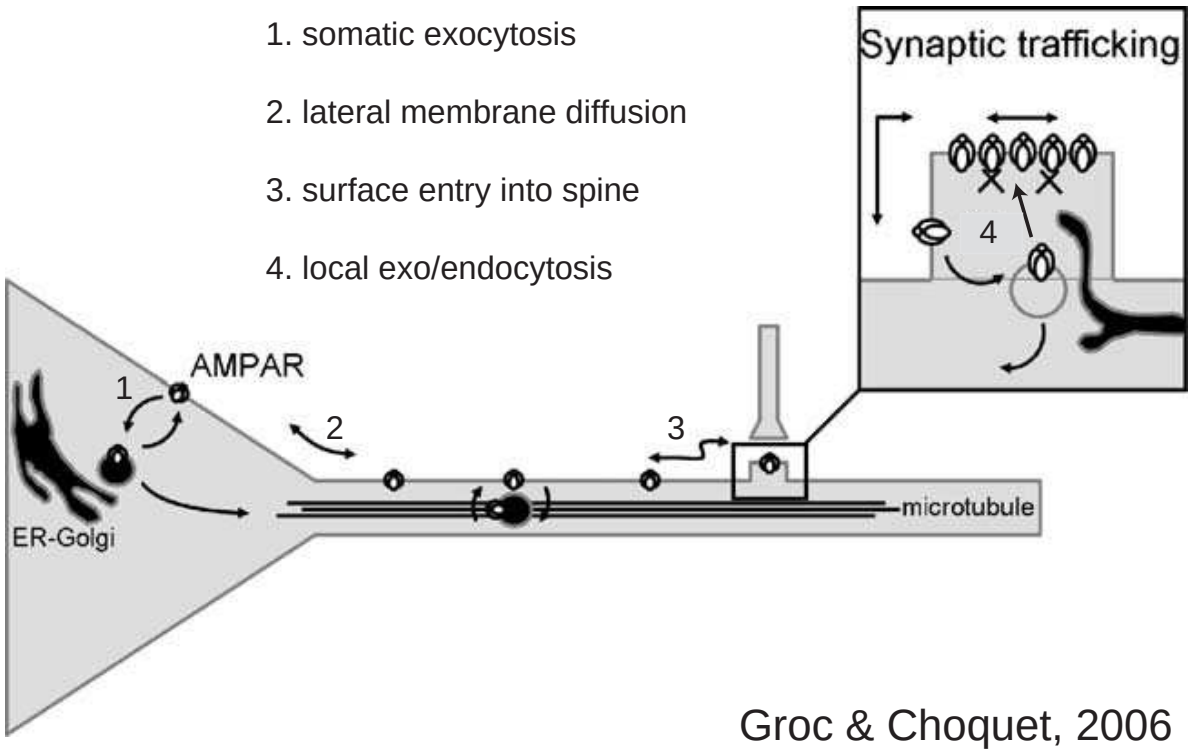
P, Q:	**unbound, bound receptor concentrations in PSD**
R, U:	**free receptor concentrations in spine head, dendrite**
C:	**number of intracellular receptors**
k, σ^{EXO}:	**rates of endocytosis, exocytosis**
σ^{DEG}, δ:	**rates of degradation, intracellular delivery**
h, μ:	**hopping rates across boundary of PSD, spine neck**
α(Z-Q):	**rate of binding to scaffolding (Z = scaffolding concentration)**
β:	**rate of unbinding from scaffolding**

AMPARs diffuse laterally between synapses



Triller & Choquet, *Nat. Rev. Neurosci.* (2003)

Long-range transport of AMPARs along spiny dendrite



Groc & Choquet, 2006

- motor transport along microtubules
- **diffusion** within dendritic membrane? (Adesnik et al., 2005)

Continuum model of 1D nonbranching dendrite

- If spines are sufficiently dense, treat them as density ρ

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

  - U = concentration of AMPARs in dendrite
  - R = concentration of AMPARs in spine
  - μ = hopping rate between dendrite and spine

Continuum model of 1D nonbranching dendrite

- If spines are sufficiently dense, treat them as density ρ

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

  - U = concentration of AMPARs in dendrite
  - R = concentration of AMPARs in spine
  - μ = hopping rate between dendrite and spine
- Boundary conditions

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

Steady-state solution: "cable" equation

- If all parameters are x-independent, then get "cable" equation for AMPAR trafficking

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

  - $\Lambda^{-1} = \sqrt{\frac{D}{\rho\widehat{\mu}}}$: length-scale of diffusive coupling
  - $\widehat{R}$, $\widehat{\mu}$: effective AMPAR spine concentration, hopping rate

Steady-state solution: "cable" equation

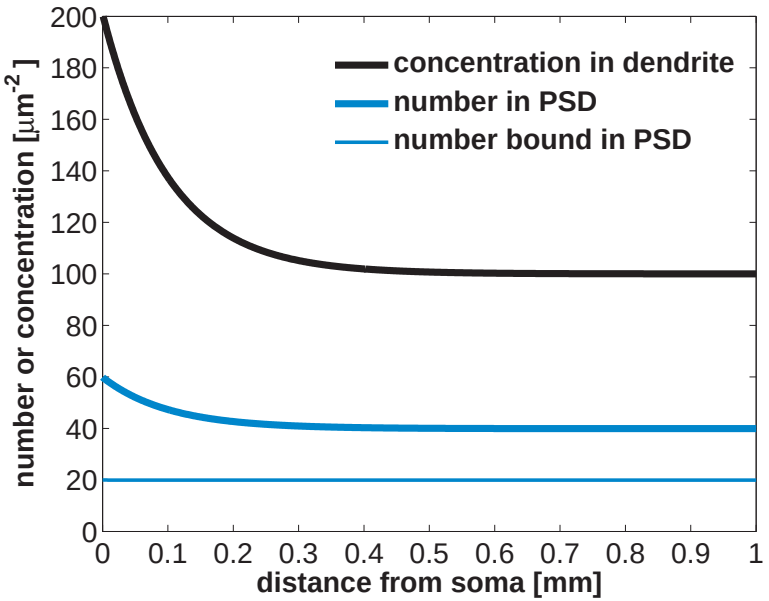
- If all parameters are x-independent, then get "cable" equation for AMPAR trafficking

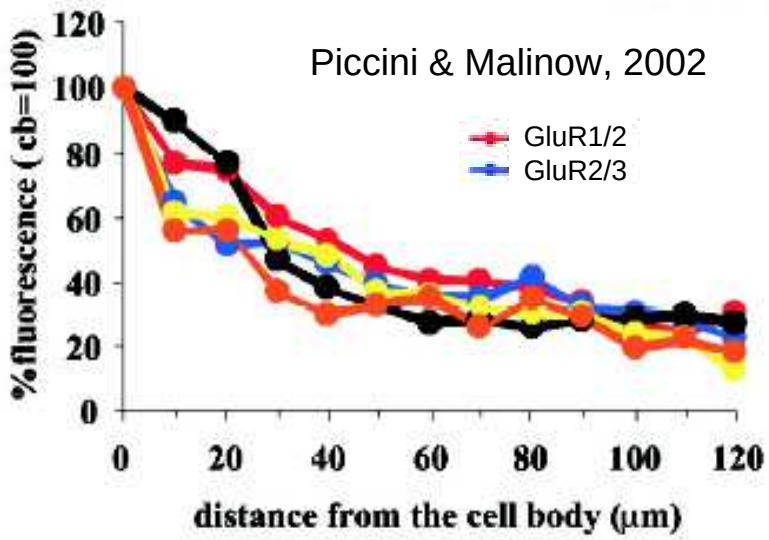
$$\frac{d^2U}{dx^2} - \Lambda^2 U = -\Lambda^2 \widehat{R}$$

  - $\Lambda^{-1} = \sqrt{\frac{D}{\rho\widehat{\mu}}}$: length-scale of diffusive coupling
  - $\widehat{R}$, $\widehat{\mu}$: effective AMPAR spine concentration, hopping rate
- Solve using Green's function methods

$$U(x) = \frac{J_{\text{soma}}}{D} \frac{\cosh(\Lambda(x-L))}{\Lambda \sinh(\Lambda L)} + \widehat{R}$$

Steady-state AMPAR profiles for identical spines

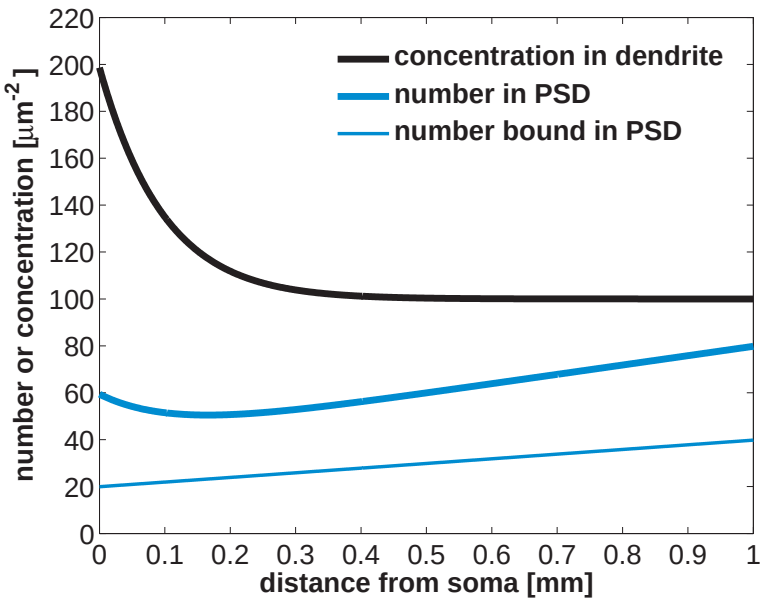




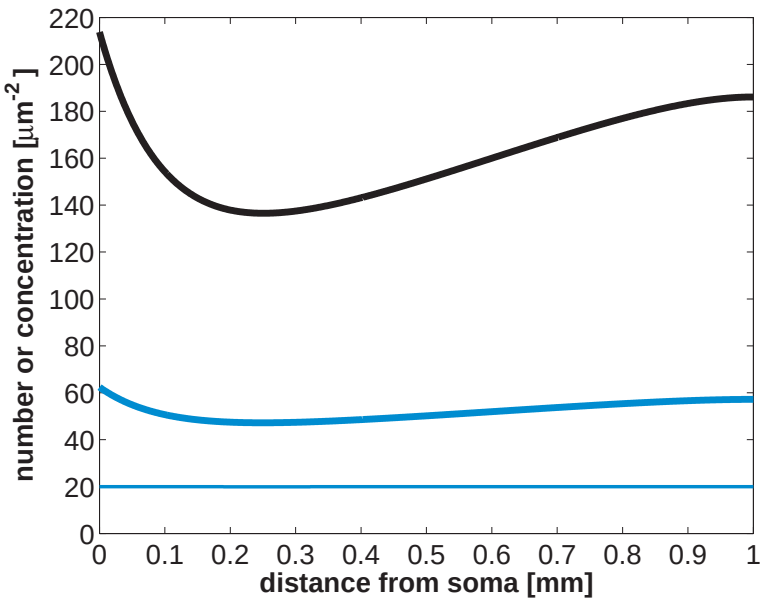
- 1,000 identical spines uniformly spaced in 1 mm dendrite
- Two sources of AMPARs
  - at soma
  - local intracellular delivery
- diffusion coefficient $D = 0.1\ \mu m^2 s^{-1}$ in dendrite

Nonidentical spines: Synaptic democracy

PSD surface area
or spine density
increases linearly

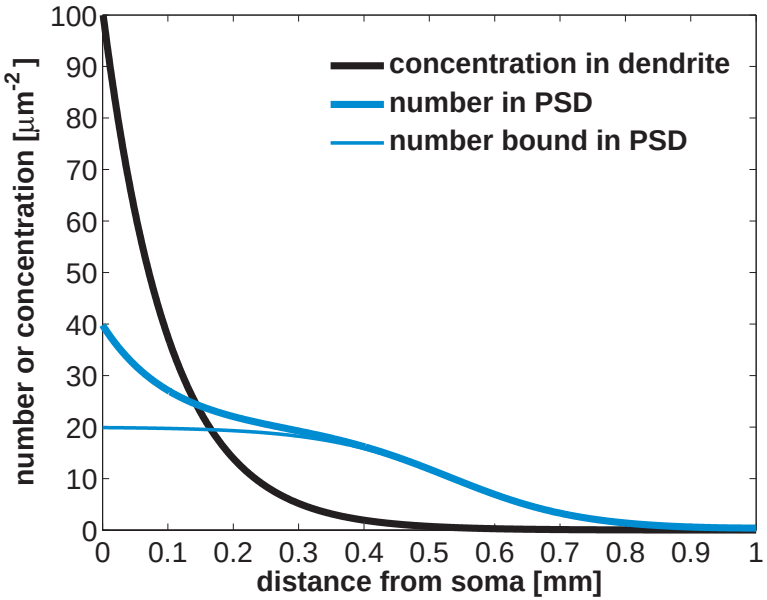


rate of delivery
or exocytosis
increases linearly

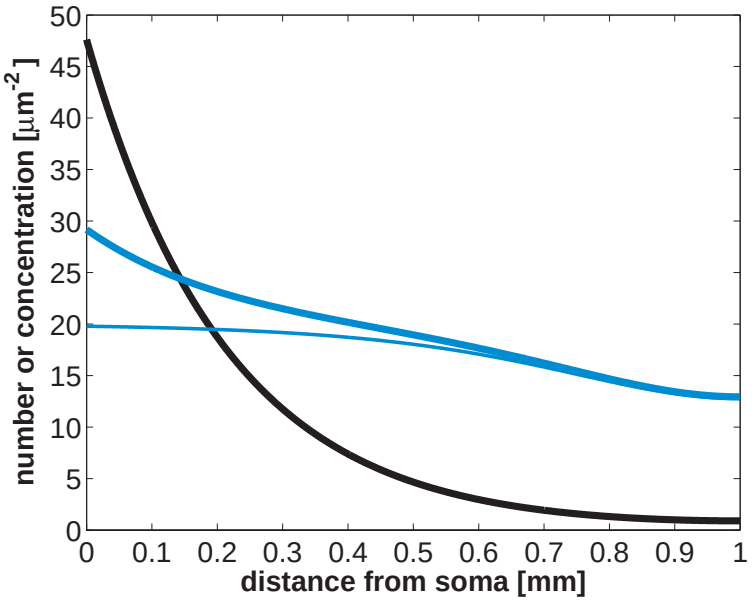


Identical spines without intracellular delivery

$D = 0.1\ \mu m^2 s^{-1}$



$D = 0.45\ \mu m^2 s^{-1}$



- Mean time to reach distance X from soma $> \frac{X^2}{2D}$
- For $D = 0.45\ \mu m^2 s^{-1}$
  - $X = 100\ \mu m \Rightarrow \frac{X^2}{2D} \sim 3$ hr
  - $X = 1\ mm \Rightarrow \frac{X^2}{2D} \sim 300$ 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 α
- unbinding rate β

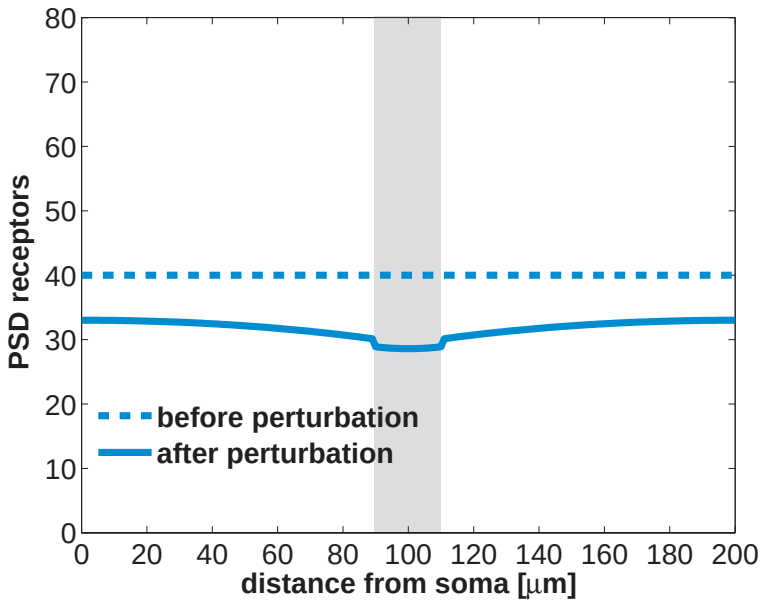
Extensive
(nonlocal effect)

- rate of exocytosis σ^{EXO}
- rate of endocytosis k
- intracellular delivery rate δ
- degradation rate σ^{DEG}

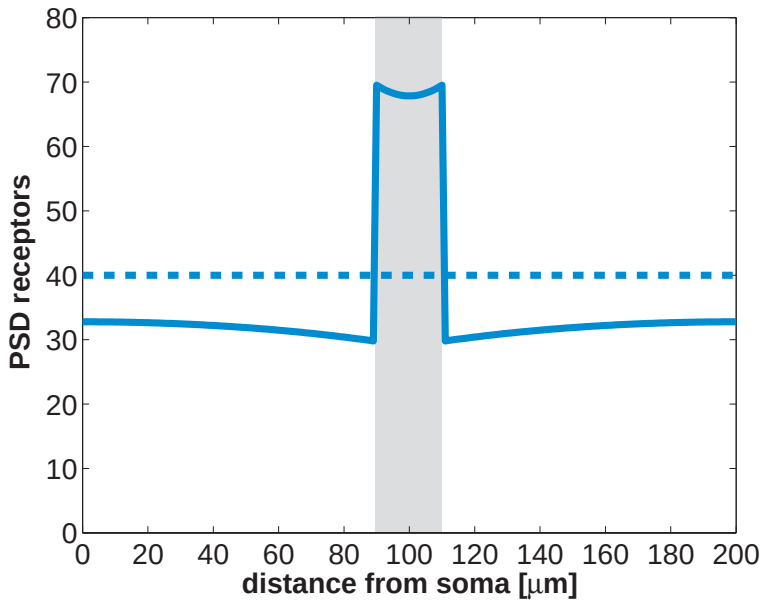
- Spine neck hopping rate Ω can be extensive, but not in current parameter regime ($\sigma^{\mathrm{EXO}} \gg \sigma^{\mathrm{DEG}}$)

Heterosynaptic dependence on constitutive recycling

10-fold reduction in rate of exocytosis in gray region



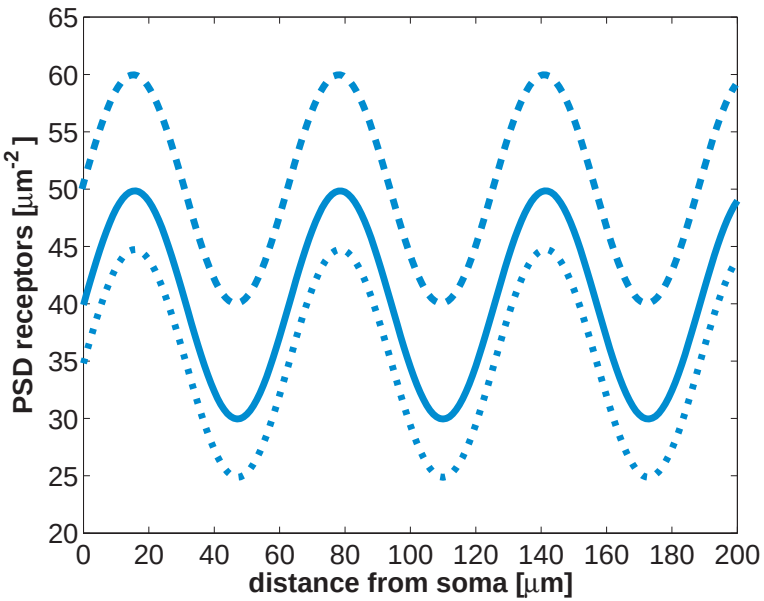
10-fold increase in rate of endocytosis in gray region

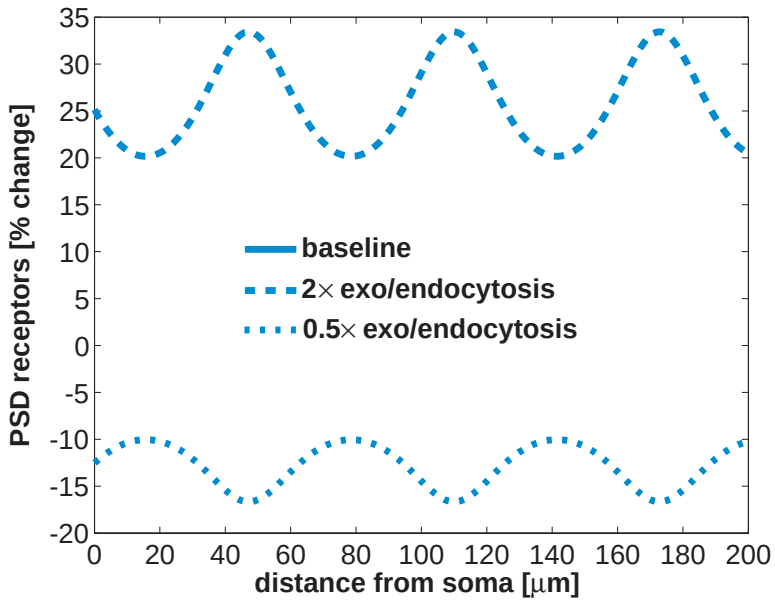


Globally scaling exo/endocytosis does not imply multiplicative scaling of synaptic AMPAR numbers

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

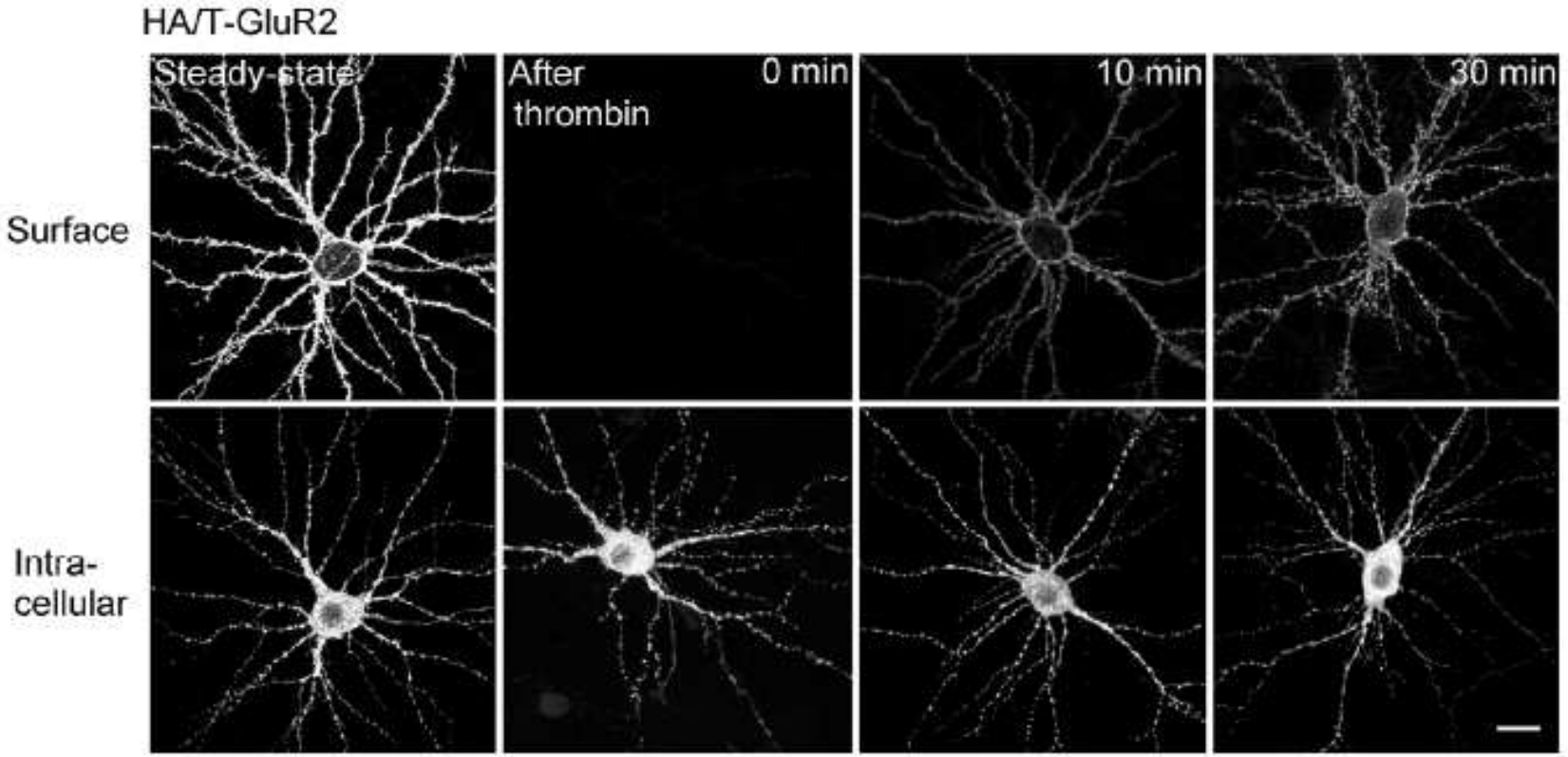
$$Z(x) = 100[2 + \sin(x/10)] \ \mu m^{-2}$$





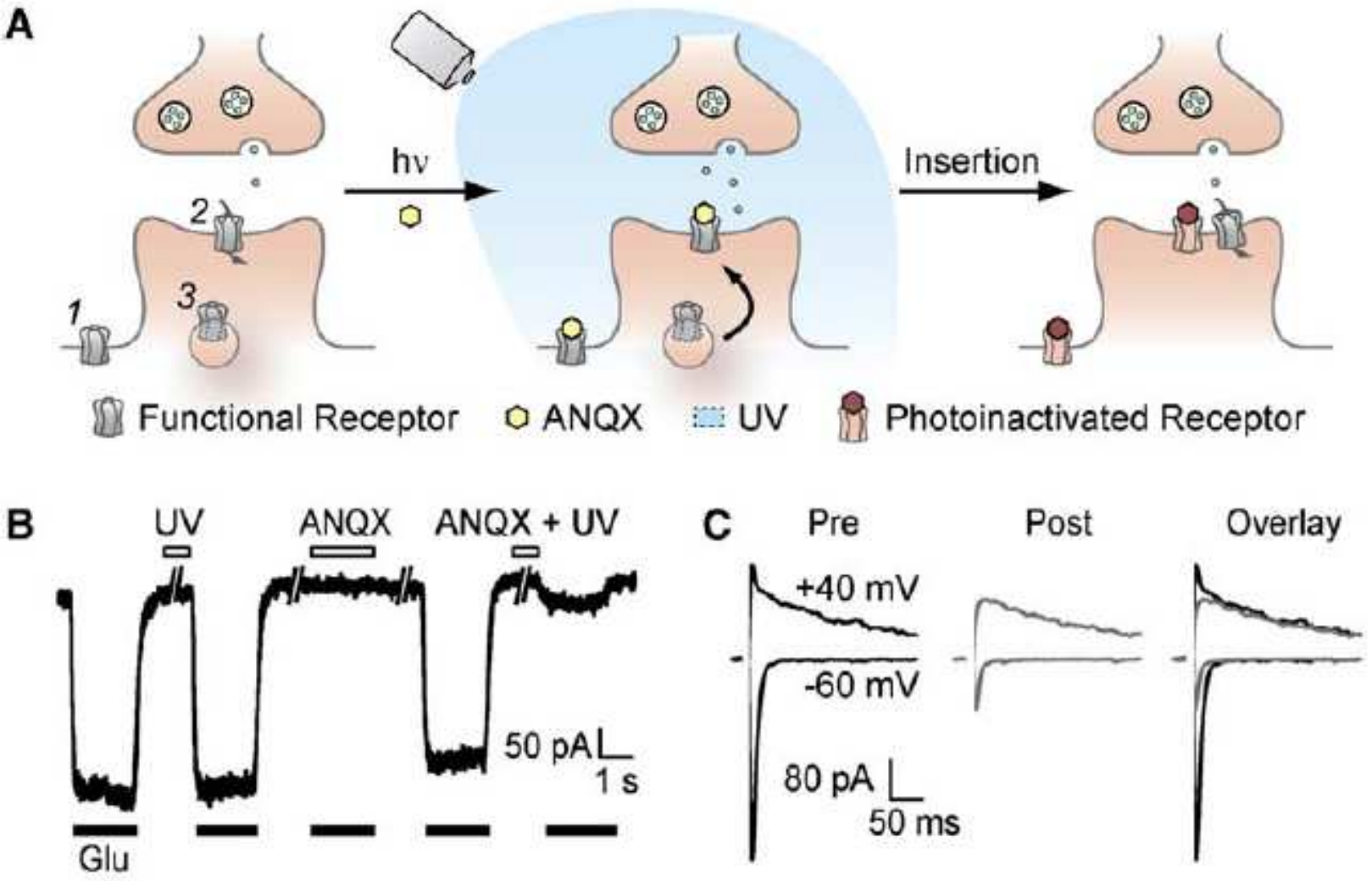
Steady-state is nice...
...but what about time-dependent phenomena?

AMPA receptor recycling via thrombin cleavage



Passafaro et al., *Nat. Neurosci.* (2001)

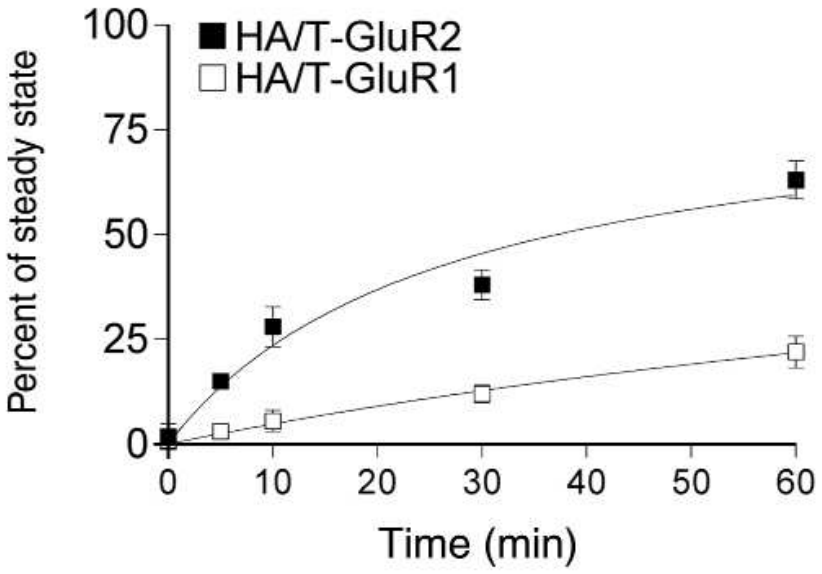
AMPA receptor recycling via photoinactivation



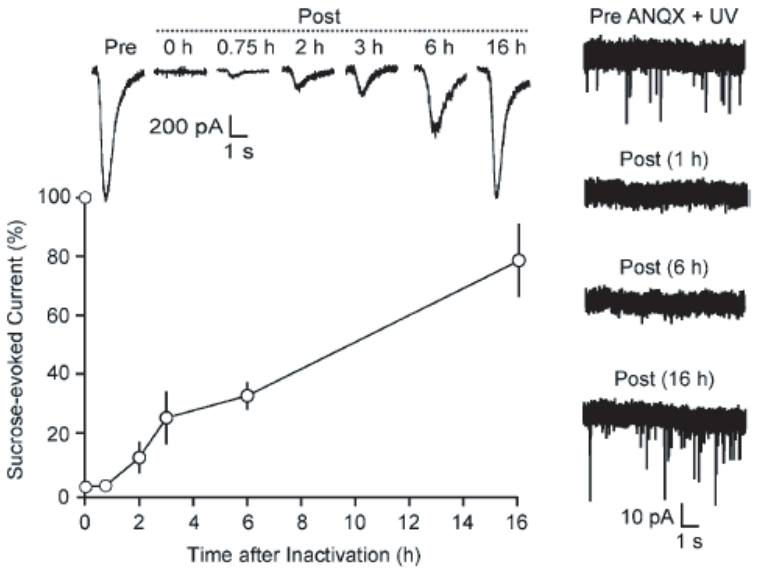
Adesnik et al., *Neuron* (2005)

Fast or slow recycling of AMPA receptors?

Passafaro et al., 2001

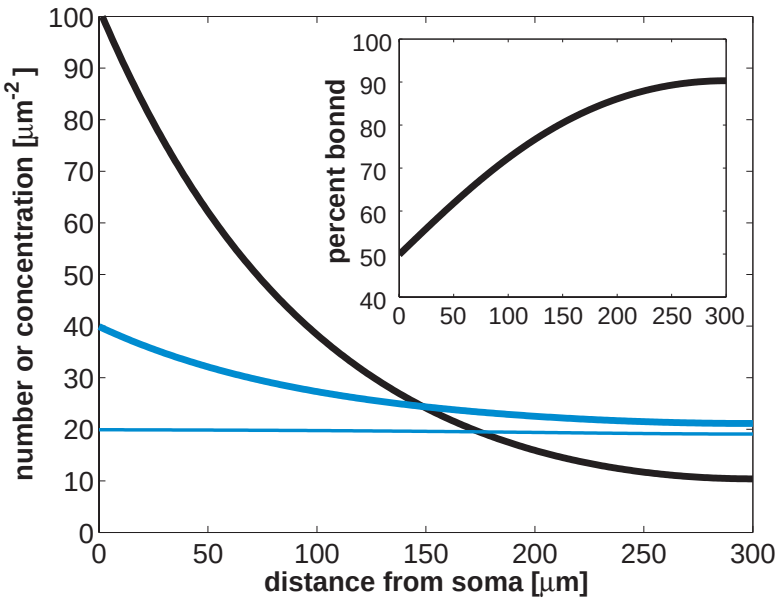


Adesnik et al., 2005



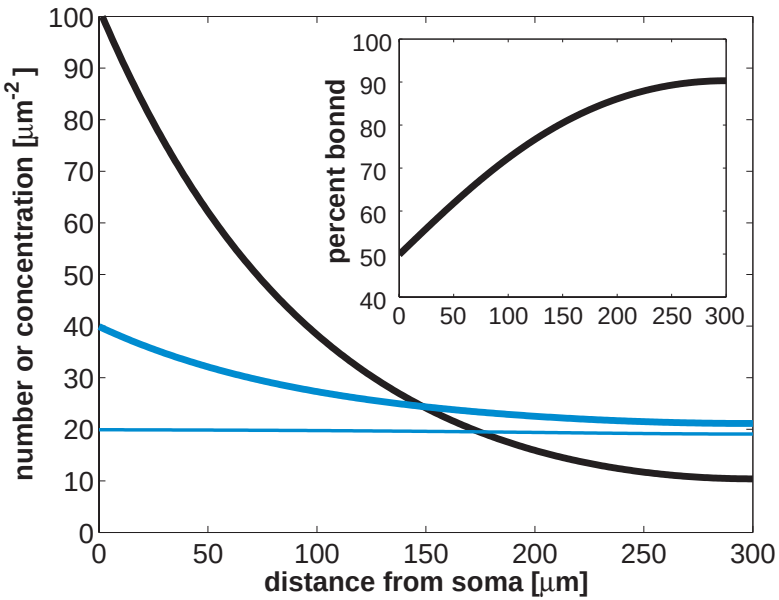
Simulation of photoinactivation of AMPA receptors

- Source at soma, but no intracellular delivery
- In steady-state for $t < 0$
- At $t = 0$ all surface AMPA receptors instantaneously "inactivated"



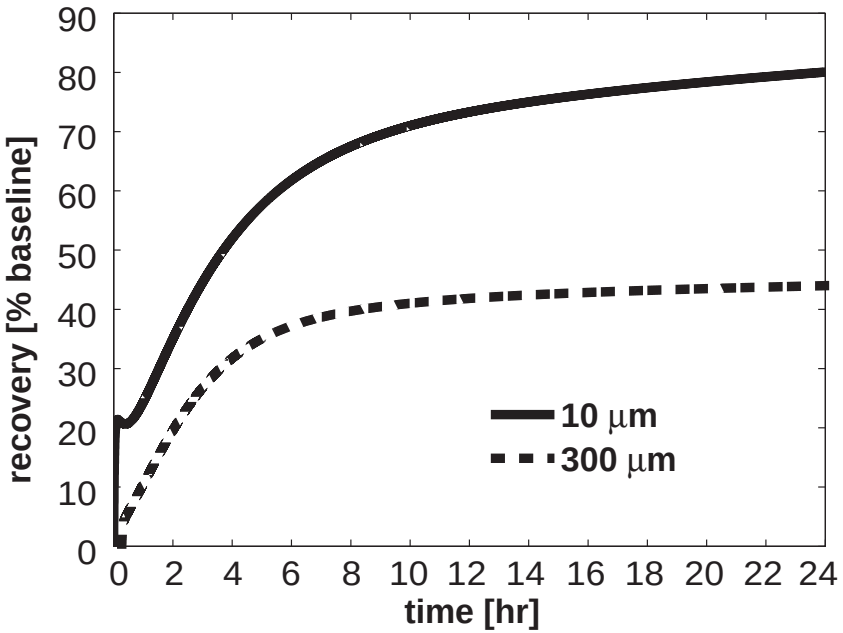
Simulation of photoinactivation of AMPA receptors

- Source at soma, but no intracellular delivery
- In steady-state for $t < 0$
- At $t = 0$ all surface AMPA receptors instantaneously "inactivated"



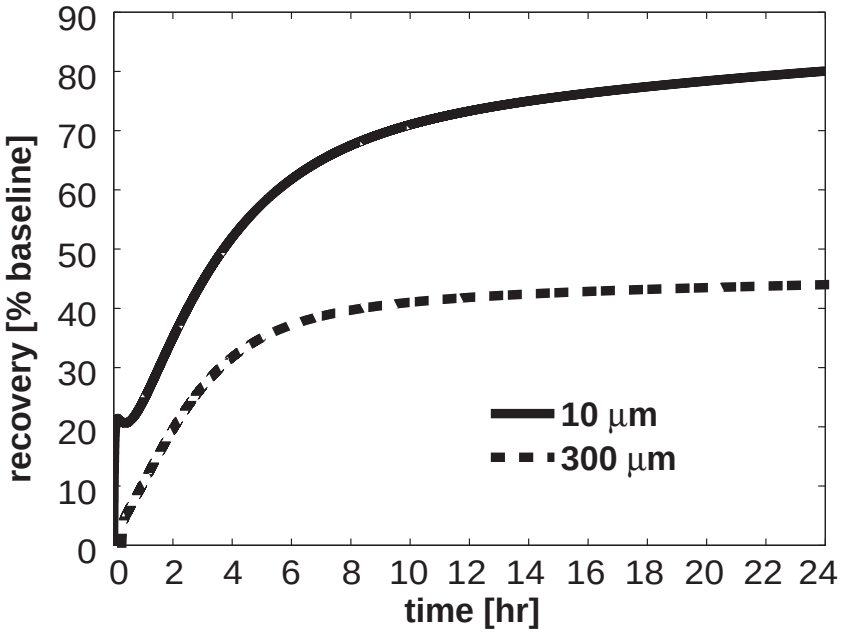
- Rates of exo/endocytosis are **fast** (10-30 mins)

Rate of recycling depends on distance from soma

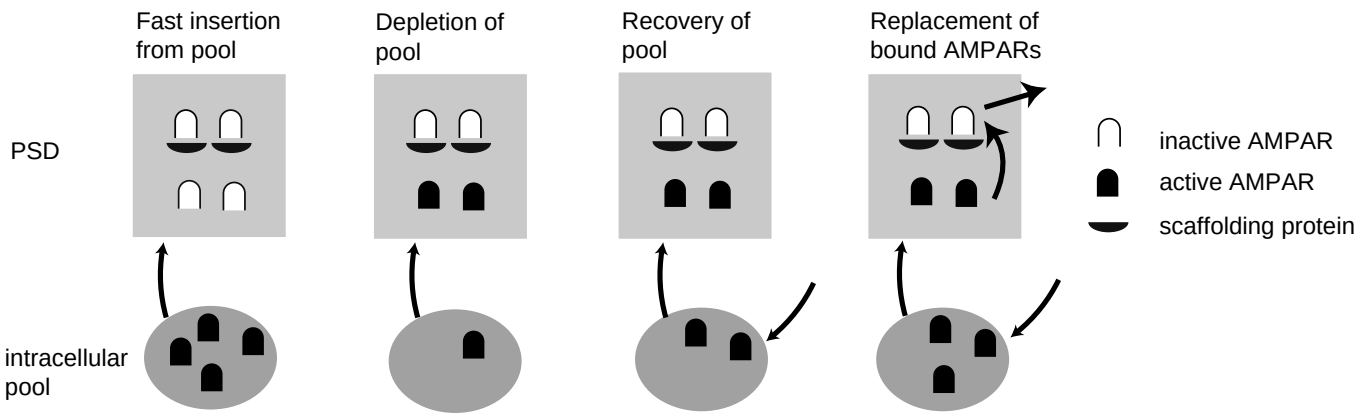


- Fast exo/endocytosis consistent with slow recycling

Rate of recycling depends on distance from soma



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



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 constitutive recycling produce nonlocal changes in synaptic AMPAR numbers
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
6. Many time scales involved in relaxation to steady-state