# Diffusion-trapping models of protein receptor trafficking along spiny dendrites

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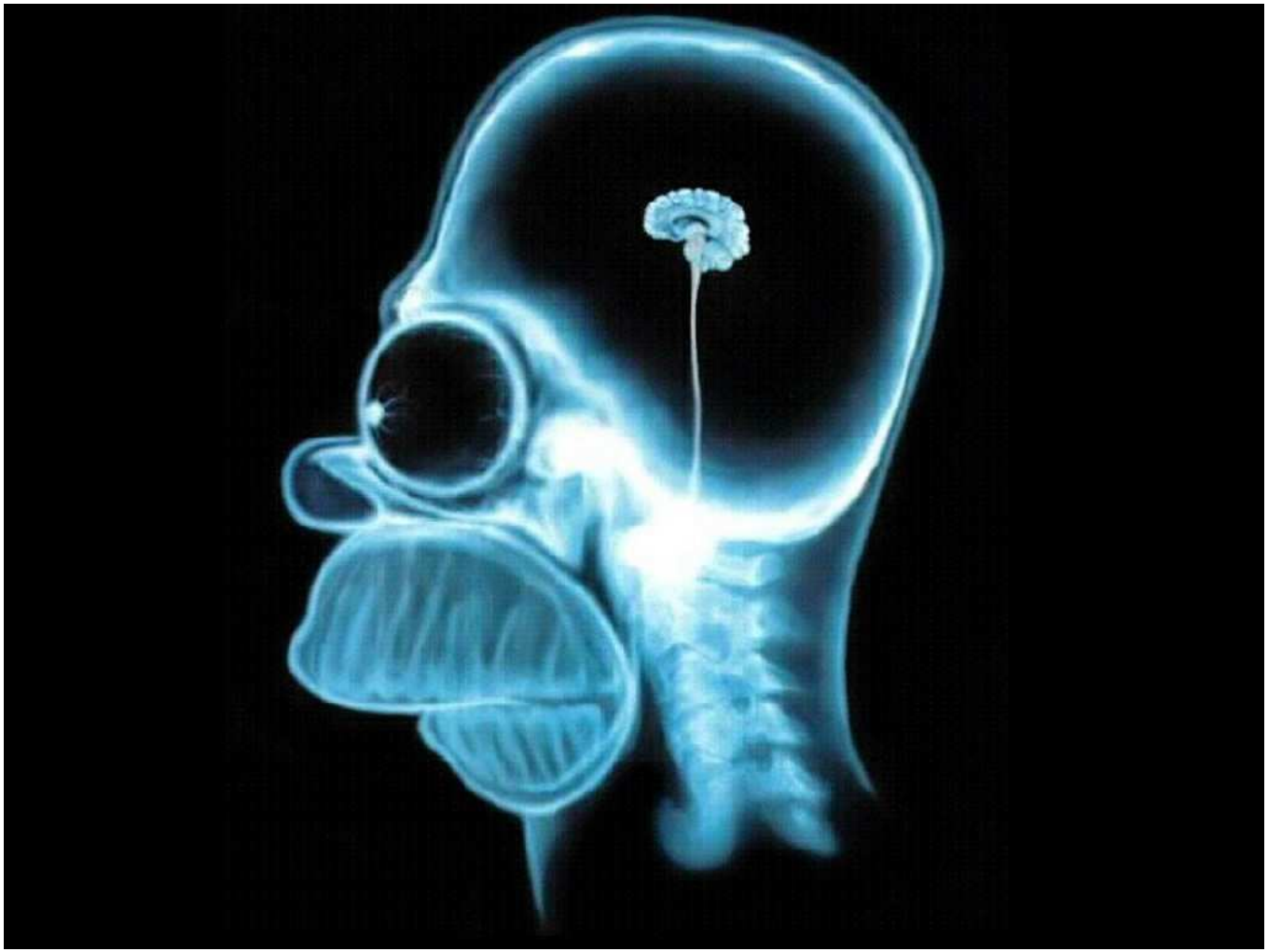
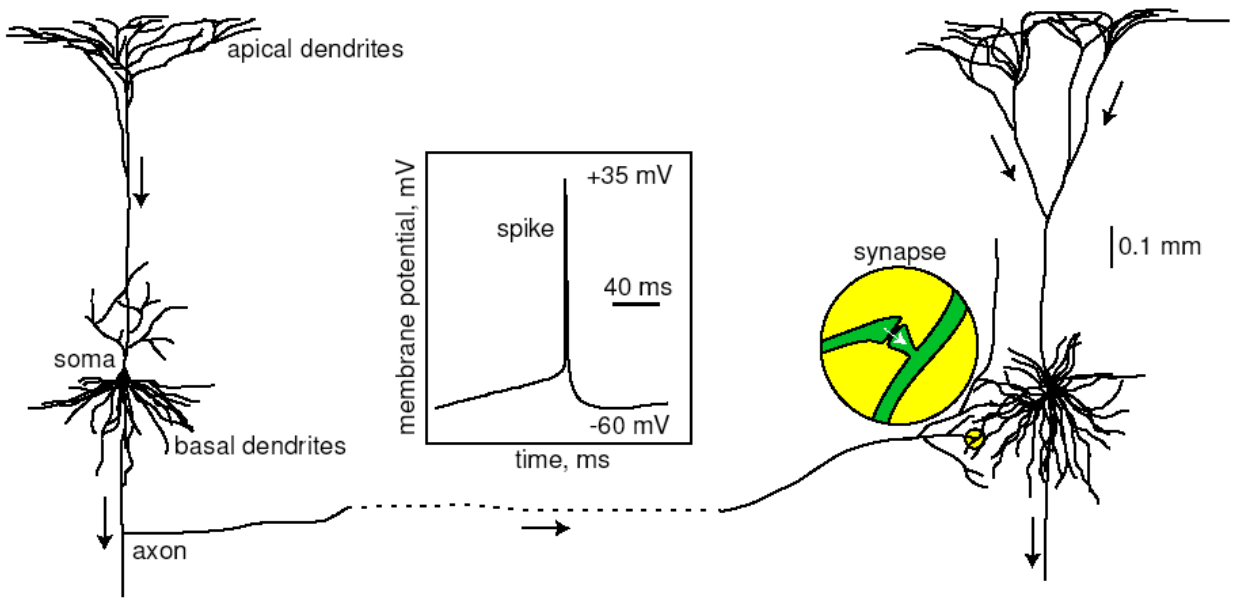
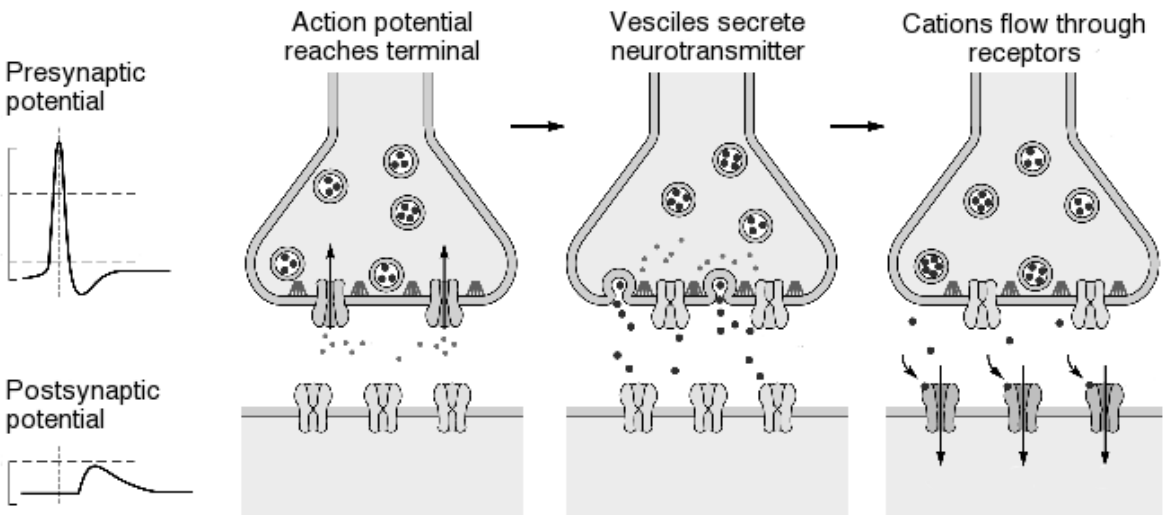
June 25, 2008

# The amazing brain



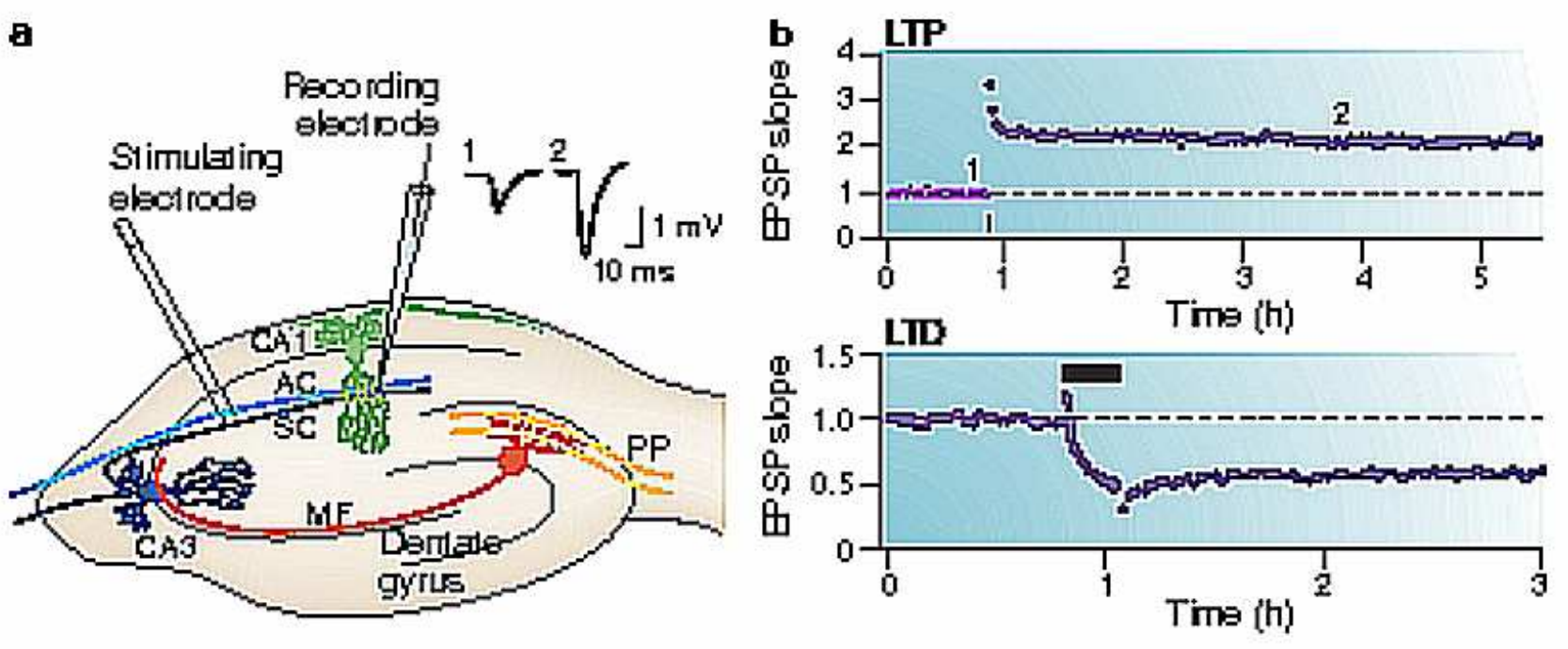
# Neurons communicate at synapses



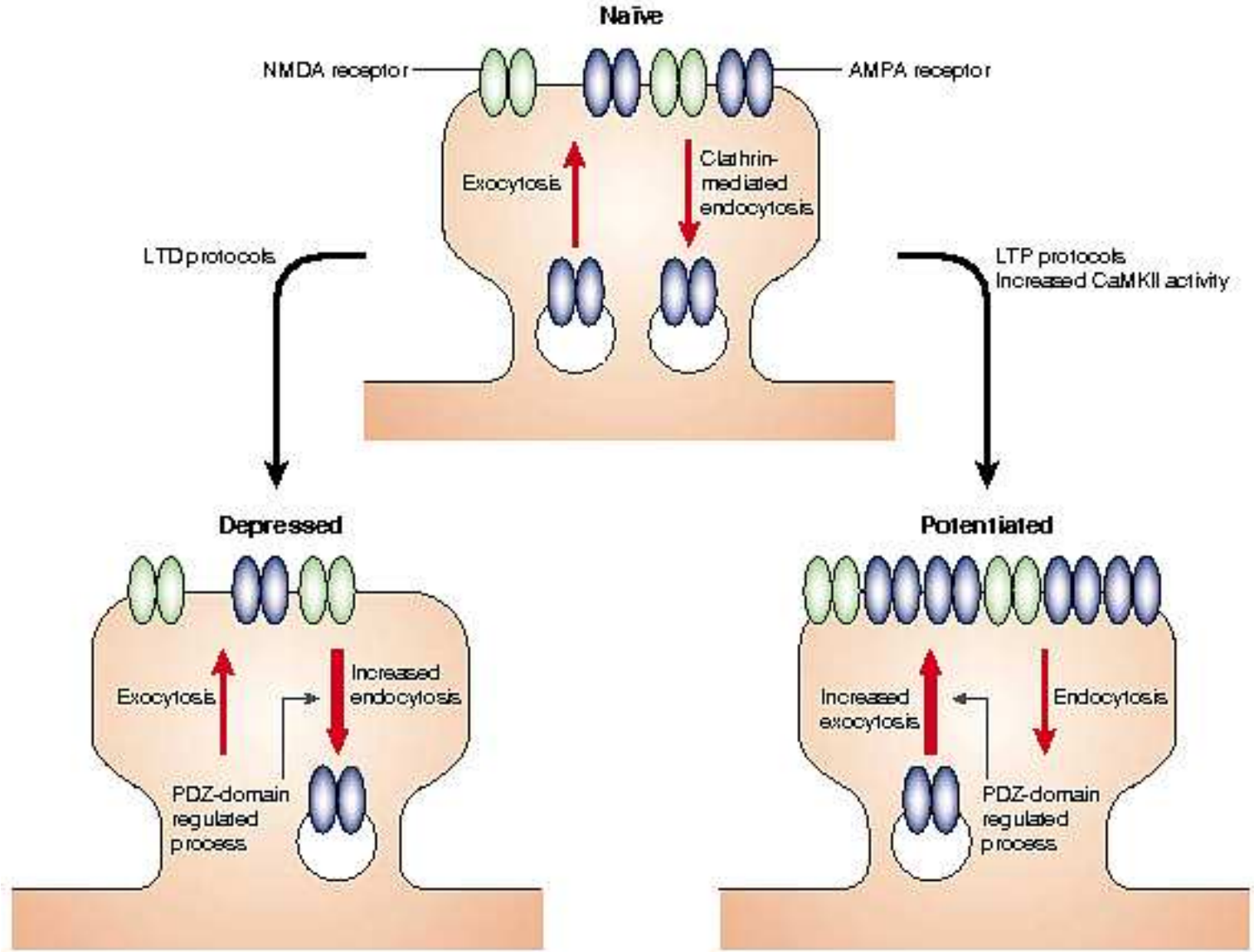

Kandel, Schwartz & Jessel (2000)

# Synapses can "learn"



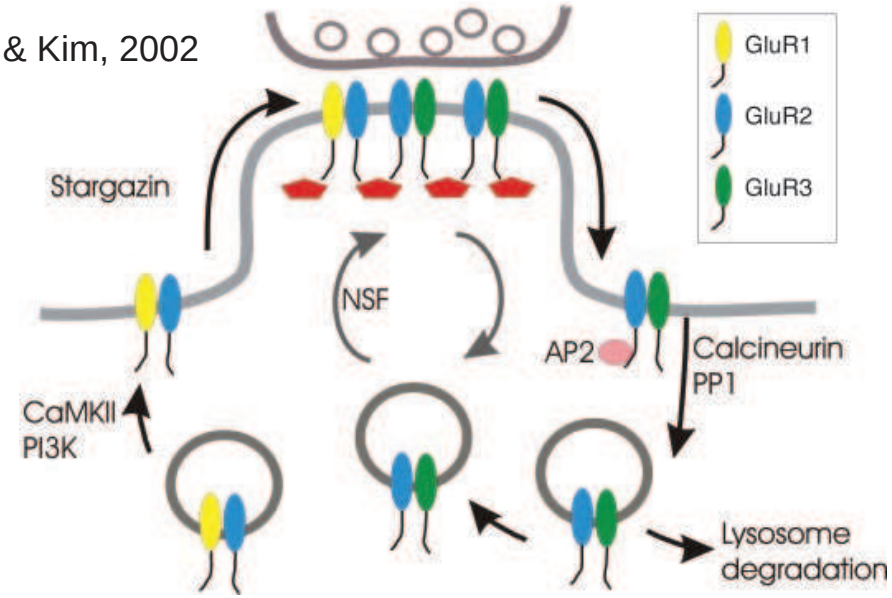

Collingridge et al., *Nat. Rev. Neurosci.* (2004)

# Synapses "learn" by regulating receptor numbers



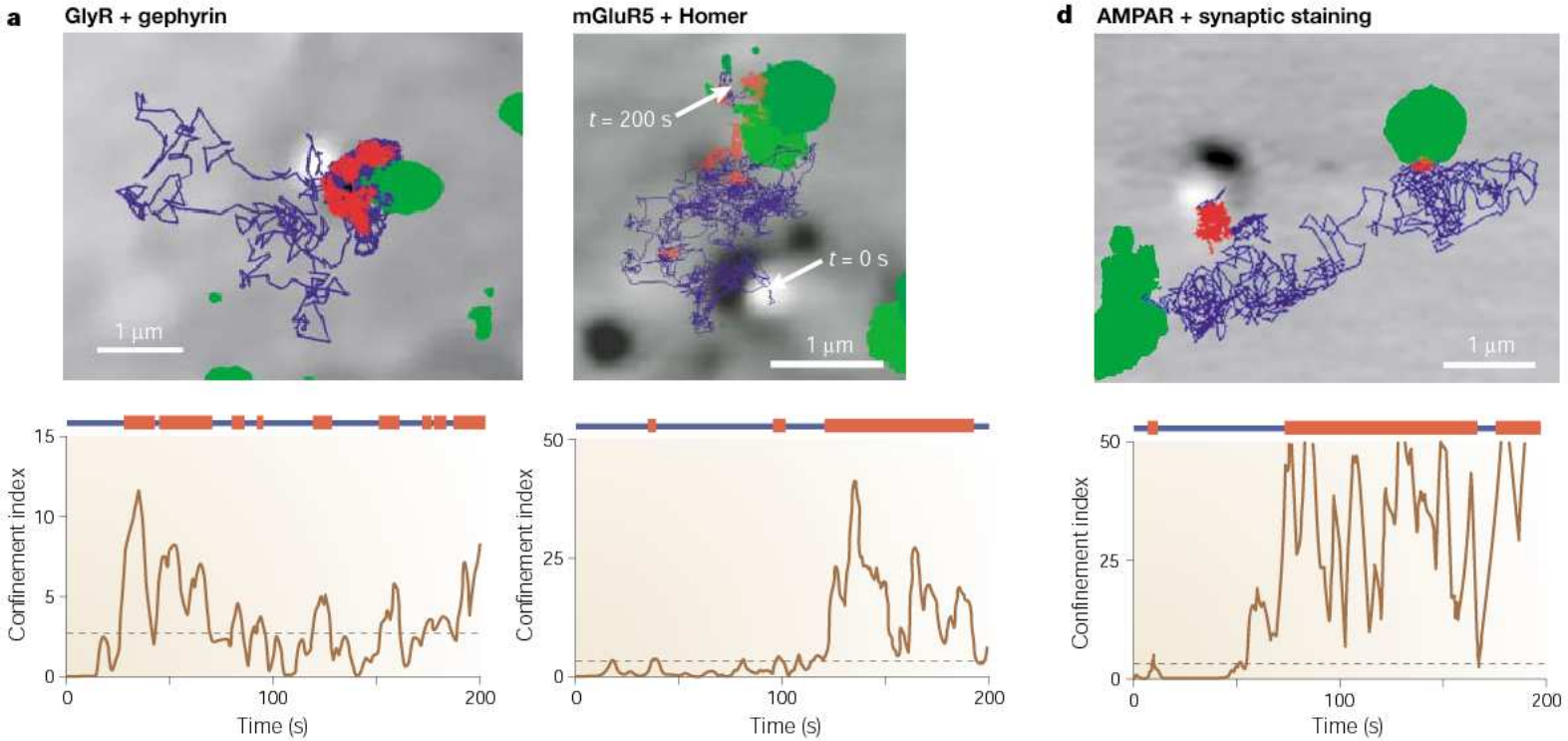

Scannevin & Huganir, *Nat. Rev. Neurosci.* (2000)

# 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

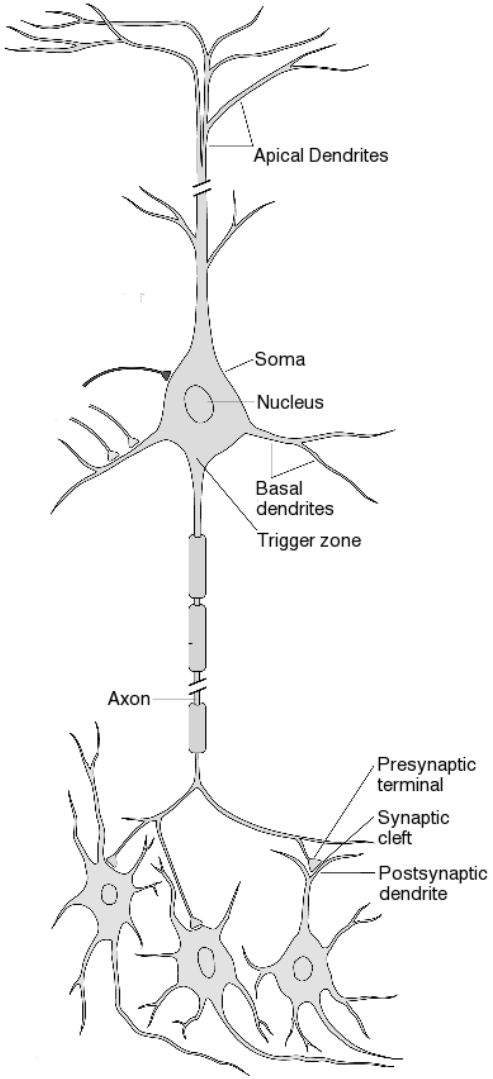
# Receptors diffuse laterally between synapses



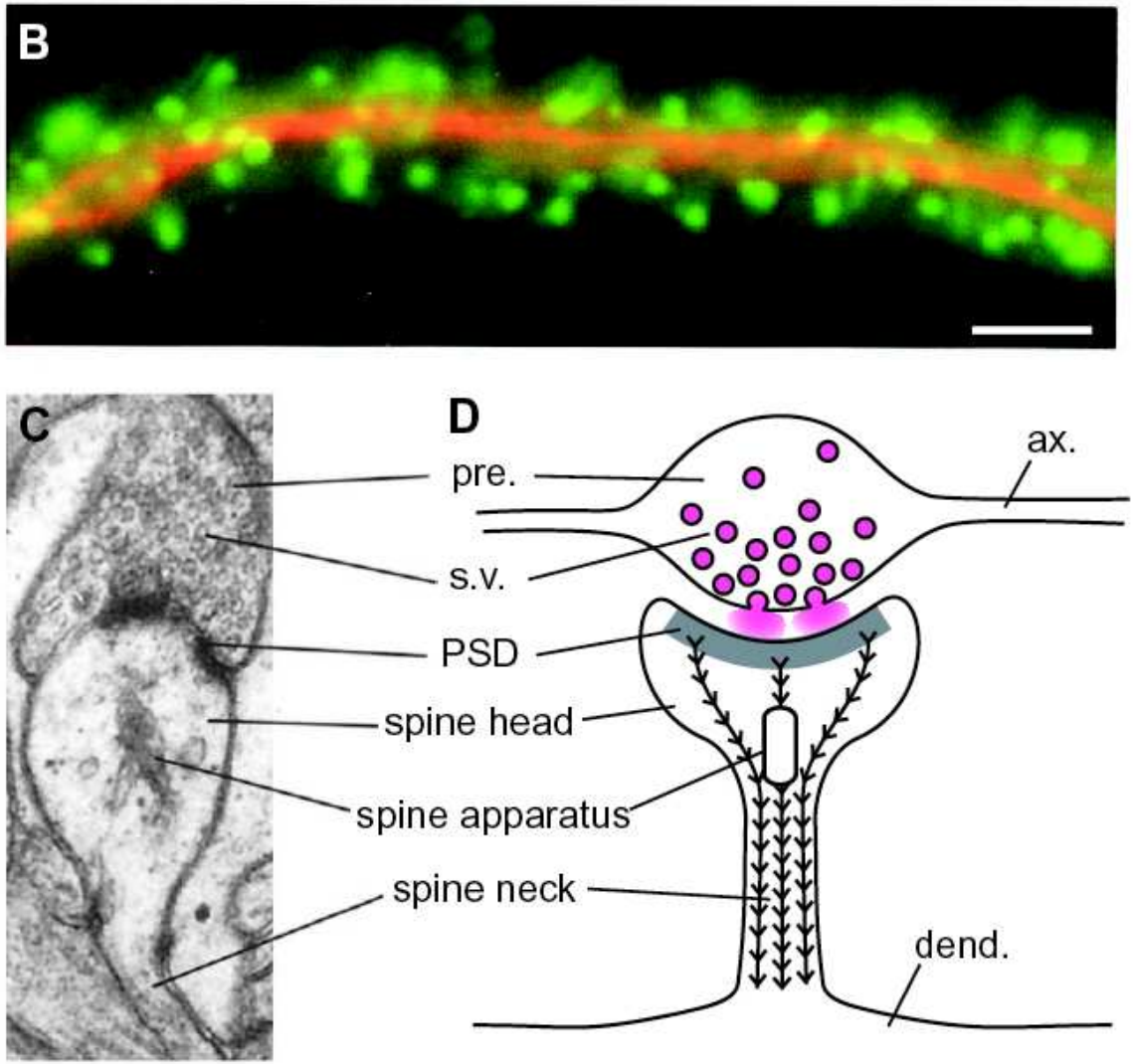

Triller & Choquet, *Nat. Rev. Neurosci.* (2003)

How are receptors transported to synapses?

# Synapses located in dendritic spines

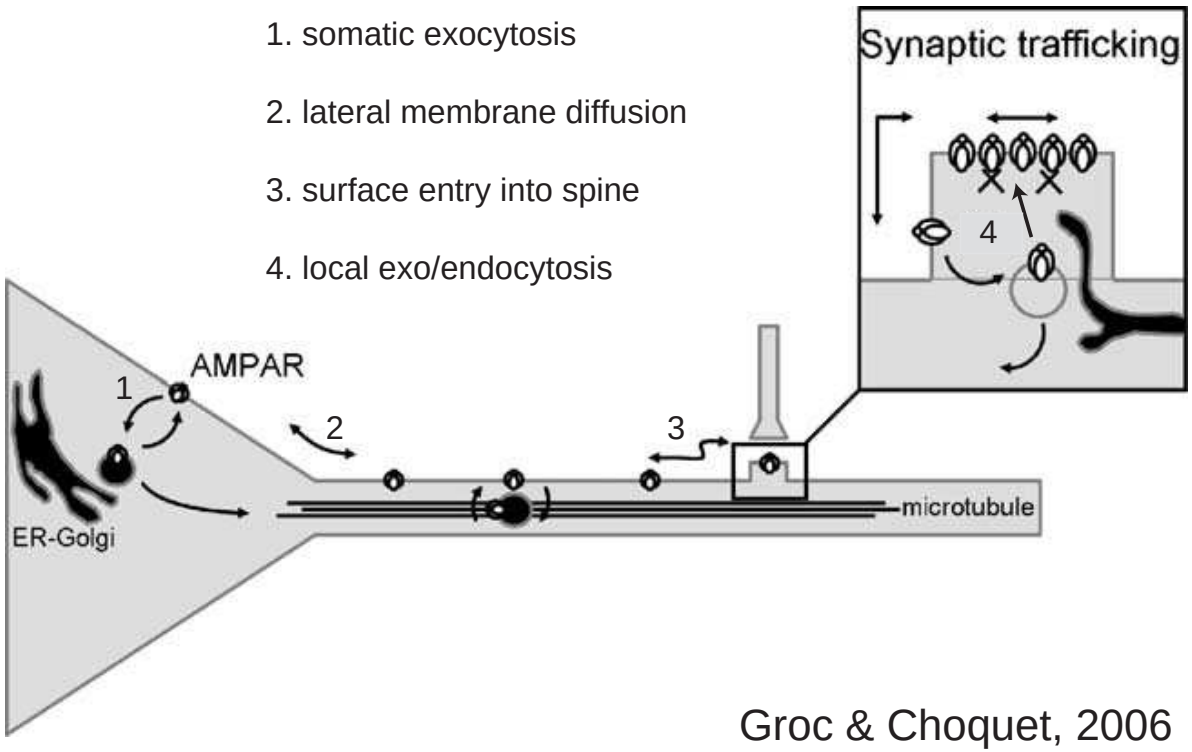



Kandel, Schwartz & Jessel (2000)




Matus, *Science* (2000)

# Long-range transport of receptors along spiny dendrite

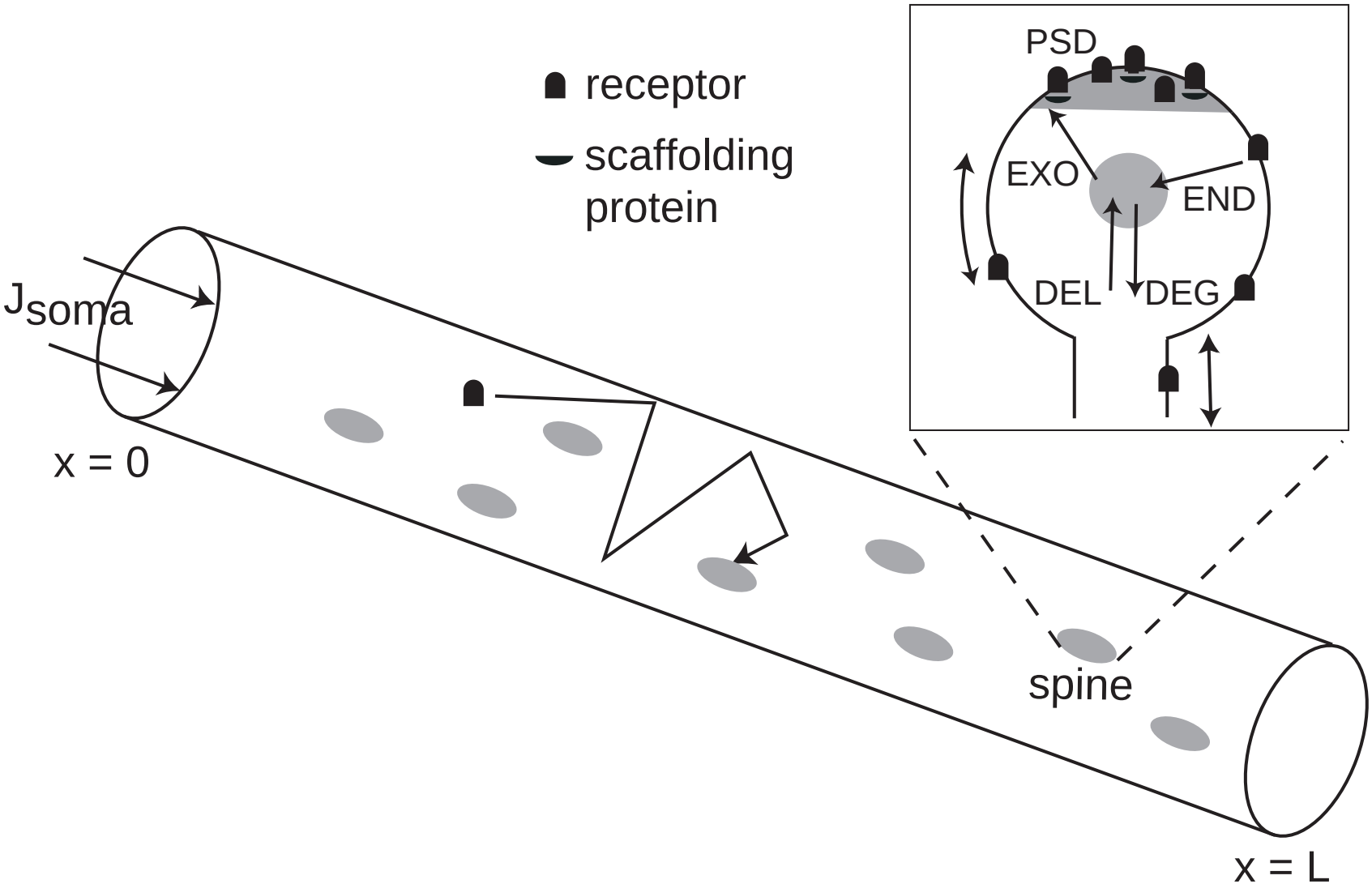



Groc & Choquet, 2006

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

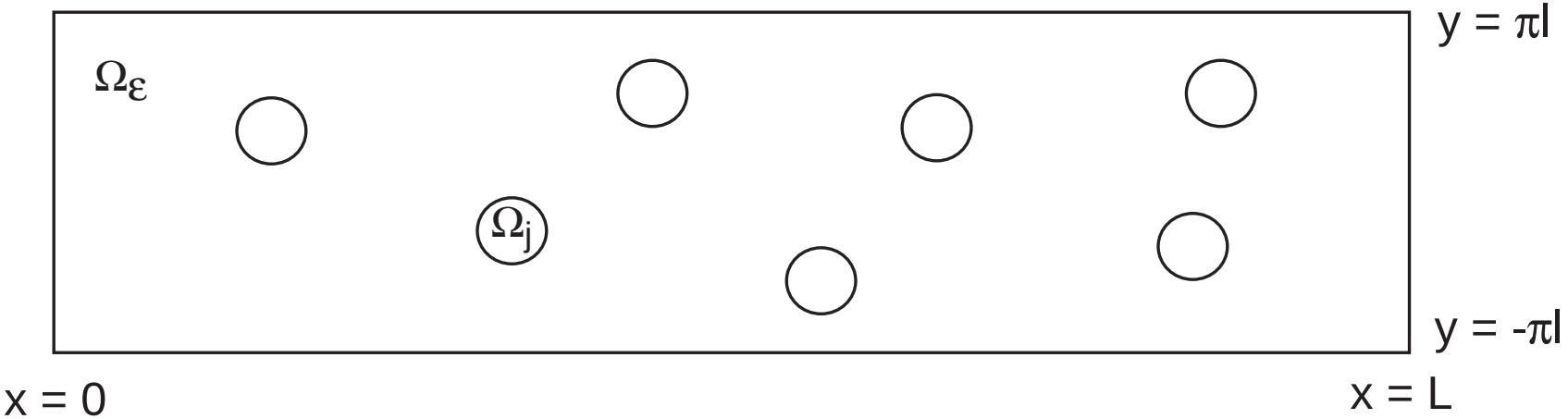
How should we model diffusion-trapping of receptors?

# Treat dendritic membrane as cylinder with holes



# 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

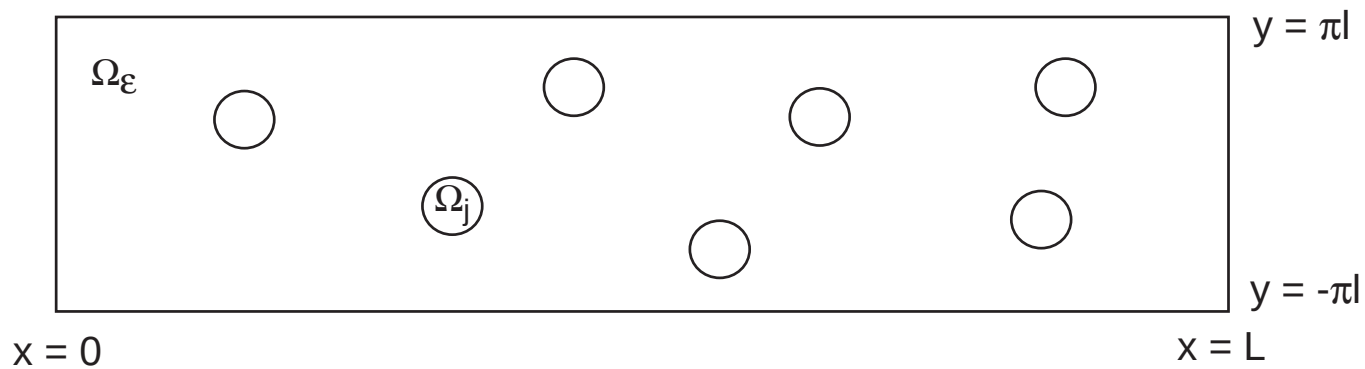
- Periodic bcs at $y = \pm \pi l$
- No-flux bc at $x = L$, and at $x = 0$

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

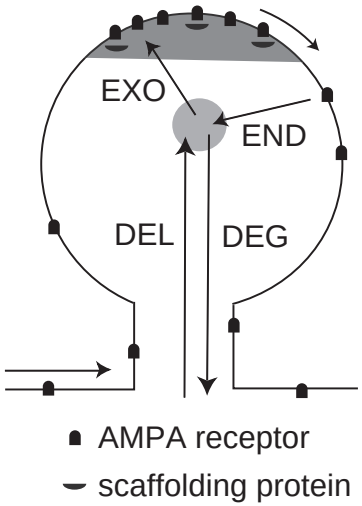
- bcs at the holes:

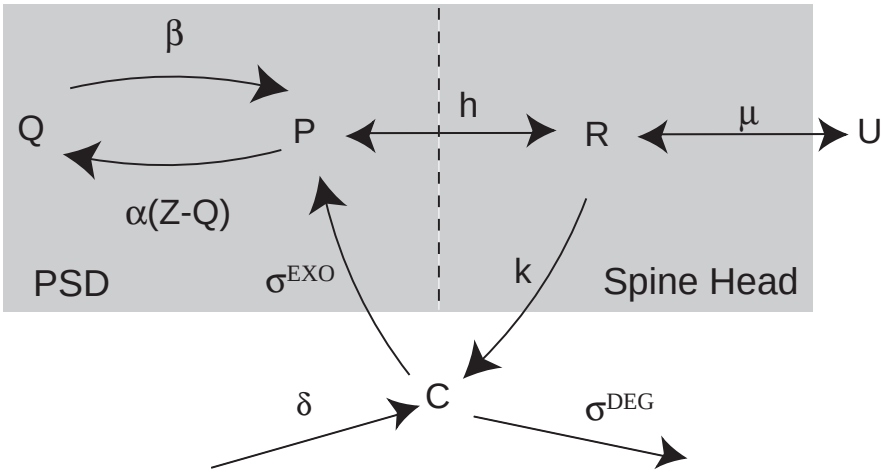
$$-\varepsilon D\frac{\partial U}{\partial \mathbf{n}}(\mathbf{r}, t) = \frac{\mu_j}{2\pi\rho}(U(\mathbf{r}, t) - R_j), \quad \mathbf{r} \in \partial\Omega_j$$

  - $\mu_j$ = 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, $\sigma^{EXO}$:** | **rates of endocytosis, exocytosis** |
| **$\sigma^{DEG}$, $\delta$:** | **rates of degradation, intracellular delivery** |
| **h**, $\mu$: | **hopping rates across boundary of PSD, spine neck** |
| **$\alpha$(Z-Q):** | **rate of binding to scaffolding (Z = scaffolding concentration)** |
| **$\beta$:** | **rate of unbinding from scaffolding** |

# Steady-state solution

- All steady-state concentrations at $j$th spine depend on the mean value of $U$ on $\partial\Omega_j$:

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

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

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

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     $$|\mathbf{r} - \mathbf{r}_j| = \mathcal{O}(\varepsilon)$$

     with Green's function singularities in outer region

     $$|\mathbf{r} - \mathbf{r}_j| = \mathcal{O}(1) \text{ for all } j$$

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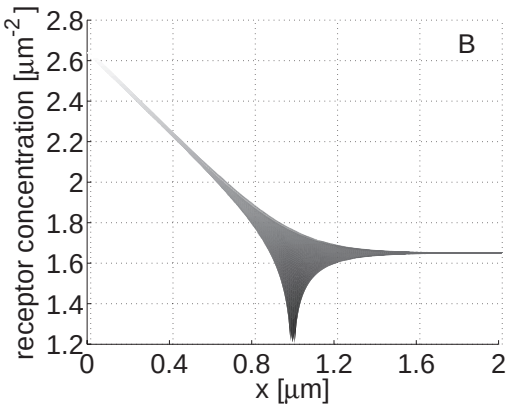
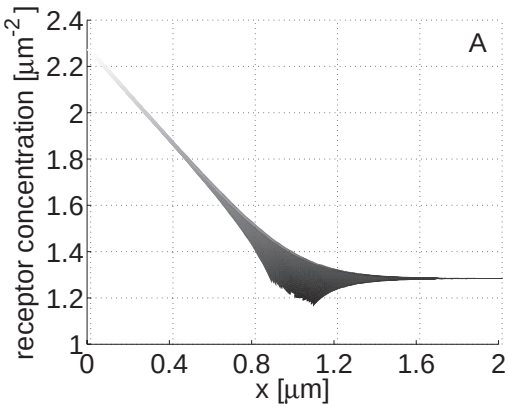
3. Conservation condition gives $(N+1)$th equation
   $$\sigma = \sum \widehat{\mu}_j \left( U_j - \widehat{R}_j \right)$$

# Effect of $\varepsilon$ on solution

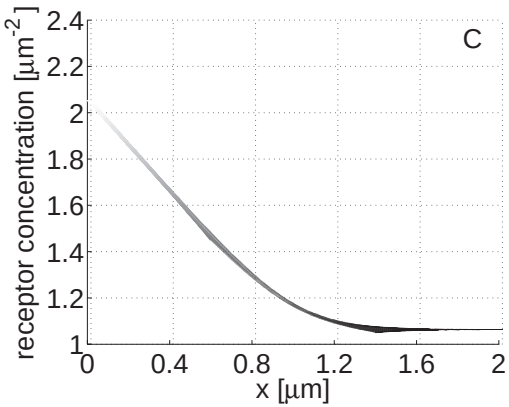
$\varepsilon\rho = 0.01$




$\varepsilon\rho = 0.1$



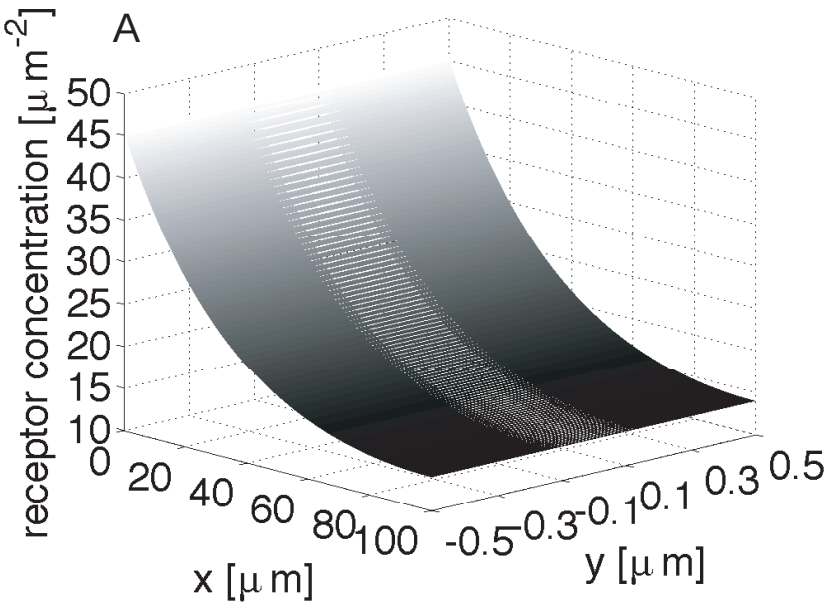

$\varepsilon\rho = 0.4$



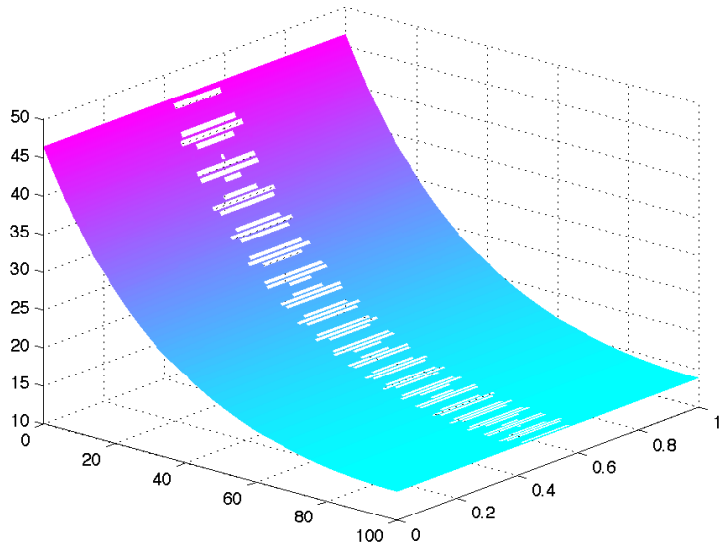

- Dendrite $2\mu$m long, circumference $1\mu$m
- One spine at $\mathbf{r} = (1, 0.5)$
- Numerical solutions look similar

# Comparison of dendritic receptor concentration

perturbation solution




numerical solution




- 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
- Solutions are almost identical!
- Similar results if spines are not identical, not in a row

Can we make things simpler?

# 2D model well-approximated by 1D model

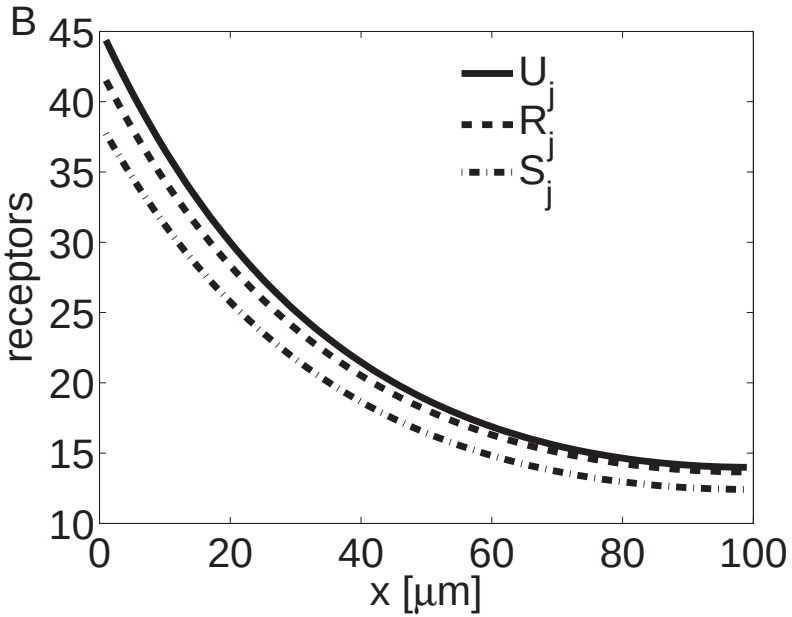
When the aspect ratio $L/l \gg 1$, we can approximate 2D model by the following 1D model

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

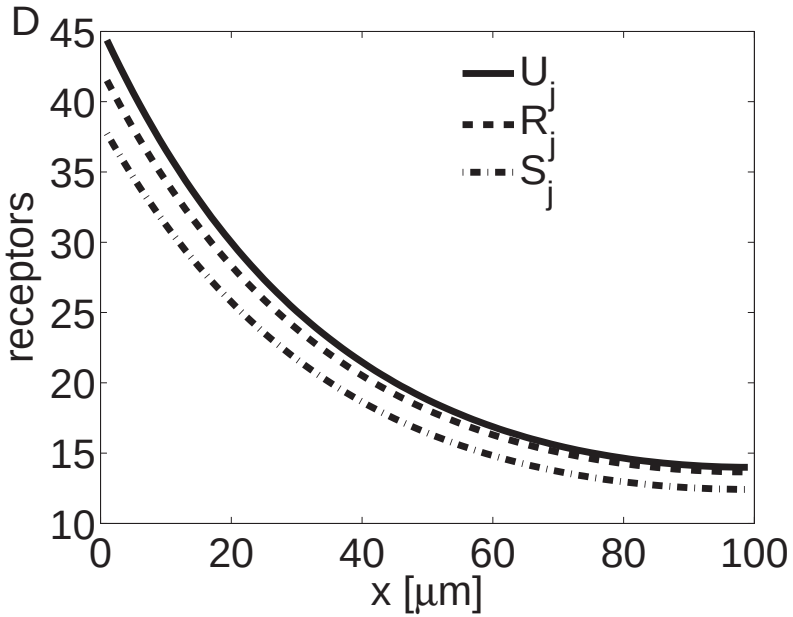
$$-D \left.\frac{\partial U}{\partial x}\right|_{x=0} = J_{\text{soma}}, \qquad \left.\frac{\partial U}{\partial x}\right|_{x=L} = 0.$$

# Comparison of models

2D model




1D model




- 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?

# Treat spine population as continuous density

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

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

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

# Steady-state solution for identical spines: "cable" equation

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

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

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

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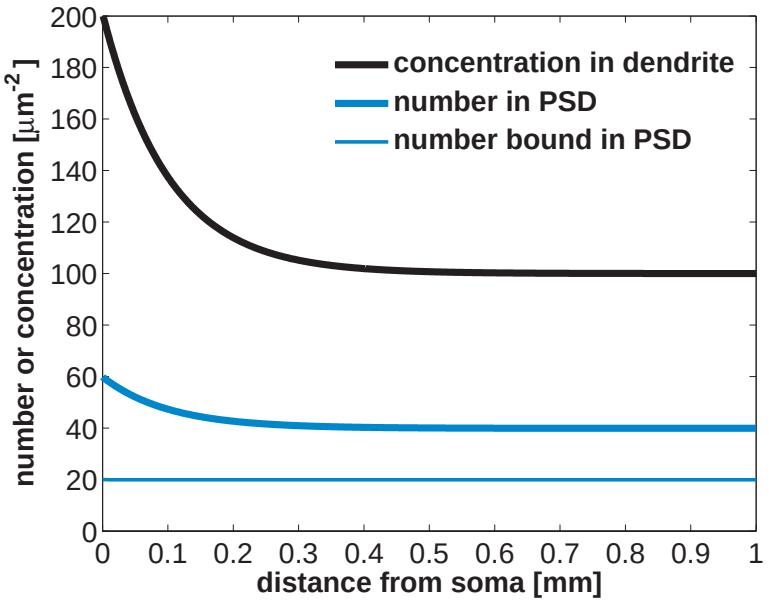
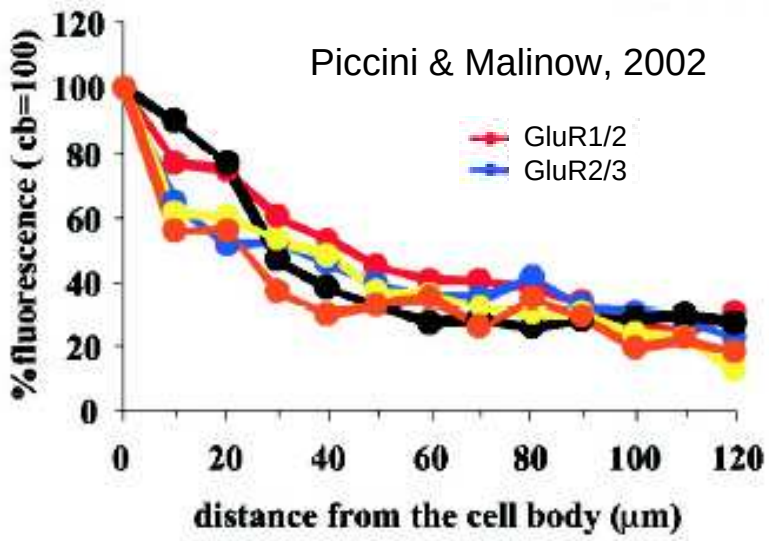
- Solve using Green's function methods

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

# Steady-state receptor concentrations for identical spines

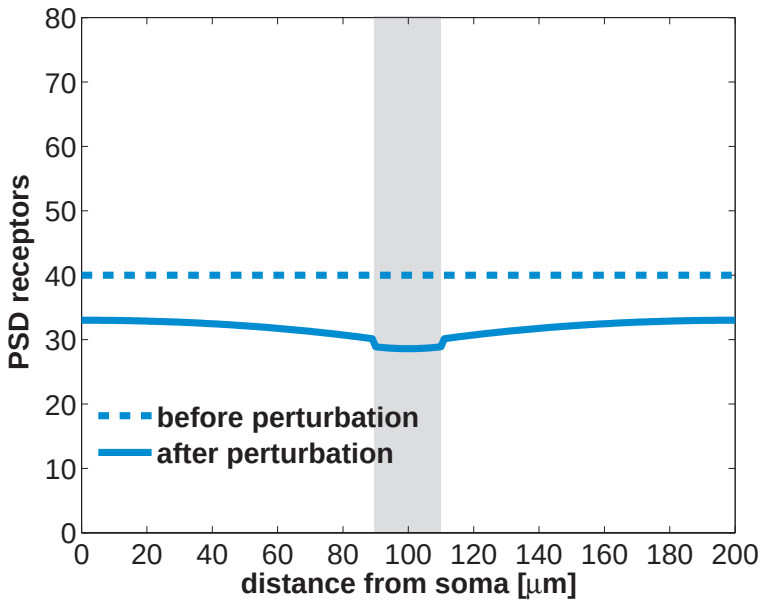



- Dendrite 1 mm long
- 1,000 identical spines spaced 1$\mu$m apart
- Two sources of receptors
  - at soma
  - local intracellular delivery

# Consequences of diffusive coupling

10-fold reduction in rate of exocytosis in gray region

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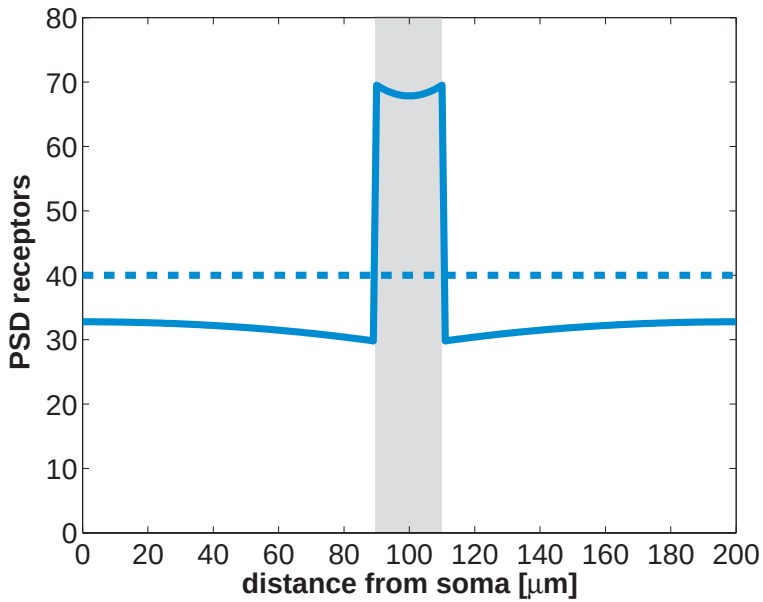
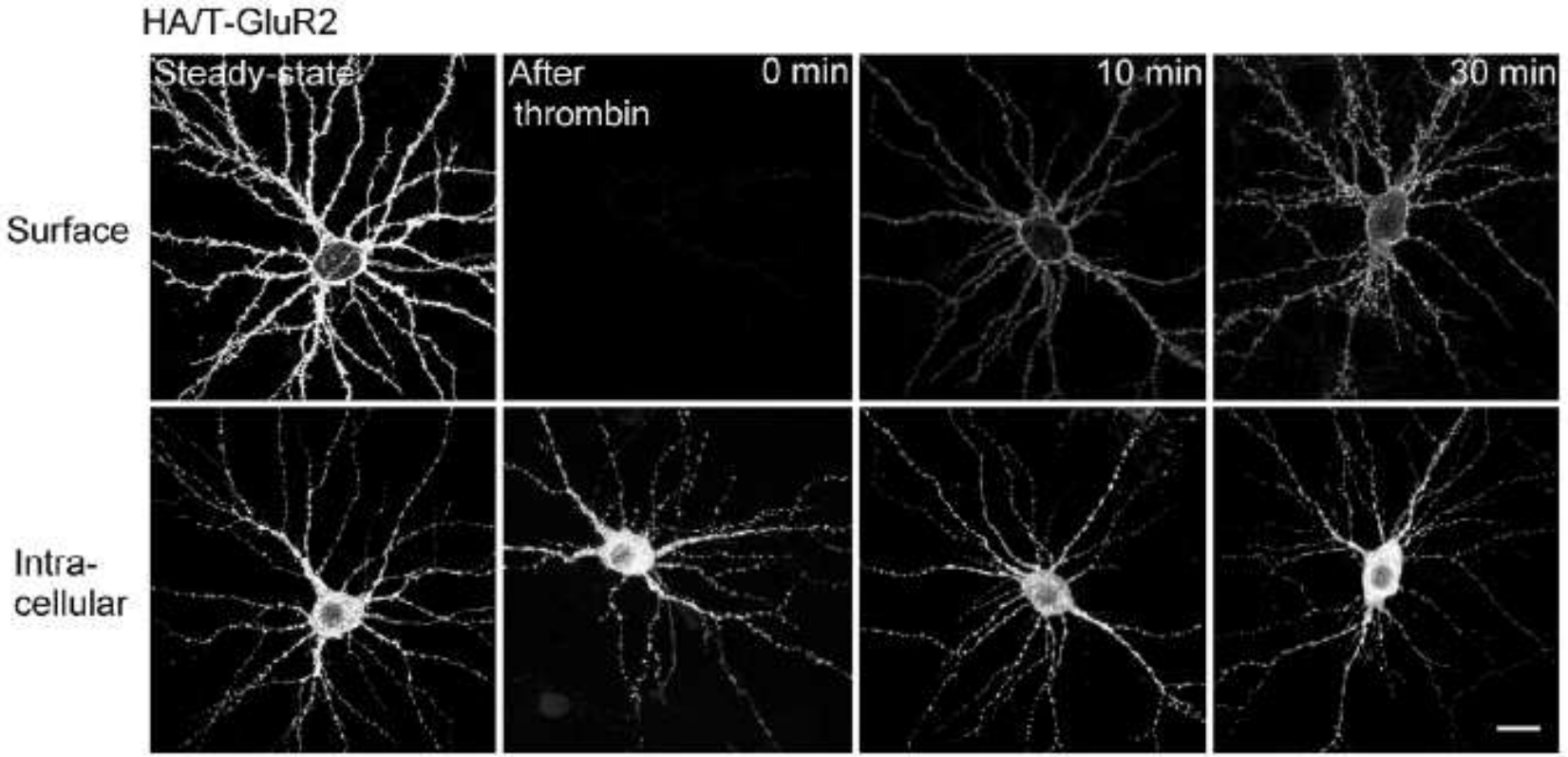


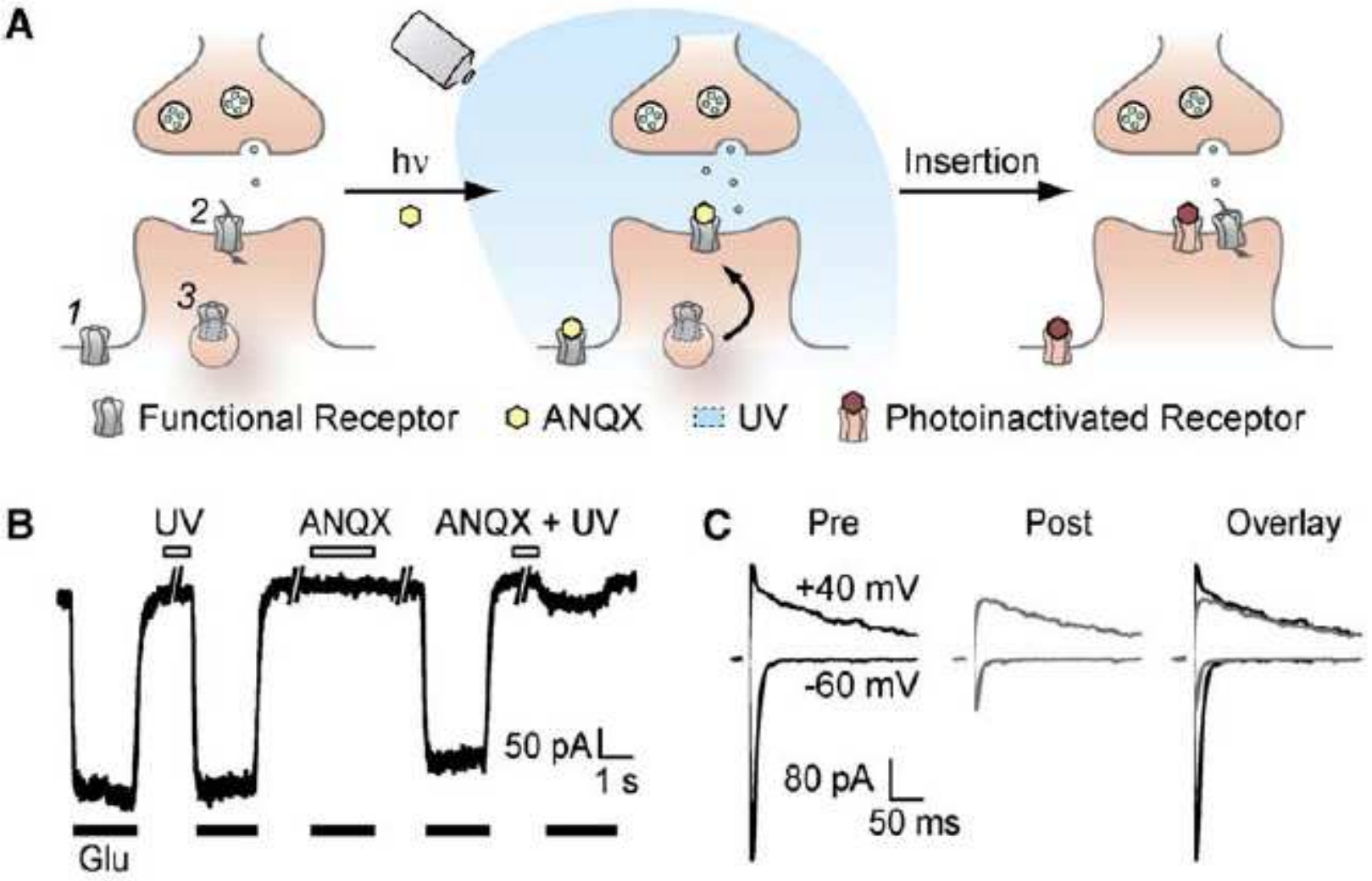
Steady-state is nice...
...but what about time-dependent phenomena?

# AMPA receptor recycling via thrombin cleavage




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

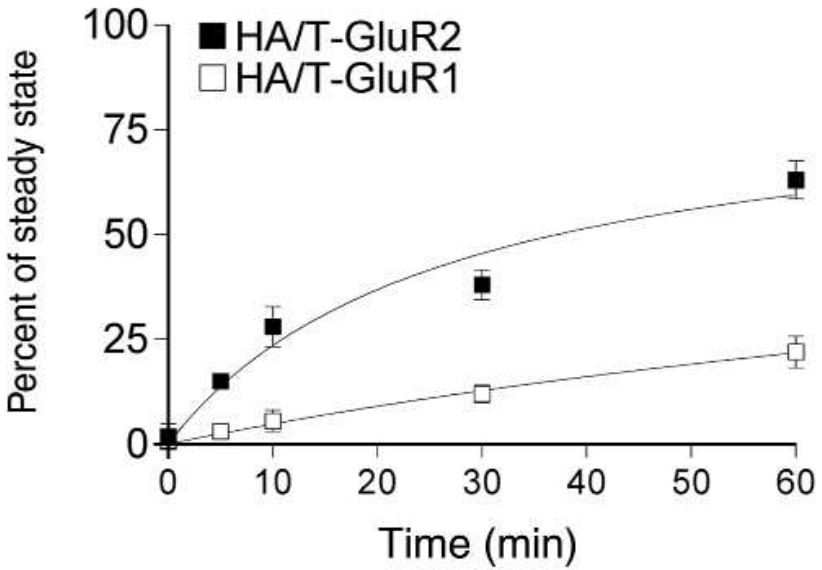
# AMPA receptor recycling via photoinactivation



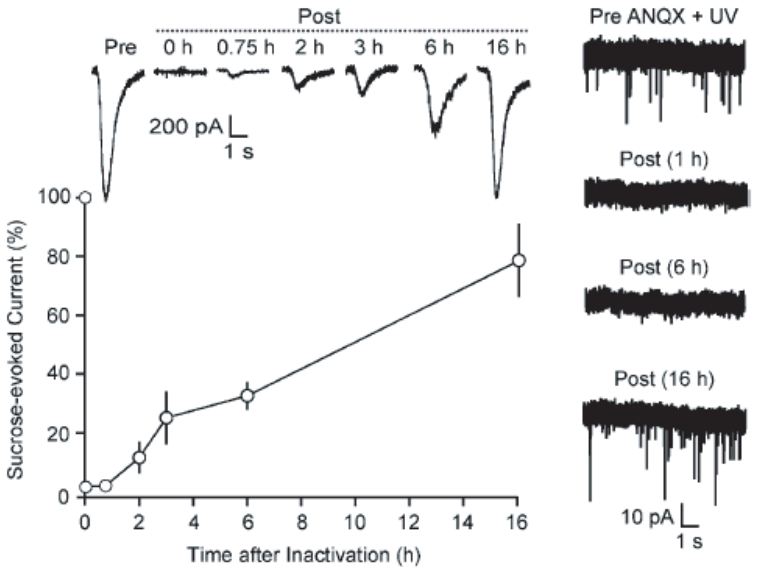

Adesnik et al., *Neuron* (2005)

# Fast or slow recycling of AMPA receptors?

Passafaro et al., 2001

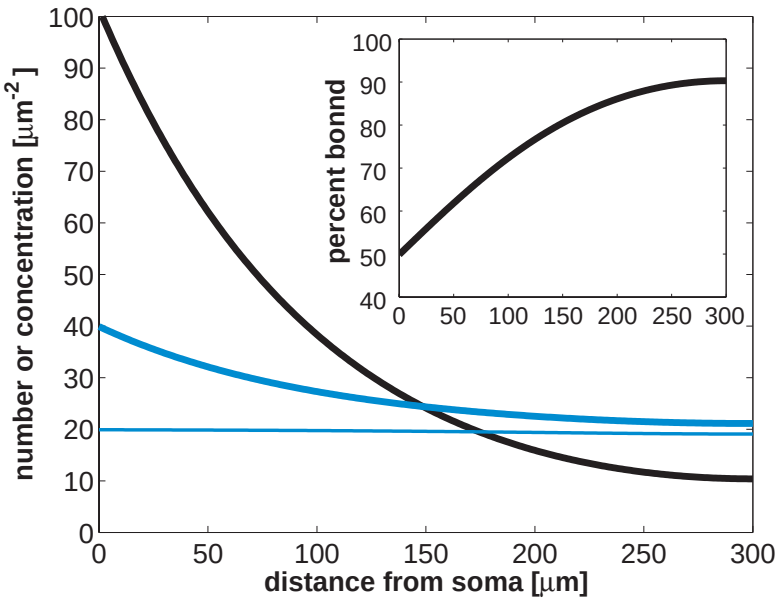



Adesnik et al., 2005



# Simulation of photoinactivation of AMPA receptors

- No intracellular delivery but source at soma
- In steady-state $t < 0$
- At $t = 0$ all surface AMPA receptors instantaneously "inactivated"



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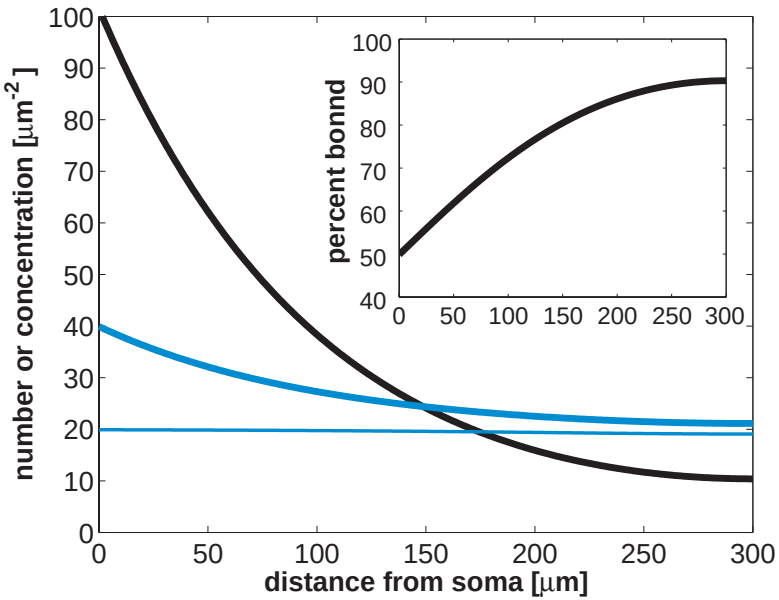
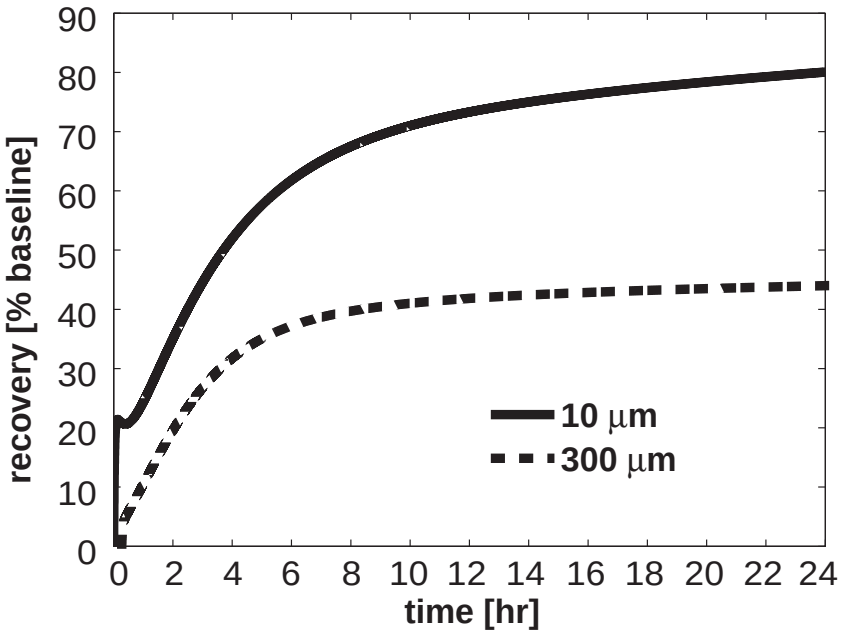
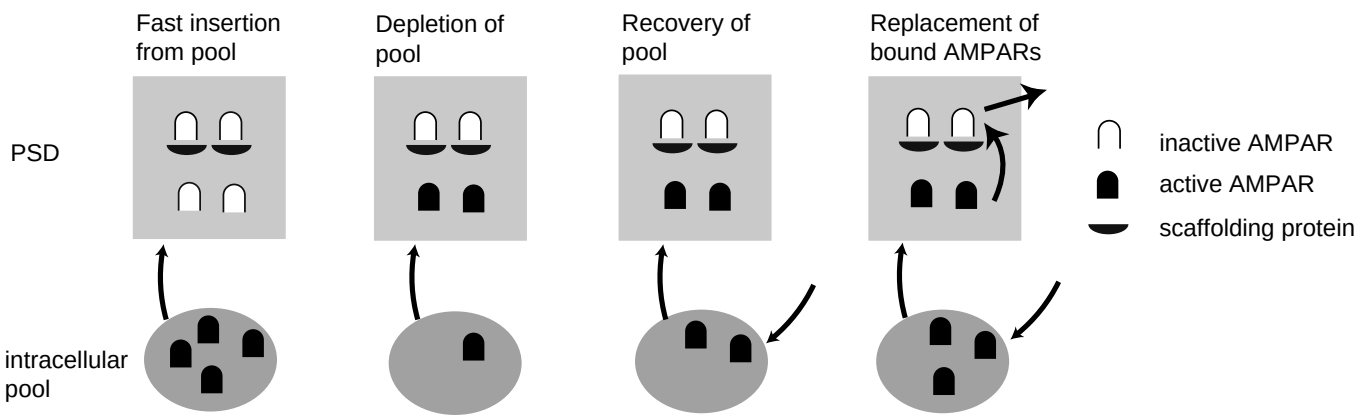



- Rates of exo/endocytosis are **fast** (10-30 mins)

# Rate of recycling depends on distance from soma



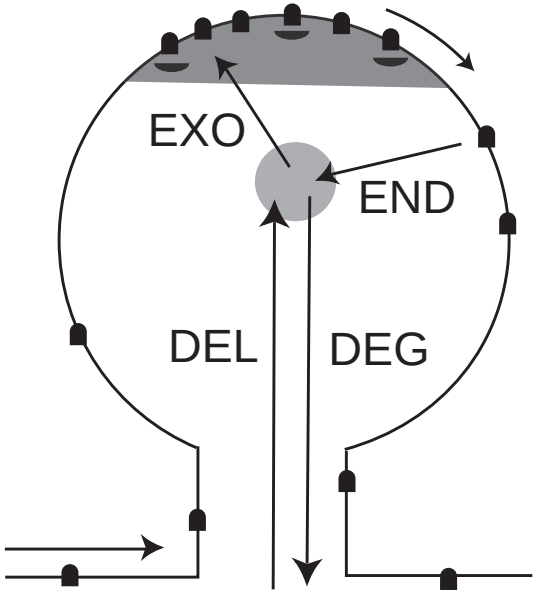

- Fast exo/endocytosis consistent with slow recycling
- There are many time scales!

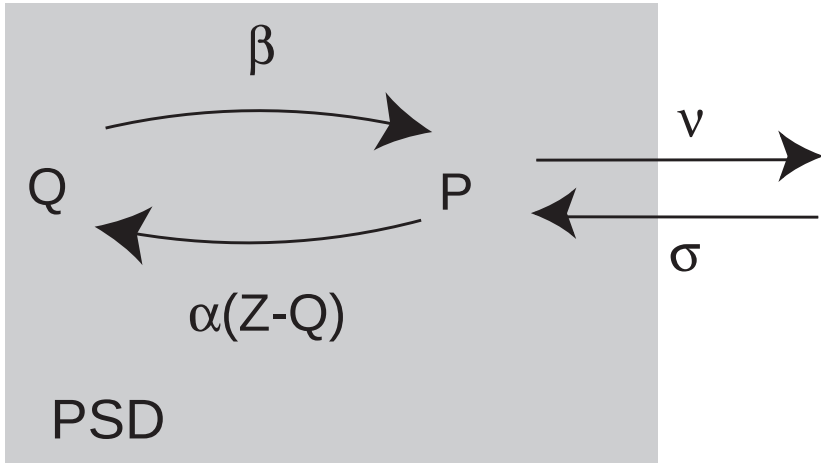


# Future directions

- 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**

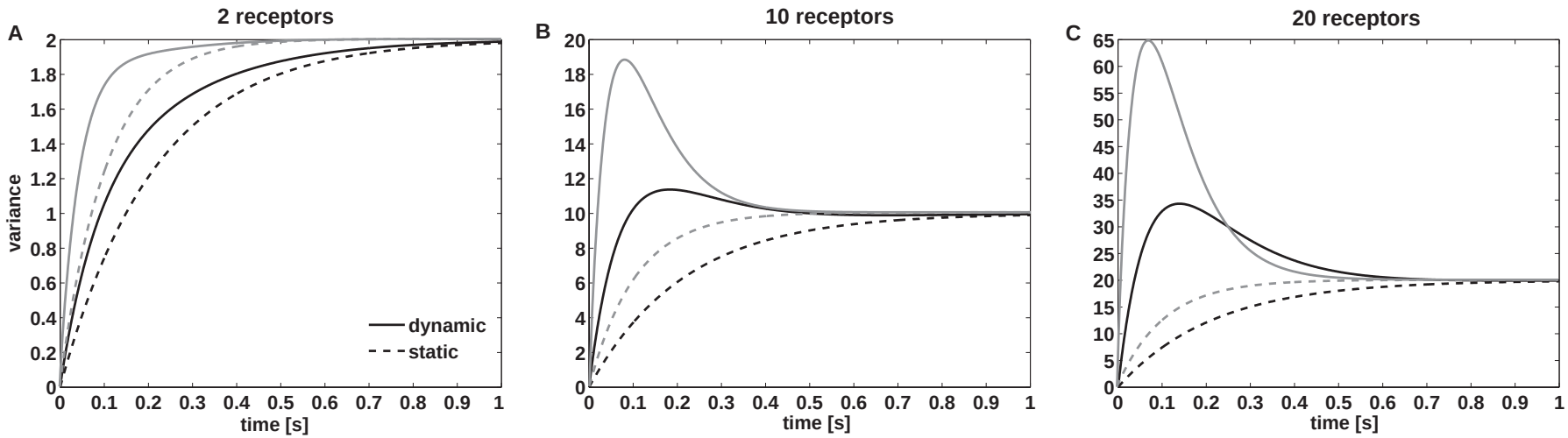
# Intrinsic vs. extrinsic noise of synaptic trafficking



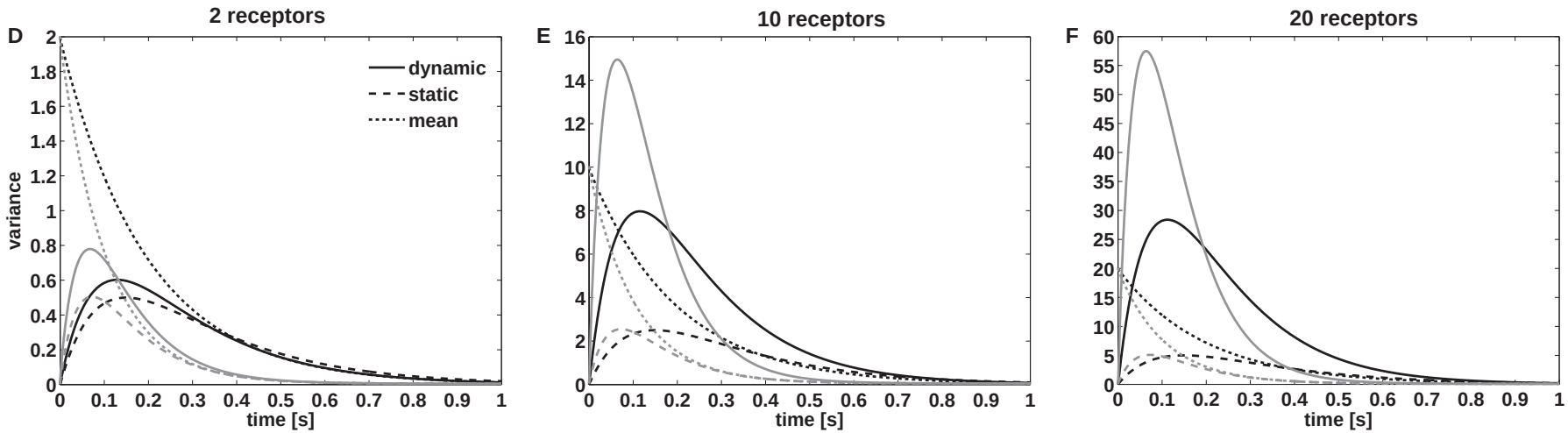

- intrinsic noise: e.g., binding/unbinding
- extrinsic noise: e.g., fluctuating gate

# 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