Multiple spatial scales of AMPA receptor trafficking

From synapse to spiny dendrite

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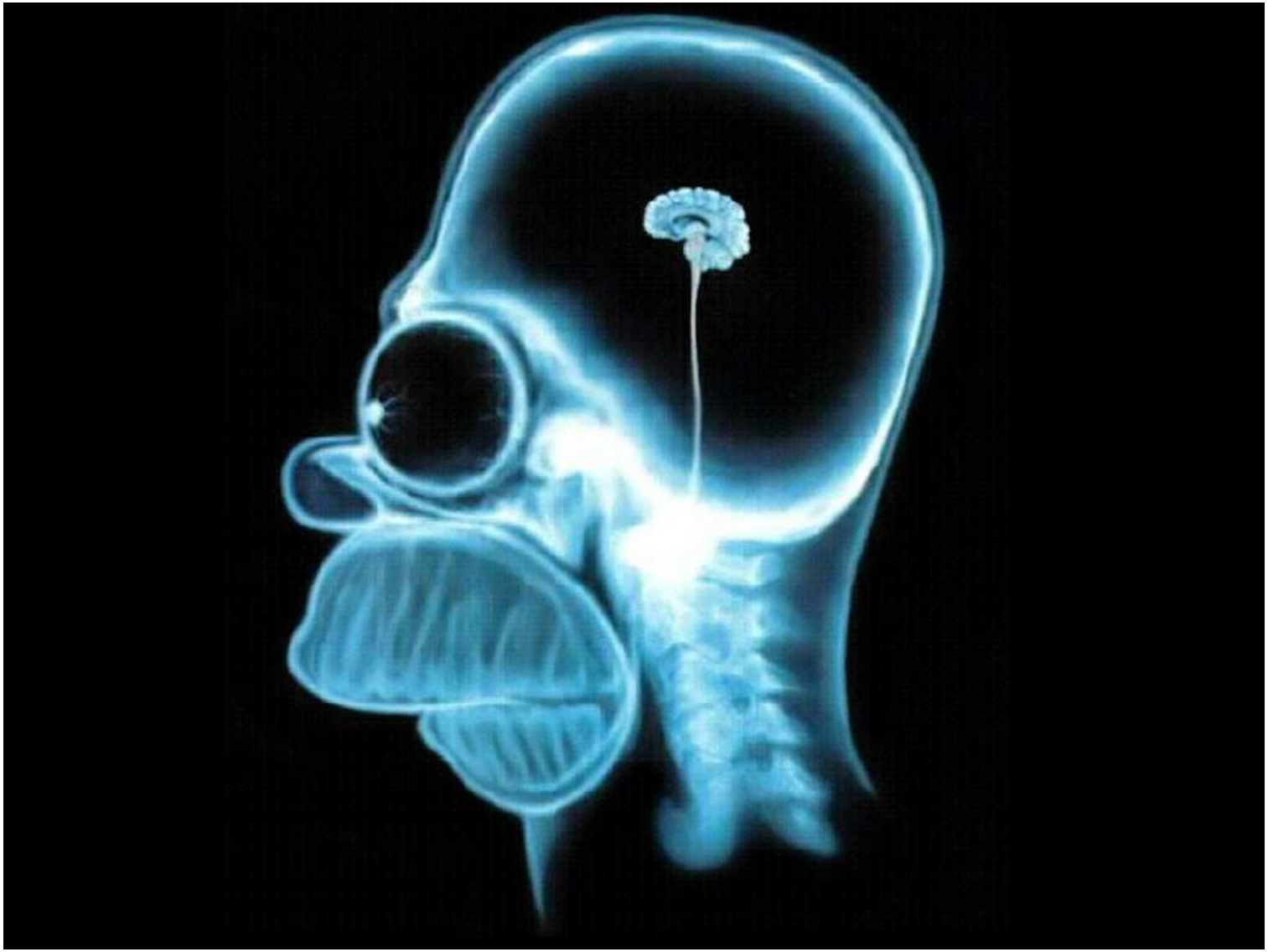
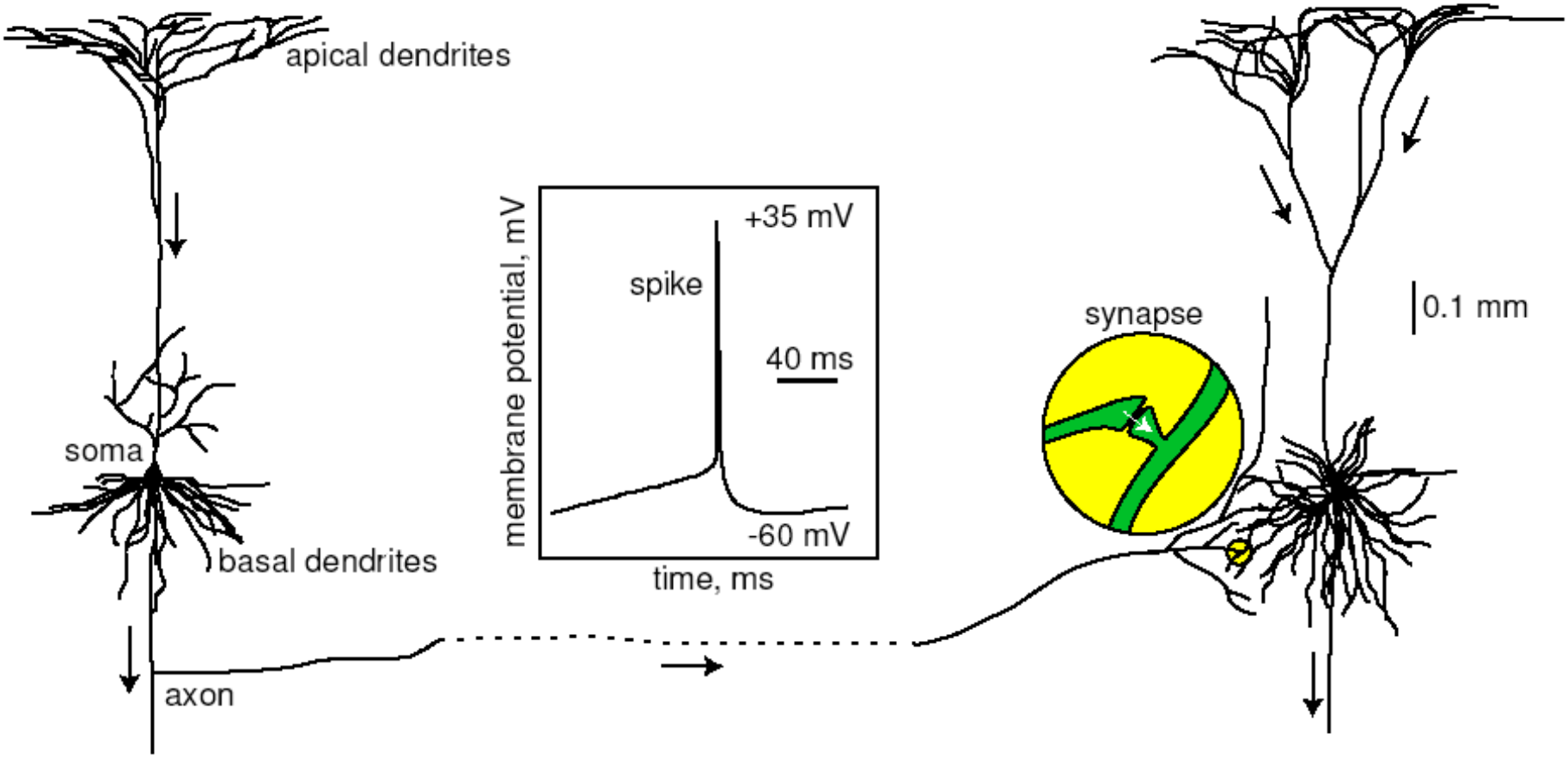
March 26, 2009

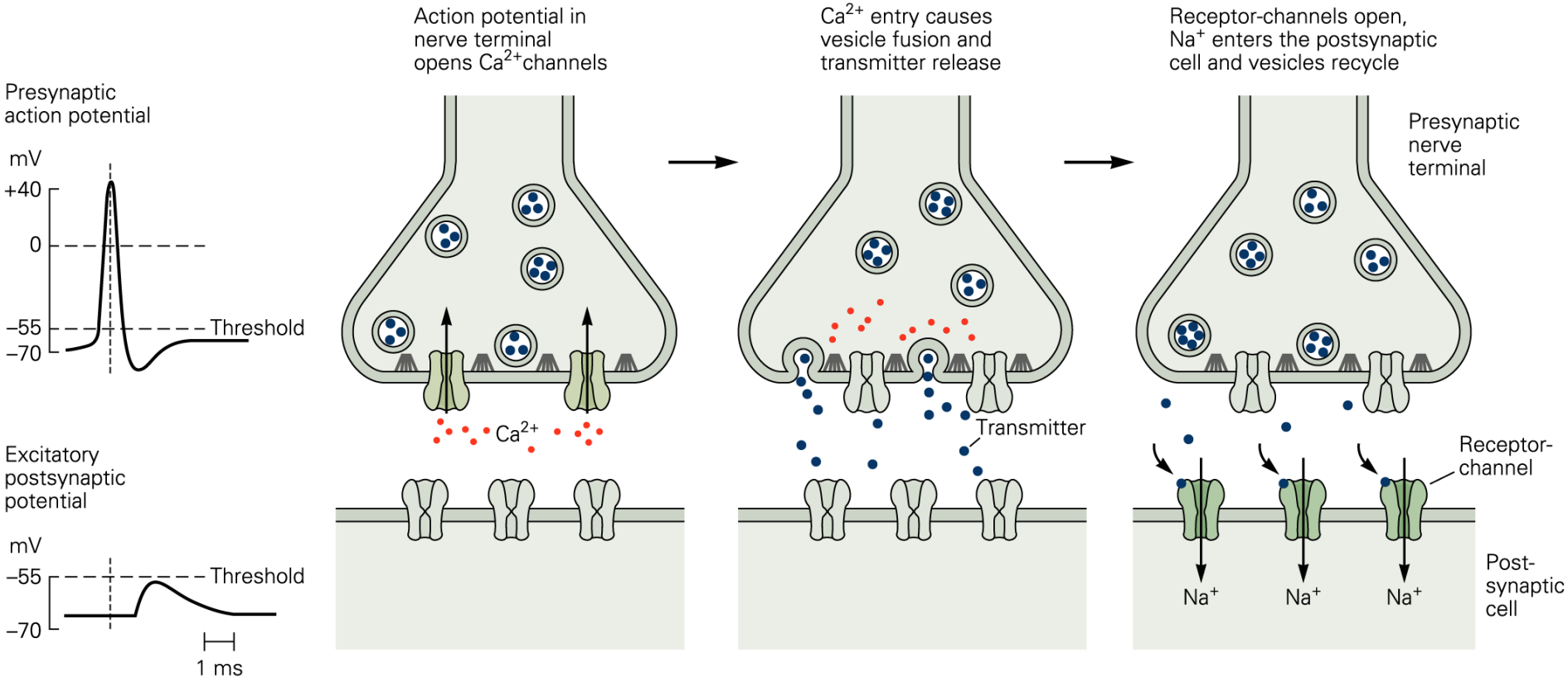
The amazing brain



Neurons communicate at synapses

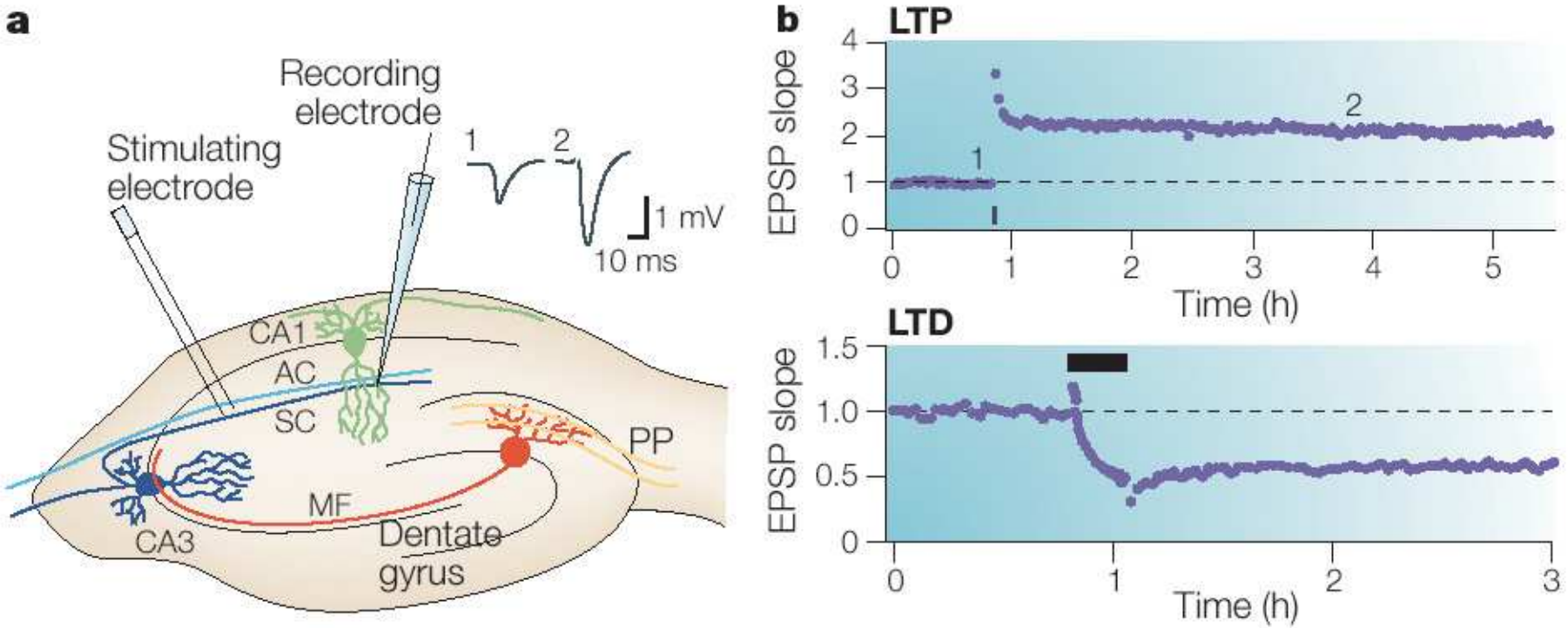


Communication at a synapse



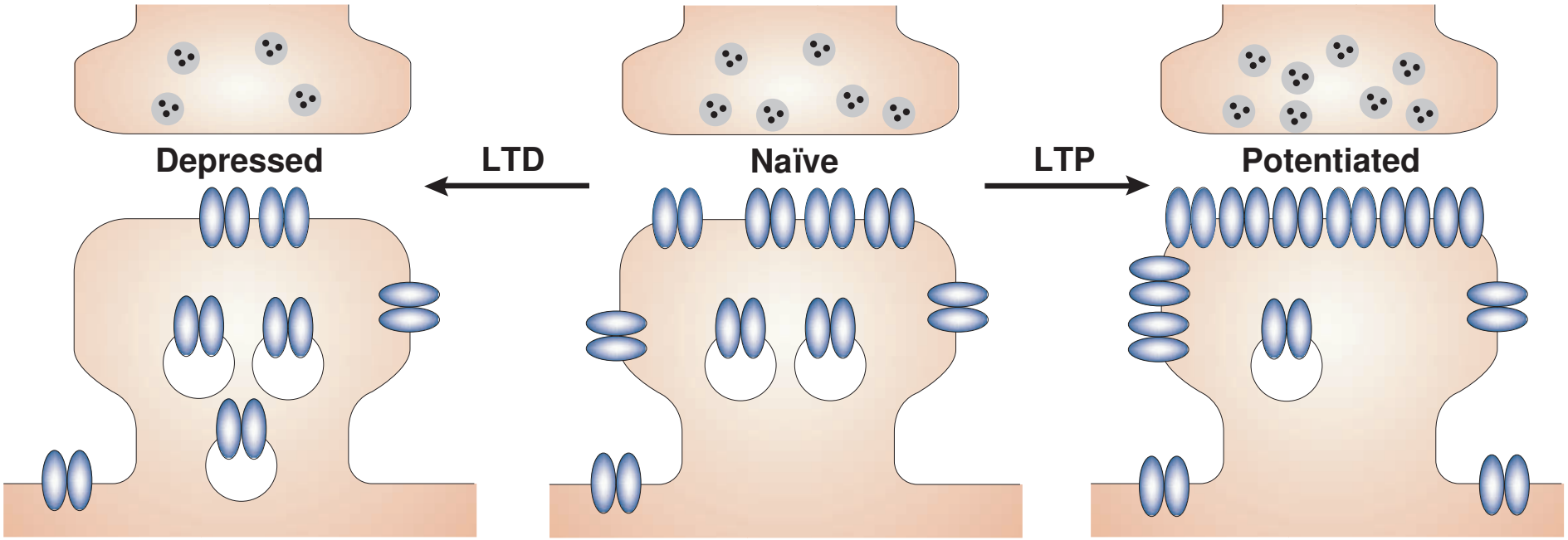
Kandel, Schwartz & Jessel (2000)

Synapses can "learn"

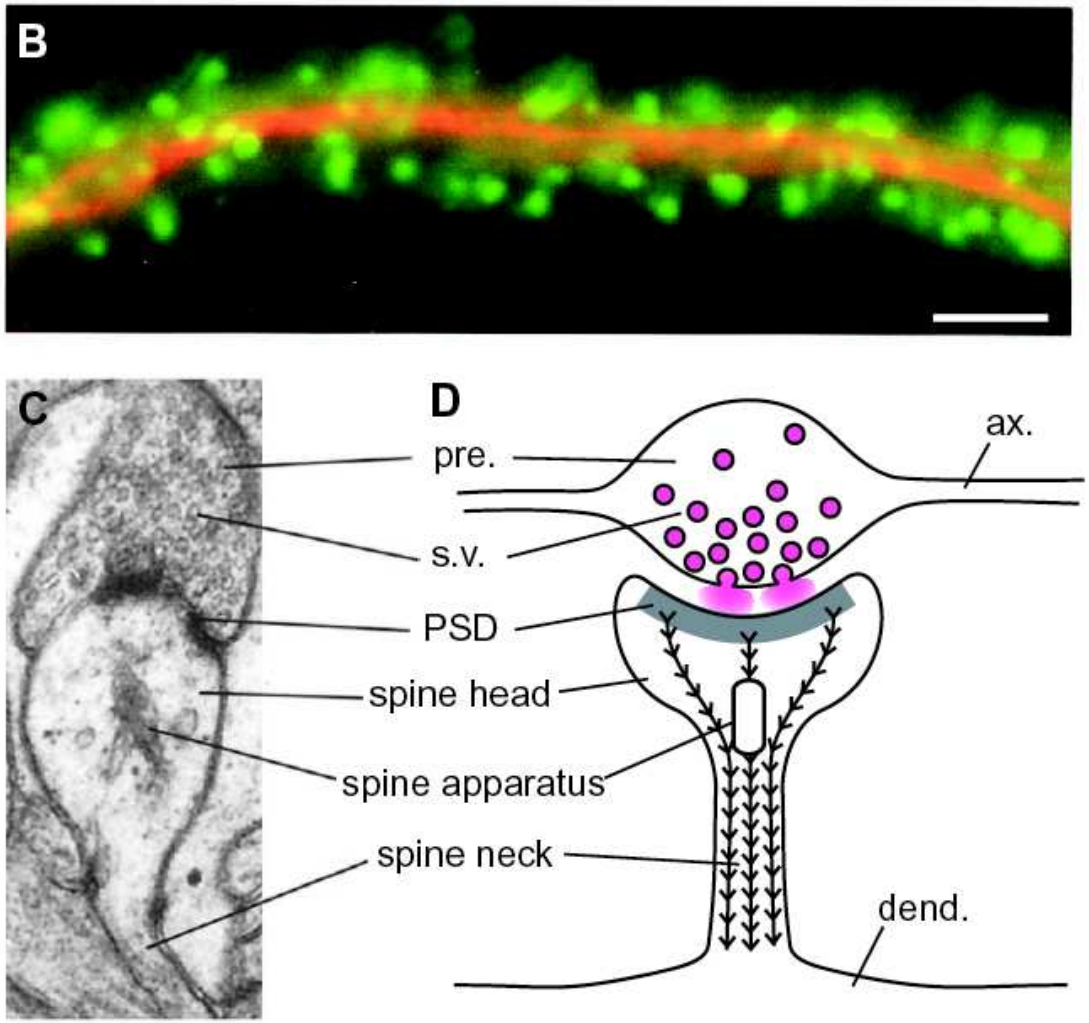


Collingridge et al., *Nat Rev Neurosci* (2004)

Synapses "learn" by regulating receptor numbers

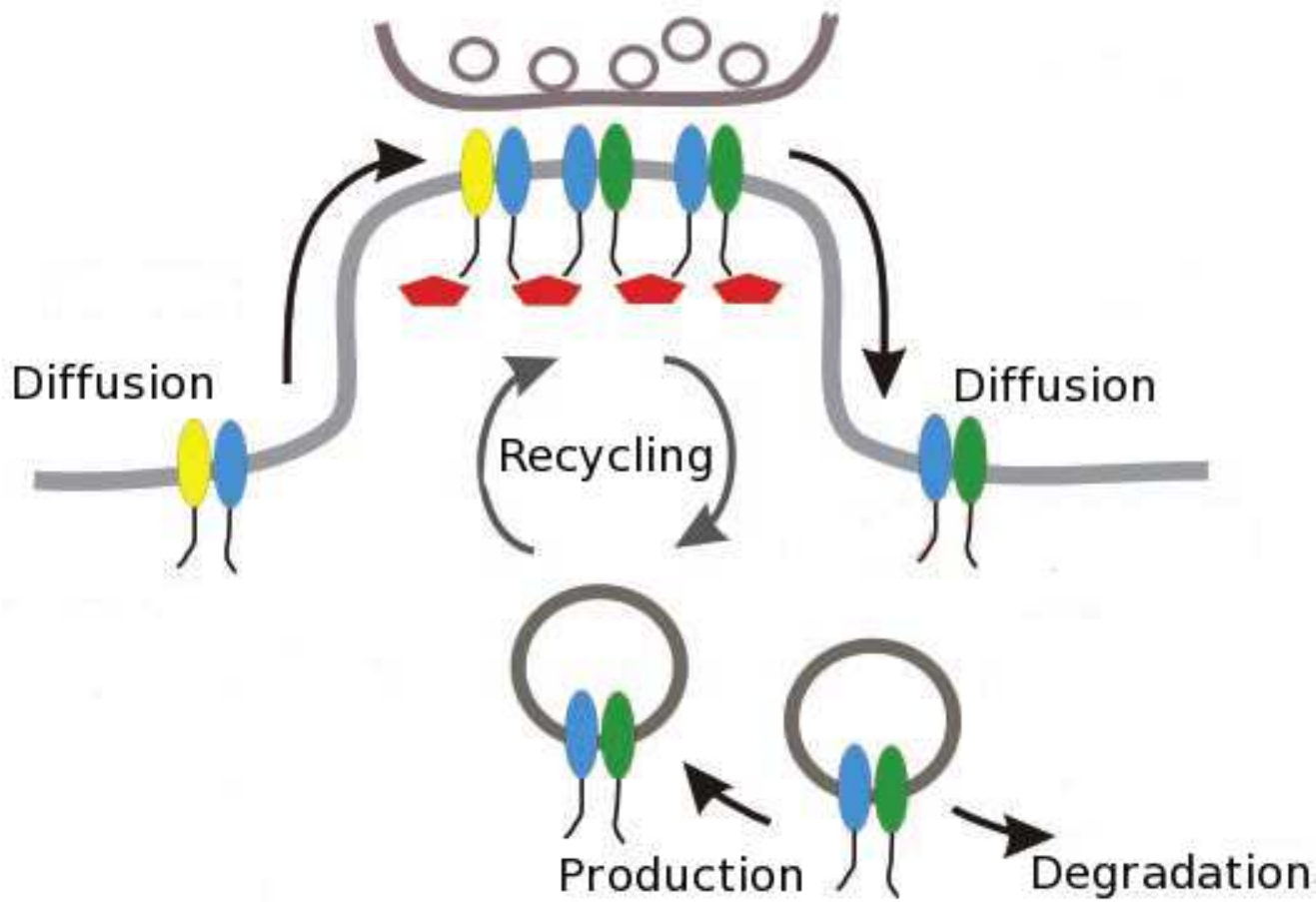


Synapses located in dendritic spines

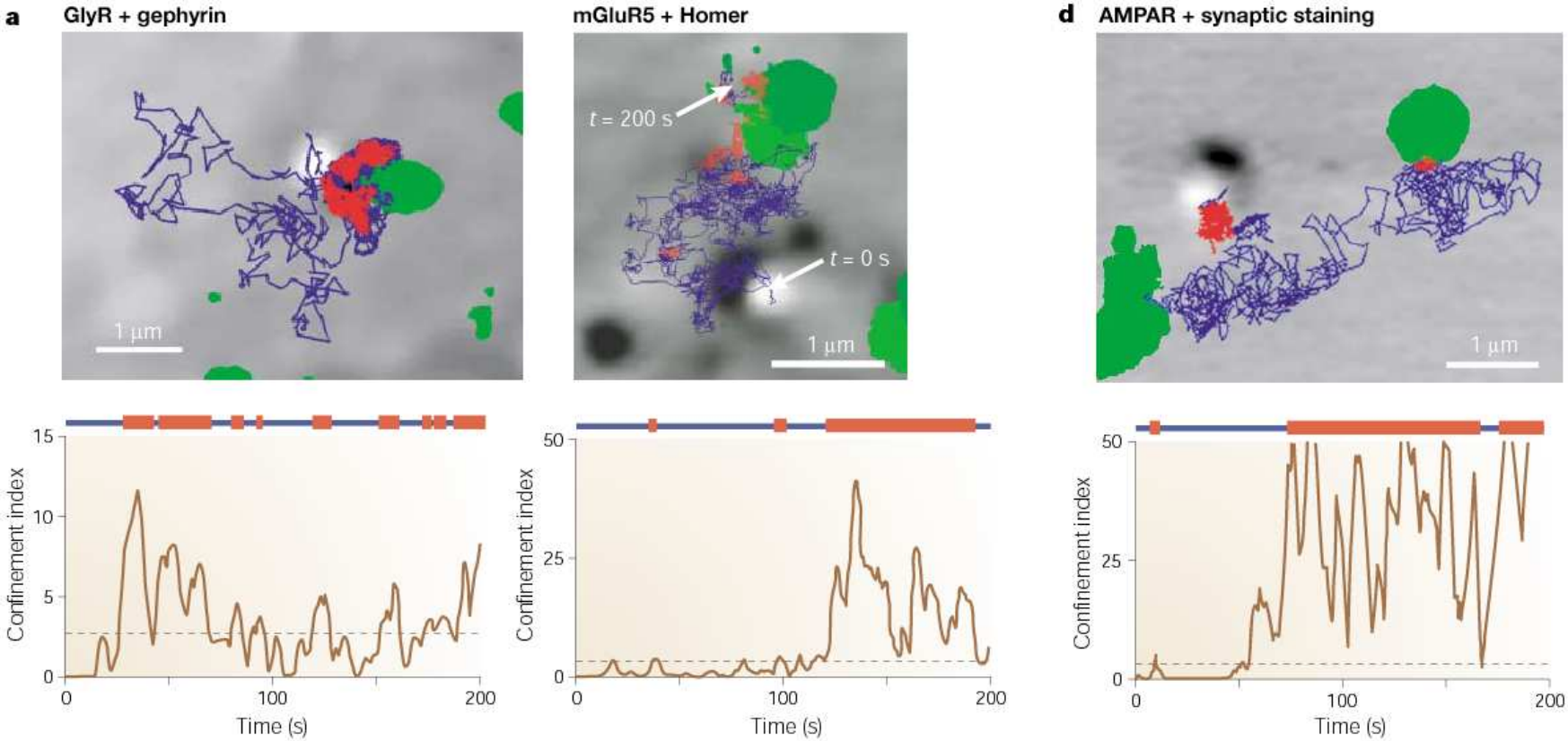


Matus, *Science* (2000)

Receptor trafficking at a synapse



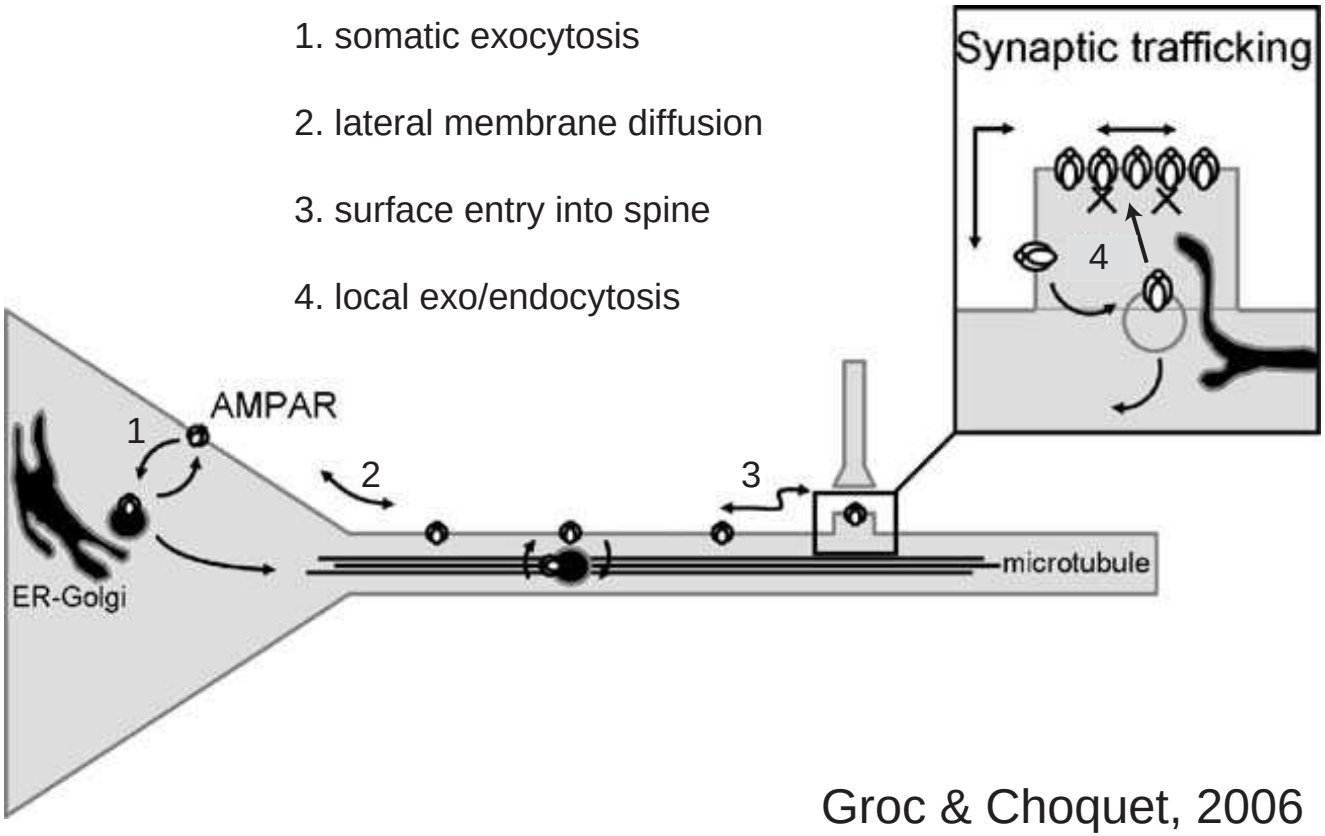
Receptors diffuse laterally between synapses



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

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

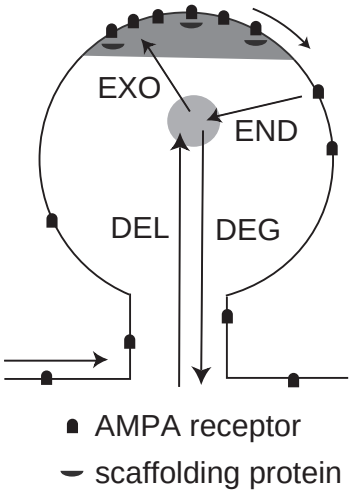
Model of single-spine AMPAR trafficking

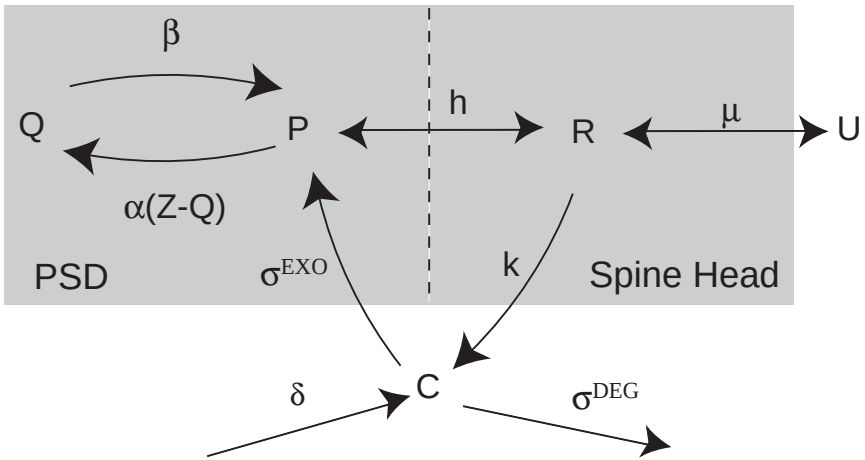
Spine head: $$\frac{dR}{dt} = \frac{1}{A}\left(\mu[U-R] - kR - h[R-P]\right)$$

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

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

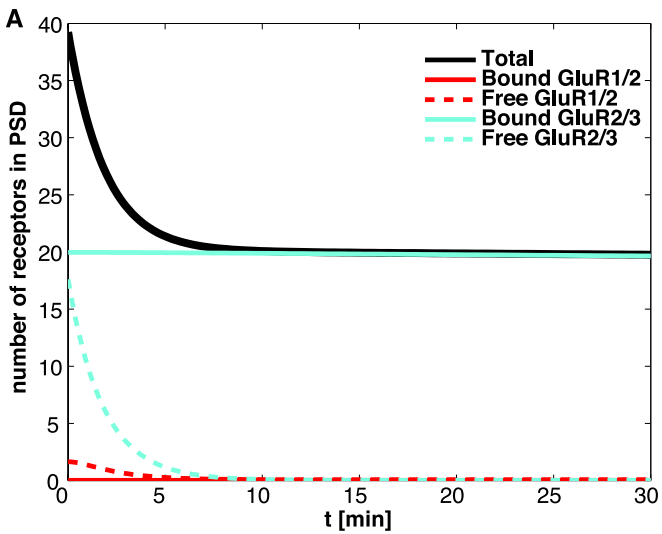
Intracellular: $$\frac{dC}{dt} = -\sigma^{\mathrm{EXO}} C - \sigma^{\mathrm{DEG}} C + kR + \delta$$

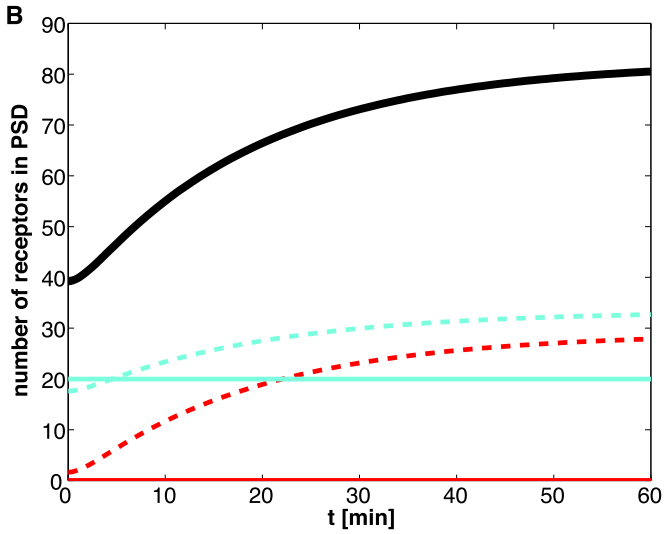


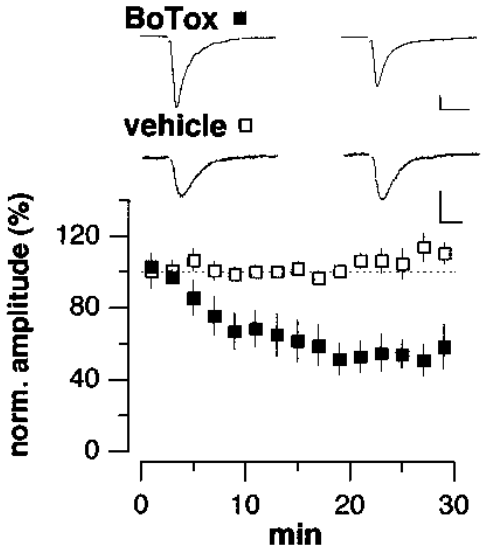


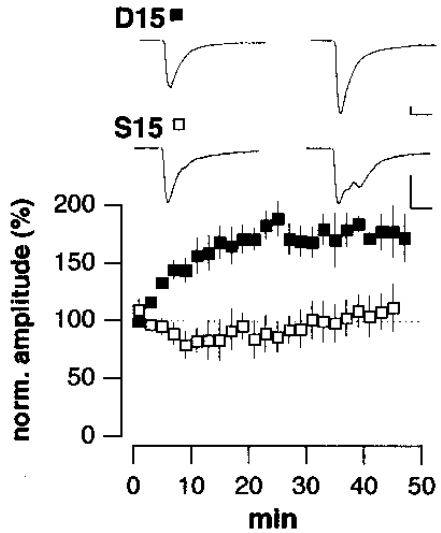
BAE & Bressloff, *J Neurosci* (2006)

Block exo/endocytosis



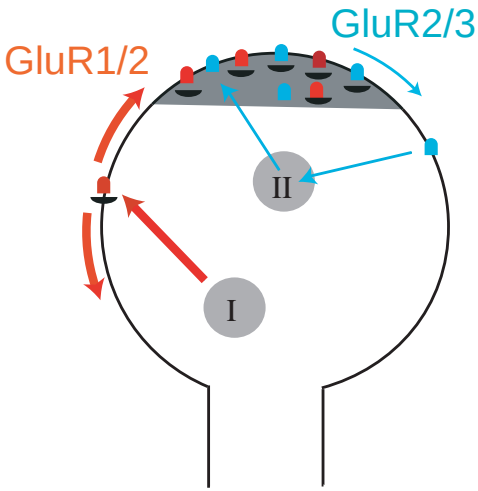




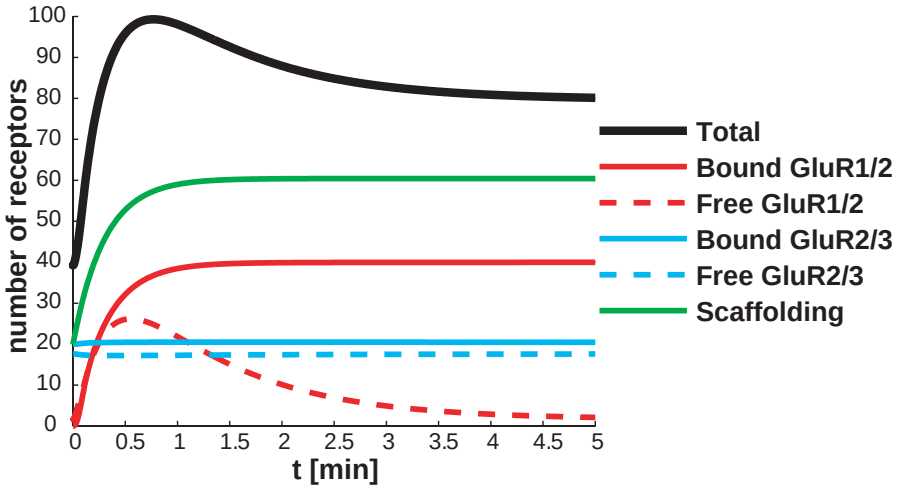


Luscher et al., *Neuron* (1999)

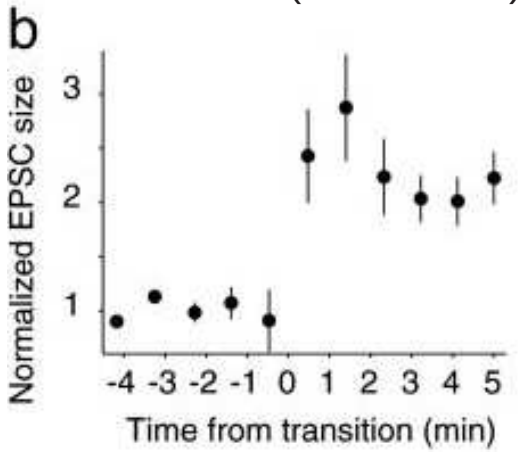
LTP simulation



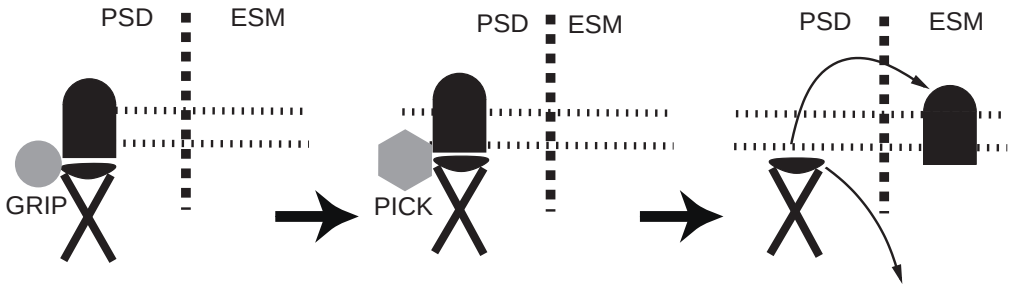
- Activation of GluR1/2 intracellular pool
- Rapid insertion of receptors into ESM
- AMPARs transport slot proteins into PSD



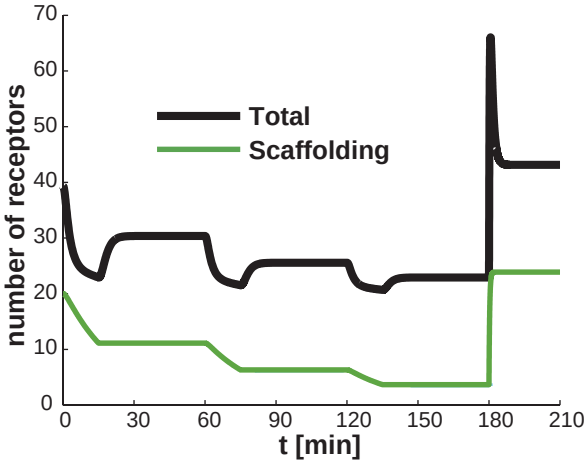
O' Connor et al (PNAS 2005)

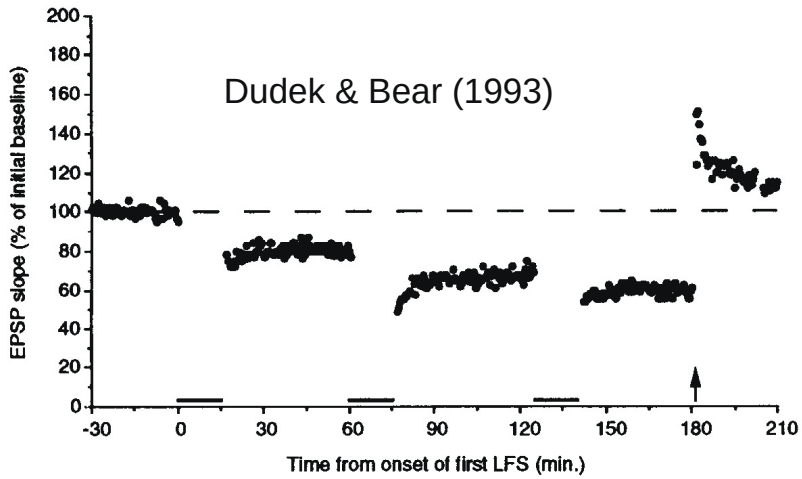


LTD simulation



- 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.





Conclusions

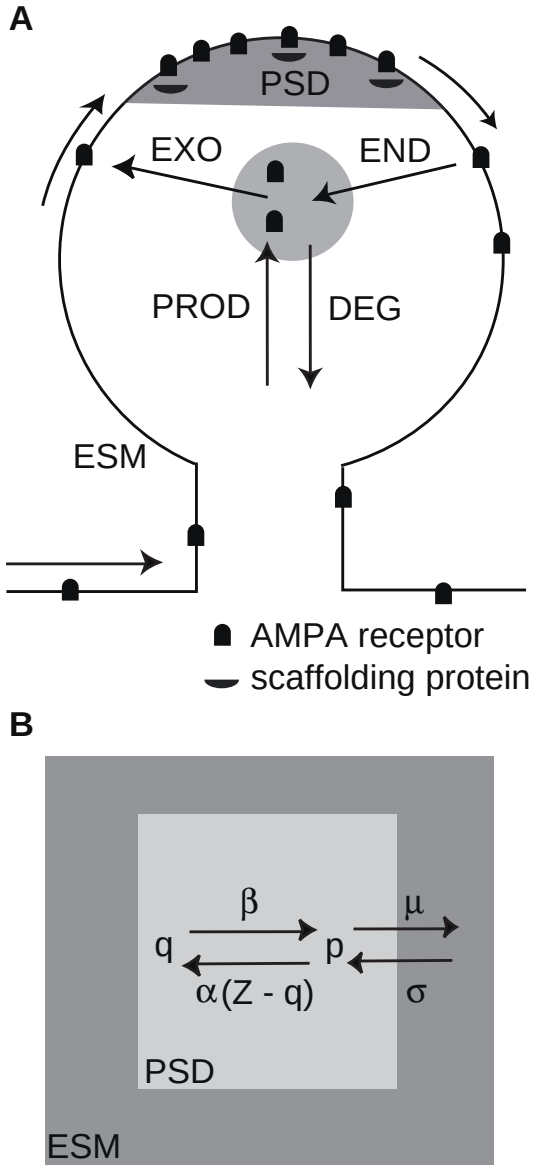
1. Significant fraction of PSD receptors are **mobile** (Groc et al., 2004; Ashby et al., 2006)
   - Requires PSD-ESM barrier (Choquet & Triller, 2003)
2. **Diffusive impedance** of spine neck is significant (Ashby et al., 2006)
3. Insertion of GluR1/2 during LTP must combine **synaptic targeting**
   - 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)
- Single-synapse model (stochastic)
- 2D diffusion model
- 1D diffusion models
- Other diffusion-trapping problems

Stochastic model of trafficking at PSD

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

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



Bressloff & BAE *Biophys J* (2009)

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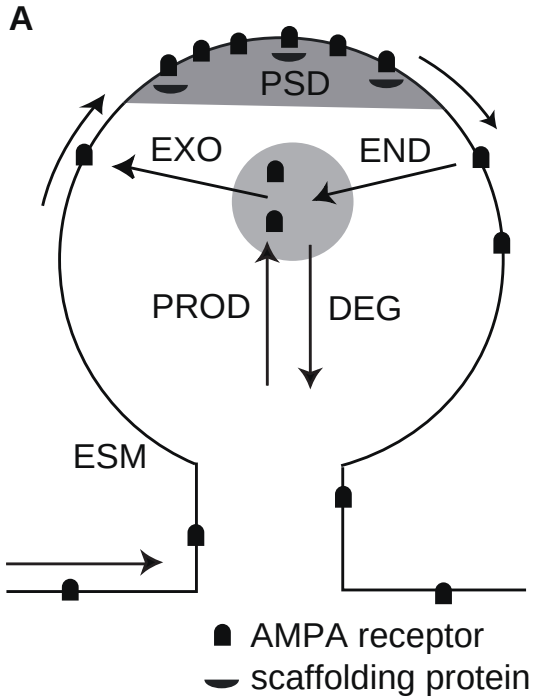

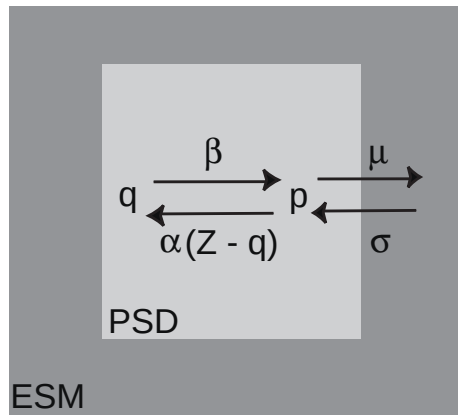

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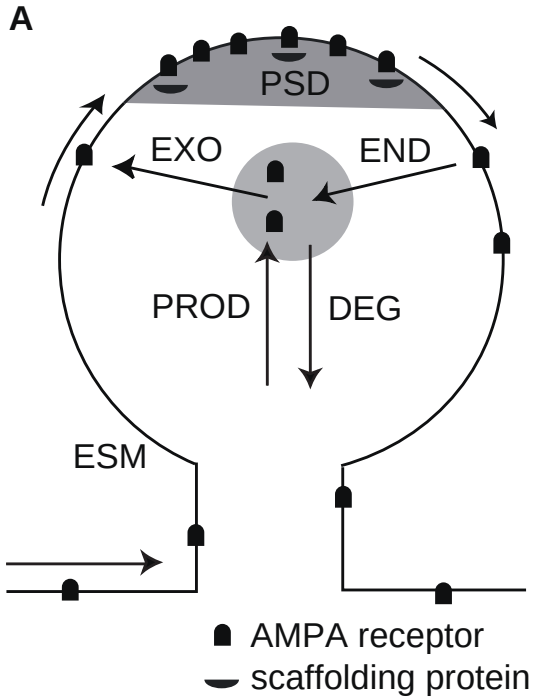
$$\begin{aligned}\frac{dP_{n,m}}{dt} &= \sigma P_{n-1,m} + \mu(n+1)P_{n+1,m} \\ &+ \alpha(n+1)[Z-(m-1)]P_{n+1,m-1} \\ &+ \beta(m+1)P_{n-1,m+1} \\ &- [\sigma + \mu n + \alpha n(Z-m) + \beta m]P_{n,m}\end{aligned}$$



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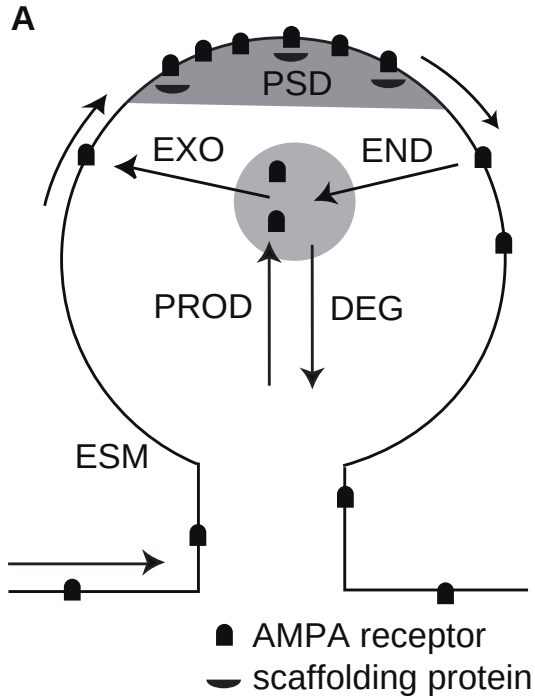
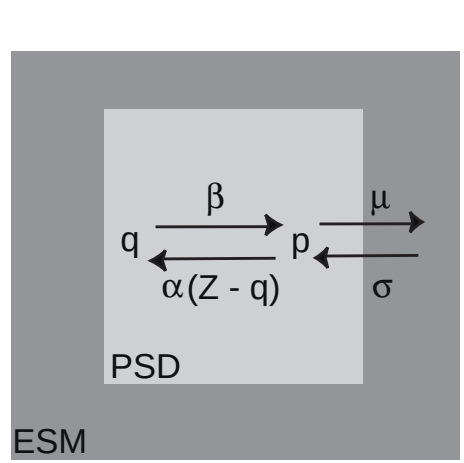
stochastic gate : $0 < \mu_{open} \underset{\gamma_+}{\overset{\gamma_-}{\rightleftarrows}} \mu_{closed} = 0$

$$\sigma(t) = C\mu(t) \quad (C \text{ bath conc.})$$





Bressloff & BAE *Biophys J* (2009)

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., $\alpha n(t) \gg \beta$)

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- 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

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

Analysis in two regimes: un/saturated binding sites

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  - Obtain mean, variance from derivatives of G

$$\mathrm{E}_\mu(n) = \left.\frac{\partial G}{\partial u}\right|_{u=v=1}, \qquad \mathrm{E}_\mu(m) = \left.\frac{\partial G}{\partial v}\right|_{u=v=1}$$

Averaging over realizations of μ

- Can show that

$$\mathrm{E}(n) \equiv \langle \mathrm{E}_\mu(n) \rangle = C + (n_0 - C)\langle \mathcal{N}_{11} \rangle + (m_0 - C\alpha Z/\beta)\langle \mathcal{N}_{21} \rangle$$
$$\mathrm{E}(m) \equiv \langle \mathrm{E}_\mu(m) \rangle = C\alpha Z/\beta + (n_0 - C)\langle \mathcal{N}_{12} \rangle + (m_0 - C\alpha Z/\beta)\langle \mathcal{N}_{22} \rangle$$

where

$$\mathcal{N}(t) = \exp\left(- \int_0^t \mathcal{M}(t')dt' \right), \quad \mathcal{M}(t) = \begin{pmatrix} \mu(t) + \alpha Z & -\alpha Z \\ -\beta & \beta \end{pmatrix}$$

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- Can derive a system of ODEs for the averages of the entries of $\mathcal{N}$ using method of Kubo and Zwanzig

Saturated binding sites

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

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

Saturated binding sites

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

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

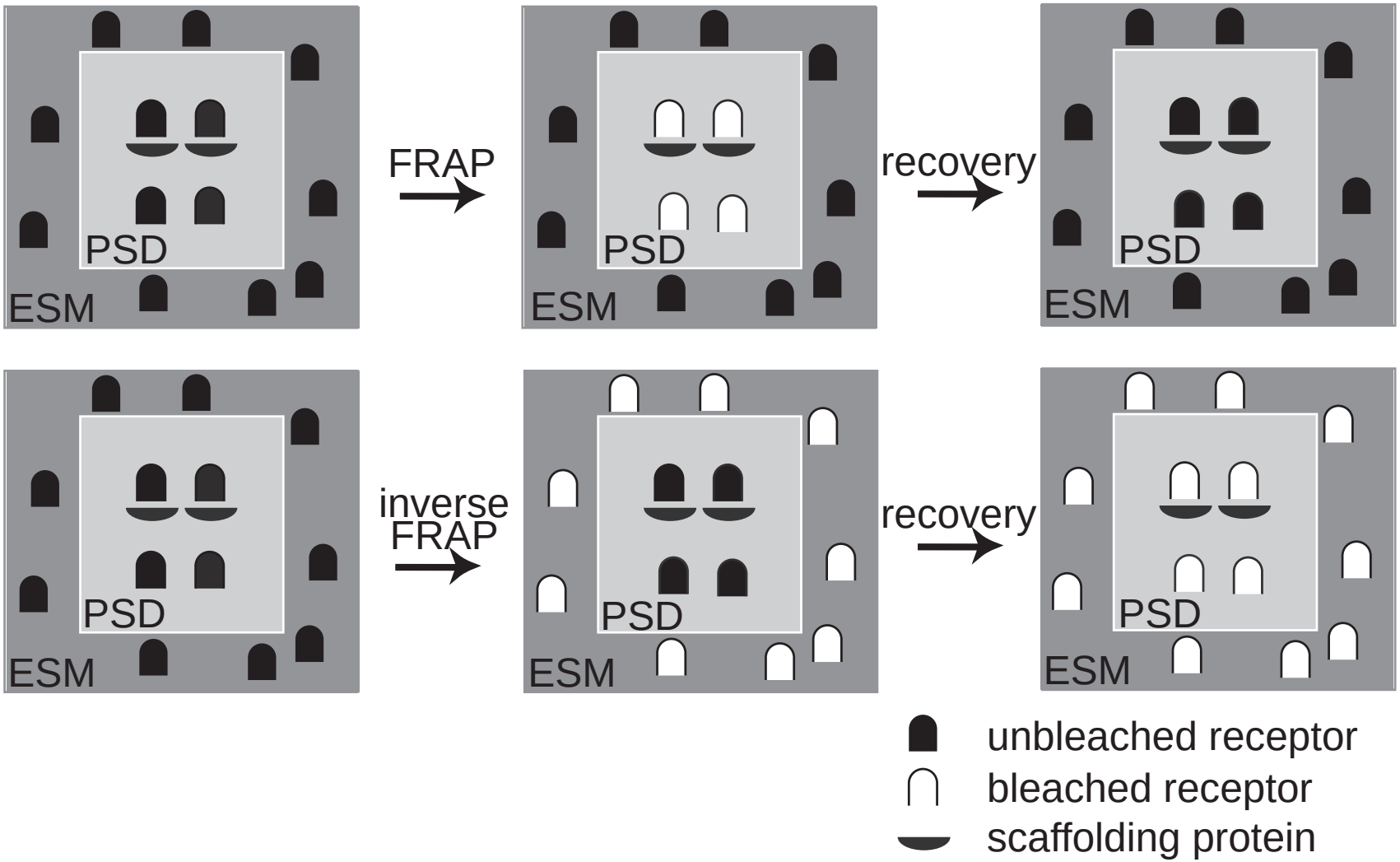
$$\mathrm{E}(n) = (n_0 - C)\langle w\rangle + C$$

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

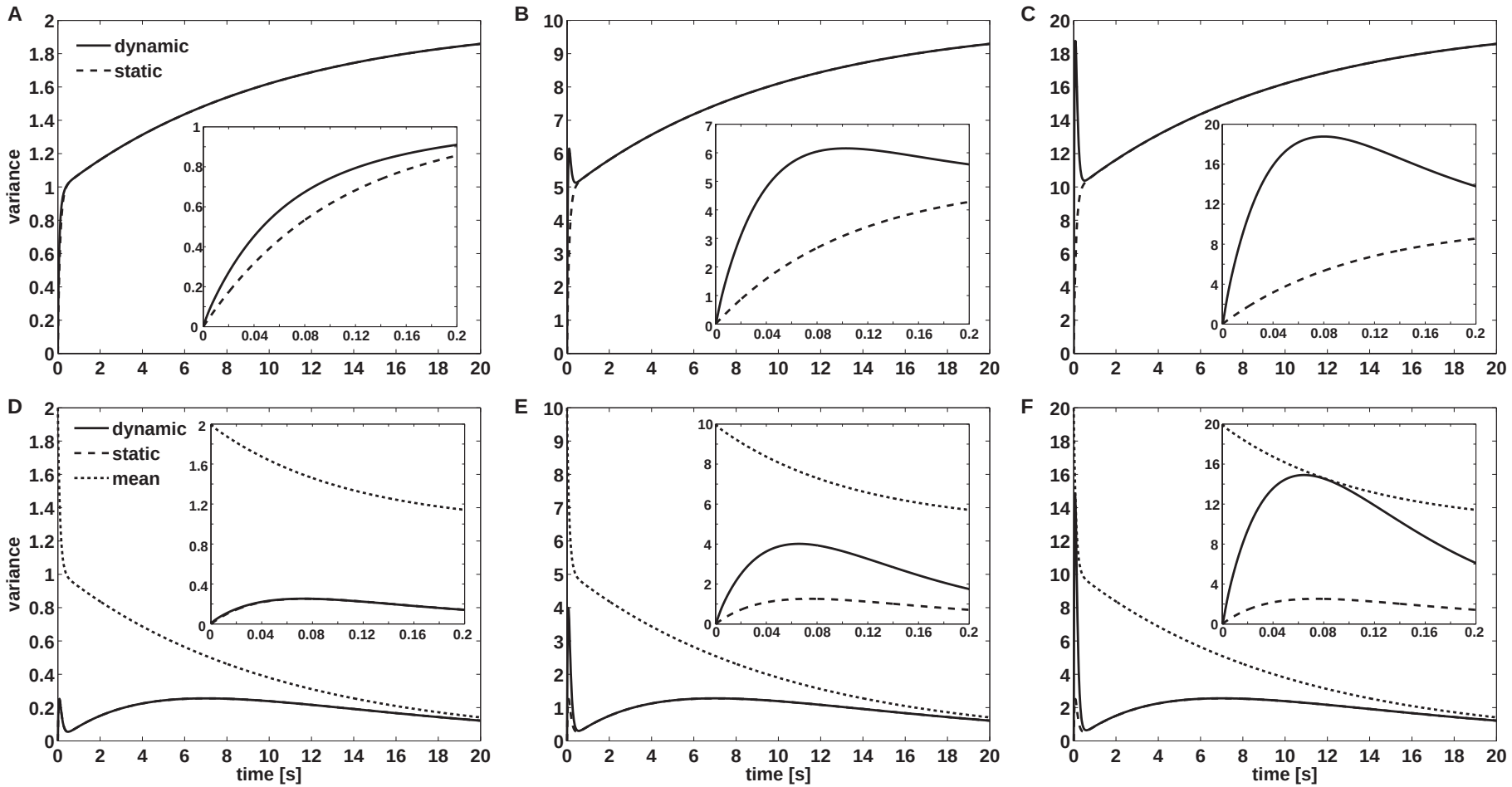
$$\left\langle w(t)^j\right\rangle = \begin{pmatrix}1\\1\end{pmatrix}^T \exp\left[-t\begin{pmatrix} j\mu_o + \gamma_- & -\gamma_+ \\ -\gamma_- & \gamma_+\end{pmatrix}\right]\begin{pmatrix}\Pi_o\\ \Pi_c\end{pmatrix}, \quad (j = 1, 2)$$

$$\Pi_o = \frac{\gamma_+}{\gamma_+ + \gamma_-}, \quad \Pi_c = \frac{\gamma_-}{\gamma_+ + \gamma_-}$$

FRAP and inverse FRAP experiments



Simulations of FRAP and inverse FRAP



- Single-spine model (deterministic)
- Single-synapse model (stochastic)
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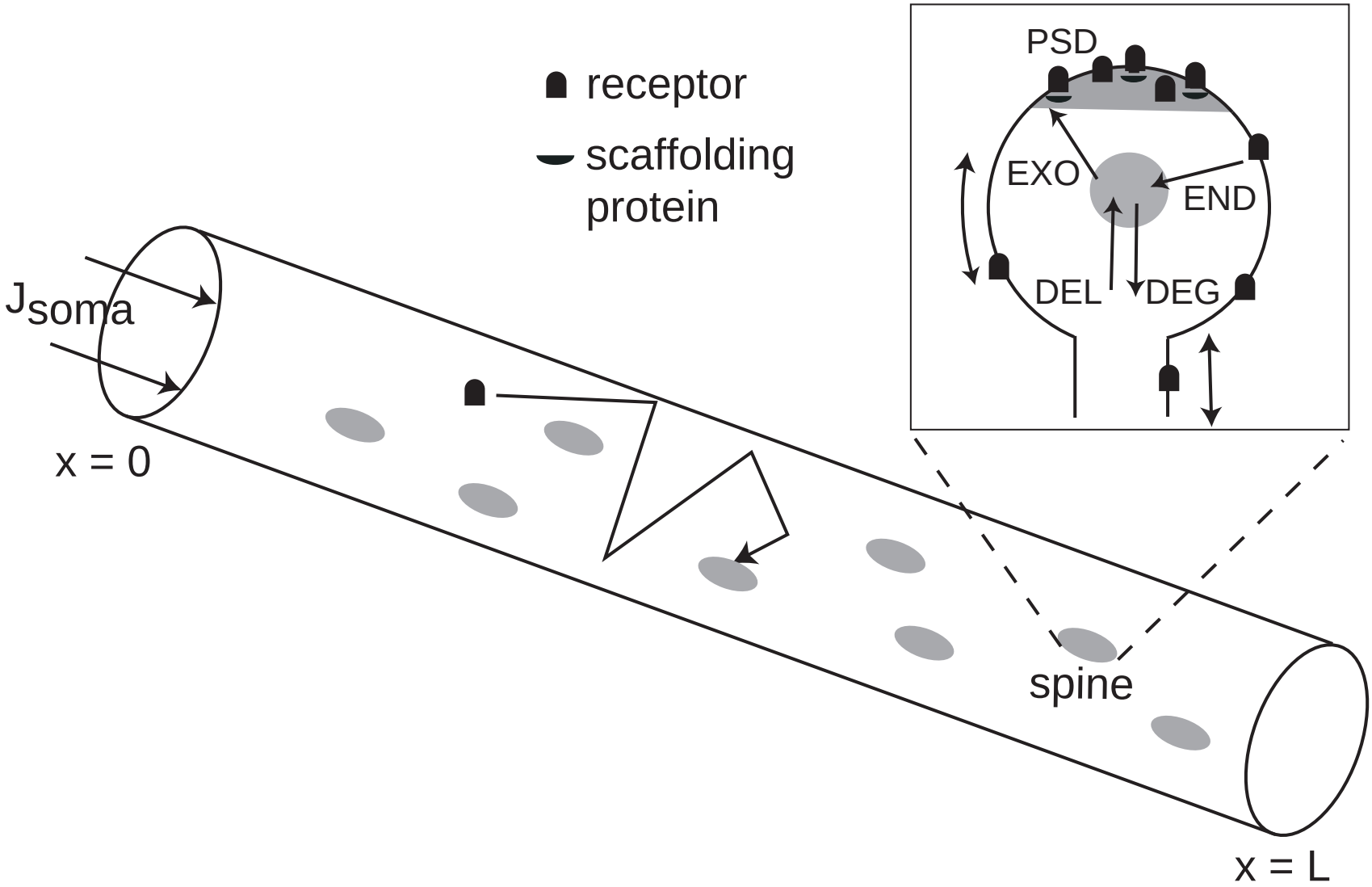
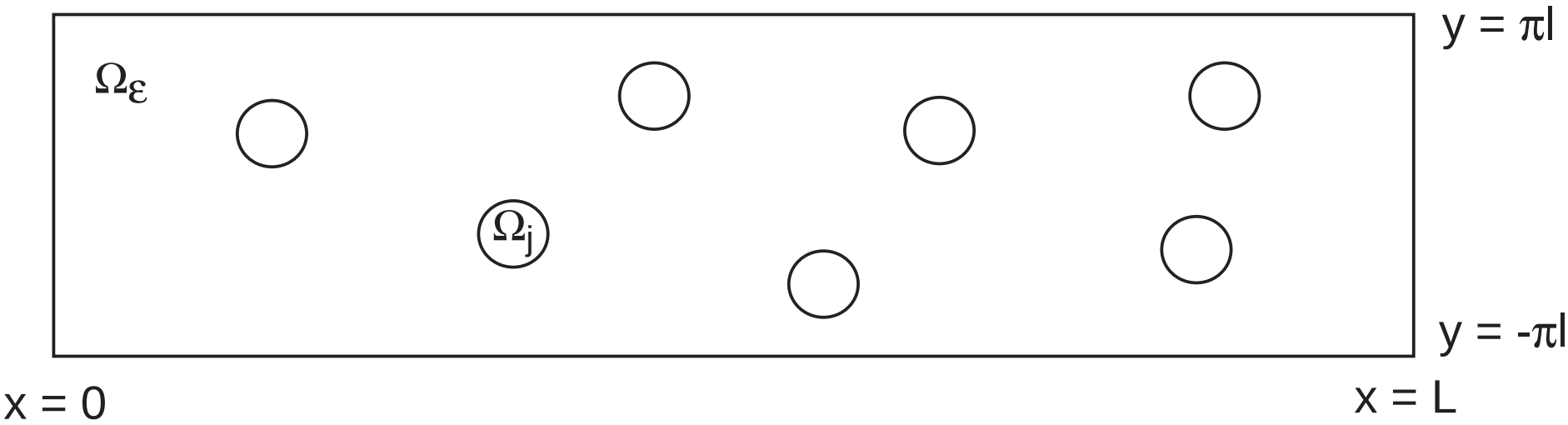
Treat dendritic membrane as cylinder with holes



Bressloff, BAE & Ward, *SIAM J Appl Math* (2008)

Diffusion equation on dendritic membrane

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



- $U =$ receptor concentration
- Ω_ε 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

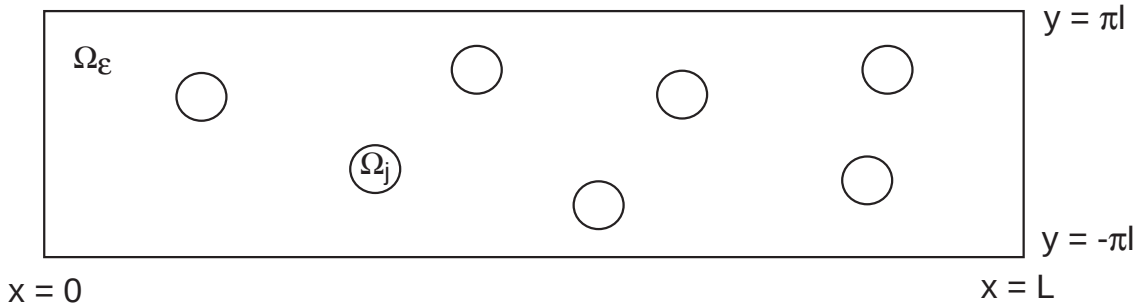
- Periodic bcs at $y = \pm \pi l$
- No-flux bc at $x = L$, and at $x = 0$

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

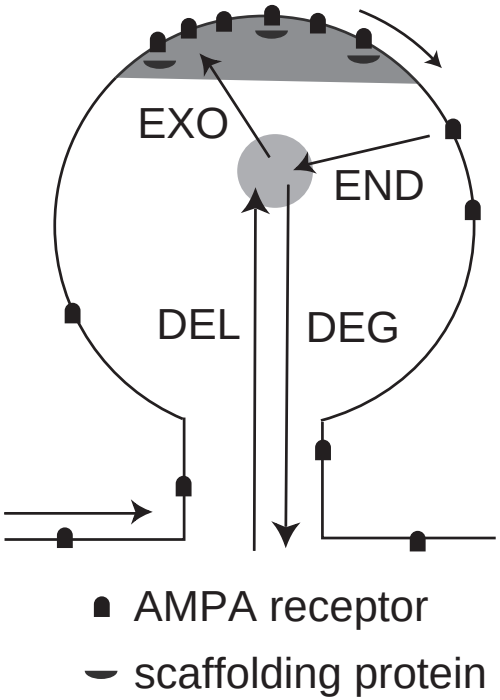
- bcs at the holes:

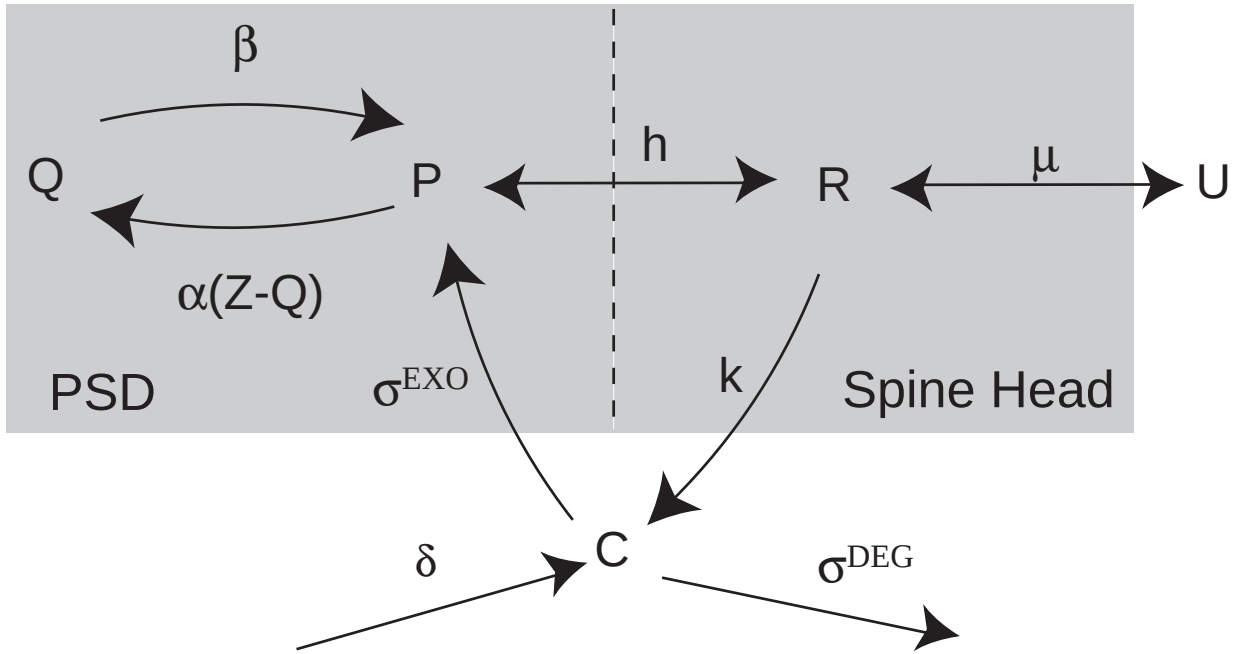
$$-D\frac{\partial U}{\partial \mathbf{n}}(\mathbf{r}, t) = \frac{\mu_j}{2\pi\varepsilon\rho}(U(\mathbf{r}, t) - R_j), \quad \mathbf{r} \in \partial\Omega_j$$

  - μ_j = spine neck hopping rate
  - R_j = receptor concentration on surface of jth spine



Treat each spine as before





Steady-state solution

- Assume concentrations in jth spine see 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 Ω_ε with boundary conditions

Steady-state solution

- Assume concentrations in jth spine see mean value of U on $\partial\Omega_j$:

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

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

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

Three steps for finding approximate steady-state solution

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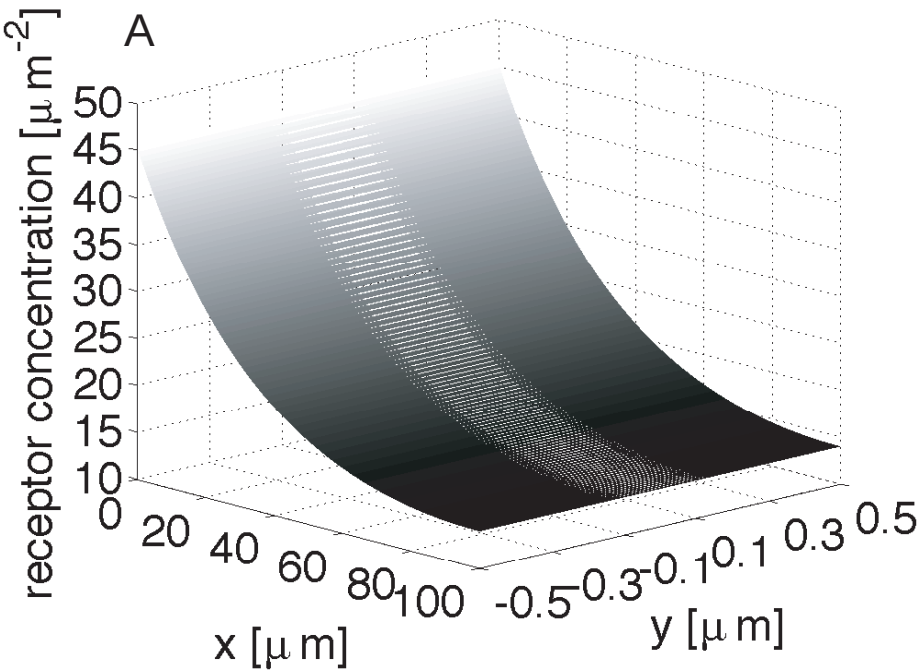
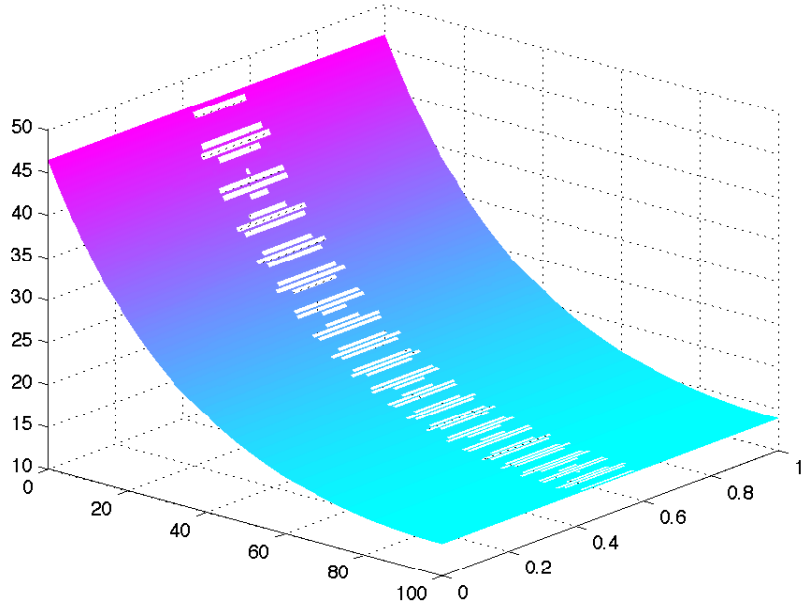
3. Conservation condition gives $(N+1)$th equation
   $$\sigma = \sum \widehat{\mu}_j \left(U_j - \widehat{R}_j \right)$$

Comparison of dendritic receptor concentration

perturbation solution



numerical solution



- 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

- Single-spine model (deterministic)
- Single-synapse model (stochastic)
- 2D diffusion model
- 1D diffusion models
- 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

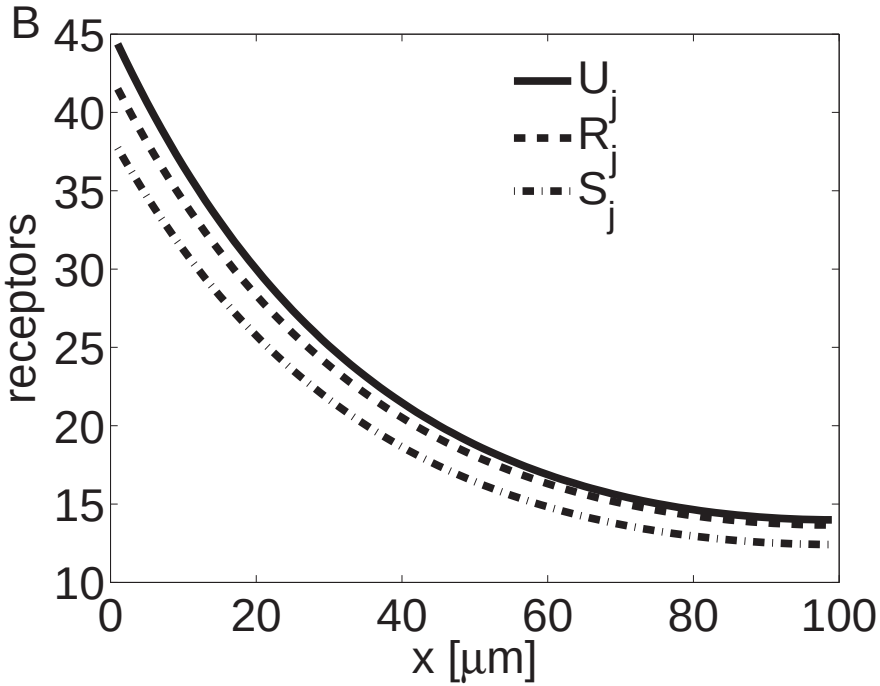
$$\frac{\partial U}{\partial t} = D\frac{\partial^2 U}{\partial x^2} - \sum_{j=1}^{N} \delta(x - x_j)\mu_j(U_j - R_j)$$

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

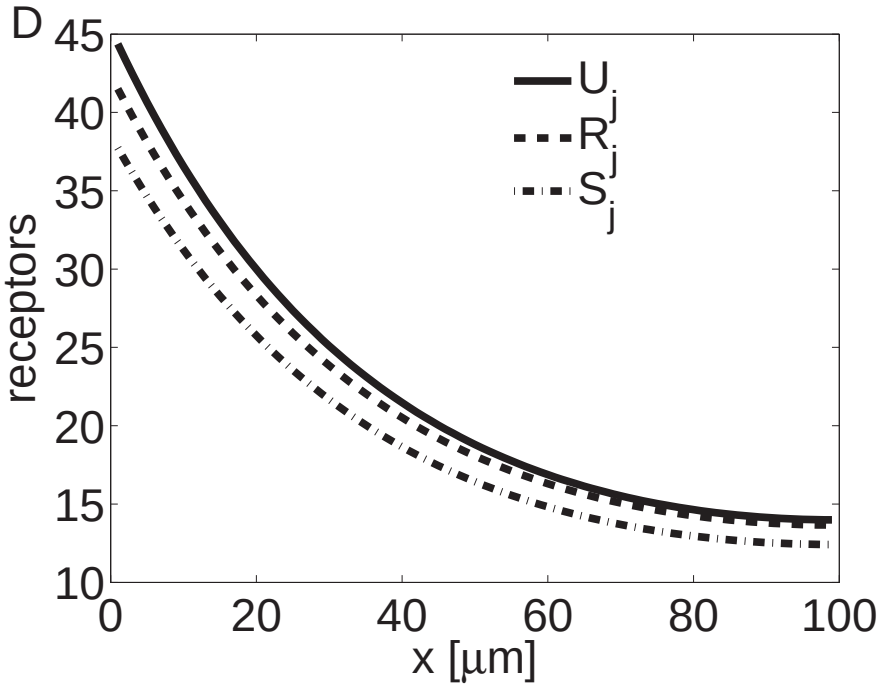
Bressloff & BAE, *PRE* (2007)

Comparison of models

2D model



1D model



- 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 η

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

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

BAE & Bressloff, *J Comput Neurosci* (2008)

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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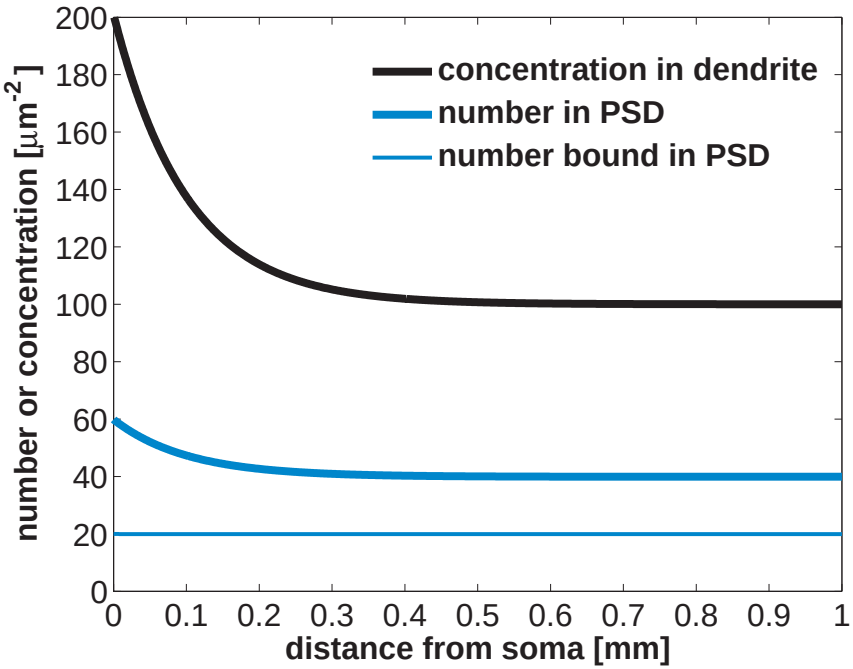
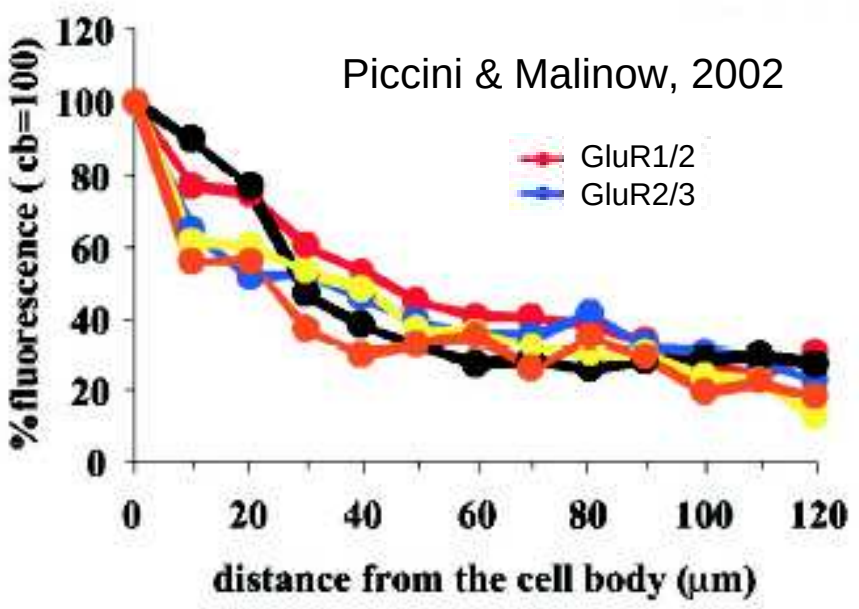
- Solve using Green's function methods

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

Steady-state receptor concentrations for identical spines

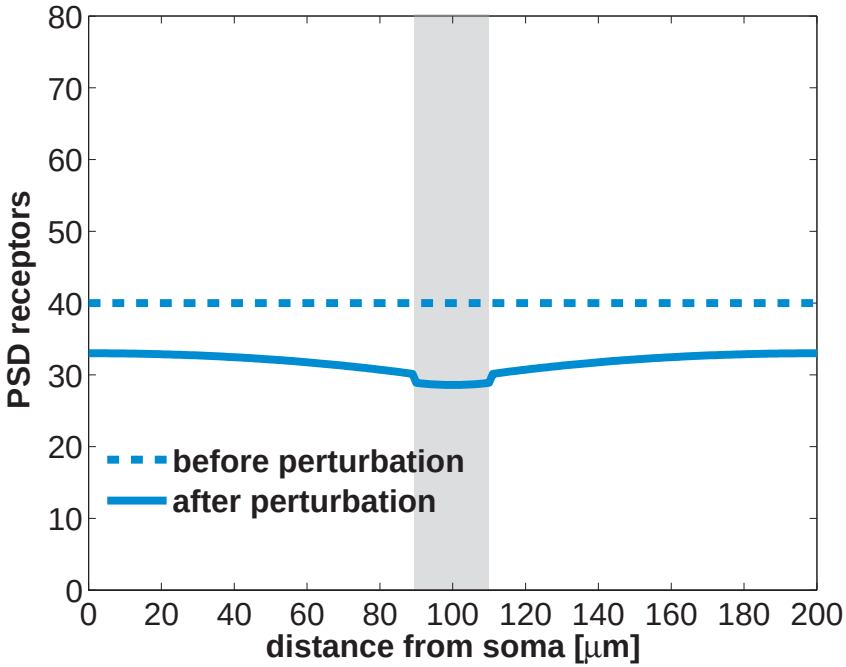




- Dendrite 1 mm long
- 1,000 identical spines spaced 1μm apart
- Two sources of receptors
  - at soma
  - local intracellular delivery

Consequences of diffusive coupling

10-fold reduction in rate of exocytosis in gray region



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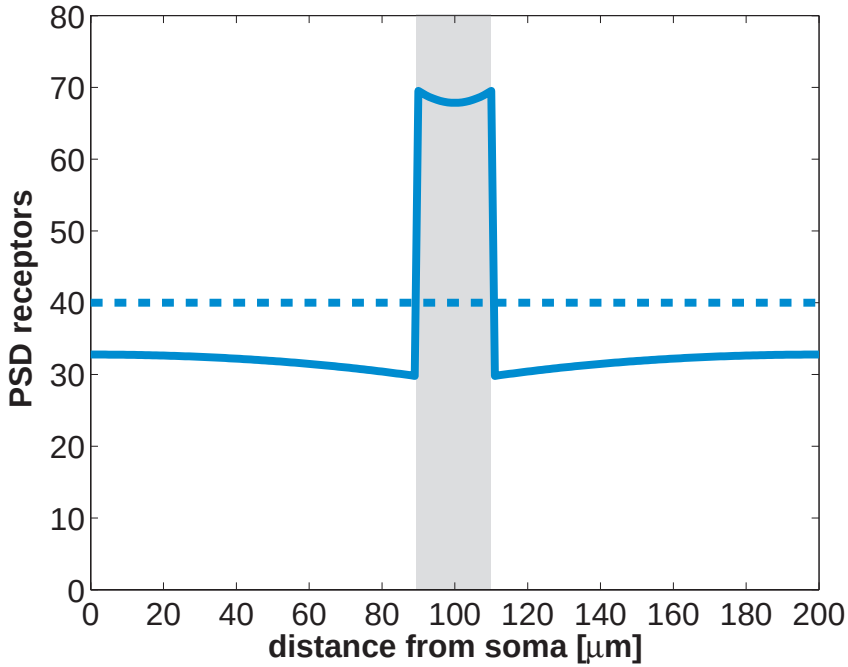
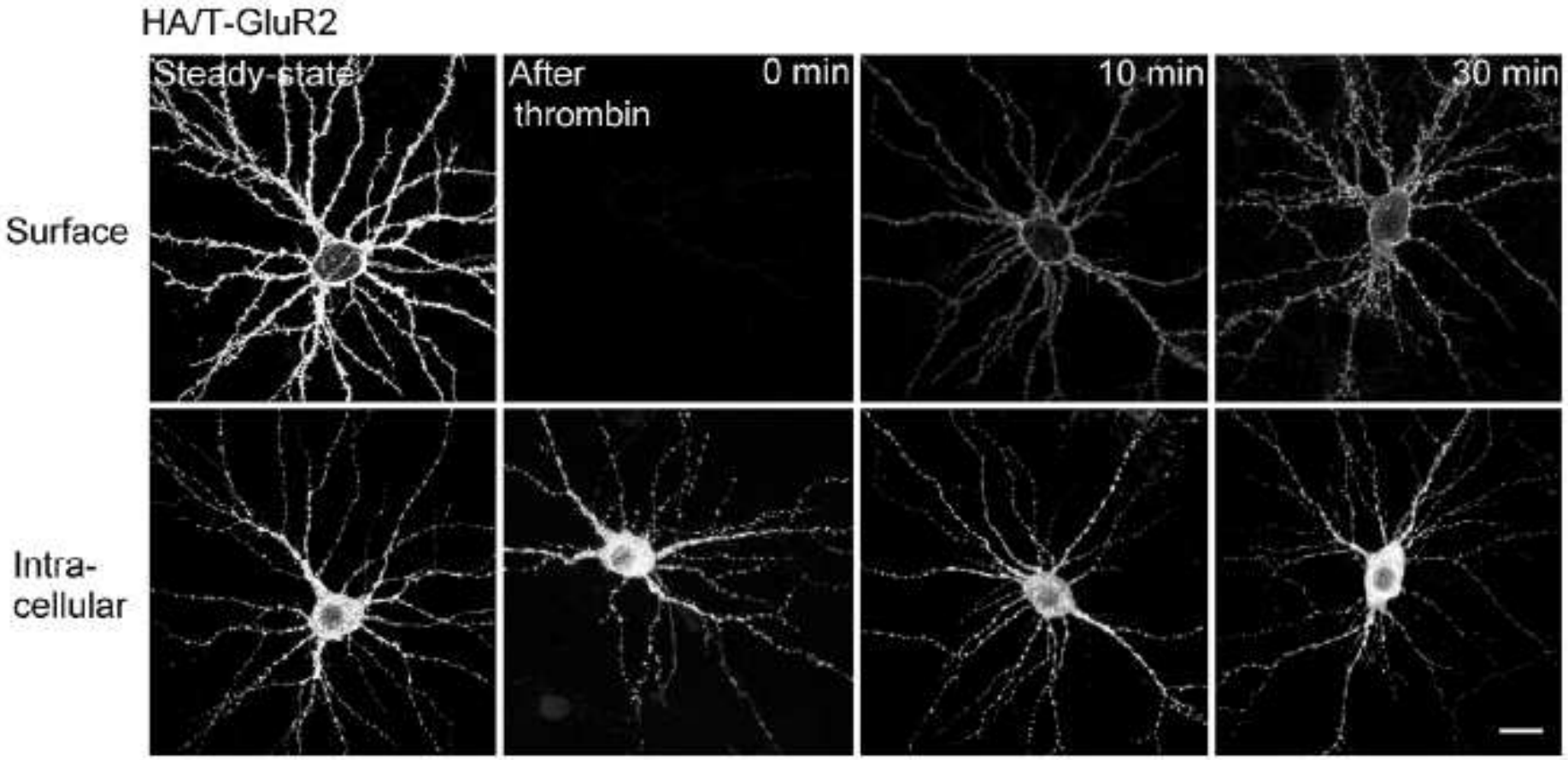


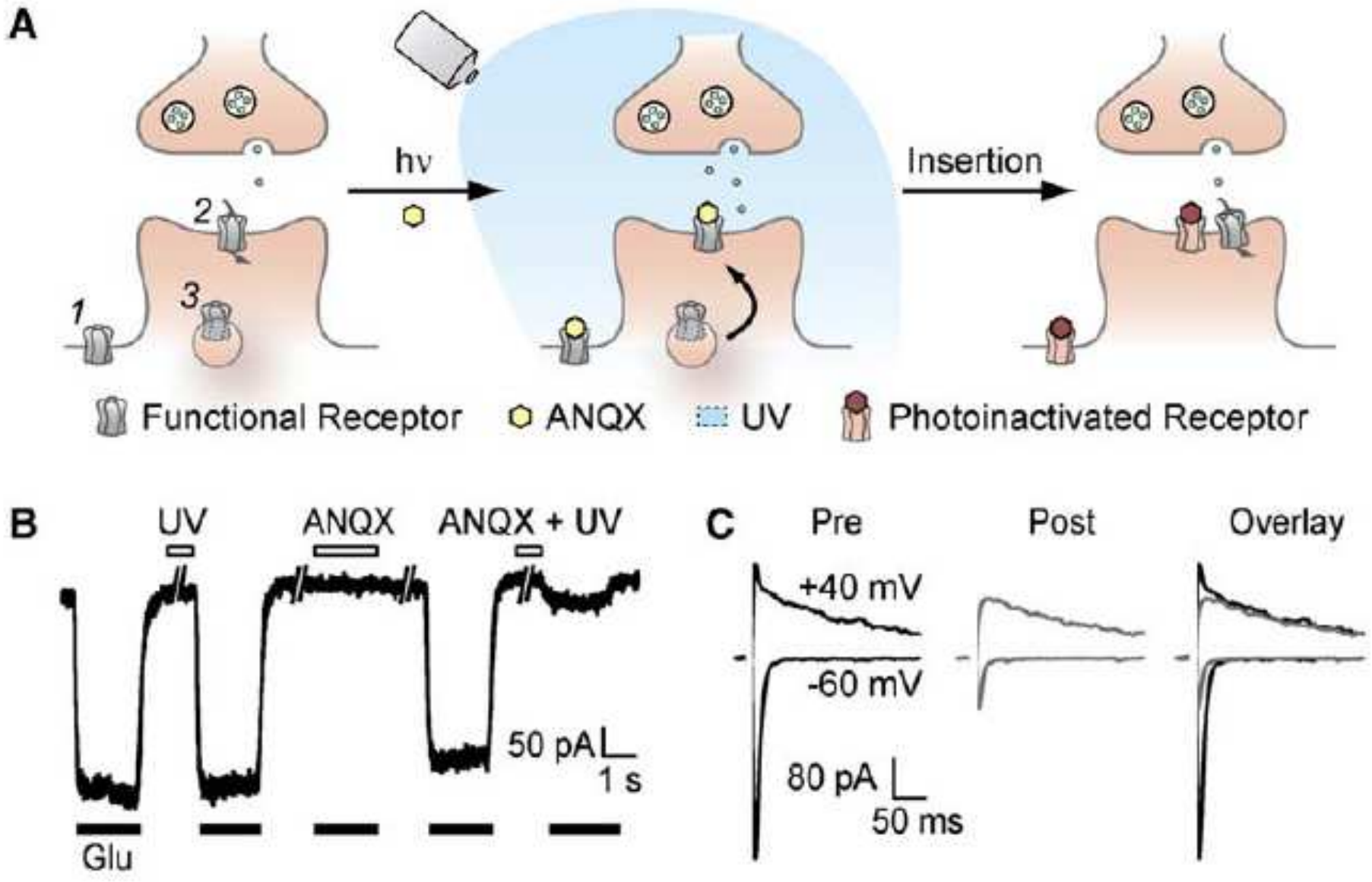
Steady-state is nice...
...but what about time-dependent phenomena?

AMPA receptor recycling via thrombin cleavage



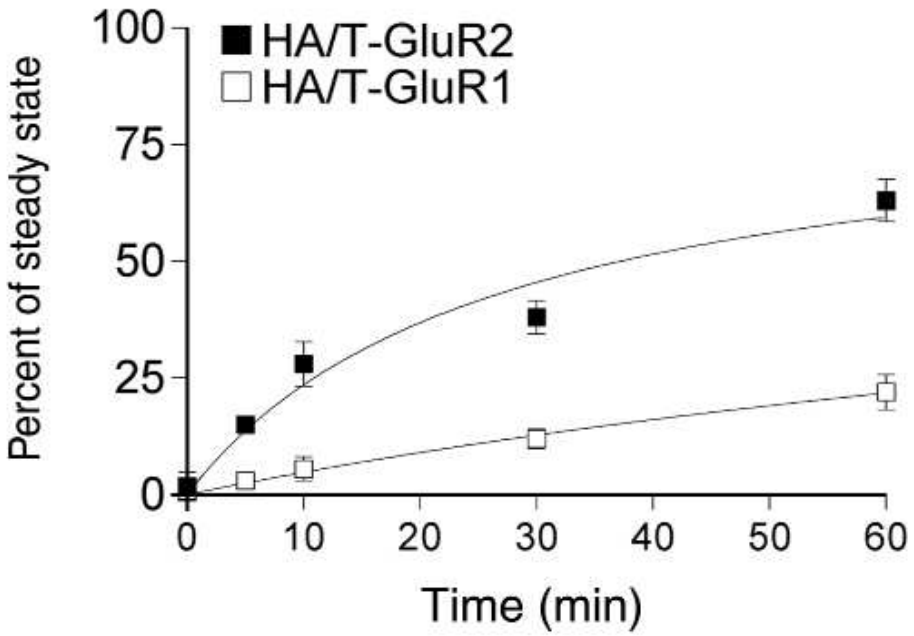
Passafaro et al., *Nat. Neurosci.* (2001)

AMPA receptor recycling via photoinactivation

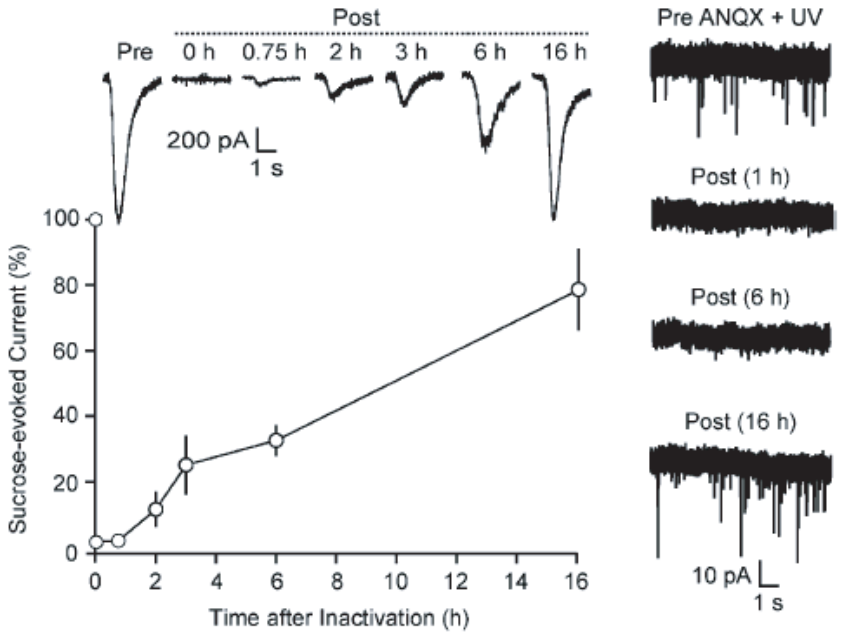


Fast or slow recycling of AMPA receptors?

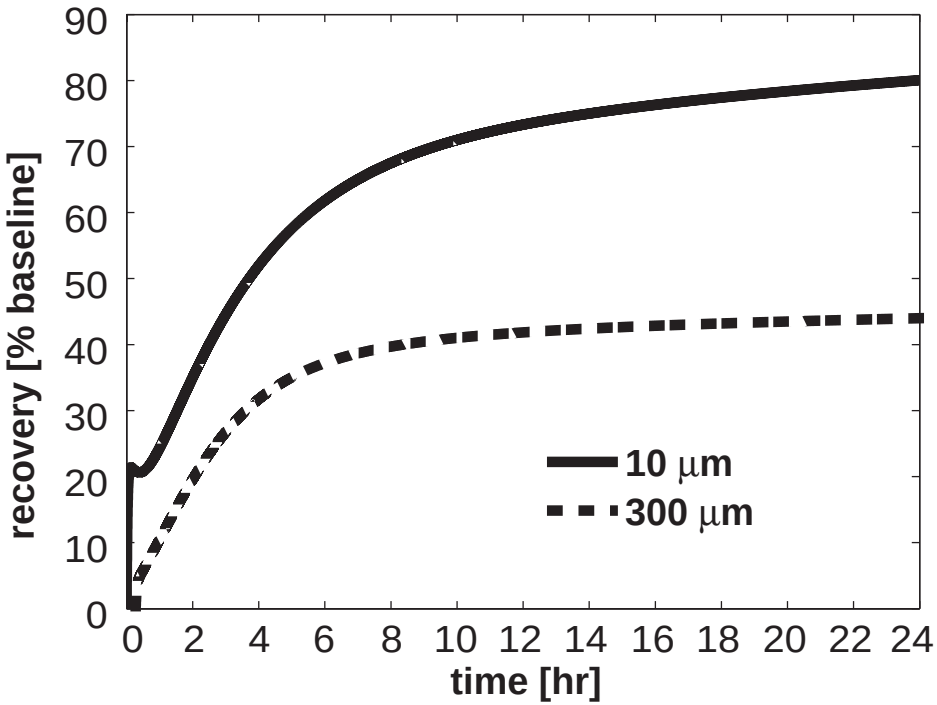
Passafaro et al., 2001

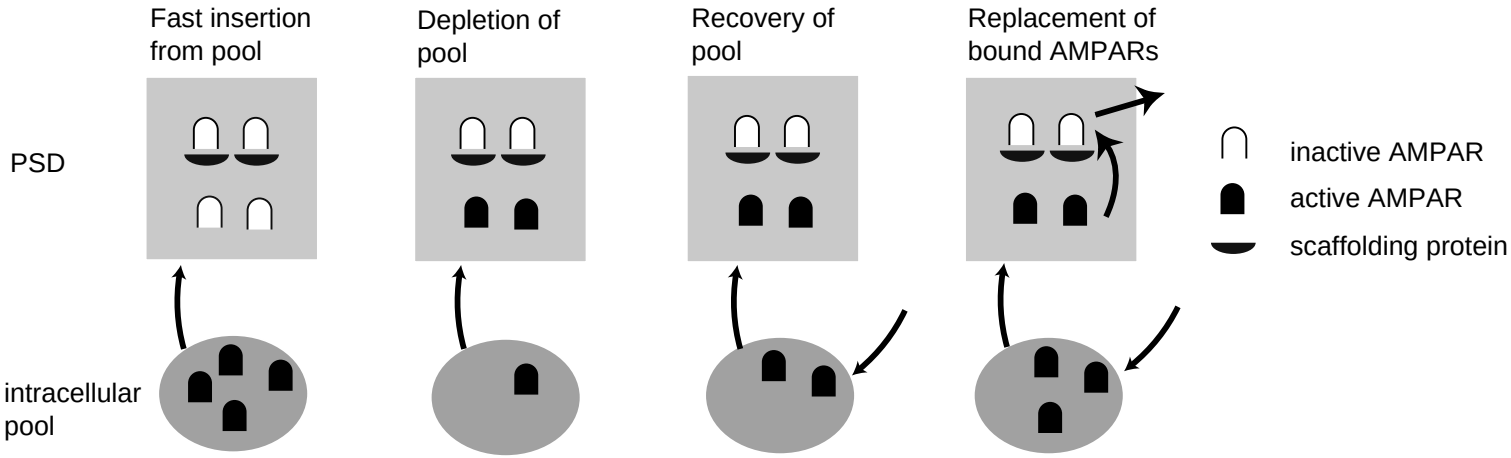


Adesnik et al., 2005



Simulation of photoinactivation of AMPA receptors





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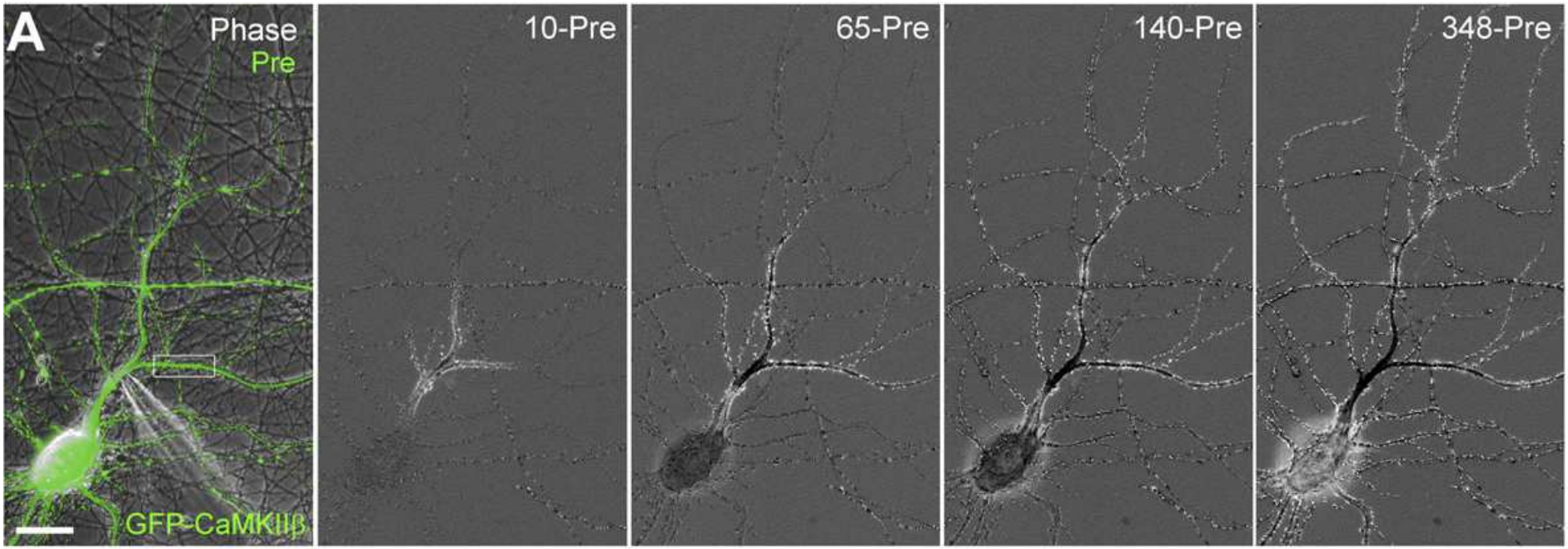
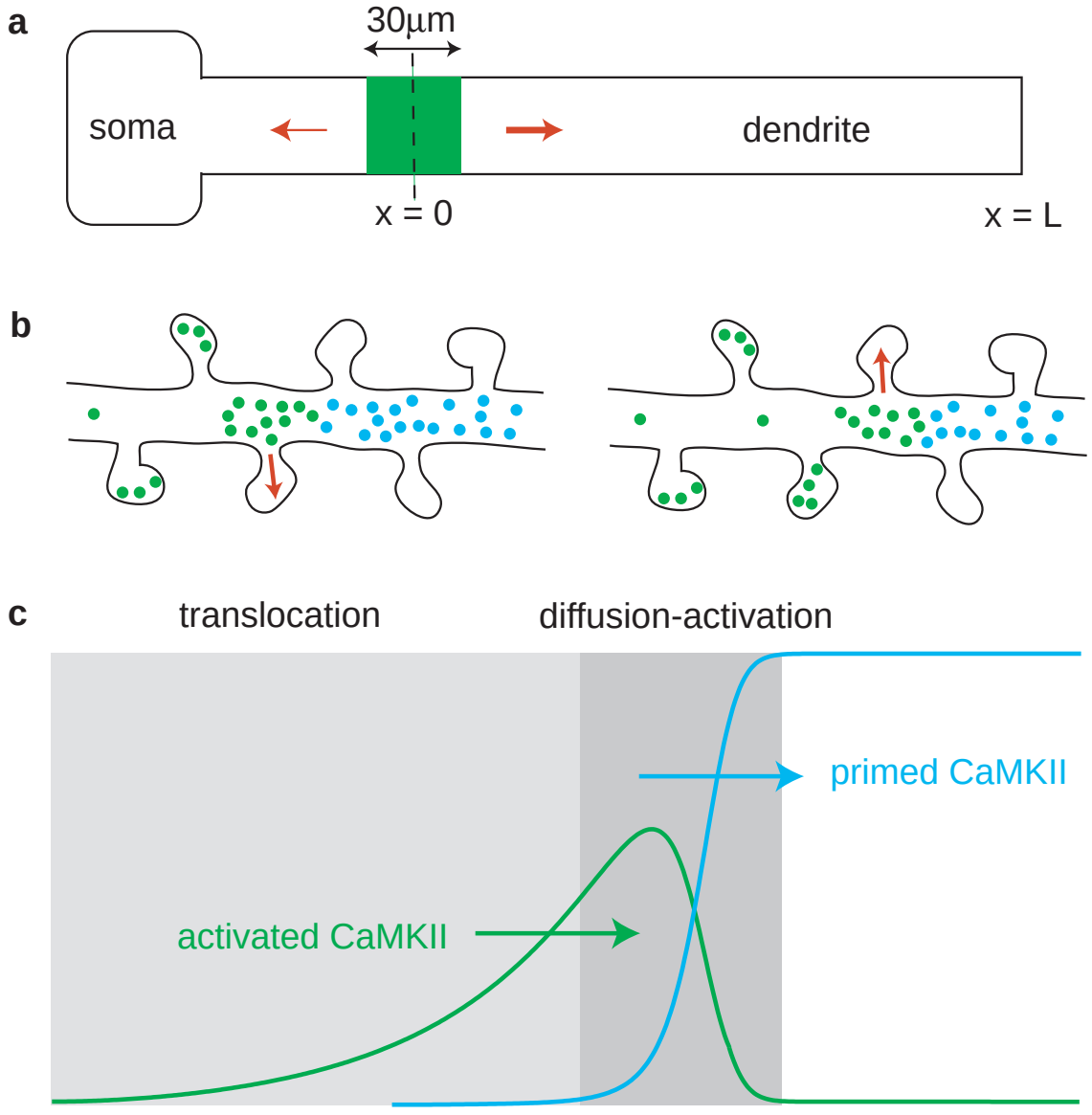
CaMKII translocation waves



Rose et al., *Neuron* (2009)

Diffusion-activation model of CaMKII translocation waves



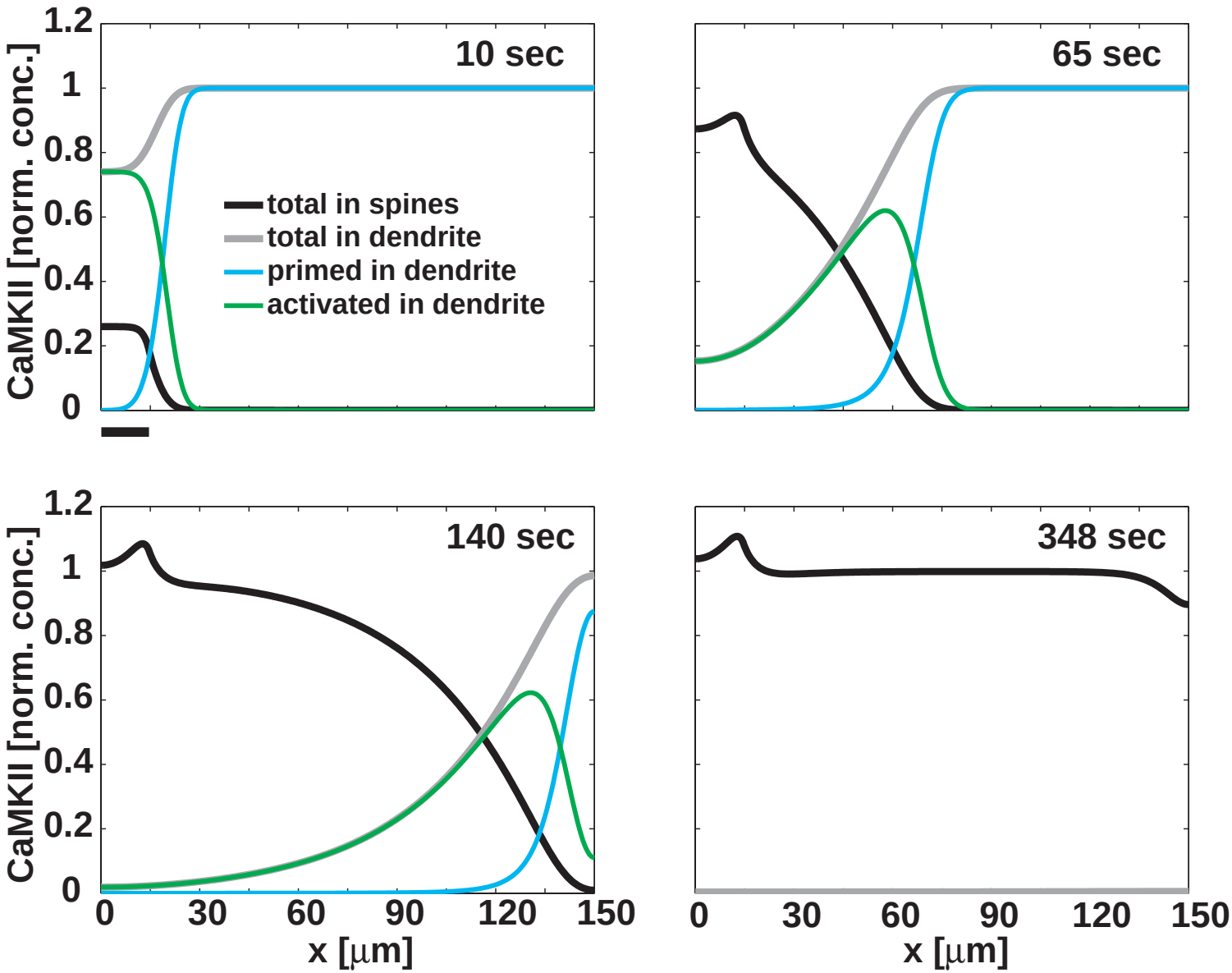
Equations for diffusion-activation model

$$\frac{\partial p}{\partial t} = D\frac{\partial^2 p}{\partial x^2} - kap$$
$$\frac{\partial a}{\partial t} = D\frac{\partial^2 a}{\partial x^2} + kap - ha$$
$$\frac{\partial s}{\partial t} = ha$$

- $p =$ 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



Calculation of wave speed

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

$$c = 2\sqrt{Dk}$$

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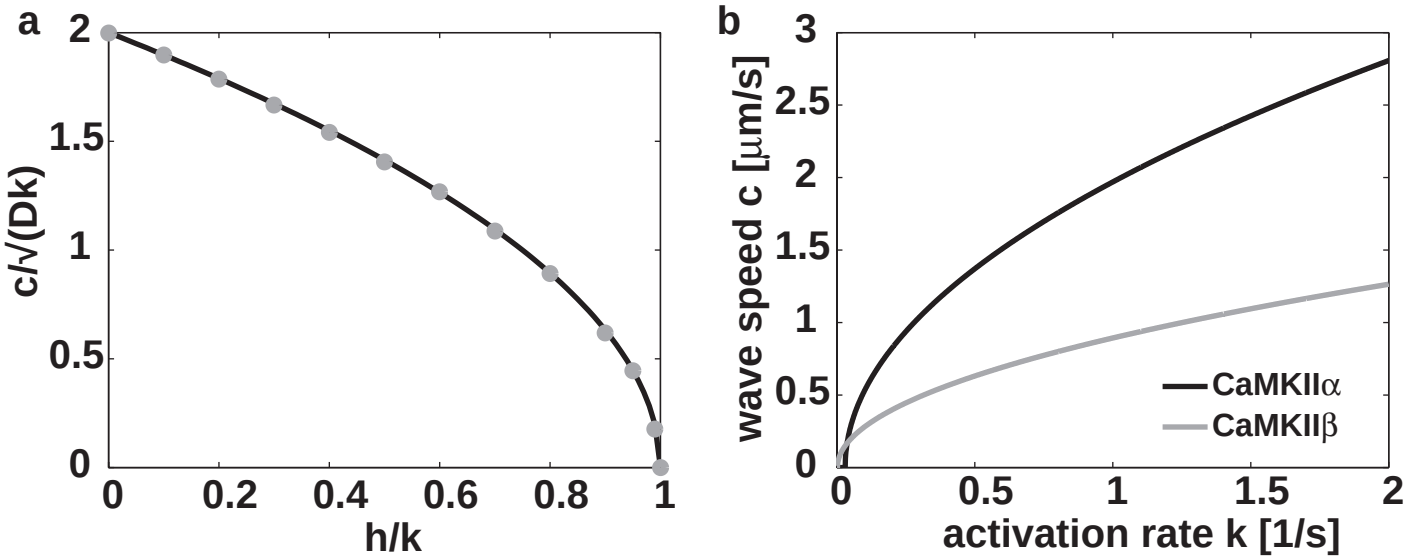

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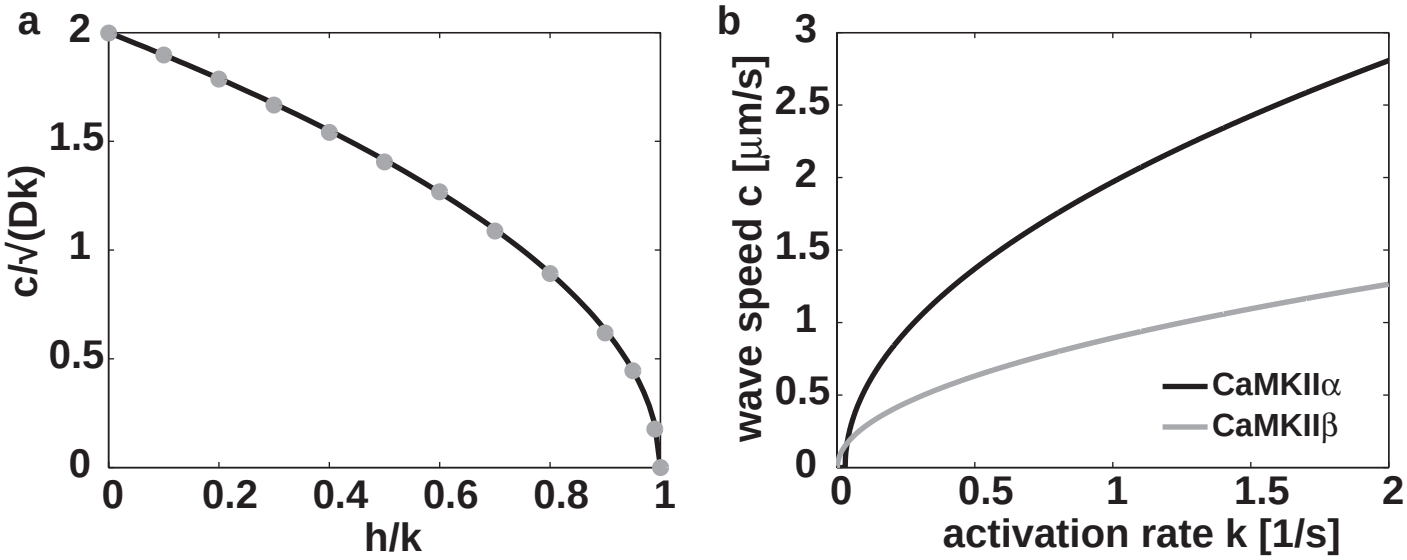

- Wave propagation failure when $k < h$

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)
- Michael Ward (UBC)
- NSF