AMPA receptor trafficking across multiple dendritic spines: heterosynaptic consequences of lateral membrane diffusion

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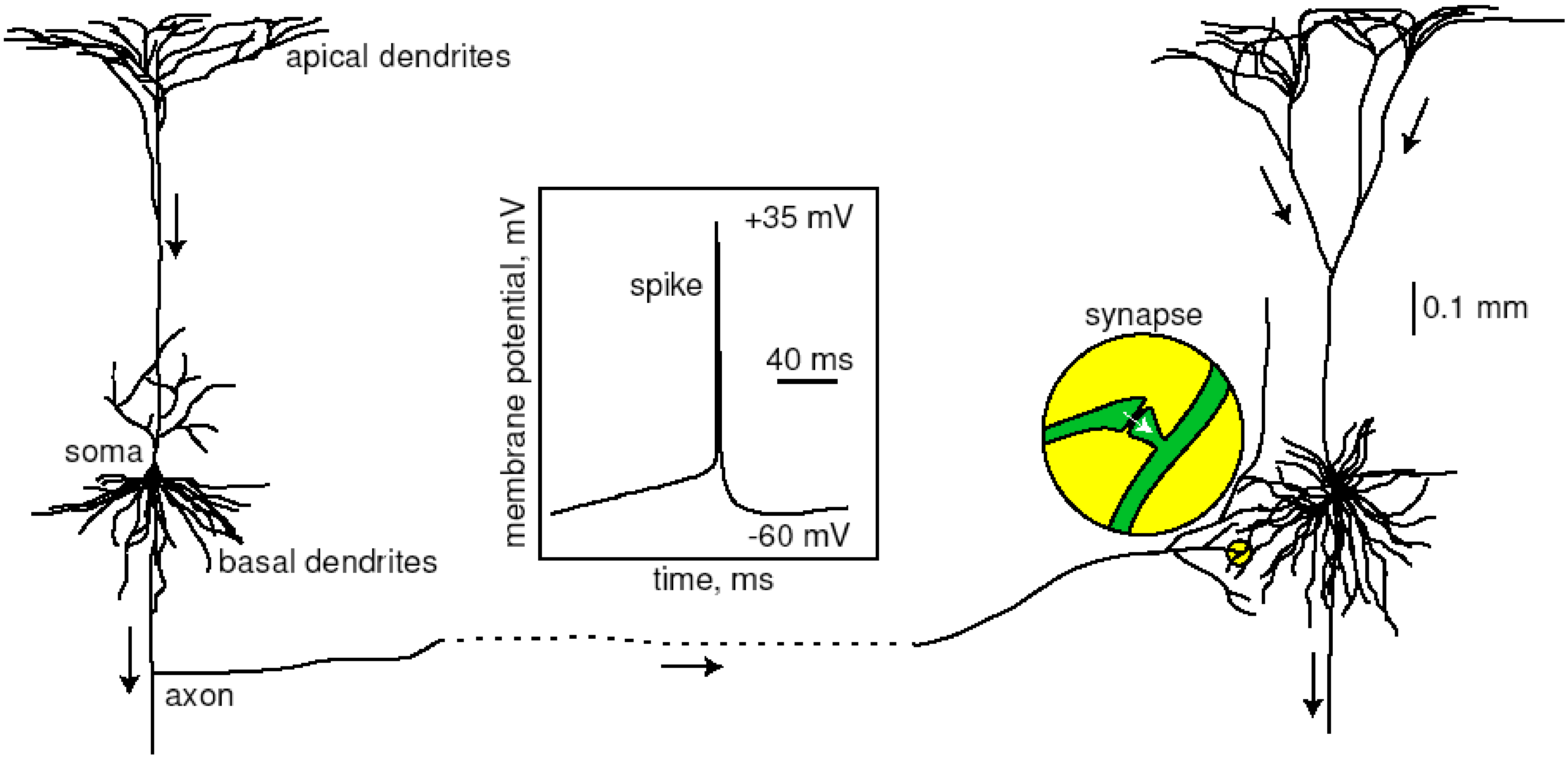
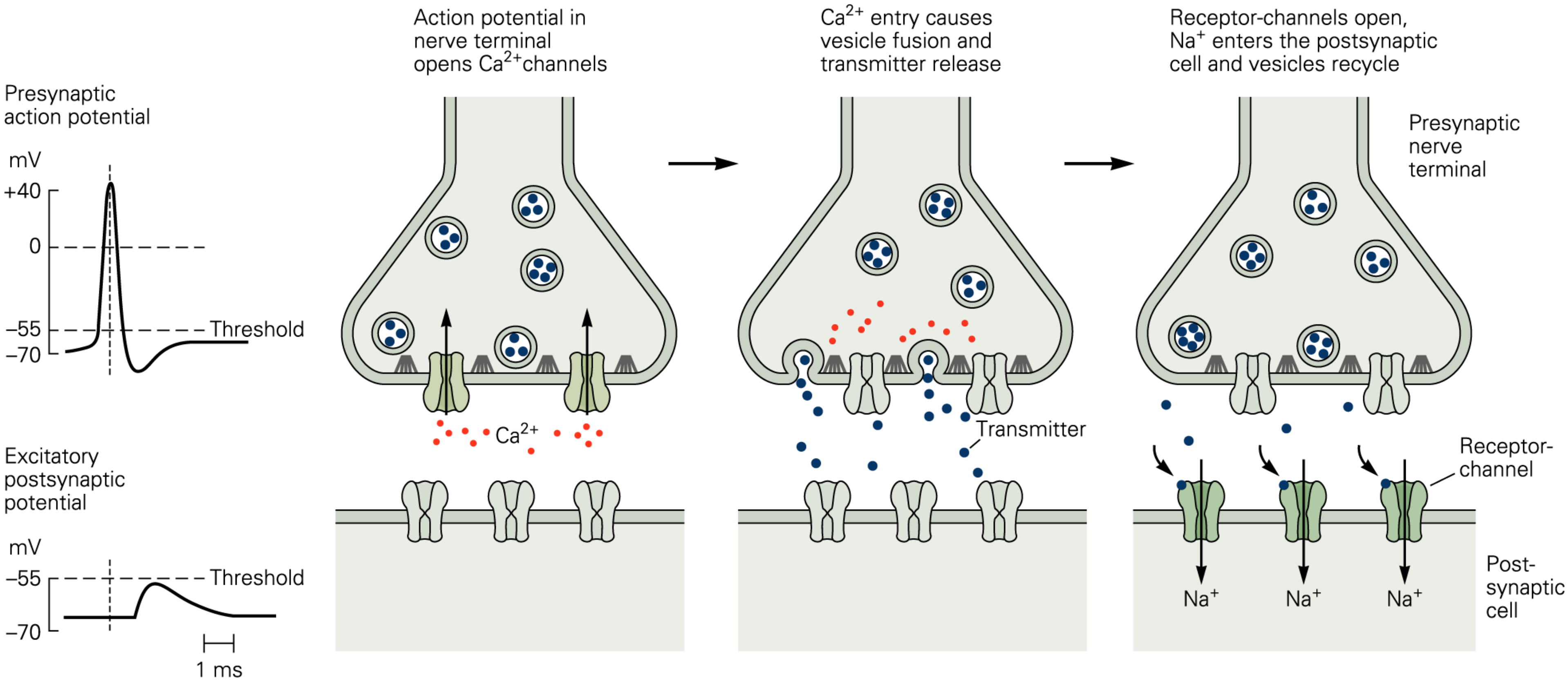
The brain: unparallel parallel computer

- 10^{11} neurons
- 10^{14} synapses
- network is plastic
- regulates behavior
- can **learn** and **remember**!

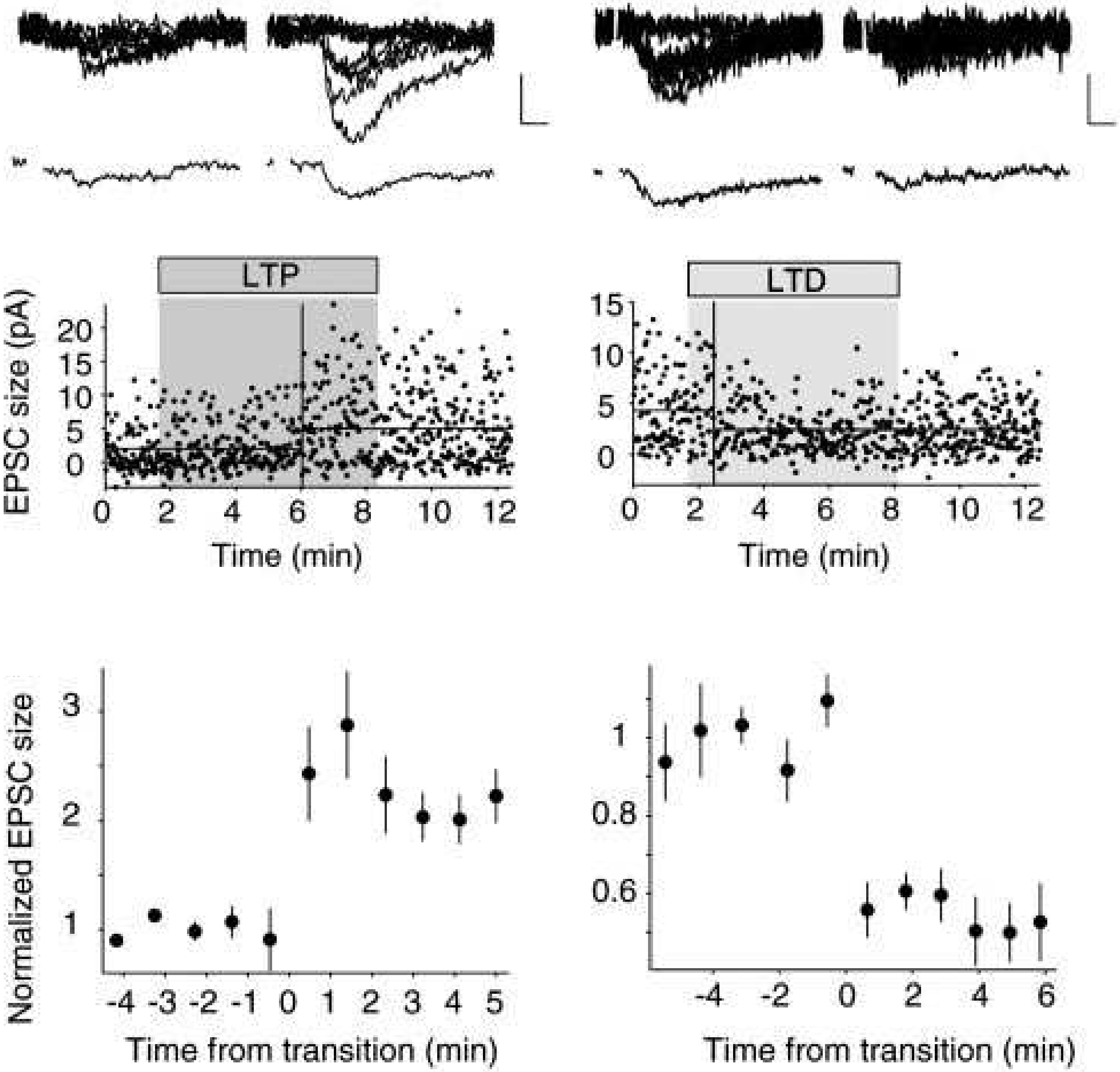
Neurons communicate via synapses



Synaptic transmission



Synaptic plasticity



1. AMPA receptor trafficking
2. 2D mathematical model
3. Steady-state analysis
4. 1D continuum model
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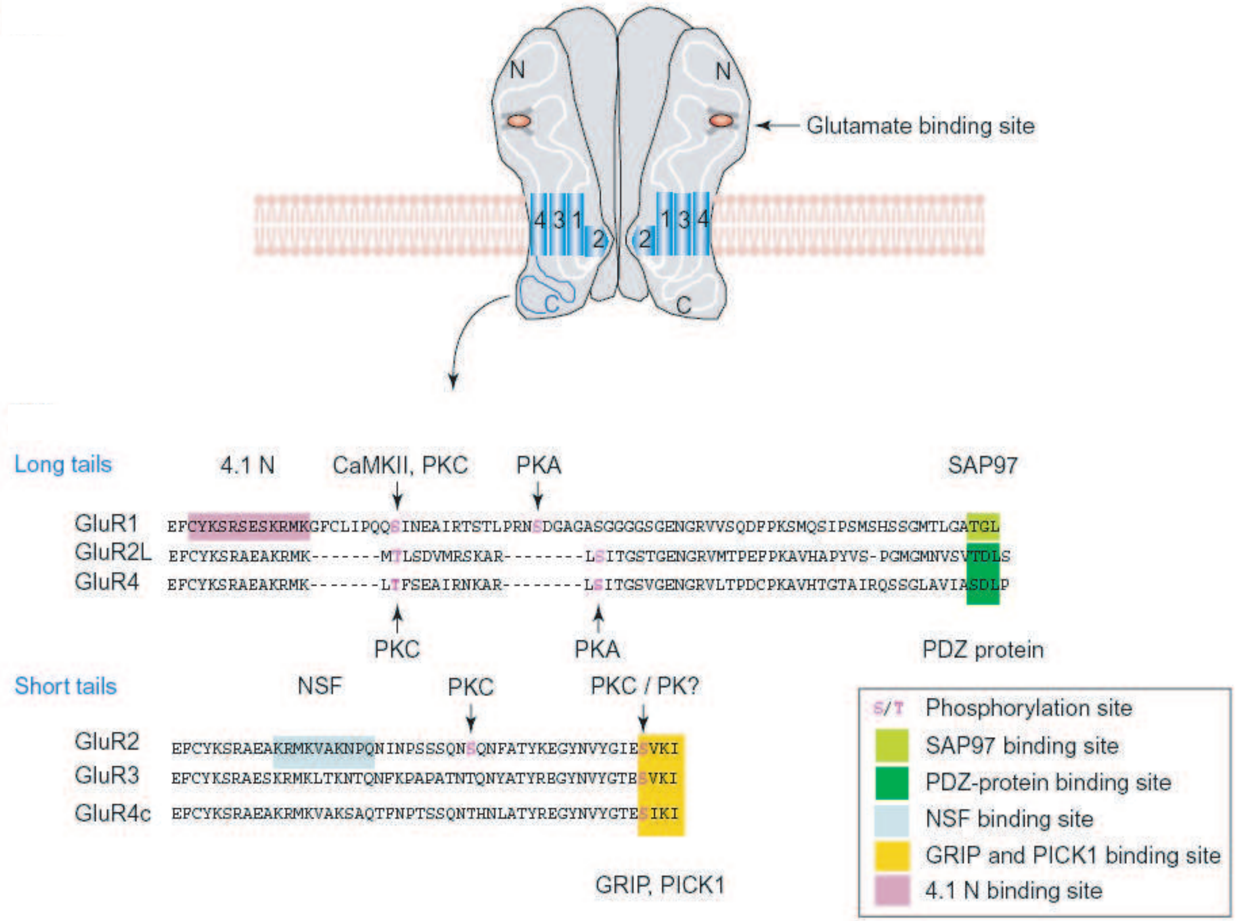
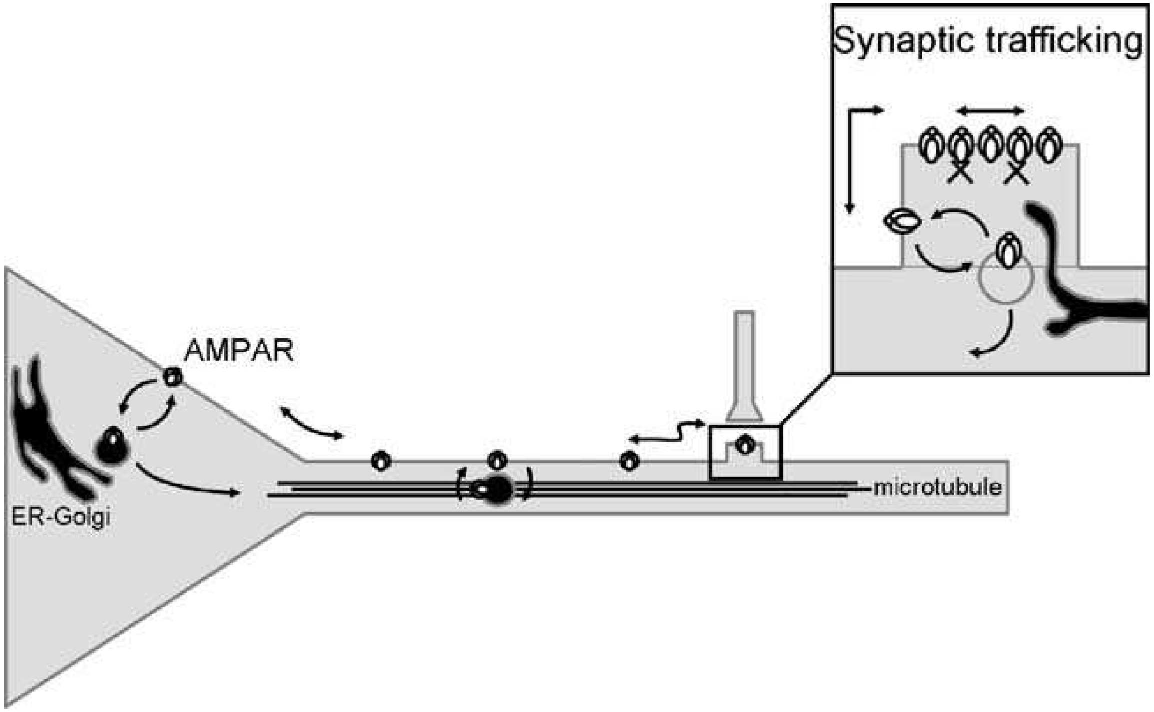
AMPA receptors



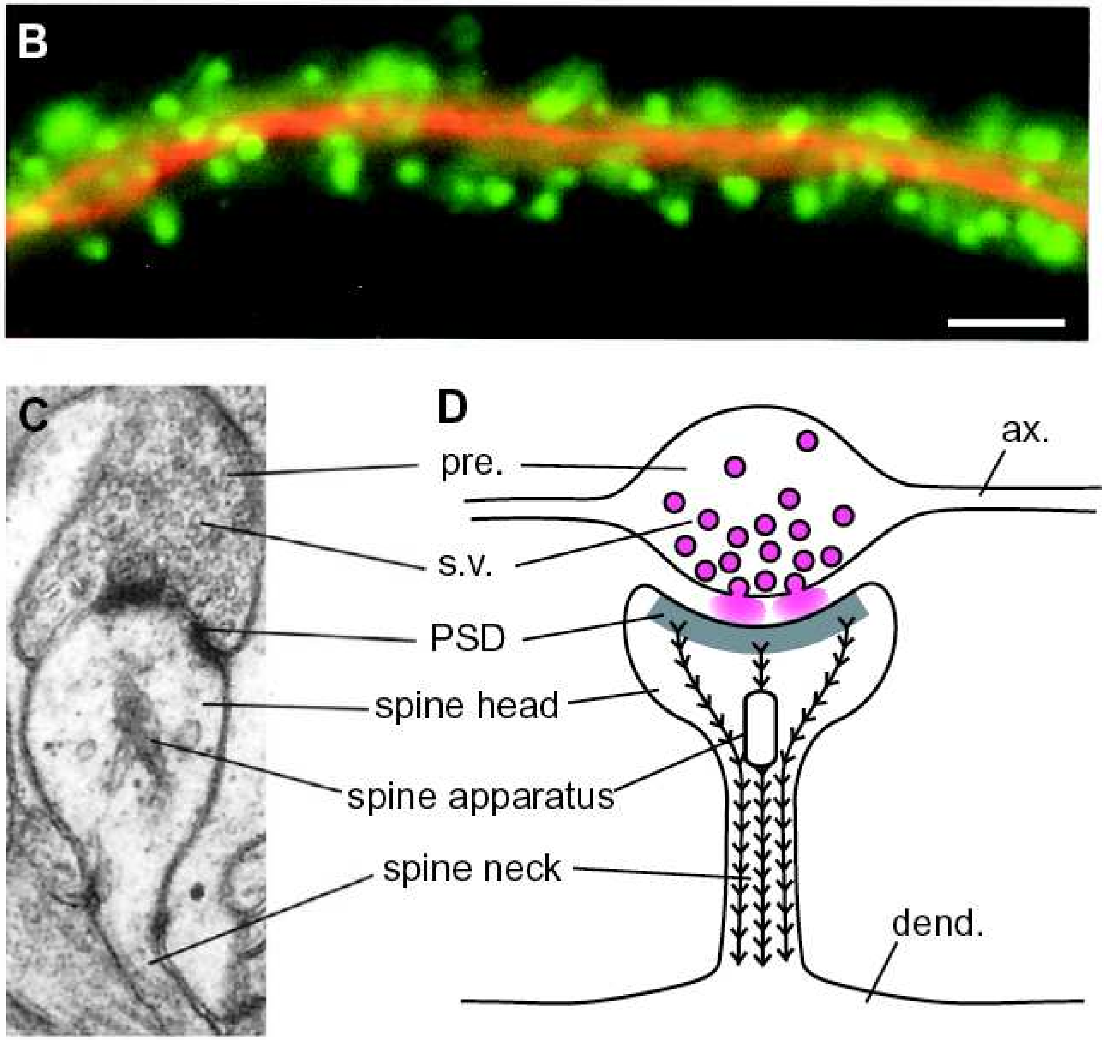
- Responsible for majority of fast synaptic transmission
- Heteromeric tetramer of subunits GluR1-GluR4
- Complexes with synaptic proteins $\longrightarrow$ trafficking

Long-range receptor trafficking



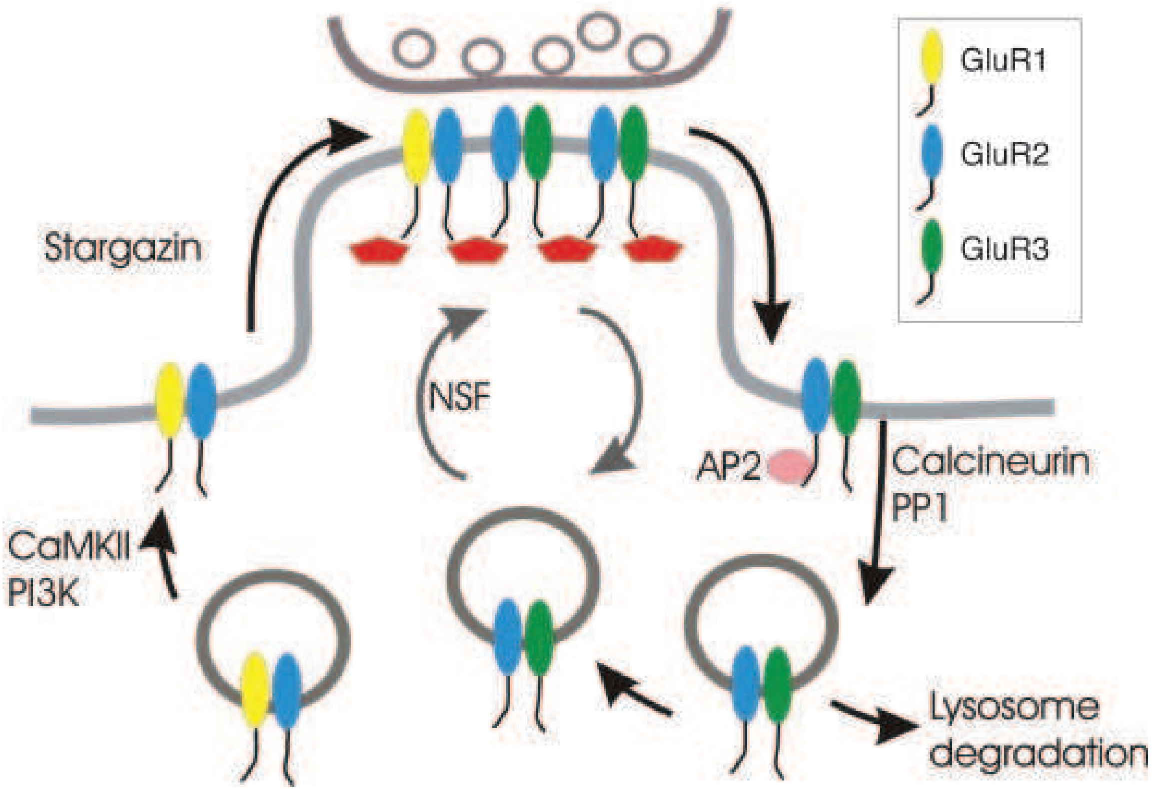
- Receptors trafficked in vesicles along microtubules
- Receptors diffuse from soma to synapse?

Dendritic spines



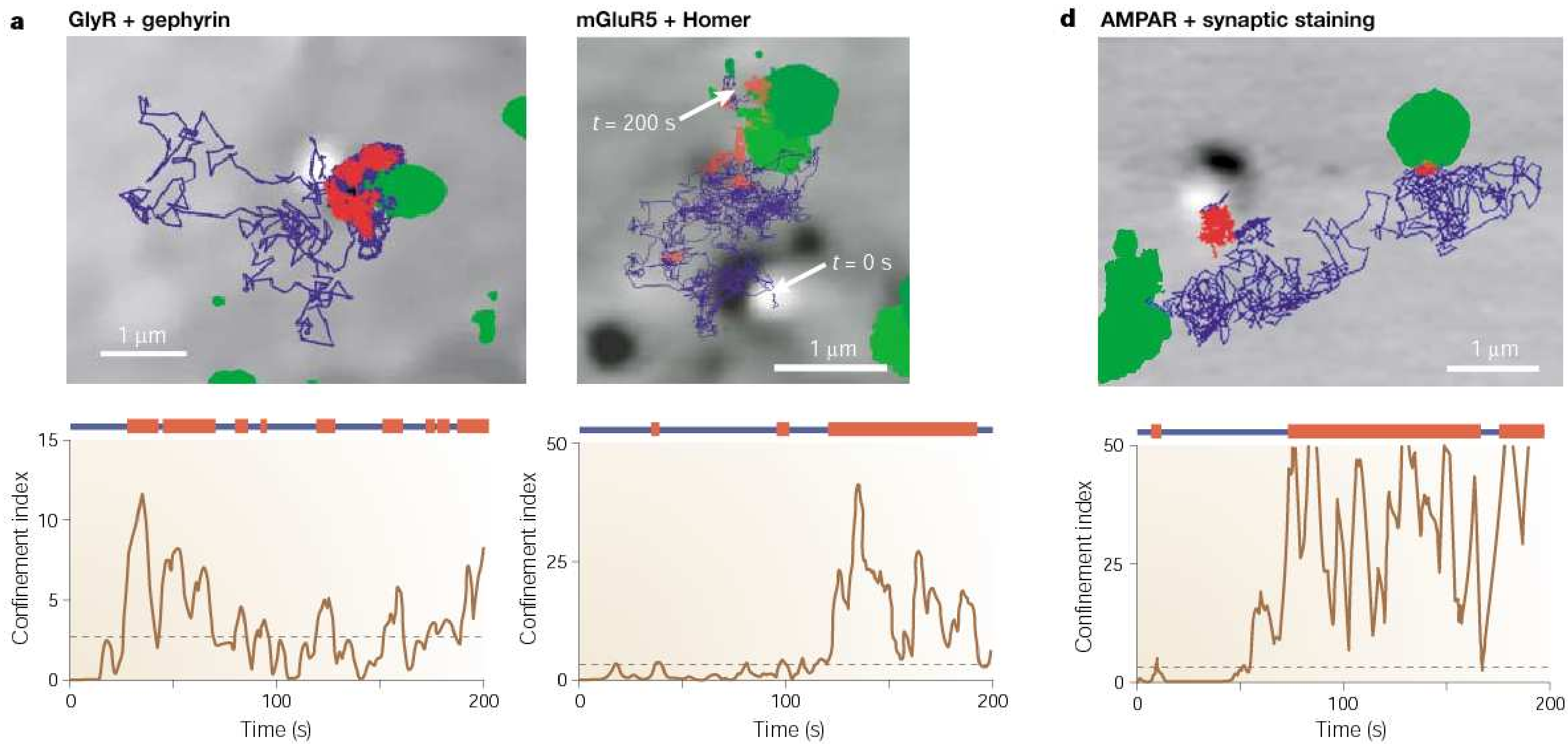
Excitatory synapses located on surface of mushroom-like protrusions of the dendritic membrane called spines

Local receptor trafficking



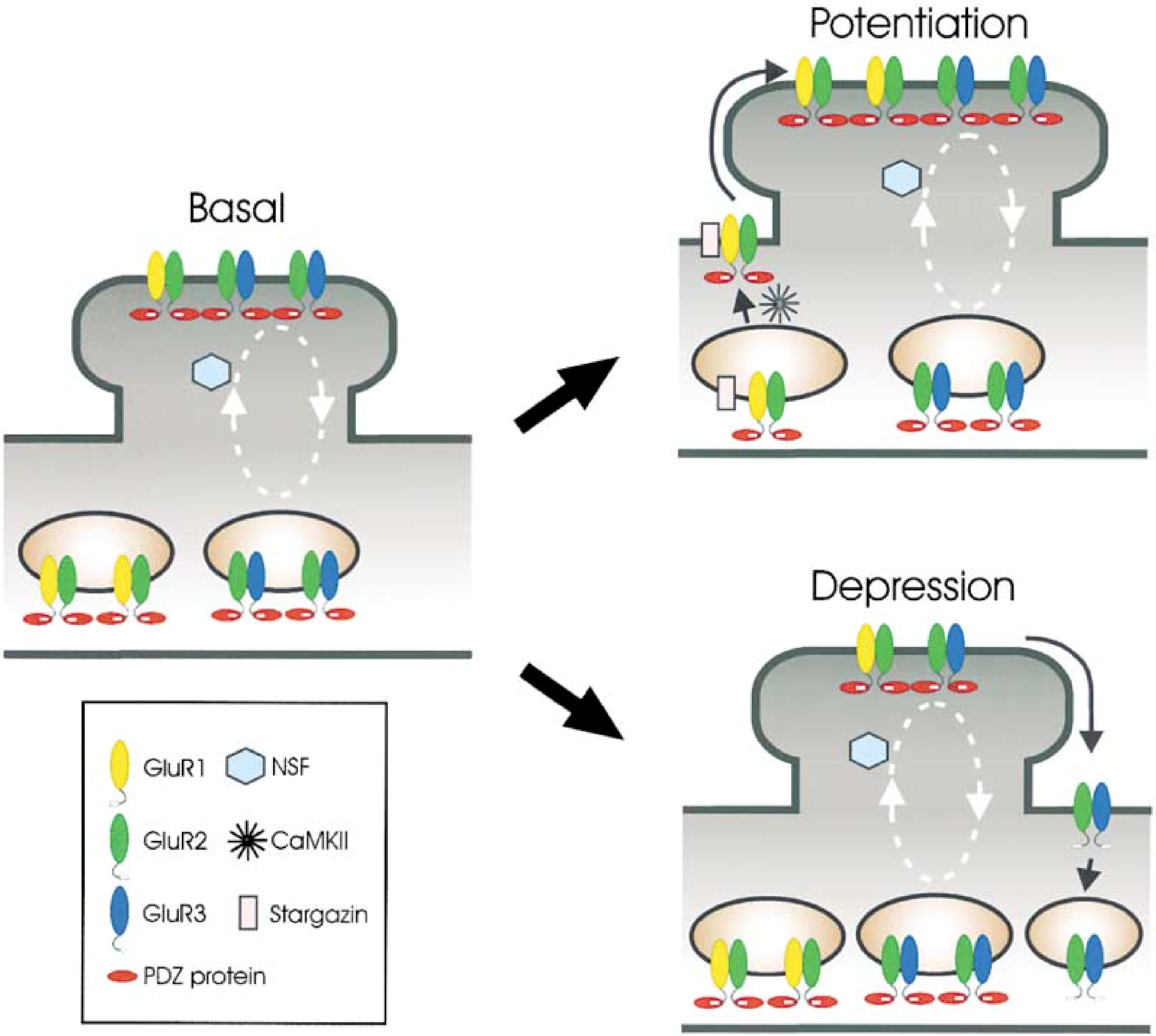
- Receptors constitutively recycled at synapse
- Crosslink to scaffolding proteins in PSD
- AMPA receptors laterally diffuse in synaptic membrane

Single-particle tracking

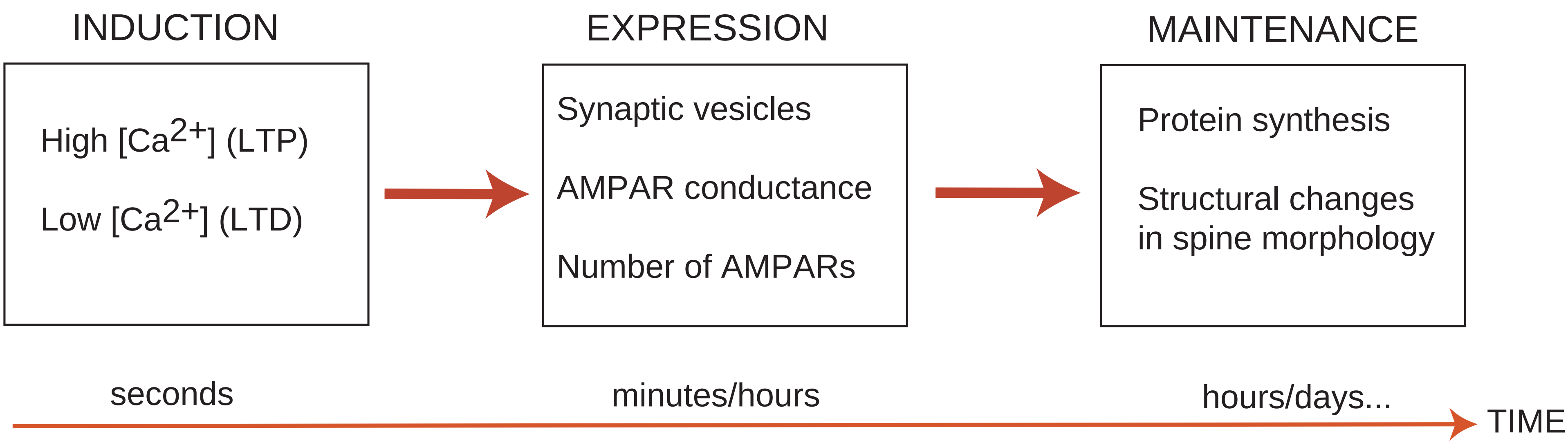


- Receptors diffuse freely away from synapses
- Confined diffusion in synapses

Expression of LTP/LTD



Separation of time-scales



- Ca^{2+} signal activates kinase/phosphotase pathways
- Phosphorylation/dephosphorylation of AMPA receptor complexes
- Regulation of AMPA receptor trafficking

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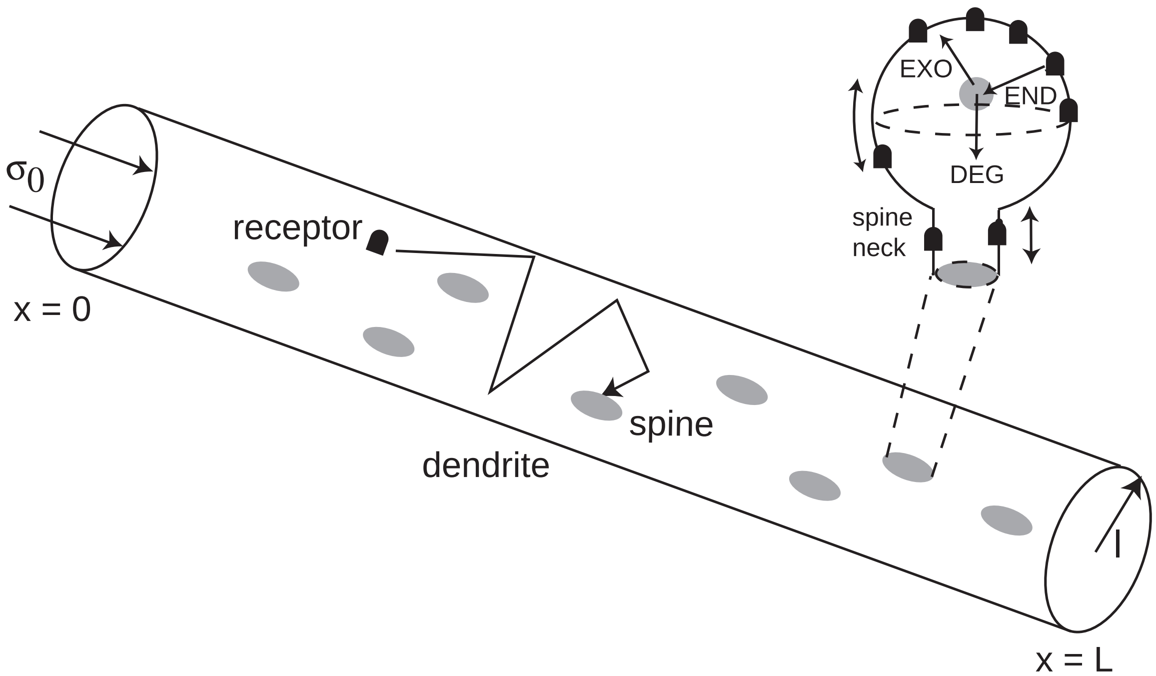
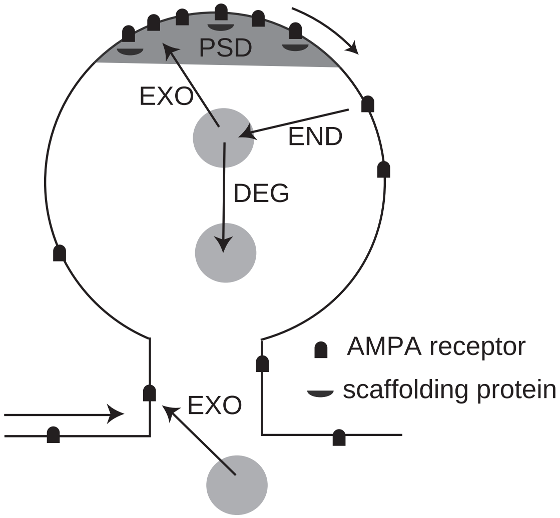
Dendritic cable model



- Treat dendritic cable as cylinder of length L, radius l
- Intersection of jth spine with dendrite as disc of radius $\epsilon\rho$ centered at $\mathbf{r}_j$, $j = 1, \ldots, N$.
- Separation of length-scales: $\varepsilon\rho \ll l \ll L$.

Single-spine model without PSD



$$\frac{dR_j}{dt} = \frac{\omega_j}{A_j}[U_j - R_j] - \frac{k_j}{A_j}R_j + \frac{\sigma_j^{rec} S_j}{A_j}.$$

$$\frac{dS_j}{dt} = -\sigma_j^{rec} S_j - \sigma_j^{deg} S_j + k_j R_j + \delta_j.$$

- R_j = free receptor concentration in jth spine
- S_j = # intracellular receptors
- $U_j = \frac{1}{2\pi\varepsilon\rho}\int_{\partial\Omega_j} U(\mathbf{r},t)d\mathbf{r}$ = mean value of U on $\partial\Omega_j$
- A_j, ω_j = surface area, hopping rate of jth spine
- k_j, σ_j^{rec} = rates of endocytosis, exocytosis at jth spine
- δ_j, σ_j^{deg} = rates of production, degradation at jth spine

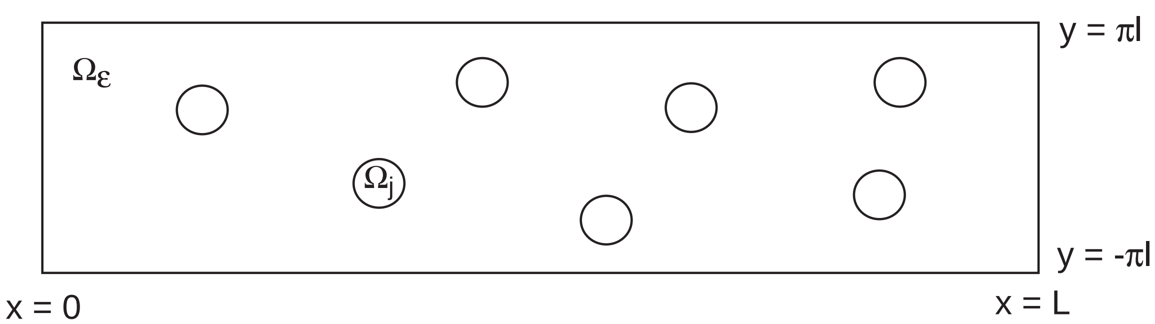
Diffusion equation

$$\partial_t U = D\nabla^2 U, \quad (\mathbf{r}, t) \in \Omega_\varepsilon \times [0, \infty)$$

- Ignore curvature
- Homogeneous surface diffusivity D
- $U(\mathbf{r}, t)$ = dendritic receptor concentration at $(\mathbf{r}, t)$
- $\Omega_\varepsilon = \Omega_0 \setminus \bigcup_{j=1}^{N} \Omega_j$, where

$$\Omega_0 = \{(x, y) : 0 < x < L, y < |\pi l|\}$$

$$\Omega_j = \{\mathbf{r} : |\mathbf{r} - \mathbf{r}_j| \leq \varepsilon\rho\}$$



Boundary conditions

- Periodic bcs at $y = \pm\pi l$:

$$U(x, \pi l, t) = U(x, -\pi l, t), \quad \partial_y U(x, \pi l, t) = \partial_y U(x, -\pi l, t)$$

- Neumann bcs at $x = 0, L$:

$$\partial_x U(0, y, t) = -\frac{\sigma_0}{2\pi l D}, \quad \partial_x U(L, y, t) = 0$$

σ_0 = # receptors per unit time entering membrane from soma

Boundary conditions

Generalized Neumann bcs at $\partial\Omega_j$:

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

- $\partial_n U$ = outward normal derivative to Ω_ε
- ω_j = effective hopping rate
- R_j = receptor concentration on surface of jth spine

Assume R_j spatially uniform since diffusion is fast

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Steady-state analysis

$$R_j = \frac{\omega_j U_j + \lambda_j \delta_j}{\omega_j + k_j(1-\lambda_j)}, \qquad S_j = \frac{k_j \lambda_j R_j}{\sigma_j^{rec}}$$

where

$$\lambda_j = \frac{\sigma_j^{rec}}{\sigma_j^{rec} + \sigma_j^{deg}}$$

To determine U_j, need to solve

$$\nabla^2 U = 0, \qquad \mathbf{r} \in \Omega_\varepsilon$$

with bcs.

Simplification of generalized Neumann bc

Assume $U(\mathbf{r}) = U_j$ on $\partial\Omega_j$, then

$$\varepsilon \partial_n U(\mathbf{r}) = -\frac{\widehat{\omega}_j}{2\pi\rho D}(U_j - \widehat{R}_j), \quad \mathbf{r} \in \partial\Omega_j$$

where

$$\widehat{\omega}_j = \frac{\omega_j k_j (1-\lambda_j)}{\omega_j + k_j(1-\lambda_j)}, \quad \widehat{R}_j = \frac{\sigma_j^{REC}}{k} \frac{\delta_j}{\sigma_j^{DEG}}$$

Integrating diffusion equation over Ω_ε and imposing bcs leads to solvability condition:

$$\sigma_0 = \sum_{j=1}^{N} \widehat{\omega}_j \left[U_j - \widehat{R}_j \right]$$

Method of solution

Solution of steady-state problem (BVP1) in two steps:

1. Solve assuming U_j's are known (BVP2)
2. Substitute solution into N generalize Neumann bcs, yielding N equations
3. Together with solvability condition, have $N+1$ equations in the $N+1$ unknowns U_j and χ

Solution of BVP1 requires matching solutions in inner region

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

and outer region

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

Inner solution

Set $\mathbf{s} = \varepsilon^{-1}(\mathbf{r} - \mathbf{r}_j)$, $V(\mathbf{s};\varepsilon) = U(\mathbf{r}_j + \varepsilon\mathbf{s};\varepsilon)$, then

$$\nabla^2_{\mathbf{s}} V = 0, \quad |\mathbf{s}| > \rho$$
$$V = U_j, \quad |\mathbf{s}| = \rho$$

which has solution

$$V = U_j + \nu A_j(\nu)\log(|\mathbf{s}|/\rho), \quad \nu = -\frac{1}{\log(\varepsilon\rho)}.$$

Thus far-field behavior of inner solution is

$$V \sim U_j + A_j(\nu) + \nu A_j(\nu)\log(|\mathbf{r} - \mathbf{r}_j|)$$

Outer solution

Decompose outer solution $U = \mathcal{U} + u$, where

$$u(\mathbf{r}) = \frac{\sigma}{2L}(x-L)^2, \quad \sigma = \frac{\sigma_0}{2\pi l D}$$

Then $\mathcal{U}$ satisfies inhomogeneous diffusion equation

$$\nabla^2 \mathcal{U} = -\frac{\sigma}{L}, \quad \mathbf{r} \in \Omega_0$$

with homogeneous bcs and asymptotic condition (as $\mathbf{r} \to \mathbf{r}_j$)

$$\mathcal{U} \sim -u(\mathbf{r}_j) + U_j + A_j(\nu) + \nu A_j(\nu) \log |\mathbf{r} - \mathbf{r}_j|.$$

Green's function

Use modified Green's function $G(\mathbf{r}, \mathbf{r}')$ to solve equation

$$\nabla^2 G = \frac{1}{|\Omega_0|} - \delta(\mathbf{r} - \mathbf{r}'), \quad \int_{\Omega_0} G(\mathbf{r}; \mathbf{r}') d\mathbf{r} = 0$$

$$G(x, \pi l; \mathbf{r}') = G(x, -\pi l; \mathbf{r}'), \quad \partial_y G(x, \pi l; \mathbf{r}') = \partial_y G(x, -\pi l; \mathbf{r}')$$

$$\partial_x G(0, y; \mathbf{r}') = 0, \quad \partial_x G(L, y; \mathbf{r}') = 0$$

G has logatrithmic singularity as $\mathbf{r}' \to \mathbf{r}$

$$G(\mathbf{r}; \mathbf{r}') = -\frac{1}{2\pi} \log |\mathbf{r} - \mathbf{r}'| + \mathcal{G}(\mathbf{r}; \mathbf{r}')$$

where $\mathcal{G}$ is regular part of G.

Outer solution

Replace equation and asymptotics for $\mathcal{U}$ by single equation

$$\nabla^2 \mathcal{U} = -\frac{\sigma}{L} + \sum_{j=1}^{N} 2\pi\nu A_j(\nu)\delta(\mathbf{r} - \mathbf{r}_j)$$

hence

$$\mathcal{U}(\mathbf{r}) = -\sum_{j=1}^{N} 2\pi\nu A_j(\nu) G(\mathbf{r}; \mathbf{r}_j) + \chi$$

where χ is a constant determined by solvability condition

$$\frac{\sigma}{L}|\Omega_0| = \sum_{j=1}^{N} 2\pi\nu A_j(\nu)$$

Inner behavior of outer solution

$\mathcal{U}$ has the near-field behavior (as $\mathbf{r} \to \mathbf{r}_j$)

$$\mathcal{U} \sim -2\pi\nu A_j(\nu)\left[-\frac{1}{2\pi}\log|\mathbf{r}-\mathbf{r}_j| + \mathcal{G}(\mathbf{r}_j;\mathbf{r}_j)\right] - \sum_{i\neq j} 2\pi\nu A_i(\nu) G(\mathbf{r}_j;\mathbf{r}_i) + \chi$$

Comparison with asymptotic conditions yields the system:

$$(1 + 2\pi\nu\mathcal{G}_{jj})A_j + \sum_{i\neq j} 2\pi\nu G_{ji} A_i = u_j - U_j + \chi$$

where $u_j = u(\mathbf{r}_j)$, $G_{ji} = G(\mathbf{r}_j;\mathbf{r}_i)$ and $\mathcal{G}_{jj} = \mathcal{G}(\mathbf{r}_j;\mathbf{r}_j)$.

Calculation of boundary concentrations U_j

Substituting inner sol. into generalized Neumann bcs gives

$$2\pi\nu A_j(\nu) = \frac{\widehat{\omega}_j}{D}[U_j - \widehat{R}_j] \equiv V_j$$

Substituting into system of equations yields

$$V_j = 2\pi\nu \sum_{i=1}^{N} M_{ji}(u_i - \widehat{R}_i + \chi)$$

where $M = (I + 2\pi\nu B)^{-1}$ and

$$B_{jj} = \frac{D}{\widehat{\omega}_j} + \mathcal{G}_{jj}, \quad B_{ji} = G_{ji},\ j \neq i$$

Calculation of χ

Substituting V_j into solvability condition yields

$$\chi = \frac{\frac{\sigma_0}{2\pi\nu D} - \sum_{i,j=1}^{N} M_{ji}(u_i - \widehat{R}_i)}{\sum_{i,j=1}^{N} M_{ji}}$$

Outer solution is

$$U(\mathbf{r}) = u(\mathbf{r}) - \sum_{j=1}^{N} \frac{\widehat{\omega}_j}{D}[U_j - \widehat{R}_j]G(\mathbf{r};\mathbf{r}_j) + \chi$$

Evaluation of Green's function

A standard (and long) calculation shows

$$G(\mathbf{r};\mathbf{r}') = -\frac{1}{2\pi}\ln|\mathbf{r}-\mathbf{r}'| + \mathcal{G}(\mathbf{r};\mathbf{r}')$$

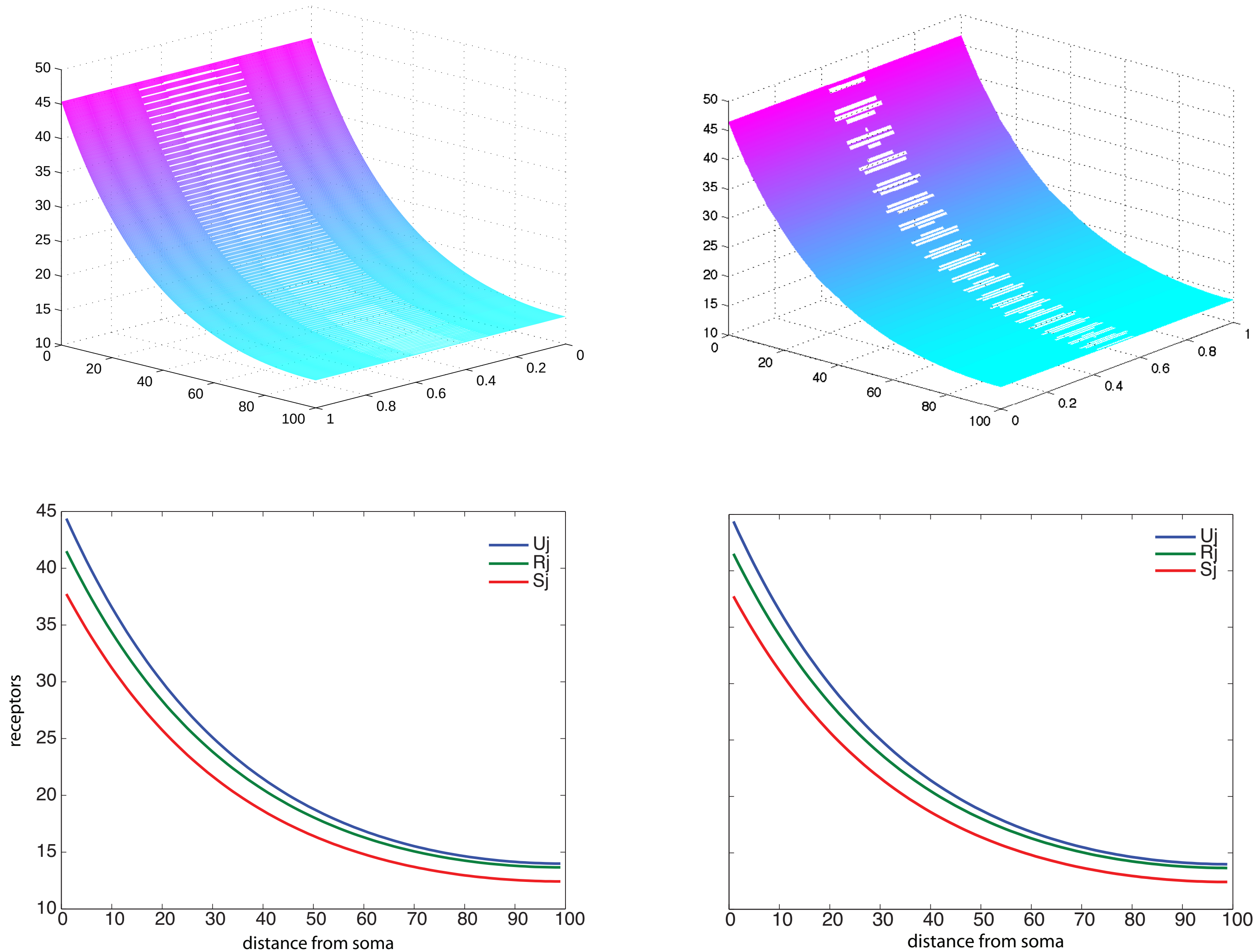
$$\mathcal{G}(\mathbf{r};\mathbf{r}') = \frac{L}{24\pi l}\left[h\left(\frac{x-x'}{L}\right) + h\left(\frac{x+x'}{L}\right)\right]$$
$$-\frac{1}{2\pi}\ln\frac{|1-\mathrm{e}^{r_+/l}||1-\mathrm{e}^{r_-/l}||1-\mathrm{e}^{\rho_+/l}||1-\mathrm{e}^{\rho_-/l}|}{|\mathbf{r}-\mathbf{r}'|} + \mathcal{O}(q)$$

$$h(\theta) = 3\theta^2 - 6|\theta| + 2$$

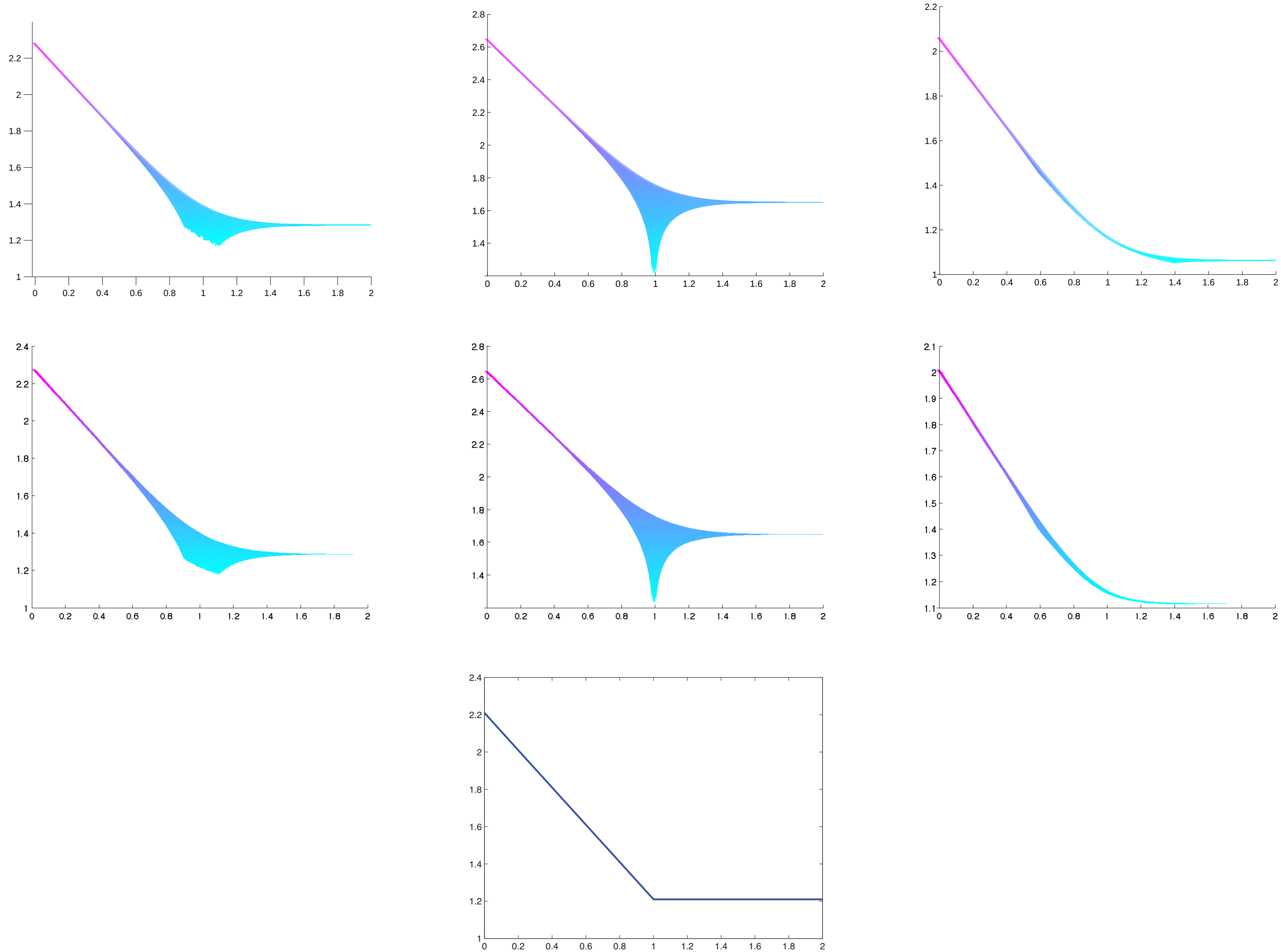
$$r_\pm = -|x \pm x'| + i(y-y'), \quad \rho_\pm = -2L + |x\pm x'| + i(y-y')$$

$$q = \mathrm{e}^{-2L/l}$$

Numerical results



Effect of ϵ



MFPT for single receptor

Can calculate MFPT for receptor to travel axial distance $X < L$ from soma, given started at $\mathbf{r}_0 = (0, y)$ and not degraded:

$$T(X|\mathbf{r}_0) = \frac{X^2}{2D} + \sum_{j=1}^{N_X} \frac{\eta_j}{D} G_X(\mathbf{r}_j; \mathbf{r}_0)$$

where

$$\eta_j = A_j + \frac{k_j}{\sigma_j^{rec}}$$

$$G_X(\mathbf{r}_j; \mathbf{r}_0) = \frac{X - x_j}{2\pi l} + \mathcal{O}(q_{x_j}), \quad q_{x_j} = \mathrm{e}^{-2x_j/l}$$

Effective and anomalous diffusion

Large number of identical spines uniformly distributed with spacing d (i.e., $N_X = X/d \gg 1$ and $x_j = jd$ for all j):

$$T \approx \frac{X^2}{2D_{eff}}, \quad D_{eff} = D\left(1 + \frac{A + k/\sigma^{rec}}{2\pi l d}\right)^{-1}$$

Suppose $x_j = d(\ln(j) + 1)$ so $N_X = \mathrm{e}^{X/d-1}$, then

$$T \approx \frac{X^2}{2D_{eff}(X)}, \quad D_{eff}(X) = D\left(1 + \frac{A + k/\sigma^{rec}}{2\pi l d}\frac{\mathrm{e}^{X/d-1}}{\frac{(X/d)^2}{2}}\right)^{-1}$$

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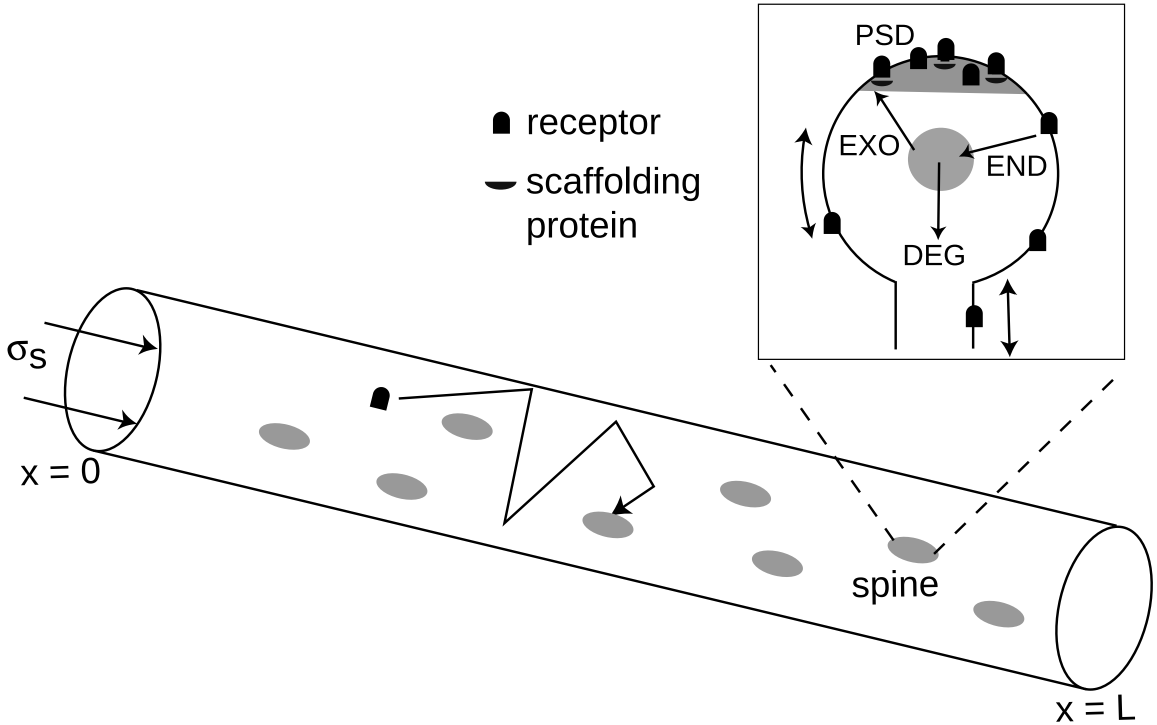
One-dimensional continuum model

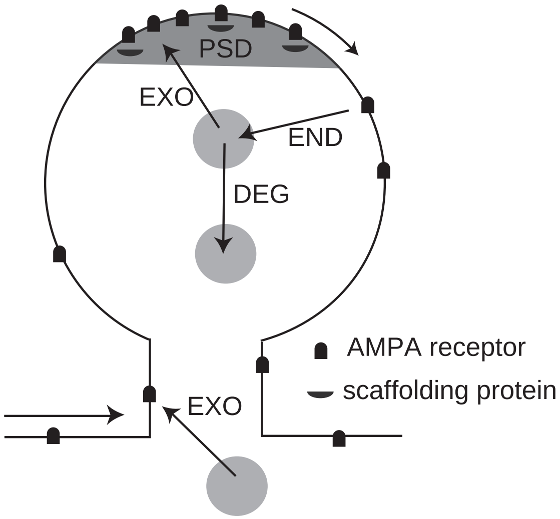
Treat spine distribution as density ρ:

$$\partial_t U = D\partial_x^2 U - \rho\omega(U - R), \quad (x,t) \in (0,L) \times [0,\infty)$$

$$\partial_x U(0,t) = -\frac{\sigma}{D}, \quad \partial_x U(L,t) = 0$$



Single-spine model with PSD



$$\frac{dR}{dt} = \frac{\omega}{A}(U - R) - \frac{k}{A}R - \frac{h}{A}(R - P)$$

$$\frac{dP}{dt} = \frac{h}{a}(R - P) - \alpha(Z - Q)P + \beta Q + \frac{\sigma^{rec} S}{a}$$

$$\frac{dQ}{dt} = \alpha(Z - Q)P - \beta Q$$

$$\frac{dS}{dt} = -\sigma^{rec} S - \sigma^{deg} S + kR + \delta$$

- P, Q = free, bound receptor concentration in PSD
- Z = concentration of scaffolding proteins
- α, β = binding, unbinding rates
- a = surface area of PSD

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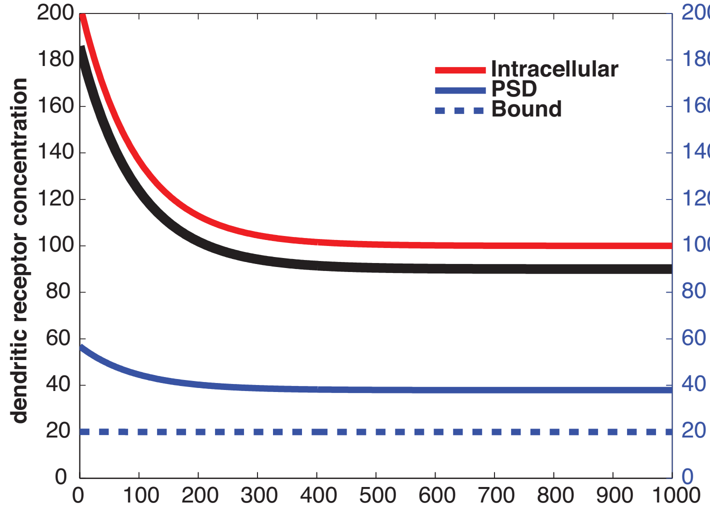
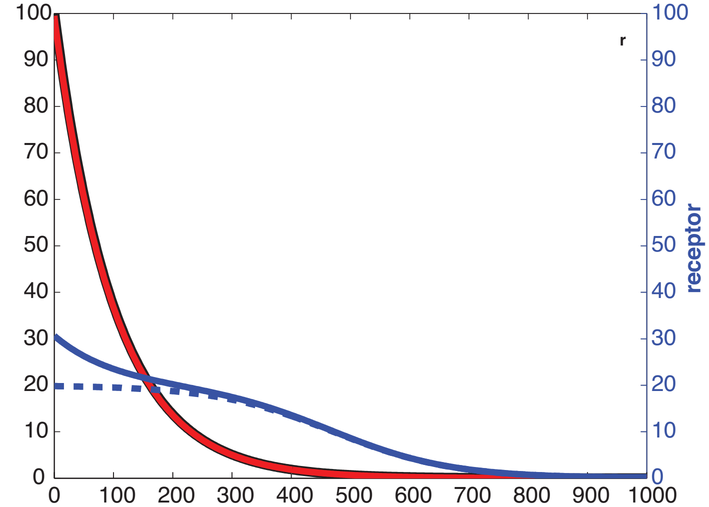
Delivery of synaptic receptors

Fast recycling, production



Slow recycling, no production



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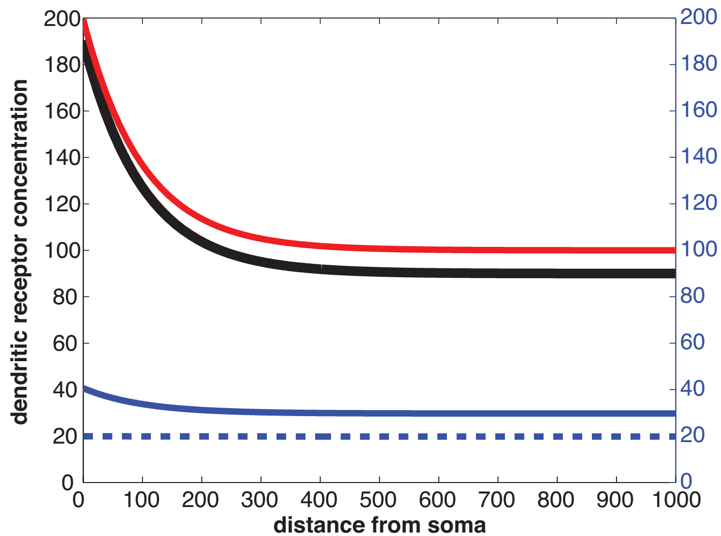

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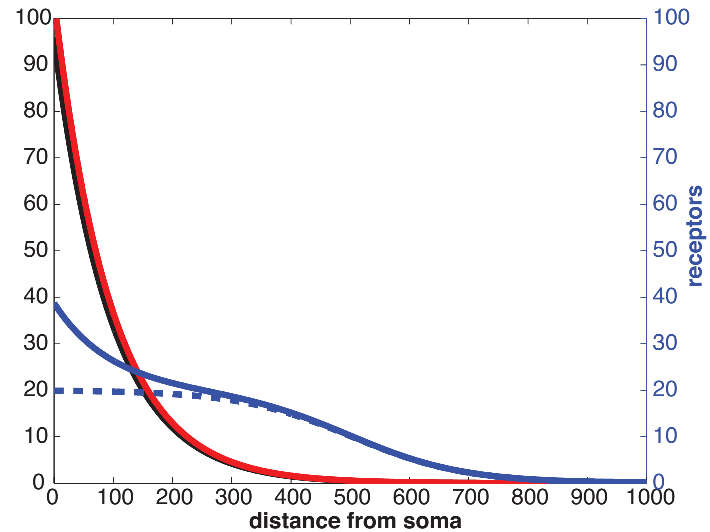
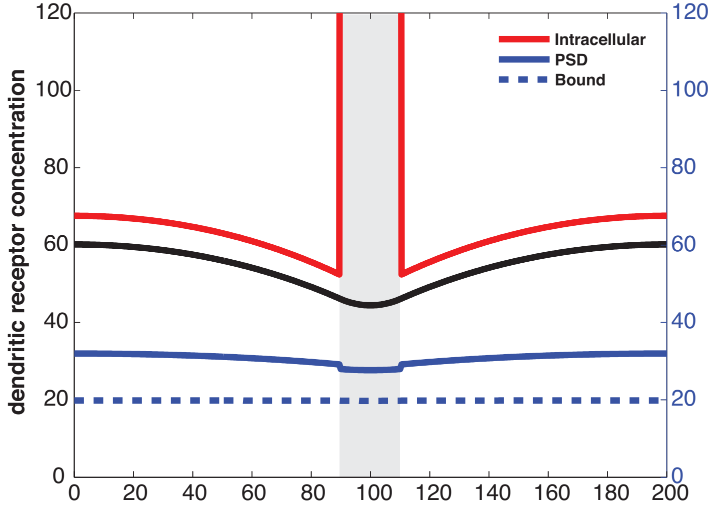
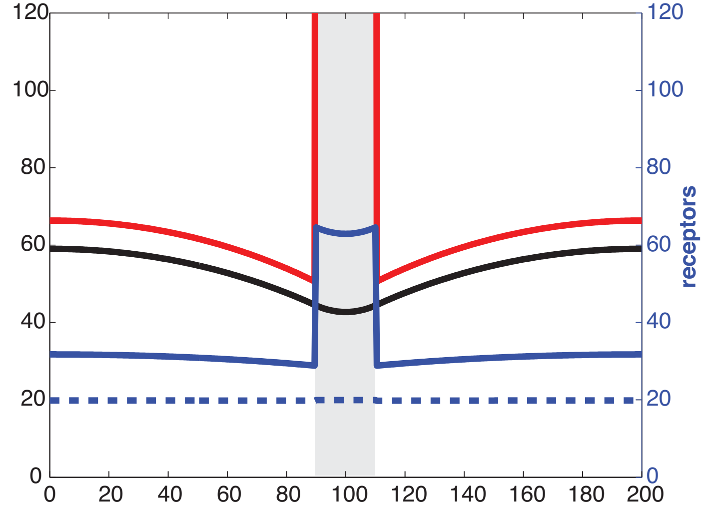


Heterosynaptic effect of constit. recycling

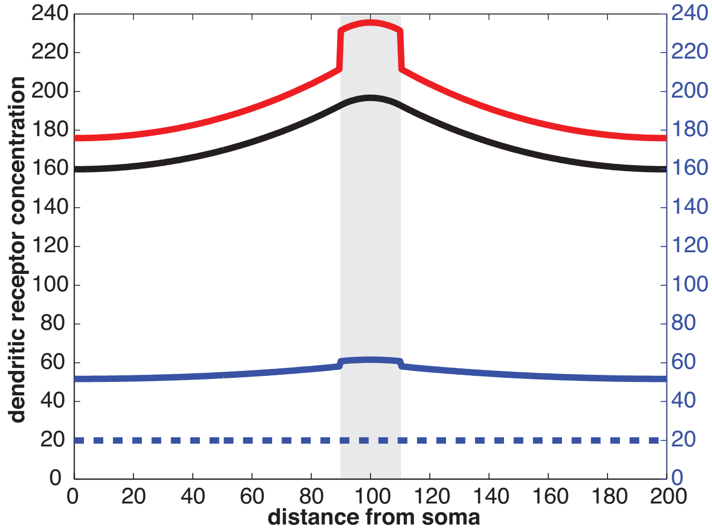
reduced σ^{rec} in gray



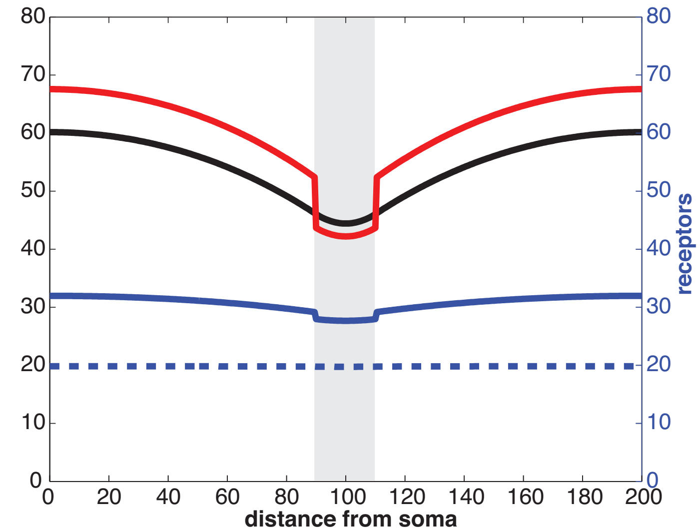
increased k in gray



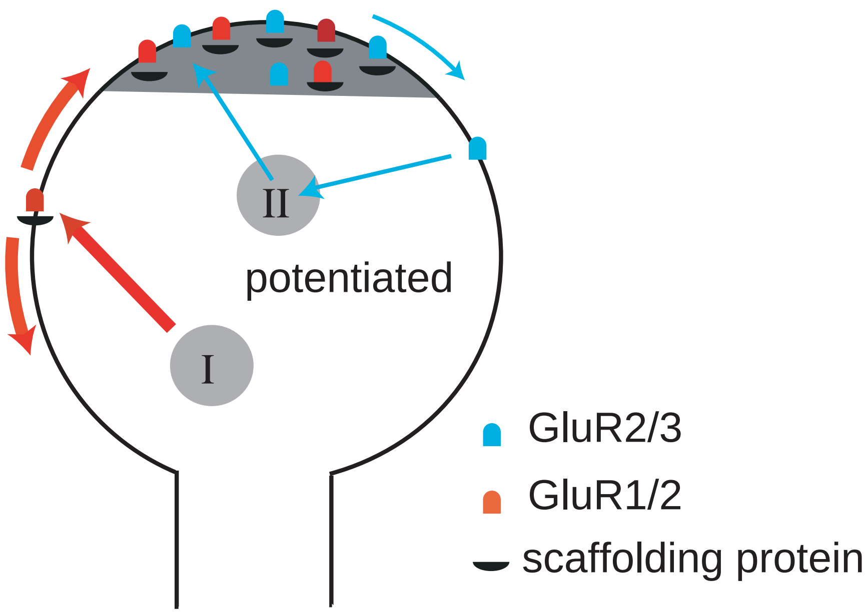
increased δ in gray

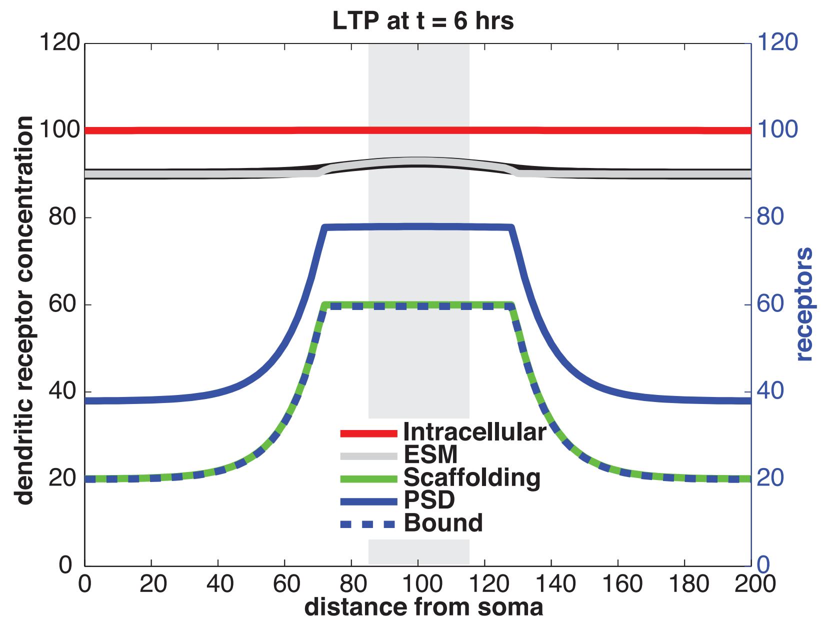


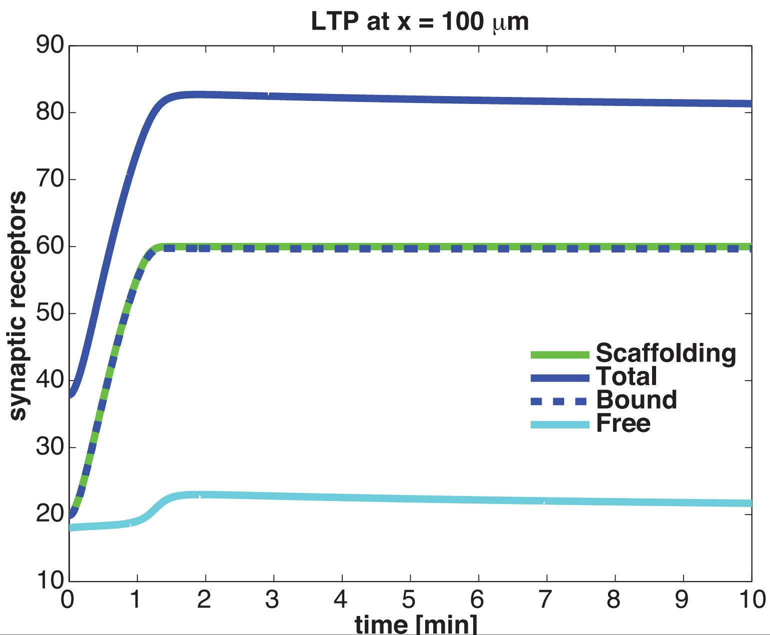
increased σ^{deg} in gray

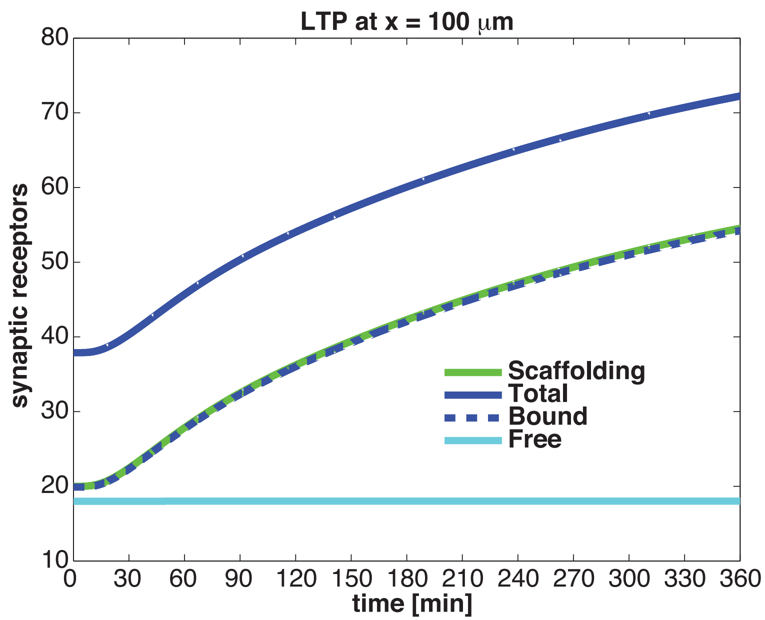


Heterosynaptic effect of LTP

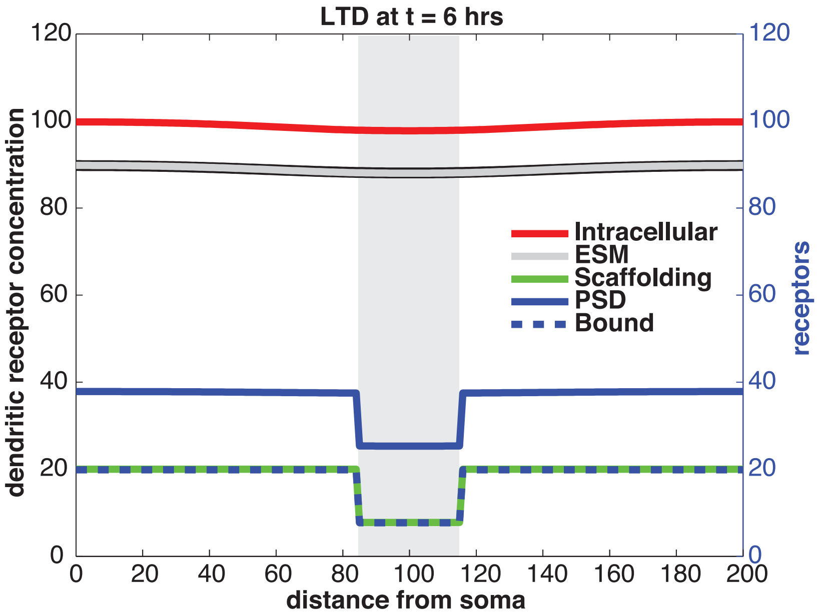


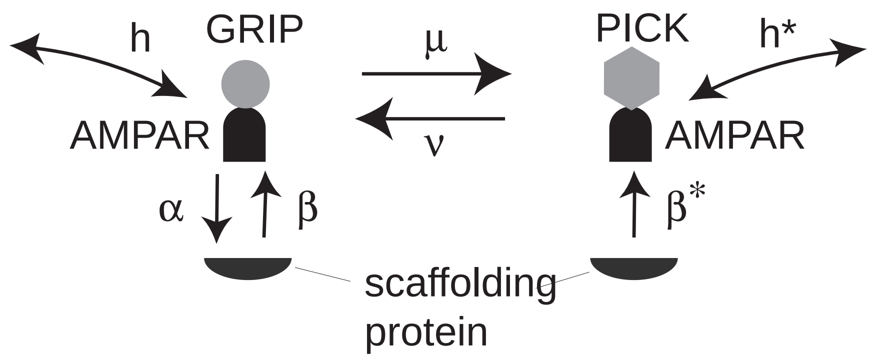


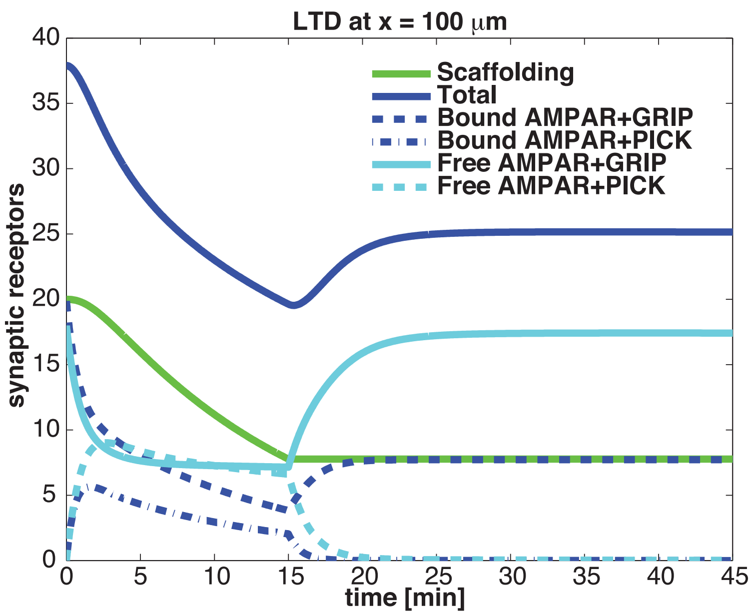


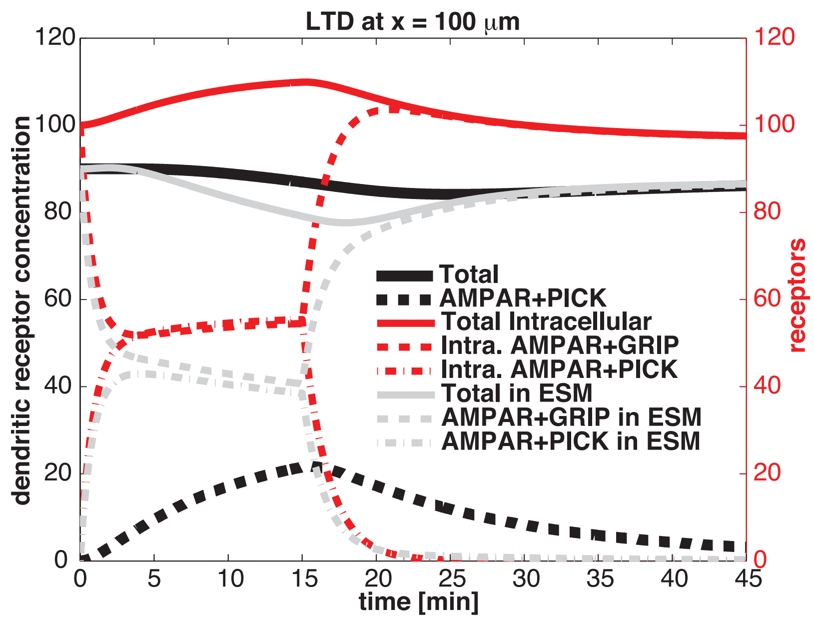


Heterosynaptic effect of LTD









Conclusions

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2. Somatic synthesis + lateral diffusion are not sufficient to supply distal synapses with receptors
3. Local changes to constitutive recycling produce non-local changes in synaptic receptor numbers
4. Lateral diffusion of AMPA receptors not responsible for heterosynaptic LTP/LTD