Biophysical models of AMPA receptor trafficking

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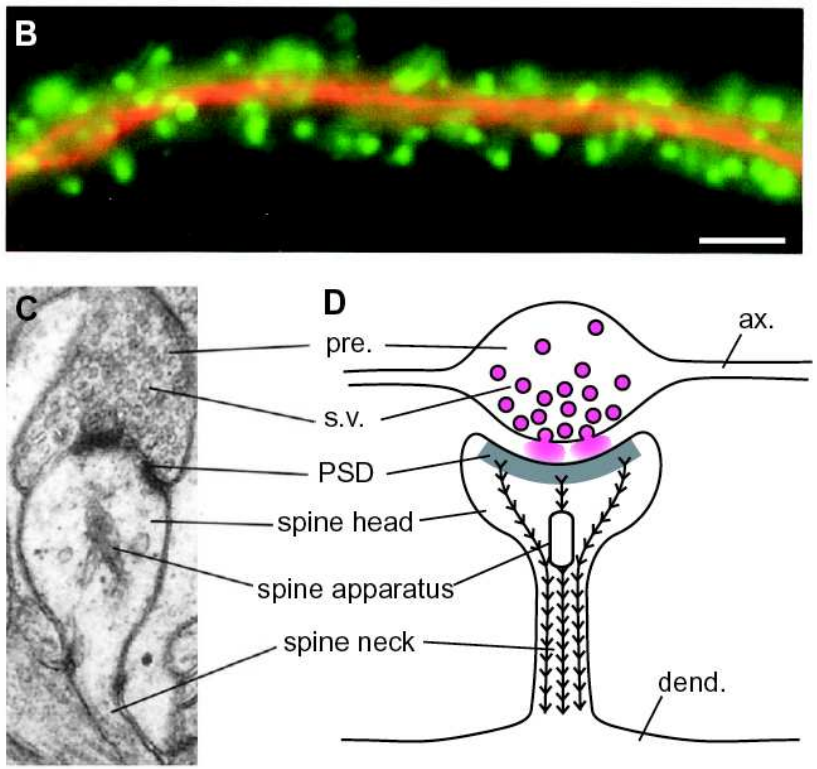
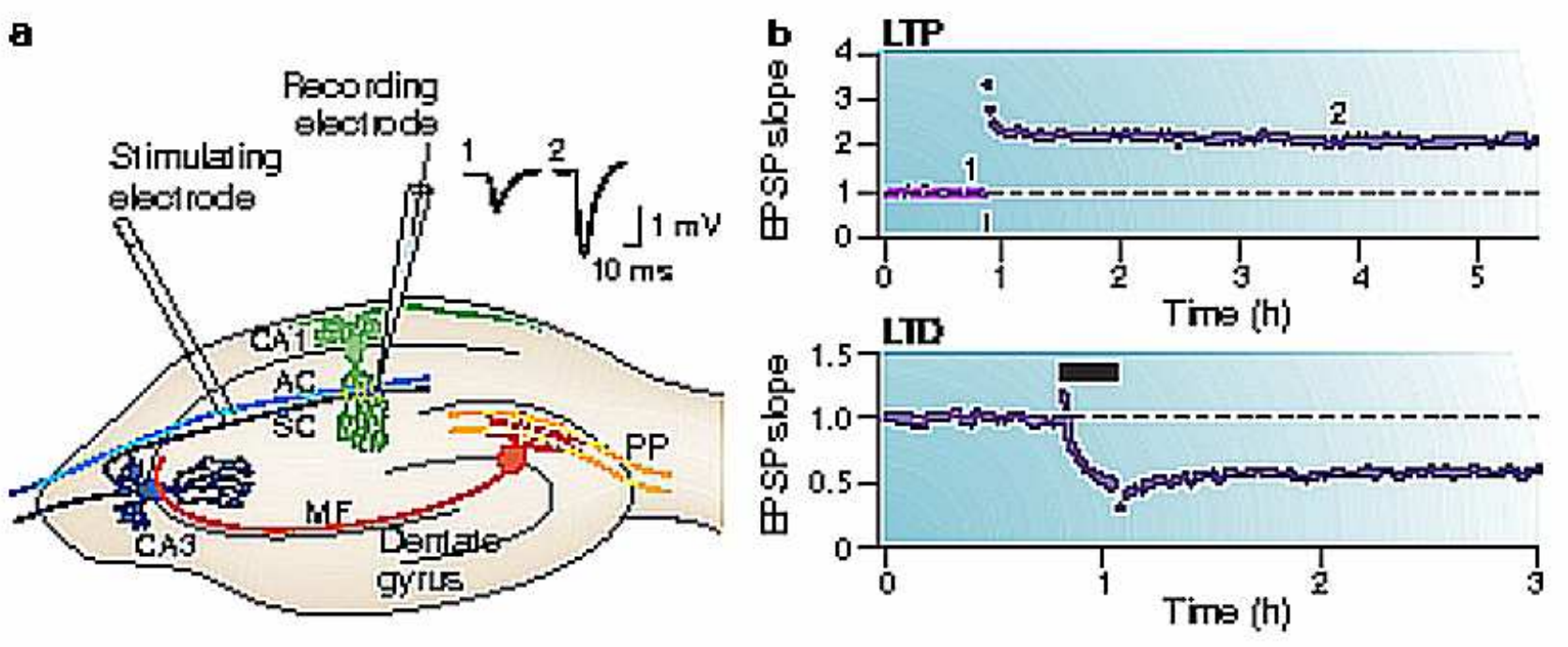
Excitatory synapses and dendritic spines



Matus, *Science* (2000)

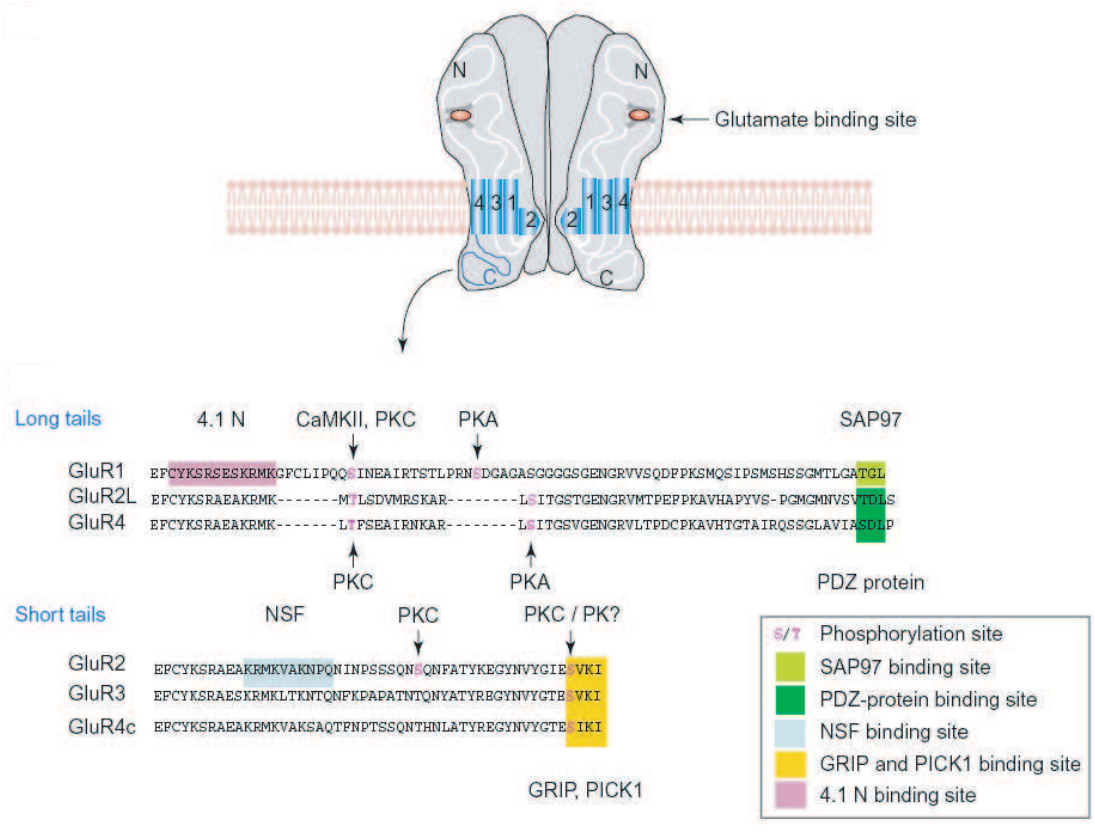
- Most excitatory synapses of CNS occur in protrusions of dendrite called spines

Synaptic plasticity



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

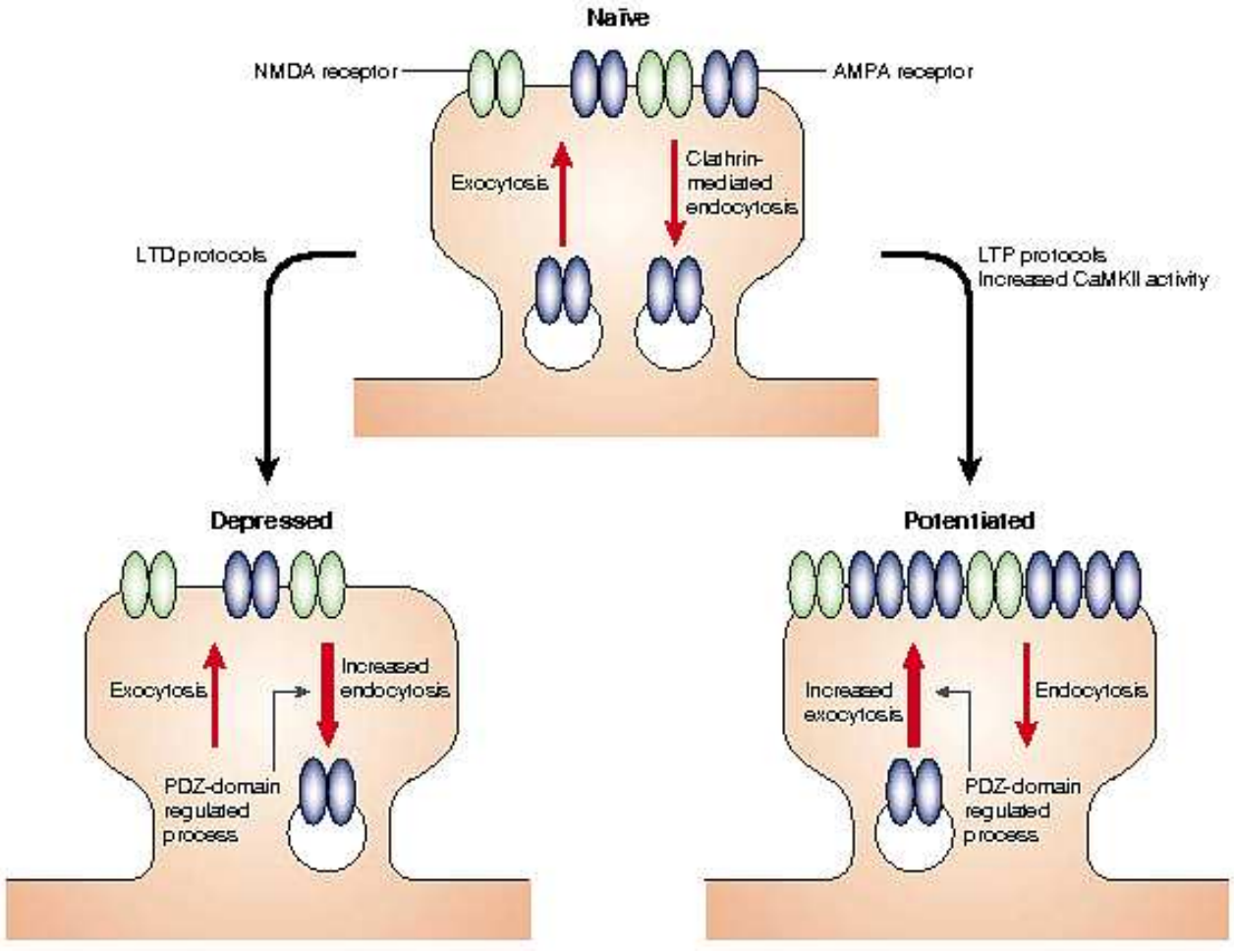
AMPA receptors



Huganir & Song, *Nat. Rev. Neurosci.* (2001)

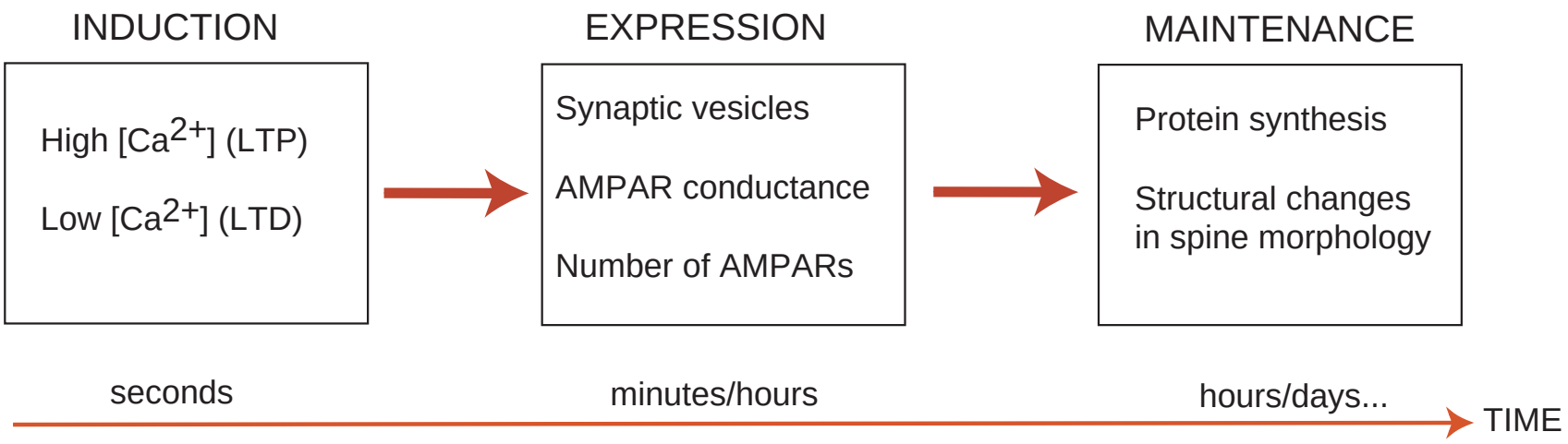
- Fast synaptic transmission
- Complexes with other proteins $\longrightarrow$ trafficking

LTP/LTD expression via AMPAR trafficking

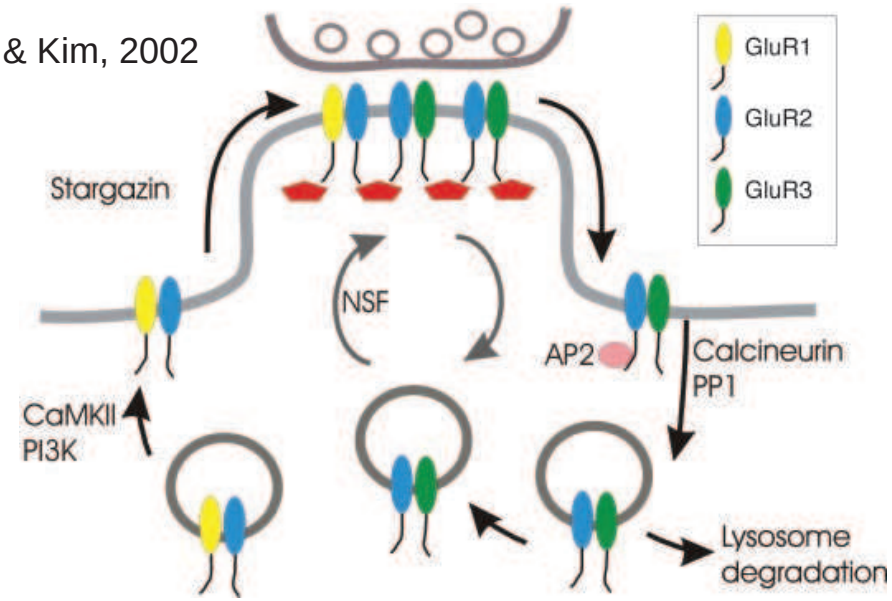


Scannevin & Huganir, *Nat. Rev. Neurosci.* (2000)

Time-scales of synaptic plasticity



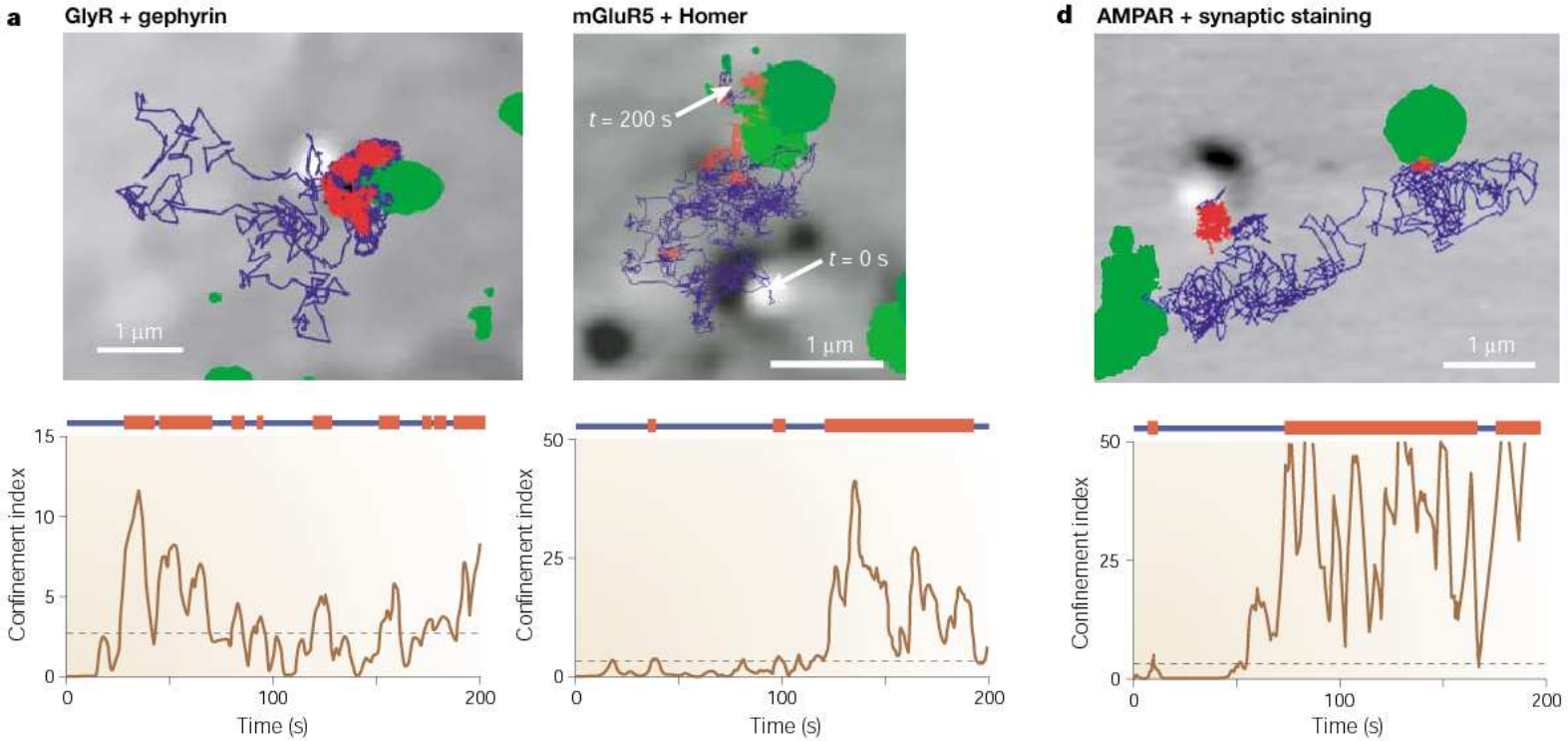
AMPA receptor trafficking at spines



Surface AMPARs

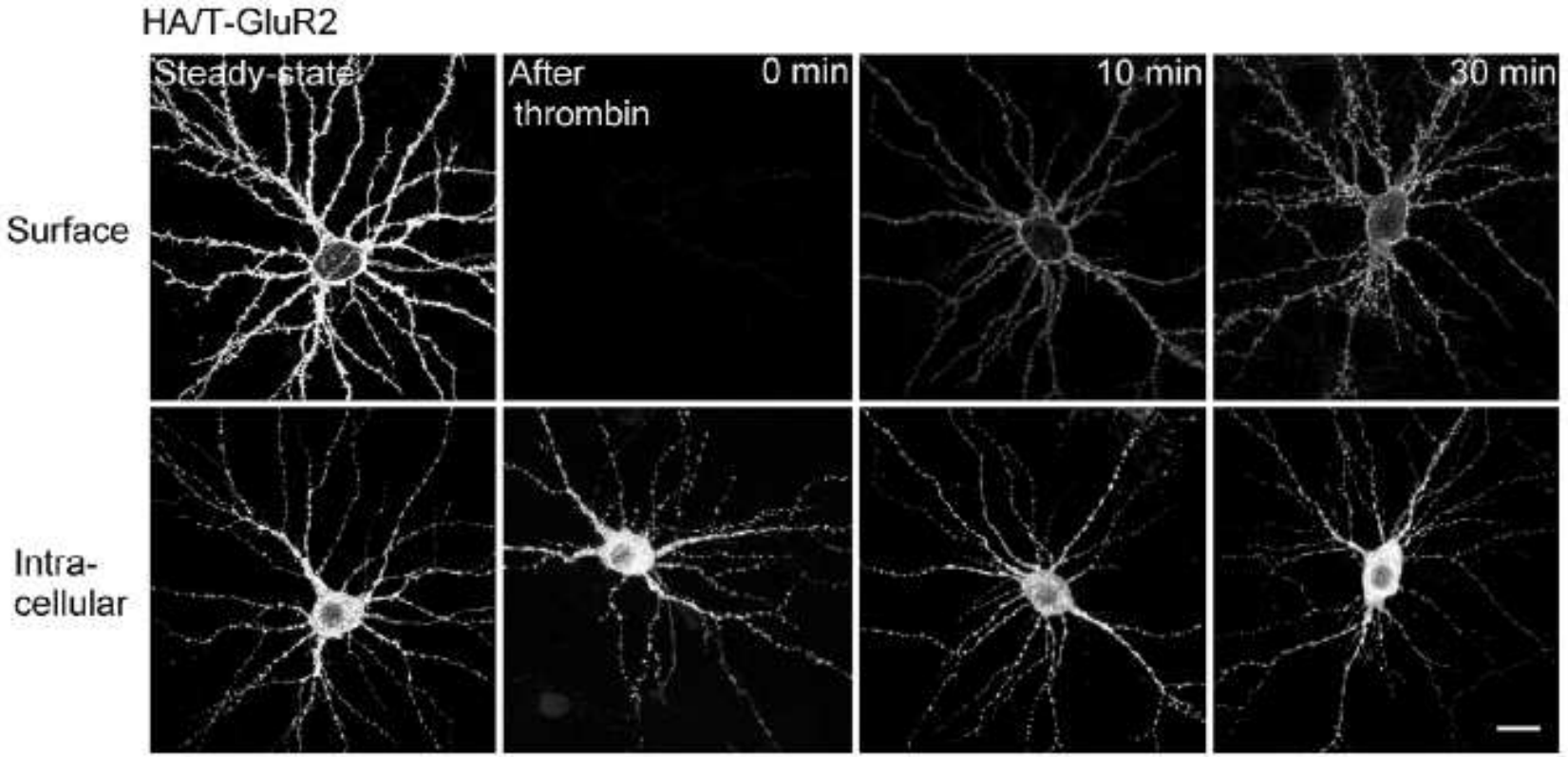
- diffuse laterally within membrane
- constitutively recycle with intracellular stores
- crosslink to scaffolding proteins in PSD

AMPAR diffusion



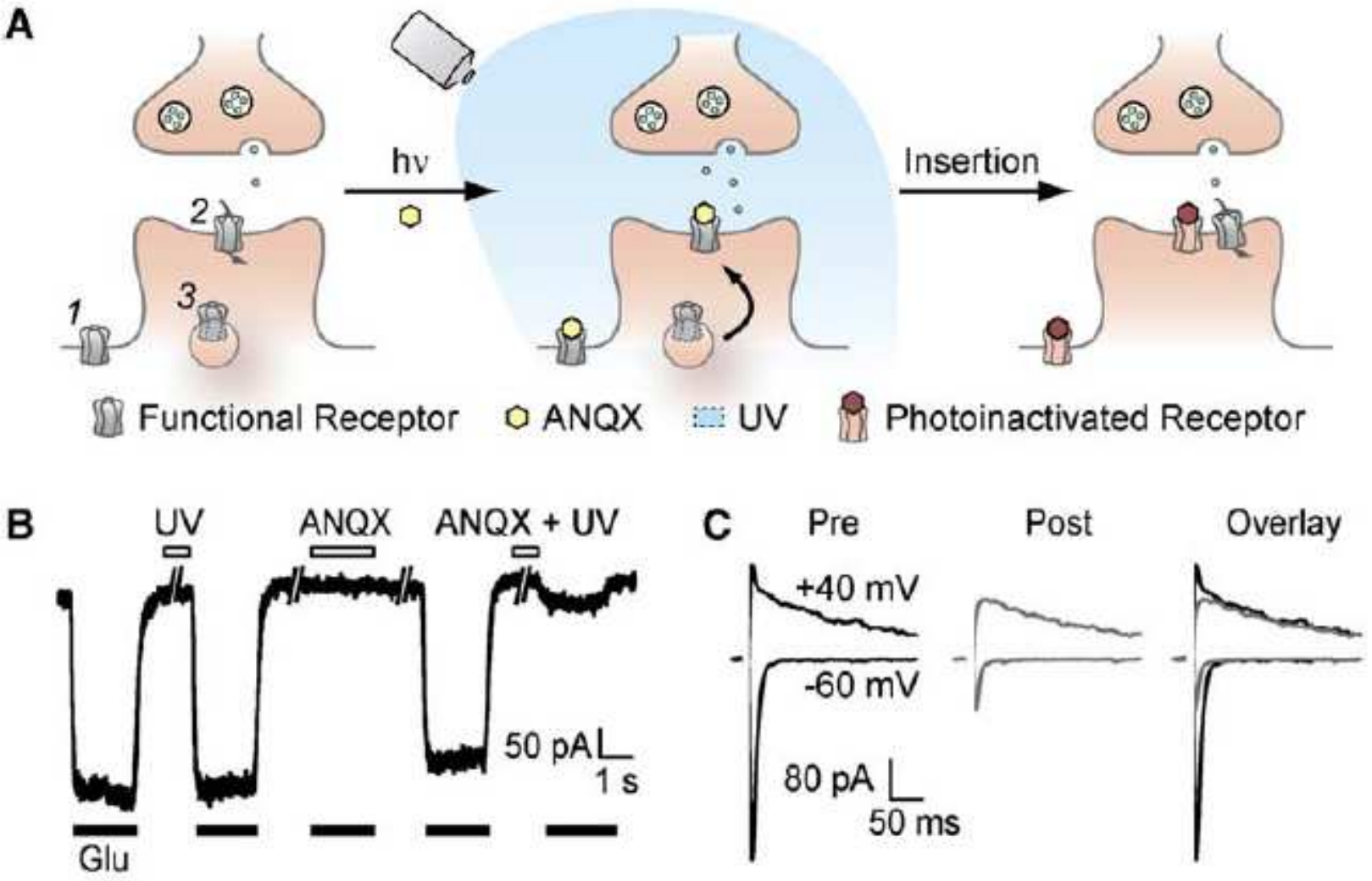
Triller & Choquet, *Nat. Rev. Neurosci.* (2003)

AMPAR recycling via thrombin cleavage



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

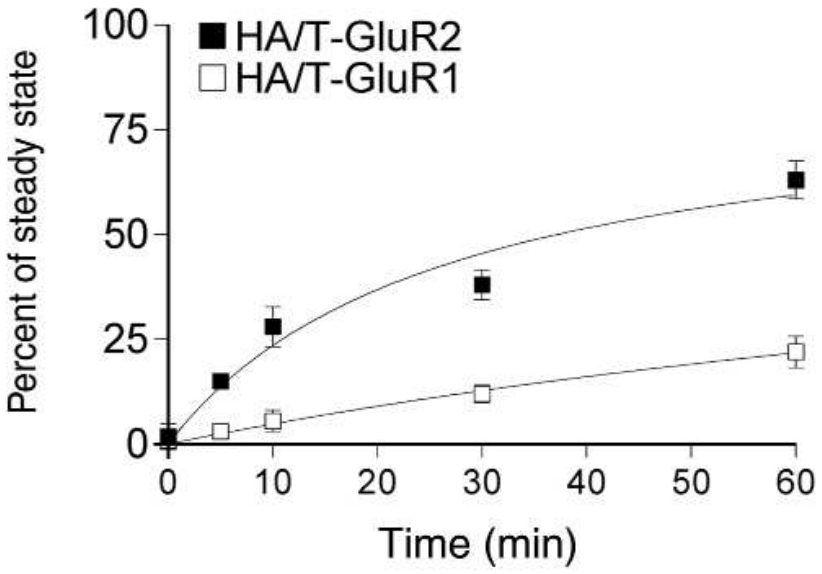
AMPAR recycling via photoinactivation



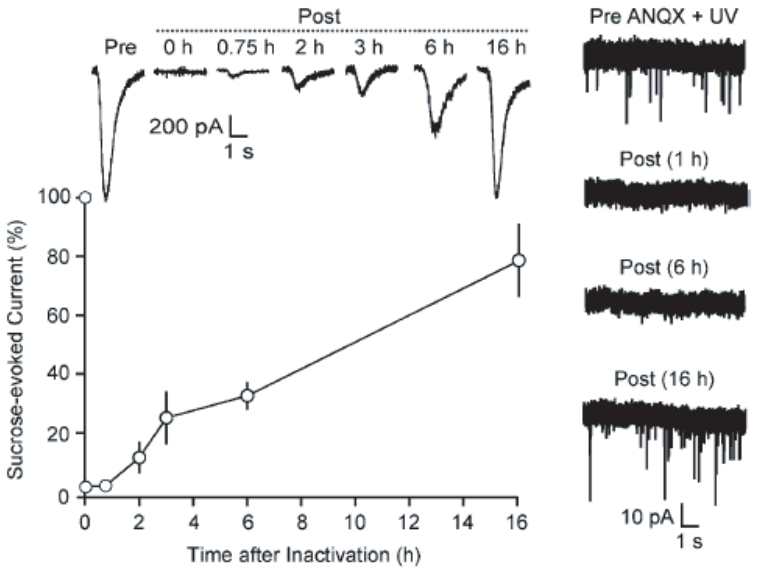
Adesnik et al., *Neuron* (2005)

Fast or slow recycling?

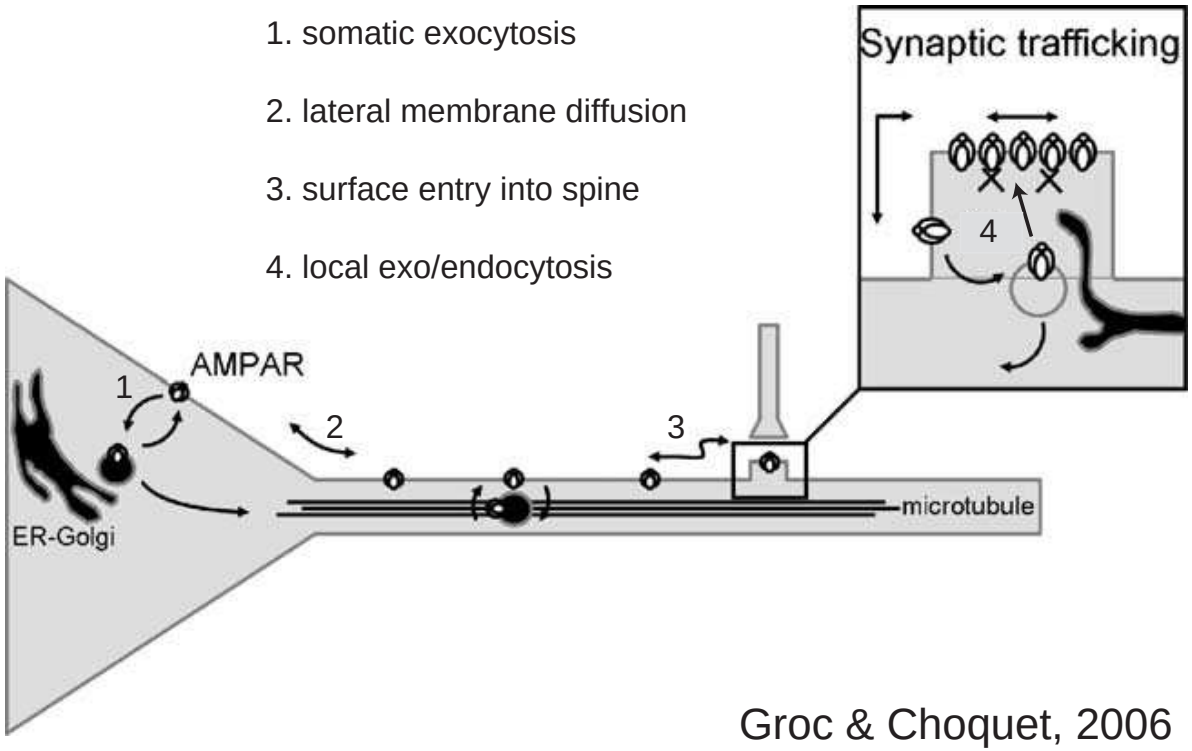
Passafaro et al., 2001



Adesnik et al., 2005



Long-range AMPAR trafficking



Groc & Choquet, 2006

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

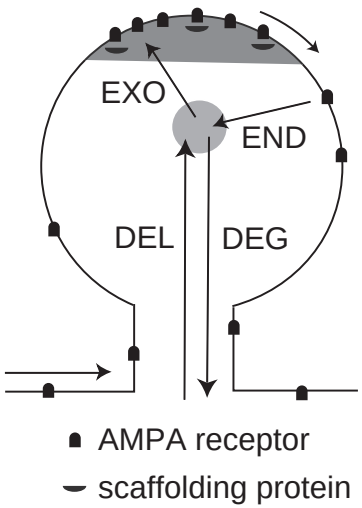
Model of single-spine AMPAR trafficking

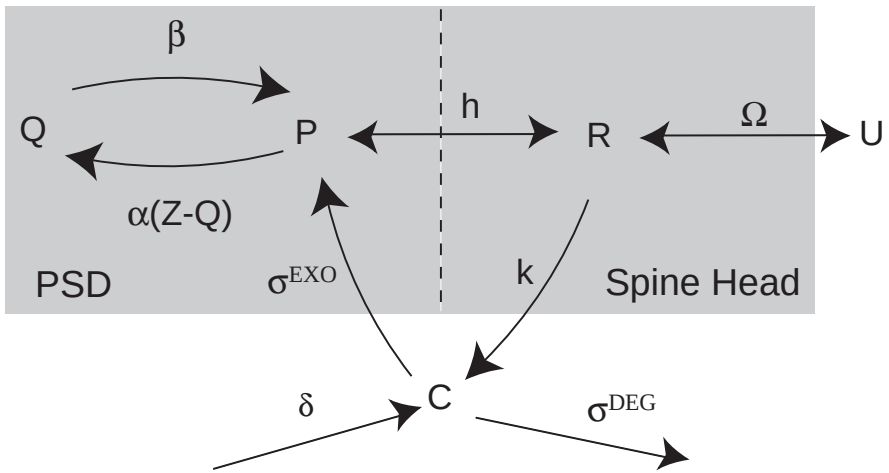
Spine head: $$\frac{dR}{dt} = \frac{1}{A}\left(\Omega[U-R] - kR - h[R-P]\right)$$

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

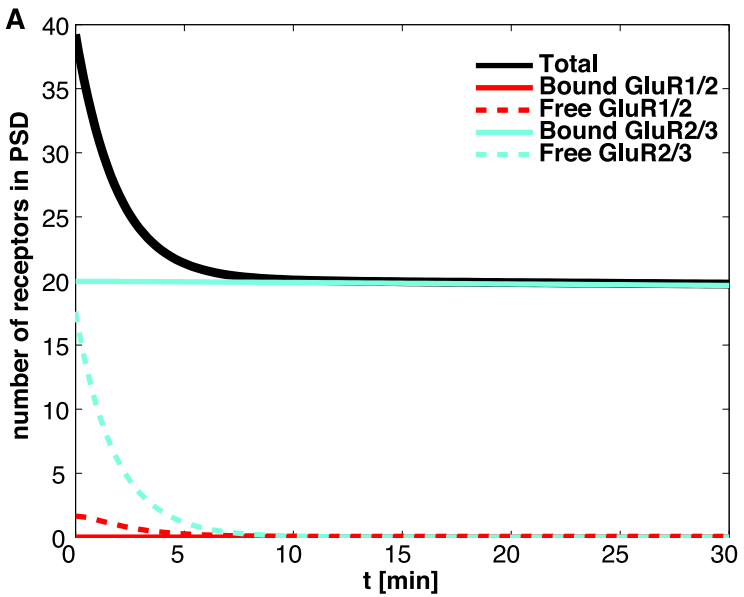
PSD bound: $$\frac{dQ}{dt} = \alpha[Z-Q]P - \beta Q$$

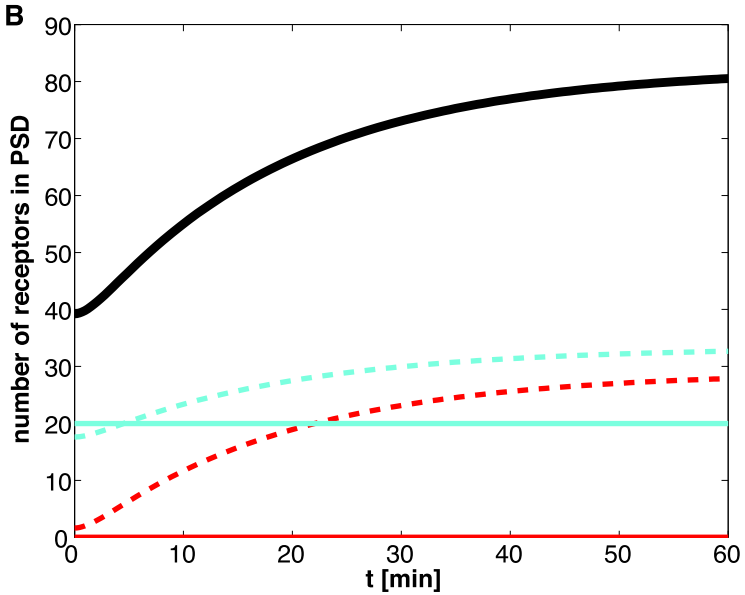
Intracellular: $$\frac{dC}{dt} = -\sigma^{\mathrm{EXO}} C - \sigma^{\mathrm{DEG}} C + kR + \delta,$$

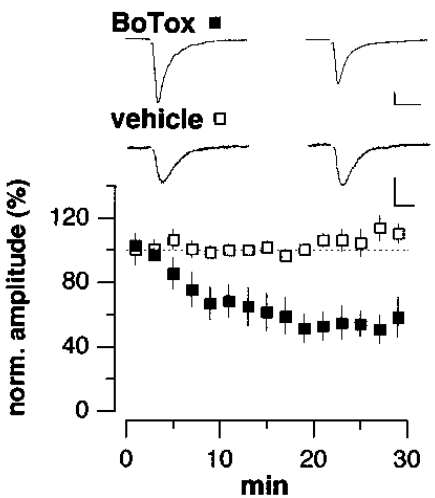


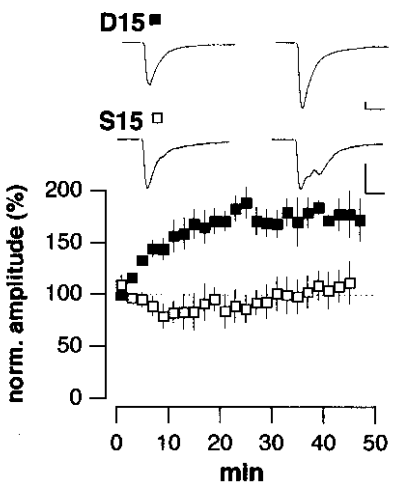


Block exo/endocytosis



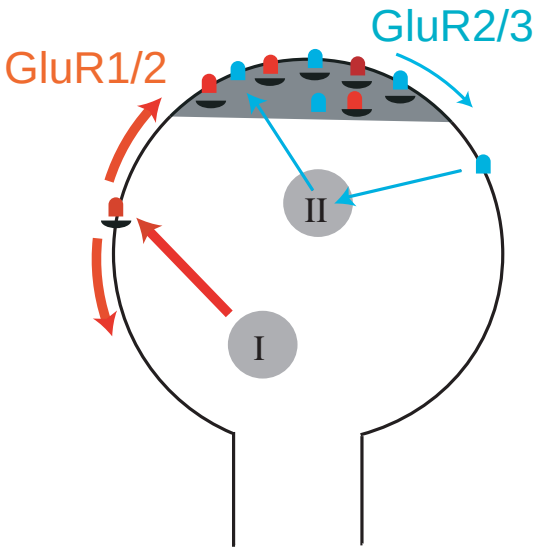




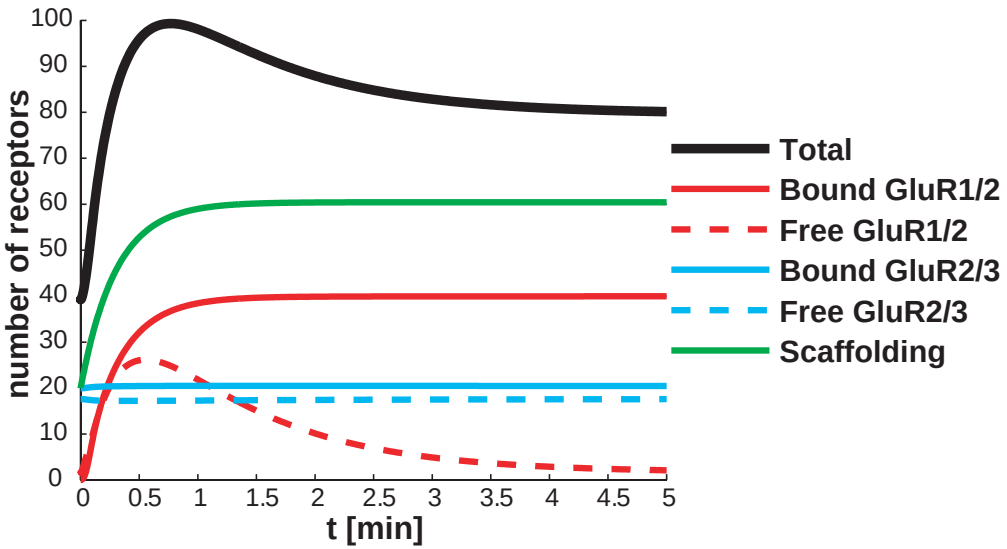


Luscher et al., *Neuron* (1999)

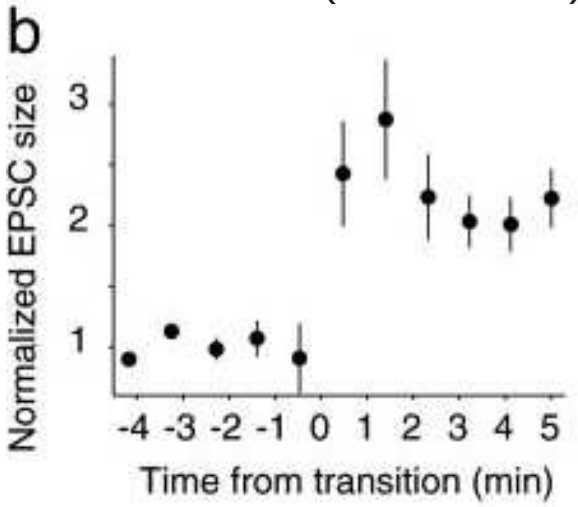
LTP simulation



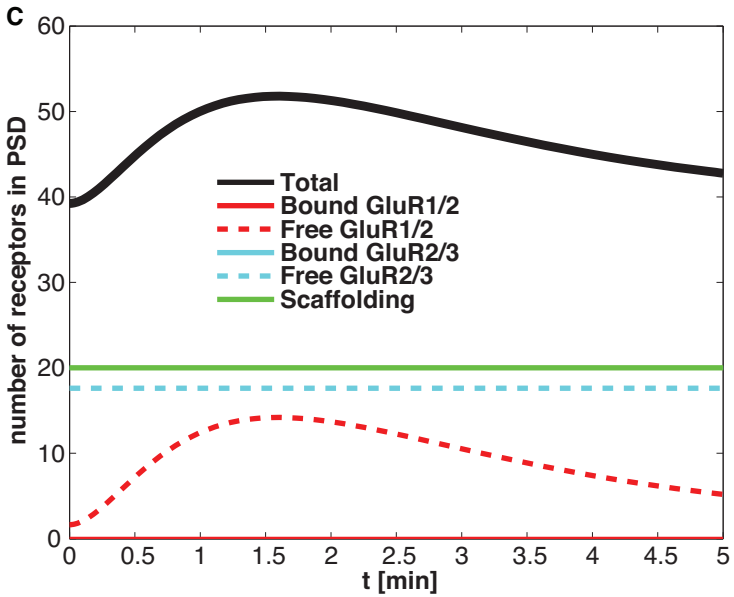
- Activation of GluR1/2 intracellular pool
- Rapid insertion of receptors into ESM
- AMPARs transport slot proteins into PSD

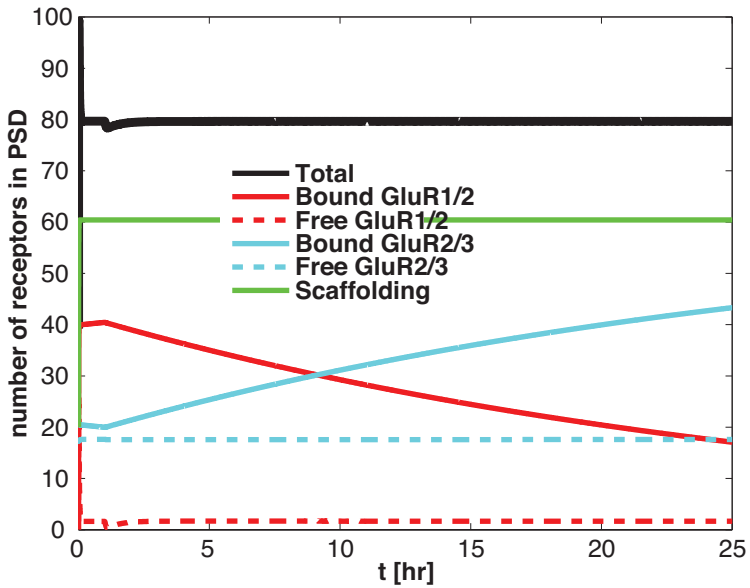


O' Connor et al (PNAS 2005)

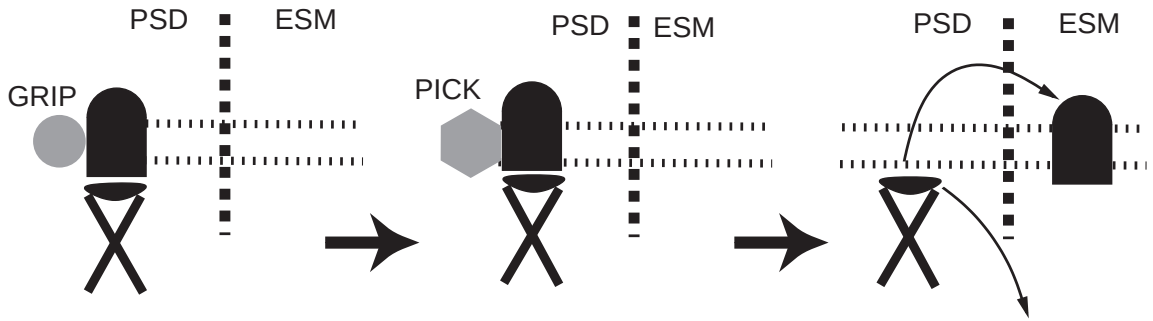


More LTP simulations

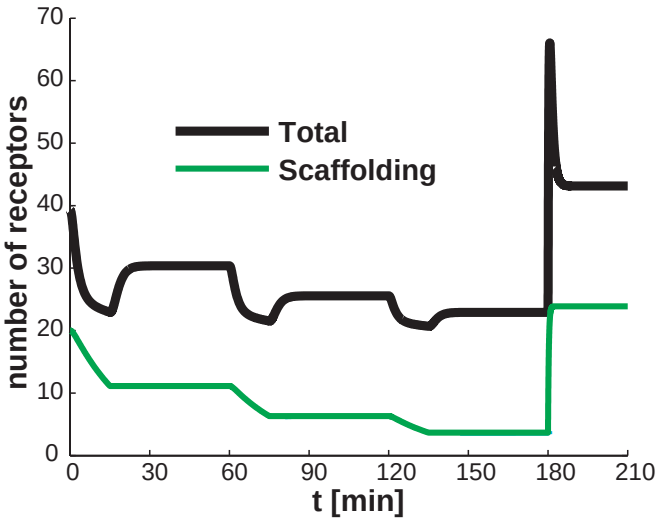


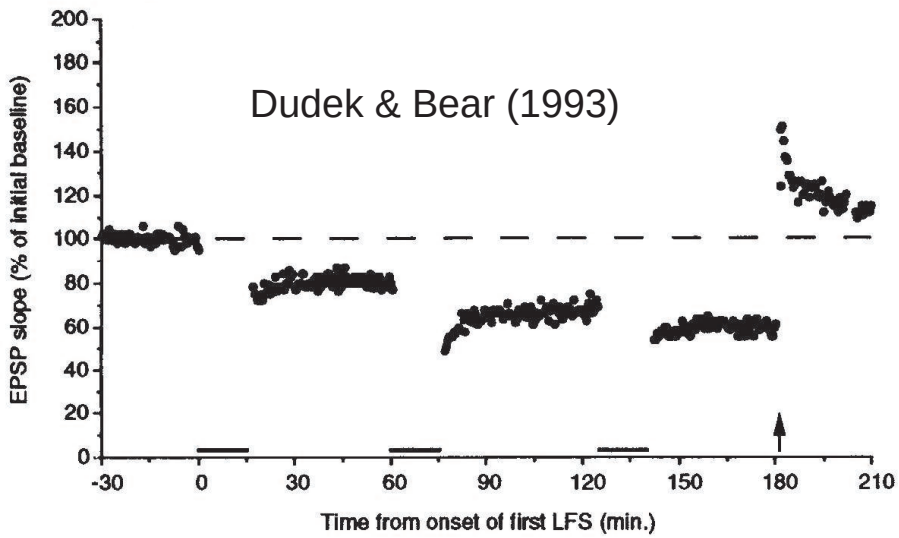


LTD simulation



- 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.

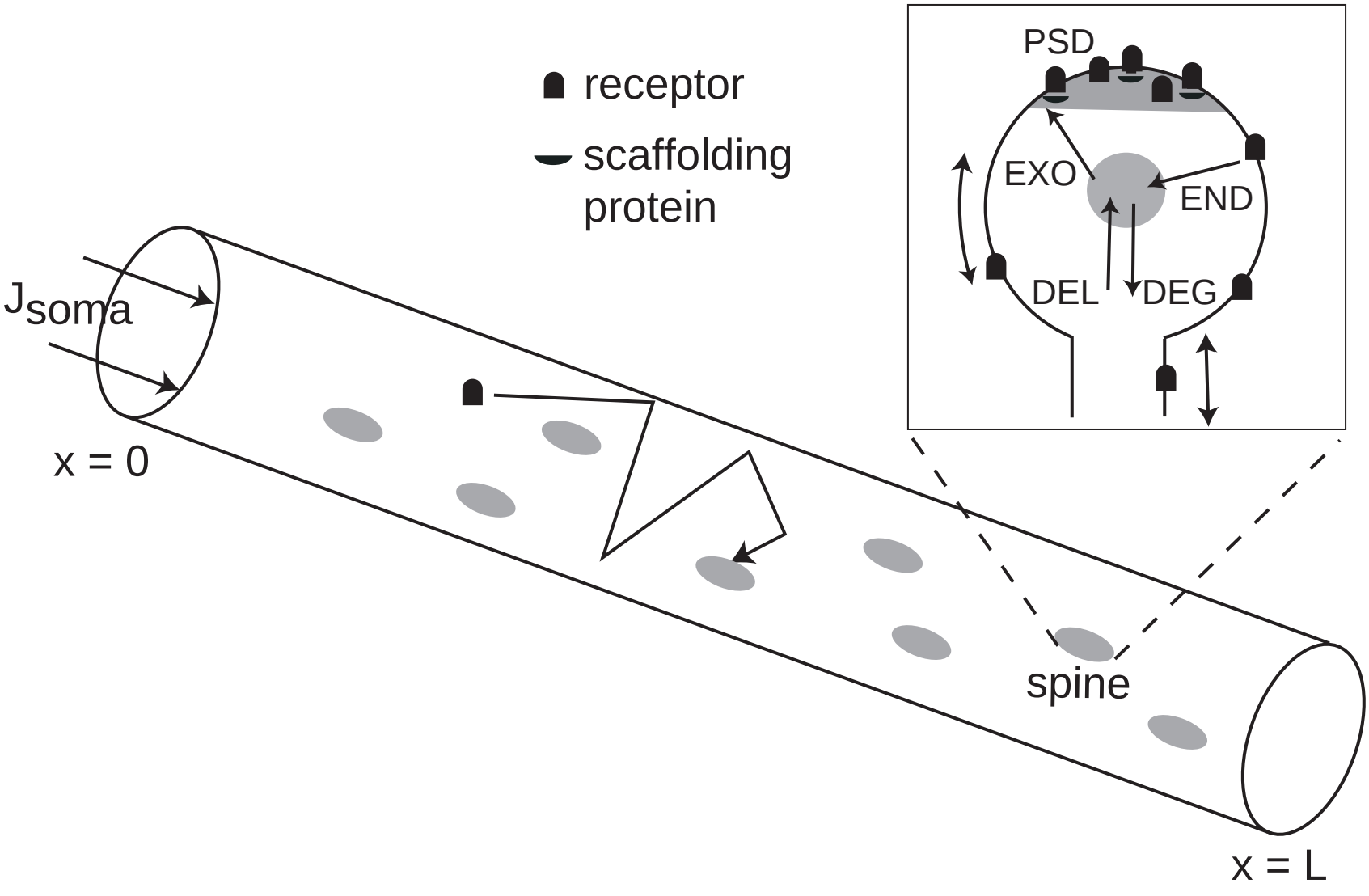




Conclusions

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



1D model: Spine population as continuous density

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

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

U = AMPAR conc. in dendritic membrane outside of spines

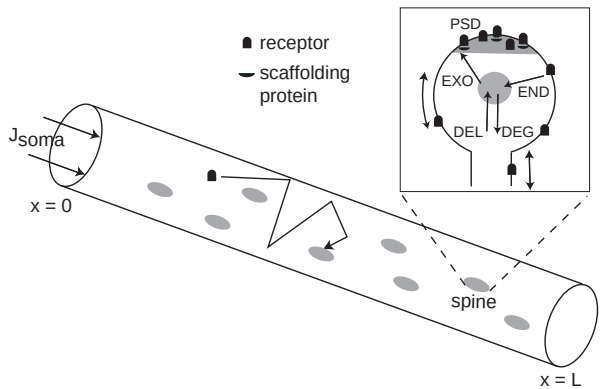
R = AMPAR conc. in extrasynaptic membrane of spine head

D = diffusion coefficient

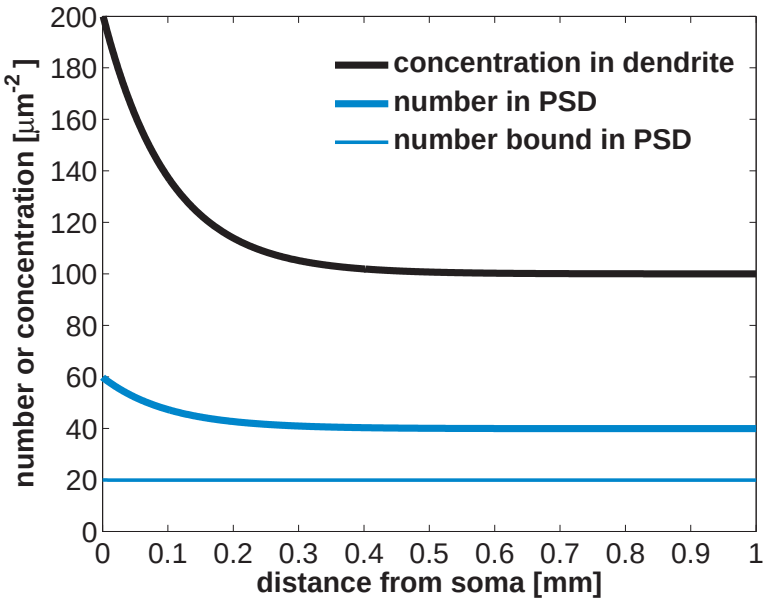
ρ = spine density

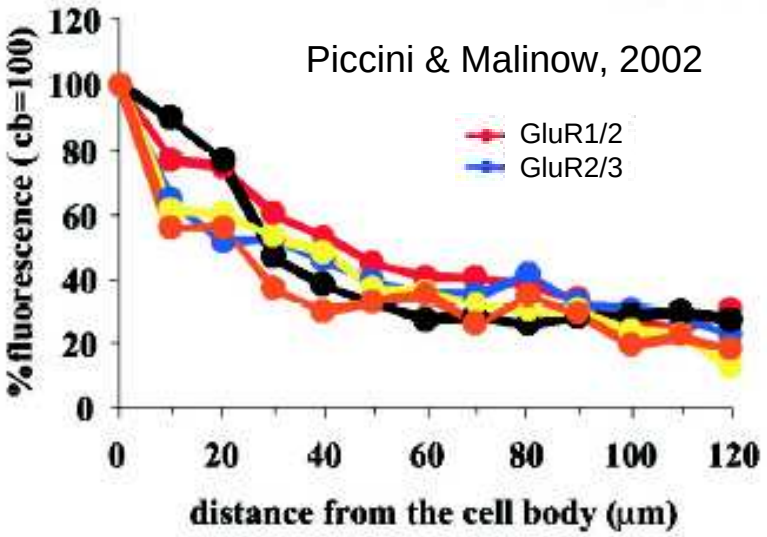
Ω = spine neck hopping rate

J_{soma} = flux of surface AMPAR from soma



Steady-state AMPAR profiles for identical spines

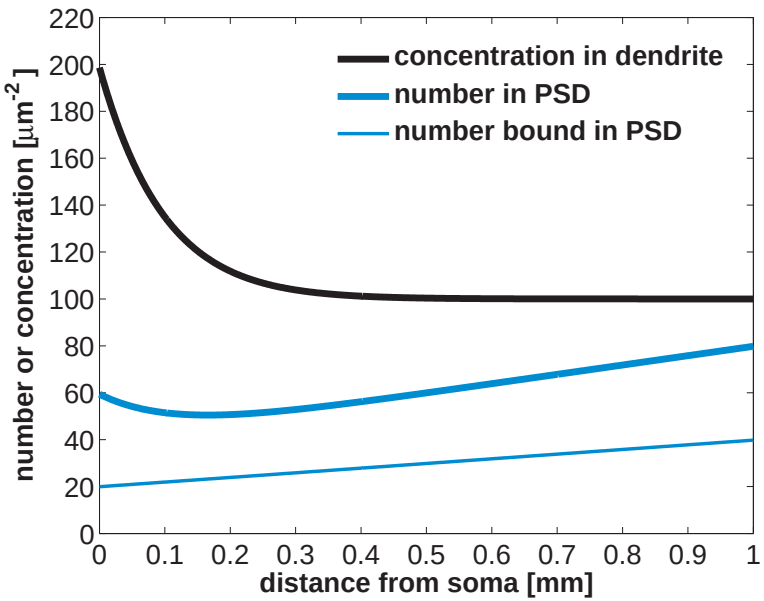




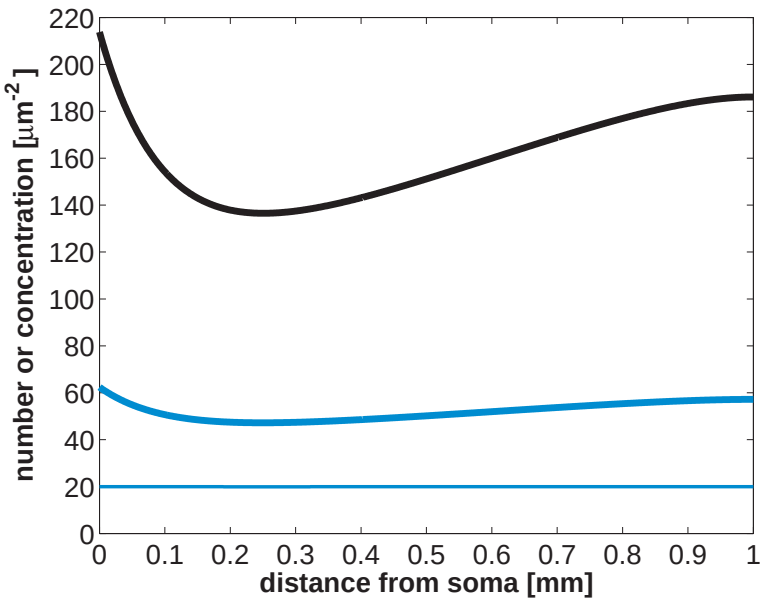
- 1,000 identical spines uniformly spaced in 1 mm dendrite
- Two sources of AMPARs
  - at soma
  - local intracellular delivery
- diffusion coefficient $D = 0.1\ \mu m^2 s^{-1}$ in dendrite

Nonidentical spines: Synaptic democracy

PSD surface area
or spine density
increases linearly

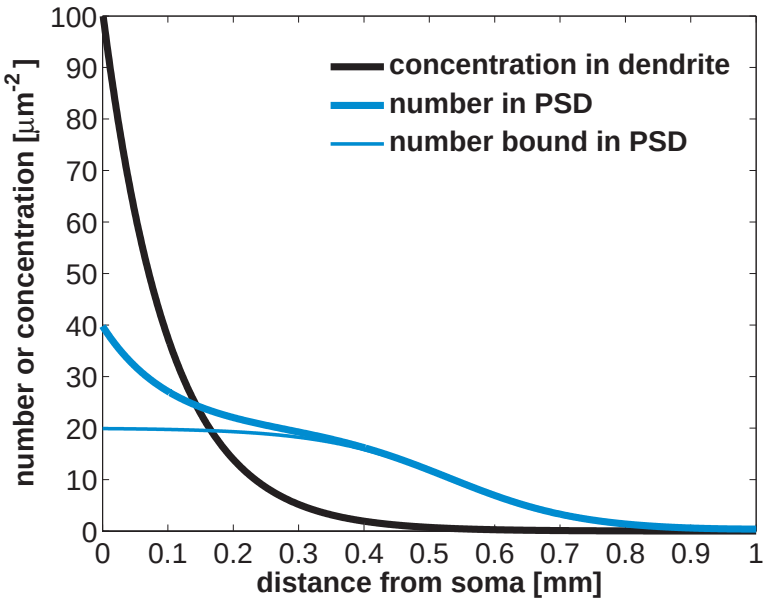


rate of delivery
or exocytosis
increases linearly

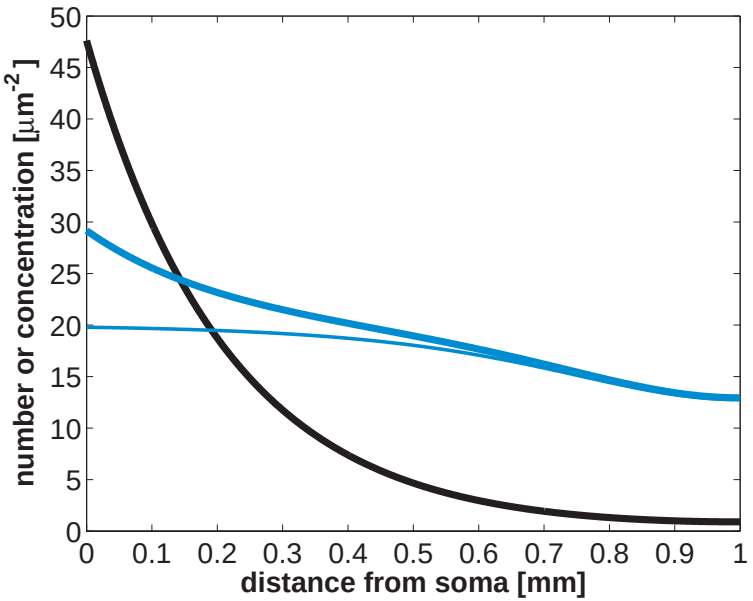


Identical spines without intracellular delivery

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



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



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

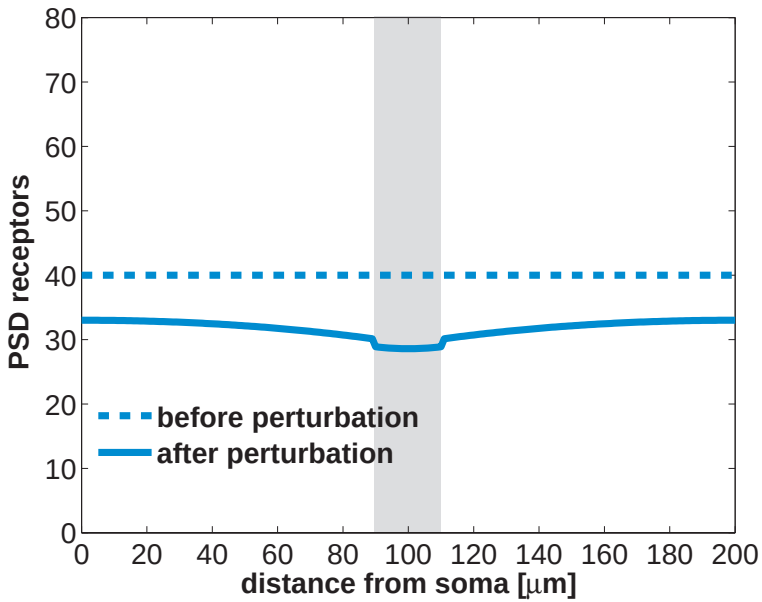
Extensive
(nonlocal effect)

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

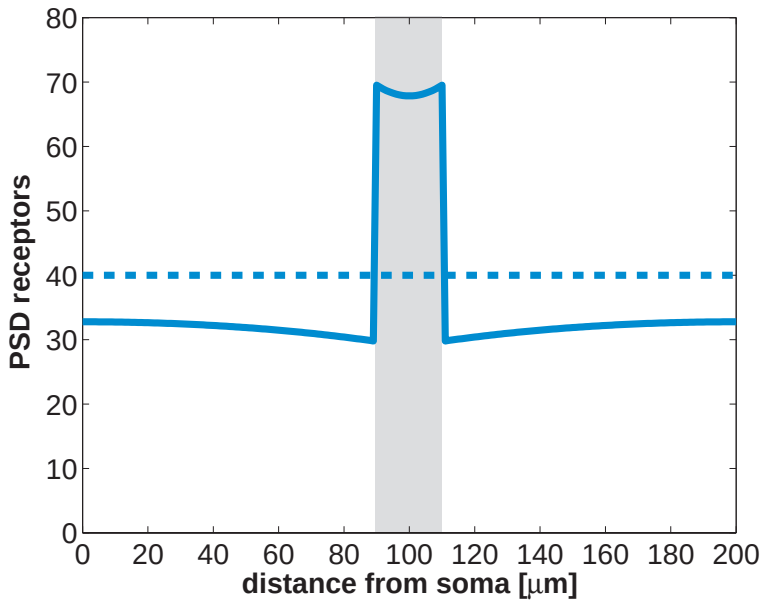
- Spine neck hopping rate Ω can be extensive, but not in current parameter regime ($\sigma^{\mathrm{EXO}} \gg \sigma^{\mathrm{DEG}}$)

Heterosynaptic dependence on constitutive recycling

10-fold reduction in rate of exocytosis in gray region



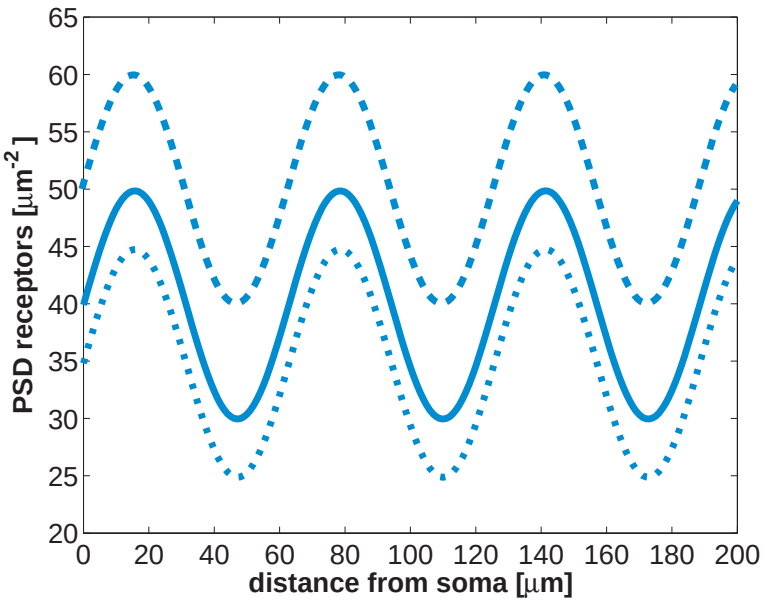
10-fold increase in rate of endocytosis in gray region

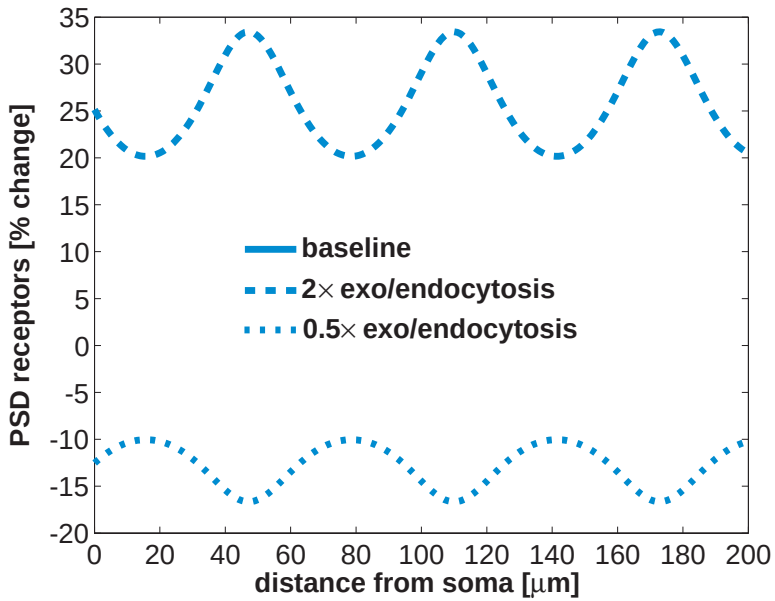


Globally scaling exo/endocytosis does not imply multiplicative scaling of synaptic AMPAR numbers

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

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

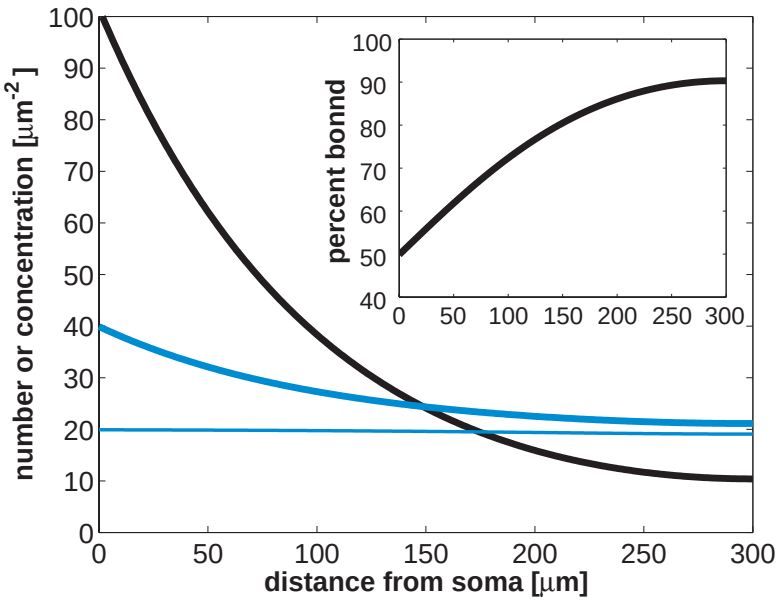




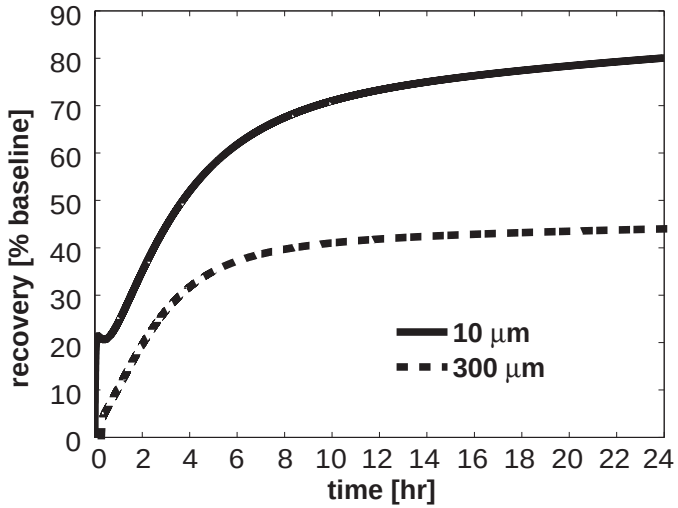
Simulation of photoinactivation

Assume

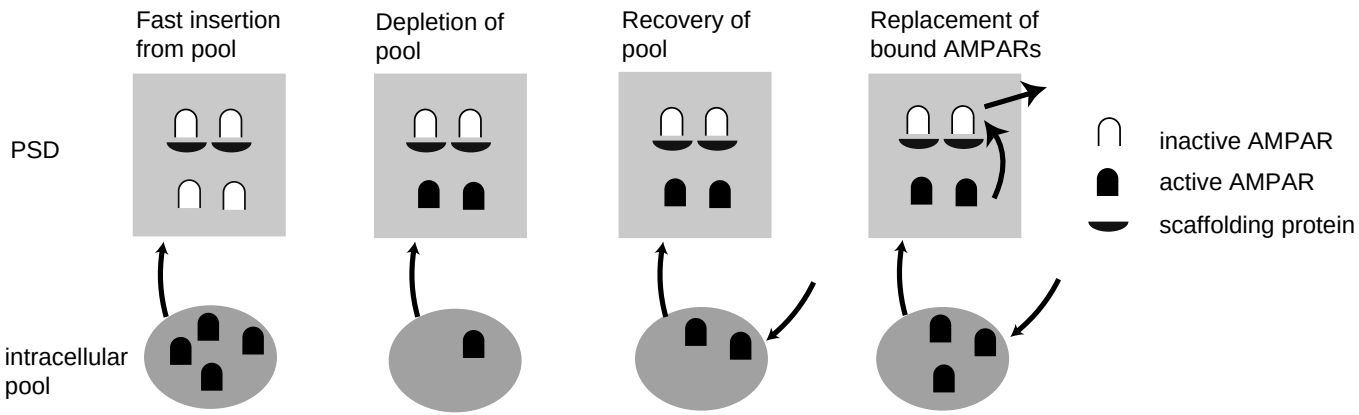
- no intracellular delivery but source at soma
- in steady-state $t < 0$
- at $t = 0$ all surface AMPARs instantaneously "inactivated"



Rate of recycling depends on distance from soma



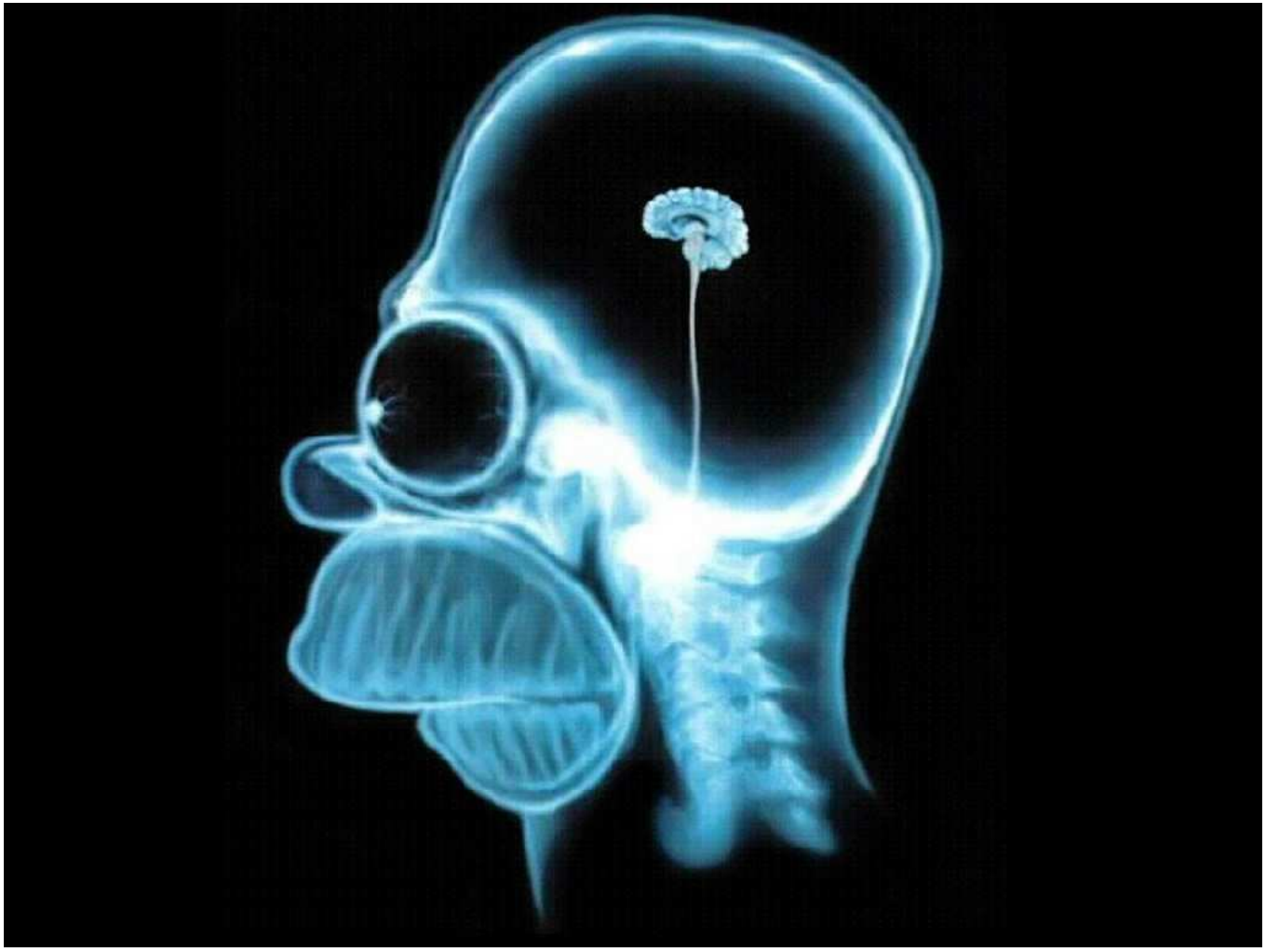
- Fast exo/endocytosis consistent with slow recycling
- Rate-limiting steps:



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

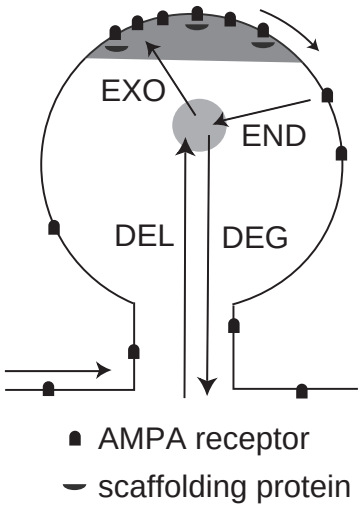
Parameter	Symbol	Value	Reference
Length of dendrite	L	1 mm	Sorra & Harris 2000
Circumference of dendrite	l	1 μm	Sorra & Harris 2000
Diffusion coefficient	D	0.1 $\mu m^2 s^{-1}$	Tardin et al. 2003
Spine density	ρ	1 μm^{-2}	Sorra & Harris 2000
Surface area of head	A	1 μm^2	Sorra & Harris 2000
Surface area of PSD	a	0.1 μm^2	Sorra & Harris 2000
Scaffolding concentration	Z	200 μm^{-2}	BE & Bressloff 2006
Binding rate	α	10^{-4} $\mu m^2 s^{-1}$	BE & Bressloff 2006
Unbinding rate	β	10^{-4} s^{-1}	BE & Bressloff 2006
PSD hopping rate	h	10^{-3} $\mu m^2 s^{-1}$	BE & Bressloff 2006
Spine neck hopping rate	Ω	10^{-3} $\mu m^2 s^{-1}$	BE & Bressloff 2006
Rate of endocytosis	k	10^{-3} $\mu m^2 s^{-1}$	Ehlers 2000
Rate of exocytosis	σ^{EXO}	10^{-3} s^{-1}	Passafaro et al. 2001
Degradation rate	σ^{DEG}	10^{-5} s^{-1}	O'Brien et al. 1999

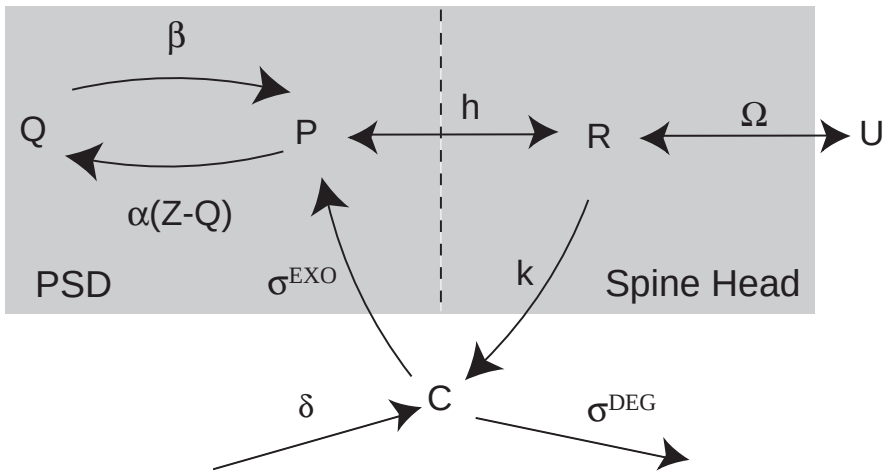
Steady-state at single spine

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

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

$$R = \frac{\Omega U + \lambda \delta}{\Omega + k(1 - \lambda)}.$$





Steady-state dendritic concentration

$$D\frac{d^2U}{dx^2} - \rho\widehat{\Omega}U = -\rho\widehat{\Omega}r$$

$$\widehat{\Omega} = \frac{\Omega k(1-\lambda)}{\Omega + k(1-\lambda)}, \quad r = \frac{\sigma^{\mathrm{EXO}}\delta}{\sigma^{\mathrm{DEG}}k}$$

One can view

- $\widehat{\Omega}$ 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

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

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

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