

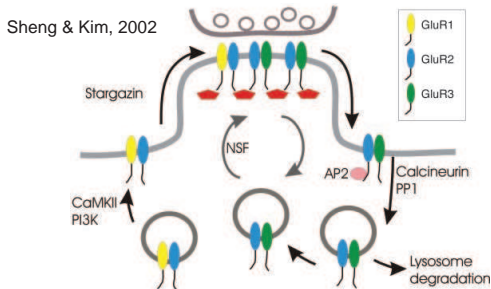
Modeling the role of lateral membrane diffusion in AMPA receptor trafficking along a spiny dendrite

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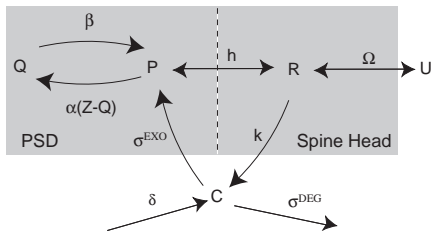
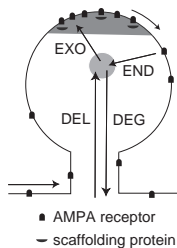
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AMPA receptor trafficking at spines



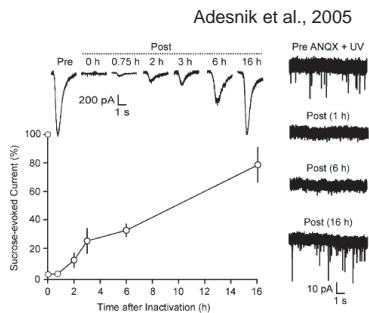
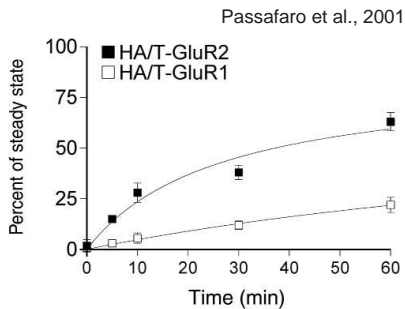
- Surface AMPARs constitutively recycle with intracellular stores
- Laterally diffuse within postsynaptic membrane
- Crosslink to scaffolding proteins in PSD

Model of trafficking at a single spine

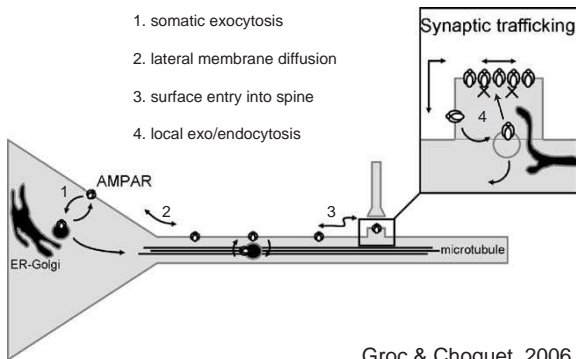


- P, Q:** unbound, bound receptor concentrations in PSD
- R, U:** free receptor concentrations in spine head, dendrite
- C:** number of intracellular receptors
- k, σ^{EXO} :** rates of endocytosis, exocytosis
- σ^{DEG} , δ :** rates of degradation, intracellular delivery
- h, Ω :** hopping rates across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

Fast or slow recycling?

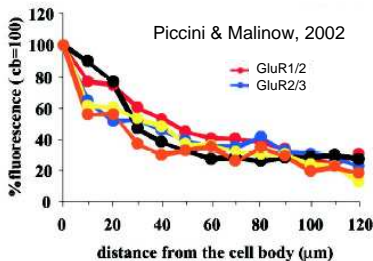
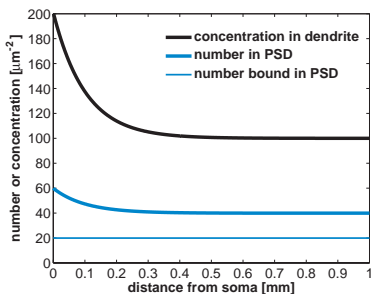


Long-range AMPA receptor trafficking



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

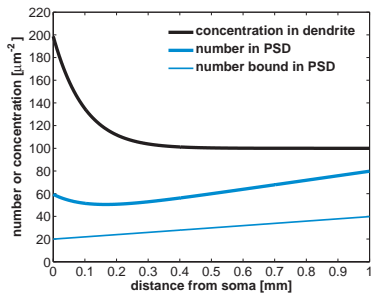
Steady-state AMPA receptor profiles for uniform cable



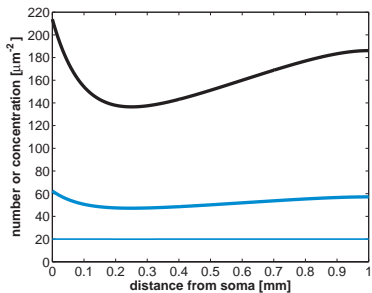
- 1,000 identical spines distributed uniformly along 1 mm dendrite
- Two sources of AMPARs
 - at soma
 - local intracellular delivery
- diffusion coefficient $D = 0.1 \mu\text{m}^2\text{s}^{-1}$

Profiles for nonuniform cable: synaptic democracy

PSD surface area
or spine density
increases linearly

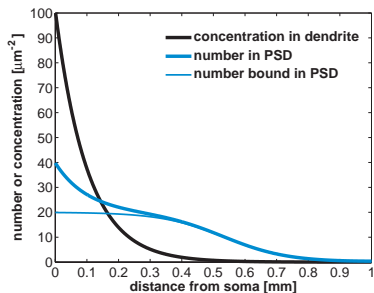


rate of delivery
or exocytosis
increases linearly

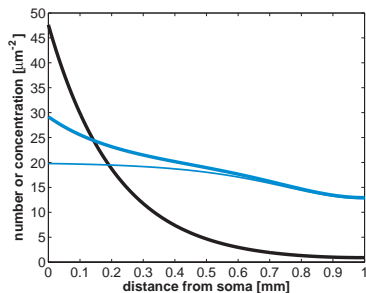


Profiles for uniform cable without intracellular delivery

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



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



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

Intensive vs. extensive parameters

- Trafficking parameters categorized into two groups: whether or not localized 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

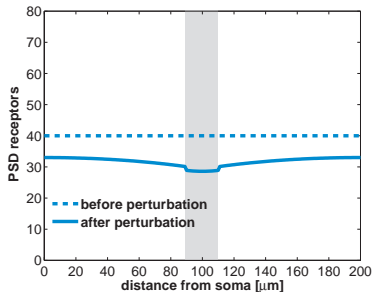
Extensive

(nonlocal effect)

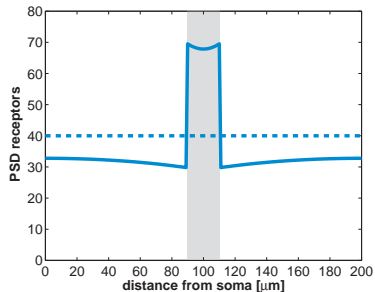
- rate of exocytosis σ^{EXO}
 - rate of endocytosis k
 - intracellular delivery rate δ
 - degradation rate σ^{DEG}
-
- Spine neck hopping rate Ω can be extensive, but not in current parameter regime ($\sigma^{\text{EXO}} \gg \sigma^{\text{DEG}}$)

Heterosynaptic dependence on constitutive recycling

10-fold reduction in
rate of exocytosis
in gray region



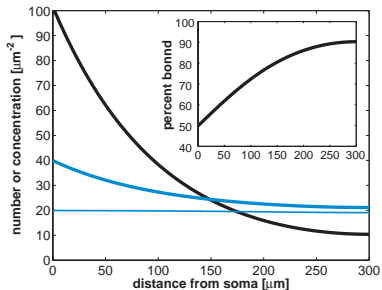
10-fold increase in
rate of endocytosis
in gray region



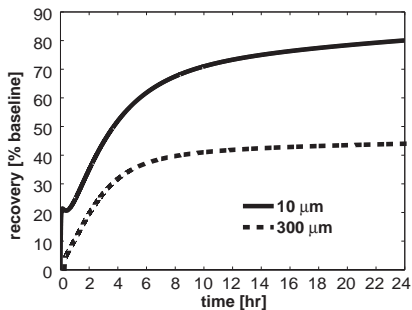
Simulation of photoinactivation

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 is consistent with slow constitutive recycling
- Rate-limiting step is unbinding from scaffolding and diffusion from PSD

Summary

- Source of AMPARs at soma implies
 - exponential decay for uniform spines
 - synaptic democracy for nonuniform spines
- Need fast lateral diffusion to deliver AMPARs to distal synapses from soma
 - Takes too long?
- Local changes in recycling produce nonlocal changes in synaptic AMPAR numbers
 - Extensive vs. intensive trafficking parameters
- Constitutive recycling rate is distance-dependent when soma is only source of AMPARs
 - fast recycling at proximal synapses
 - slow recycling at distal synapses

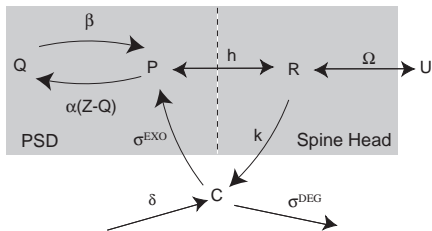
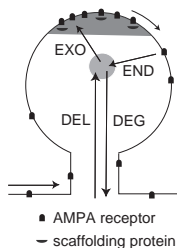
Model of trafficking at a single spine

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

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

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

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

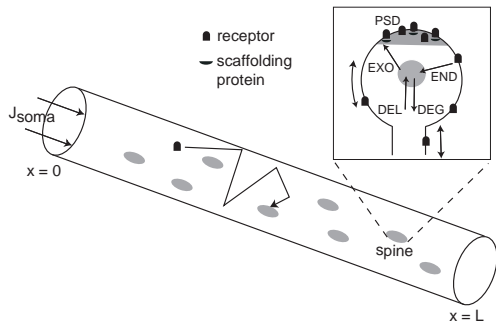


Model of trafficking along a spiny dendrite

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

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

D = diffusion coefficient, $\rho(x)$ = spine density at x
 J_{soma} = surface flux from soma



Baseline parameter values

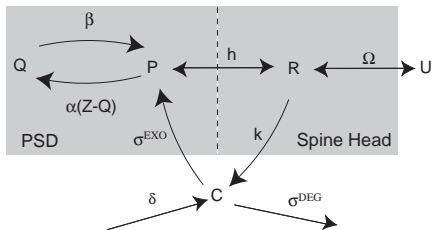
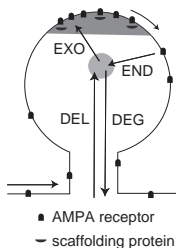
Parameter	Symbol	Value	Reference
Length of dendrite	L	1 mm	Sorra & Harris 2000
Circumference of dendrite	l	1 μm	Sorra & Harris 2000
Diffusion coefficient	D	0.1 $\mu\text{m}^2\text{s}^{-1}$	Tardin et al. 2003
Spine density	ρ	1 μm^{-2}	Sorra & Harris 2000
Surface area of head	A	1 μm^2	Sorra & Harris 2000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

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

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

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



Steady-state dendritic concentration

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

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

One can view

- $\hat{\Omega}$ as effective spine neck hopping rate
- r as effective ESM receptor concentration

Solution for uniform cable: “cable” equation

- Assume all parameters are x -independent, then get “cable” equation for receptor trafficking

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

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

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