

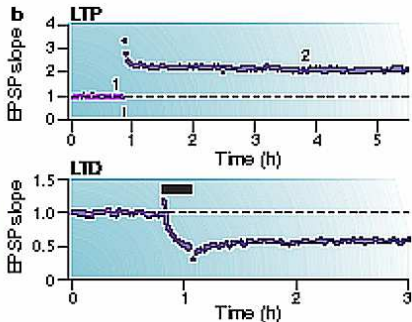
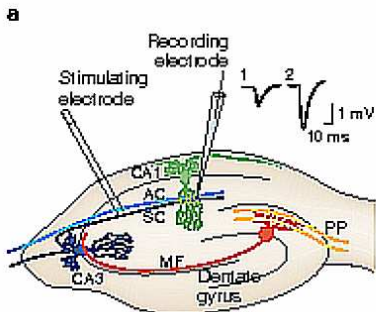
Diffusion-trapping model of AMPA receptor trafficking along a spiny dendrite

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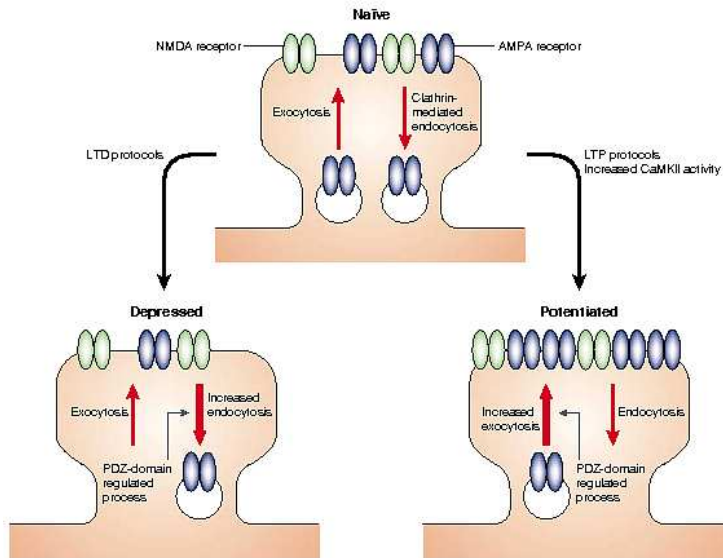
August 4, 2008

Synapses can “learn”

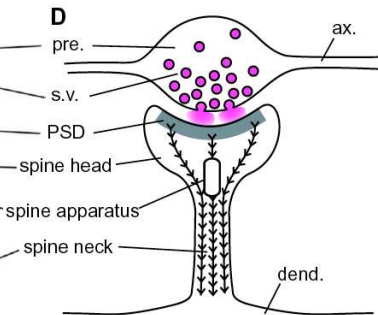
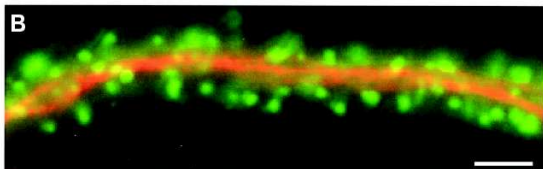


Collingridge et al., *Nat. Rev. Neurosci.* (2004)

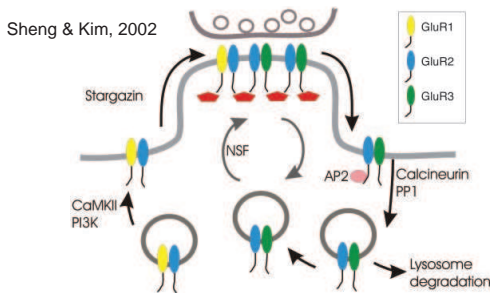
Synapses “learn” by regulating AMPA receptor numbers



Synapses located in dendritic spines

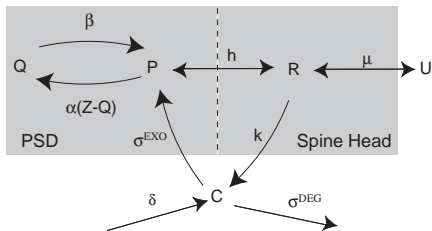
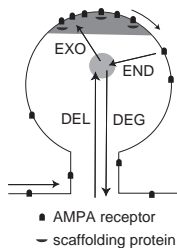


AMPA receptor trafficking at spines



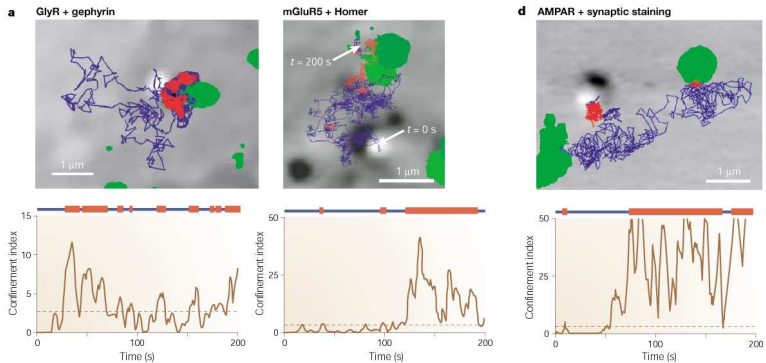
- constitutively recycled with intracellular stores
 - turned over in 10-30 mins (or 16 hrs?)
- immobilized by scaffolding proteins in synapse
- **diffuse** laterally within membrane

Model of AMPAR 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
 $\sigma^{\text{DEG}}, \delta$: rates of degradation, intracellular delivery
h, μ : 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

AMPA receptors diffuse laterally between synapses



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

Continuum model of 1D nonbranching dendrite

- If spines are sufficiently dense, treat them as density ρ

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

- U = concentration of AMPARs in dendrite
- R = concentration of AMPARs in spine
- μ = hopping rate between dendrite and spine

Continuum model of 1D nonbranching dendrite

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- U = concentration of AMPARs in dendrite
- R = concentration of AMPARs in spine
- μ = hopping rate between dendrite and spine
- Boundary conditions

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

Steady-state solution: “cable” equation

- If all parameters are x -independent, then get “cable” equation for AMPAR trafficking

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

- $\Lambda^{-1} = \sqrt{\frac{D}{\rho \hat{\mu}}}$: length-scale of diffusive coupling
- $\hat{R}, \hat{\mu}$: effective AMPAR spine concentration, hopping rate

Steady-state solution: “cable” equation

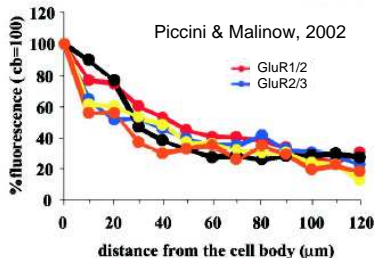
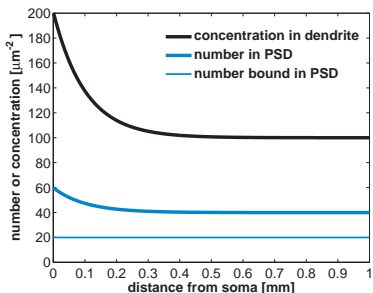
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- $\Lambda^{-1} = \sqrt{\frac{D}{\rho \hat{\mu}}}$: length-scale of diffusive coupling
- $\hat{R}, \hat{\mu}$: effective AMPAR spine concentration, hopping rate
- Solve using Green's function methods

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

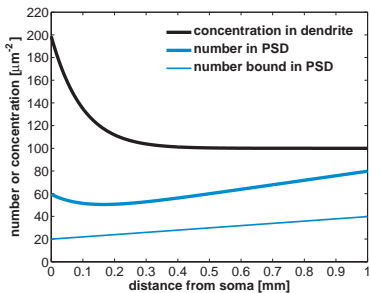
Steady-state AMPAR profiles for identical spines



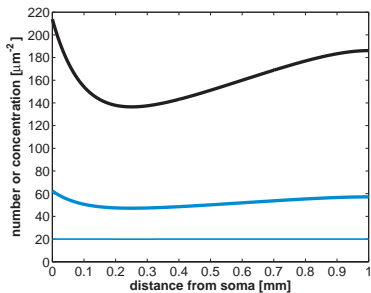
- 1,000 identical spines uniformly spaced in 1 mm dendrite
- Two sources of AMPARs
 - at soma
 - local intracellular delivery
- diffusion coefficient $D = 0.1 \mu m^2 s^{-1}$ in dendrite

Nonidentical spines: Synaptic democracy

PSD surface area
or spine density
increases linearly

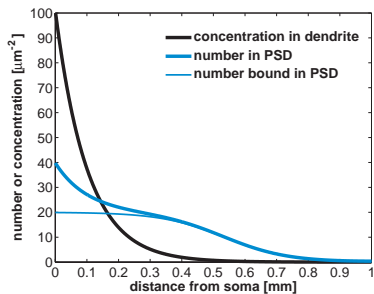


rate of delivery
or exocytosis
increases linearly

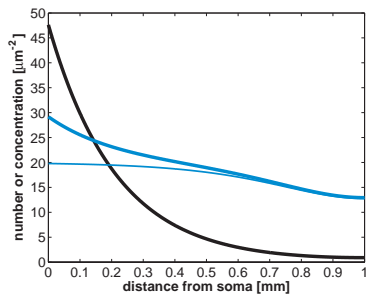


Identical spines without intracellular delivery

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



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



- 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:
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

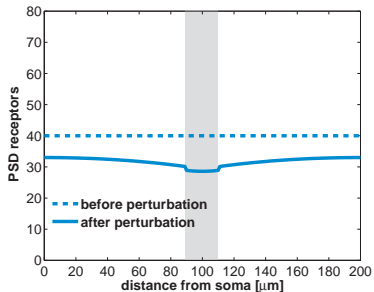
Extensive

(nonlocal effect)

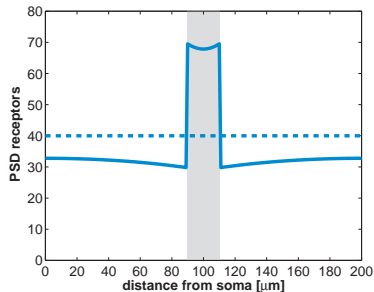
- rate of exocytosis σ^{EXO}
 - rate of endocytosis k
 - intracellular delivery rate δ
 - degradation rate σ^{DEG}
-
- Spine neck hopping rate Ω can be extensive, but not in current parameter regime ($\sigma^{\text{EXO}} \gg \sigma^{\text{DEG}}$)

Heterosynaptic dependence on constitutive recycling

10-fold reduction in
rate of exocytosis
in gray region



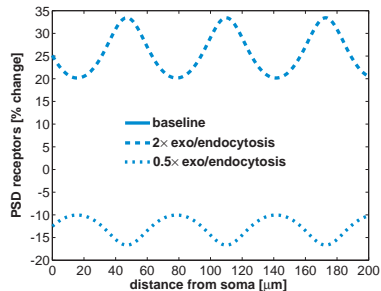
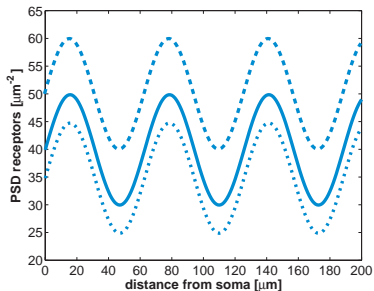
10-fold increase in
rate of endocytosis
in gray region



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

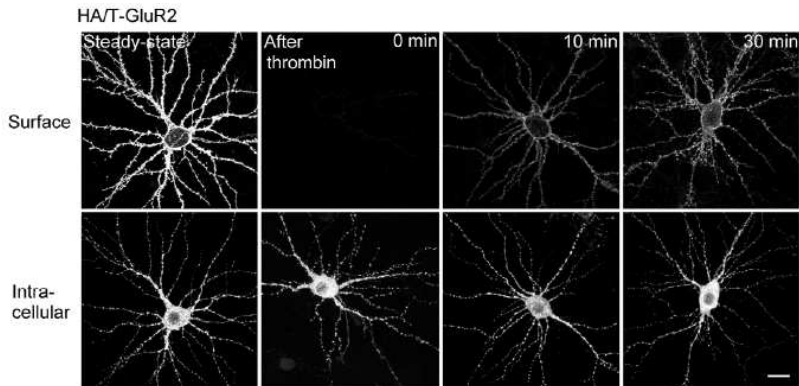
- True if spine properties vary along dendrite
- E.g., identical spines except scaffolding concentration is

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



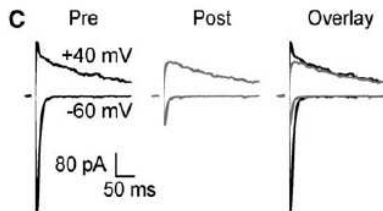
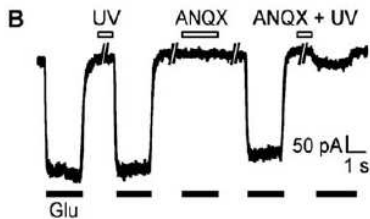
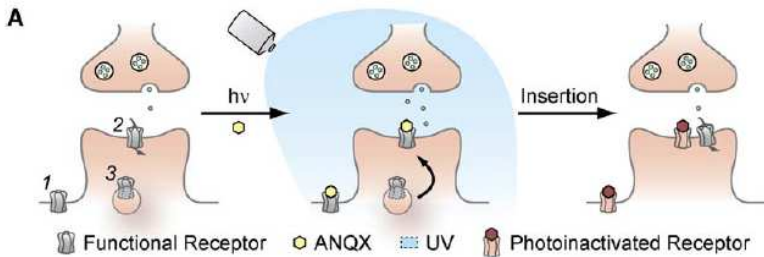
Steady-state is nice...
...but what about time-dependent phenomena?

AMPA receptor recycling via thrombin cleavage

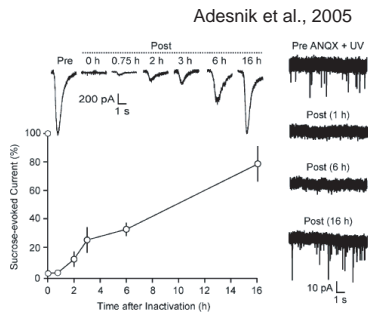
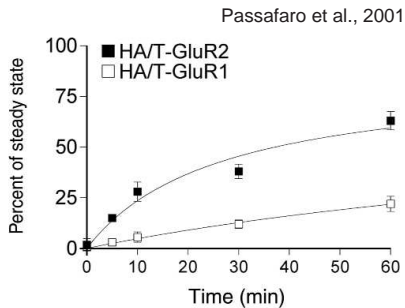


Passafaro et al., *Nat. Neurosci.* (2001)

AMPA receptor recycling via photoinactivation

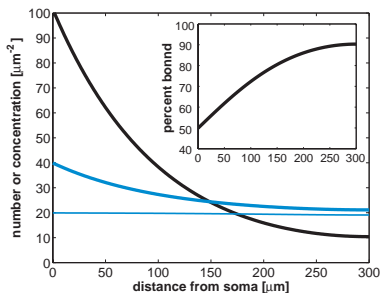


Fast or slow recycling of AMPA receptors?



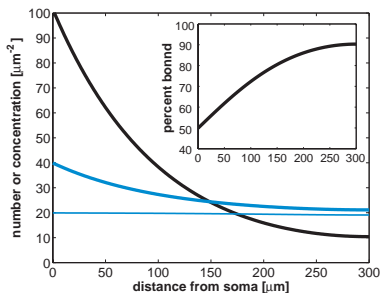
Simulation of photoinactivation of AMPA receptors

- Source at soma, but no intracellular delivery
- In steady-state for $t < 0$
- At $t = 0$ all surface AMPA receptors instantaneously “inactivated”



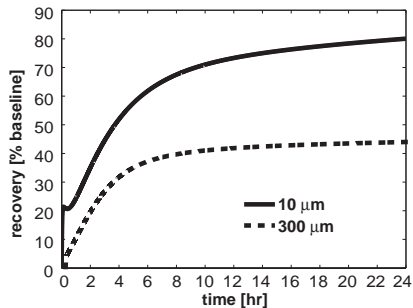
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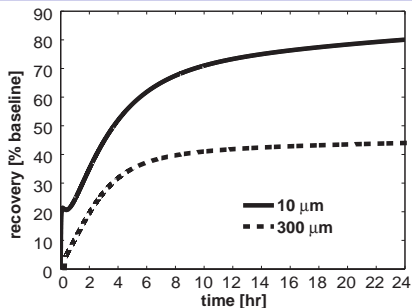
- Rates of exo/endocytosis are **fast** (10-30 mins)

Rate of recycling depends on distance from soma

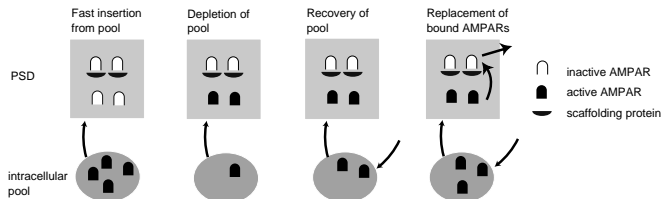


- Fast exo/endocytosis consistent with slow recycling

Rate of recycling depends on distance from soma



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



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 constitutive recycling produce nonlocal changes in synaptic AMPAR numbers
- 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
- 6 Many time scales involved in relaxation to steady-state