Model of AMPA Receptor Trafficking Across Multiple Dendritic Spines

Berton A. Earnshaw and Paul C. Bressloff
Department of Mathematics, University of Utah, Salt Lake City, Utah

Introduction

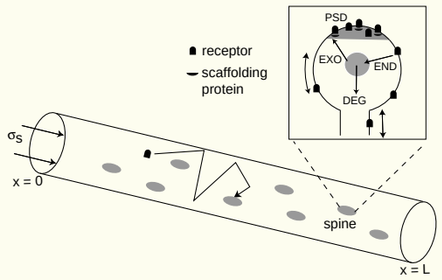
AMPA receptors (AMPARs) mediate the majority of fast excitatory synaptic transmission in the CNS. AMPAR trafficking contributes to activity-dependent changes in synaptic strength (e.g., during LTP/LTD) which are thought to be necessary components of learning and memory. AMPARs can be delivered to synapses via motor-assisted transport along microtubules or lateral diffusion from the soma within the dendritic membrane, and there is currently some dispute over which is the major source of synaptic AMPARs. The lateral diffusion of AMPARs could also mediate heterosynaptic interactions between synapses. We propose and analyze a mathematical model of AMPAR trafficking in order to address the issues of synaptic AMPAR delivery and heterosynaptic interactions.

Mathematical Model[4]

Lateral diffusion of AMPARs in dendritic cable

Concentration in cable surface: $\frac{\partial U}{\partial t} = D\frac{\partial^2 U}{\partial x^2} - \rho\Omega(U-R), \quad 0<x<L$

Receptor flux at cable ends: $J(0)=\sigma,\ J(L)=0 \quad \left(J=-D\frac{\partial U}{\partial x}\right)$



AMPAR trafficking at spines

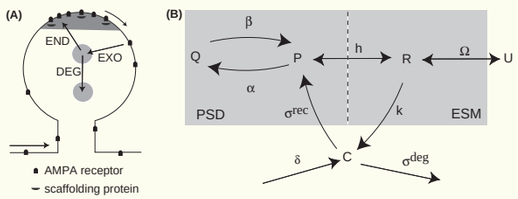
Concentration in ESM: $\frac{dR}{dt} = \frac{\Omega}{A}(U-R) - \frac{k}{A}R - \frac{h}{A}(R-P)$

Free concentration in PSD: $\frac{dP}{dt} = \frac{h}{a}(R-P) - \alpha(Z-Q)P + \beta Q + \frac{\sigma^{rec}}{a}(1-f)C$

Bound concentration in PSD: $\frac{dQ}{dt} = \alpha(Z-Q)P - \beta Q$

Intracellular receptors: $\frac{dC}{dt} = -\sigma^{rec}(1-f)C - \sigma^{deg} fC + kR + \delta$

(Abbreviations: ESM, extrasynaptic membrane of spine head; PSD, postsynaptic density)



P, Q: free and bound receptor concentrations in PSD

R, U: free receptor concentration in ESM and dendrite

C: number of intracellular receptors

k, σ^{rec}, σ^{deg}, δ: **rates of endo/exocytosis, deg/syn**

h, Ω: **hopping rates**

α, β: **rates of binding/unbinding to scaffolding proteins**

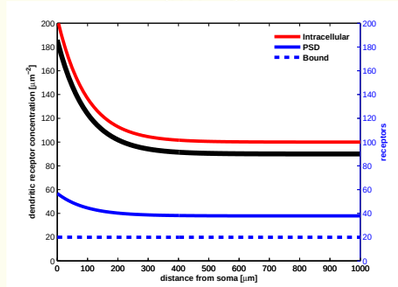
Parameter definitions and baseline values

Diffusivity	D	0.1 $\mu m^2 s^{-1}$
Receptor flux from soma	σ	0.1 receptors $\mu m^{-1} s^{-1}$
Spine density	ρ	1 μm^{-2}
Surface area of ESM	A	1 μm^2
Surface area of PSD	a	0.1 μm^2
Concentration of scaffolding proteins	Z	200 μm^{-2}
Rate of binding to scaffolding	α	10^{-4} $\mu m^2 s^{-1}$
Rate of unbinding from scaffolding	β	10^{-4} s^{-1}
Cable-ESM hopping rate	Ω	10^{-3} $\mu m^2 s^{-1}$
ESM-PSD hopping rate	h	10^{-3} $\mu m^2 s^{-1}$
Rate of endocytosis	k	10^{-3} $\mu m^2 s^{-1}$
Rate of exocytosis	σ^{rec}	10^{-3} s^{-1}
Rate of degradation	σ^{deg}	10^{-4} s^{-1}
Fraction sorted for degradation	f	0.1
Rate of production	δ	10^{-3} receptors s^{-1}

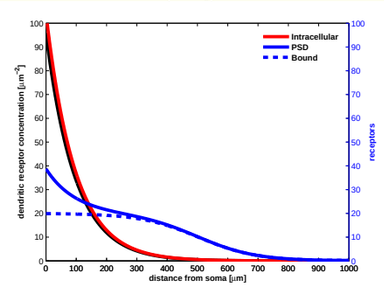
Delivery of Synaptic AMPARs

Steady-state AMPAR profiles are plotted as functions of distance from the soma. Baseline parameter values correspond to fast constitutive recycling[1,2] and generic intracellular production (e.g., vesicular transport from soma, dendritic synthesis) while slow recycling[3] corresponds to a 10-fold decrease of the exo- and endocytic rates. Without intracellular production, neither fast nor slow recycling can supply distal synapses.

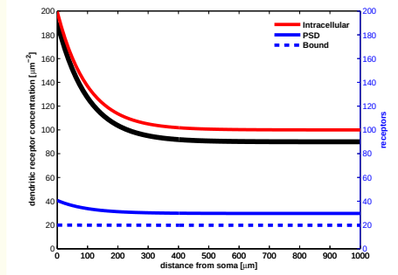
Fast recycling, intracellular production (baseline)



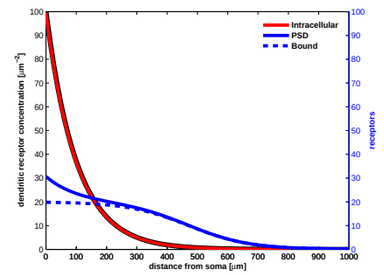
Fast recycling, no production ($\delta = 0$)



Slow recycling, intracellular production ($\sigma^{rec} = k = 10^{-4}$)

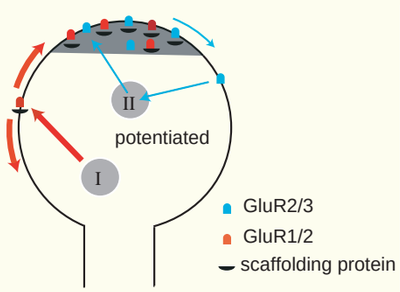


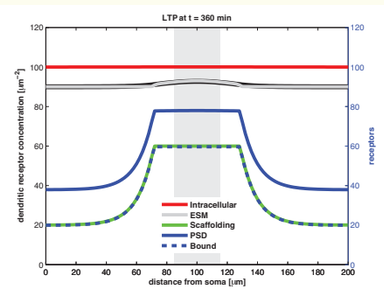
Slow recycling, no production ($\sigma^{rec} = k = 10^{-4}$, $\delta = 0$)

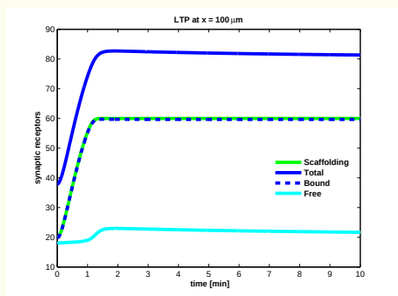


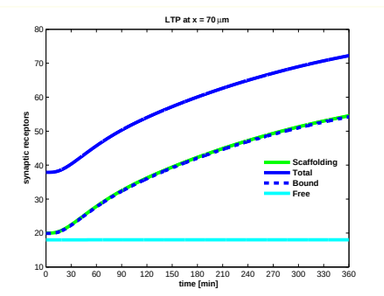
Heterosynaptic Effect of LTP

At time $t = 0$, 100 AMPAR-scaffolding complexes are inserted into each spine in gray (85-115 μm from soma). Each spine is assumed to have capacity for only 60 scaffolding proteins (3x baseline). After $t = 6$ hrs, synapses ≤ 15 μm away are as potentiated as those in gray region.









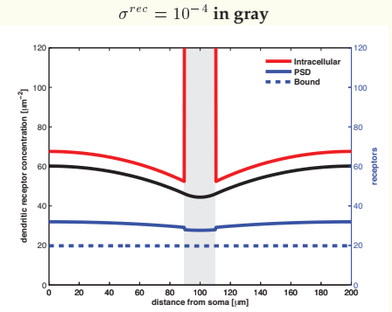
Acknowledgements

This work was supported by the NSF (DMS-0515725 and RTG-0354259).

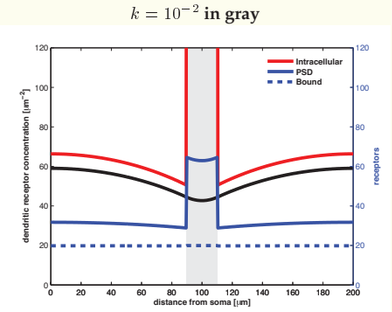
Heterosynaptic Effect of Constitutive Recycling

Steady-state AMPAR profiles are plotted as functions of distance from the soma. All spines use baseline parameter values except those in gray (90-110 μm from the soma), which have a single parameter changed as indicated. Any deviation from the baseline number of AMPARs in the PSD (38) at synapses outside the perturbed region is considered a heterosynaptic effect.

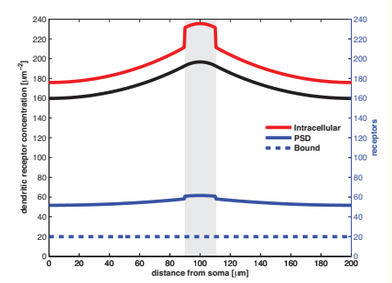
$\sigma^{rec} = 10^{-4}$ **in gray**



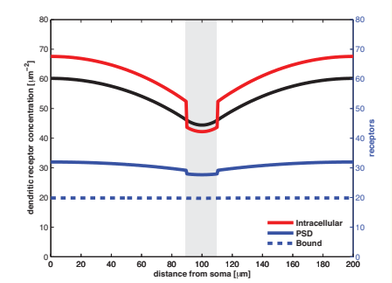
$k = 10^{-2}$ **in gray**



$\delta = 10^{-2}$ **in gray**

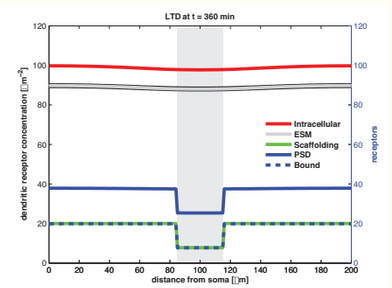


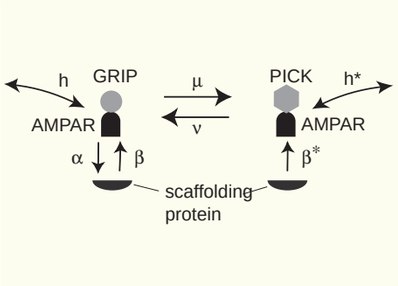
$\sigma^{deg} = 10^{-3}$ **in gray**

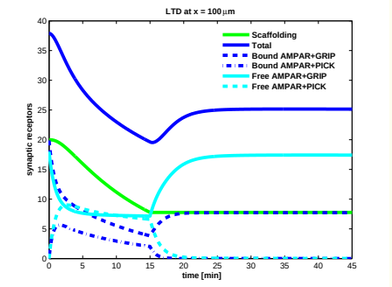


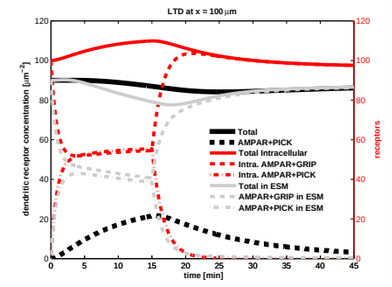
No Heterosynaptic Effect of LTD

At time $t = 0$, AMPARs change association from GRIP to PICK and are steadly removed from each spine in gray (85-115 μm from soma). Scaffolding proteins are also steadly degraded as they become free. After $t = 6$ hrs, only those synapses in gray region have been depressed.









References

1. Lin *et al. Nat. Neurosci.* **4** (2000).
2. Passafaro *et al. Nat. Neurosci.* **4** (2001).
3. Adesnik *et al. Neuron* **48** (2005).
4. Earnshaw & Bressloff. *J. Neurosci.* **26** (2006); Bressloff & Earnshaw. *Phys. Rev. E* **To appear** (2007).