Biophysical model of AMPA receptor trafficking and its regulation during LTP/LTD

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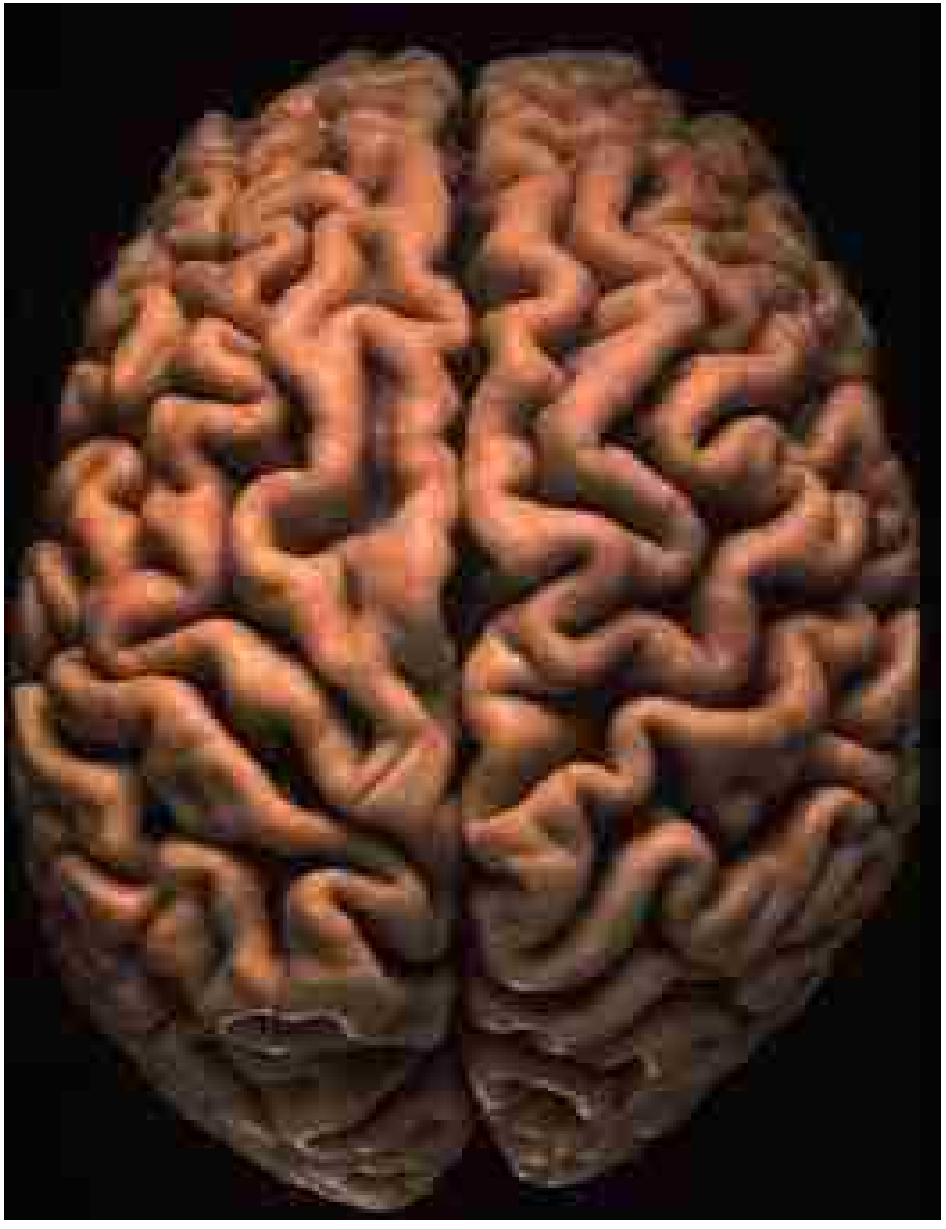
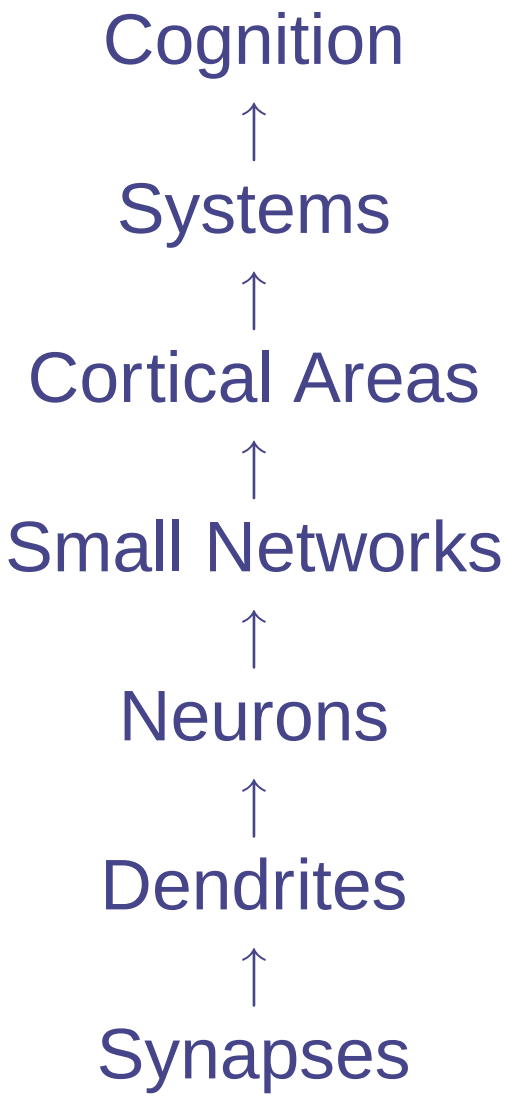
The brain: unparalled parallel computer

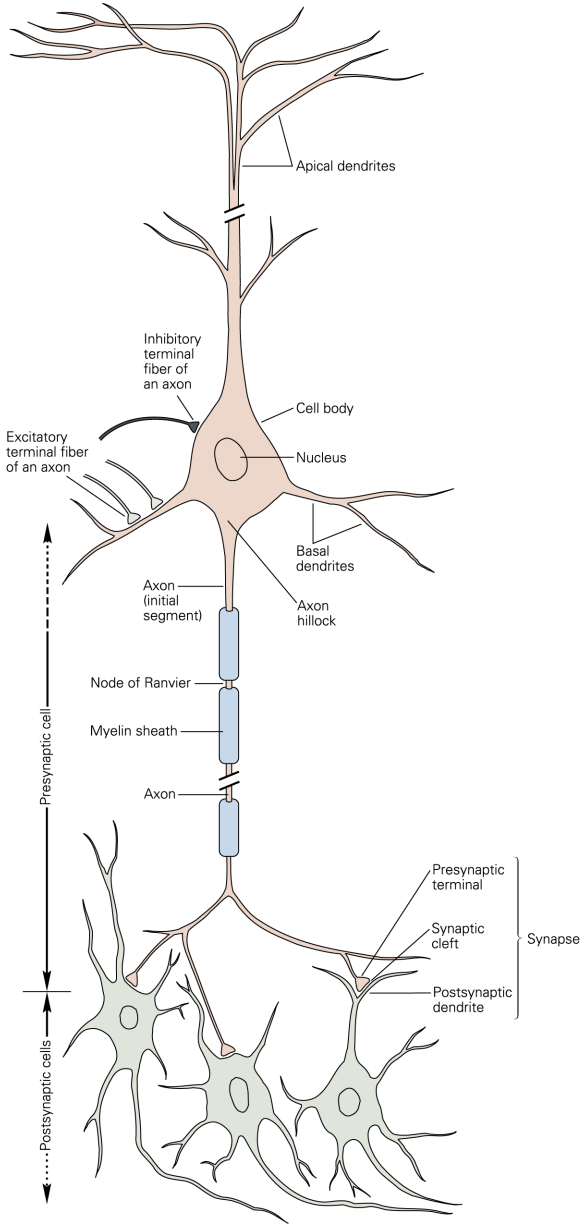


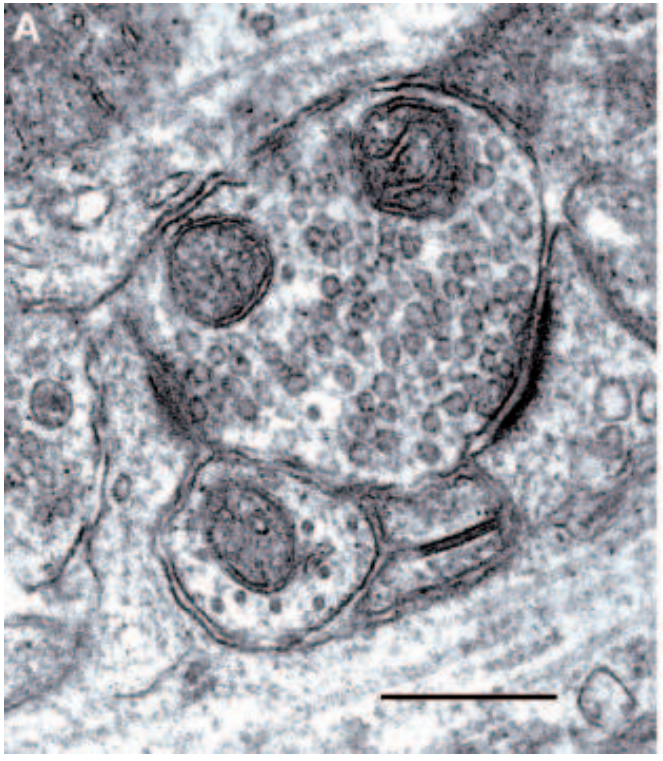
- 10^{11} neurons
- $\sim 10 - 10,000$ synapses/neuron
- network is plastic
- regulates behavior
- can **learn** and **remember**!

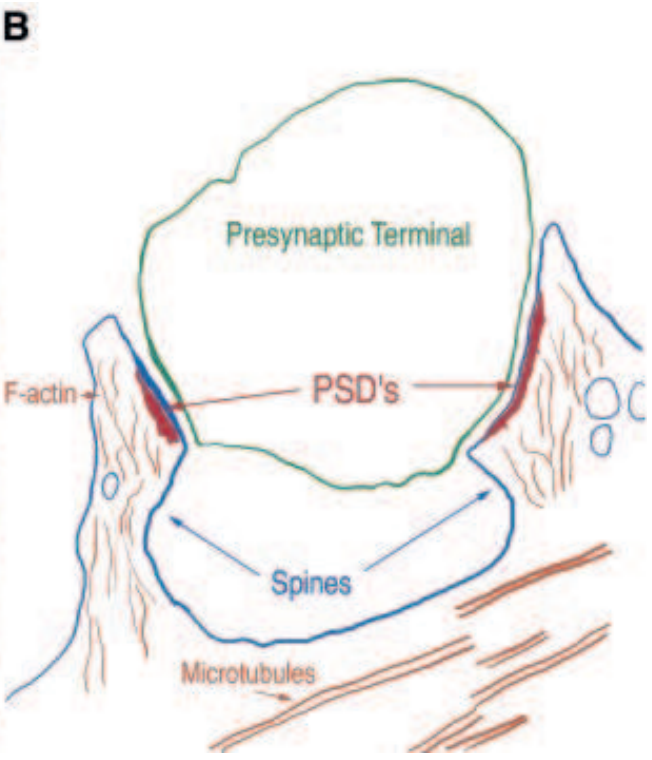
Mathematical Neuroscience at Utah



The Synapse



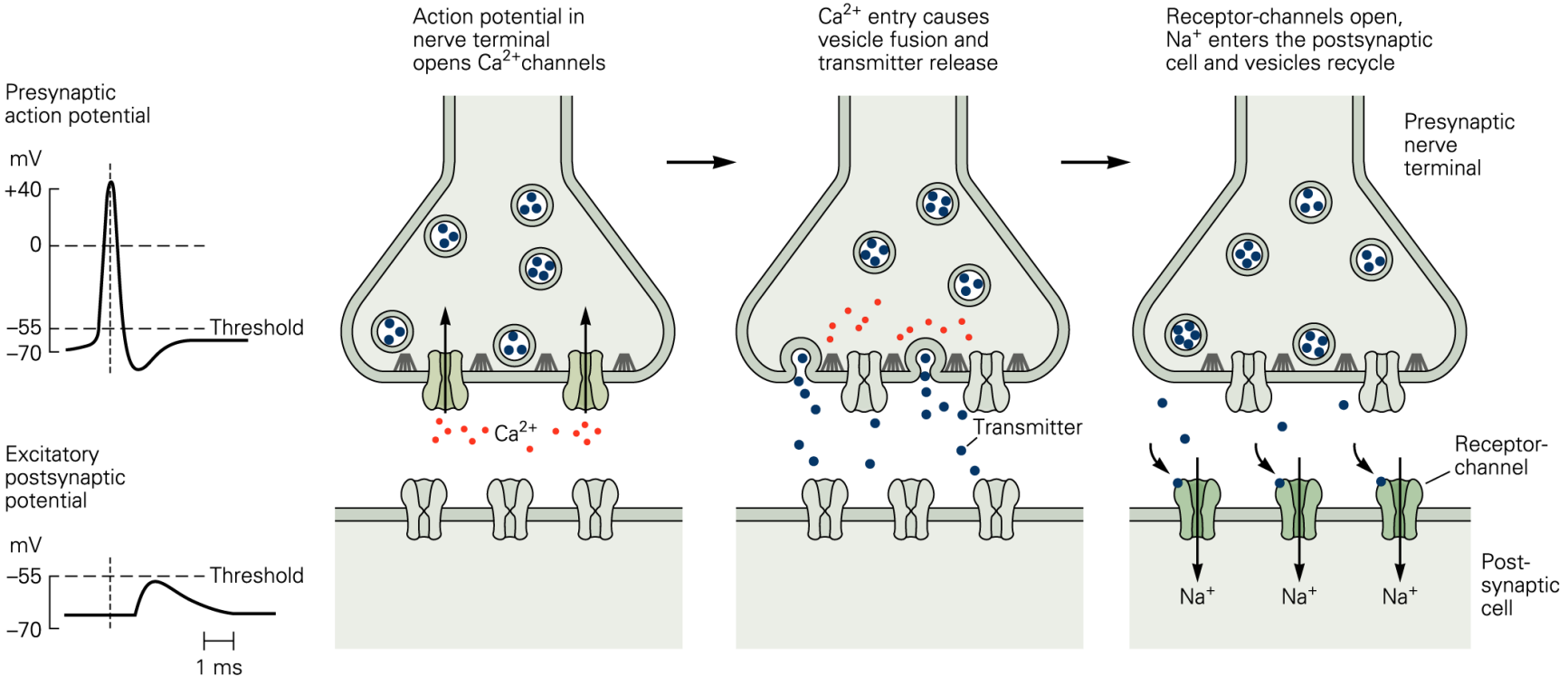




E.R. Kandel et al. Principles of Neural Science. 2000.

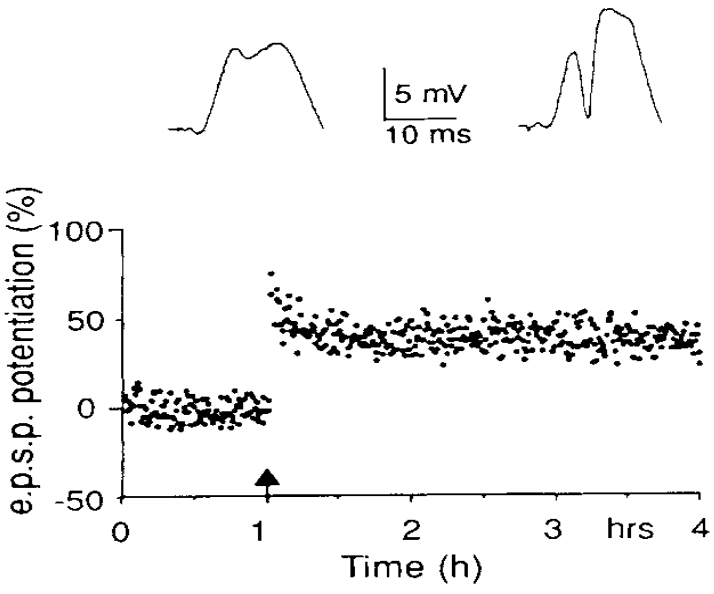
M.B. Kennedy. *Science* **290** 750–754 (2000).

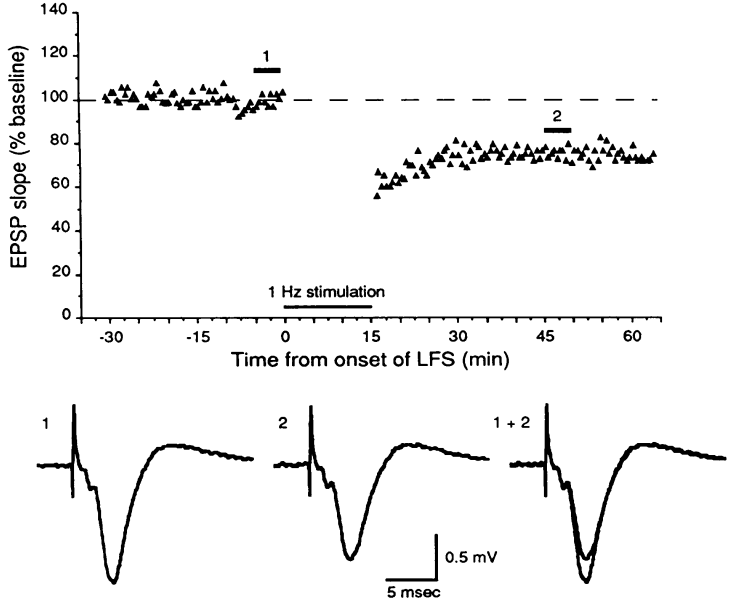
Synaptic transmission



E.R. Kandel et al. Principles of Neural Science. New York: McGraw-Hill. 2000.

LTP/LTD: Long-term potentiation/depression



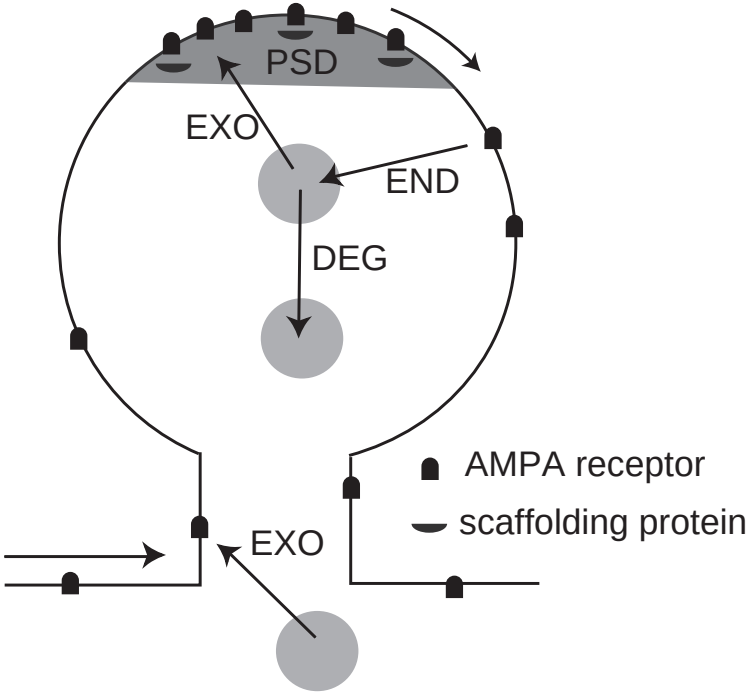


T.V.P. Bliss and G.L. Collingridge. *Nature* **361** 31–39 (1993).

S.M. Dudek and M.F. Bear. *PNAS* **89** 4363–4367 (1992).

AMPA receptor trafficking

- **Exo/endocytosis** $\tau \sim$10-30min
- **Lateral diffusion**
  - Brownian in ESM: $\sim 0.1 \mu m^2/s$
  - Confined in PSD: $\sim 0.01 \mu m^2/s$
  - PSD is confinement domain
  - Spine neck impedance
- **Immobilization** by scaffolding
- **Synthesis/degradation**



M.D. Ehlers. *Neuron* **28** 511–525 (2000).

M. Passafaro et al. *Nat. Neurosci.* **4** 917–926 (2001).

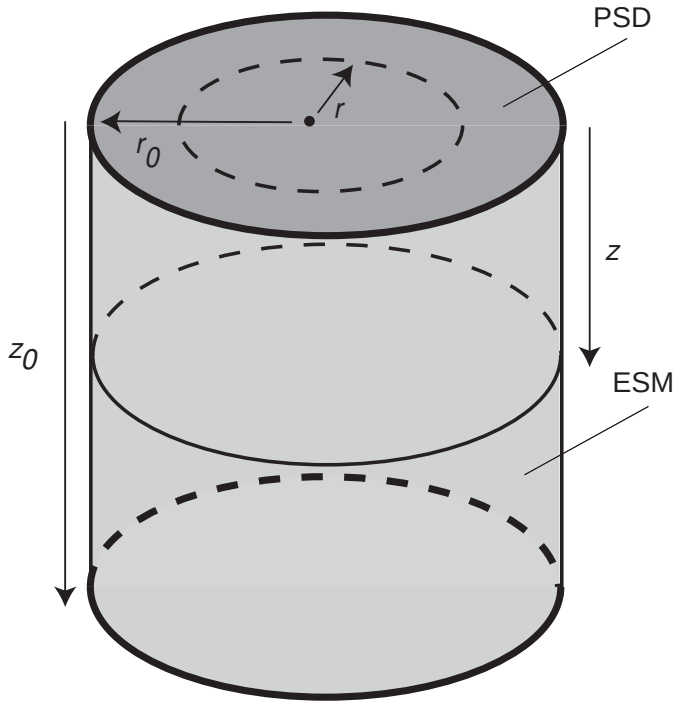
C. Tardin et al. *EMBO J.* **22** 4656–4665 (2003).

L. Groc et al. *Nat. Neurosci.* **7** 695–696 (2004).

M.C. Ashby et al. *J. Neurosci.* **26** 7046–7055 (2006).

Model – Spine geometry

- **Cylinder**
  - Radius: $r_0 = 0.2\mu$m
  - Length: $z_0 = 1.0\mu$m
  - Body: ESM ($A_{ESM} = 1.257\mu\text{m}^2$)
  - Top: PSD ($A_{PSD} = 0.1257\mu\text{m}^2$)
  - Bottom: dendrite junction
- **Diffusion is fast**
  - Time constant of diffusion: $\tau = A/D \sim 10$s
  - Other time constants: $\tau \geq 10$min
  - $\Rightarrow$ uniform concentrations



Model – Trafficking

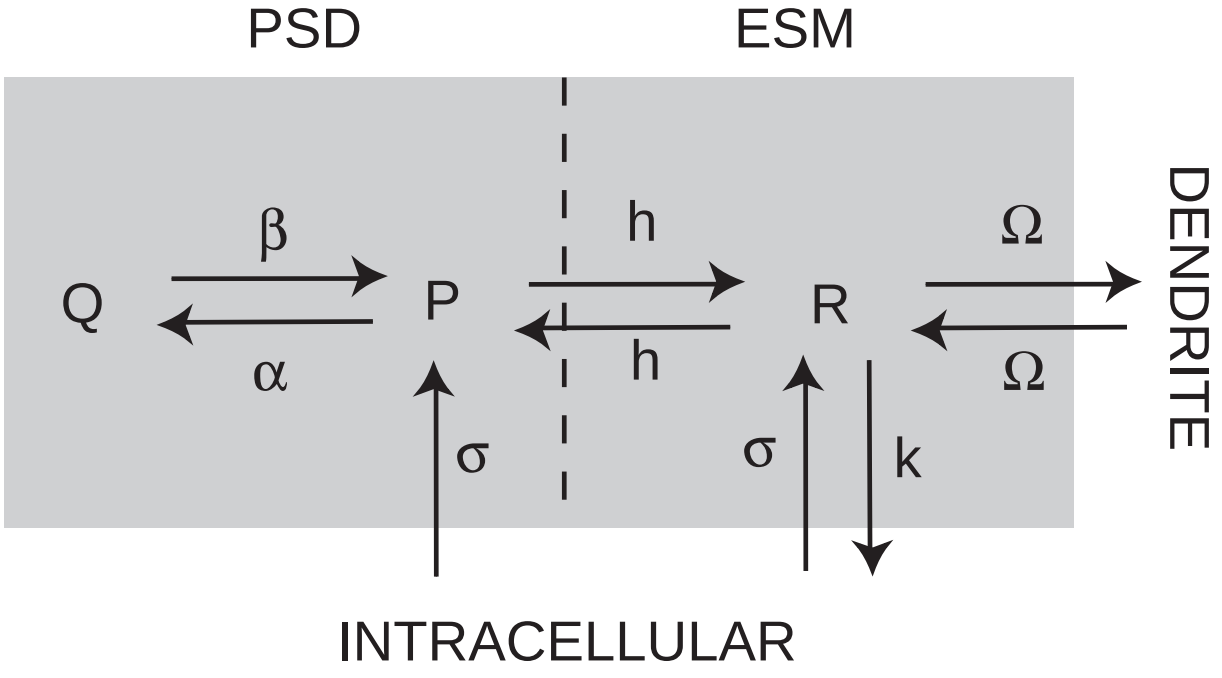
P, Q: Free/Bound AMPAR concentration in PSD

R: Free AMPAR concentration in ESM

α, β: Binding/unbinding rate

σ, k: Exo/endocytosis

h, Ω: PSD-ESM/ESM-dendrite hopping rate



Model Equations – AMPAR in PSD

$$\frac{dP_I}{dt} = -\alpha_I(L - Q_I - Q_{II})P_I + \beta_I Q_I - \frac{h_I}{A_{PSD}}(P_I - R_I)$$

$$\frac{dP_{II}}{dt} = -\alpha_{II}(L - Q_I - Q_{II})P_{II} + \beta_{II} Q_{II} - \frac{h_{II}}{A_{PSD}}(P_{II} - R_{II}) + \frac{\sigma_{II}}{A_{PSD}}$$

$$\frac{dQ_I}{dt} = \alpha_I(L - Q_I - Q_{II})P_I - \beta_I Q_I$$

$$\frac{dQ_{II}}{dt} = \alpha_{II}(L - Q_I - Q_{II})P_{II} - \beta_{II} Q_{II}$$

Subscripts: I = GluR1/2, II = GluR2/3

L = scaffolding protein concentration (e.g. PSD-95)

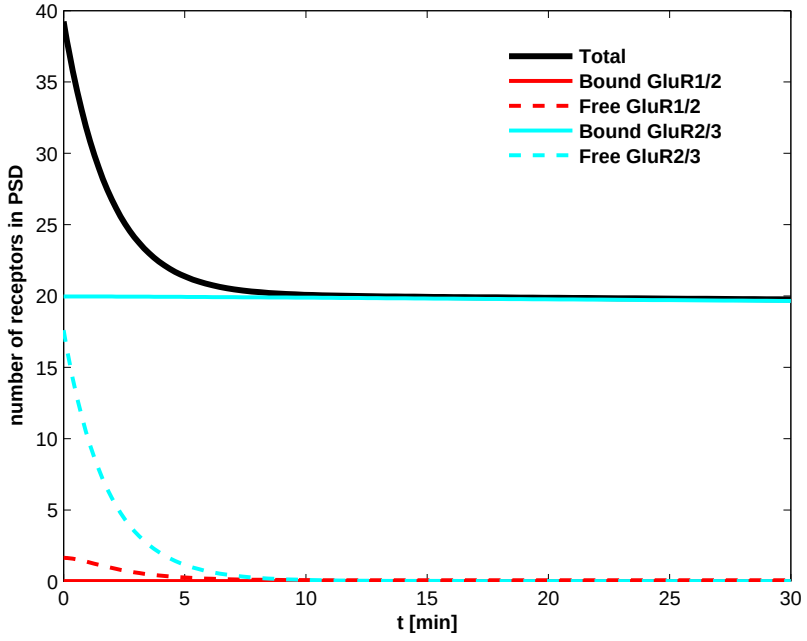
Model Equations – AMPAR in ESM

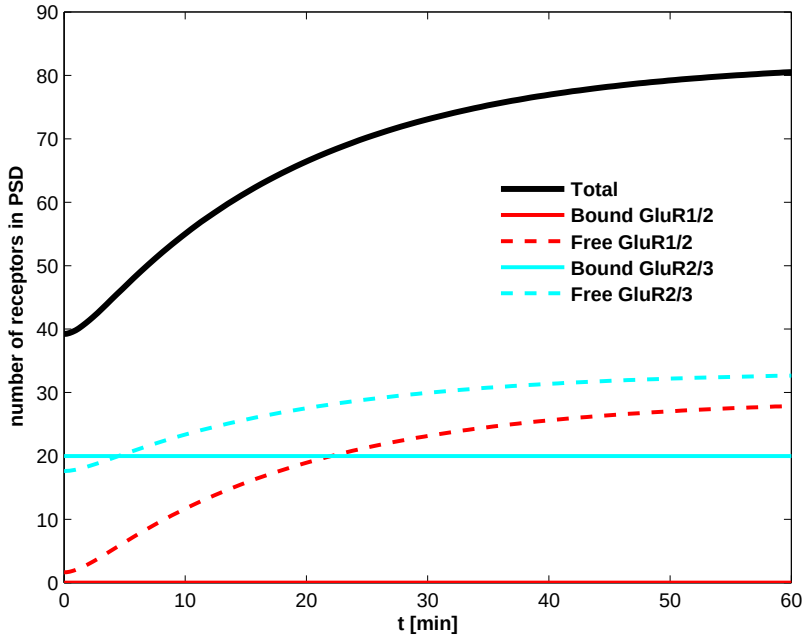
$$\frac{dR_I}{dt} = \frac{h_I}{A_{ESM}}(P_I - R_I) - \frac{\Omega_I}{A_{ESM}}(R_I - \overline{R}_I) - k_I R_I + \frac{\sigma_I}{A_{ESM}}$$

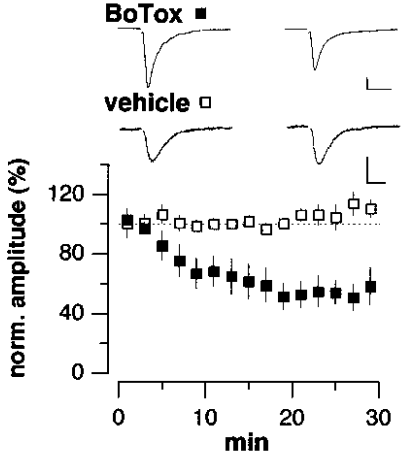
$$\frac{dR_{II}}{dt} = \frac{h_{II}}{A_{ESM}}(P_{II} - R_{II}) - \frac{\Omega_{II}}{A_{ESM}}(R_{II} - \overline{R}_{II}) - k_{II} R_{II}$$

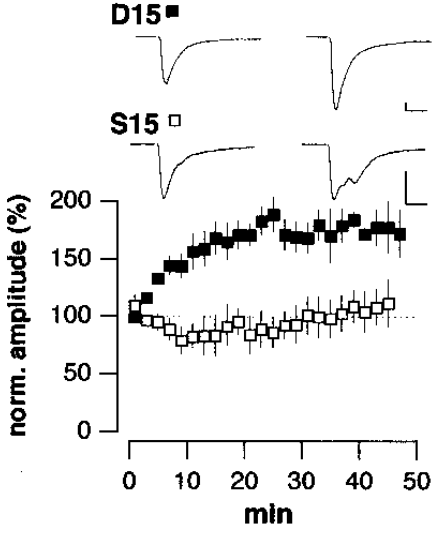
$\overline{R} =$ background AMPAR concentration in dendritic spine

Blocking exo/endocytosis



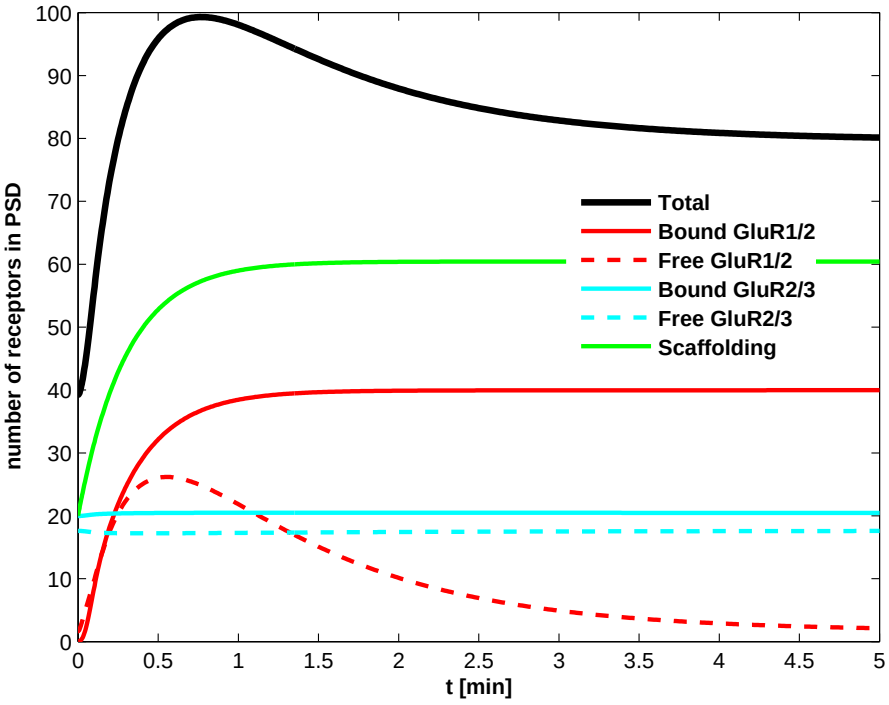


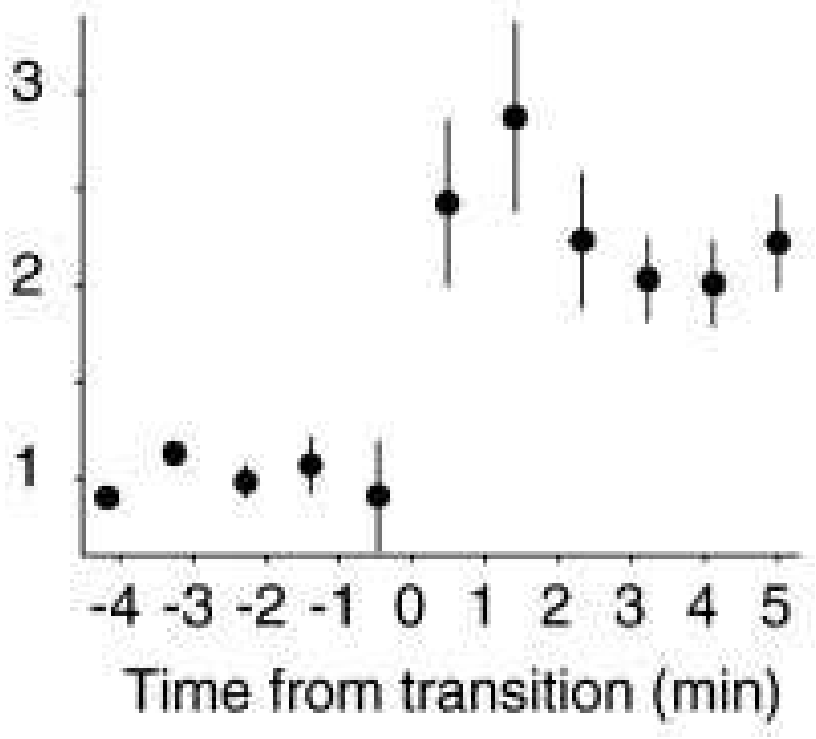




C. Luscher et al. *Neuron* **24** 649–658 (1999).

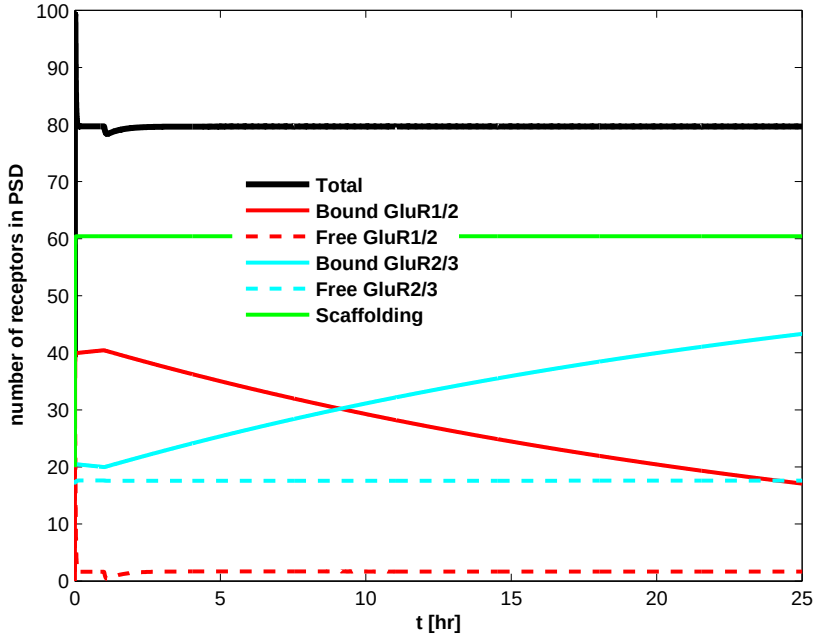
LTP trafficking

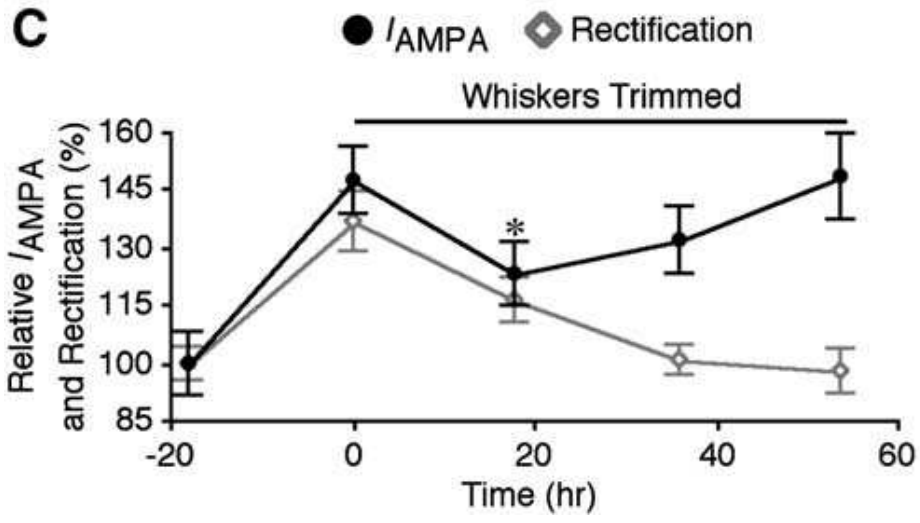




D.H. O'Connor et al. *PNAS* **102** 9679–9684 (2005).

Exchange of GluR1/2 with GluR2/3

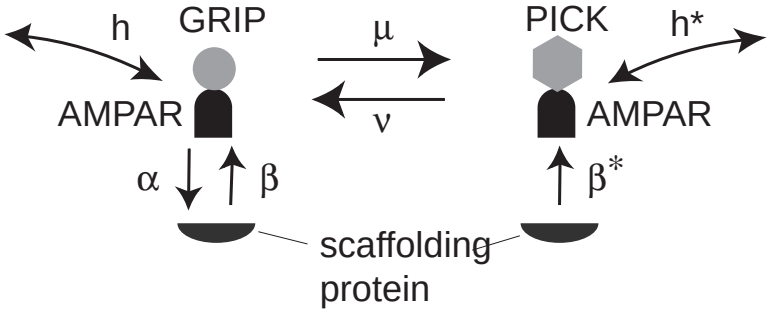


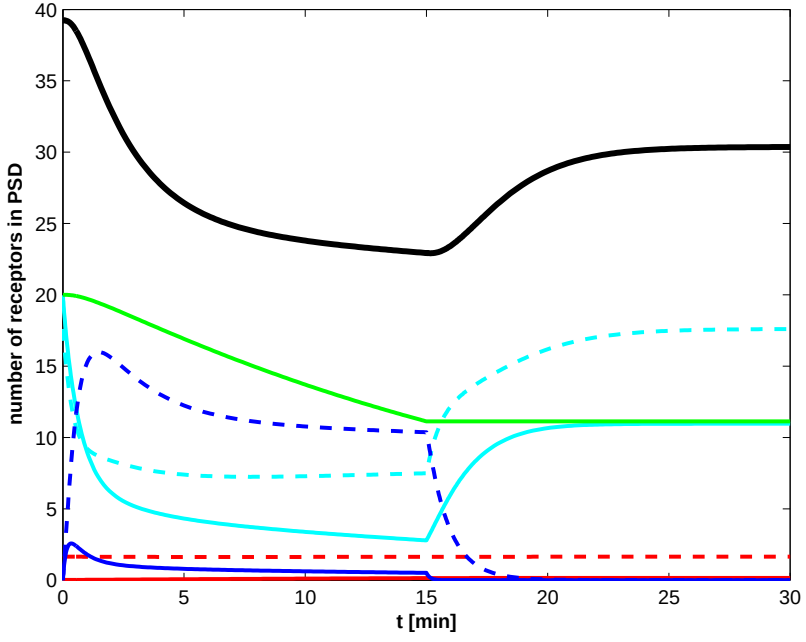


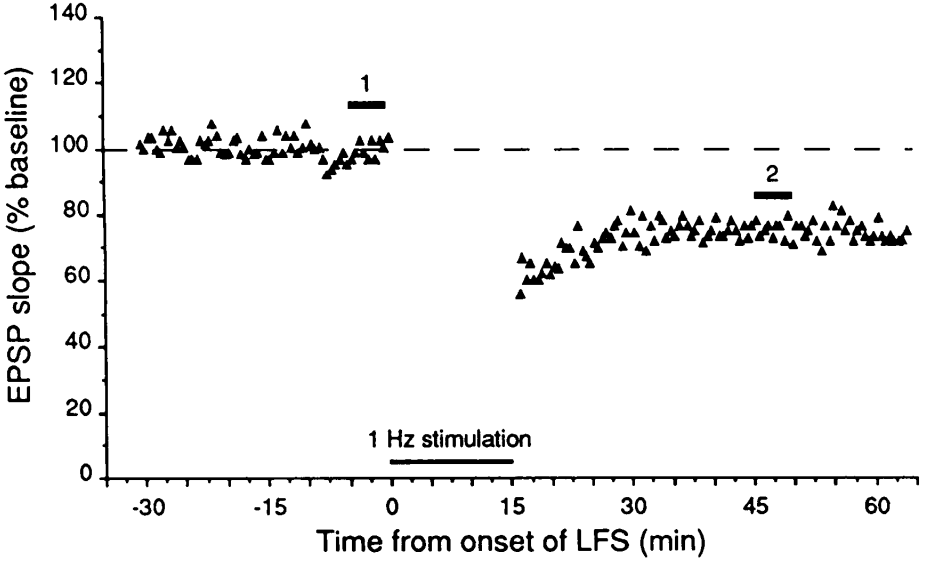
S.G. McCormack et al. *Neuron* **50** 75–88 (2006).

LTD trafficking

During induction of LTD, AMPAR+GRIP → AMPAR+PICK



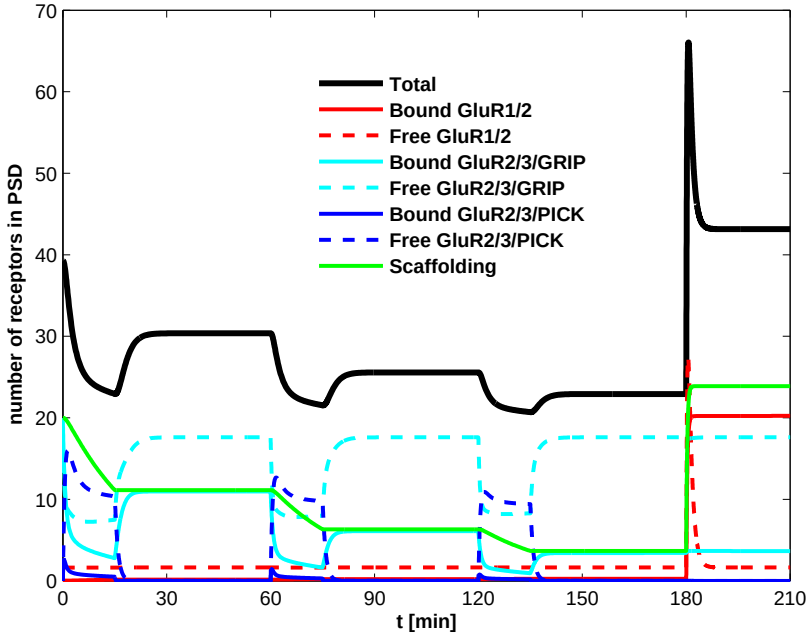


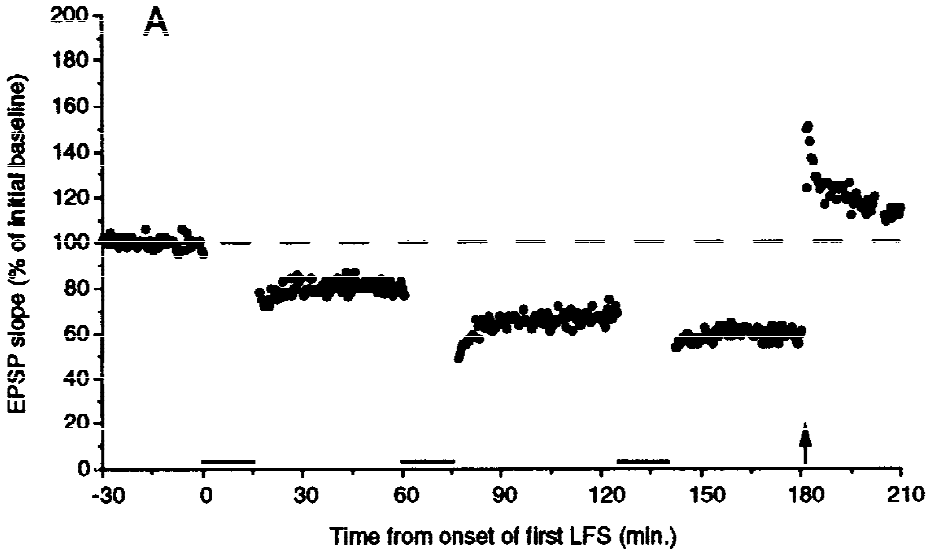


S.M. Dudek and M.F. Bear. *PNAS* **89** 4363–4367 (1992).

Saturation of LTD

Induce LTD 3 times, then LTP





S.M. Dudek and M.F. Bear. *J. Neurosci.* **13** 2910–2918 (1993).

Review – Experiments reproduced

1. Basal AMPAR numbers (Cottrell et al., 2000)
2. Changes in synaptic strength after blocking exo/endocytosis (Luscher et al., 1999)
3. Changes in synaptic strength during LTP expression (O'Connor et al., 2005)
4. Slow exchange of GluR1/2 with GluR2/3 after LTP (McCormack et al., 2006)
5. Changes in synaptic strength during LTD expression, stimulation frequency dependence (Dudek and Bear, 1992)
6. Saturation of LTD (Dudek and Bear, 1993).

Conclusions

1. Significant fraction of **PSD receptors are mobile**
   - Consistent with Groc et al., 2004; Ashby et al., 2006
   - Requires PSD-ESM barrier
   - Required for exocytosis blockade time-course
   - Required for LTD saturation
2. Significant **diffusive impedance at spine neck**
   - Consistent with Ashby et al., 2006
   - Required for endocytosis blockade time-course
   - Required for LTP time-course

Conclusions

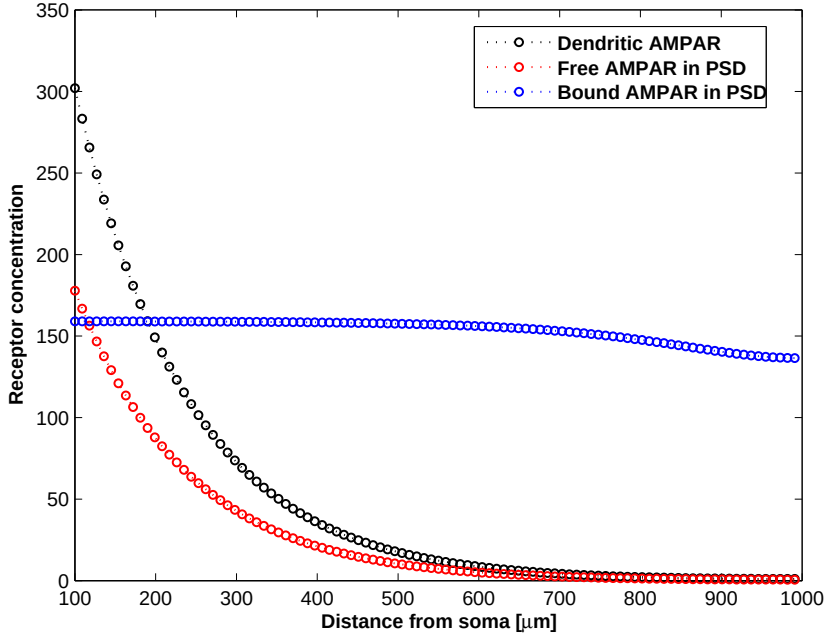
3. Available **scaffolding proteins are saturated** with AMPAR under basal conditions
   - Required for just about everything
   - Hypothesis: “slot proteins” encode memory
4. Exocytosis of intracellular GluR1/2 during LTP must combine **synaptic targeting**
   - Consistent with Schnell et al., 2002
   - Requires increased hopping, binding rate (e.g. stargazin)
   - Requires **additional scaffolding proteins**
   - Required for LTP time-course

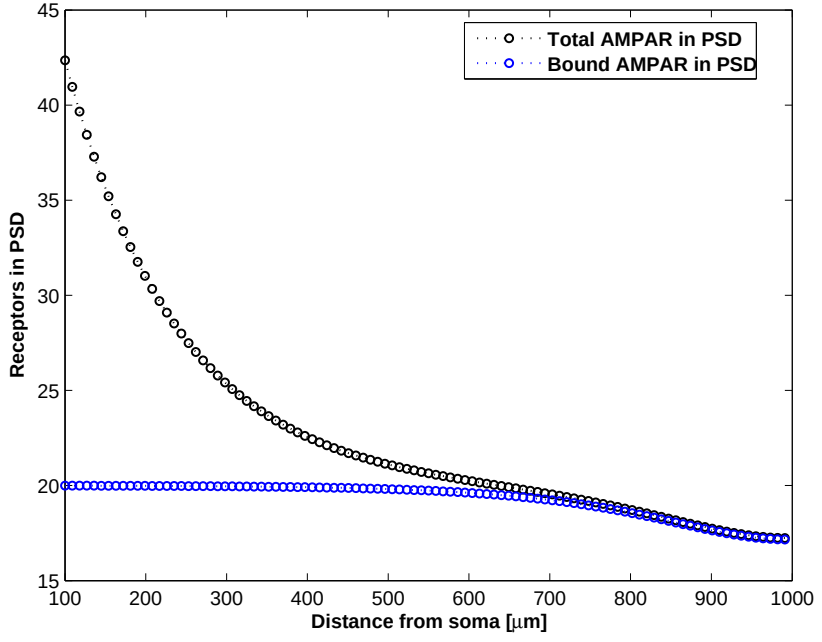
Conclusions

5. Slow exchange of GluR1/2 with GluR2/3 after LTP requires **maintenance of additional scaffolding proteins**
   - Required for exchange time-course
6. GRIP to PICK1 exchange must be accompanied by **loss of scaffolding proteins**
   - Consistent with Colledge et al., 2003
   - Required for LTD time-course and saturation

Current work

- **Multiple synapse model**
  - Single-synapse model distributed on dendritic cable
  - Exo/endocytosis at soma (Adesnik et al., 2005)
  - Homeostatic plasticity (Turrigiano et al., 1998)
  - Heterosynaptic plasticity/competition (Royer and Paré, 2003)





Current work

- **Effects of membrane curvature**
  - Curvature may affect receptor diffusion
  - Estimate Ω
- **Stochastic model**
  - Estimate variance in EPSP recordings

The end