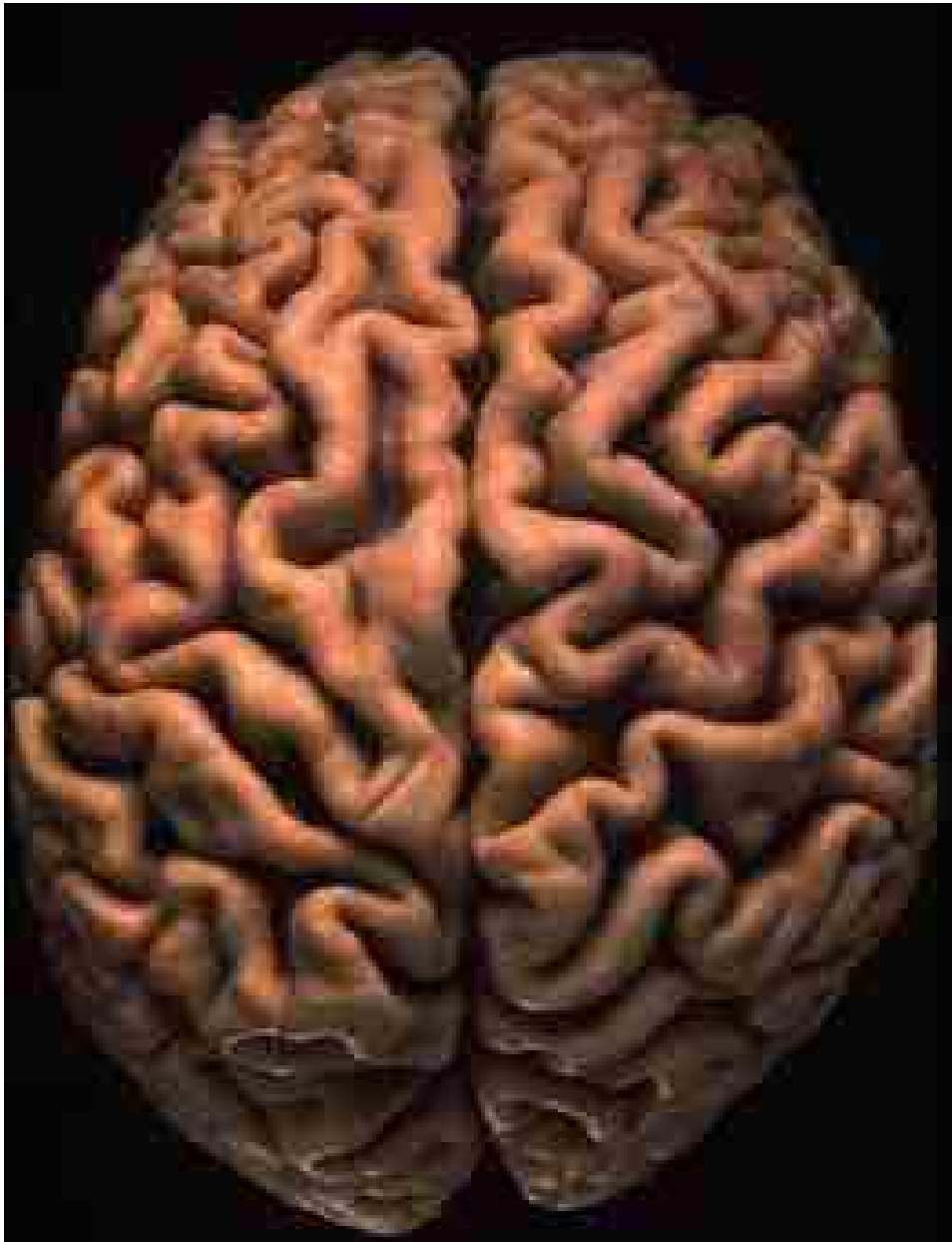


Biophysical model of AMPA receptor trafficking and its regulation during LTP/LTD

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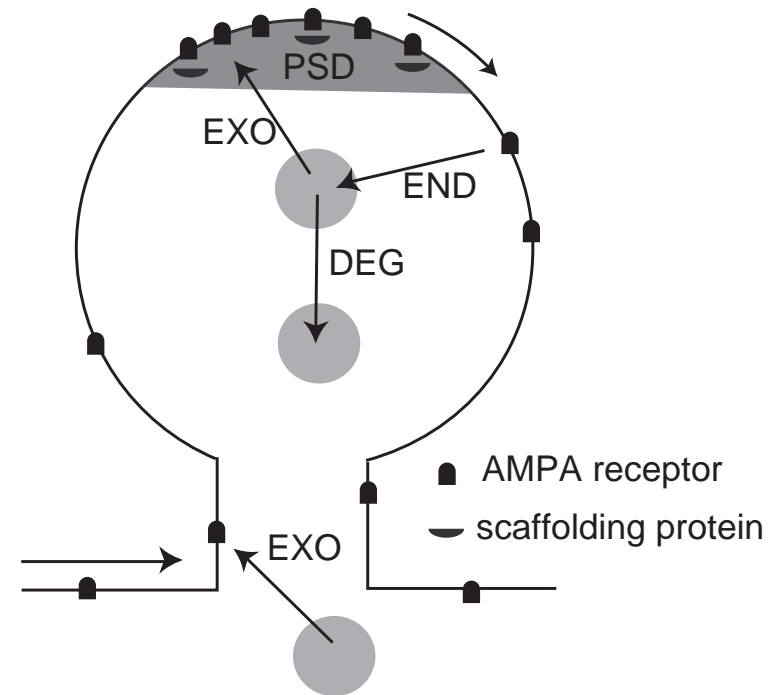
The brain: unparalleled parallel computer



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

AMPA receptor trafficking

- **Exo/endocytosis** $\tau \sim 10\text{-}30\text{min}$
- **Lateral diffusion**
 - Brownian in ESM $\sim 0.1 \mu\text{m}^2/\text{s}$
 - Confined in PSD $\sim 0.01 \mu\text{m}^2/\text{s}$
 - PSD-ESM boundary barrier
 - Spine neck impedance
- **Immobilization by scaffold**
- **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).

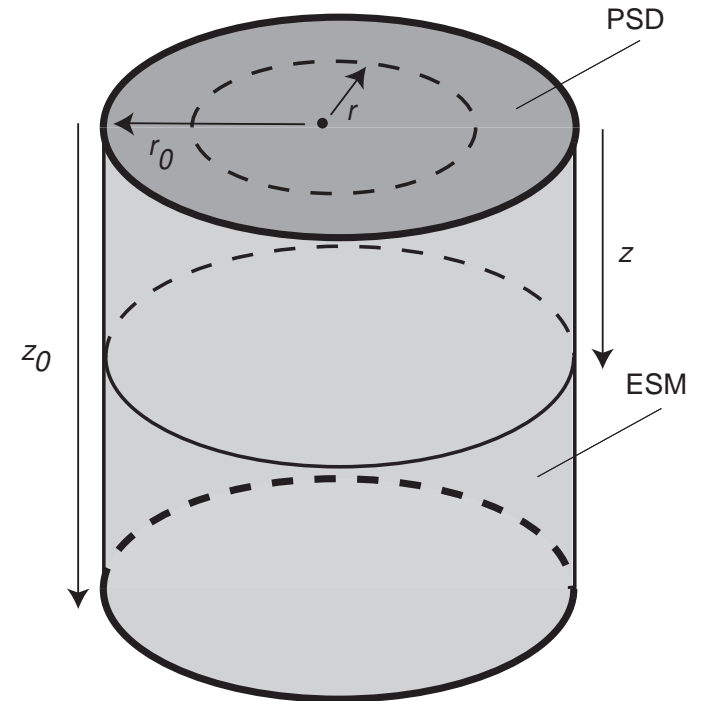
Model – Spine geometry

- **Cylinder**

- Radius: $r_0 = 0.2\mu\text{m}$
- Length: $z_0 = 1.0\mu\text{m}$
- Body: ESM ($A_{ESM} = 1.257\mu\text{m}^2$)
- Top: PSD ($A_{PSD} = 0.1257\mu\text{m}^2$)
- Bottom: dendrite junction

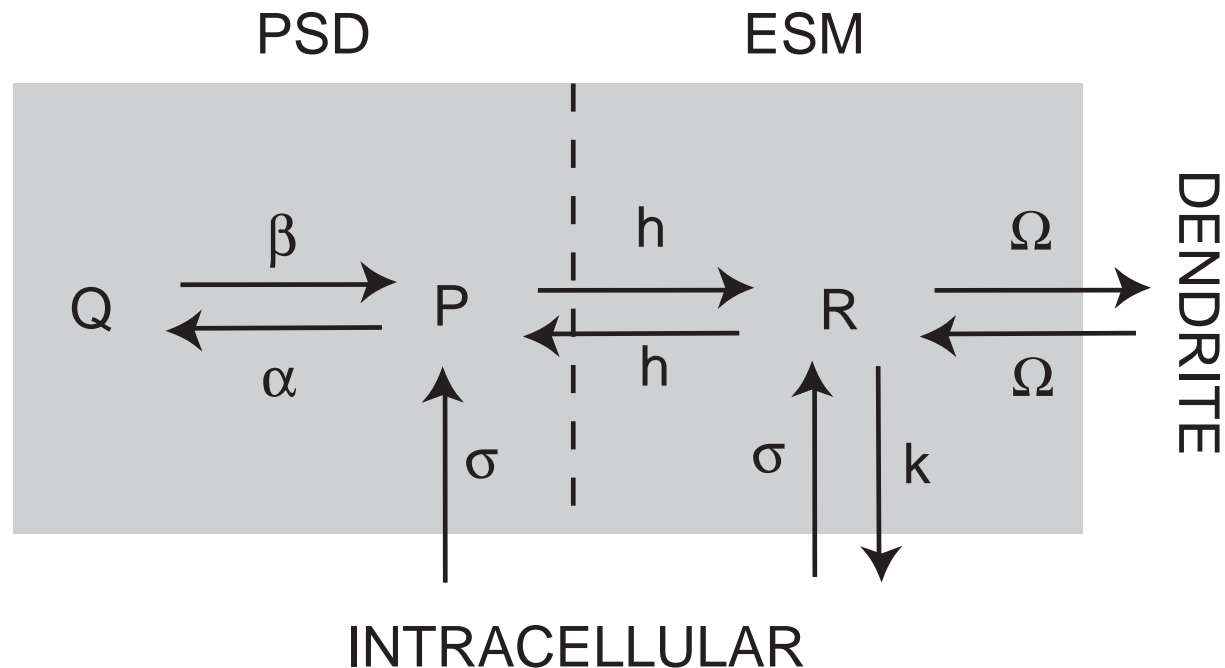
- **Diffusion is fast**

- Time constant of diffusion:
 $\tau = A/D \sim 10\text{s}$
- Other time constants: $\tau \geq 10\text{min}$
- \Rightarrow uniform concentrations

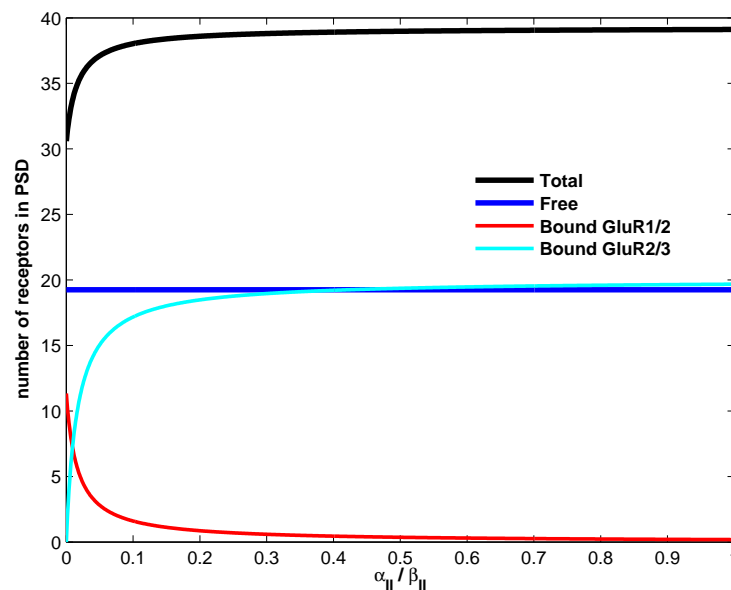
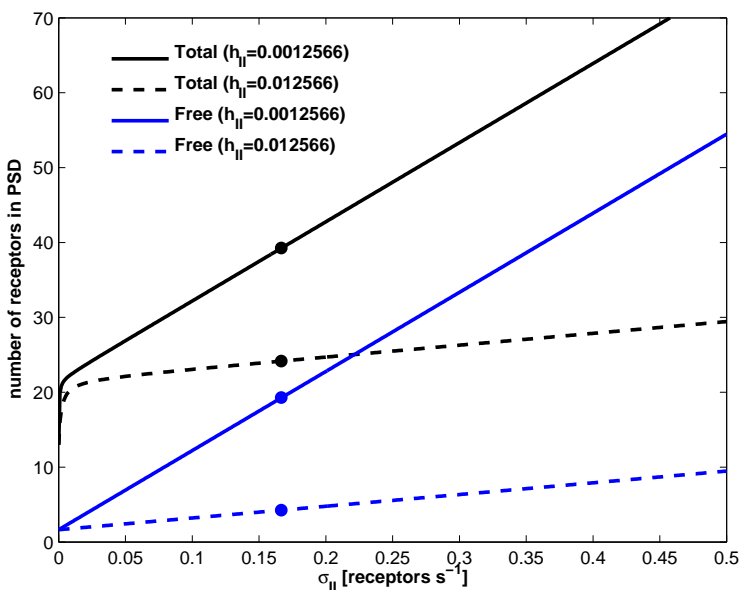
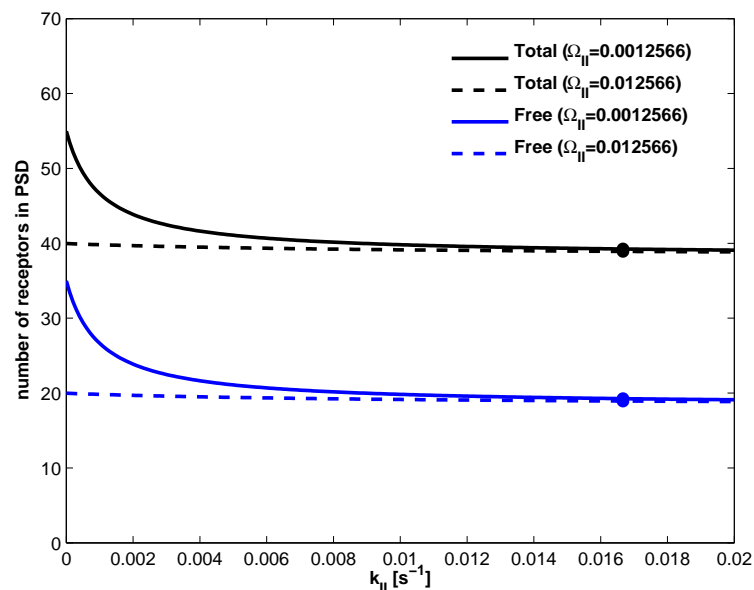
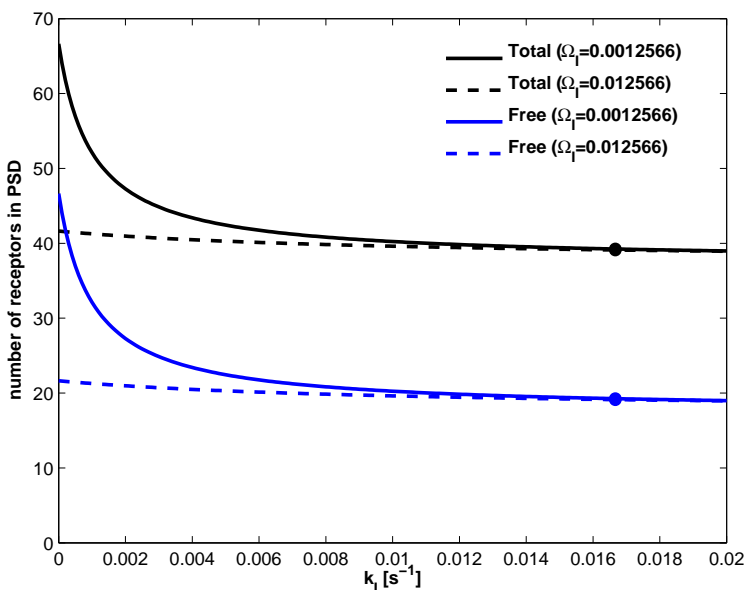


Model – Trafficking

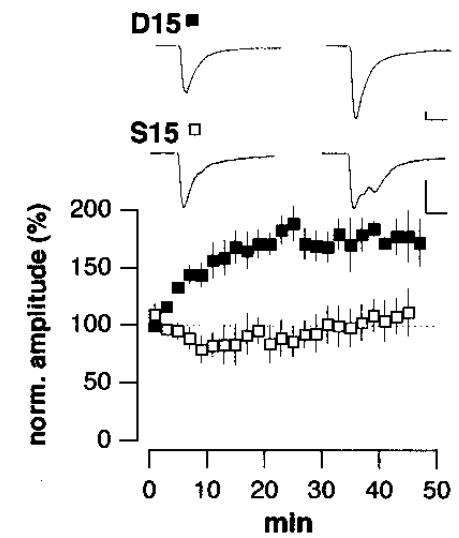
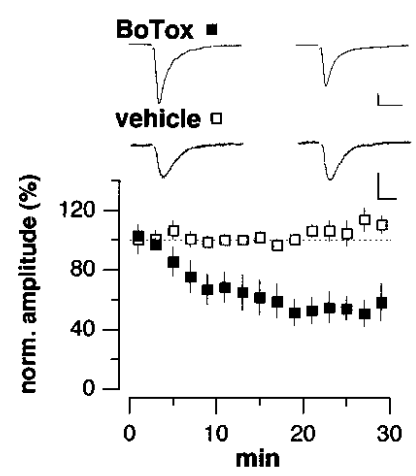
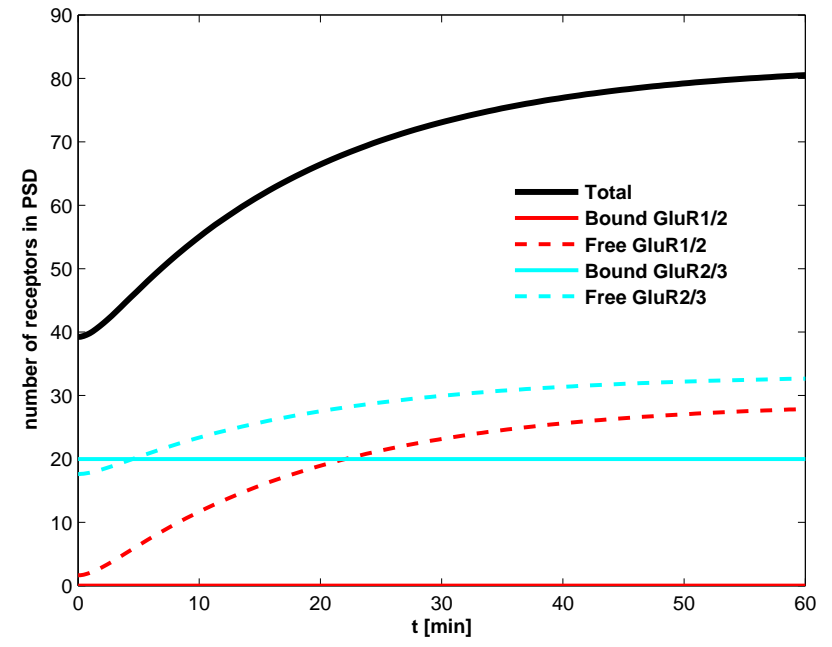
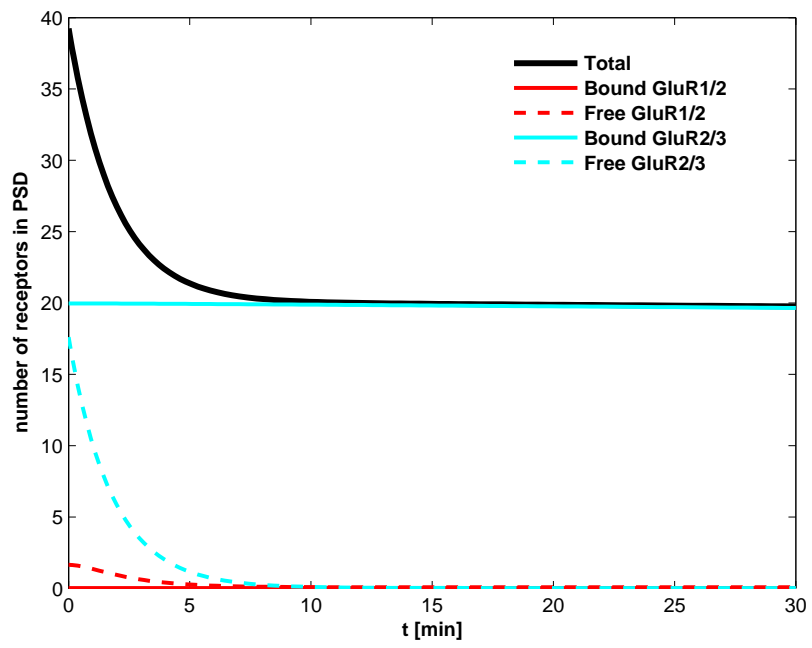
- P, Q : Free/Bound AMPAR concentration in PSD
 R : Free AMPAR concentration in ESM
 α, β : Binding/unbinding rate
 σ, k : Exo/endocytosis
 h, Ω : PSD-ESM/ESM-dendrite hopping rate



Steady-state dependence on parameters



Blocking exo/endocytosis

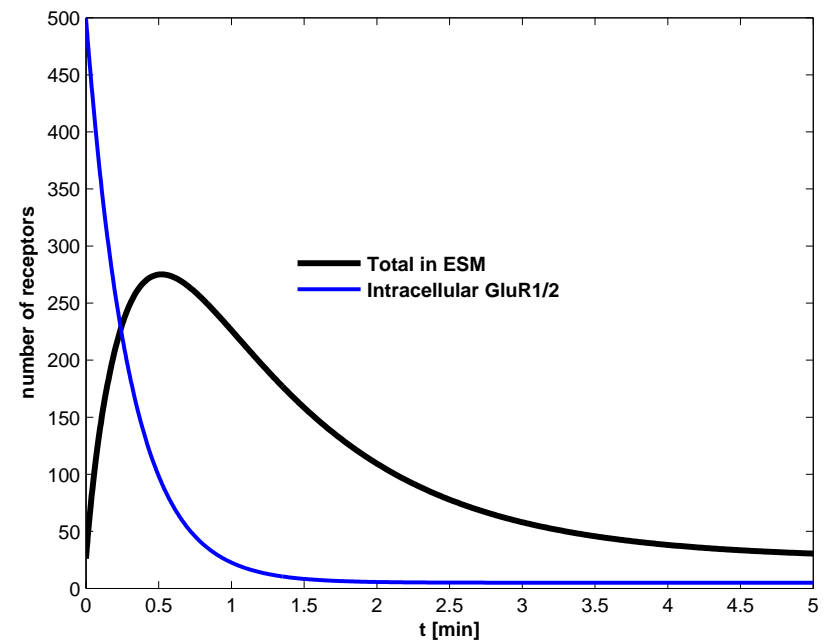
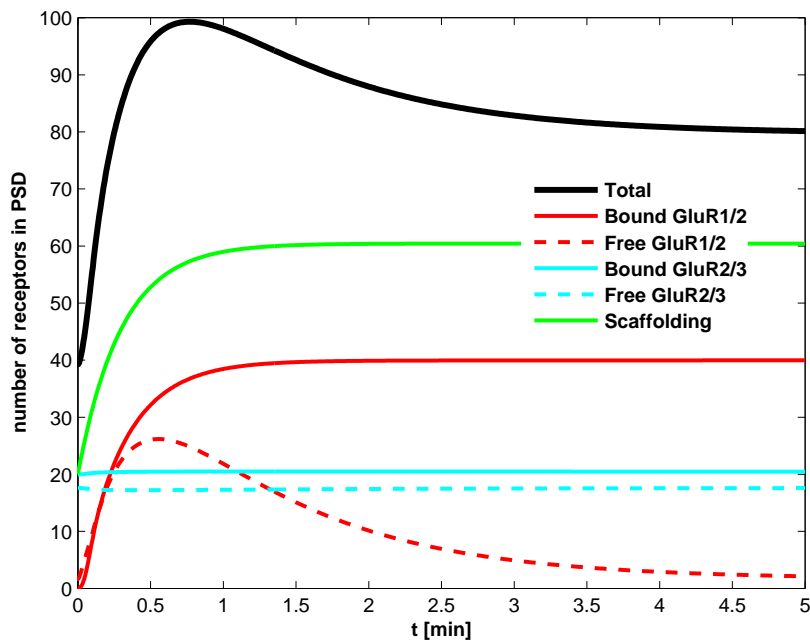


C. Luscher et al. *Neuron* 24 649–658 (1999).

LTP trafficking

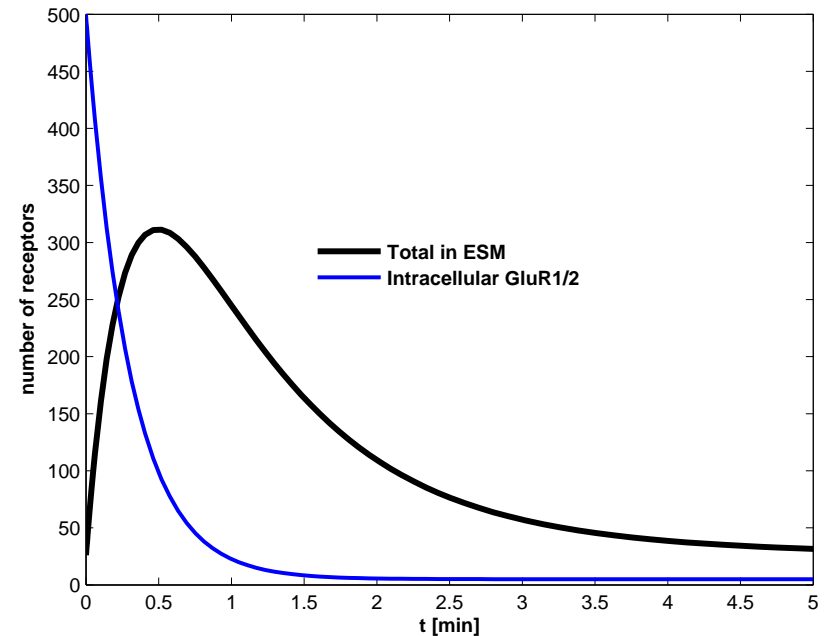
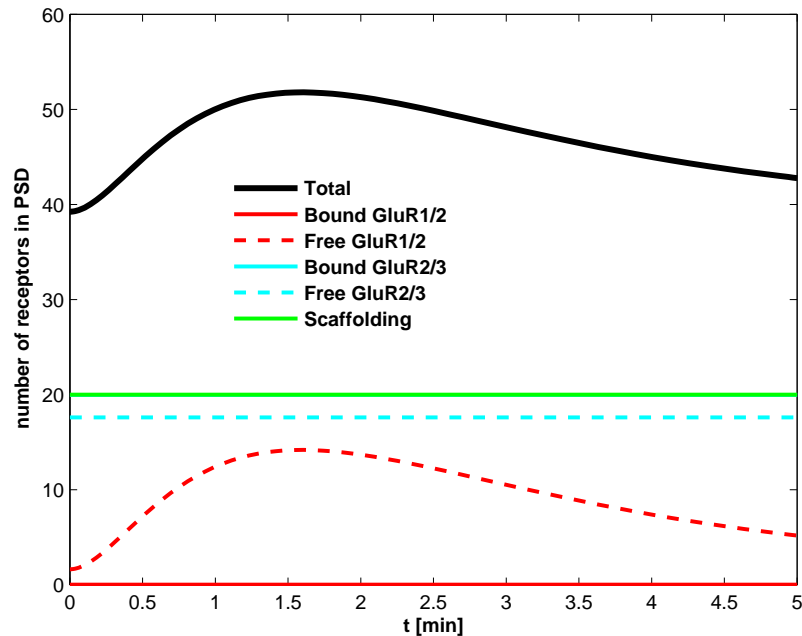
Time-scale of induction **faster** than expression \rightarrow parameters change instantaneously at $t = 0$:

- GluR1/2+stargazin insertion, hopping and binding increase
- Increase in scaffolding protein



Stargazin-only trafficking

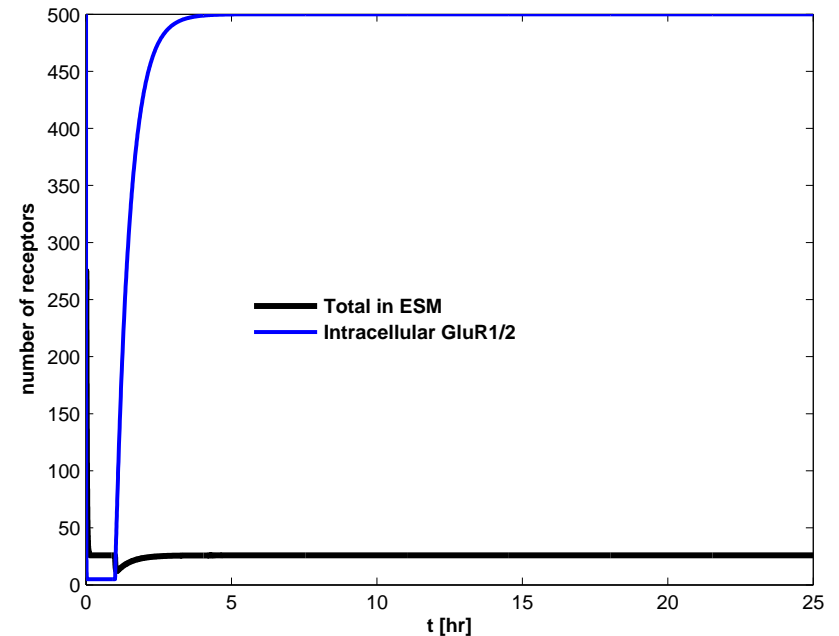
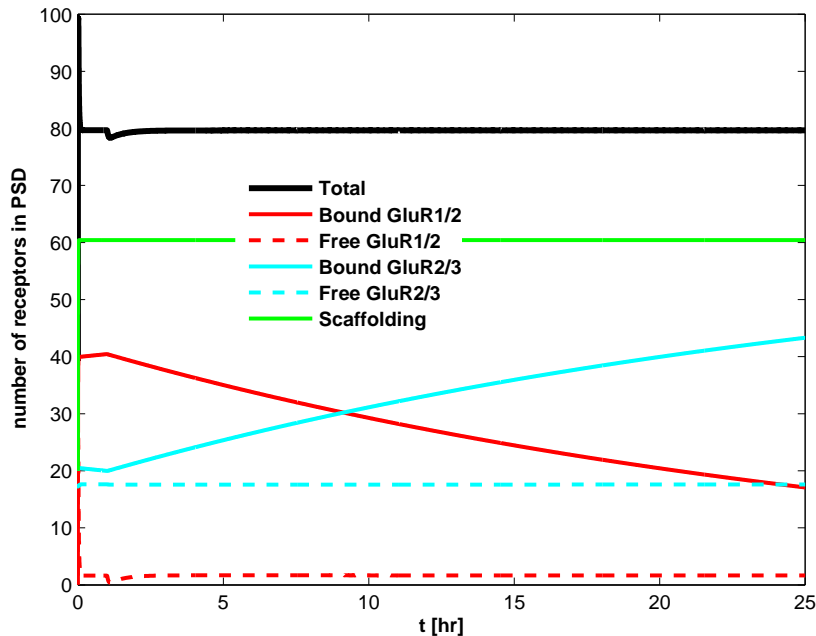
Express stargazin, but no increase in scaffolding (e.g. PSD-95) → only increase exocytosis



E. Schnell et al. *PNAS* 99 13902–13907 (2002).

Exchange of GluR1/2 with GluR2/3

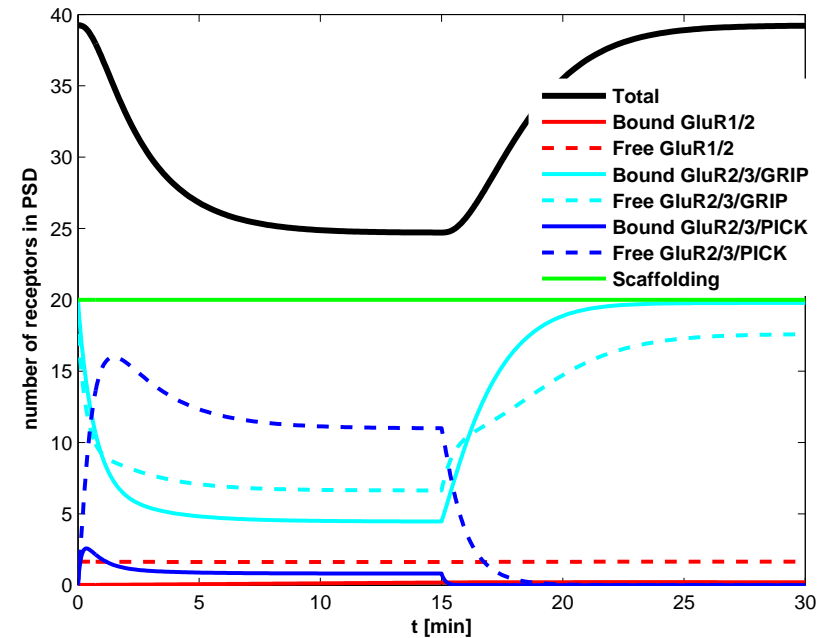
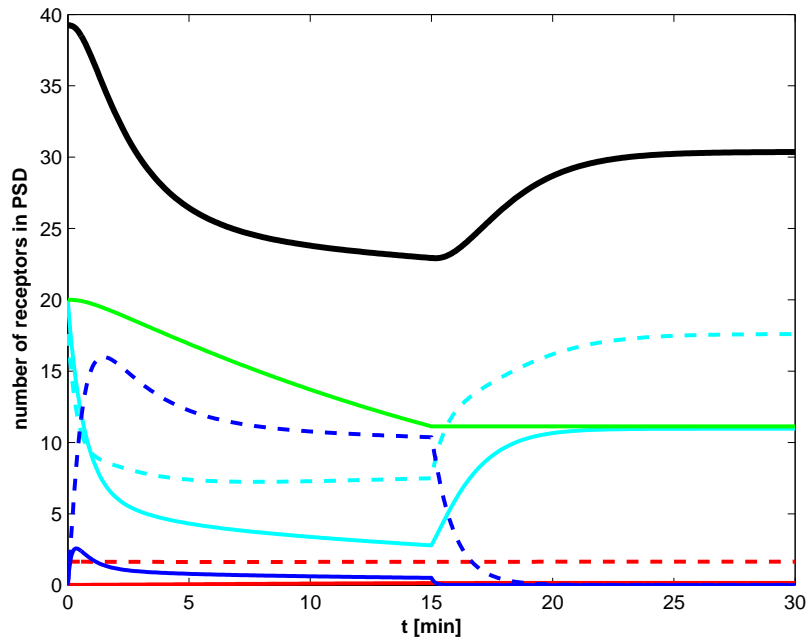
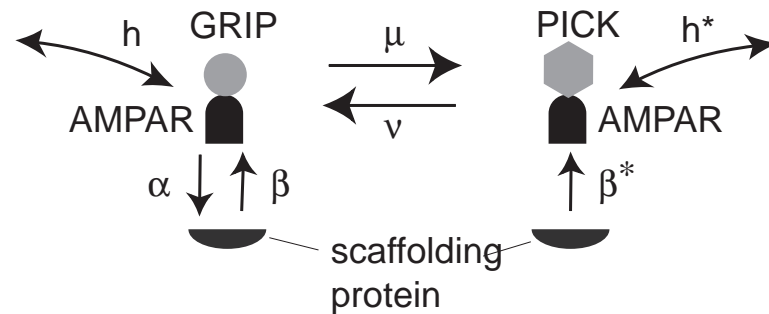
At $t = 1$ hr, all parameters return to basal values, but fix scaffolding concentration



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

LTD trafficking

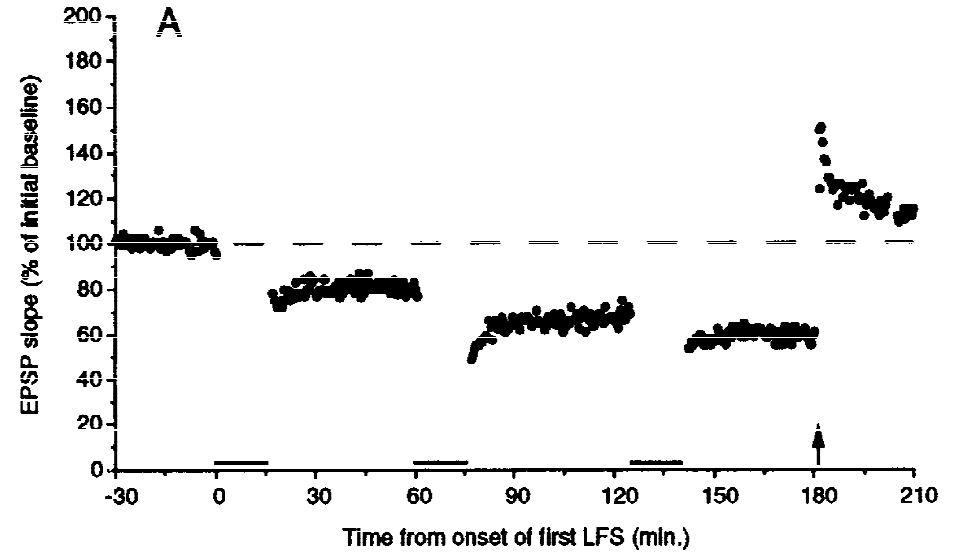
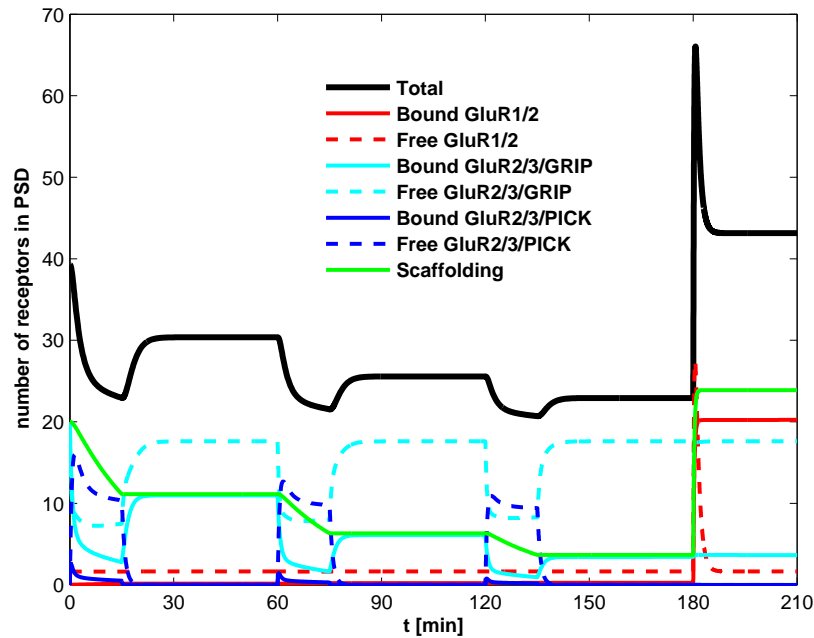
During induction of LTD, AMPAR+GRIP \rightarrow AMPAR+PICK



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

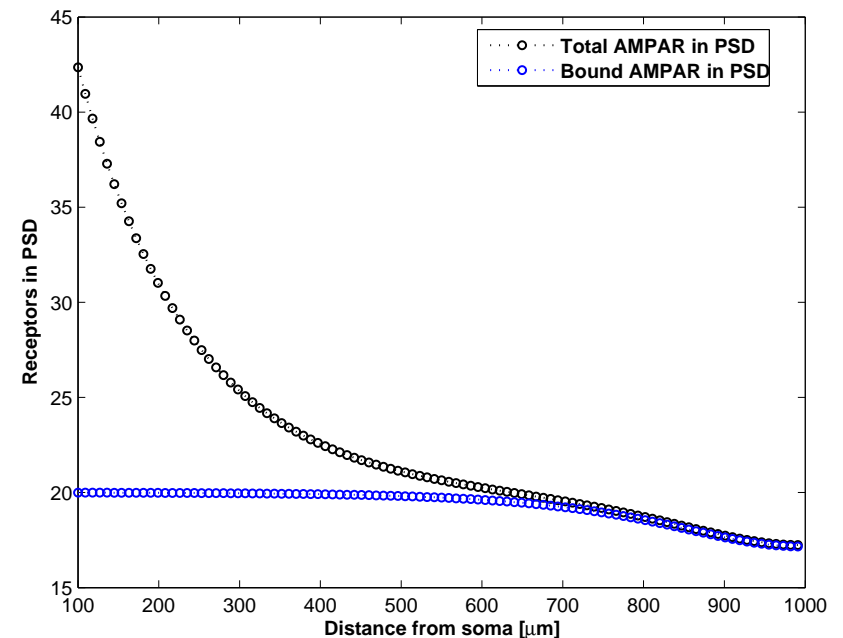
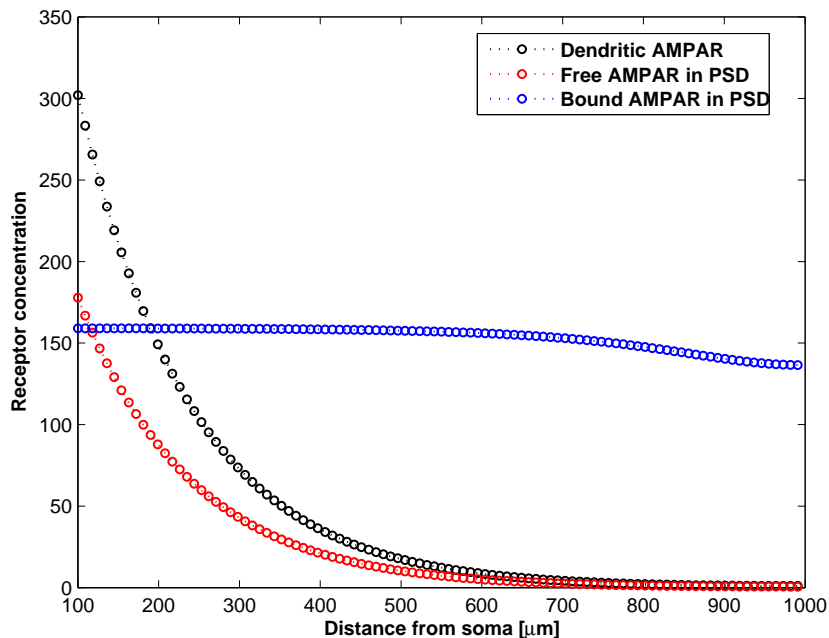
Conclusions

3. Exocytosis of intracellular GluR1/2 during LTP must combine **synaptic targeting**
 - Consistent with Schnell et al., 2002
 - Requires increased hopping, binding rate
 - Requires additional scaffolding proteins
 - Required for LTP time-course
4. Slow exchange of GluR1/2 with GluR2/3 after LTP requires **maintenance of additional binding sites**
 - Required for exchange time-course
5. GRIP to PICK1 exchange must be accompanied by **loss of binding sites**
 - Consistent with Colledge et al., 2003
 - Required for LTD time-course and saturation

Future directions

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)



Future directions

- **Effects of membrane curvature**
 - Curvature may affect receptor diffusion (Faraudo, 2002)
 - Estimate for Ω
- **Stochastic model**
 - Estimate variance in EPSP recordings

The end

