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

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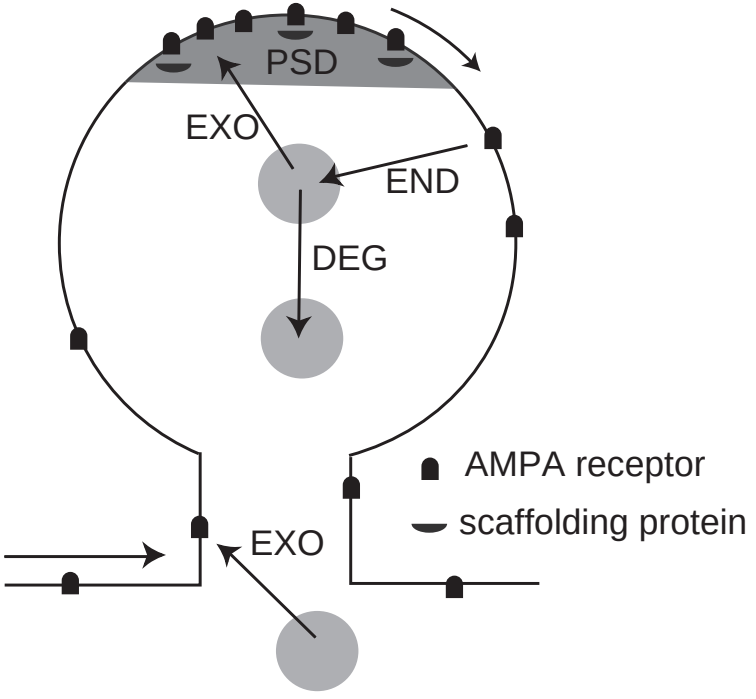
# The brain: unparalled parallel computer

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

# 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-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).

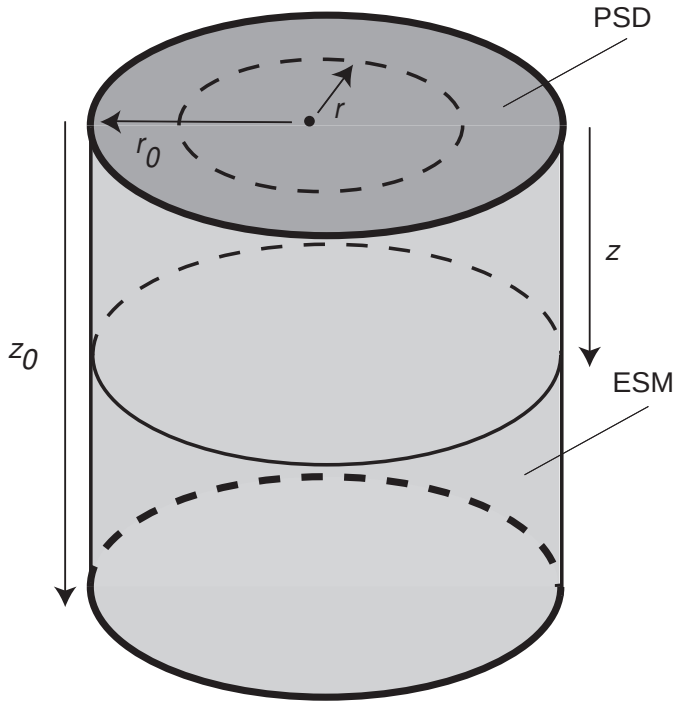
C. Tardin et al. *EMBO J.* **22** 4656–4665 (2003).

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: $r_0 = 0.2\mu$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

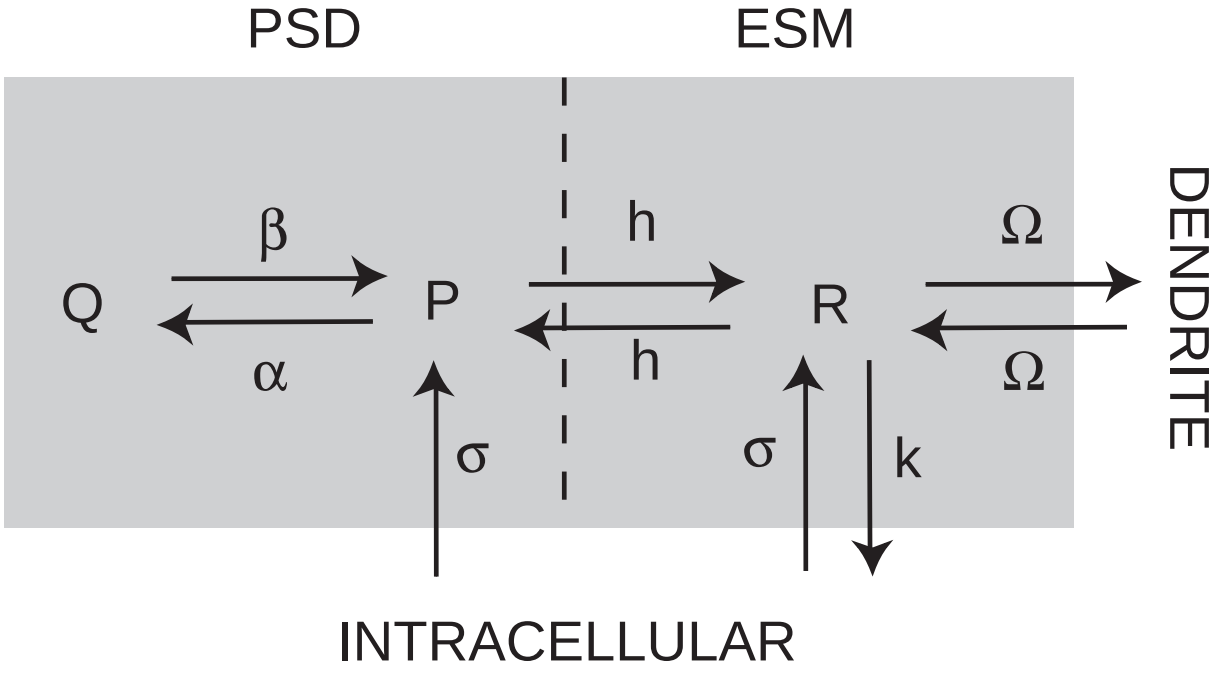
$P, Q$: Free/Bound AMPAR concentration in PSD

$R$: Free AMPAR concentration in ESM

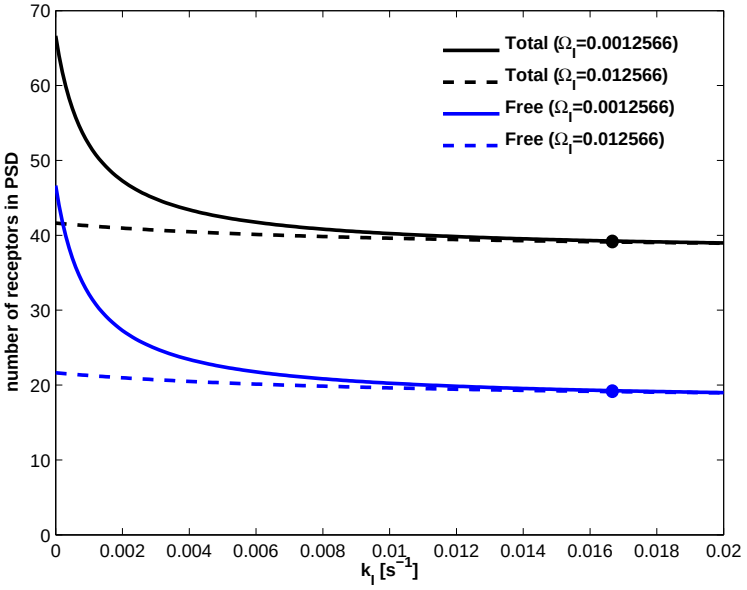
$\alpha, \beta$: Binding/unbinding rate

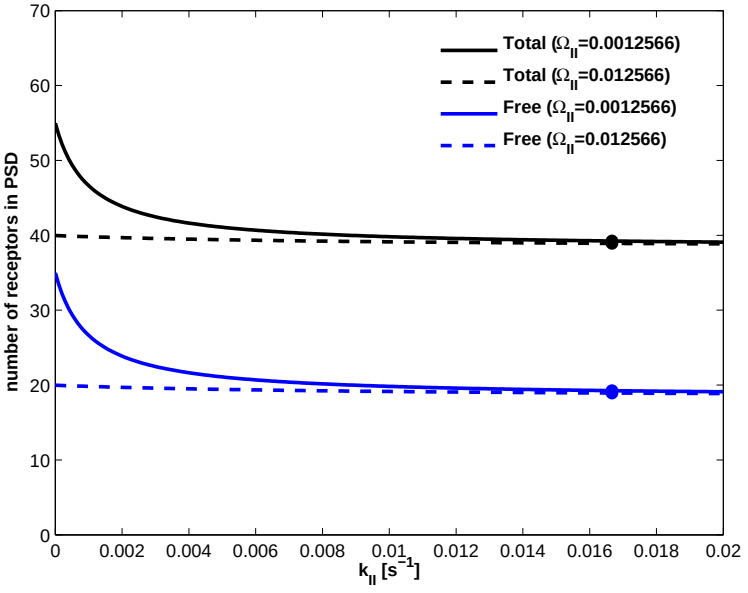
$\sigma, k$: Exo/endocytosis

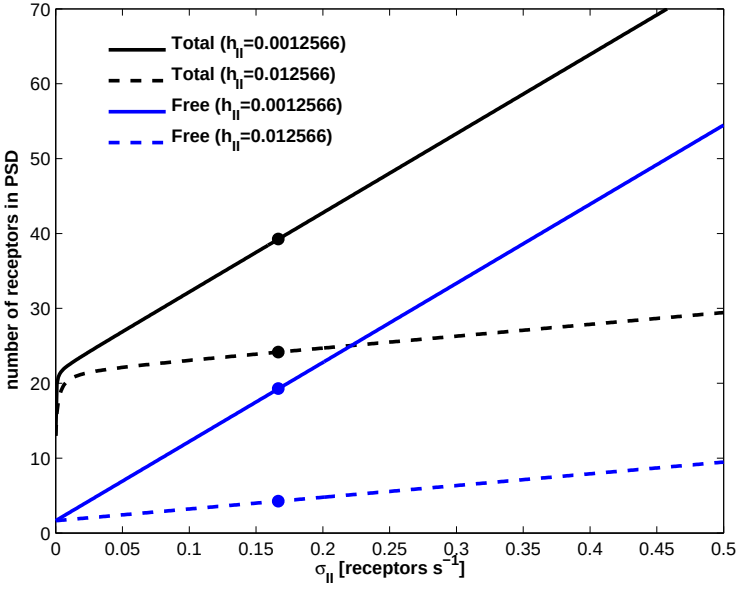
$h, \Omega$: PSD-ESM/ESM-dendrite hopping rate

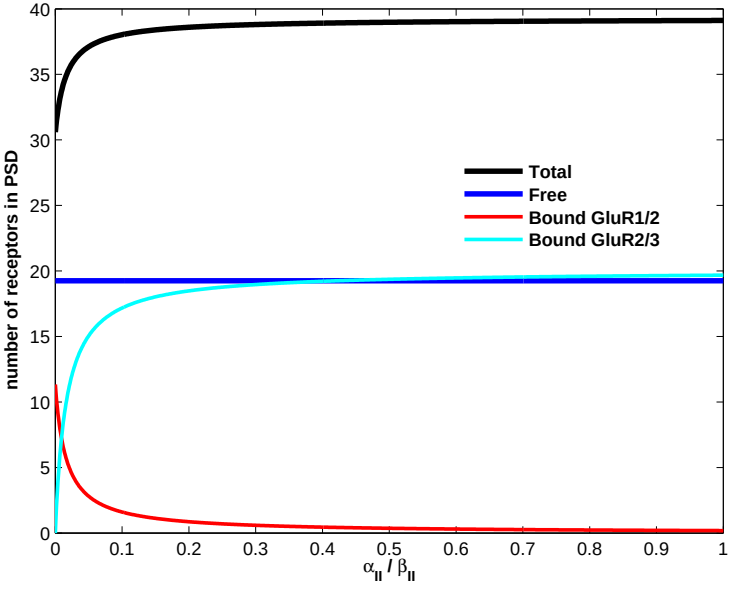


# Steady-state dependence on parameters

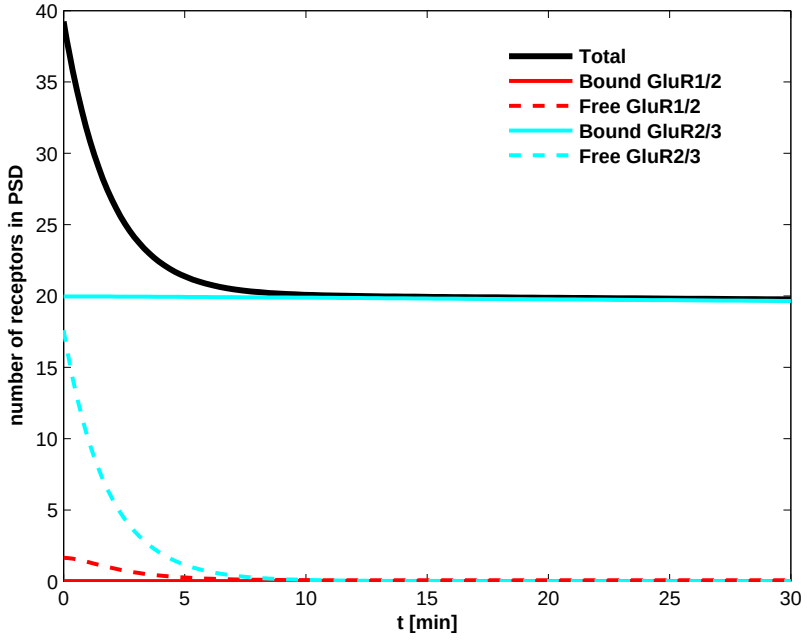


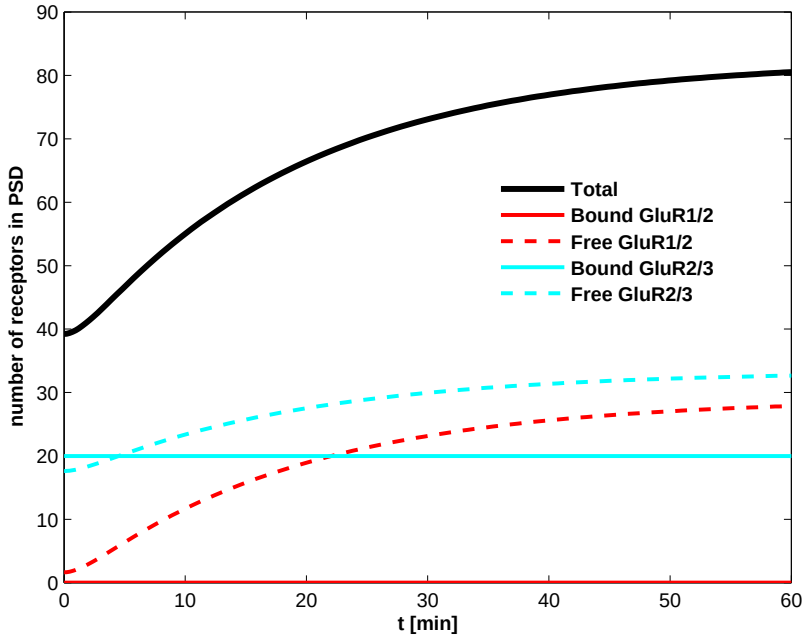



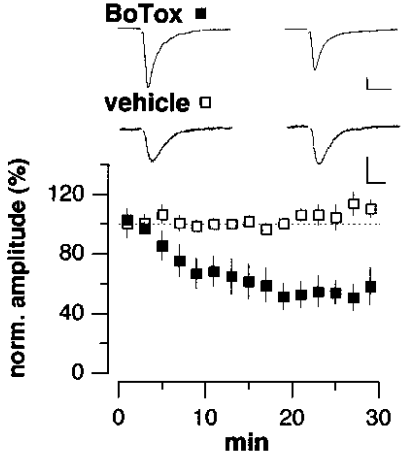



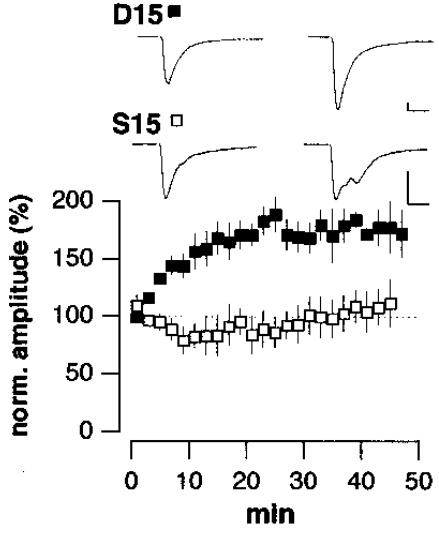



# Blocking exo/endocytosis



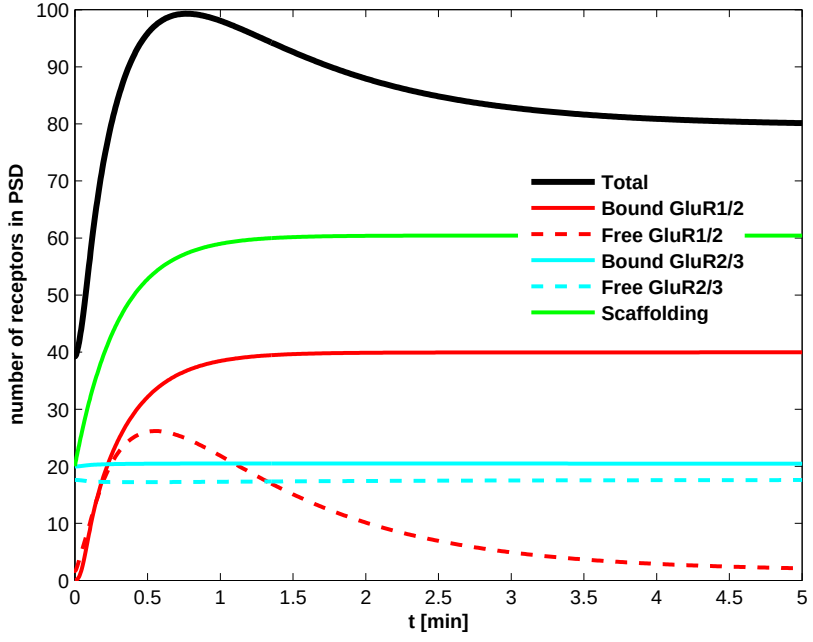



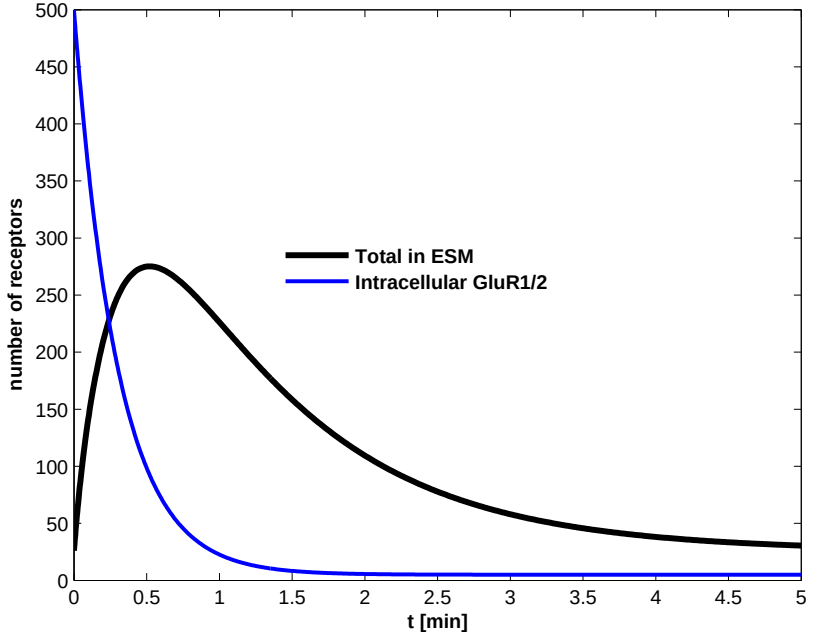

C. Luscher et al. *Neuron* **24** 649–658 (1999).

# LTP trafficking

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

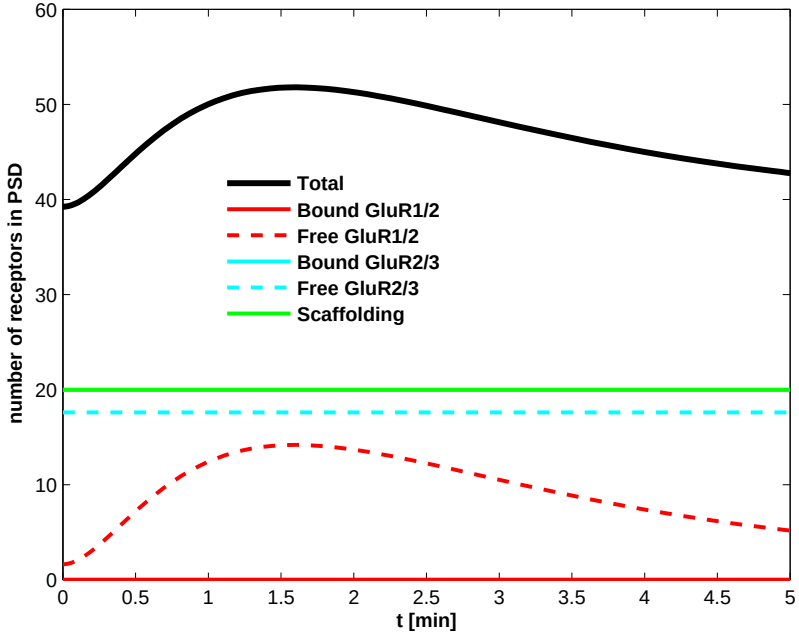
- GluR1/2+stargazin insertion, hopping and binding increase
- Increase in scaffolding protein

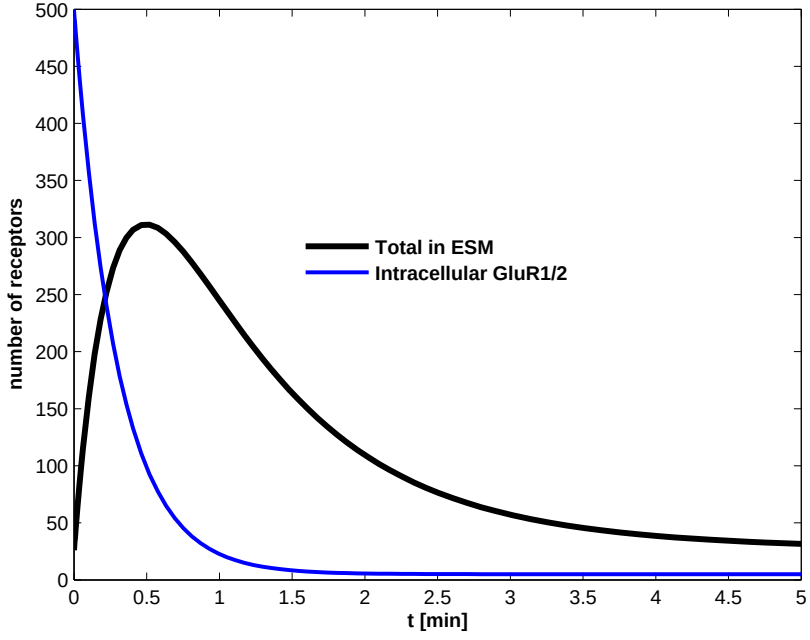


# Stargazin-only trafficking

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

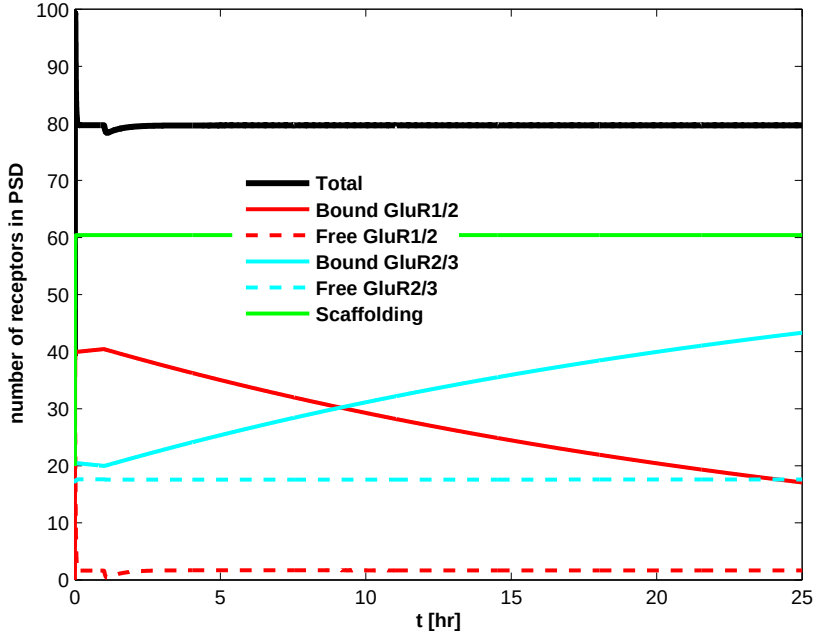


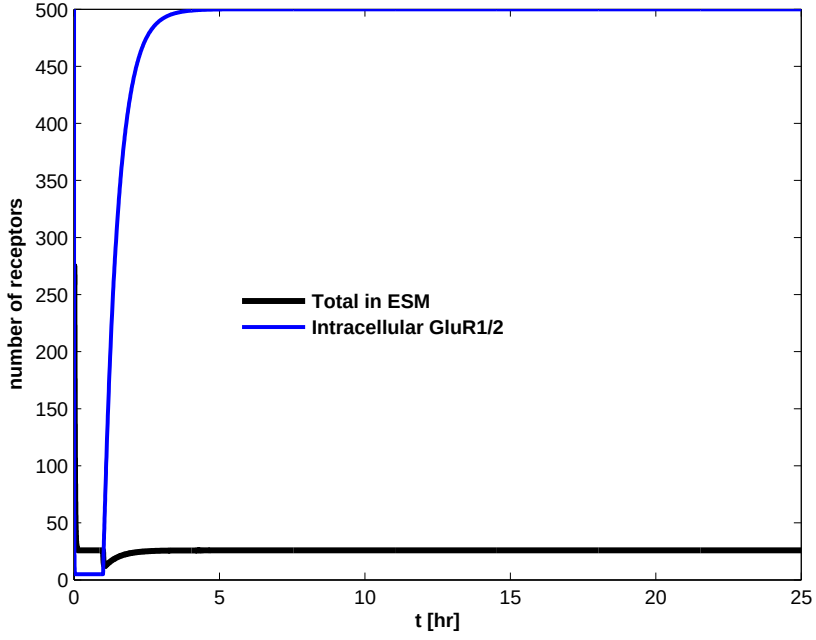




E. Schnell et al. *PNAS* **99** 13902–13907 (2002).

# Exchange of GluR1/2 with GluR2/3

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

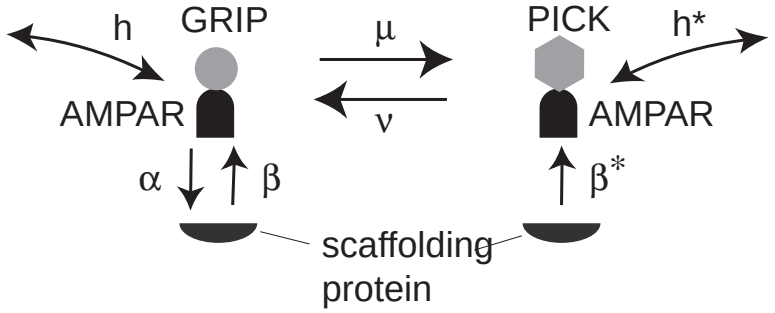


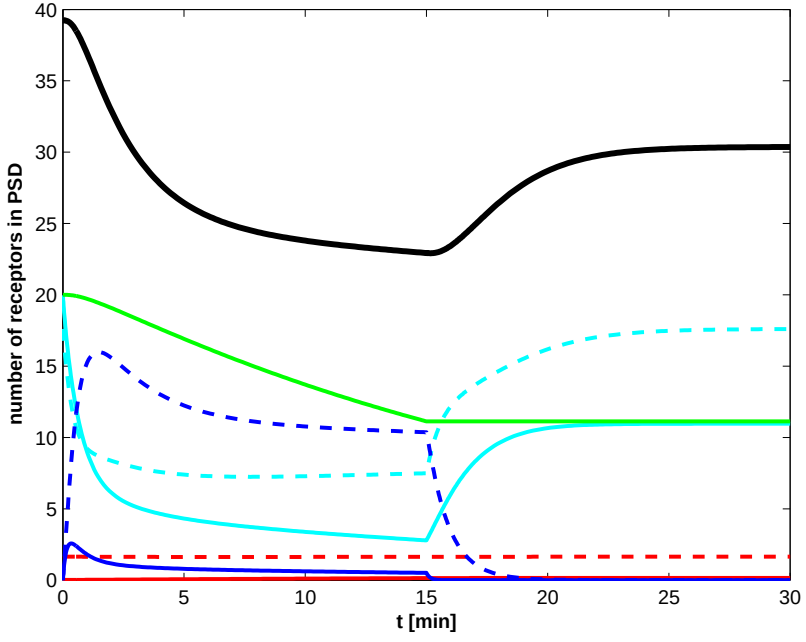



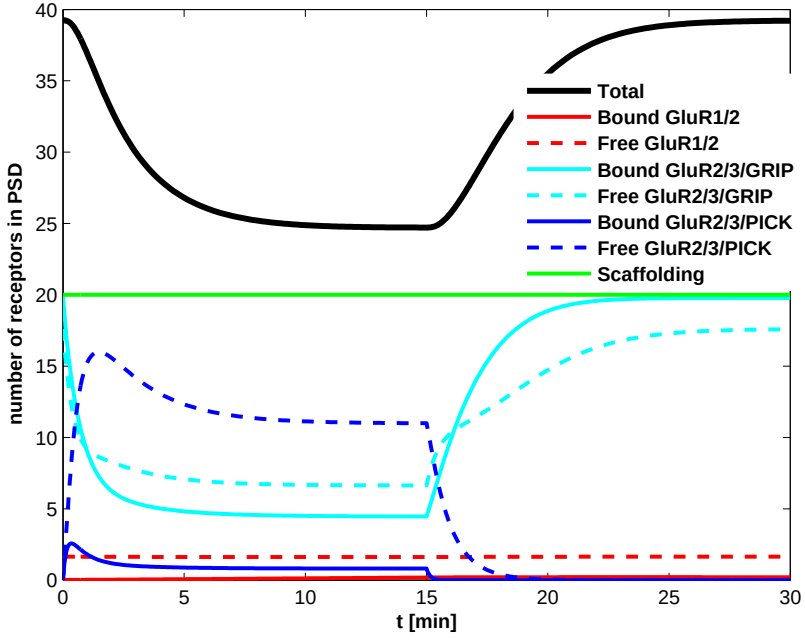

S.G. McCormack et al. *Neuron* **50** 75–88 (2006).

# LTD trafficking

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



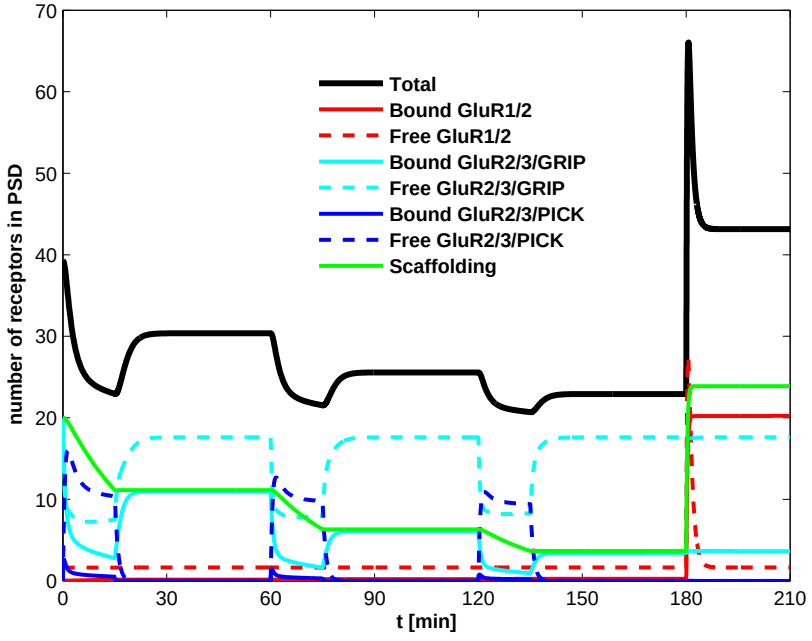



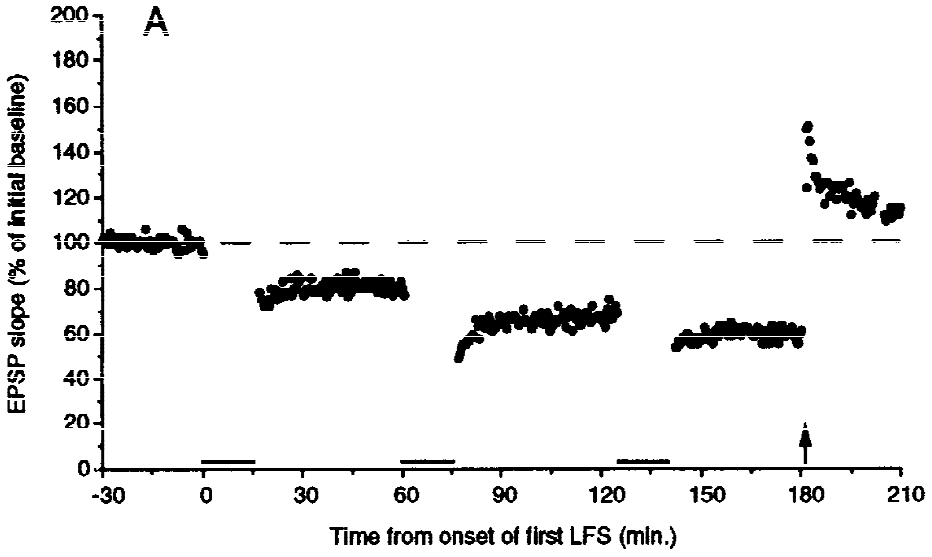




S.M. Dudek and M.F. Bear. *PNAS* **89** 4363–4367 (1992).

# 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

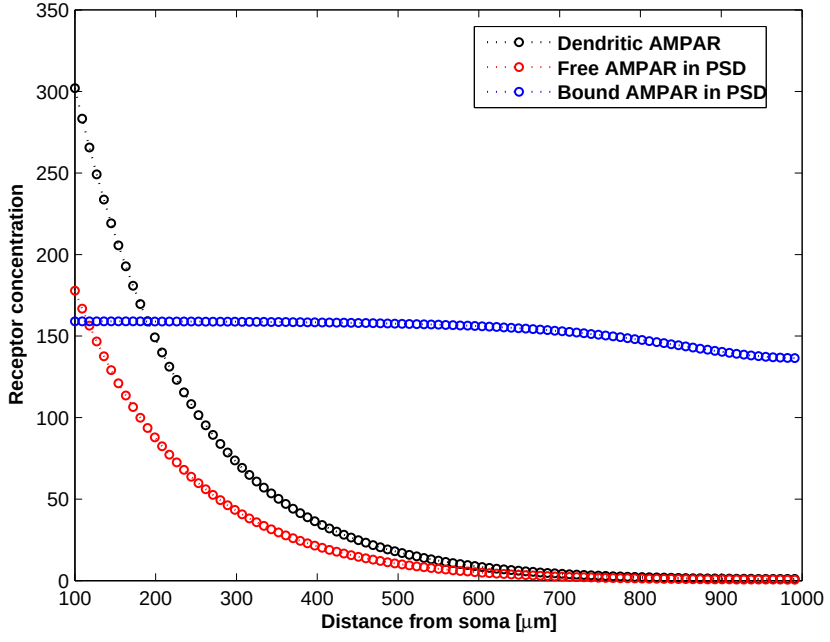
1. Significant fraction of **PSD receptors are mobile**
   - Consistent with Groc et al., 2004; Ashby et al., 2006
   - Requires PSD-ESM barrier
   - Required for exocytosis blockade time-course
   - Required for LTD saturation
2. Significant **diffusive impedance at spine neck**
   - Consistent with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

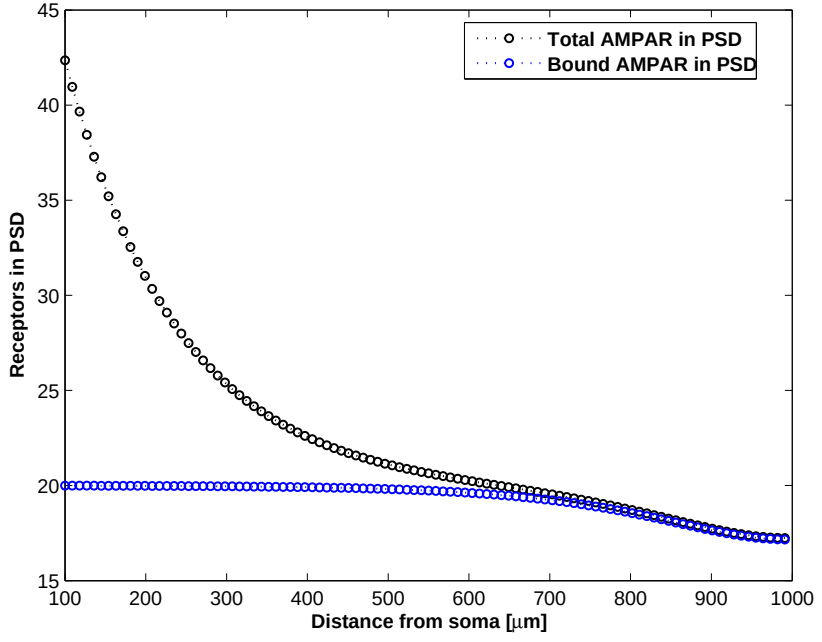
# Conclusions

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 $\Omega$
- **Stochastic model**
  - Estimate variance in EPSP recordings

# The end