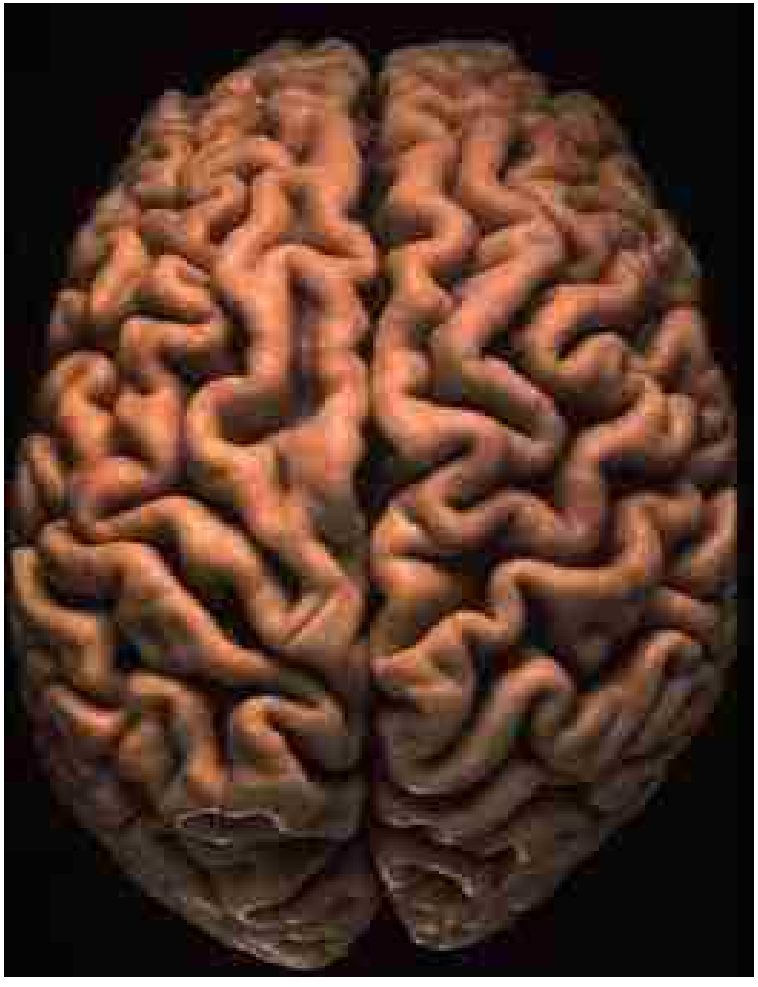
# Biophysical model of AMPA receptor trafficking and its regulation during LTP/LTD

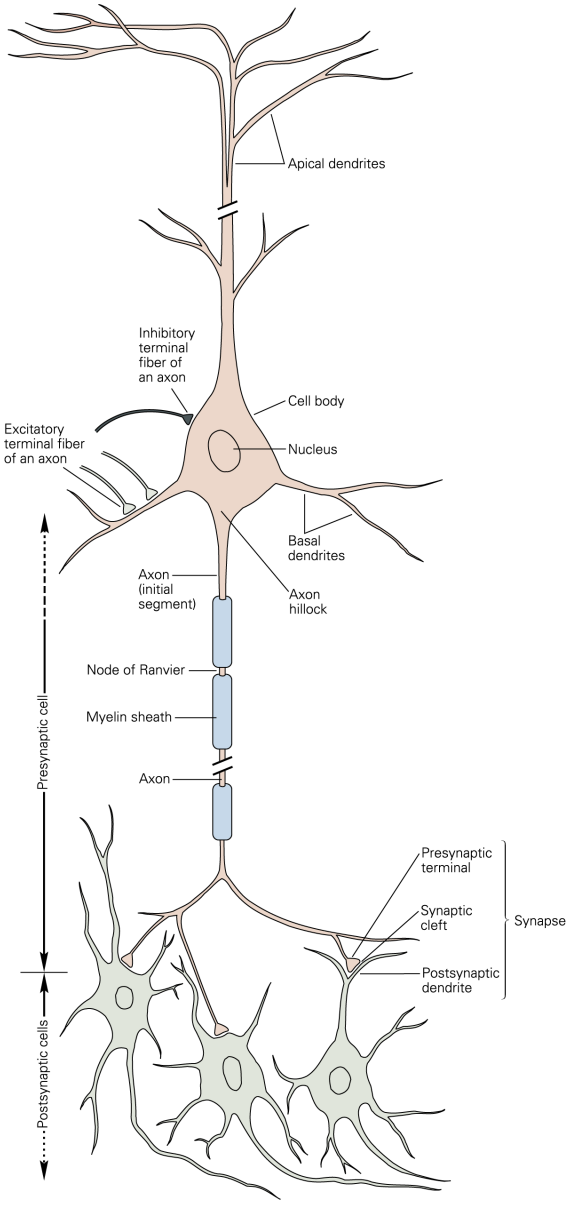
Berton A. Earnshaw and Paul C. Bressloff

Department of Mathematics, University of Utah

Salt Lake City, Utah 84112

# The brain: unparalled parallel computer

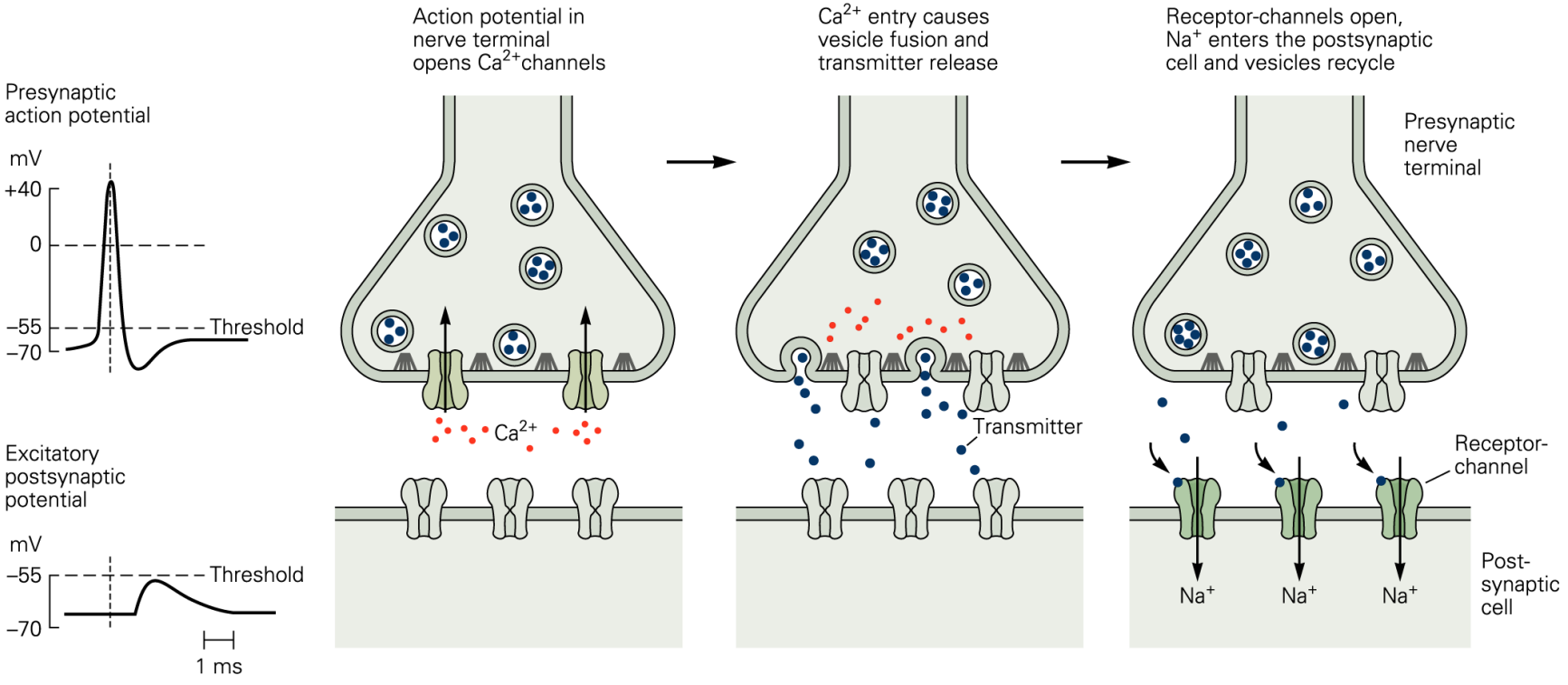





- $10^{11}$ neurons
- $\sim 10 - 10,000$ synapses/neuron
- network is plastic
- regulates behavior
- can **learn** and **remember**!

# Synaptic transmission

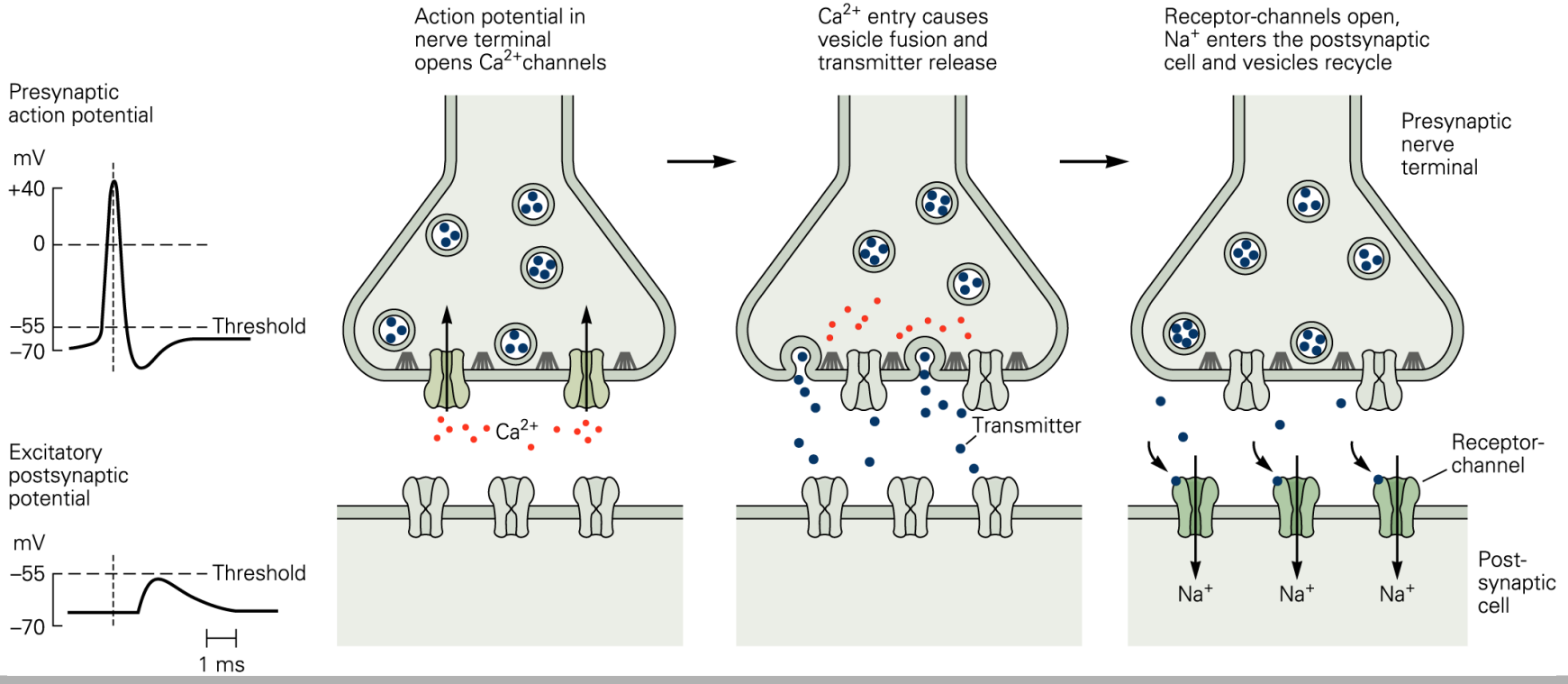
- Action potential causes neurotransmitter release
- Neurotransmitter binds to receptors
- Receptors mediate influx/efflux of ions
- **Excitatory/inhibitory**: de/hyperpolarize membrane




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

# AMPA receptors and trafficking

- Glutamate-gated, cation channel ($Na^+$ and $K^+$)
- Mediate **excitatory synaptic transmission** in CNS
- AMPAR trafficking **regulates synaptic strength** by changing AMPA receptor numbers
- Synaptic plasticity implicated in **learning** and **memory**



# Why model AMPAR trafficking and plasticity

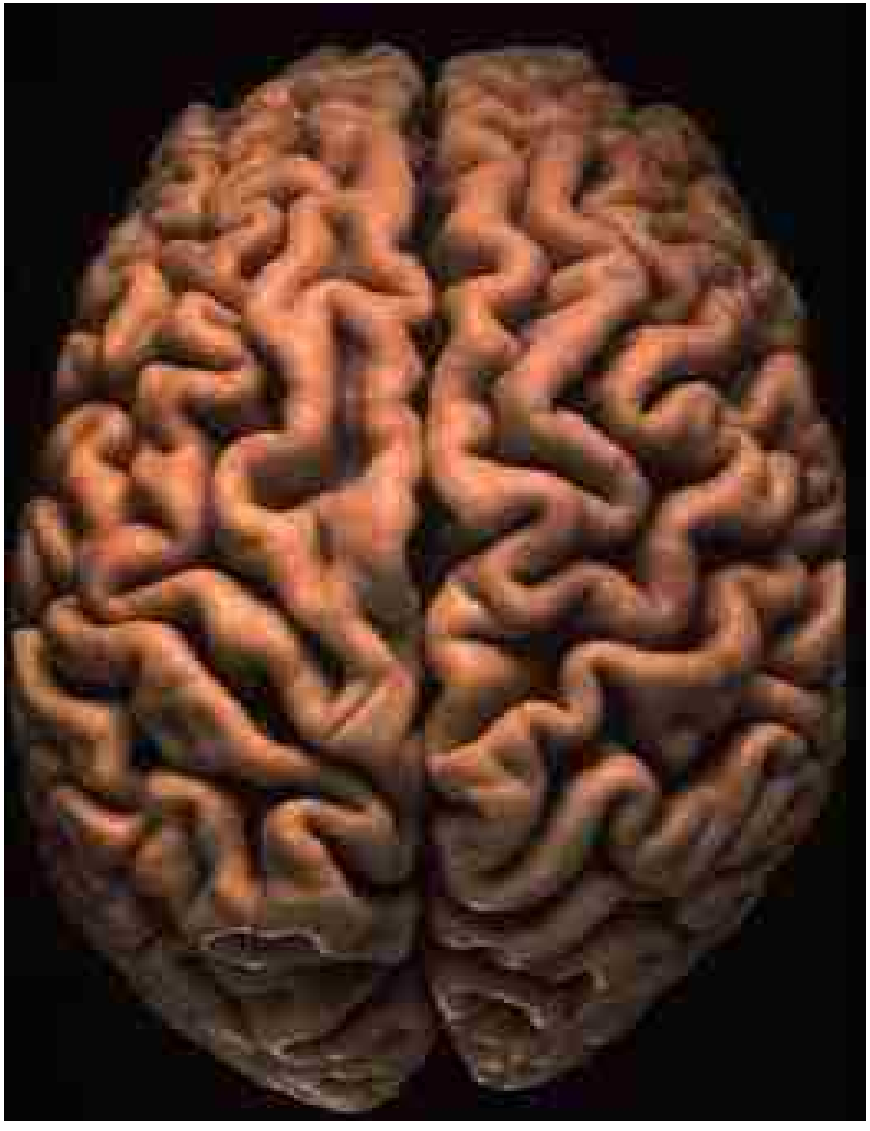
- Explain **experimental data** (validate **folk story**)
- Make **useful predictions**

There are other models, but either

- **ignore biophysics** (e.g., lateral diffusion), or
- focus on **induction** of synaptic plasticity rather than expression (confounded time-scales?), or
- **too simplistic** to capture diverse data.


G.C. Castellani et al. *PNAS* **98** 12772–12777 (2001).
H.Z. Shouval et al. *PNAS* **99** 10831–10836 (2002).
H.Z. Shouval et al. *Biol. Cybern.* **87** 383–391 (2002).
D. Holcman and Z. Schuss. *J. Stat. Phys.* **117** 976–1014 (2004).
A. Hayer and U.S. Bhalla. *PLoS Comput. Biol.* **1** 137–154 (2005).
H.Z. Shouval. *PNAS* **102** 14440–14445 (2005).
A.M. Zhabotinsky et al. *J. Neurosci.* **26** 7337-7347 (2006).
D. Holcman and A. Triller. *Biophys. J.* **91** 2405-2415 (2006).

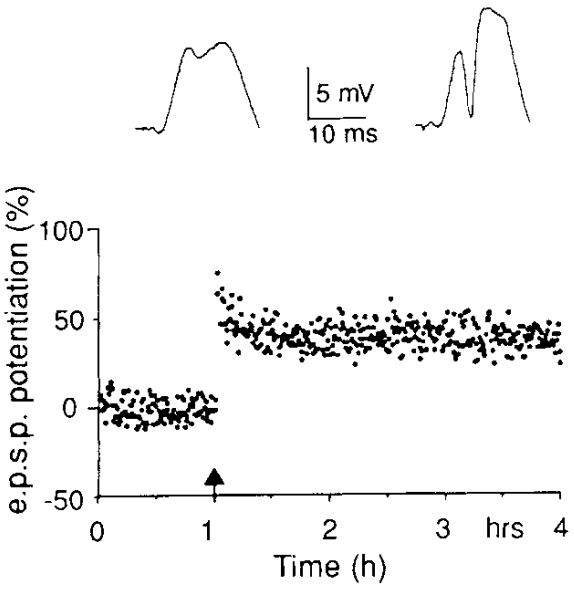
# Outline

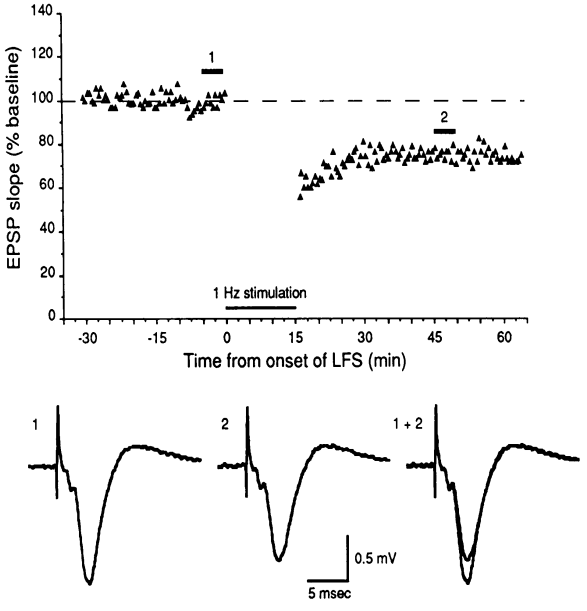


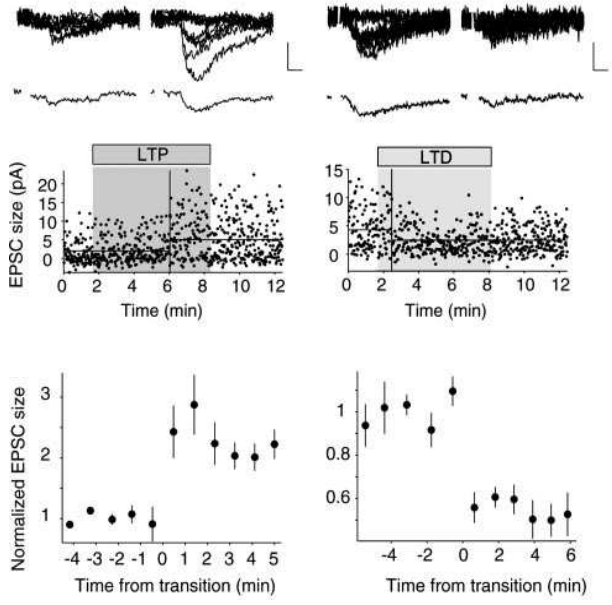
- Review synaptic plasiticty and AMPAR trafficking
- Model and assumptions
- Results
- Conclusions
- Future directions

# LTP/LTD: Long-term potentiation/depression

- Increase/decrease in the amplitude of evoked synaptic potentials lasting >1 hr
- Induced by correlations/anti-correlations in pre- and postsynaptic activity





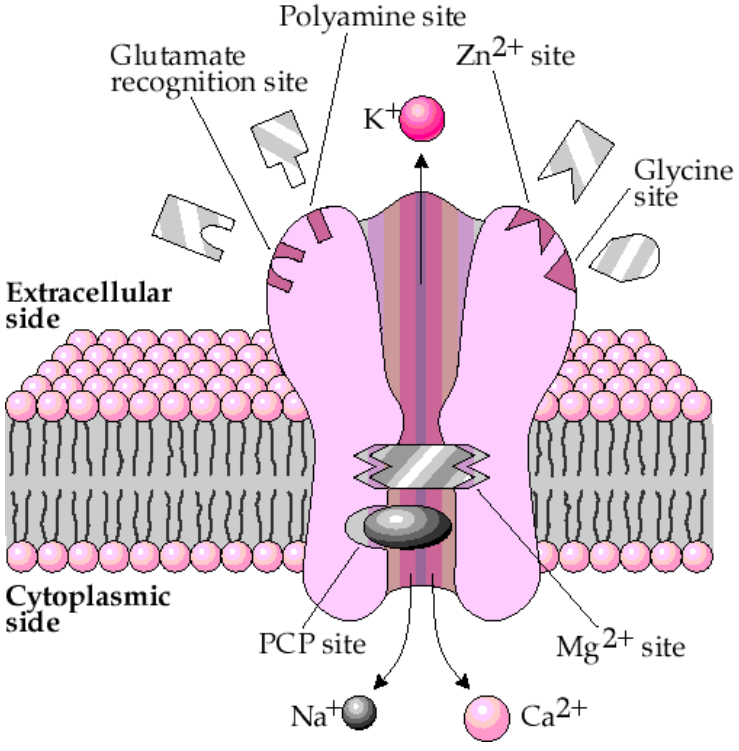
T.V.P. Bliss and G.L. Collingridge. *Nature* **361** 31–39 (1993).

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

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

# NMDA receptor-mediated LTP/LTD

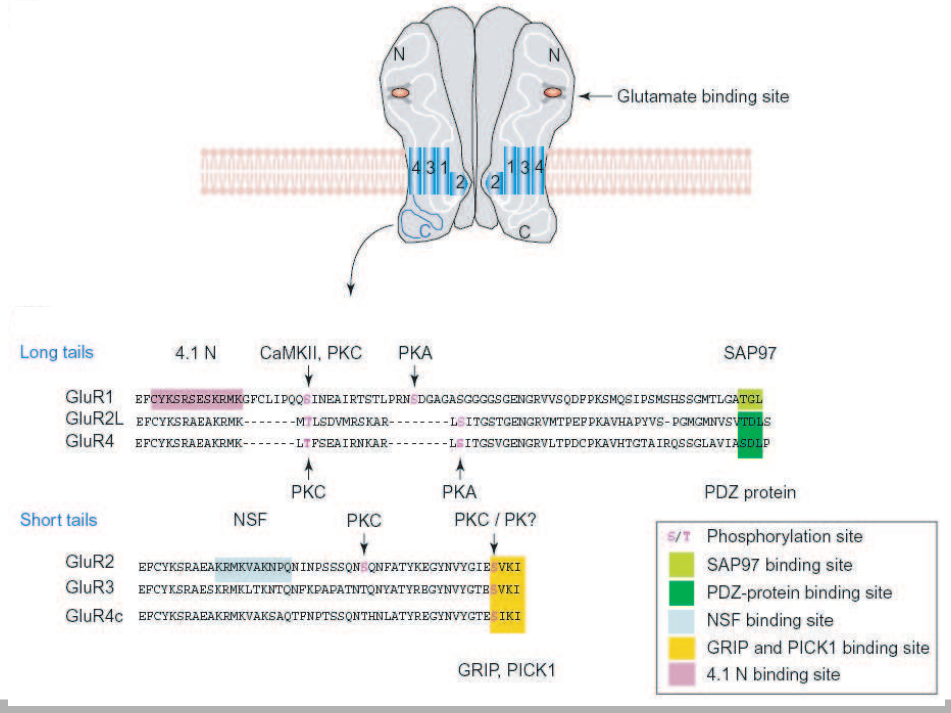
- Ubiquitous, prototypical in CNS
- Logical AND gate - have 2 $Ca^{2+}$ gates:
  - neurotransmitter gate (requires glutamate, agonist)
  - voltage-sensitive $Mg^{2+}$ binding site
- Detect coincidence of pre- and postsynaptic activity
- Integrated $Ca^{2+}$ signal encodes correlations in activity by regulating second-messenger pathways




L.F. Quenzer and R.S. Feldman. Fundamentals of Neuropsychopharmacology. Sunderland: Sinauer Associates Inc. 1984.

# AMPAR trafficking depends on subunits

- Hetero-tetramer composed of subunits GluR1-GluR4
- Subunit composition determines trafficking:
  - Only short C-termini (GluR2 or GluR3): activity-independent, constitutive recycling
  - At least one long C-terminus (GluR1 or GluR4): activity-dependent, transient

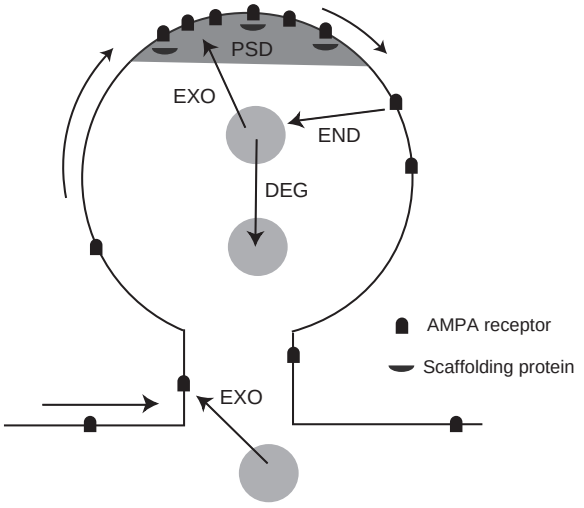


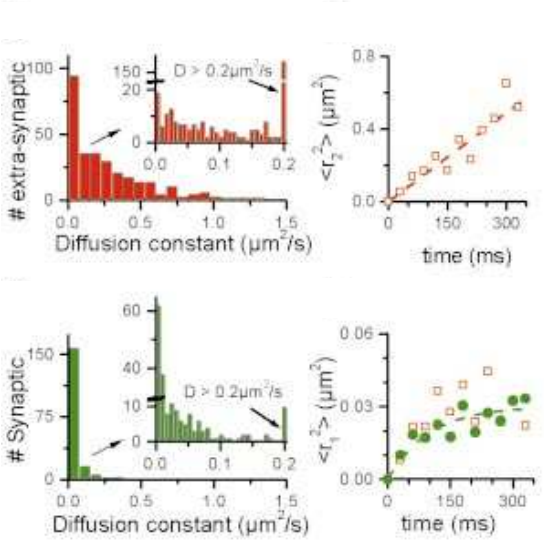

- C-terminus interact with other proteins (e.g., SAP-97, PSD-95, NSF, GRIP, PICK1, 4.1N)

I. Song and R.L. Huganir. *Trends Neurosci.* **25** 578–588 (2002).

# 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 PSD 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).

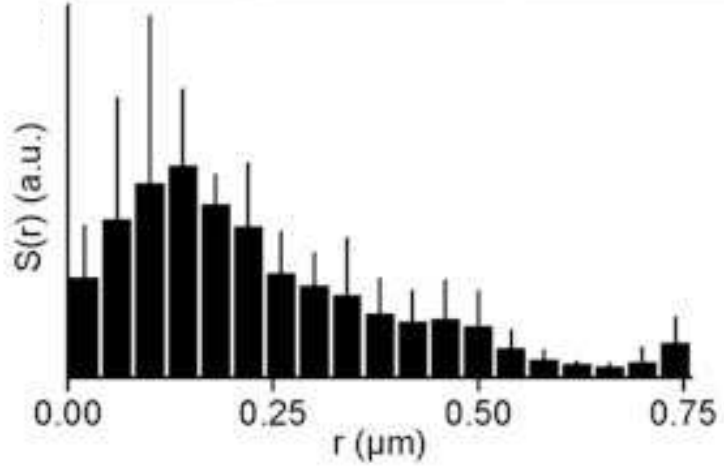
D. Choquet and A. Triller. *Nat. Rev. Neurosci.* **4** 251–265 (2003).

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

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

# Basal concentrations, constitutive cycling

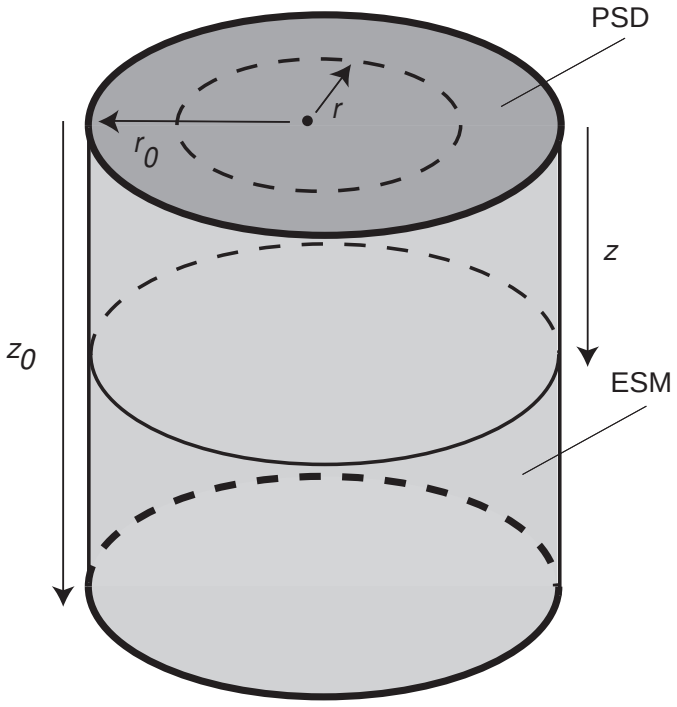
- **PSD**
  - high concentration $\sim$100-1000 receptors/$\mu$m$^2$
  - mostly GluR2/3, constitutive cycling
  - $\sim$50% receptors mobile
- **ESM**
  - low concentration $\sim$1-20 receptors/$\mu$m$^2$
  - mostly GluR1/2 and GluR2/3
- **Intracellular pool** $\sim$80%-90% of total receptors




J.R. Cottrell et al. *J. Neurophysiol.* **84** 1573–1587 (2000).
C. Tardin et al. *EMBO J.* **22** 4656–4665 (2003).
D.S. Bredt and R.A. Nicoll. *Neuron* **40** 361–379 (2003).
M.C. Ashby et al. *J. Neurosci.* **26** 7046–7055 (2006).

# Model – Spine geometry and state variables

- **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
- **State variables**
  - $P$: free concentration in PSD
  - $Q$: bound concentration in PSD
  - $R$: free concentration in ESM
  - $S$: number in intracellular pools
- **Subscripts**: $I$ = GluR1/2, $II$ = GluR2/3



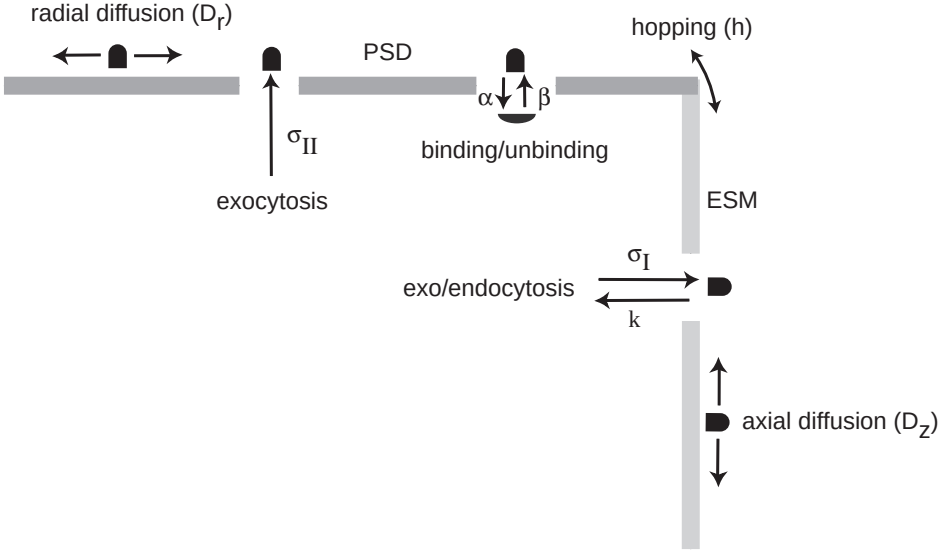

K.E. Sorra and K.M. Harris. *Hippocampus* **10** 501–511 (2000).

# Diffusion is fast!

- **PSD**
  - Spatial scale: $\lambda_{PSD} \sim 0.1\mu\text{m}^2$
  - Diffusion coefficient: $D_{PSD} \sim 0.01\mu\text{m}^2\text{s}^{-1}$
  - Diffusion time constant: $\tau_{PSD} = \sqrt{\lambda_{PSD}/D_{PSD}} \sim 10\text{s}$
- **ESM**
  - Spatial scale: $\lambda_{ESM} \sim 1.0\mu\text{m}^2$
  - Diffusion coefficient: $D_{ESM} \sim 0.1\mu\text{m}^2\text{s}^{-1}$
  - Diffusion time constant: $\tau_{ESM} = \sqrt{\lambda_{ESM}/D_{ESM}} \sim 10\text{s}$
- Time constants of other trafficking: $\tau \sim 10$min-1hr
- Diffusion is fast - assume uniform concentrations

# Model – Basal trafficking parameters

- **Exocytosis ($\sigma$):** $\sigma_I = 0.2778$, $\sigma_{II} = 0.1667$ receptors $s^{-1}$
- **Endocytosis ($k$):** $k_I = 0.01667$, $k_{II} = 0.1667$ $s^{-1}$
- **PSD-ESM hopping ($h$):** $h_I = h_{II} = 10^{-3}\mu m^2 s^{-1}$
- **ESM-dendrite hopping ($\Omega$):** $\Omega_I = \Omega_{II} = 10^{-3}\mu m^2 s^{-1}$
- **Binding:** $P + L \underset{\beta}{\overset{\alpha}{\rightleftharpoons}} Q$
  - **Scaffolding:**
    $L = 159.15\mu m^{-2}$
    *20 sites, uniform conc.*
  - **Binding:** $\alpha_I = 10^{-6}$,
    $\alpha_{II} = 10^{-4}\mu m^2 s^{-1}$
  - **Unbinding:**
    $\beta_I = \beta_{II} = 10^{-5} s^{-1}$



# Model – Equations for GluR1/2

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

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

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

$$\frac{dS_I}{dt} = -\kappa_I S_I + \delta_I \quad (\sigma_1 = \kappa_1 S_1)$$

Assume that in steady-state, $S_1 = 500$ receptors

$\Rightarrow$ basal values: $\kappa_I = 5.556 \times 10^{-4}\text{s}^{-1}$, $\delta_I = 0.2778$ rec. s$^{-1}$.

$\overline{R}_I = 10$ receptors $\mu$m$^{-2}$: AMPAR concentration in dendrite (assumed constant)

# Model – Equations for GluR2/3

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

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

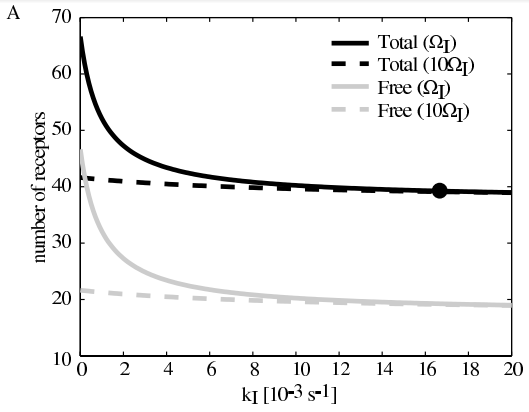
$$\frac{dR_{II}}{dt} = \frac{h_{II}}{A_{ESM}}(P_{II} - R_{II}) - \frac{\Omega_{II}}{A_{ESM}}(R_{II} - \bar{R}_{II}) - k_{II}R_{II}$$

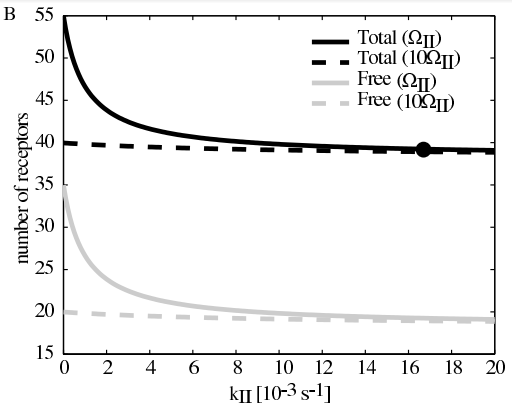
Assume $S_2$, and hence $\sigma_2$, is constant.

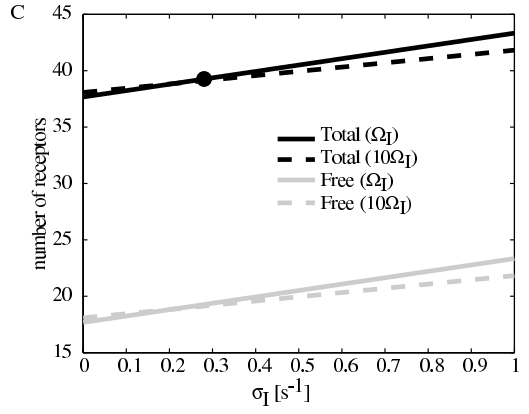
$\overline{R}_{II} = 0$ receptors $\mu$m$^{-2}$: AMPAR concentration in dendrite (assumed constant)

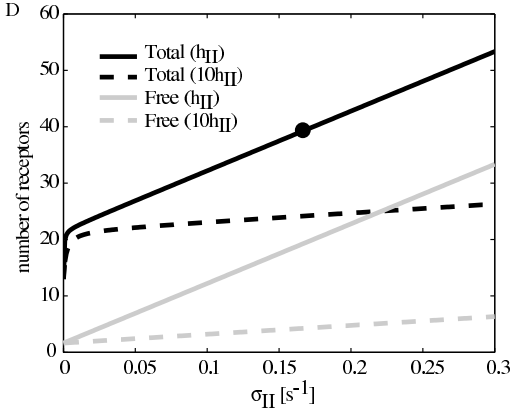
# Model – Steady-state

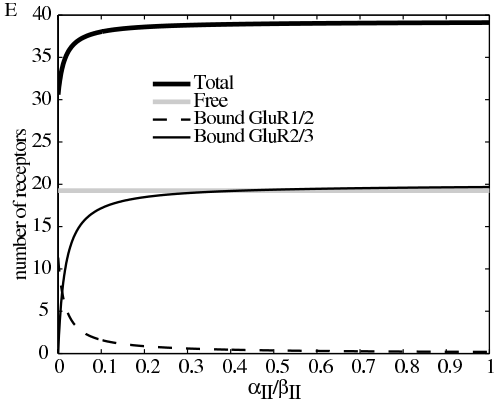
- **PSD**
  - Total ≈40, Bound ≈20
  - GluR1/2 ≈2, GluR2/3 ≈38
- **ESM**
  - Total ≈25
  - GluR1/2 ≈16, GluR2/3 ≈9
- **Sensitive** to GluR2/3 trafficking and hopping rates



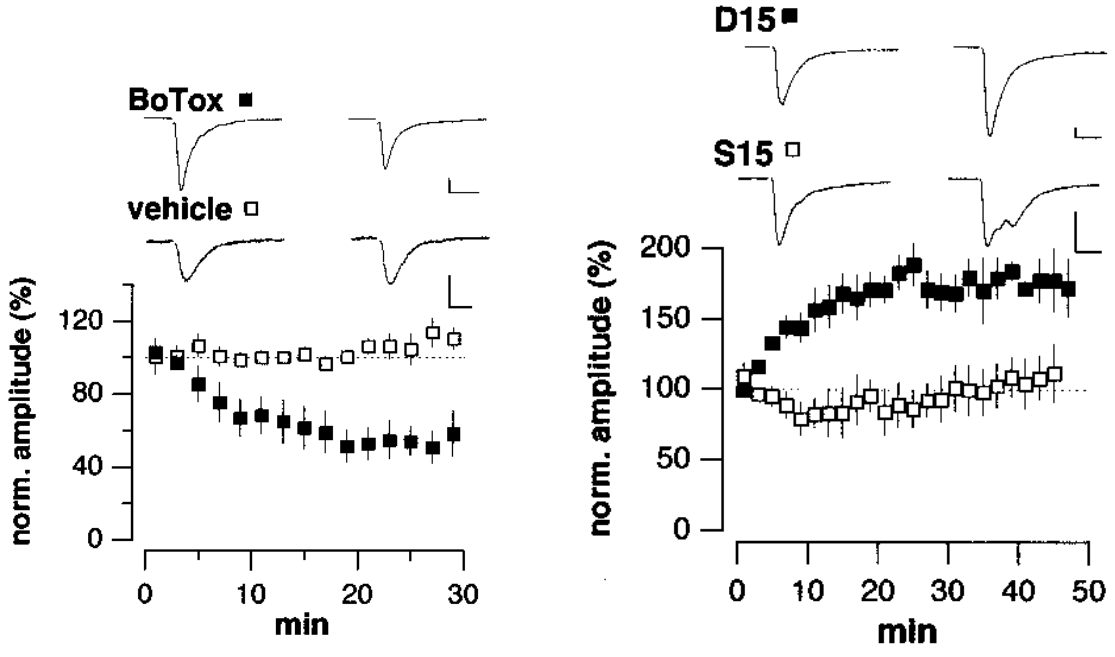



# Experiment – Blocking exo/endocytosis

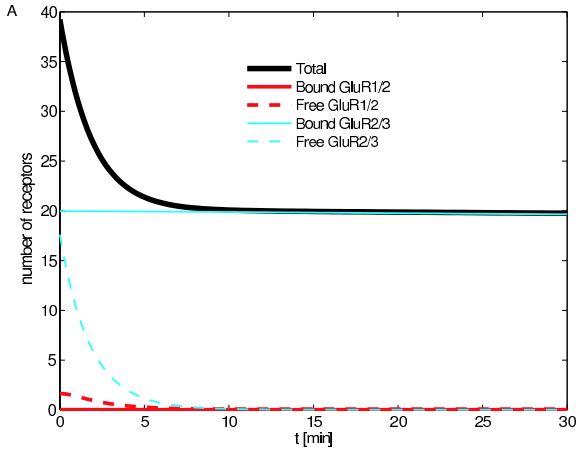
- **Block exocytosis**: ∼50% reduction in field EPSPs over ∼10-20min
- **Block endocytosis**: ∼100% increase in field EPSPs over ∼10-20min
- Dynamic balance of basal fluxes!

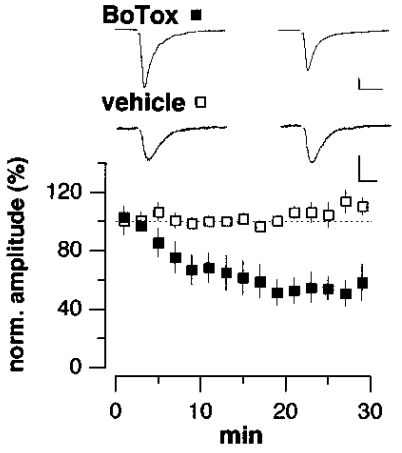


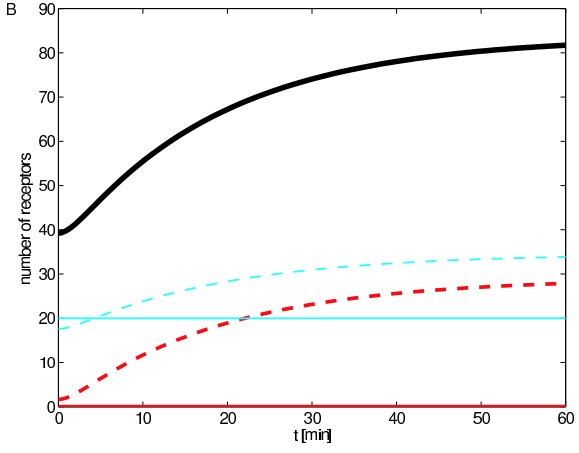

C. Luscher et al. *Neuron* **24** 649–658 (1999).

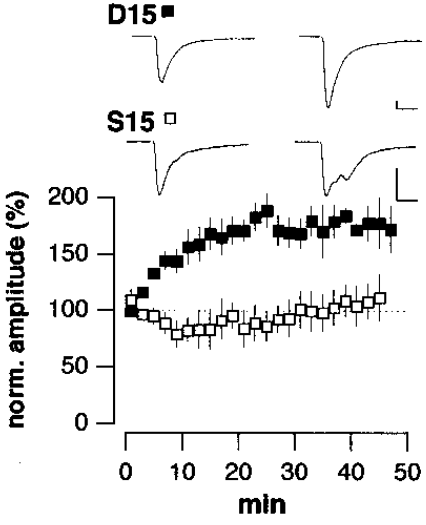
# Model – Blocking exo/endocytosis

- **Block exocytosis:**
  $\sigma_I = \sigma_{II} = 0$ at $t = 0$
  - Climb to $\approx$84 receptors in $\sim$1 hr
- **Block endocytosis:**
  $k_I = k_{II} = 0$, $R_{II,0} = 10$ at $t = 0$
  - Drop to $\approx$20 receptors in $\sim$10 min
  - Drop to $\approx$1 receptor as $t \to \infty$



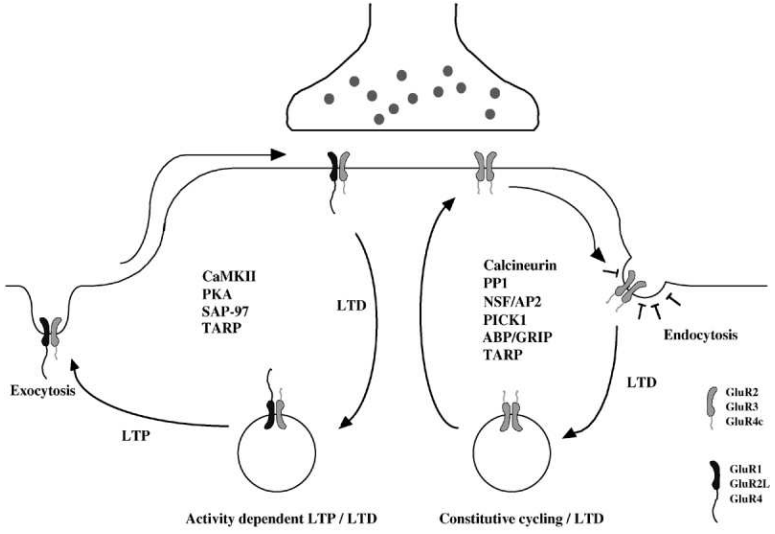



# LTP trafficking

- Large $[Ca^{2+}]$ transient **activates CaMKII**
- CaMKII phosphorylates SAP-97 and TARPs (e.g., stargazin) $\rightarrow$ **GluR1/2 exocytosis** into ESM
- TARPs **target PSD** by binding to PSD-95
- **Hypothesis**: PSD-95 increased during GluR1/2 exocytosis $\rightarrow$ additional binding sites
  - Include dynamics for $L$:

$$\frac{dL}{dt} = -c\frac{dS}{dt}$$





A.E. El-Husseini et al. *Science* **290** 1364–1368 (2000).

S.H. Shi et al. *Cell* **105** 331–343 (2001).

J. Lisman et al. *Nat. Rev. Neurosci.* **3** 175–190 (2002).

D.S. Bredt and R.A. Nicoll. *Neuron* **40** 361–379 (2003).

S. Tomita et al. *Neuron* **45** 269–277 (2005).

# Model – LTP trafficking

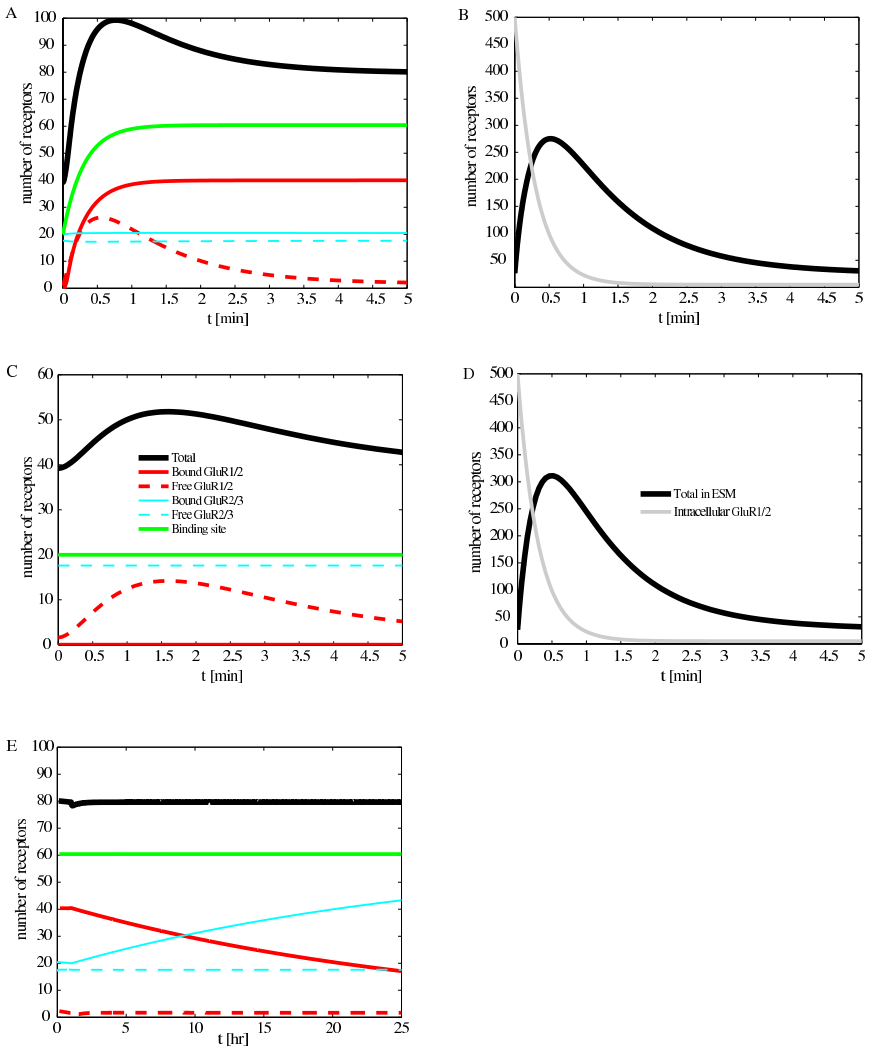
Time-scale of induction **much faster** than expression $\rightarrow$ parameters change instantaneously at $t = 0$:

- $\alpha_I = 10^{-2} \mu\text{m}^2\text{s}^{-1}$ ($10^4\times$ increase)
- $\kappa_I = 0.0556\ \text{s}^{-1}$ ($100\times$ increase)
- $h_I = 0.01\ \mu\text{m s}^{-1}$ ($10\times$ increase)

We assume $c = 0.65$

# Model – LTP trafficking: numbers

- **LTP**
  - Peak at $\approx$100 in $\sim$1 min
  - Settles to $\approx$80 in $\sim$4 min
  - $L$ triples in $\sim$1 min
- **Stargazin**
  - Only increase $\kappa_I$
- **Exchange**
  - At $t = 1$ hr, all parameters set to basal
  - GluR2/3 replaces GluR1/2





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

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

# LTD trafficking

- Small sustained increase in $[Ca^{2+}]$ **activates calcineurin** and **PP1**
- GluR2/3 phosphorylated, changes association **from GRIP/ABP to PICK1**
- Phosphorylation promotes **endocytosis of GluR2/3**
- PSD-95 degraded during LTD $\rightarrow$ **fewer binding sites**
- Include dynamics for $L$:

$$\frac{dL}{dt} = -\gamma(L - Q_I - Q_{II} - Q_{II}^*)$$

- $\gamma = 10^{-3}\mathrm{s}^{-1}$ (*on during LTD induction*)


R.M. Mulkey et al. *Science* **261** 1051–1055 (1993).
R.M. Mulkey et al. *Nature* **369** 486–488 (1994).
C.H. Kim et al. *PNAS* **98** 11725–11730 (2001).
J.L. Perez et al. *J. Neurosci.* **21** 5417–5428 (2001).
S.H. Lee et al. *Neuron* **36** 661–674 (2002).
M. Colledge et al. *Neuron* **40** 595–607 (2003).

# Model – Extended LTD equations for GluR2/3

$P^*_{II}$, $Q^*_{II}$ and $R^*_{II}$ denote GluR2/3-PICK1 concentrations

$$\frac{dP_{II}}{dt} = -\alpha_{II}(L - Q_I - Q_{II})P_I + \beta_{II}Q_{II} - \frac{h_{II}}{A_{PSD}}(P_{II} - R_{II}) + \frac{\sigma_{II}}{A_{PSD}} - \mu P_{II} + \nu P^*_{II}$$

$$\frac{dP^*_{II}}{dt} = -\frac{h^*_{II}}{A_{PSD}}(P^*_{II} - R^*_{II}) + \mu P_{II} - \nu P^*_{II}$$

$$\frac{dQ_{II}}{dt} = \alpha_{II}(L - Q_I - Q_{II})P_{II} - \beta_{II}Q_{II} - \mu Q_{II} + \nu Q^*_{II}$$

$$\frac{dQ^*_{II}}{dt} = -\beta^*_{II}Q^*_{II} + \mu Q_{II} - \nu Q^*_{II}$$

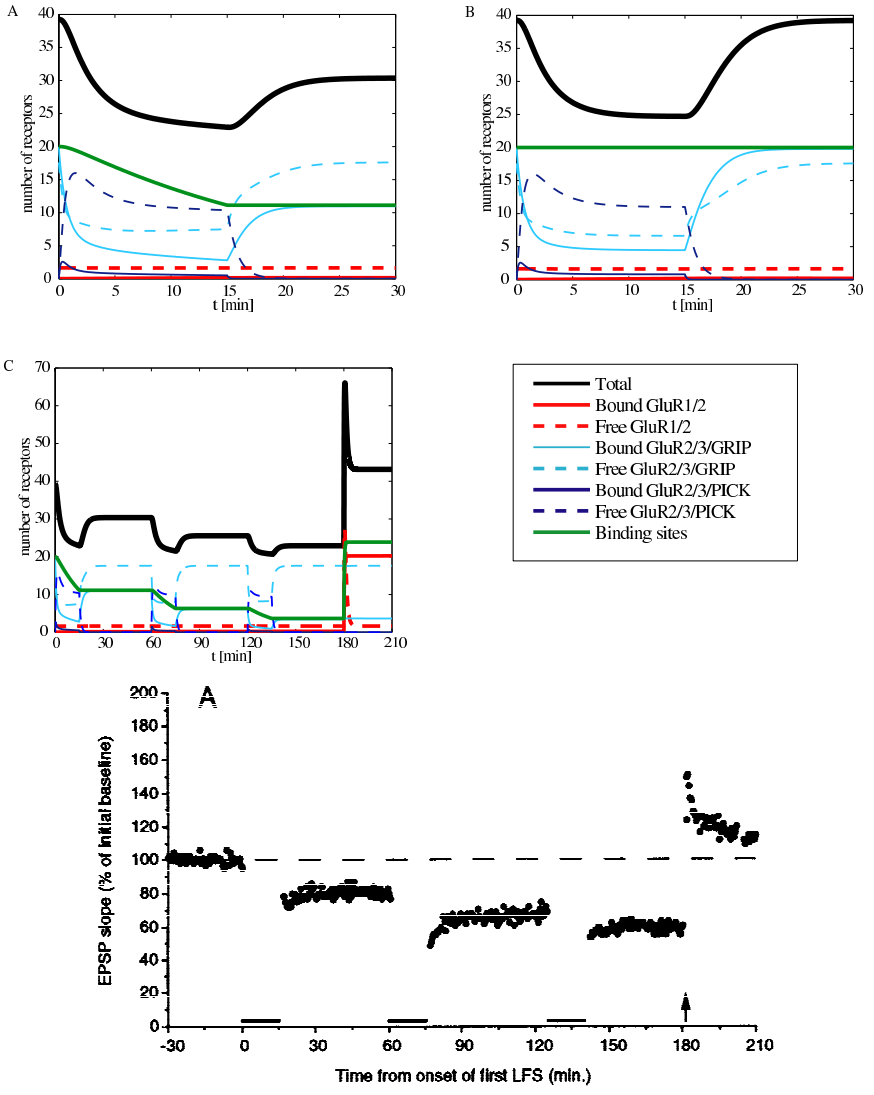
$$\frac{dR^*_{II}}{dt} = \frac{h^*_{II}}{A_{ESM}}(P^*_{II} - R^*_{II}) - k^*_{II}R^*_{II}$$

$\nu = 10^{-2}\text{s}^{-1}$, $\beta^*_{II} = 0.1\ \text{s}^{-1}$, $k^*_{II} = 0.1667\ \text{s}^{-1}$ (*always on*)

$\mu = 10^{-4}\text{s}^{-1}$ (*on during LTD induction*)

# Model – LTP trafficking: numbers

- **LTD:** LFS (e.g, 1 Hz)
  - Loss during induction
  - Recovery to lower state
- **LTD:** MFS (e.g, 10 Hz)
  - Only GRIP→PICK1, no scaffolding loss
  - Recovery to original state
- **Saturation:**
  - 15 min induction, 45 min rest (3×)
  - Due to scaffolding loss





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

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

# Review – experiments reproduced

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

# Conclusions

- Significant fraction of PSD receptors are **mobile** under basal conditions (Groc et al., 2004; Ashby et al., 2006)
  - Requires PSD-ESM barrier (Choquet and Triller, 2003)
  - Required for exocytosis blockade time-course (Luscher et al., 1999) and LTD saturation (Dudek and Bear, 1993)
- **Diffusive impedance** at spine neck significant (Ashby et al., 2006)
  - Required for endocytosis blockade time-course (Luscher et al., 1999) and LTP time-course (O'Connor et al., 2005)

# Conclusions

- Exocytosis of intracellular GluR1/2 during LTP must combine **synaptic targeting**
  - Requires increased hopping and binding rate (Schnell et al., 2002) and scaffolding (Shi et al., 2001)
  - Required for LTP time-course (O'Connor et al., 2005)
- Slow exchange of GluR1/2 with GluR2/3 after LTP requires **maintenance of additional binding sites**
  - Required for exchange time-course (McCormack et al., 2006)
- GRIP to PICK1 exchange must be accompanied by **loss of binding sites** (Colledge et al., 2003)
  - Required for LTD time-course (Dudek and Bear, 1992) and LTD saturation (Dudek and Bear, 1993)

# Future directions

- **Multiple synapse model**
  - Mesoscopic version of single-synapse model on non-branching dendritic cable
  - Exo/endocytosis at soma (Adesnik et al., 2005)
  - Homeostatic plasticity (Turrigiano et al., 1998)
  - Heterosynaptic competition
- **Effects of membrane curvature**
  - Curvature may modulate receptor diffusion (Faraudo, 2002)
  - Estimate for $\Omega$
- **Stochastic model**
  - Estimate variance in EPSP recordings

# The end