Modeling the role of AMPA receptor trafficking in the expression of long-term potentiation/depression

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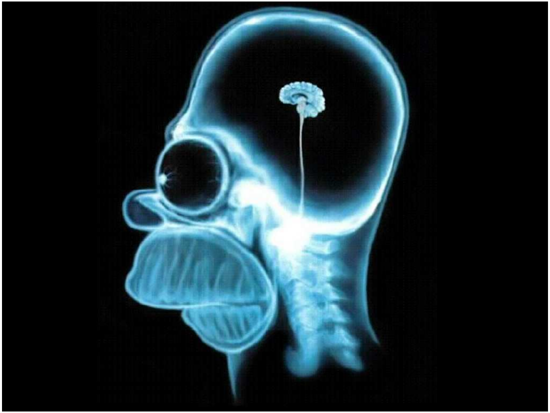
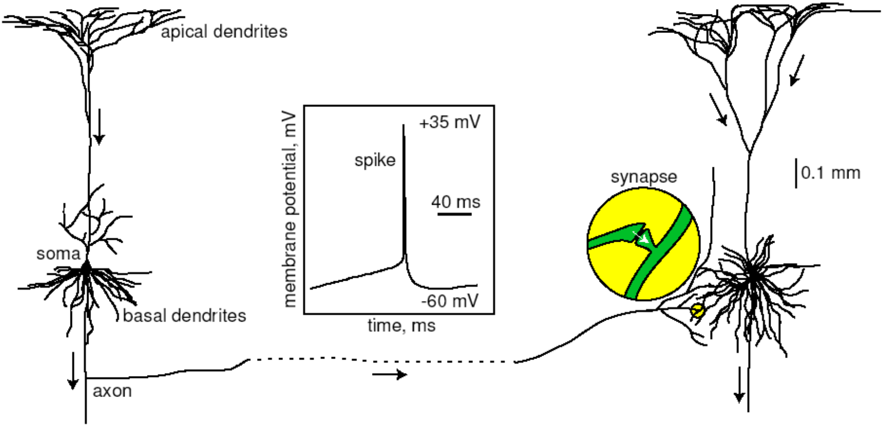
The amazing brain

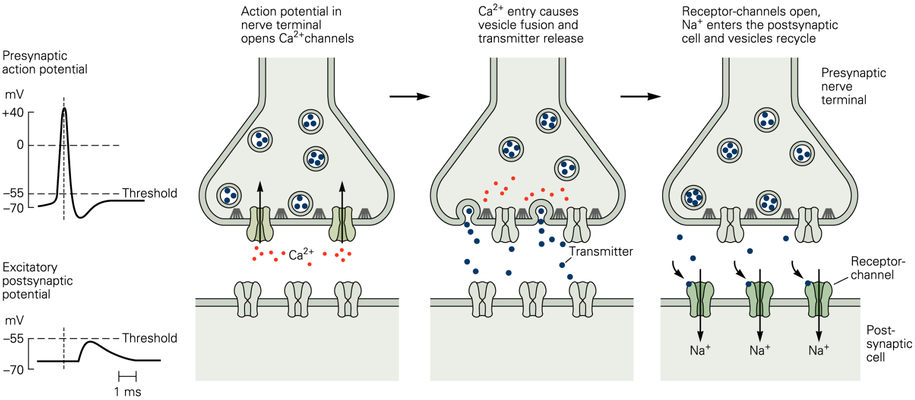


- 10^{11} neurons
- $10 - 10,000$ synapses/neuron
- regulates body, behavior
- can learn, remember
- conscious experience

Neurons communicate at synapses

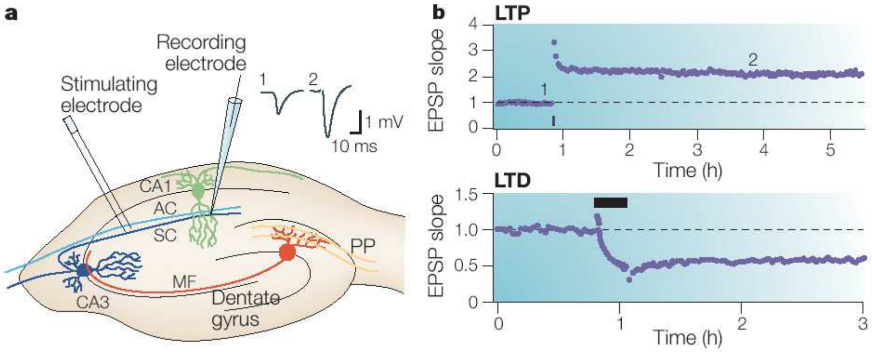


Communication at a synapse



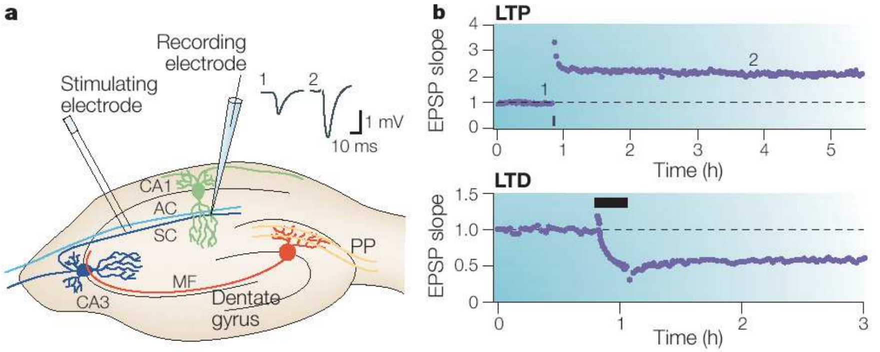
Kandel, Schwartz & Jessel (2000)

Synapses can "learn" – synaptic plasticity



Collingridge et al., *Nat Rev Neurosci* (2004)

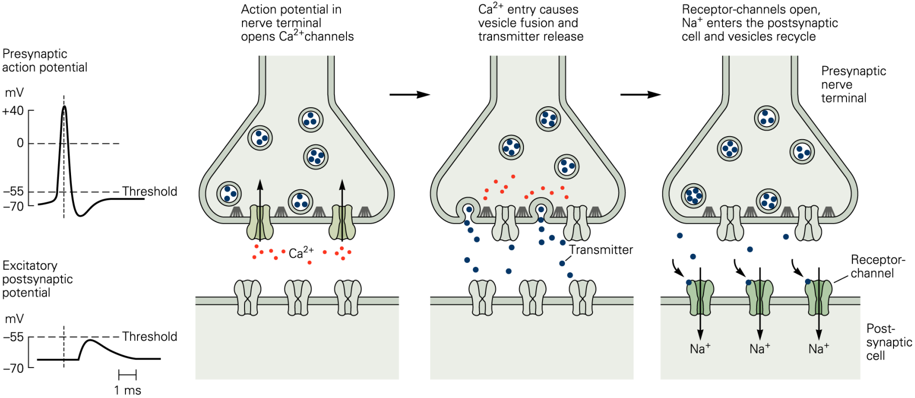
Synapses can "learn" – synaptic plasticity



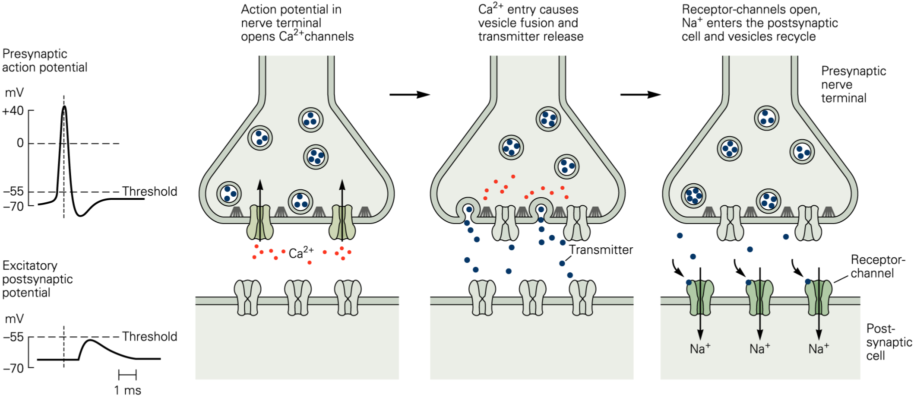
Collingridge et al., *Nat Rev Neurosci* (2004)

- LTP = long-term potentiation (strengthens synapse)
- LTD = long-term depression (weakens synapse)

How/where does synaptic plasticity occur?

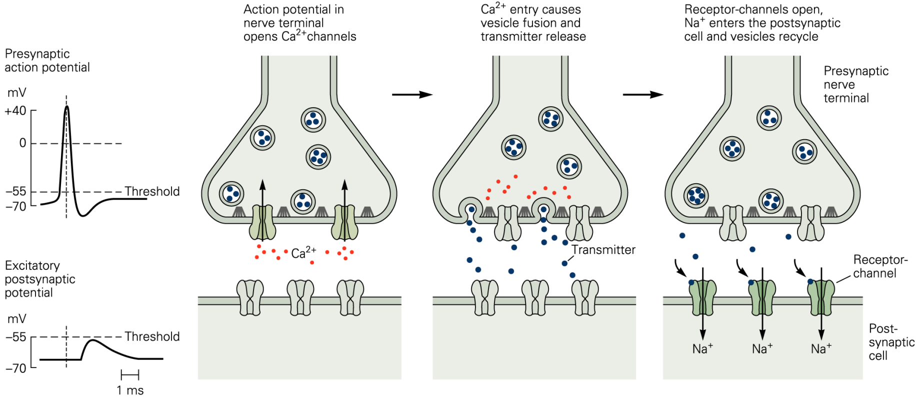


How/where does synaptic plasticity occur?



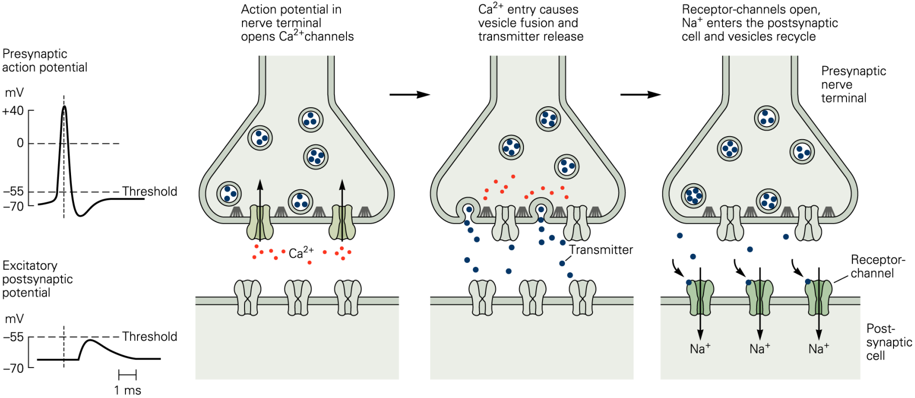
- Two major hypotheses:

How/where does synaptic plasticity occur?



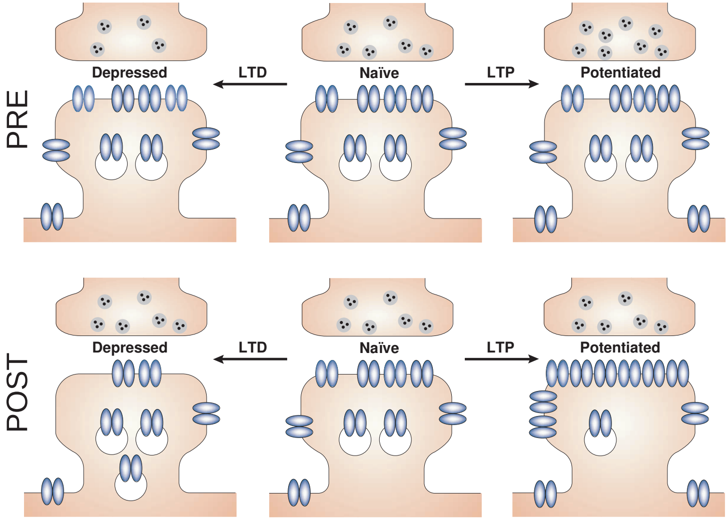
- Two major hypotheses:
    1. Presynaptic: change in the number of vesicles/probability of release

How/where does synaptic plasticity occur?

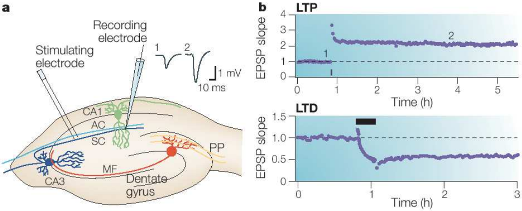


- Two major hypotheses:
  1. Presynaptic: change in the number of vesicles/probability of release
  2. Postsynaptic: change in the number/conductance of receptors

Presynaptic vs. postsynaptic mechanisms



Presynaptic vs. postsynaptic debate



...long-term plasticity...is expressed overwhelmingly via presynaptic changes in reliability of transmitter release.

–Enoki et al., *Neuron* (2009)

Therefore, LTP is the recruitment of new [receptors] to synapses...

–Kerchner & Nicoll, *Nat. Rev. Neurosci.* (2008)

Can modeling help?

Can modeling help?

That depends on who you talk to!

Can modeling help?

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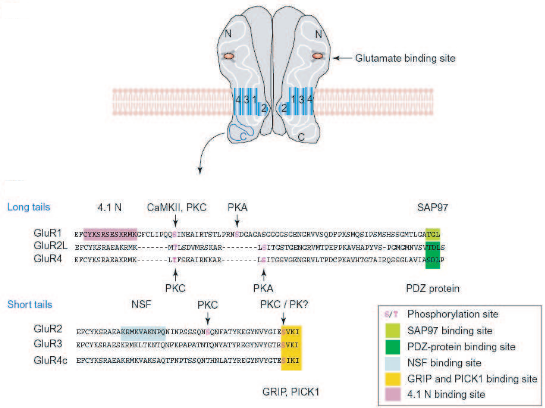
Question to answer...

Can LTP/LTD data be explained by postsynaptic receptor trafficking alone?

Outline for rest of talk

- Introduce AMPA receptors
- Describe AMPA receptor trafficking
- Propose model of AMPA receptor trafficking
- Present results from model
- Conclusions & future directions

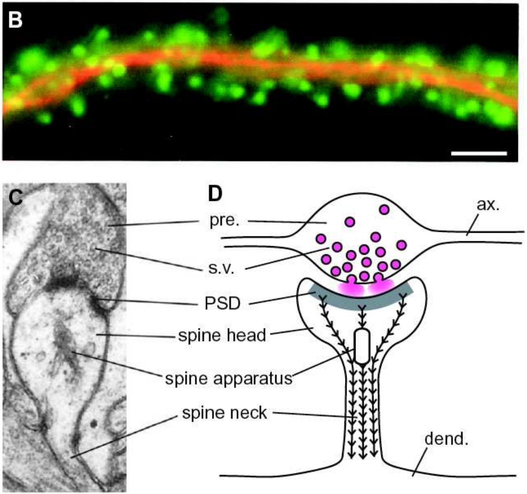
AMPA receptors



Huganir & Song, *Nat. Rev. Neurosci.* (2002)

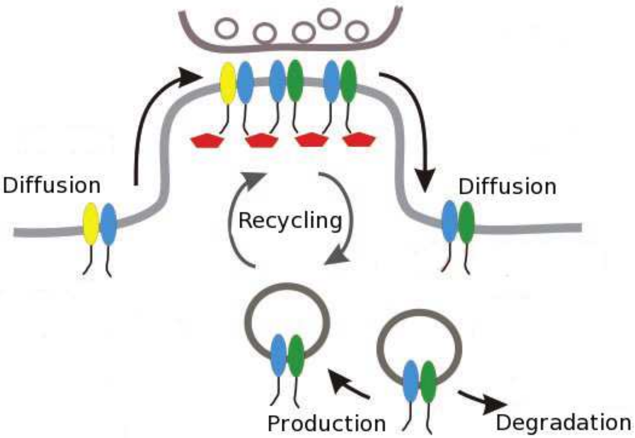
- Responsible for excitable synaptic transmission in CNS
- Formed from four subunits: GluR1 to GluR4
- Dominant heteromers: GluR1/2 and GluR2/3

Excitable synapses located in dendritic spines

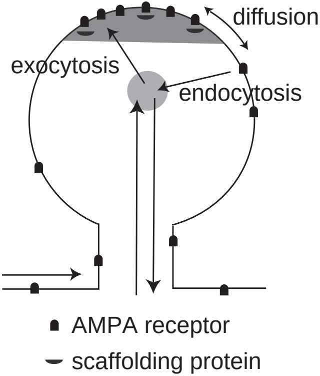


Matus, *Science* (2000)

AMPA receptor trafficking at a spine



Model of AMPA receptor trafficking at a single spine



Cottrell et al., *J. Neurophysiol.* (2000)
Sorra & Harris, *Hippocampus* (2000)
Ehlers, *Neuron* (2000)
Passafaro et al., *Nat. Neurosci.* (2001)
Groc et al., *Nat. Neurosci.* (2004)

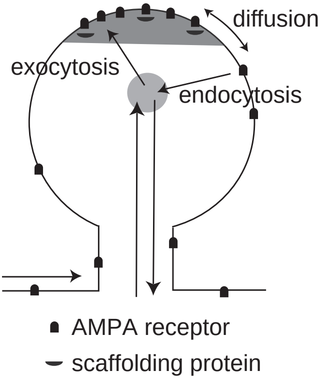
Time constants

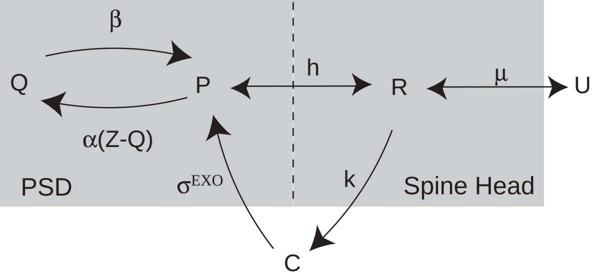
- Exo/endocytosis: 10-30 min
- Diffusion: 10 s
  - Surface area of PSD: 0.1 μm^2
  - Surface area of spine head: 1 μm^2
  - Diffusion coefficient: 0.01-0.1 μm^2/s
- Binding/unbinding to scaffolding: unknown
- Production/degradation: unknown

Other constants

- Intracellular AMPAR number: 100-500
- AMPAR concentration in dendrite: 10-100/μm^2
- Scaffolding concentration: unknown

State diagram





Variables

P = free AMPAR concentration in PSD

Q = bound AMPAR concentration in PSD

R = AMPAR concentration in spine head

Constants

C = intracellular AMPAR number

U = AMPAR concentration in dendrite

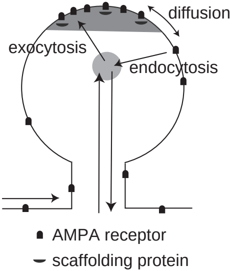
Z = scaffolding protein concentration

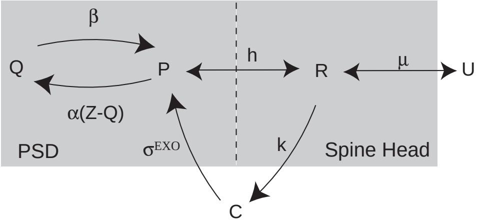
Model equations

PSD free: $$\frac{dP}{dt} = h(R-P) - \alpha(Z-Q)P + \beta Q + \sigma^{\mathrm{EXO}}\frac{C}{a}$$

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

Spine head: $$\frac{dR}{dt} = \mu(U-R) - h(R-P) - kR$$





BAE & Bressloff, *J. Neurosci.* (2006)

Parameter values

Known parameter values:

- Rate of exocytosis, endocytosis: $\sigma^{\mathrm{EXO}}, k = 10^{-3}/\mathrm{s}$
- Surface area of PSD, spine head: $a = 0.1\ \mu\mathrm{m}^2$, $A = 1\ \mu\mathrm{m}^2$
- Hopping rate between PSD and spine head: $h = 0.1/\mathrm{s}$
- Hopping rate between spine head and dendrite: $\mu = 0.005/\mathrm{s}$
    - Ashby et al., *J. Neurosci.* (2006)
- Intracellular AMPA receptor number: $C = 100$
- AMPA receptor concentration in dendrite: $U = 20/\mu\mathrm{m}^2$

Unknown parameter values:

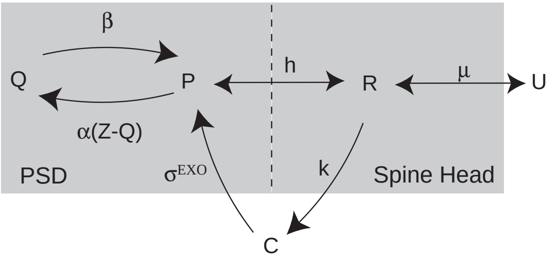
- Binding/unbinding rates α and β
    - Constitutive recycling $\sim 10 - 30$ min $\Rightarrow \alpha = \beta = 10^{-3}/\mathrm{s}$
- Scaffolding protein concentration Z
    - Approx. half AMPARs in PSD are bound $\Rightarrow Z = 200/\mu\mathrm{m}^2$

Steady-state

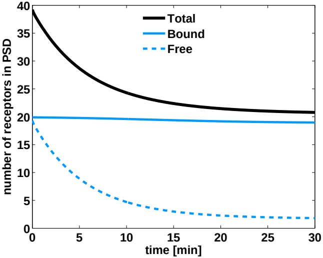
PSD free: $P = R + \frac{\sigma^{\text{EXO}}}{h}\frac{C}{a} \approx 193/\mu m^2$

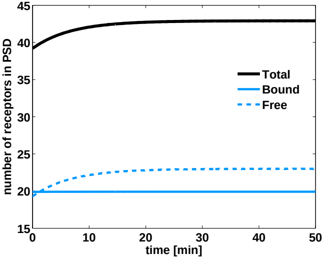
PSD bound: $Q = \frac{\alpha P}{\alpha P + \beta} Z \approx 199/\mu m^2$

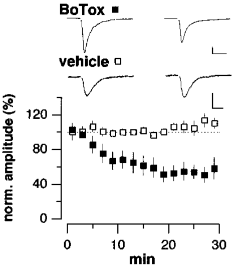
Spine head: $R = \frac{\mu U + \sigma^{\text{EXO}}\frac{C}{a}}{\mu + k} \approx 183/\mu m^2$

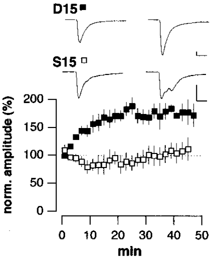


Block exo/endocytosis



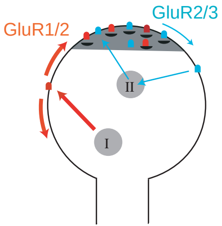




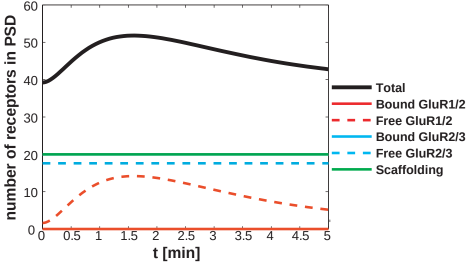


Luscher et al., *Neuron* (1999)

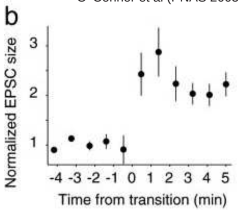
LTP simulation



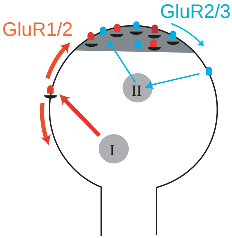
- Activation of GluR1/2 intracellular pool
- Rapid insertion of receptors into ESM



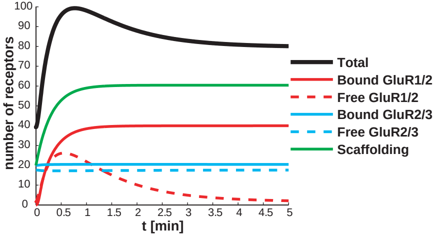
O' Connor et al (PNAS 2005)



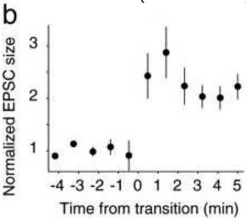
LTP simulation with increase in scaffolding



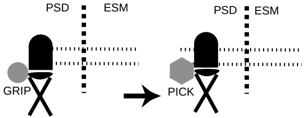
- Activation of GluR1/2 intracellular pool
- Rapid insertion of receptors into ESM
- AMPARs transport slot proteins into PSD



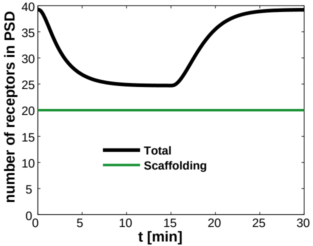
O' Connor et al (PNAS 2005)

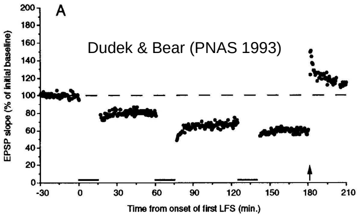


LTD simulation

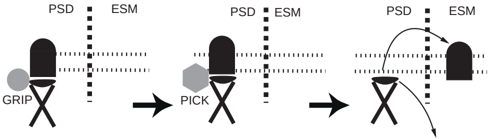


- Switch from AMPA-GRIP to AMPA-PICK receptor-protein complexes
- Rapid unbinding from PSD and trafficking to ESM followed by endocytosis.

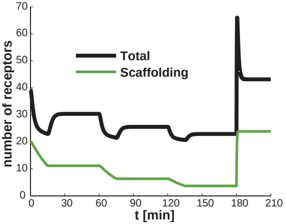


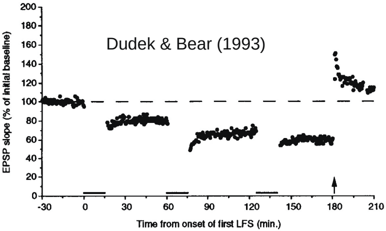


LTD simulation with decrease in scaffolding



- Switch from AMPA-GRIP to AMPA-PICK receptor-protein complexes
- Rapid unbinding from PSD and trafficking to ESM followed by endocytosis.
- Unbound scaffolding proteins are degraded.





Conclusions

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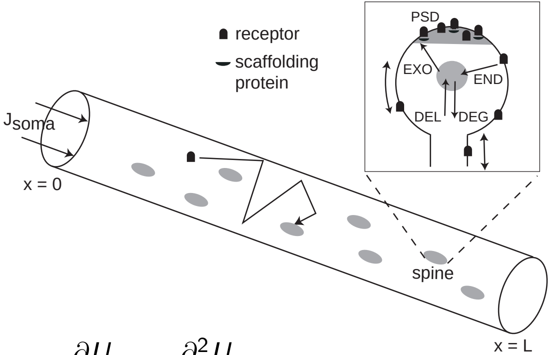
Can LTP/LTD data be explained by postsynaptic receptor trafficking alone?

- LTP/LTD data can be reproduced within our model of AMPA receptor trafficking
  - LTP requires increase in scaffolding (Shi et al., *Cell* 2001)
  - LTD requires decrease in scaffolding (Colledge et al., *Neuron* 2003)

Future directions – AMPAR trafficking along dendrite



$$\frac{\partial U}{\partial t} = D\frac{\partial^2 U}{\partial x^2} - \eta(x)\mu(x)(U - R)$$

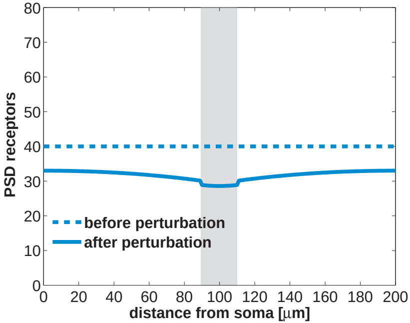
$$-D\left.\frac{\partial U}{\partial x}\right|_{x=0} = J_{\mathrm{soma}}, \qquad \left.\frac{\partial U}{\partial x}\right|_{x=L} = 0.$$

Bressloff, BAE, Ward, *SIAM J Appl Math* (2008)
BAE & Bressloff, *J Comput Neurosci* (2008)

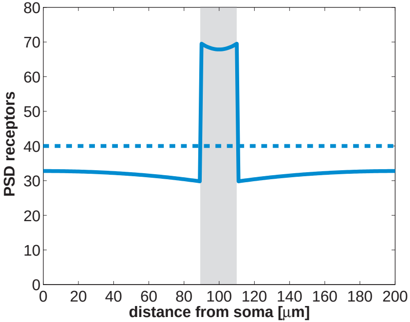
Future directions – AMPAR trafficking along dendrite

Consequences of diffusive coupling

10-fold reduction in rate of exocytosis in gray region



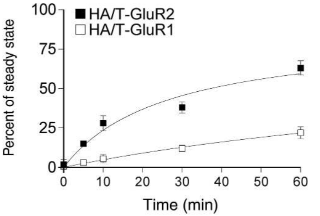
10-fold increase in rate of endocytosis in gray region



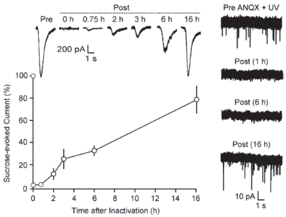
Future directions – AMPAR trafficking along dendrite

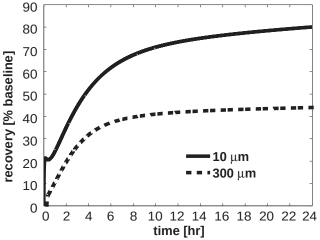
Fast or slow recycling?

Passafaro et al., 2001



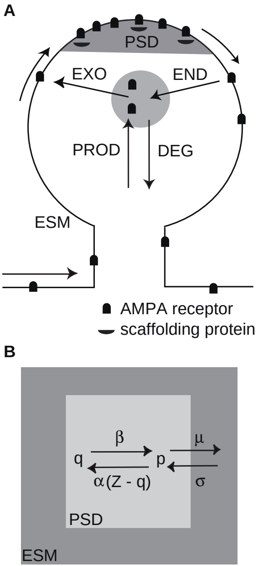
Adesnik et al., 2005





Future directions – stochastic models

$$\frac{dp}{dt} = -\alpha(Z-q)p + \beta q - \mu p + \sigma$$
$$\frac{dq}{dt} = \alpha(Z-q)p - \beta q$$



Bressloff & BAE *Biophys J* (2009)

Future directions – stochastic models

$$\frac{dp}{dt} = -\alpha(Z-q)p + \beta q - \mu p + \sigma$$
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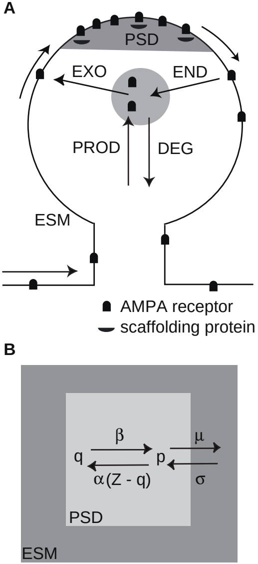
$$P_{n,m}(t) = \text{Prob}\{n \text{ unbound}, m \text{ bound at time } t\}$$



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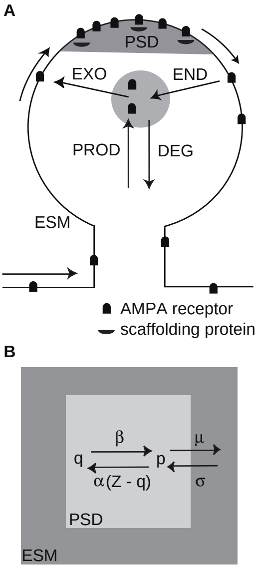
$$\frac{dP_{n,m}}{dt} = \sigma P_{n-1,m} + \mu(n+1)P_{n+1,m} + \alpha(n+1)[Z-(m-1)]P_{n+1,m-1} + \beta(m+1)P_{n-1,m+1} - [\sigma + \mu n + \alpha n(Z-m) + \beta m]P_{n,m}$$



Bressloff & BAE *Biophys J* (2009)

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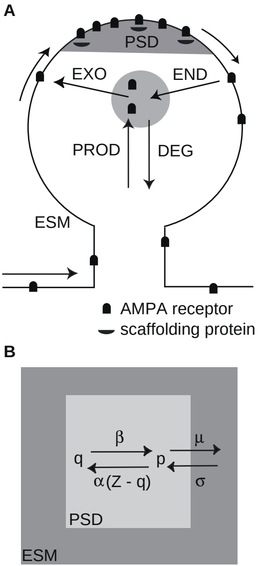
$$\begin{aligned}\frac{dP_{n,m}}{dt} &= \sigma P_{n-1,m} + \mu(n+1)P_{n+1,m} \\ &+ \alpha(n+1)[Z-(m-1)]P_{n+1,m-1} \\ &+ \beta(m+1)P_{n-1,m+1} \\ &- [\sigma + \mu n + \alpha n(Z-m) + \beta m]P_{n,m}\end{aligned}$$

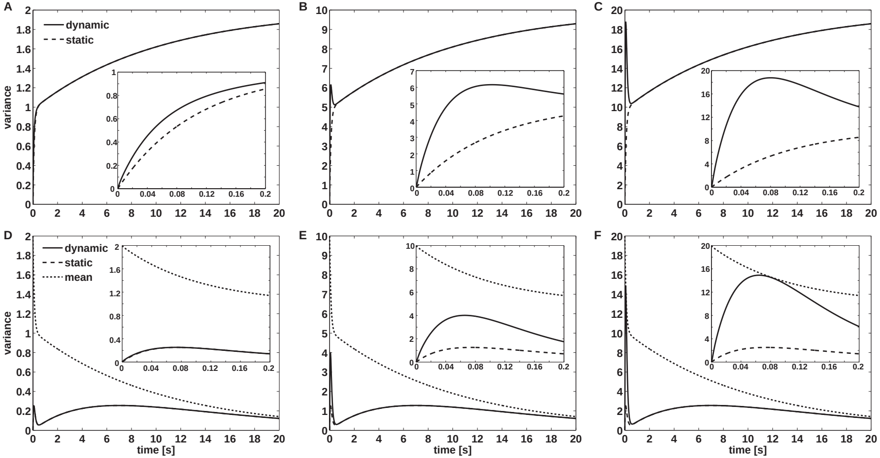
$$\text{stochastic gate}: \quad 0 < \mu_{open} \underset{\gamma_+}{\overset{\gamma_-}{\rightleftarrows}} \mu_{closed} = 0$$

$$\sigma(t) = C\mu(t) \quad (C \text{ bath conc.})$$

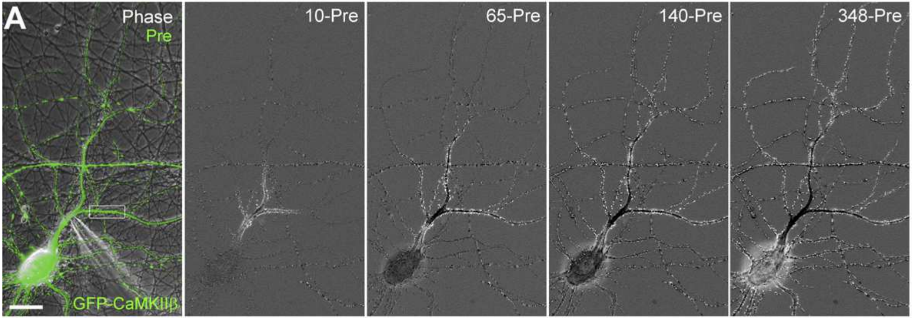


Bressloff & BAE *Biophys J* (2009)

Future directions – stochastic models



Future directions – trafficking of other proteins

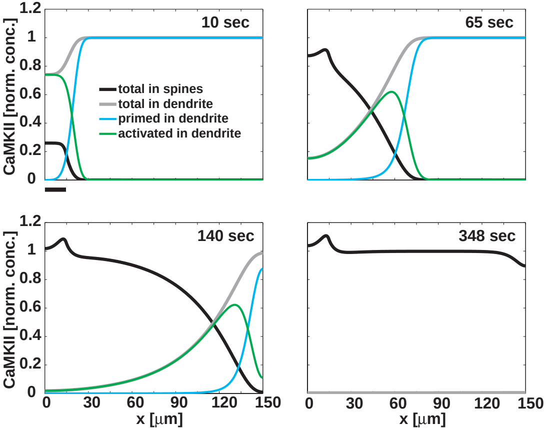


Rose et al., *Neuron* (2009)

Future directions – trafficking of other proteins

$$\frac{\partial p}{\partial t} = D\frac{\partial^2 p}{\partial x^2} - kap$$
$$\frac{\partial a}{\partial t} = D\frac{\partial^2 a}{\partial x^2} + kap - ha$$
$$\frac{\partial s}{\partial t} = ha$$

BAE & Bressloff, *J. Comput. Neurosci.*



Thank you!

Thanks to

- Paul Bressloff (Oxford)
- Michael Ward (UBC)
- National Science Foundation