What I do
(and what I want to do)

Berton Earnshaw

Department of Mathematics, University of Utah
Salt Lake City, Utah 84112

March 1, 2008

Current projects

- What I do
  - AMPA receptor trafficking
  - Synaptic plasticity

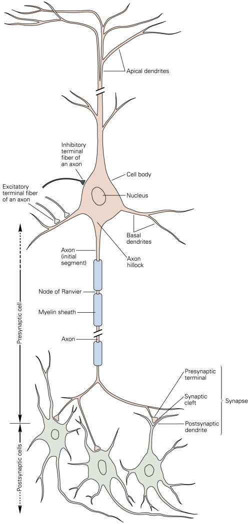
Current projects

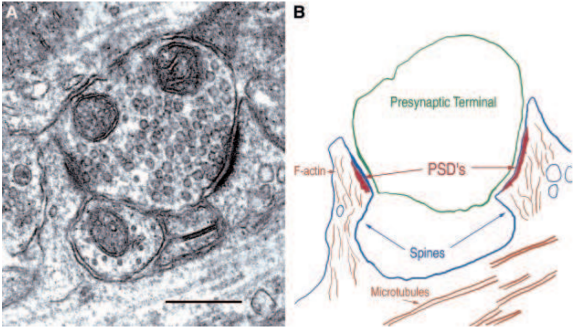
- What I do
  - AMPA receptor trafficking
  - Synaptic plasticity
- What I want to do
  - Just count things

Mathematical neuroscience at Utah

Cognition
↑
Systems
↑
Cortical Areas
↑
Small Networks
↑
Neurons
↑
Dendrites
↑
Synapses

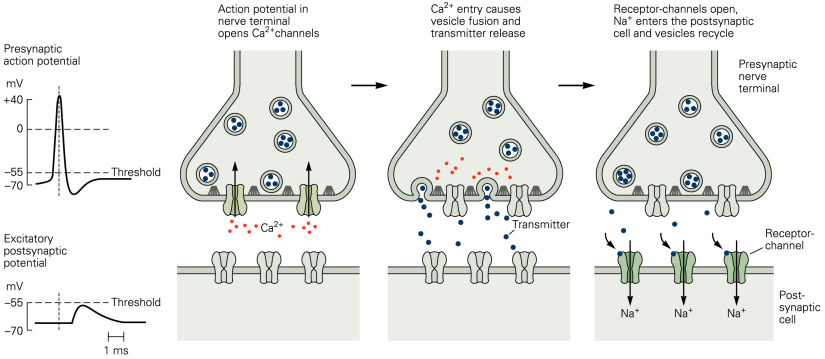
The synapse





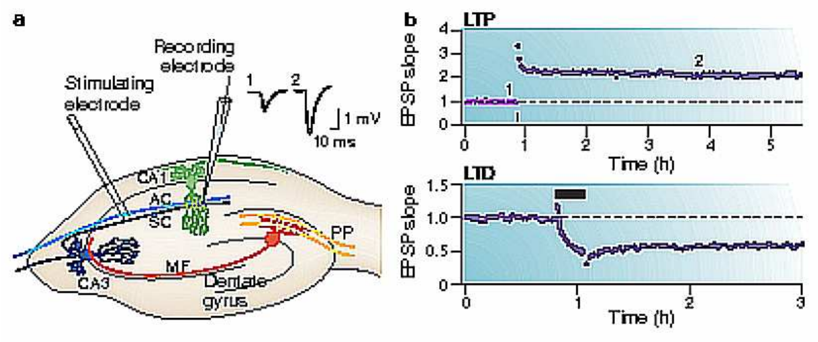
E.R. Kandel et al. *Principles of Neural Science* (2000)
M.B. Kennedy *Science* (2000)

Synaptic transmission



E.R. Kandel et al. *Principles of Neural Science* (2000)

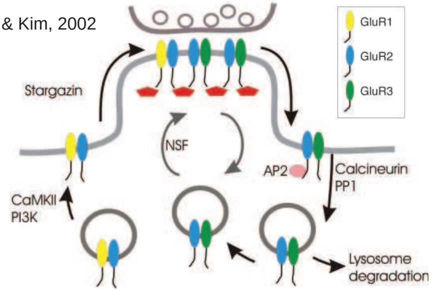
Synaptic plasticity



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

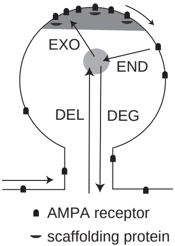
AMPA receptor trafficking at a single spine

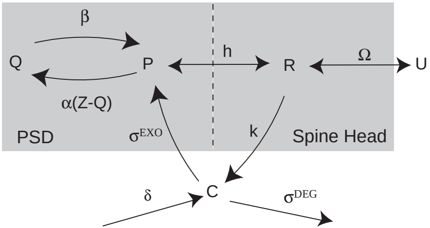
Sheng & Kim, 2002



- Surface AMPARs constitutively recycle with intracellular stores
- Laterally diffuse within postsynaptic membrane
- Crosslink to scaffolding proteins in PSD

Model of trafficking at a single spine





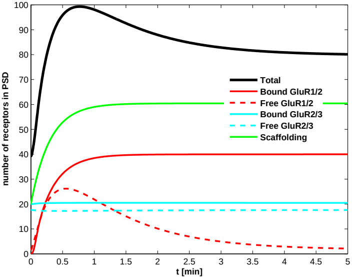
Spine head: $$\frac{dR}{dt} = \frac{1}{A}\left(\Omega[U-R] - kR - h[R-P]\right)$$

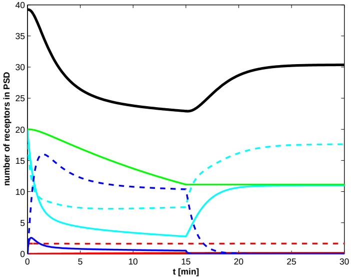
PSD unbound: $$\frac{dP}{dt} = \frac{h}{a}[R-P] - \alpha[Z-Q]P + \beta Q + \frac{\sigma^{\mathrm{EXO}} C}{a}$$

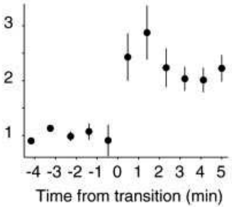
PSD bound: $$\frac{dQ}{dt} = \alpha[Z-Q]P - \beta Q$$

Intracellular: $$\frac{dC}{dt} = -\sigma^{\mathrm{EXO}} C - \sigma^{\mathrm{DEG}} C + kR + \delta,$$

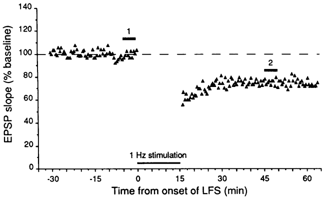
Trafficking during LTP/LTD







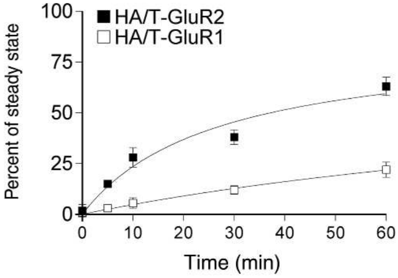
O'Connor et al. *PNAS* (2005)



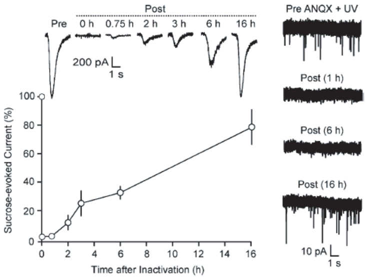
Dudek & Bear *PNAS* (1992)

Fast or slow recycling?

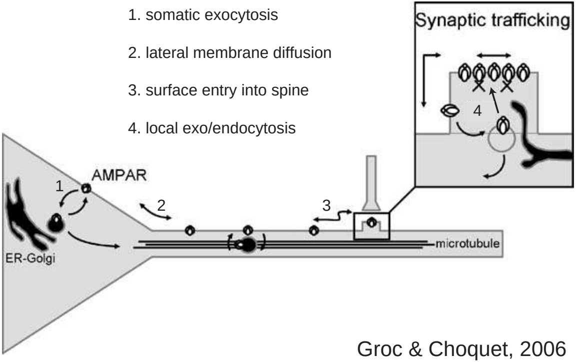
Passafaro et al., 2001



Adesnik et al., 2005



AMPA receptor trafficking along a spiny dendrite



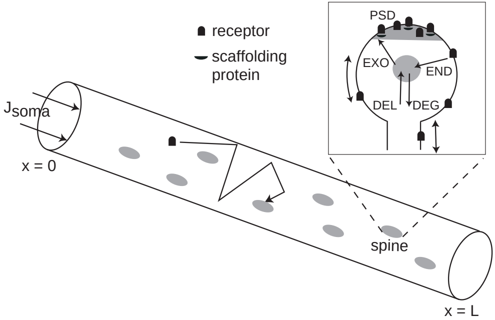
Groc & Choquet, 2006

- AMPARs trafficked in vesicles along microtubules?
- AMPARs diffuse from soma to synapse?

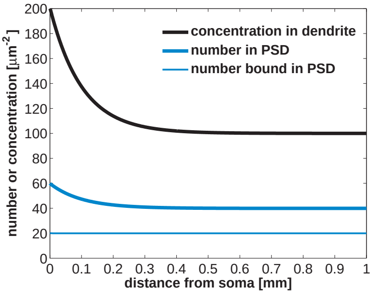
Model of trafficking along a spiny dendrite

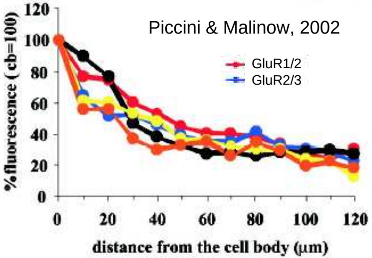
$$\frac{\partial U}{\partial t} = D\frac{\partial^2 U}{\partial x^2} - \rho(x)\Omega(x)[U(x,t) - R(x,t)]$$

$$\rho(x) = \text{spine density at } x$$



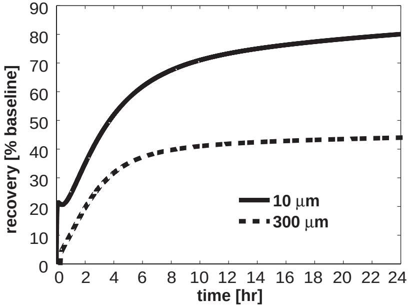
Steady-state receptor concentrations





- 1,000 identical spines distributed uniformly
- Two sources of AMPARs
  - at soma
  - local intracellular delivery

Recovery rate depends on distance from soma

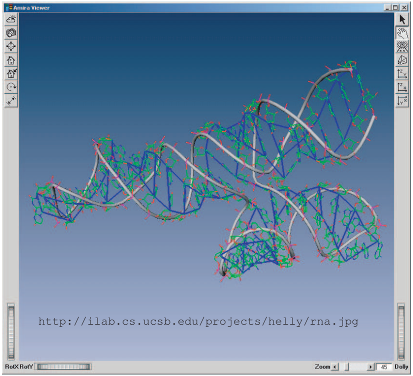


- Recovery exhibits many time-scales!

Now that we're done with that...

...let's count something!

A single strand of RNA



- Primary structure: sequence of bases (A,G,U,C)
- Secondary structure: pairing of bases
  - Watson-Crick pairs: A-U, G-C (less often U-G)
- Tertiary structure: resulting 3D molecule
  - Different tertiary structures $\Rightarrow$ different enzymatic properties

A single strand of RNA: An example

- Primary structure:

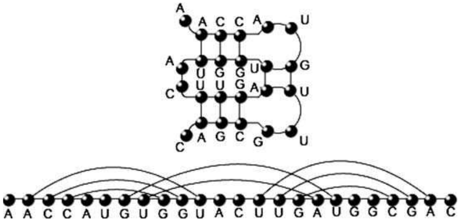
AACCAUGUGGUACUUGAUGGCGAC

A single strand of RNA: An example

- Primary structure:

  AACCAUGUGGUACUUGAUGGCGAC

- Secondary structure:

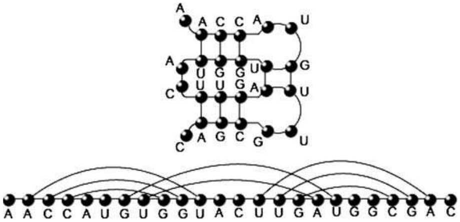


A single strand of RNA: An example

- Primary structure:

  AACCAUGUGGUACUUGAUGGCGAC

- Secondary structure:



- Tertiary structure: extremely difficult to predict (probably NP-hard)

RNA secondary structure as k-noncrossing arch diagram

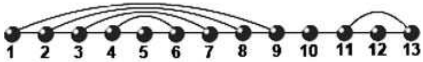
- k-noncrossing arch diagram of order n
  - graph on vertex set $\{1, \ldots, n\}$
  - all vertices have degree ≤ 1
  - there do not exist k arches $\{i_1, j_1\}, \ldots, \{i_k, j_k\}$ such that

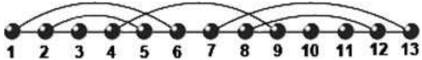
$$i_1 < \cdots < i_k < j_1 < \cdots < j_k$$

RNA secondary structure as k-noncrossing arch diagram

- k-noncrossing arch diagram of order n
  - graph on vertex set $\{1, \ldots, n\}$
  - all vertices have degree ≤ 1
  - there do not exist k arches $\{i_1, j_1\}, \ldots, \{i_k, j_k\}$ such that

$$i_1 < \cdots < i_k < j_1 < \cdots < j_k$$

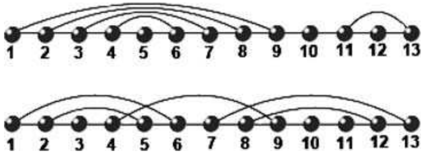




RNA secondary structure as k-noncrossing arch diagram

- k-noncrossing arch diagram of order n
  - graph on vertex set $\{1, \ldots, n\}$
  - all vertices have degree ≤ 1
  - there do not exist k arches $\{i_1, j_1\}, \ldots, \{i_k, j_k\}$ such that

$$i_1 < \cdots < i_k < j_1 < \cdots < j_k$$



- RNA secondary structure of n bases, pseudoknot type $k-2$
  - k-noncrossing (but not $k-1$) arch diagram of order n
  - no 1-arches $\{i, i+1\}$
  - "abstract" secondary structure (no primary structure)

k-noncrossing arch diagrams and walks in Weyl chamber

- Walk in $\mathbb{Z}^m$ of length n
  - sequence of vectors $\mathbf{x}_0, \mathbf{x}_1, \ldots, \mathbf{x}_n \in \mathbb{Z}^m$ s.t. $|\mathbf{x}_{i+1} - \mathbf{x}_i| = 0$ or 1

k-noncrossing arch diagrams and walks in Weyl chamber

- Walk in $\mathbb{Z}^m$ of length n
  - sequence of vectors $\mathbf{x}_0, \mathbf{x}_1, \ldots, \mathbf{x}_n \in \mathbb{Z}^m$ s.t. $|\mathbf{x}_{i+1} - \mathbf{x}_i| = 0$ or 1
- Weyl chamber
  - subset of vectors $\mathbf{x} = (x_1, \ldots, x_m) \in \mathbb{Z}^m$ s.t. $x_1 > \cdots > x_m > 0$

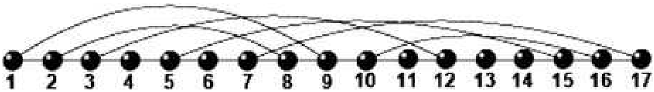
k-noncrossing arch diagrams and walks in Weyl chamber

- Walk in $\mathbb{Z}^m$ of length n
  - sequence of vectors $\mathbf{x}_0, \mathbf{x}_1, \ldots, \mathbf{x}_n \in \mathbb{Z}^m$ s.t. $|\mathbf{x}_{i+1} - \mathbf{x}_i| = 0$ or 1
- Weyl chamber
  - subset of vectors $\mathbf{x} = (x_1, \ldots, x_m) \in \mathbb{Z}^m$ s.t. $x_1 > \cdots > x_m > 0$

Theorem (Chen et al. (2007) *Trans. Am. Math. Soc.* 359)

There exists a bijection between k-noncrossing arch diagrams of order n and walks of length n in $\mathbb{Z}^{k-1}$ which start and end at $\mathbf{a} = (k-1, k-2, \ldots, 1)$ and remain in the Weyl chamber.

Idea of proof: The bijection



$$\varnothing \quad \begin{array}{c}1\end{array} \quad \begin{array}{cc}1&2\end{array} \quad \begin{array}{cc}1&2\\3&\end{array} \quad \begin{array}{cc}1&2\\3&\end{array} \quad \begin{array}{cc}1&2\\3&\\5&\end{array} \quad \begin{array}{cc}1&2\\3&\\5&\end{array} \quad \begin{array}{cc}1&2\\3&\\5&\\7&\end{array} \quad \begin{array}{c}1\\3\\5\\7\end{array}$$

$$\begin{array}{c}3\\5\\7\end{array} \quad \begin{array}{cc}3&10\\5&\\7&\end{array} \quad \begin{array}{cc}3&10\\5&\\7&\end{array} \quad \begin{array}{cc}5&10\\7&\end{array} \quad \begin{array}{cc}5&10\\7&\end{array} \quad \begin{array}{cc}5&10\\7&\end{array} \quad \begin{array}{cc}7&10\end{array} \quad \begin{array}{c}7\end{array} \quad \varnothing$$

$(4,3,2,1)$, $(5,3,2,1)$, $(6,3,2,1)$, $(6,4,2,1)$, $(6,4,2,1)$, $(6,4,2,1)$

$(6,4,3,1)$, $(6,4,3,1)$, $(5,4,3,1)$, $(5,4,3,2)$, $(6,4,3,2)$, $(6,4,3,1)$

$(6,4,3,1)$, $(6,4,2,1)$, $(6,4,2,1)$, $(6,3,2,1)$, $(5,3,2,1)$, $(4,3,2,1)$

Counting k-noncrossing RNA secondary structures

- Set

$$A_k(n,l) = \#\ k\text{-nc arch diagrams of order } n,\ l \text{ isolated nodes}$$
$$B_k(n,l) = \#\ k\text{-nc RNA structures of } n \text{ bases},\ l \text{ isolated bases}$$

Counting k-noncrossing RNA secondary structures

- Set

$$A_k(n,l) = \# \; k\text{-nc arch diagrams of order } n,\ l \text{ isolated nodes}$$
$$B_k(n,l) = \# \; k\text{-nc RNA structures of } n \text{ bases, } l \text{ isolated bases}$$

Theorem (Jin, Qin & Reidys, 2008)

$$B_k(n,l) = \sum_{b=0}^{(n-l)/2} (-1)^b \binom{n-b}{b} A_k(n-2b,l)$$

where $A_k(n,l)$ is given by the generating function

$$\sum_{n=1}^{\infty}\sum_{l=0}^{n} A_k(n,l)\frac{x^n}{n!} = \mathrm{e}^x \det[I_{i-j}(2x) - I_{i+j}(2x)]|_{i,j=1}^{k-1}$$

and $I_r(2x) = \sum_{j=0}^{\infty} x^{2r+j}/(j!(r+j)!)$ is hyperbolic Bessel function of 1st kind of order r.

The end

Thank you!