

Sophisticated Synapses and Cells - A look at the complex components of neural networks

Herbert Levine UCSD/CTBP

S. Nadkarni, V. Volman; T. Bartol and T. Sejnowski (Salk)

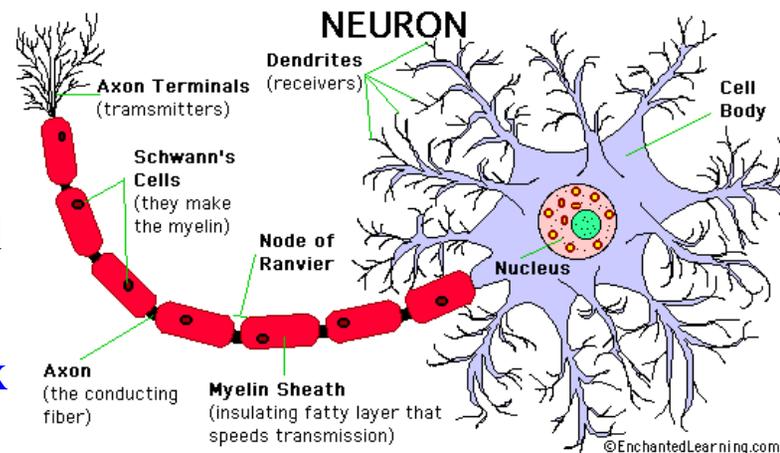
- Introduction: The complexity of real neural components
 - My bias as a theorist coming from microorganisms
 - Implications from evolution studies
- CA3-CA1 presynaptic calcium dynamics (Nadkarni)
 - Structure-function relationship
 - Asynchronous versus phasic release
 - Coupling to the astrocyte; optimized information transfer?
- Consequences of the dynamical synapse (Volman)
 - Gain modulation (in point neurons)
 - Fluctuations in active dendrites

Simple vs Complex

- Neural networks date back to McCullough-Pitts (1943)

$$S_i = \Theta(\sum W_{ij} S_j + b_i)$$

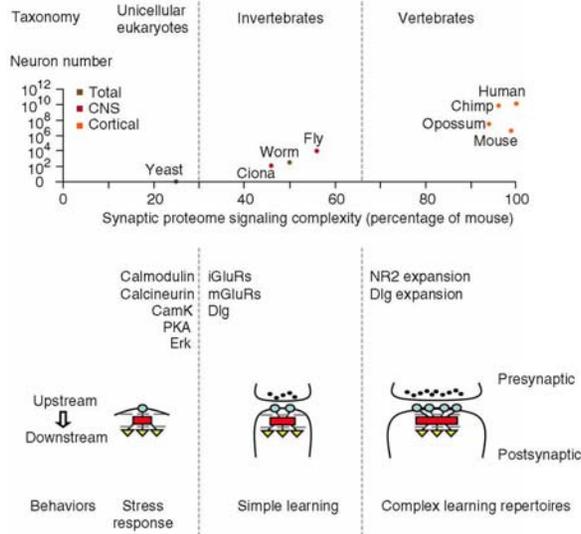
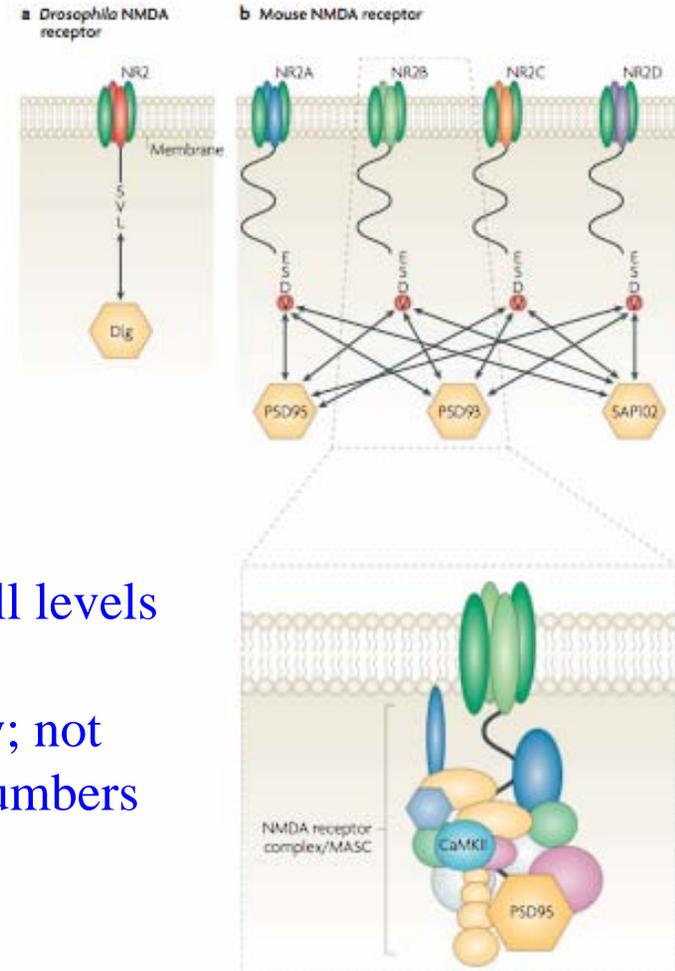
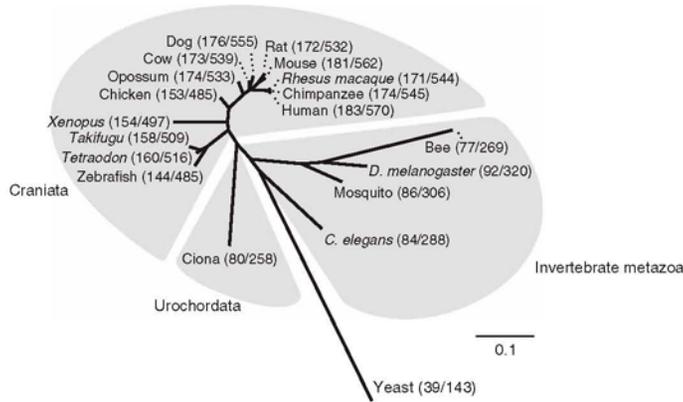
- Binary neurons (firing or not)
 - Passive synapses
 - Input is summed and then thresholded
 - History of simple models (Hopfield, IF,..)
 - Conductance based-model still are often 0d
- Real neurons are immensely more complex
 - Myriads of ion channels
 - Extensive dendritic trees
 - Huge variety of morphologies, neurotransmitters etc.



Lessons from simpler cells: Individual cells do extremely complex computations to determine their actions - why should we expect any less from neurons?

SN Grant and co-workers
 Nat. Neuro (2008)

Evolution is relentless

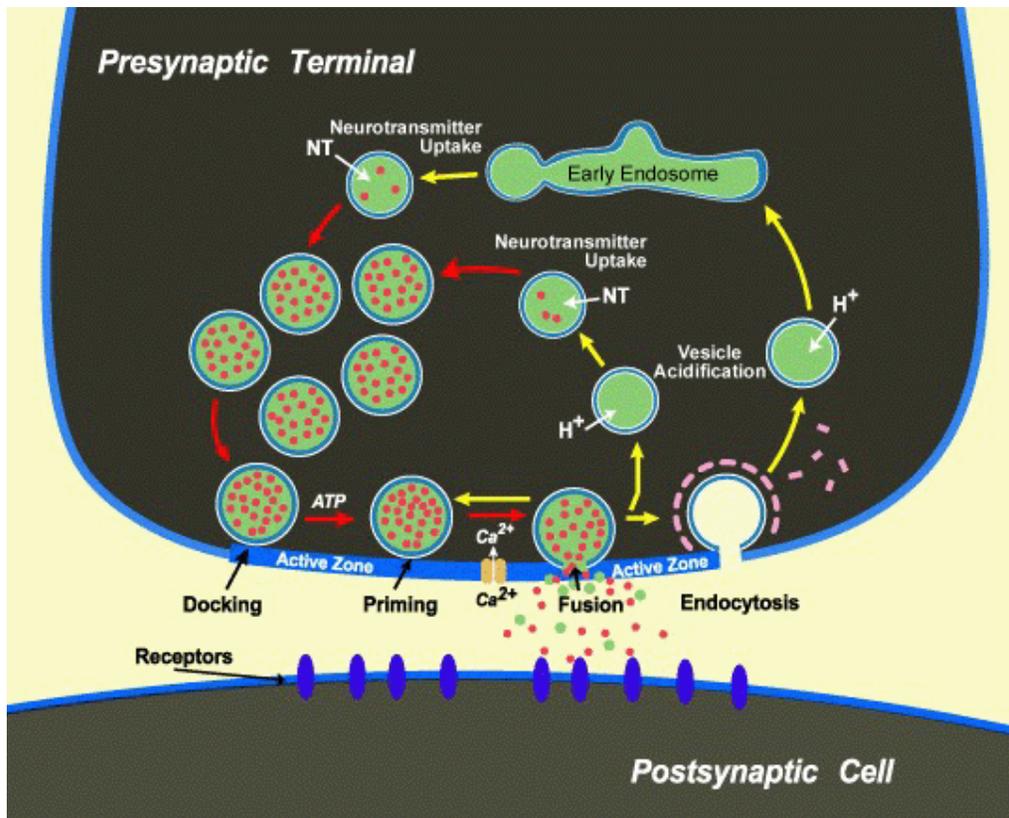


Complexity at all levels
 increases in a
 coordinated way; not
 just increased numbers
 and connections

Our research program

- Devise biophysical models which incorporate more sophisticated views of these neural components
- Calibrate/test these models with physiology data (synapses, dendrites, astrocytes)
- Work towards understanding the implications of component sophistication for network dynamics
- Disclaimer: this is a new field for me and I am very much on the steep part of the learning curve

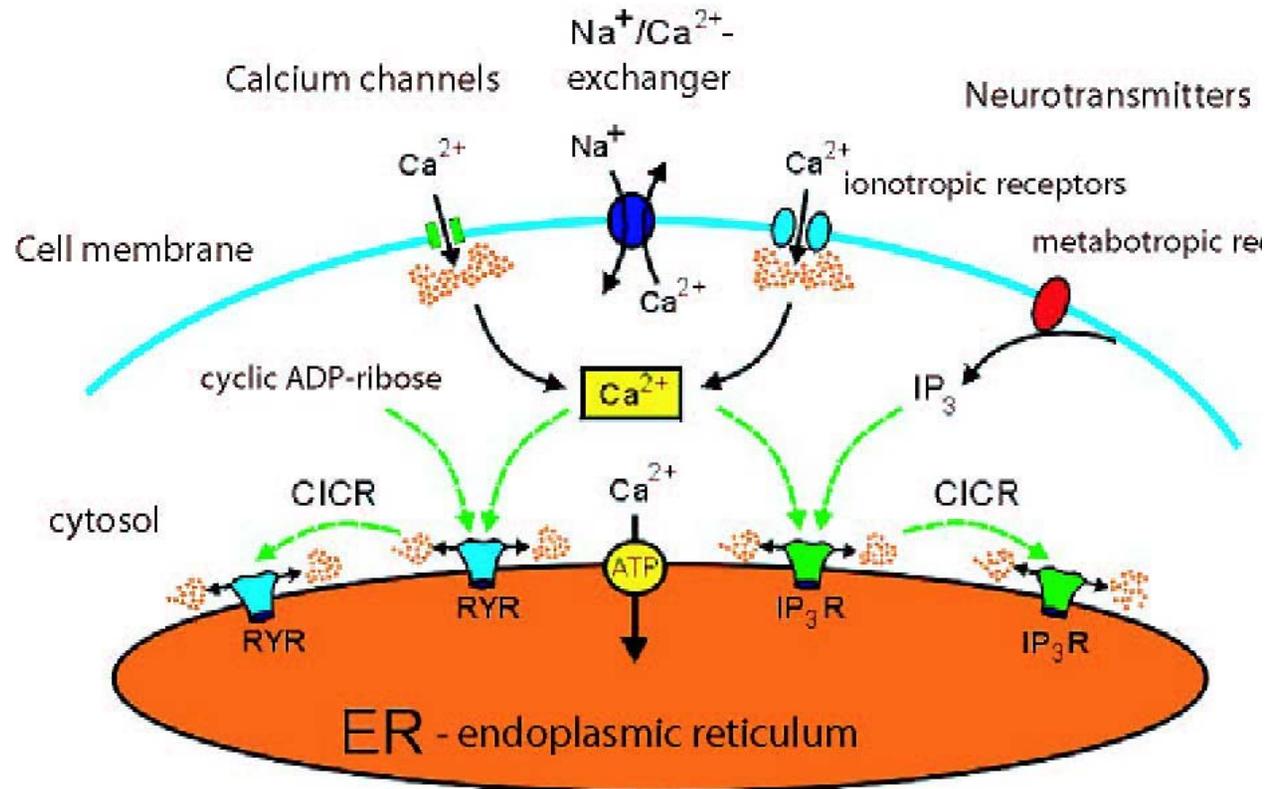
The pre-synaptic terminal



From T. Sudhof

- Vesicles dock at an active zone; finite supply can be depleted
- Different synapses have different numbers of active zones
 - Calyx of Held - 100's
 - CA3-CA1 Hippocampus 1-5
- Fusion mediated by calcium binding to “sensor” proteins
- Calcium dynamics is an inherently spatially-extended nonlinear dynamical process

Intracellular Calcium handling



Positive feedback via CICR - excitable dynamics

Neurotransmitter depletion only

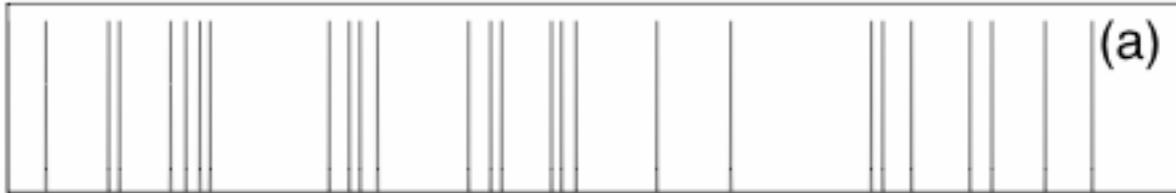
Tsodyks and Markram model (depression)

$$\frac{dX}{dt} = \frac{(1 - X - Y)}{\tau_{rec}} - uX\delta(t - t_{spike})$$
$$\frac{dY}{dt} = -\frac{Y}{\tau_{inactive}} + uX\delta(t - t_{spike})$$

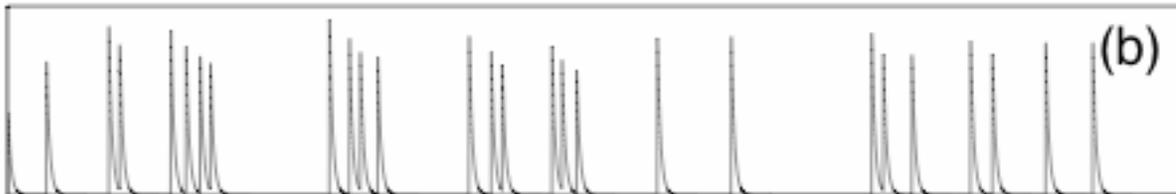
X = available resources
Y = released level

governed by 2 times;
recovery ~ 800ms
inactivation ~ 3ms

u = resource utilization



Presynaptic firing



Postsynaptic current
(TM model)

Can add facilitation by phenomenologically increasing u after each use

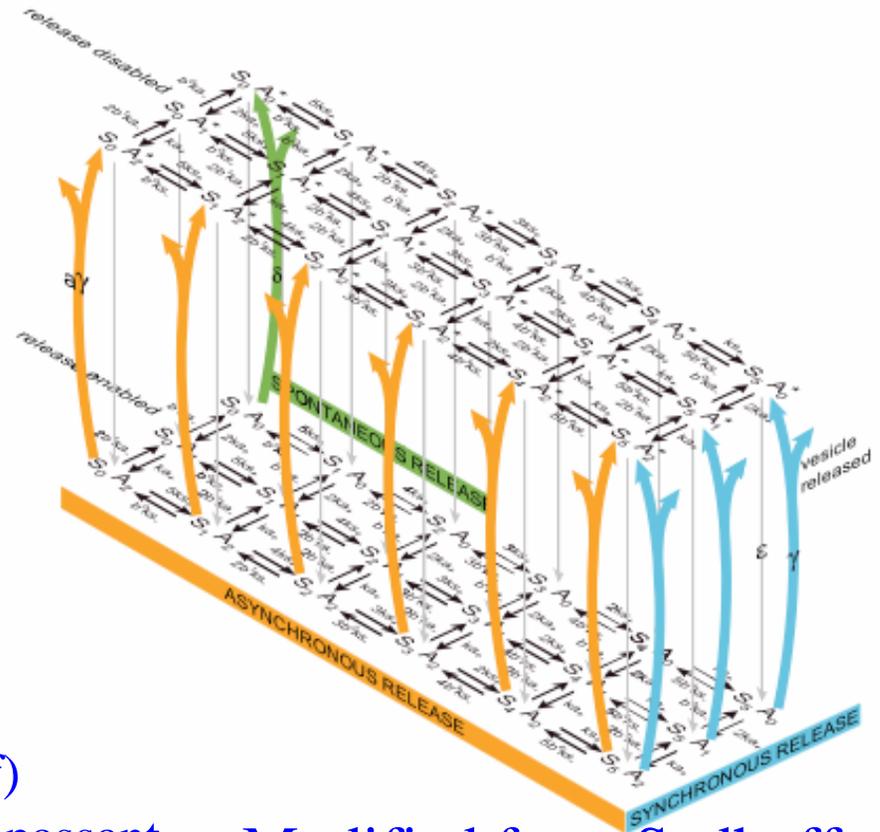
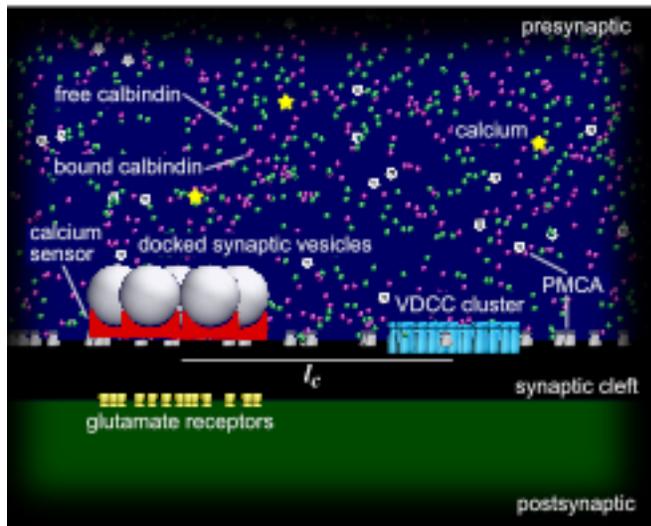
Calcium dynamics

- TM model has very simplified Ca^{2+} facilitation
- Also, no stochasticity; but in fact vesicle release is actually far from deterministic
 - CA3-CA1 synapse has only a few active zones
 - Each spike has release probability of 25-50%
 - Release can occur spontaneously/asynchronously
- We can proceed in two different ways
 - Detailed biophysical models of the pre-synaptic zone
 - Phenomenological modifications/extensions to TM approach

"When you come to a fork in the road, take it."

Yogi Berra

Presynaptic model

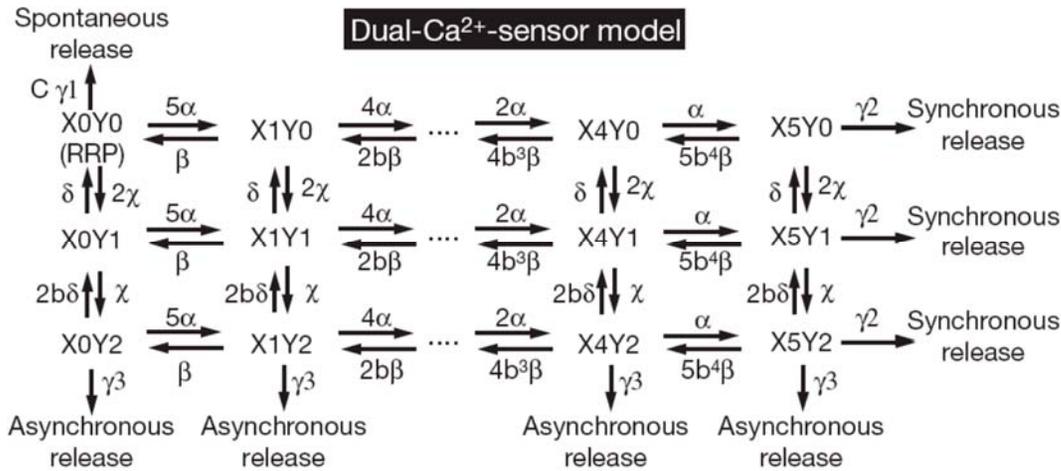


- Dual-release sensor model (Sudhoff)
- 4 micron x .5 micron x .5 micron en passant
- VDC's; pumps; buffers
- Solved by explicit particle tracking (Mcell)

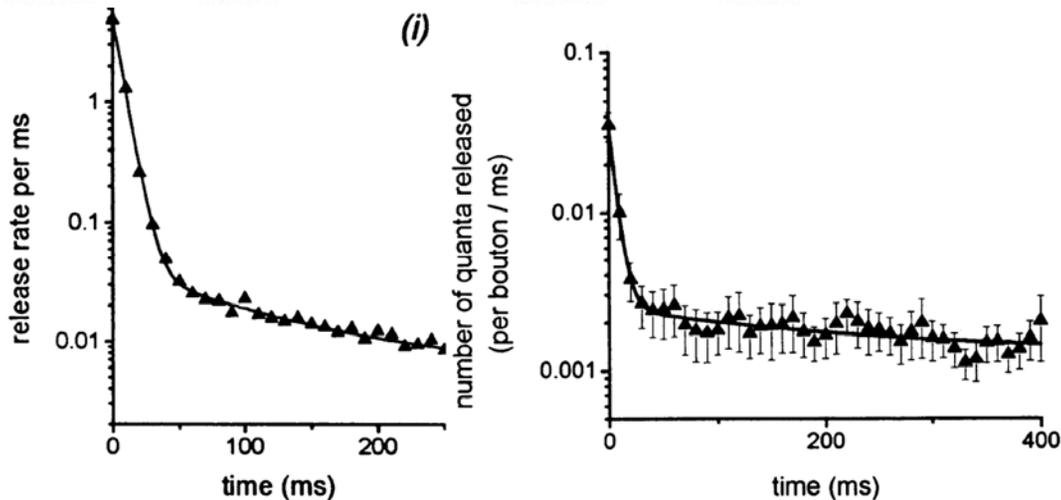
Modified from Sudhoff et al

Nadkarni et al PLoS CompBio (2010 to appear)

Details of the Ca sensor



Modification of model for Calyx of Held due to Sun et al (Nature 2007)

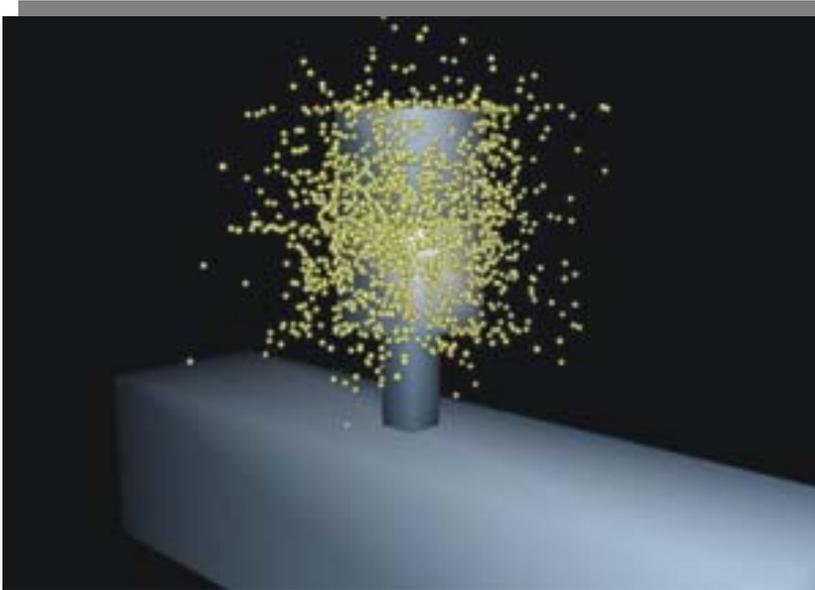


Can be calibrated by using data of Goda and Stevens, PNAS (1994)

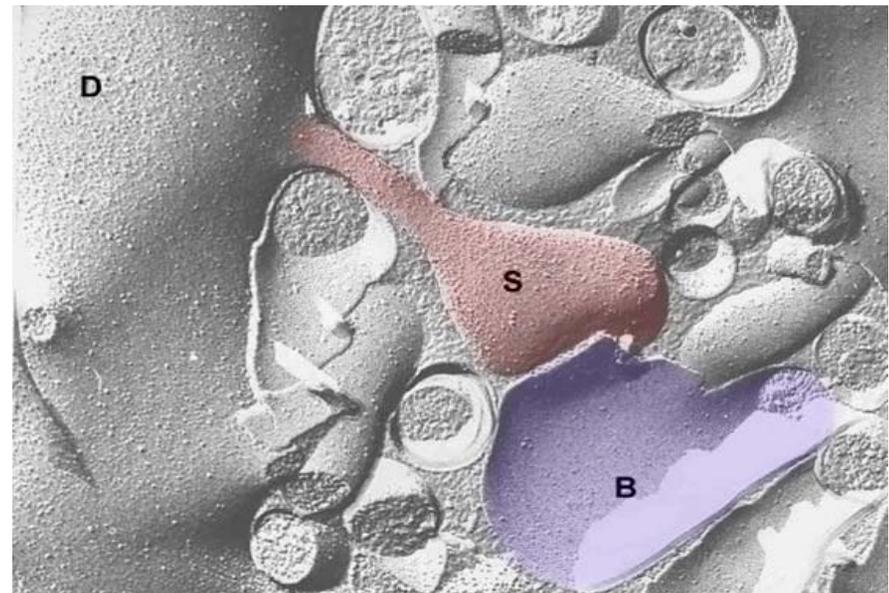
MCell

Monte Carlo Simulator of Microphysiology

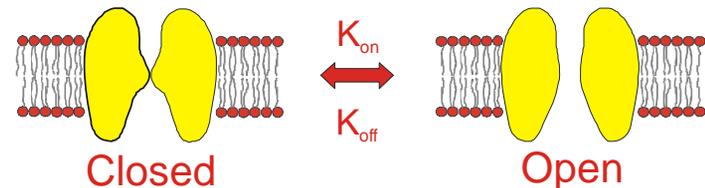
- Random walk diffusion



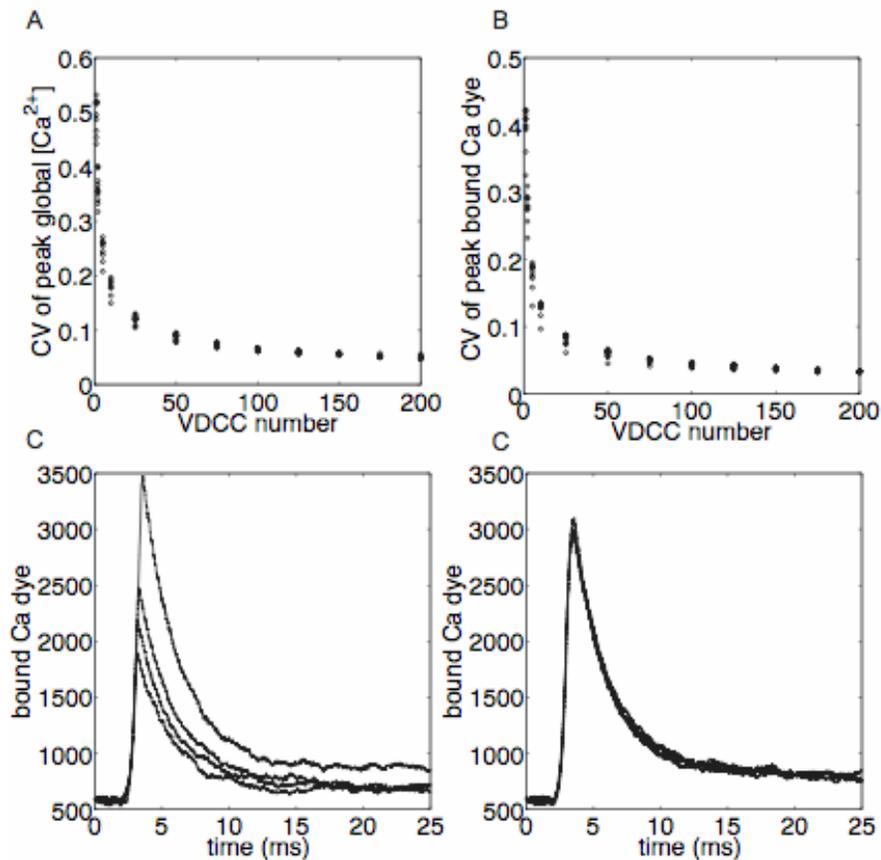
- Realistic 3D Geometry



- Stochastic biochemical kinetic state transitions



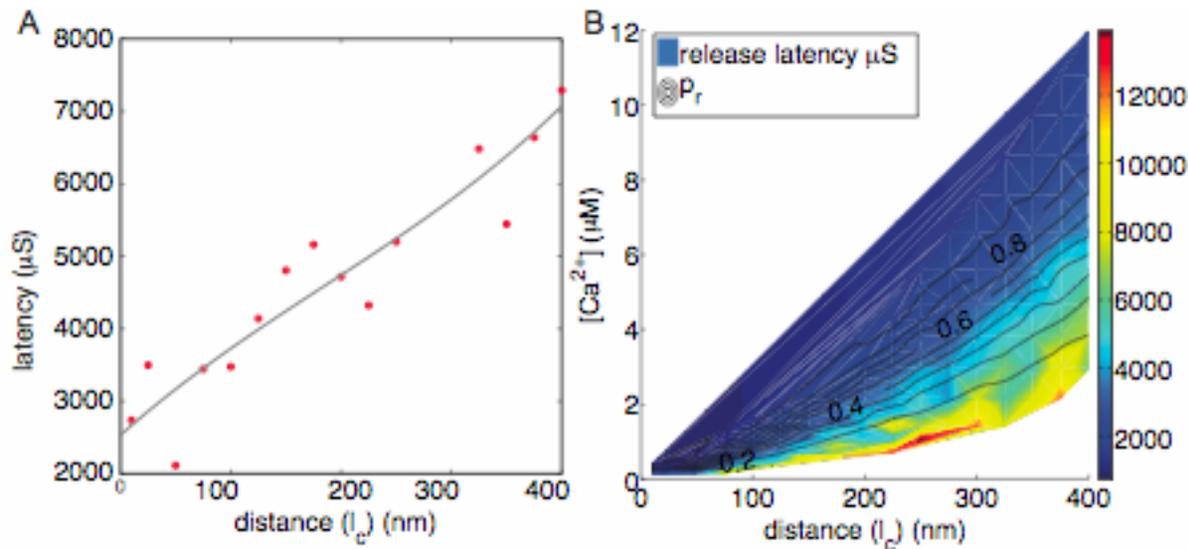
Structure-function relations



The Coefficient of Variation of the global Ca signal depends exclusively on VDCC number

- A. Total number of ions
- B. Predicted fluorescence
- C. Ca time course with 1 Ca channel
- D. Predicted time course with 200 channels (with smaller flux so as to give same mean)

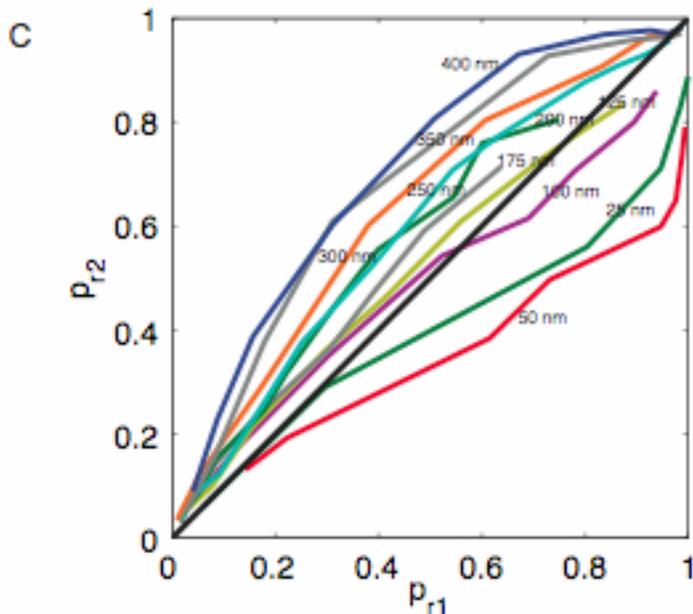
Structure-function cont'd



If we measure latency (time to release) and also measure either release probability or global $[Ca]$, can infer distance between the sensor and the Calcium channels.

Short-term Facilitation/Depression

- Once we have determined the synaptic structure, we can predict response to pp protocol



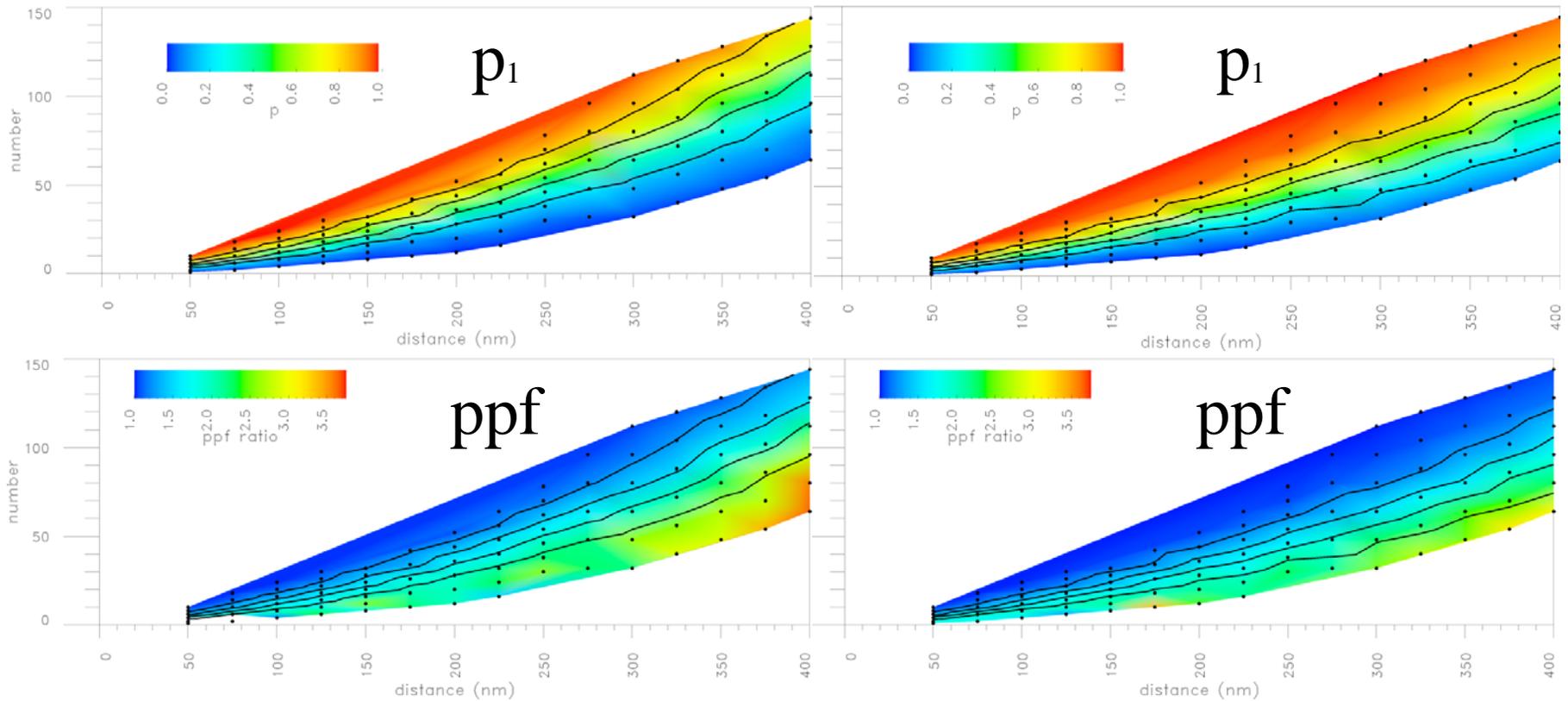
Basic physics

- If L_c is large, need large global Ca signal to reach threshold at sensor, implies facilitation of next pulse
- If L_c is small, tight coupling allows release with localized peak, which decays quickly; depletion dominates at large p_r

Paired Pulse Facilitation a Measure of Plasticity

Stores On

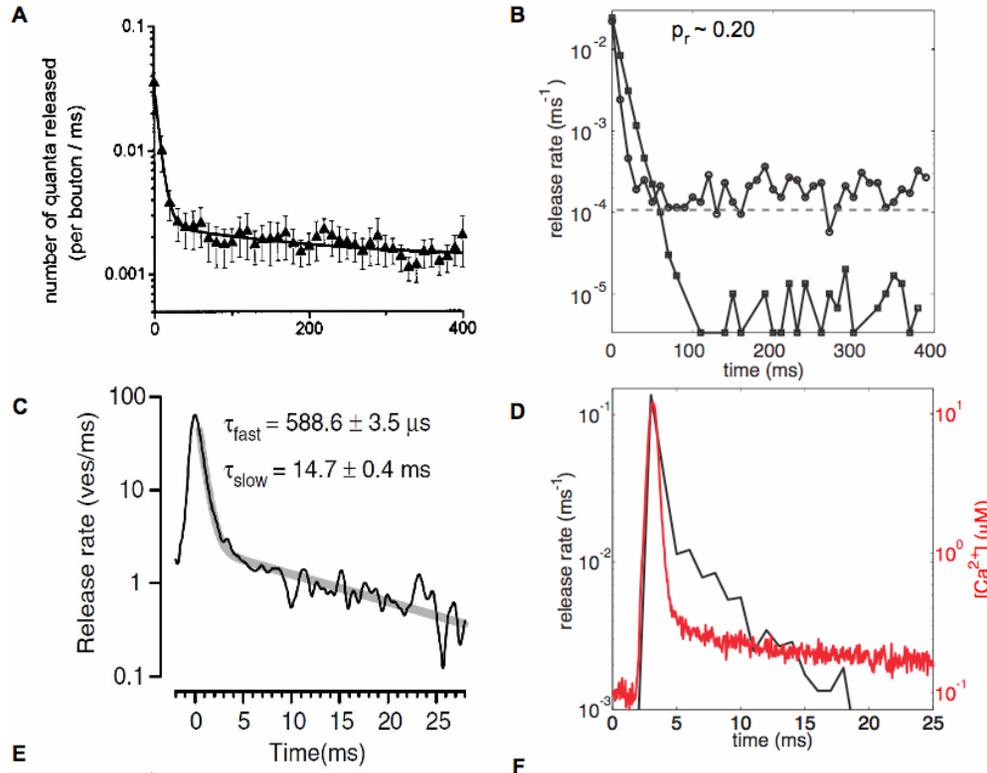
Stores Off



Lower Probability of release on first pulse, however HIGHER ppf for stores:
buffer saturation

Release time scales

Figure 3



The black line shows that release occurs with two main time scales;
7.5 msec “phasic” response
160 msec “asynchronous” release

A closer look shows that there is actually a very fast decay (.5 msec) directly caused by local Ca, which is then taken over by the sensor kinetic response

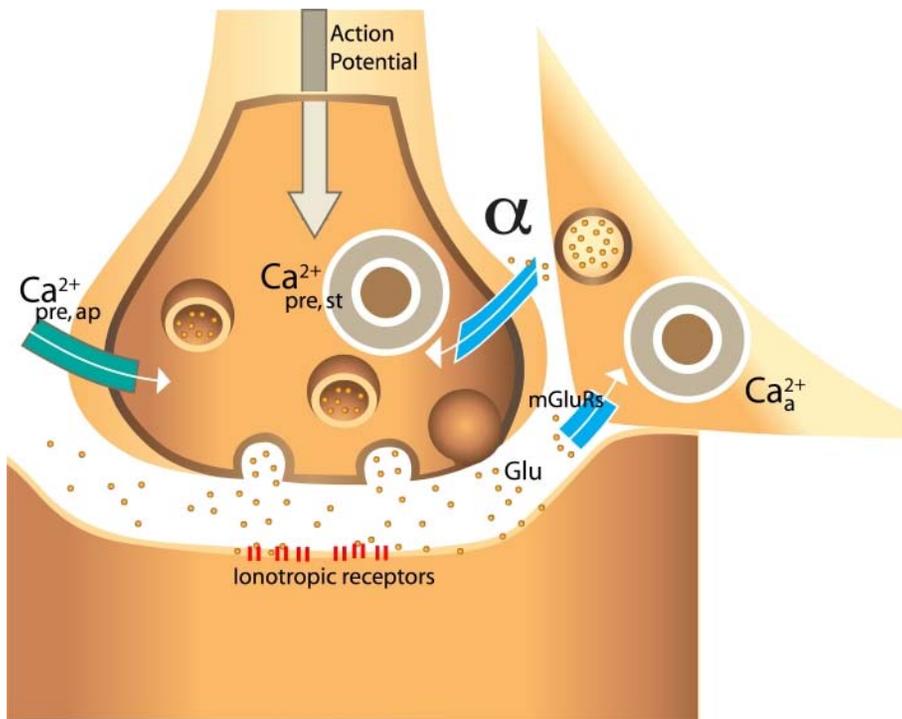
Decay rates are independent of release probability, in agreement with data

Data from Goda and Stevens;
Schuess and Neher (Caylx)

Results

- We have a new microphysical model of the pre-synaptic Ca dynamics
- Can investigate the interplay between geometry and synaptic facilitation
- Predicts that synapses with greater than 2-3 fold facilitation must contain ER, which allows for calcium amplification

Tripartite synapse model

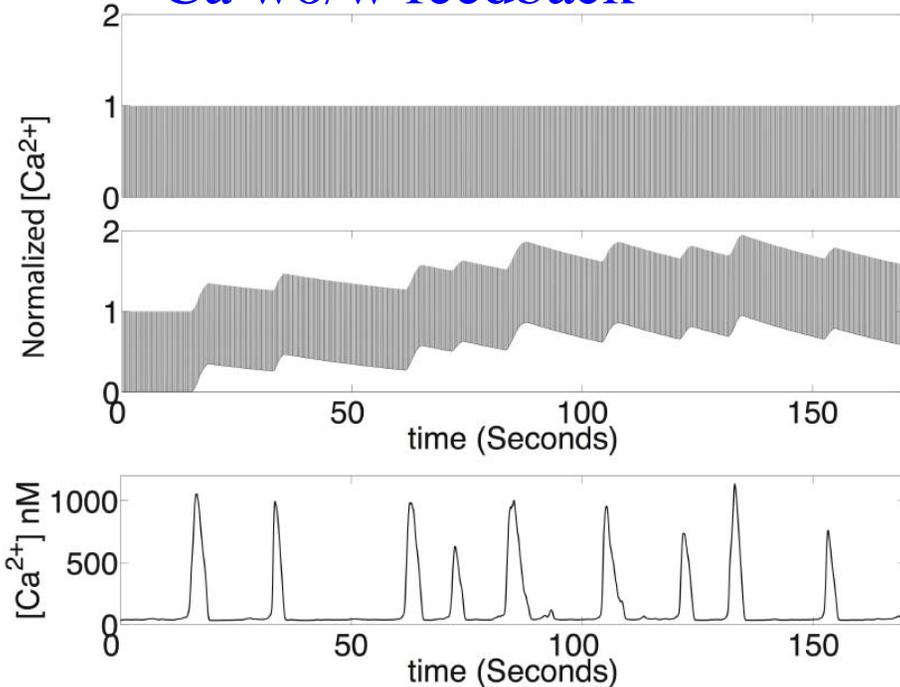


Add to TM model:

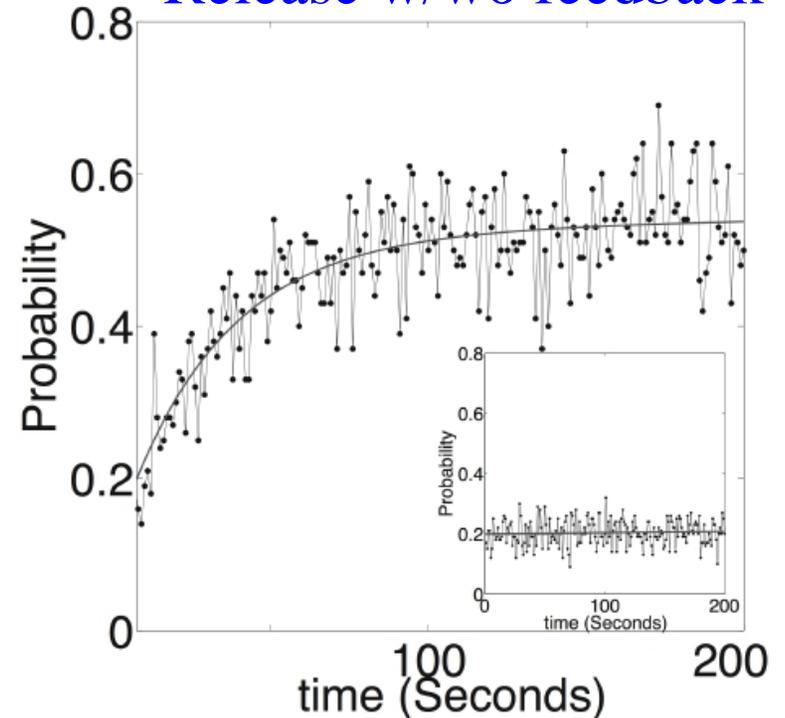
- Kinetic model (Bertram et al) of Ca^{2+} -dependent phasic release
- Spontaneous release as a Poisson process with measured rates
- Astrocyte senses neurotransmitter via mGlu receptors, which increase IP_3
- Calcium system is activated, leading to release of glutamate and increase in presynaptic calcium

Coupled dynamics

Ca wo/w feedback

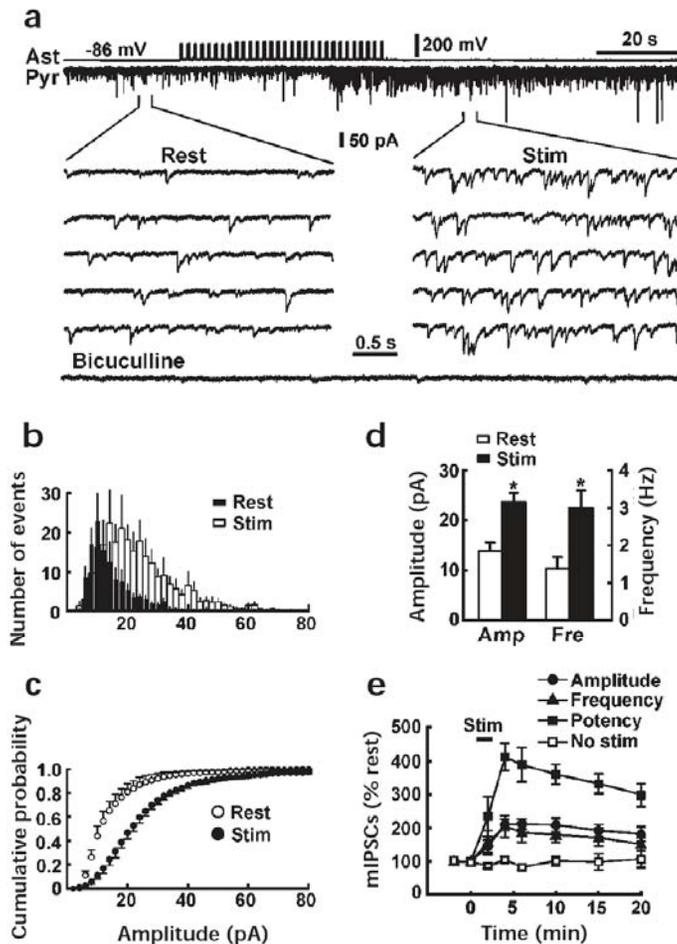


Release w/wo feedback



As the neuron fires, the astrocyte becomes excited and via feedback to the presynaptic cells, raised the release probability

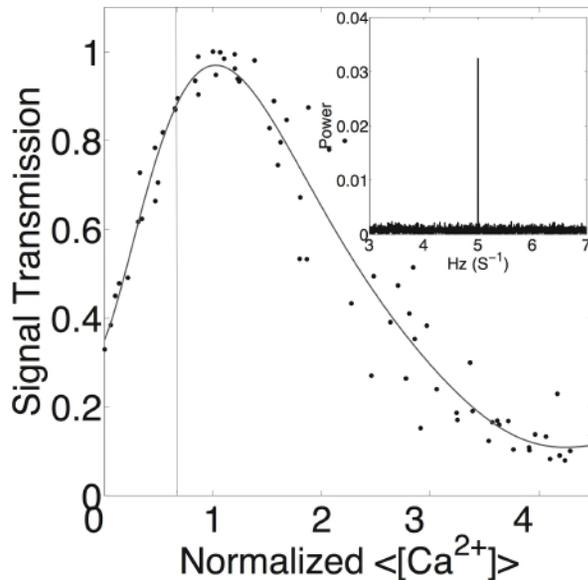
Enhanced spontaneous release



From Kang et al, 1998, Nat
Neurosci., 1, 683-692

Fig. 3. Increase in miniature inhibitory postsynaptic currents (mIPSCs) induced by astrocyte stimulation in hippocampal CA1 pyramidal neurons. **(a)** A representative experiment showing an increase in the frequency of mIPSCs in pyramidal neurons. Neuronal mIPSCs increased (Pyr) following stimulation of a neighboring astrocyte (Ast). The middle traces indicate five continuous recordings before (Rest) and after (Stim) astrocytic stimulation. The bottom trace shows that mIPSCs were blocked by bicuculline (30 μ M), indicating that the events were mediated by GABA_A receptors. **(b)** Amplitude histograms of mIPSCs (bin width, 2 pA, 100-s trace) before (solid bars) and 5 min after (open bars) astrocytic stimulation. Data are mean \pm standard error ($n = 10$ responding cells). **(c)** Cumulative amplitude distributions of the data in (b). The curve was shifted to the right following astrocytic stimulation (solid circles). **(d)** Mean values of the amplitude (Amp) and frequency (Fre) before (open bars) and five min after (solid bars) astrocytic stimulation. * $p < 0.01$ compared with rest ($n = 10$ responding cells, paired t -test). **(e)** Time course of the increase in mIPSCs. Normalized values (percent of rest) of the amplitude (solid circles), frequency (solid triangles), potency (product of amplitude and frequency, solid squares) and potency without stimulation (open squares) of mIPSCs (100-s trace) are plotted against time. Data are mean \pm standard error ($n = 5$ cells for both groups). The potency of mIPSCs five min after stimulation was significantly larger than that at rest ($p < 0.001$, paired t -test) or in the unstimulated group ($p < 0.01$, t test).

Optimum transmission



Define signal transmission as
output spectrum at driving rate

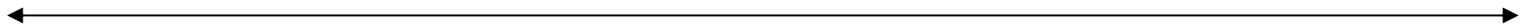
If calcium is too low - small
phasic release probability

If calcium is too high - increase
in spontaneous release

Experimentally measured astrocytic coupling makes the
transmission close to optimal when the neuron is active

Beyond synaptic physiology

- Are there important functions of neurons or neural networks that depend on a more sophisticated synapse?
- We have looked at several issues to try to get a handle on this question
 - Point-like neurons simulated by Morris-Lecar 2 component model
 - CA1 dendritic tree with multi-compartment conductance model



Physics

Modeling Philosophy

Neuroscience

- Synapses described with an TM model extended to include (stochastic) asynchronous release which depends on pre-synaptic calcium (extra dynamical variable)

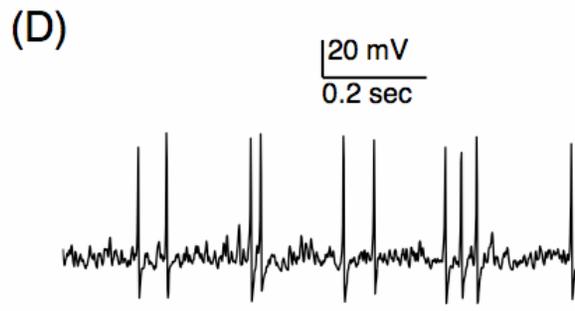
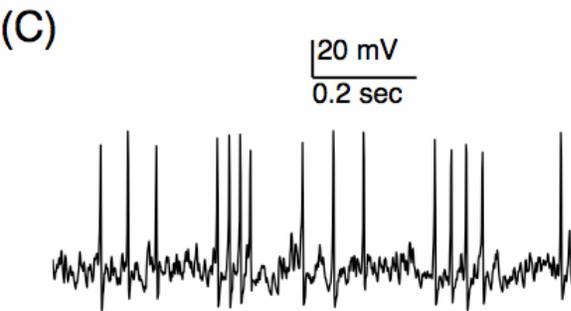
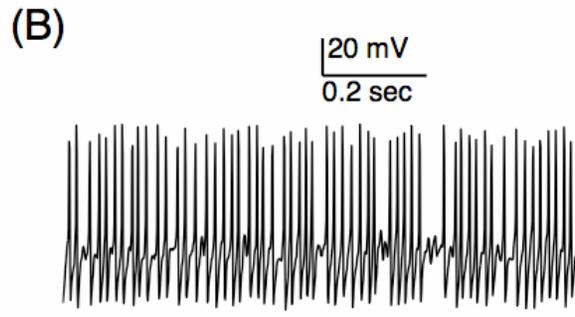
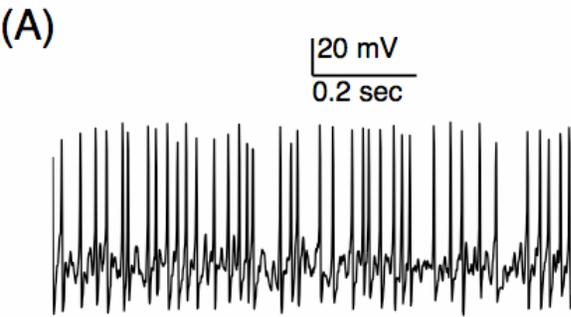
Neuronal gain

- Gain is the slope of the input-output curve, for example for firing rates
- Gain can be modulated by a variety of physiological mechanisms
 - Balanced Input (Chance, Abbott and Reyes, 2002)
 - Shunting Inhibition (Mitchell and Silver, 2003)
 - Synaptic Depression (Abbott, Varela, Sen and Nelson, 1997)
- Previous work had assumed that short-term synaptic plasticity and noise act independently
 - Here, “noise” is due to asynchronous release and contributes to short-term depression (same vesicle pool)
- We will use a simple Morris-Lecar two component point neuron model
- We will model the synaptic model into the cell, arising from both phasic release and asynchronous release (AR)

Input Model

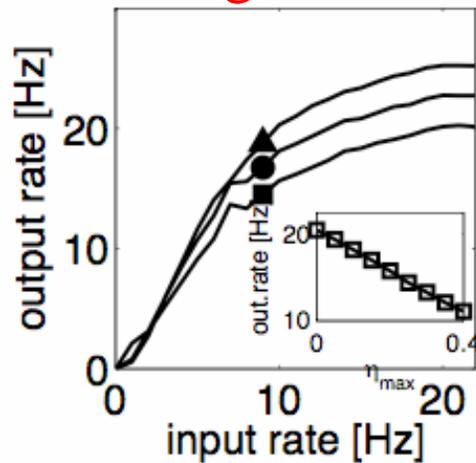
- Assume initially that there are 10^4 synaptic inputs (active zones) onto the cell in question
- Represent these by 100 TM model synapses coming from Poisson neurons, by assuming 1% synchrony of original inputs (can compare to full model to validate basic findings)
- $U=.3$ represents 30% release probability
- Relative AR obtained from scaling Goda and Stevens data from hippocampal culture
- Volman, Sejnowski and Levine PLoS CompBio (2010 to appear)

Results

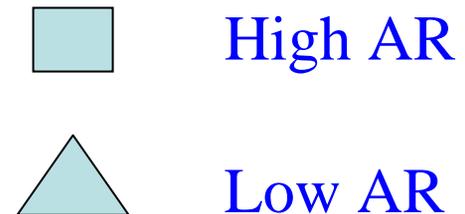
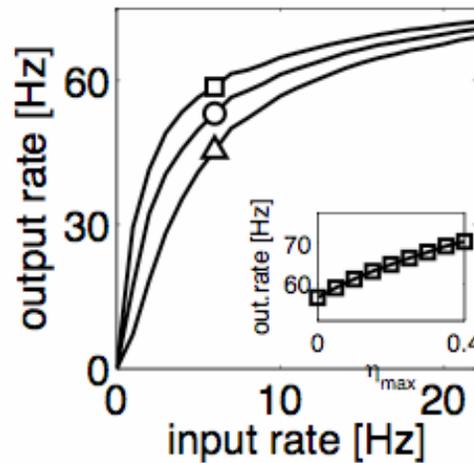


- A. Low shunt, no AR
- B. Low Shunt, AR
- C. High Shunt, no AR
- D. High Shunt, AR

High Shunt

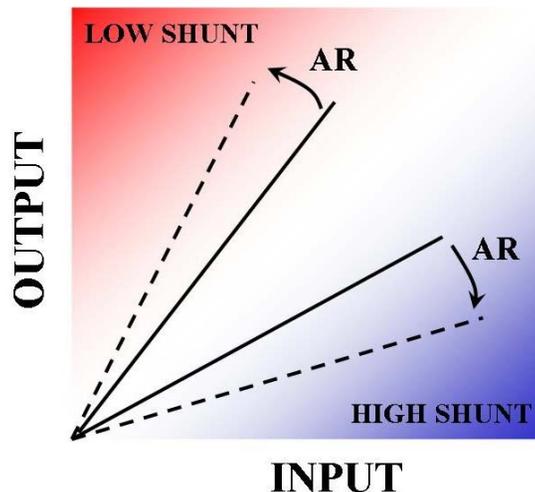


Low Shunt



Comments

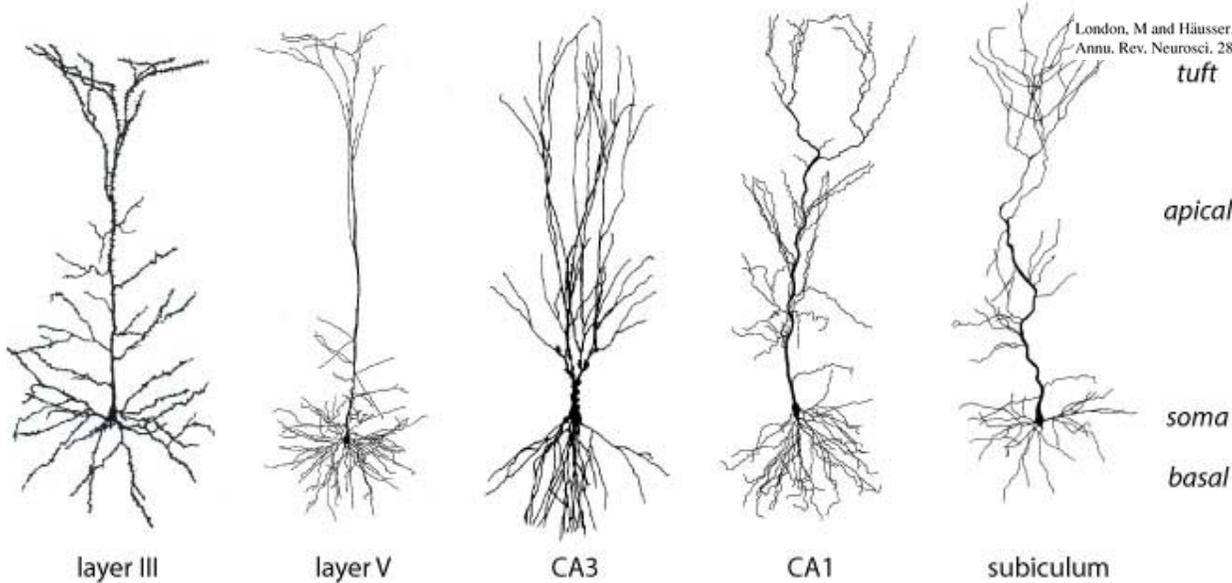
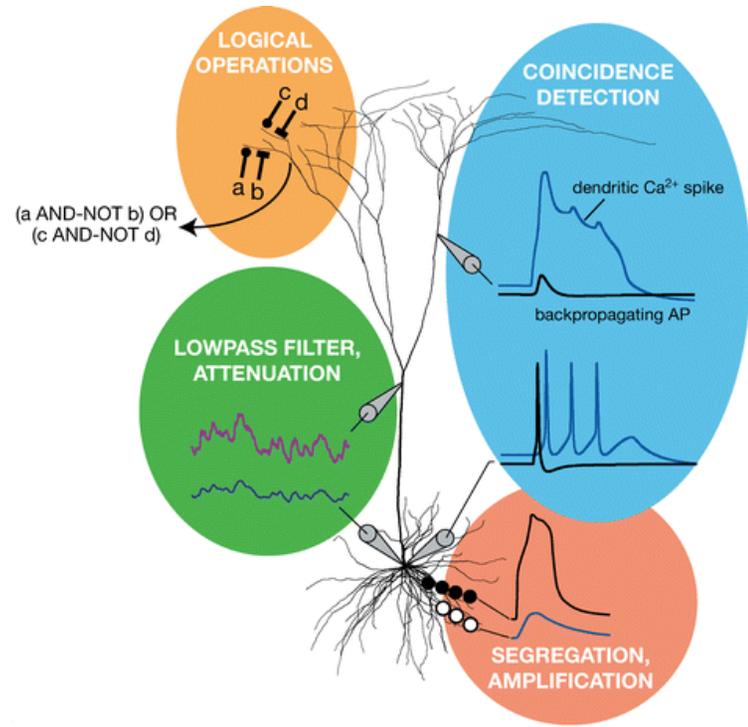
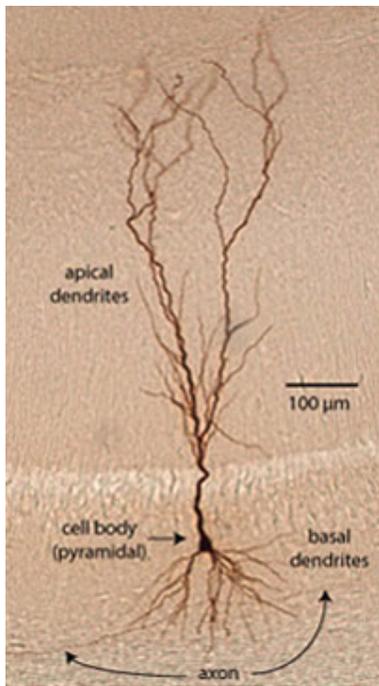
- In low shunt region, neuron acting as integrator; mean input above threshold
 - AR increases mean input and hence increases firing rate and gain
- In high shunt region, neuron acts as coincidence detector; mean below threshold
 - AR makes it harder for phasic releases to be coincident by enhancing depletion; gain is reduced



- Effect goes away if AR comes from different pool

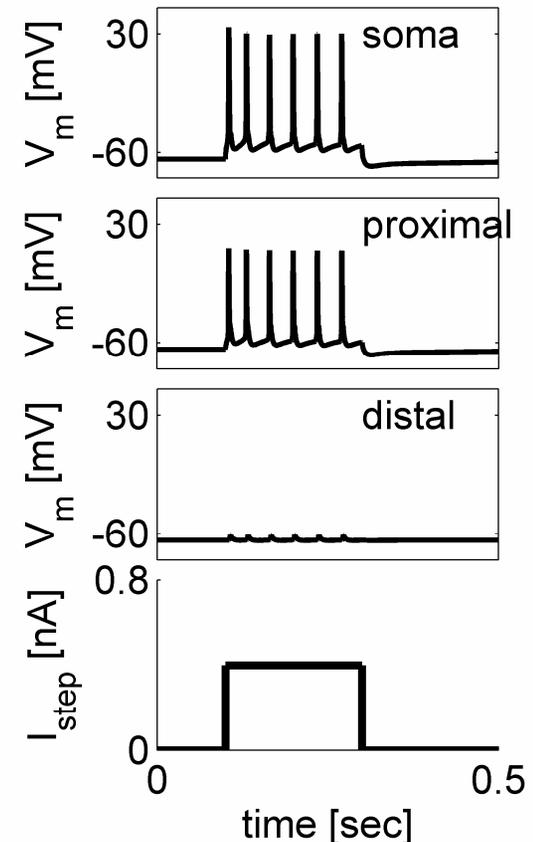
- Also has effects on the role of input correlations

Pyramidal dendrite

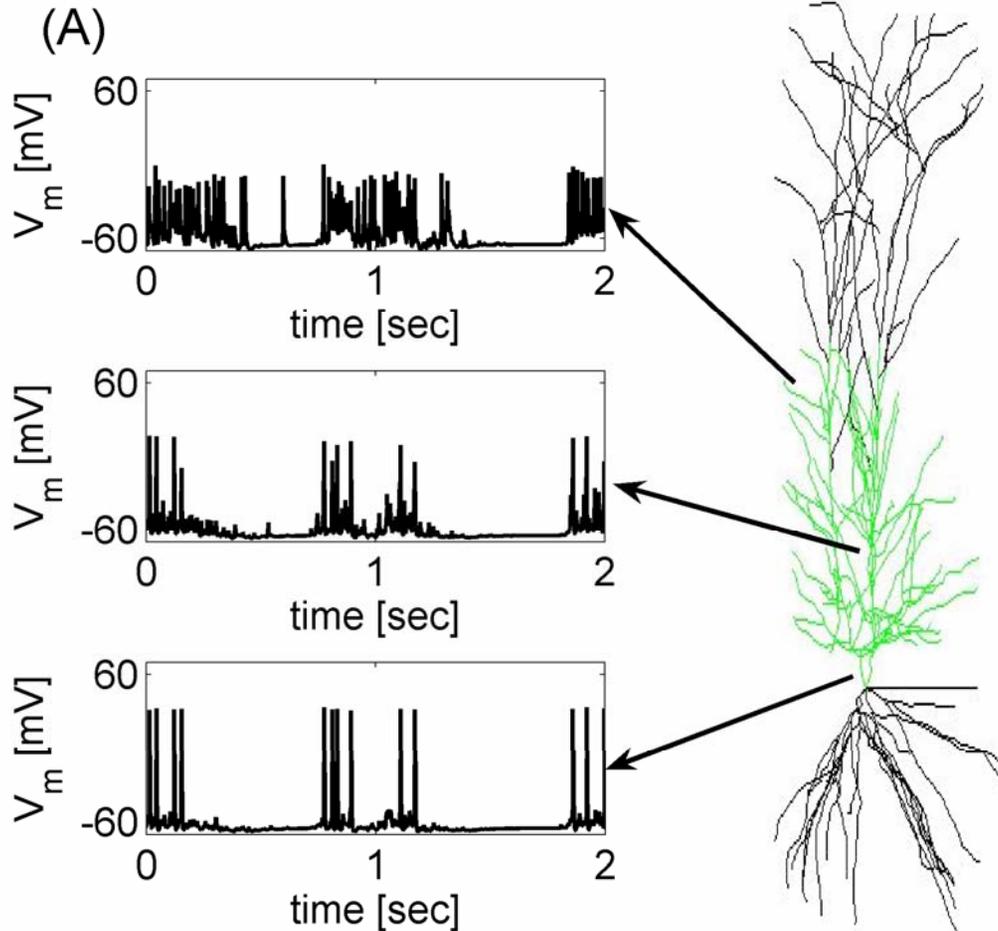


CA1 Model

- CA1 dendritic tree geometry taken from database
- Spatial distribution of active conductances
- 100 synapses distributed uniformly on proximal region of apical dendrite
- Synapses described by Bertram model with refractory synapses and finite RRP
 - Both facilitation and depression, but deterministic
 - Scaling of synapses to account for passive decay to soma
- Volman, Levine, Ben-Jacob and Sejnowski (J Neurophys 2009)

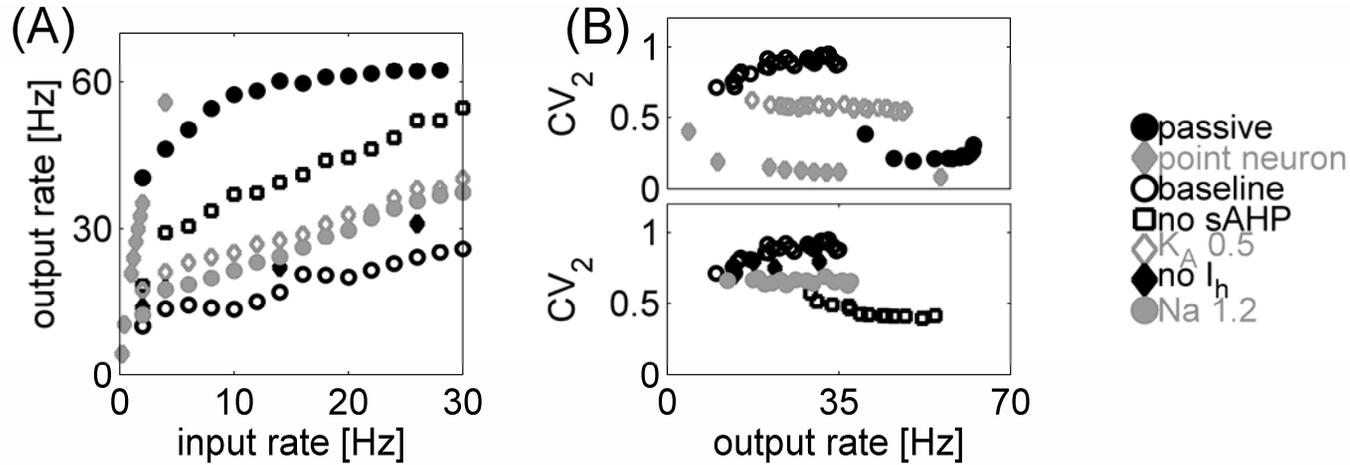


Results



- Complex synapses convert Poisson presynaptic spiking into correlated input
- Processing by active dendrites lead to high variability in somatic firing
- Alternate mechanism to inhibitory balance (NB no inhibitory input is included in this calculation)

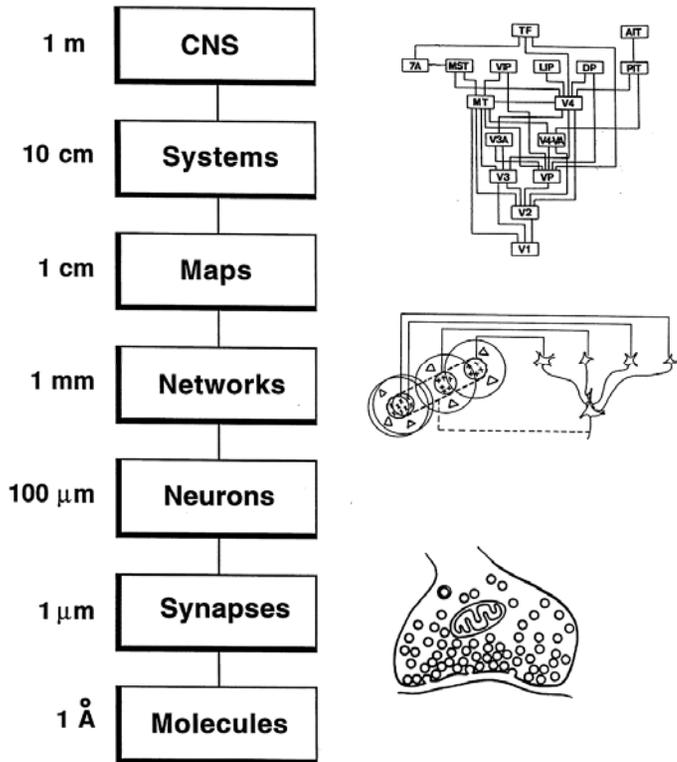
Mechanism



- Large variability depends on interaction of active dendritic branches with synaptic degrees of freedom
 - Most important channel seems to be sAHP, since its time scale (100's msec is compatible with the correlations in the input created by synaptic plasticity)
 - Channel is activated by local spread of dendritic spikes (and backprop AP's)
 - sAHP is creating localized dendritic regions which detect synaptic fluctuations
- Could this be connected to observed variability of place cell? Is the actual spiking pattern carrying additional information??

Conclusions

Levels of Investigation



- Components of neural systems have their own hierarchical complexity
- Models of real synapses, astrocytes, dendritic trees etc. can be built based on increasing biophysical knowledge
- Challenge will be to figure out which of these degrees of freedom are essential for which types of information processing