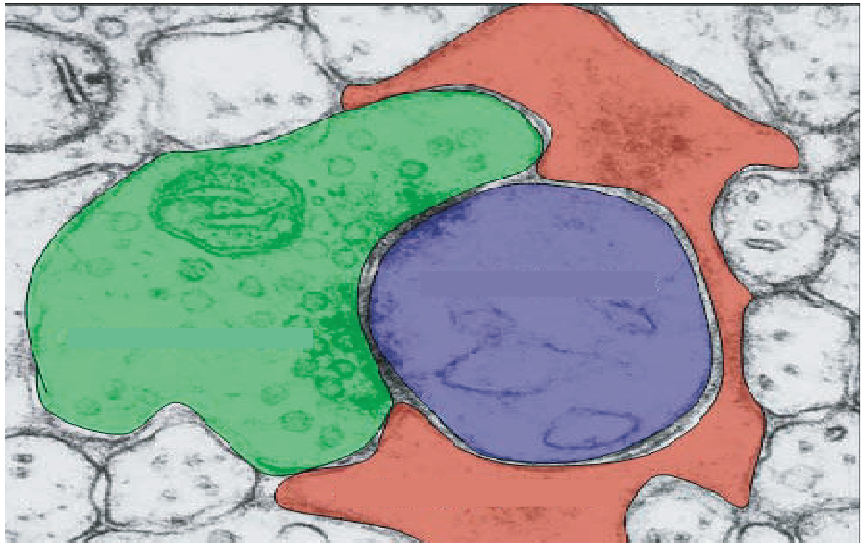
Sophisticated Synapses - a quantitative insight into complex components of neuronal networks



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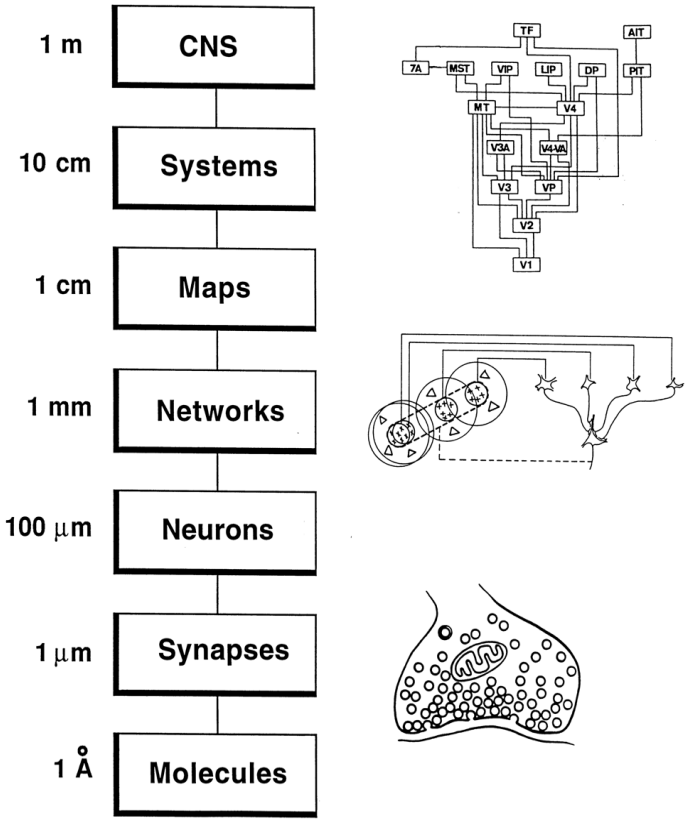
Levels of Investigation



- General approach is

1. devise biophysical models which incorporate a more sophisticated view of these neural components.

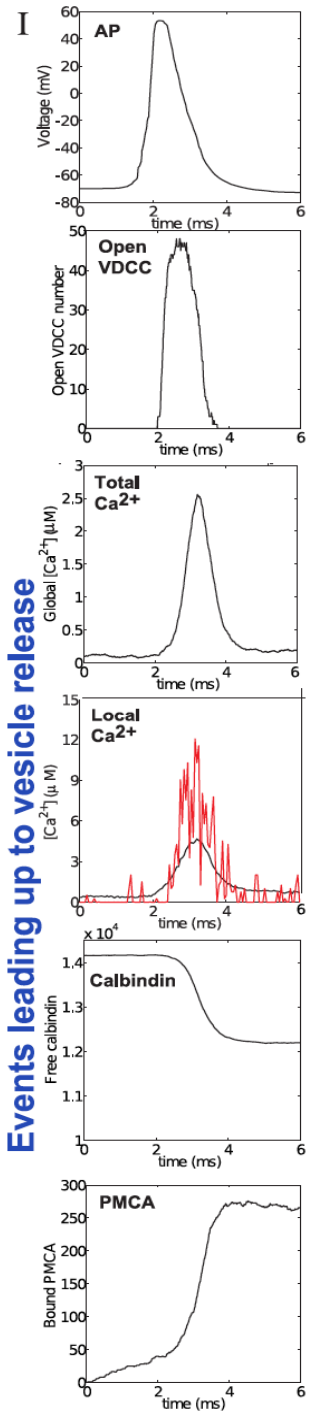
2. calibrate and test these models with experimental data that can then be used to make testable predictions

3. work towards understanding the implications of component sophistication for network dynamics.

Simple vs Complex

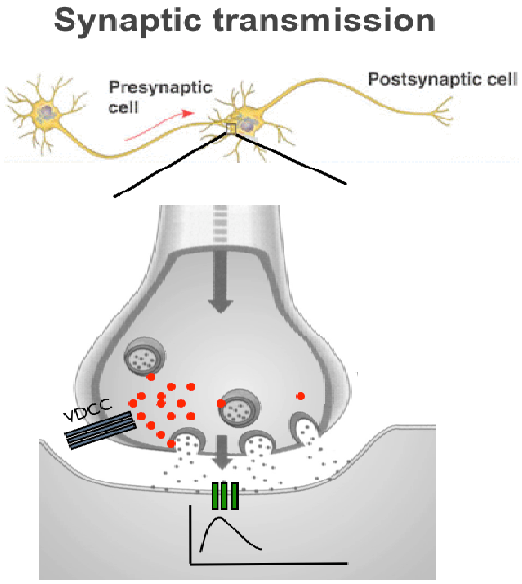
- Synapses are immensely complex - a large number of ion channels and a plethora of neurotransmitters and receptors operating over multiple of timescales.

- This complexity contributes to the rich spatiotemporal repertoire of the nervous system required to respond appropriately to complex patterns of stimulus and carry out extensive computations.



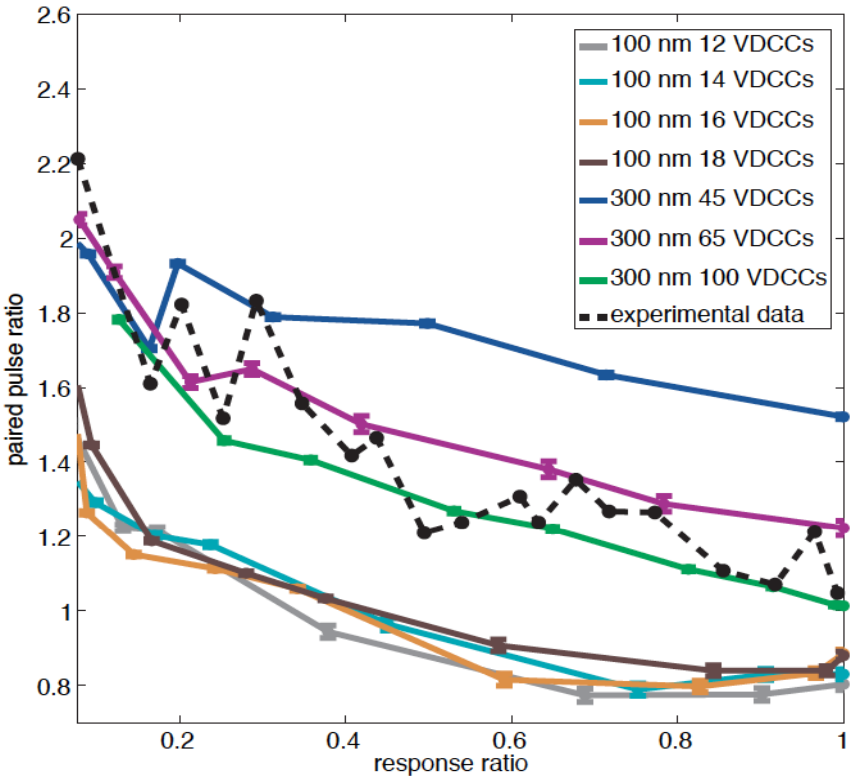
In-Silico experiments on CA3-CA1 synapse

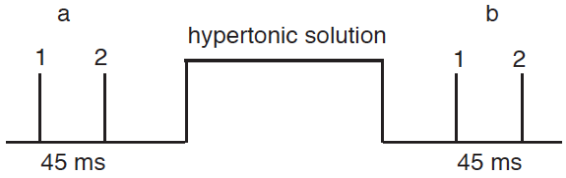
- Time series data on chronology of events leading up to a vesicle release.
- Concentrations, kinetics rates and diffusion constants are well constrained by physiologic data.
- Effective diffusion constant of Ca^{2+} that falls out of the model synapse is consistent with measured experimental values - validates the model.



Its Alive!

Response ratio is a predictor of synaptic ultrastructure





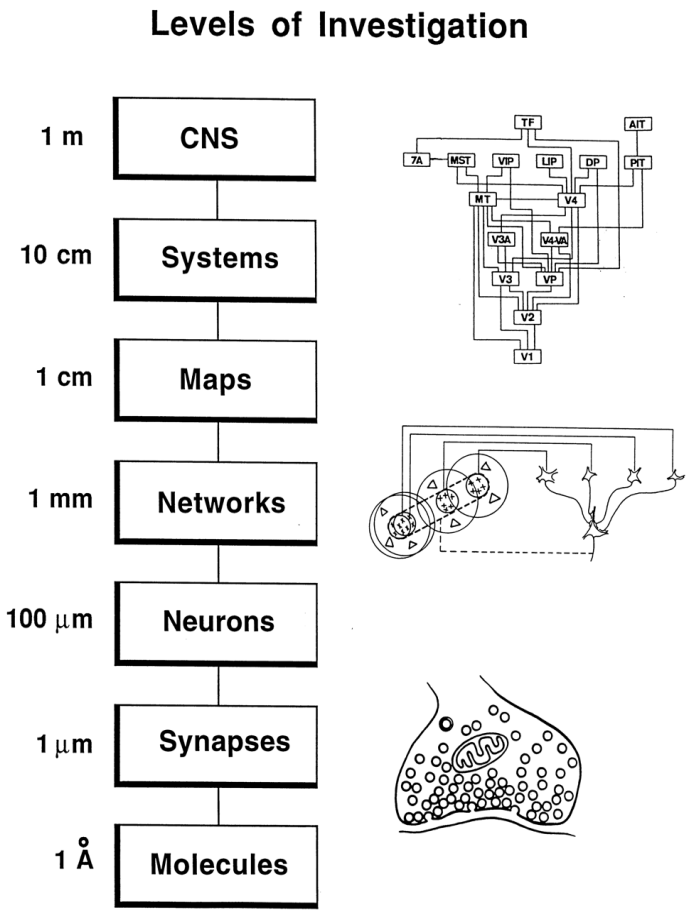
Response ratio ($EPSC1_b/EPSC1_a$) a measure of vesicles available for release

Most depleted synapses indicating small p_r lead to larger PPF

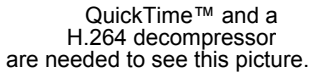
Model predicts Lc of ~ 300 nm and ~70 VDCCs regulate synaptic transmission in CA3-CA1 presynaptic terminal

Experimental data: Sullivan and Stevens, in prep

Outlook



- The goal is to arrive at general principles as well as unique features of synaptic transmission across systems, an understanding of influence of structure on function, cohesively bring together diverse experimental data and quantify pathways for function and those implicated in diseases.


QuickTime™ and a
H.264 decompressor
are needed to see this picture.

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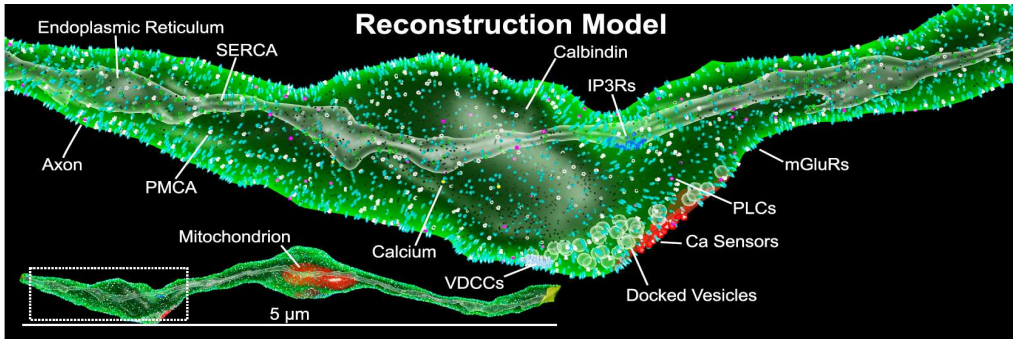
Understanding the Human Brain

LIKE MOST FIELDS IN BIOLOGY, NEUROSCIENCE IS SUCCUMBING TO AN "EPIDOMIC" OF DATA collecting. There are major projects under way to completely characterize the proteomic, metabolomic, genomic, and methylomic signatures for all of the different types of neurons and glial cells in the human brain. In addition, "connectomics" plans to provide the complete network structure of brains, and "synaptomics" aims to uncover all molecules and their interactions at synapses. This is a good time to pause and ask ourselves what we expect to find at the end of this immense omic brainbow.

Terrence J. Sejnowski is

Future Directions

Investigating the role of intracellular calcium signal remodeling in the pathogenesis of Alzheimer's disease (AD)



- Aberrational extracellular buildup of amyloid fibrils and plaques formed by polymerization of β-amyloid (Aβ) is a signature of AD.

- Two types of AD, sporadic AD and a rare familial (FAD) that develops much faster. FAD can be caused by mutation in the gene presenilin (PS) an integral membrane protein in the ER involved in the amyloid pathway-increase in production of Aβ.

Role played by PS in the calcium handling of the ER is the central tenet of the calcium hypothesis.

Berridge, Eur J of Physiol, 2010

Remodeling of presynaptic Ca^{2+} leads to aberrant LTP in PS KO

- Ca^{2+} remodeling in PS1 mutant - (1) increase in [Ca^{2+}] in the ER (2) increase in the expression of RyR (3) Increased open probability of IP_3Rs (4) Down regulation of the calcium buffer Calbindin (5)Reduced PPF in presynaptic PS1 mutants leading to aberrant LTP.

- Quantify calcium signal remodeling seen in FAD PS1 mutants leading to altered plasticity

Defects in cognition occur long before structural changes. The focus of all AD research so far has been on reducing the production of Aβ and increasing its extrusion. The calcium hypothesis provides a novel therapeutic view point.

Zhang et al Nature, 2008
Zhang et al. J of NeuSci, 2010