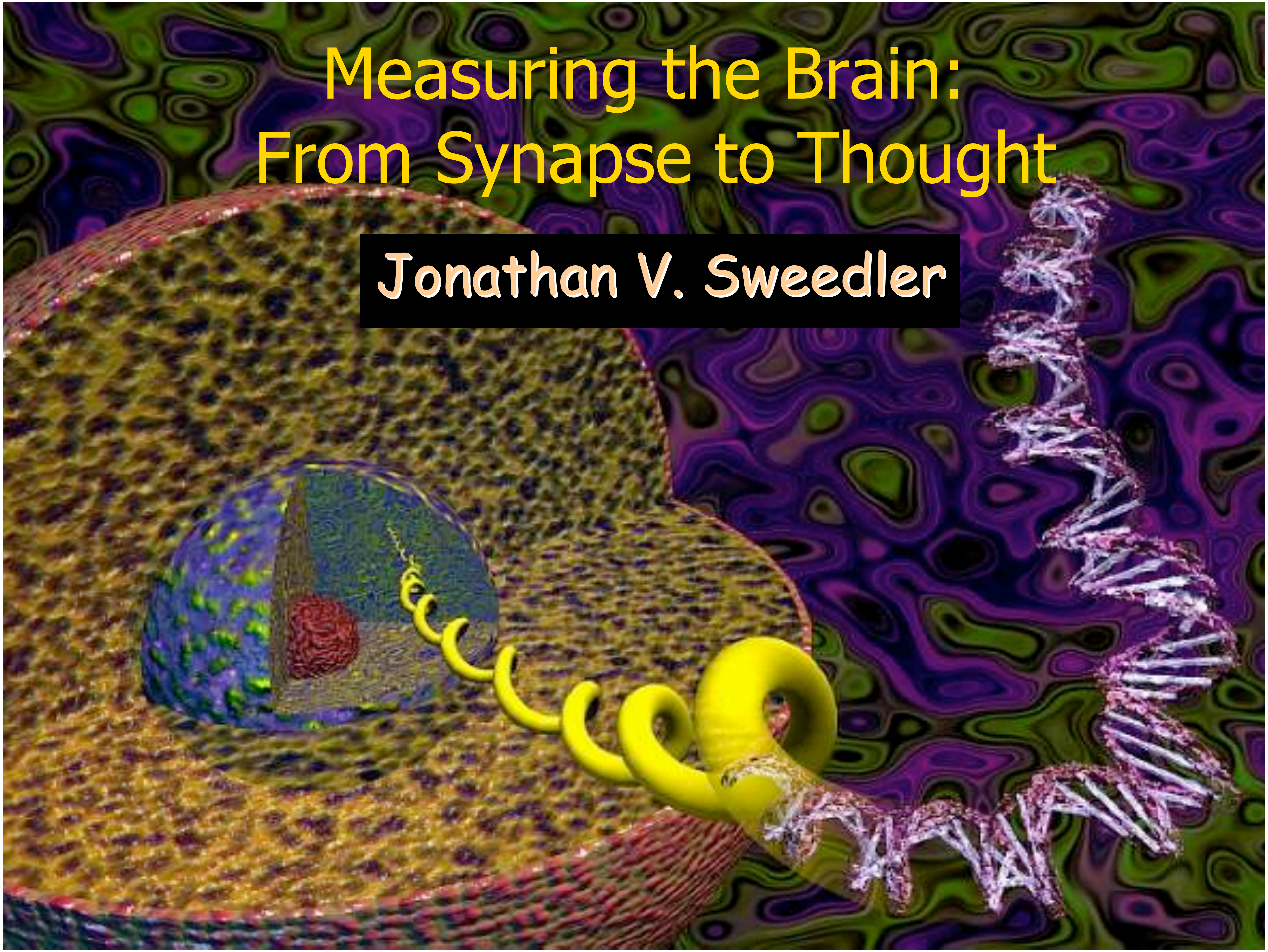
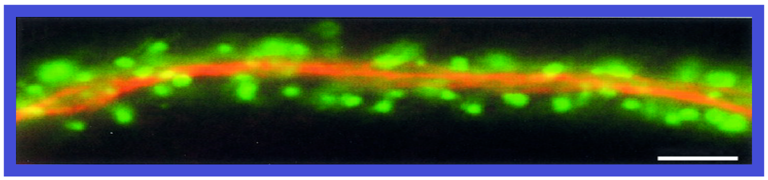
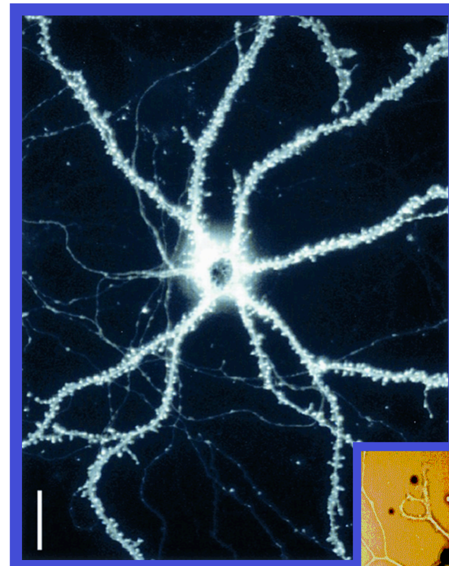
Measuring the Brain: From Synapse to Thought

Jonathan V. Sweedler

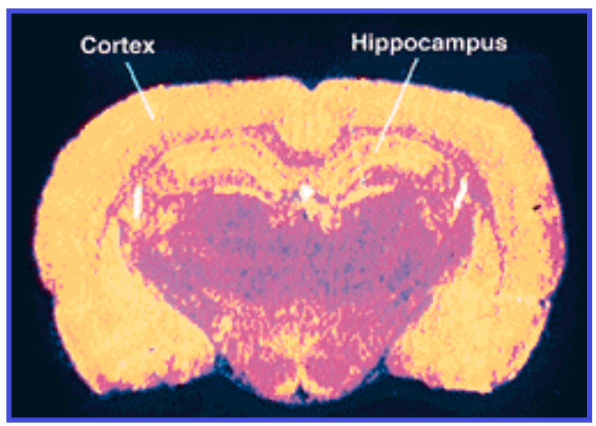


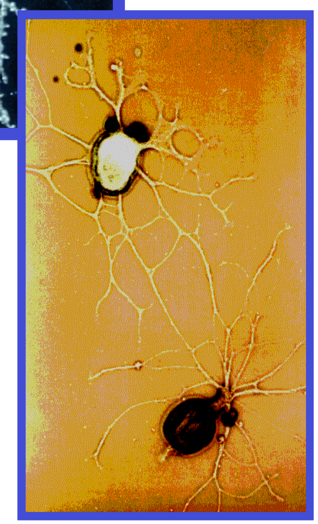
From dendritic spines, to neurons, to networks, to the intact brain





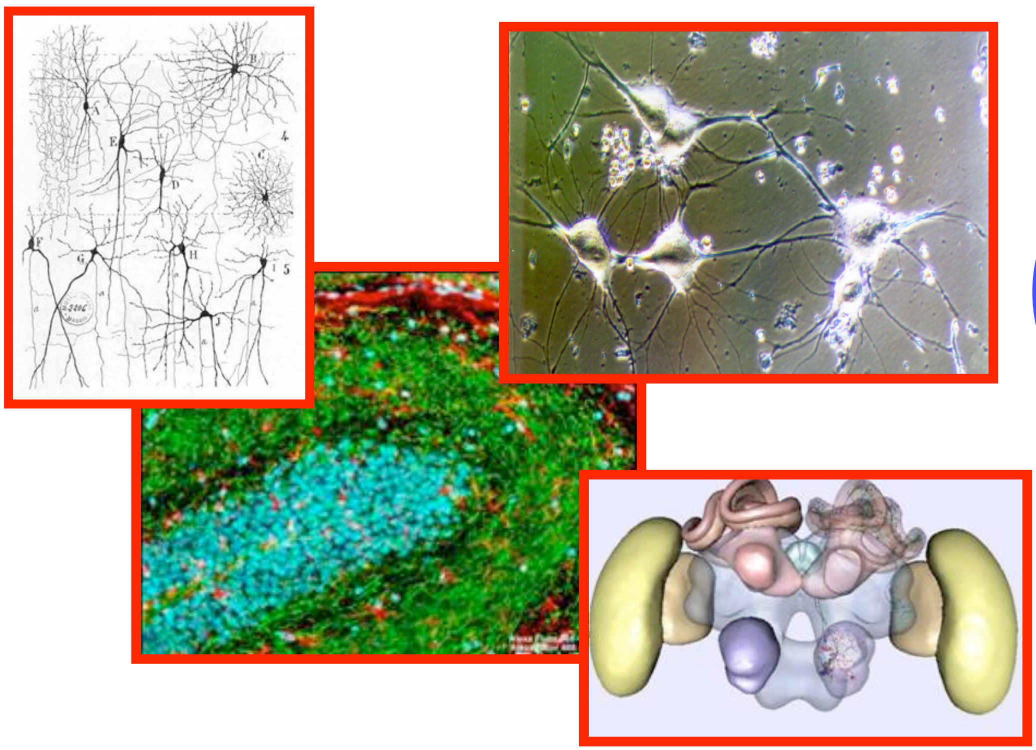
The neuron is the basic building block of our brain, and yet our understanding of even simple neuronal networks containing limited numbers of cells is not complete, partly because we lack methods to probe many of the dynamic processes occurring within them.

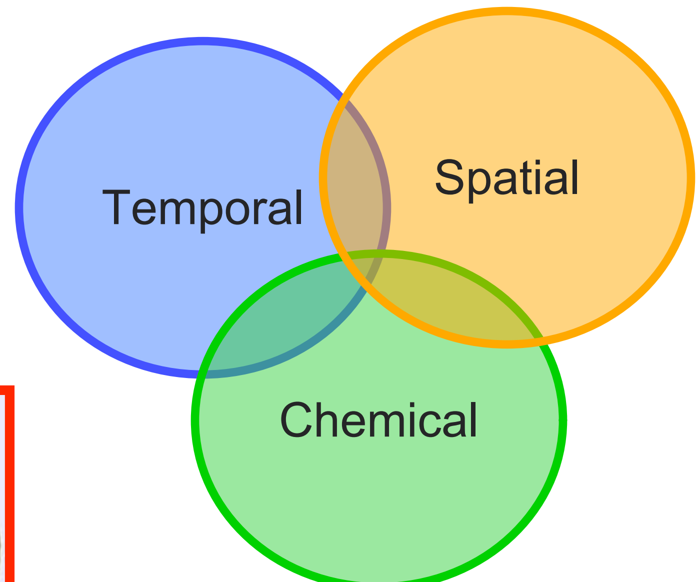




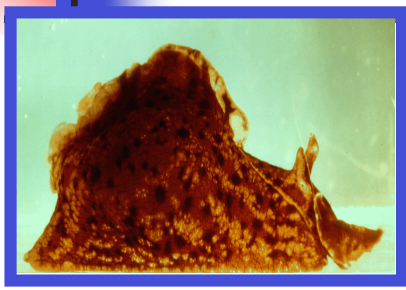
The Molecular Nature of Learning and Behavior

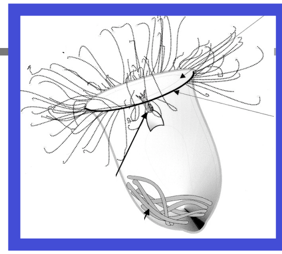
Complete characterization of even a simple neuronal network requires techniques that provide spatial, chemical and temporal information on the signaling and related compounds used by the neuronal networks.





What Models To Use?





From “Simpler” To “Complex”

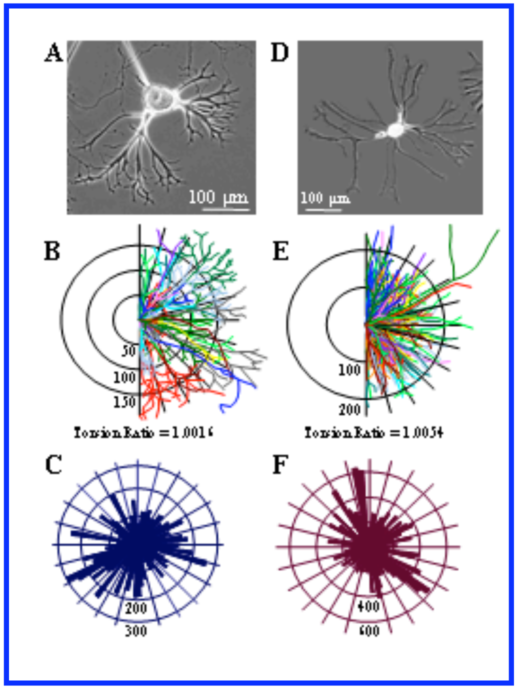
- Mollusks with a simple CNS: ~10,000 larger neurons and a million synaptic connections
- Insects with social behaviors
- Arthropods with networks with well-defined / function
- Mammals that are relevant to understanding our brain and how we think

Choose the Ideal System:

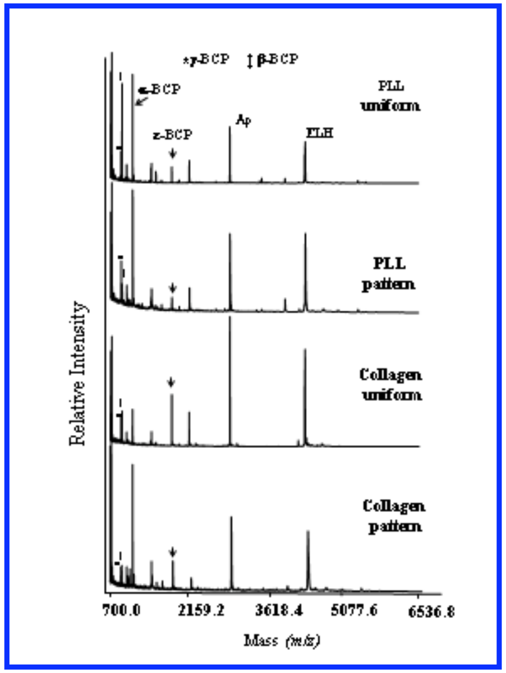
- Learning and memory
- Neuronal control of behavior
- Neuronal repair
- Novel cell-cell signaling pathways
- And do not forget, match the tool!

Combine measurement modalities across information domains

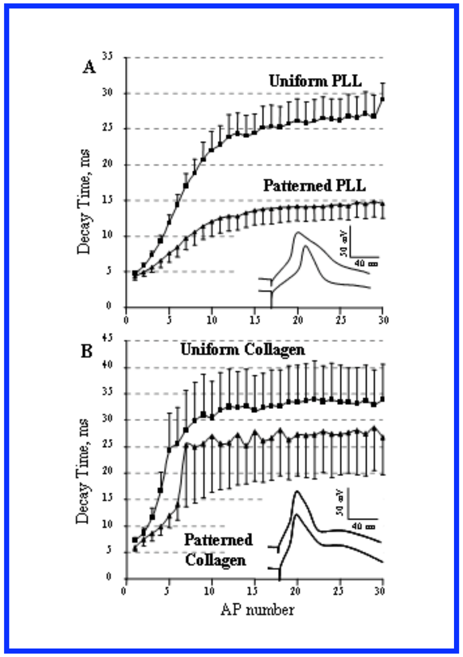
- Morphology



- Signaling molecules

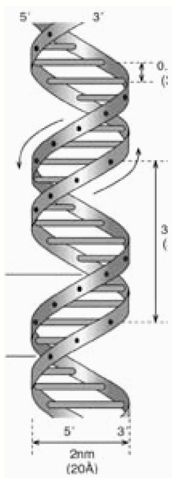


- Electrophysiology



Why is the chemistry so complex? From one gene, many protein forms

DNA



SNP

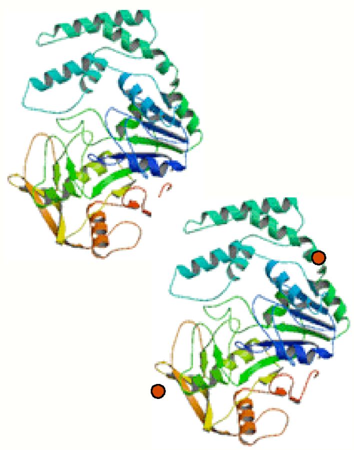
~30,000 human genes

mRNA

Alternative splicing

>100,000 RNA messages

Protein

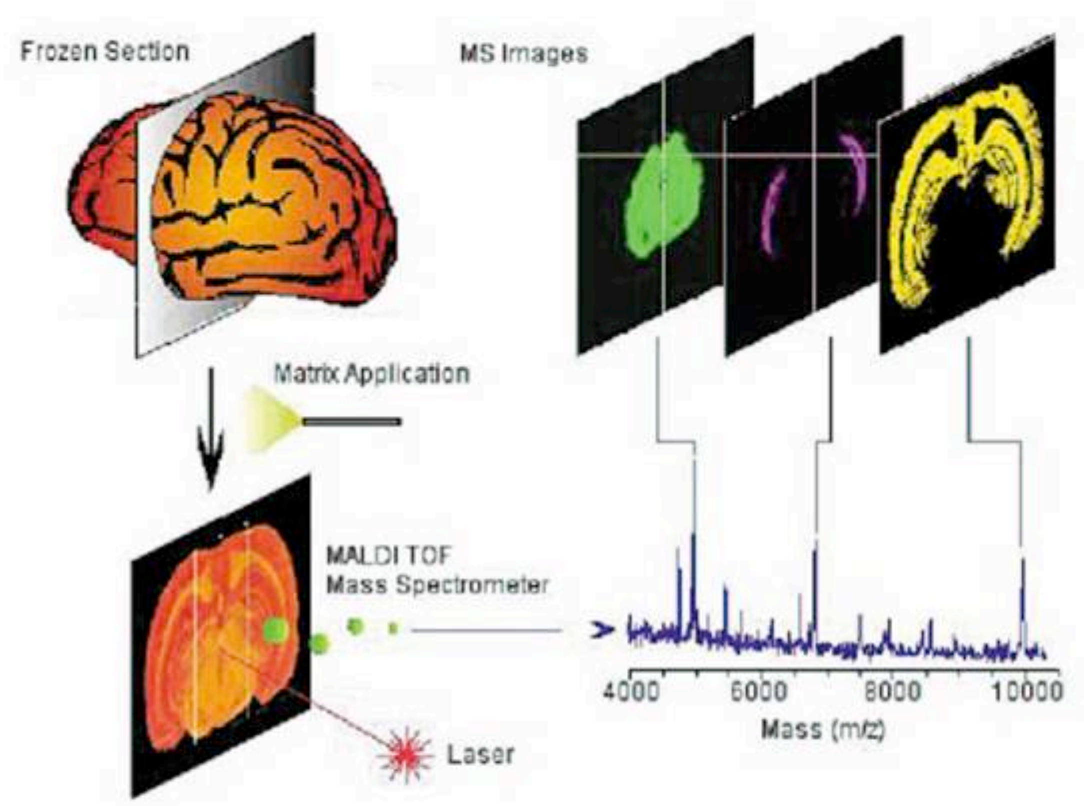


Covalent Modification

>1,000,000 distinct protein forms

Can we follow the interactions and localization of these million forms non-destructively in real time? Can we even characterize them?

One new technology: imaging tissues with mass spectrometry

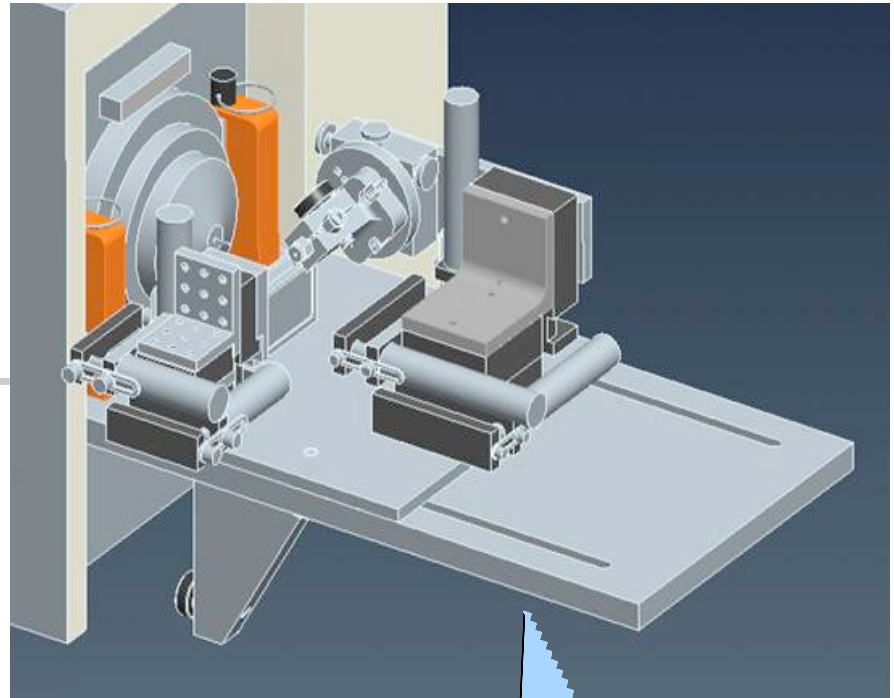


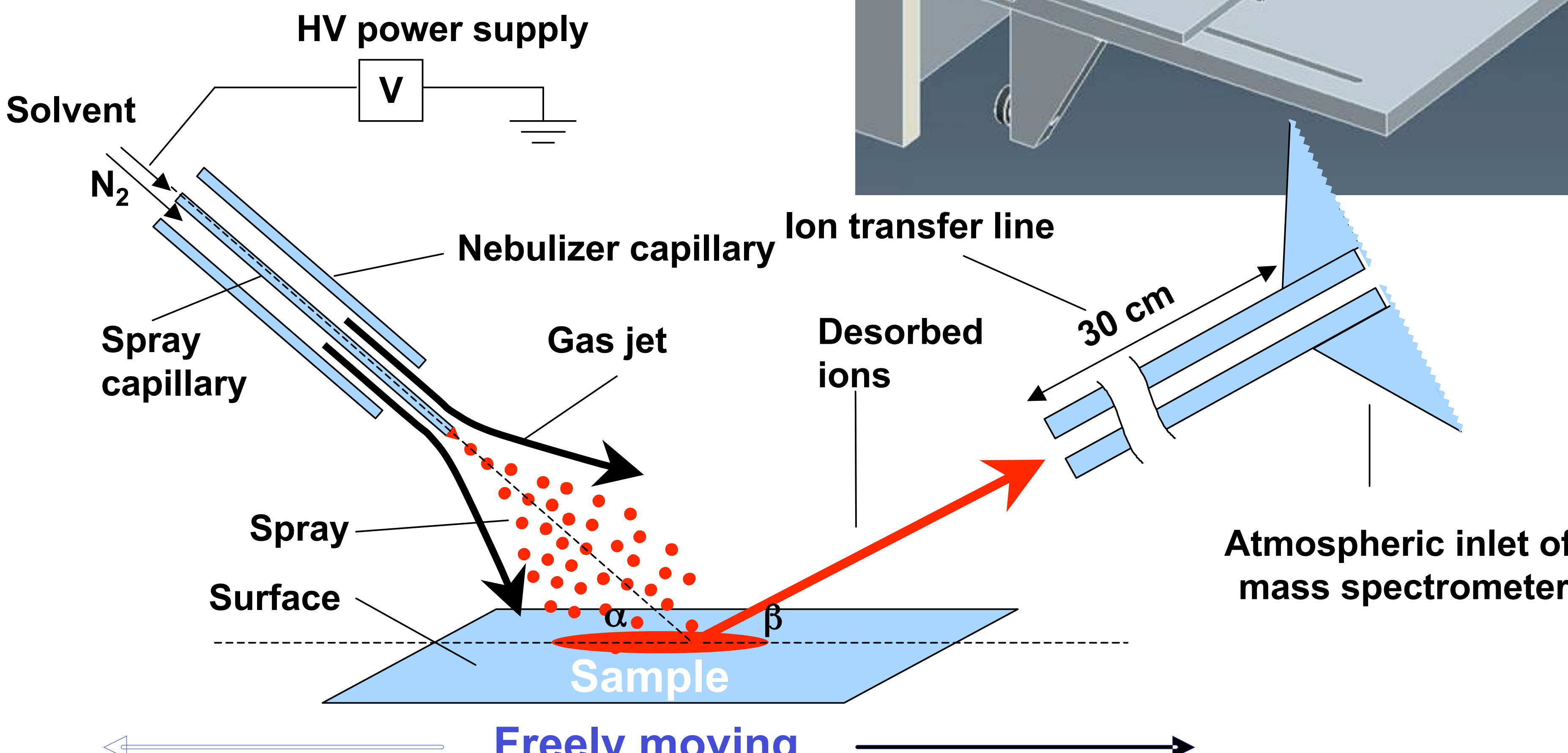
The Players in Cell-Cell Communication

NO, ATP, Acetylcholine
Amino acids
Indolamines
Catacholamines
Neuropeptides
Proteins

From Caprioli' s group: Nature Medicine, 2001, 7, 493.

Desorption Electrospray Ionization (DESI)

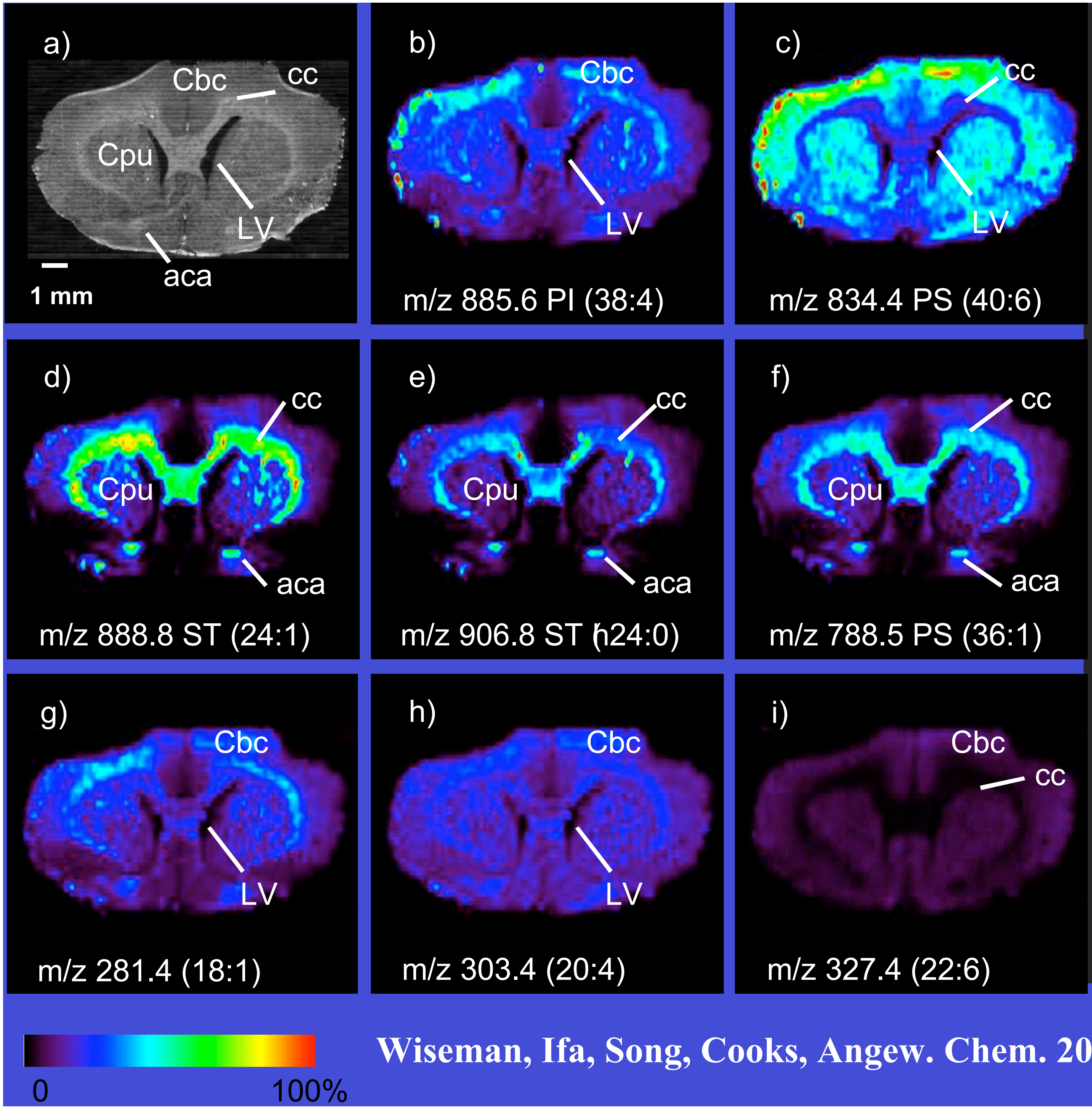




Graham Cooks, Purdue, IL

Takats et al *Science*. 2004

DESI Molecular Images



Molecular ion images of specific lipids in 13 x 10mm rat brain tissue section

a) Optical image coronal section, CC corpus callosum;

Cpu striatum; Cbc cellebelar commisure; LV left ventricle;

aca anterior part of anterior commissure

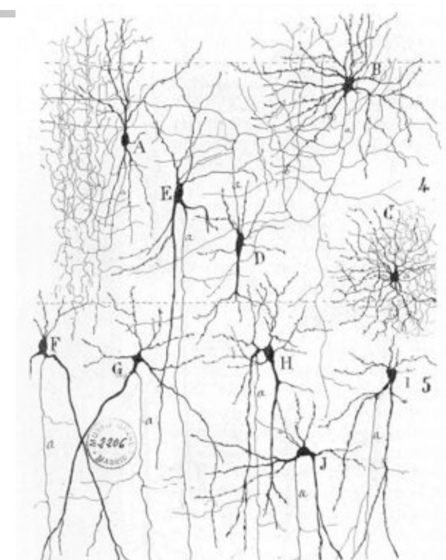
b-i) ion images

PI (38:4), PS (40:6), ST (24:1), ST (h24:1), PS (36:1), oleate (18:1), arachidonate (20:4), docosahexaenoate (22:6)

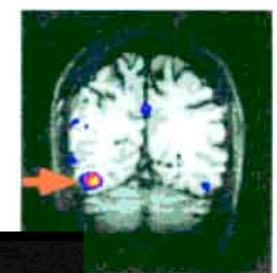
Wiseman, Ifa, Song, Cooks, Angew. Chem. 2006

The "Omics of a Neuronal Circuit: what changes during network activity or learning in a "simple" network

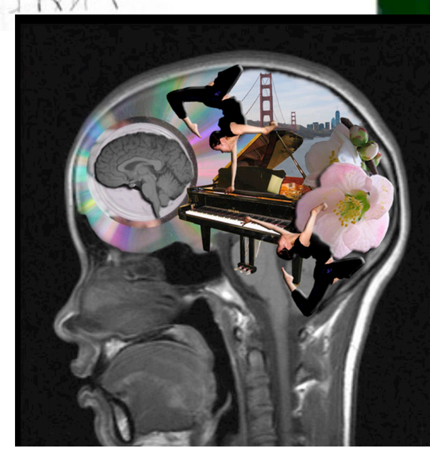
- Transcriptomics: what genes turn on and off for each cell
- Proteomics: which proteins or levels are modified, and in what cellular compartments?
- Metabolomics: how do transmitter levels and their release change during network activity?
- Connectivity: does the wiring change? Can we generate electrical maps of activity?
- Can we repeat all measurements as we scale the network complexity upwards from simple to complex?



From "Texture of the Nervous System of Man and the Vertebrates" by Santiago Ramón y Cajal.



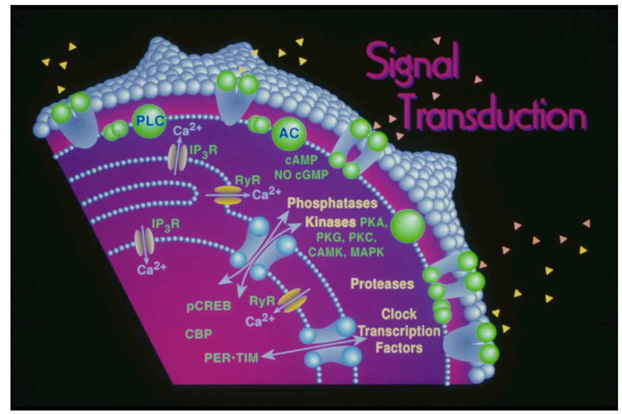
If functional MRI can image the brain, can we map neuronal wiring, chemistry or activity to the synaptic level? Why not?

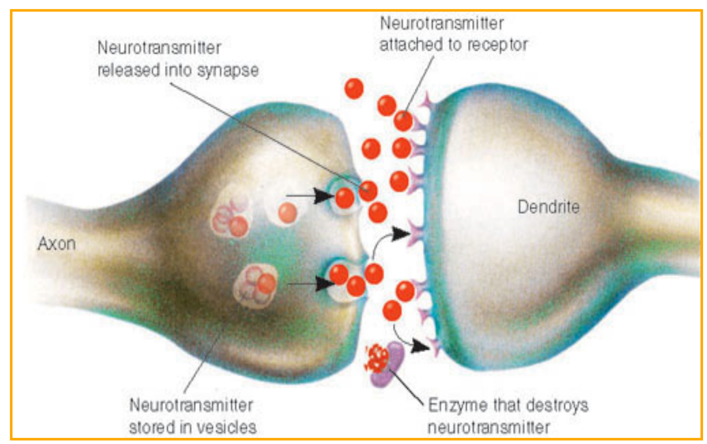


Mindy Chang, Stanford

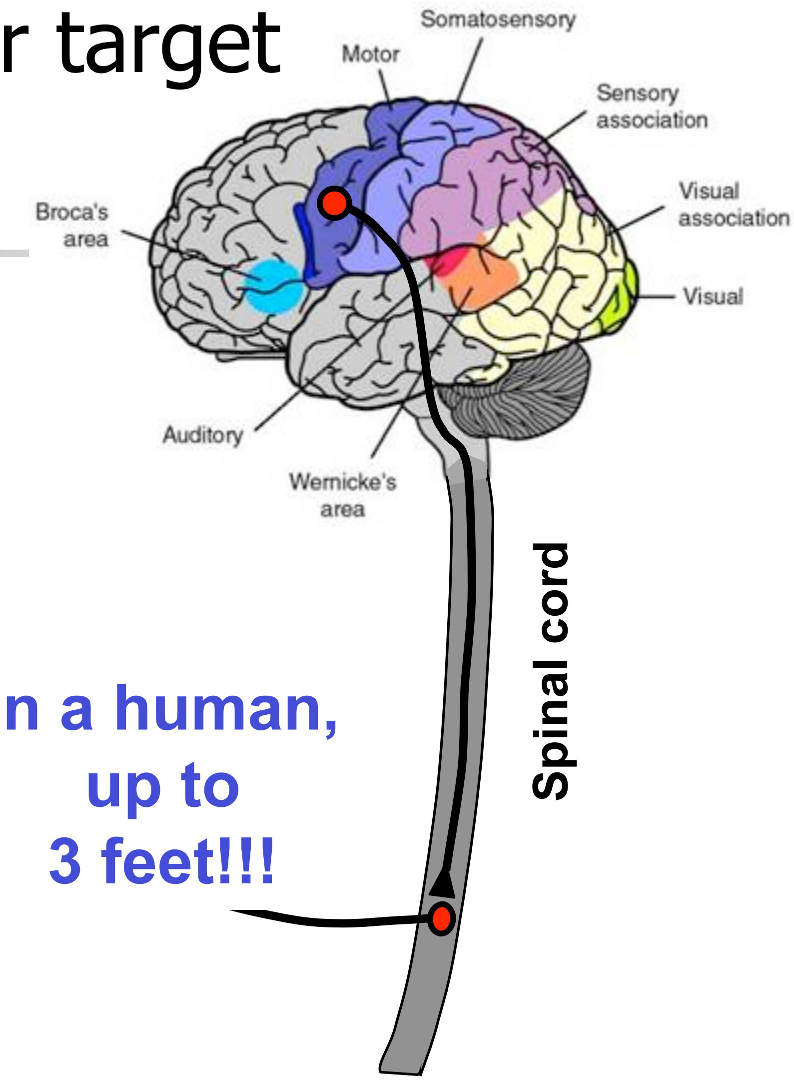
An Engineering Perspective: the brain as a machine

- Discover the parts lists of the brain and define their function
- How do these parts assemble and interact?
- From cells, to networks
- What are the emergent system properties?





Axons project over long distances to reach their target



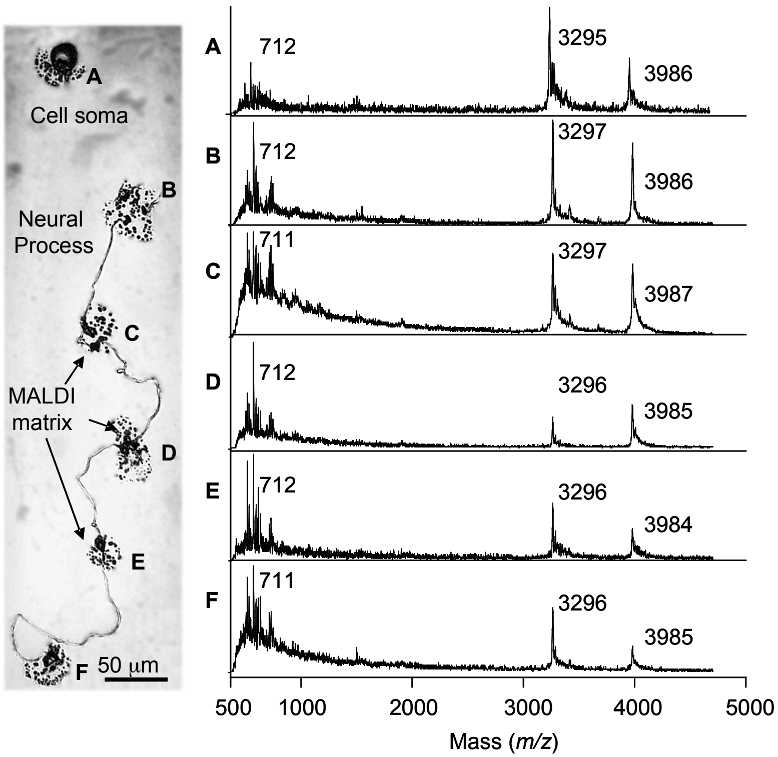
In a human, up to 3 feet!!!

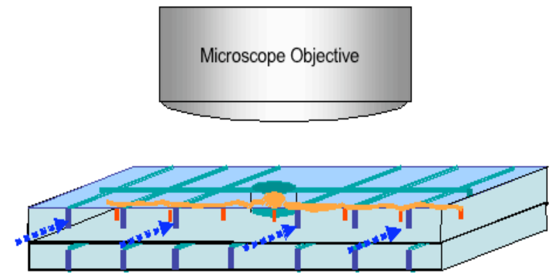
How can axons reach their targets in such a precise manner?

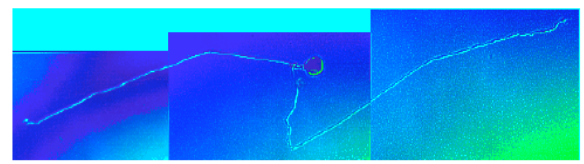
Axon guidance

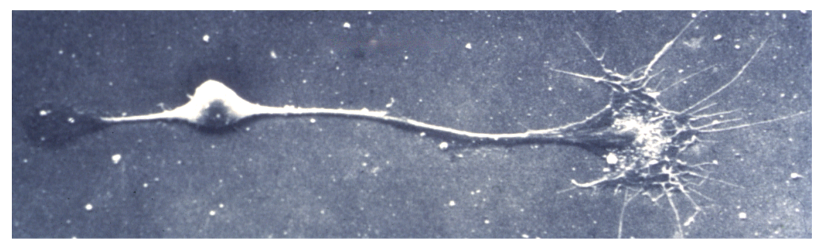
Slide adapted from F. Charon
Stanford University

Use engineering tools to create defined networks, follow path finding, synapse formation and repair

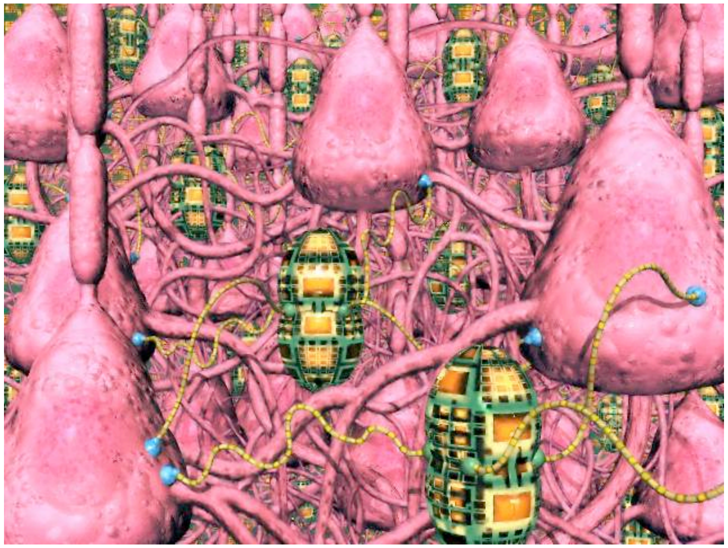






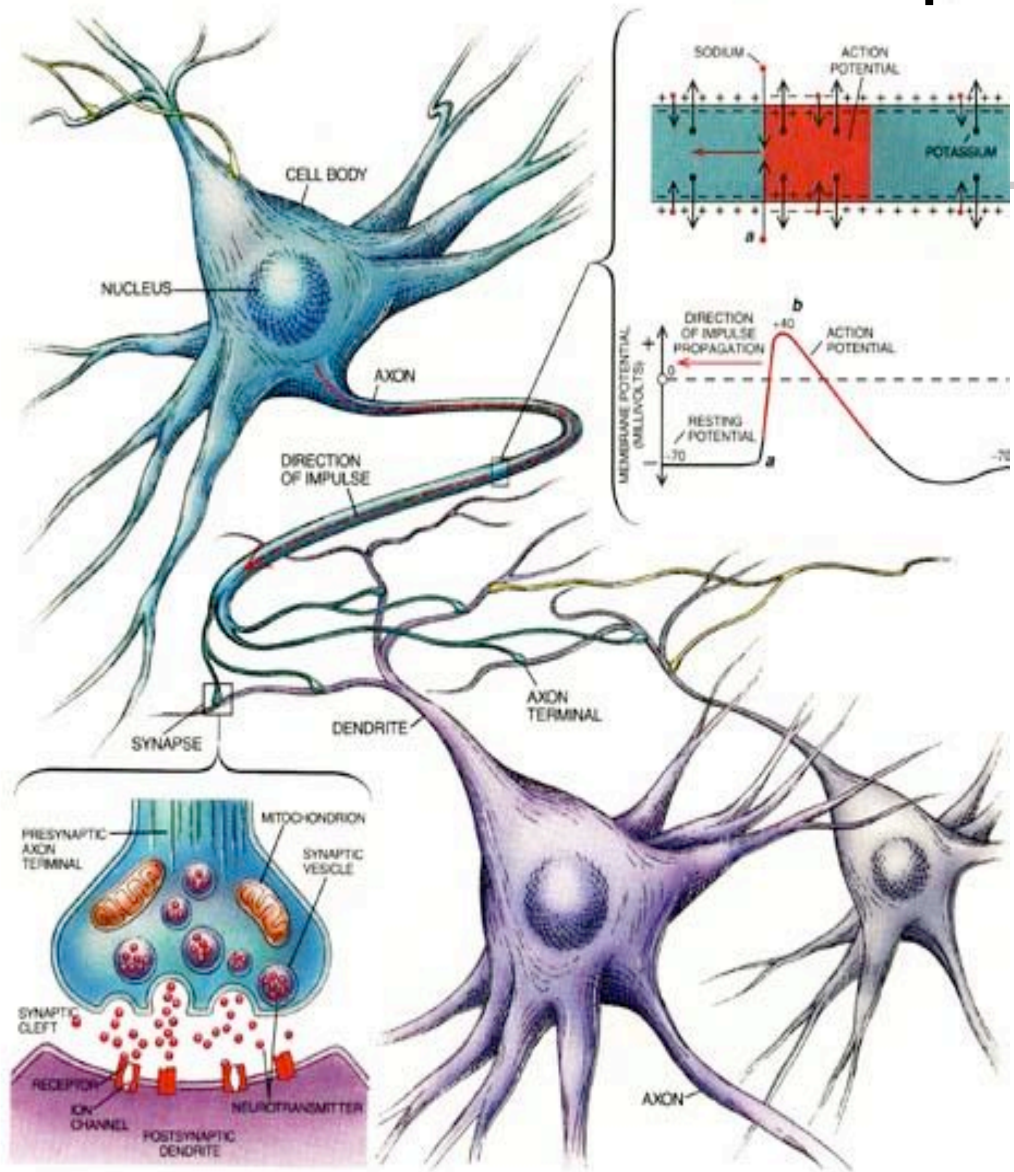


Of course, all this has been done, at least in the popular literature.



www.nanotech-now.com/Art_Gallery/tim-fonseca.htm

Despite our impressive tool box, advances are needed to enable important measurements



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Measuring the brain from synapse to thought

break-out discussion group

Irv Epstein
Chris Gall
Martha Gillette
Lingjun Li
Anna Lin
Tom Meade
Gordon Sheperd
Jonathan Sweedler
Harold Szu
Mark Wightman