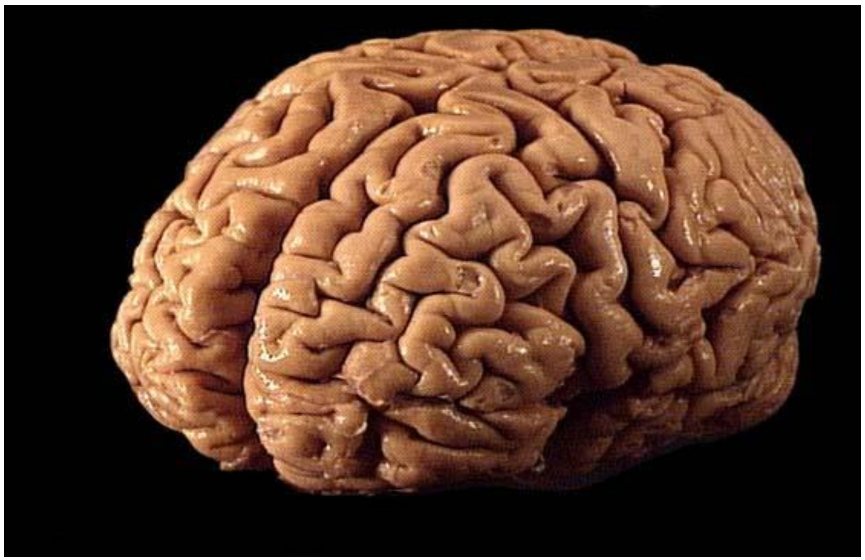
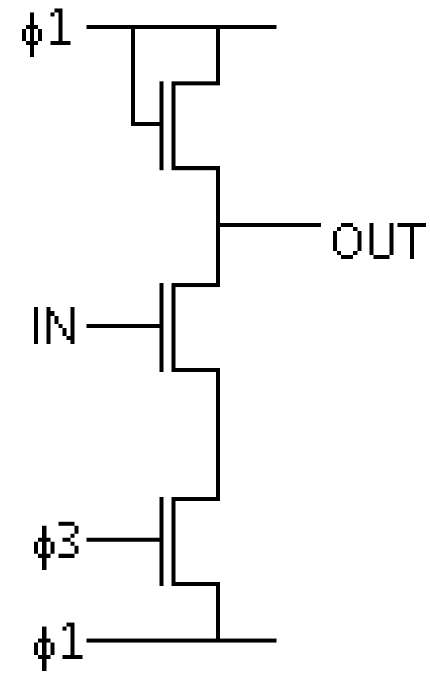
Lessons from the Neurons Themselves





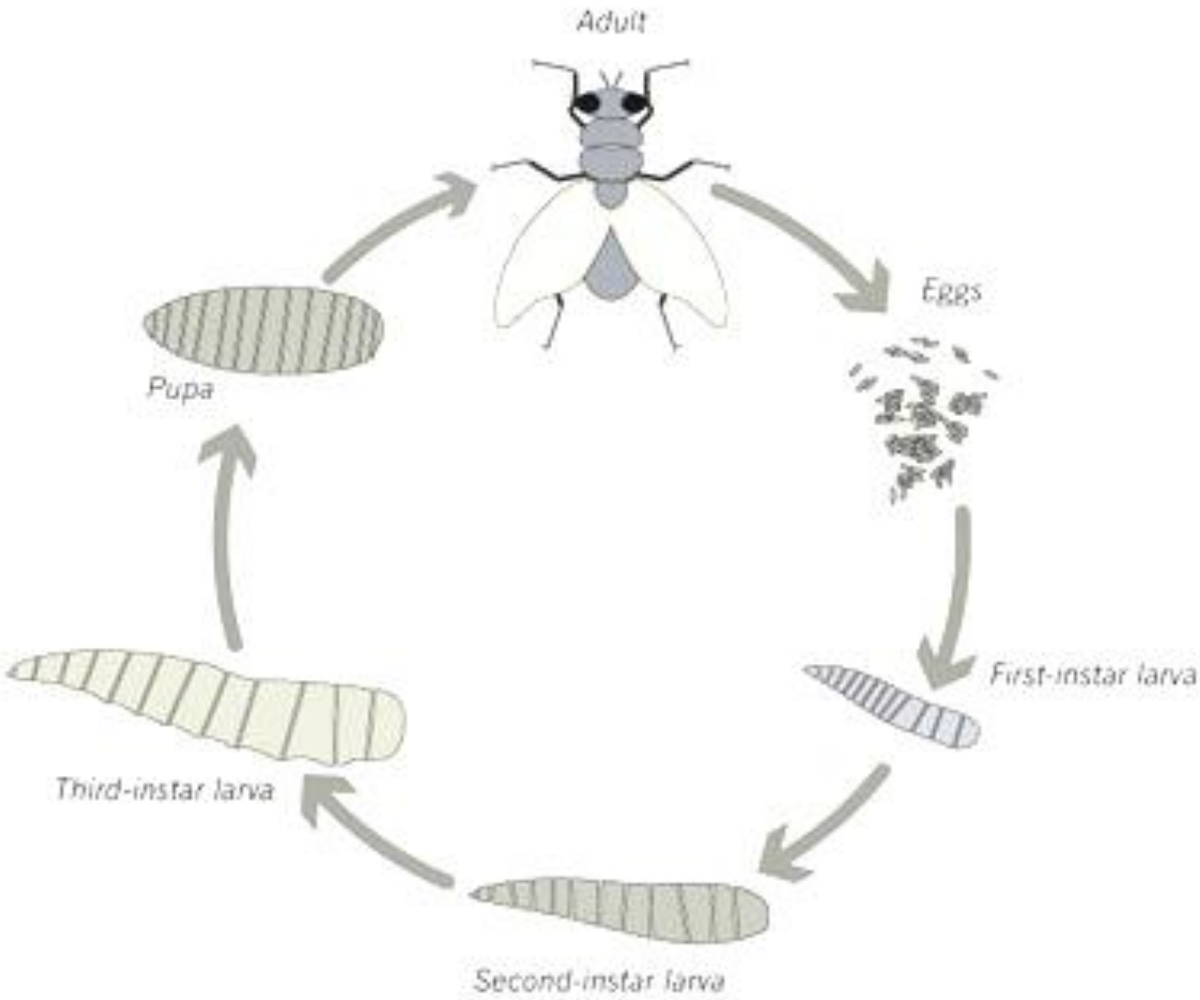
Lou Scheffer

Howard Hughes Medical Institute

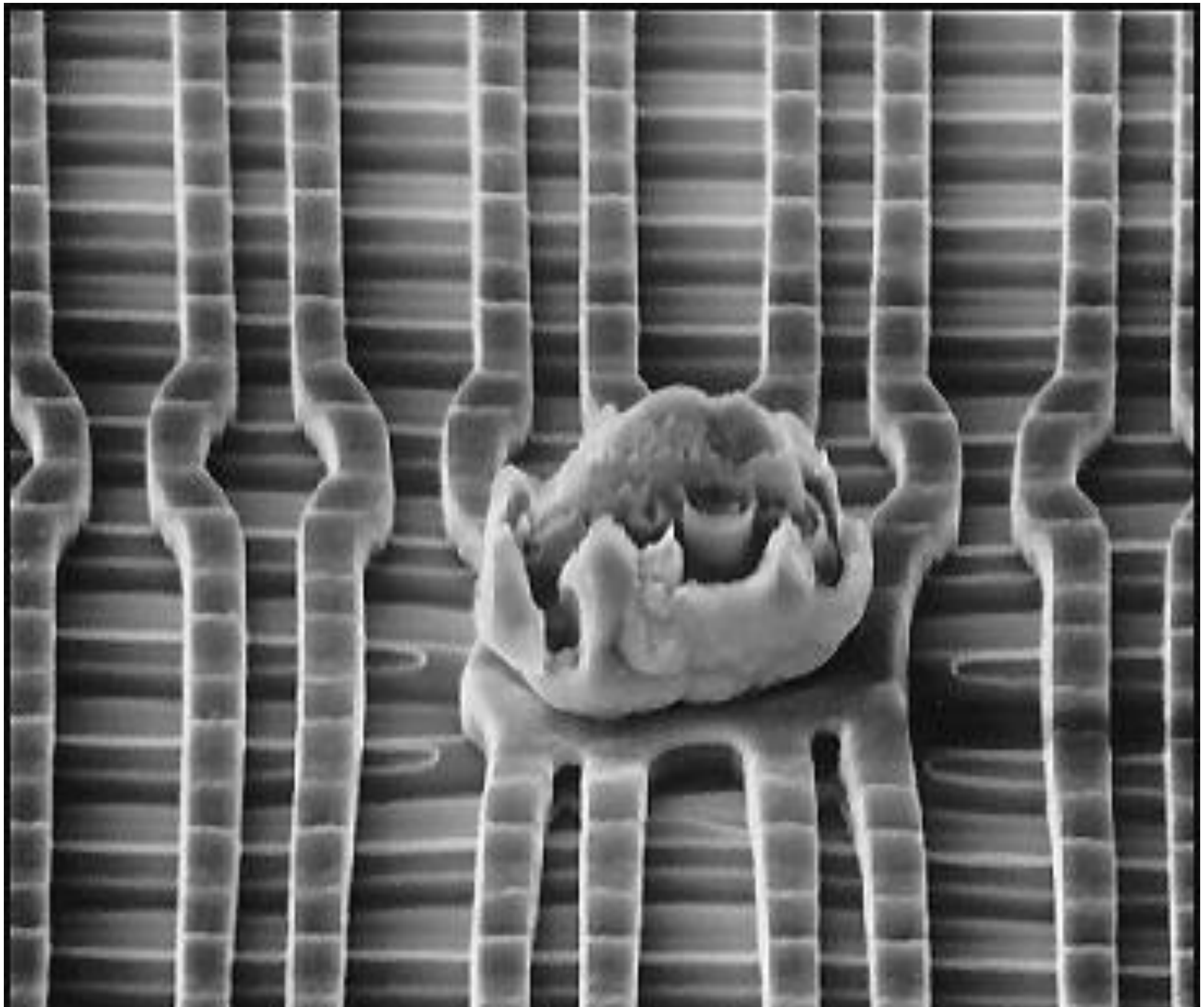
Overview

- Properties of neural circuits
- Studying the brain
- What we know so far
- Applications to neuromorphic computation

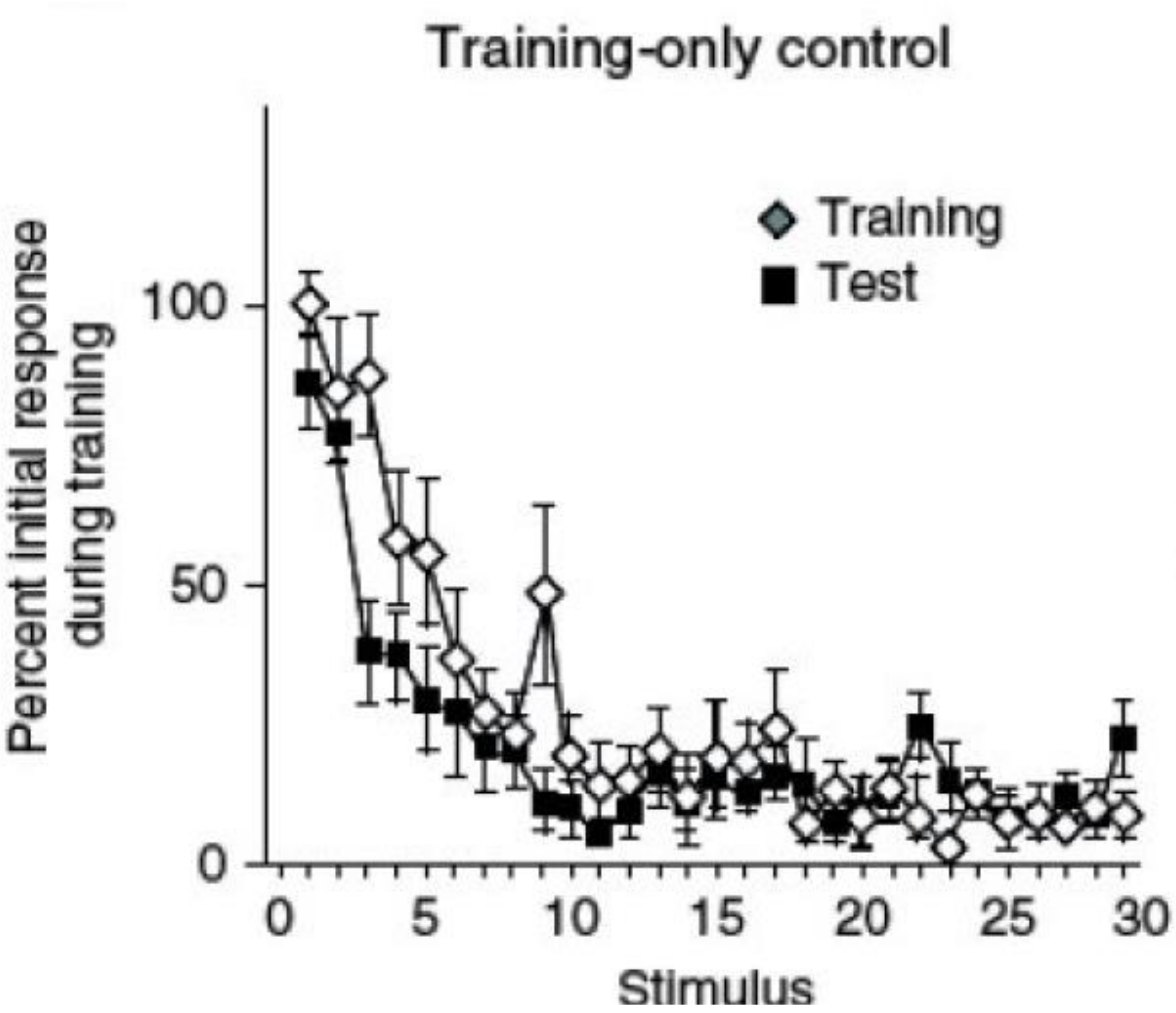
- Cool feature #1:   Grow, not built. Nanometer features with no $6B factory.
- Connections not specified in advance



- Cool feature #2: systems are extremely robust
  - Both in construction and operation

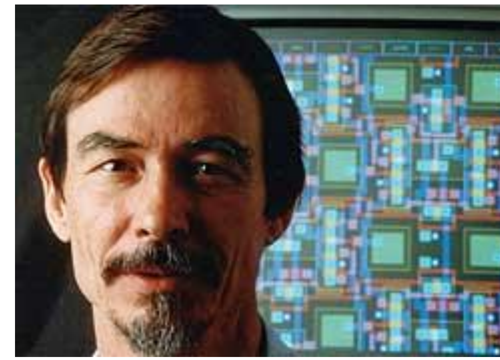


Cool feature #3: Biological systems adapt and learn



Neuromorphic Computing

- “Computing like the brain does”
  - Example: “The Silicon Retina”, Mahowald and Mead, Scientific American, 1991

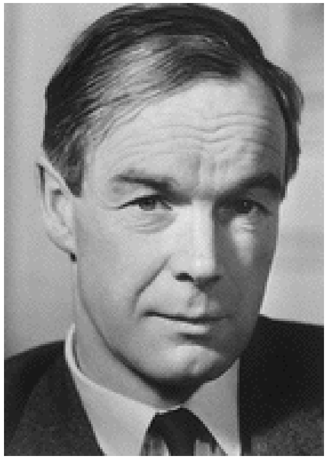


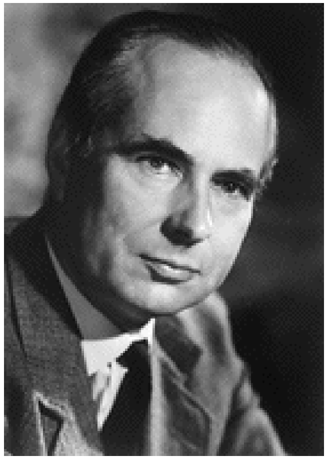
- Good plan, but one significant drawback
  - With very few exceptions, <u>we don’t know how the brain computes.</u>

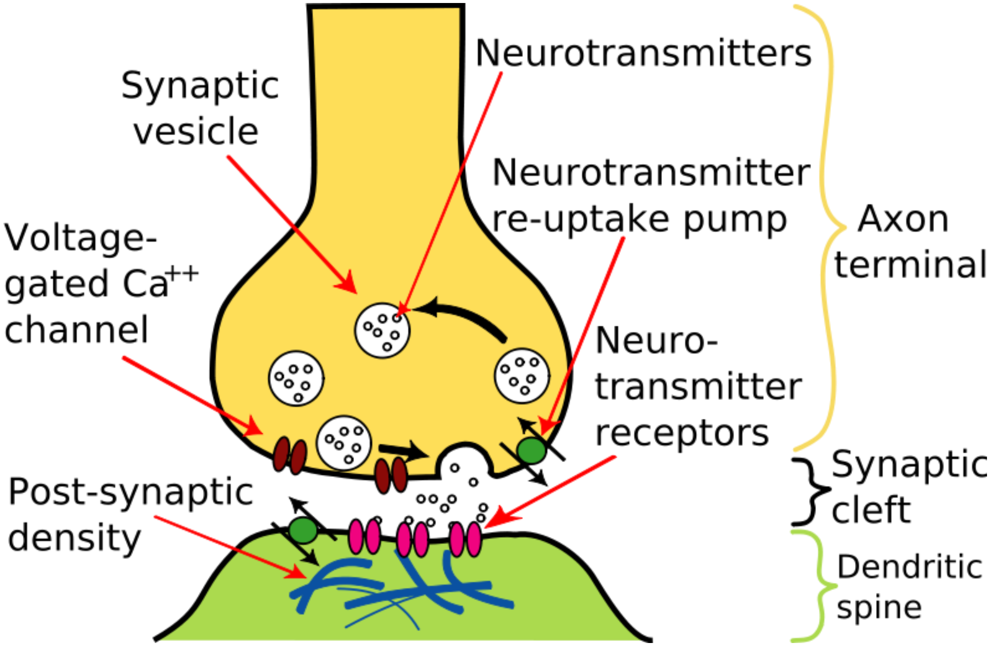
Even politicians recognize this is a good problem to work on!

History – Basic Science

- Caton saw electrical activity in animal brains, 1875
- Berger produced first EEGs of humans in 1924
- Hodgkin-Huxley Nobel-winning model in 1953
  - Established basic model of how the brain works

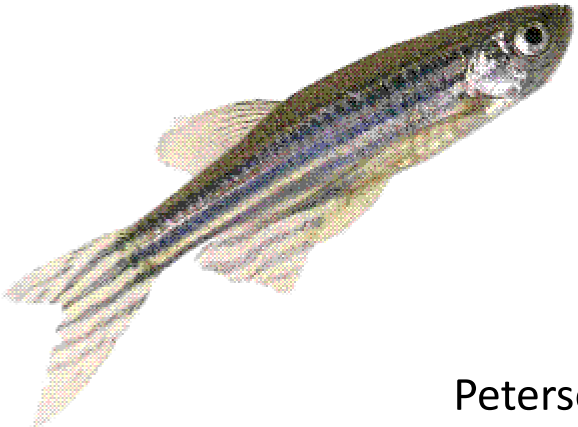






Model organisms

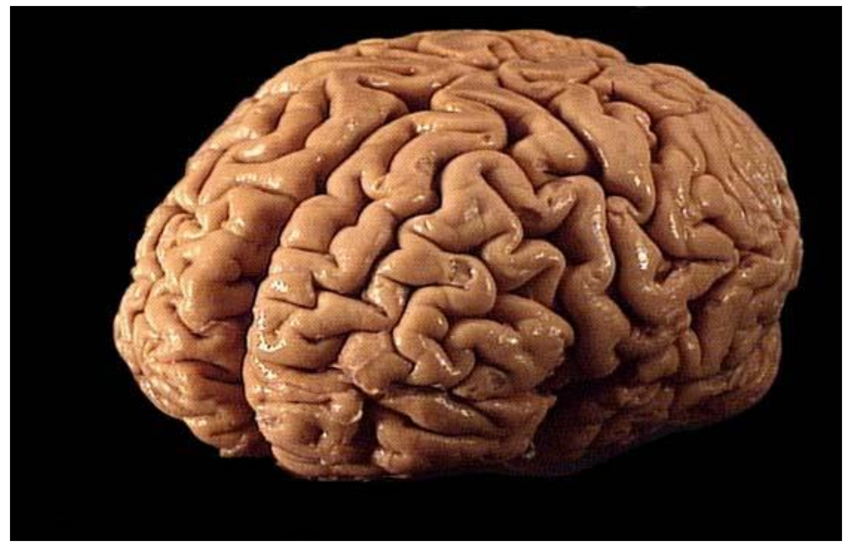
- Fruit fly
  - Breeds quickly, cheap, excellent genetics
- Zebrafish
  - Vertebrate, larva transparent
- Mouse
  - Mammal, good genetics



Peterson lab, U Texas

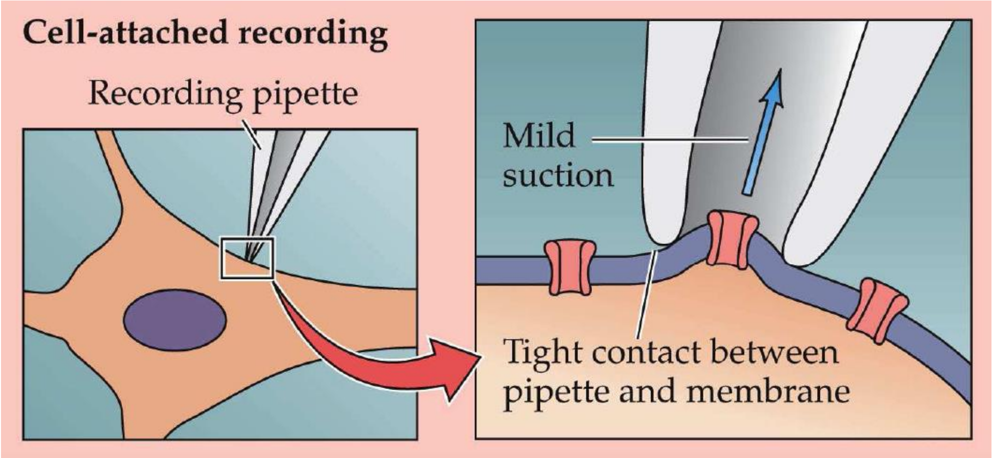
Figuring out how the brain works

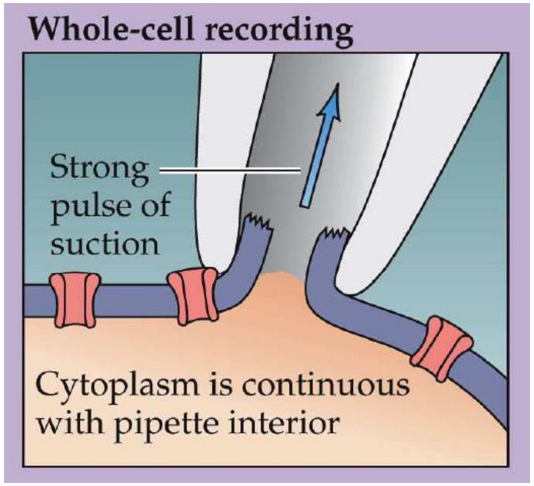
- Hot topic – many methods are being used
  - Structural – reverse engineering
  - Genetic
  - Behavioral
  - Electrophysiology
  - Imaging
  - Lineage
  - Combinations of these techniques



Electrical: single cell recording

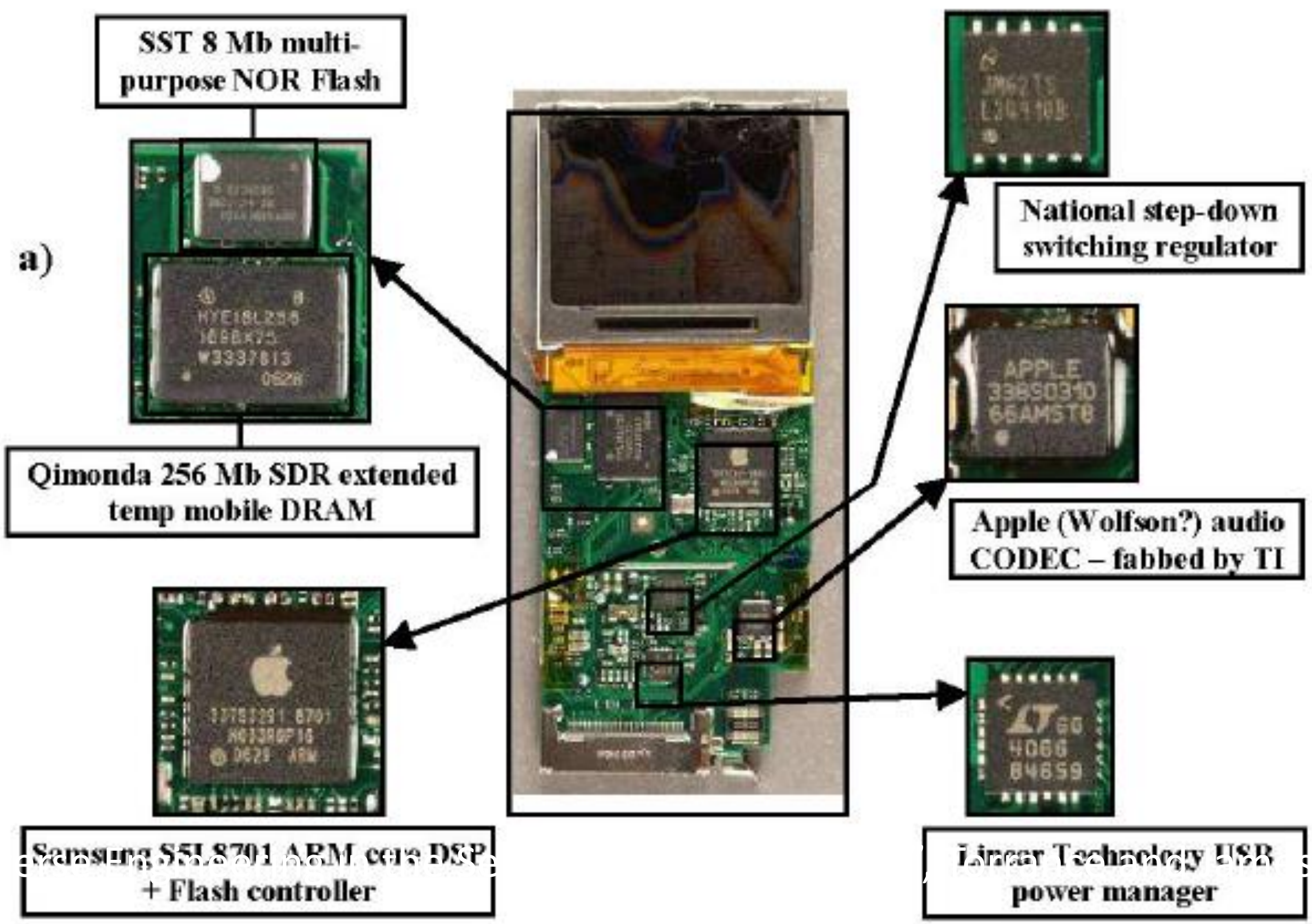
- Perfect resolution
- Input and output
- Drawbacks
  - Invasive
  - Hard to connect to desired cell
  - Short life (1/2 hour)
  - Not easy to parallelize

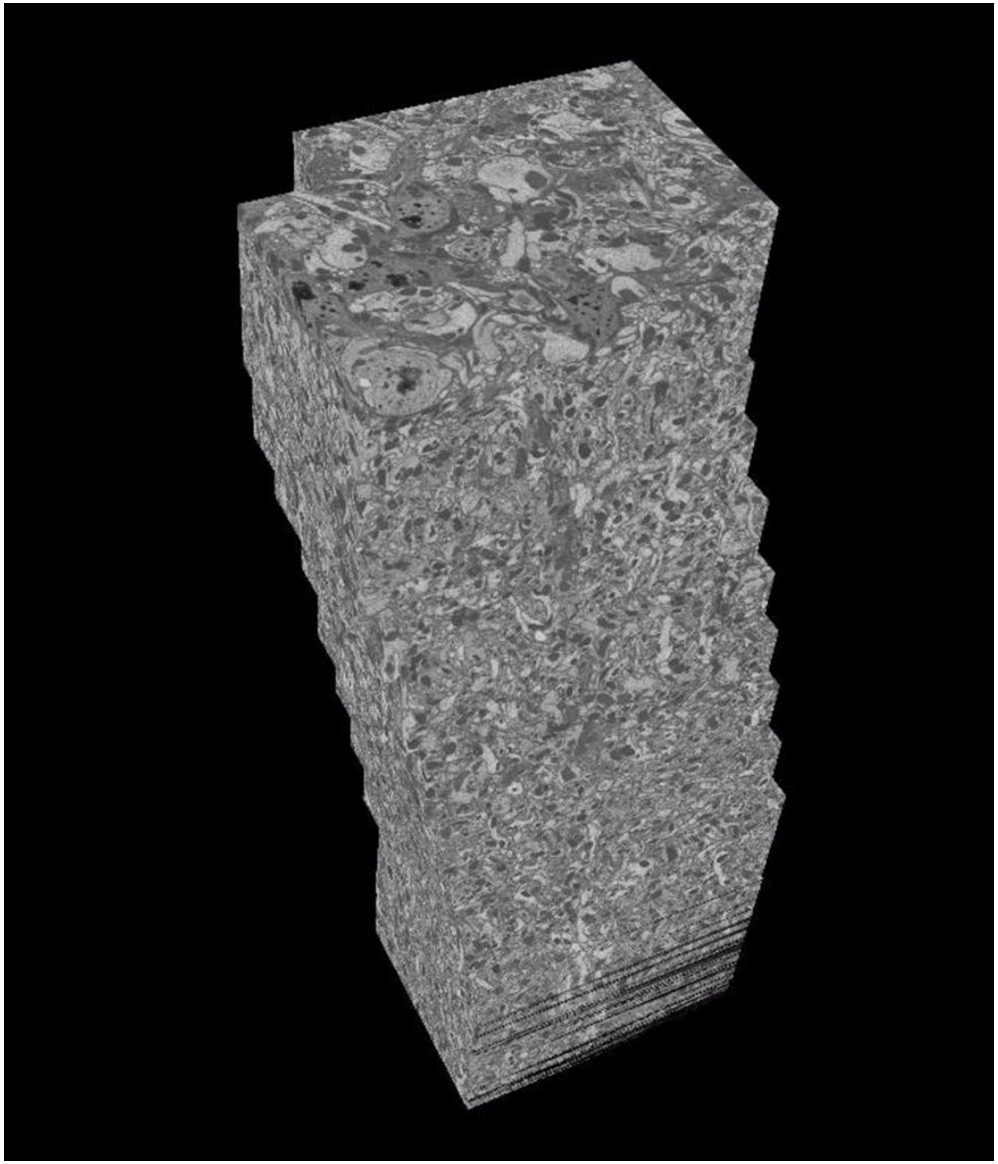




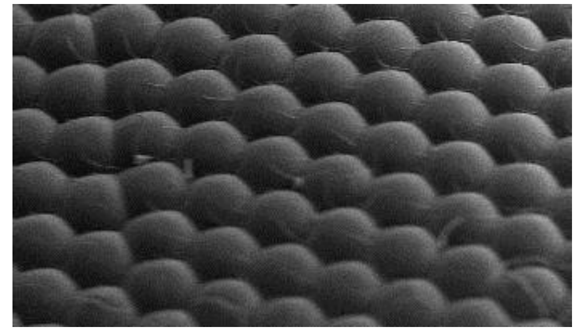
Structural – Reverse Engineering

- Just like reverse engineering electronics





Neuron Reconstruction



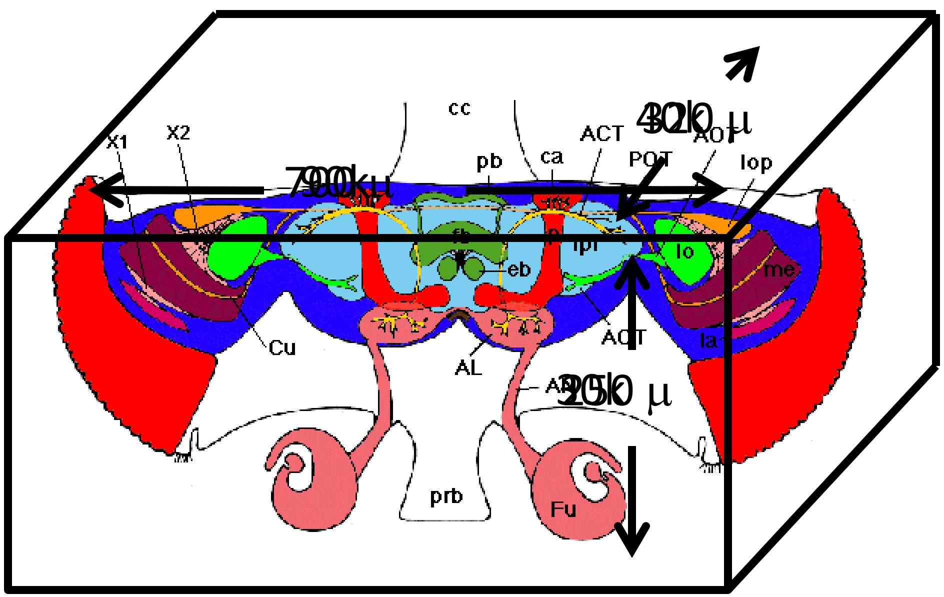
7 columns of the fruit fly medulla.

Each column is the second stage of processing behind each facet of the eye

800 columns in total on each side of a 1 mm fly

Further out

- Fly brain fits in this box
- Assume 8nm isotropic voxels
- Will have netlist of whole fly brain in 5-10 years



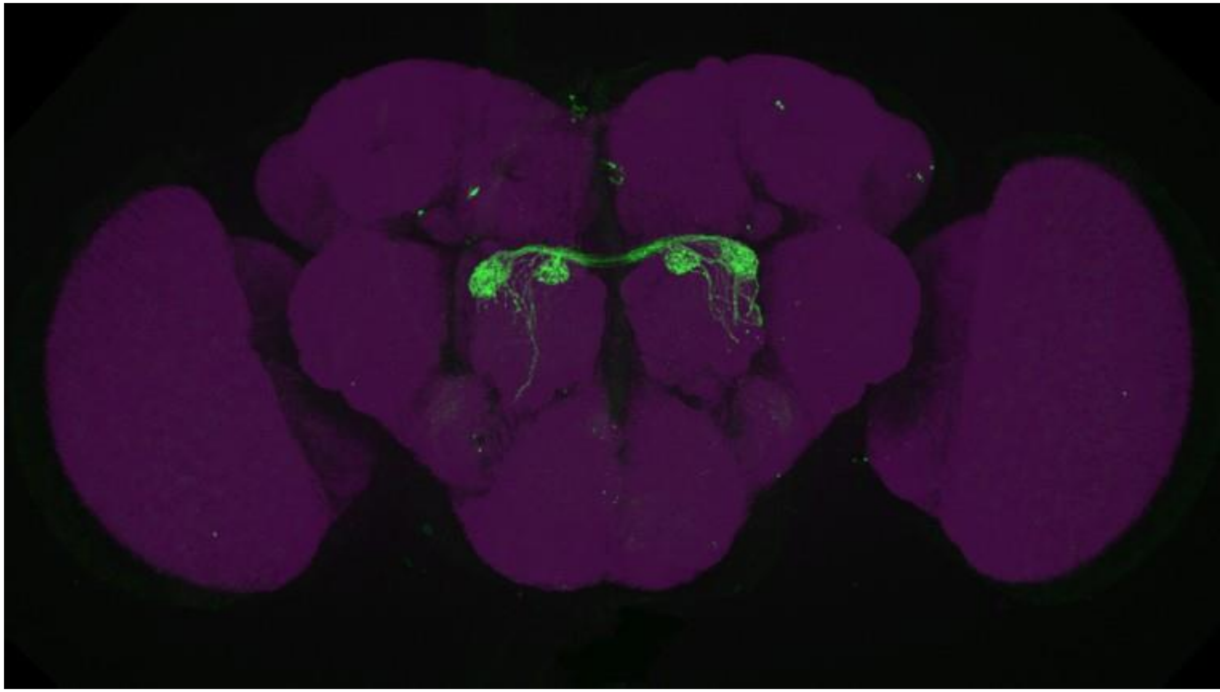
About 100 Tb of images

1500 person-years to analyze

http://filab.biologie.uni-freiburg.de/Atlas

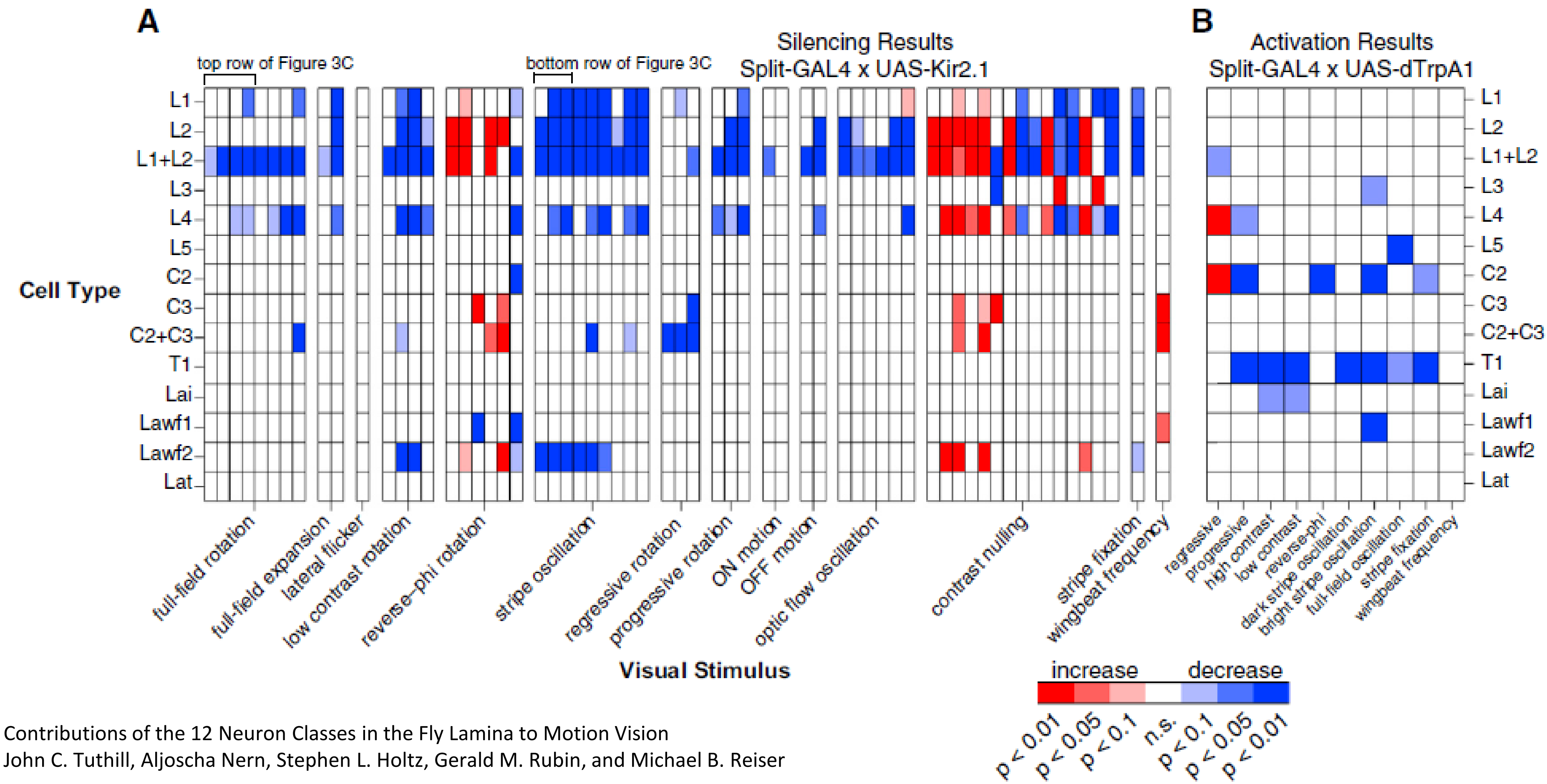
Genetic techniques

- Can create specific modification of a subset of neurons by crossing animals
  - Permanently on or off
  - By temperature
  - Optogenetically
  - Small molecule



Automated behavioral analysis

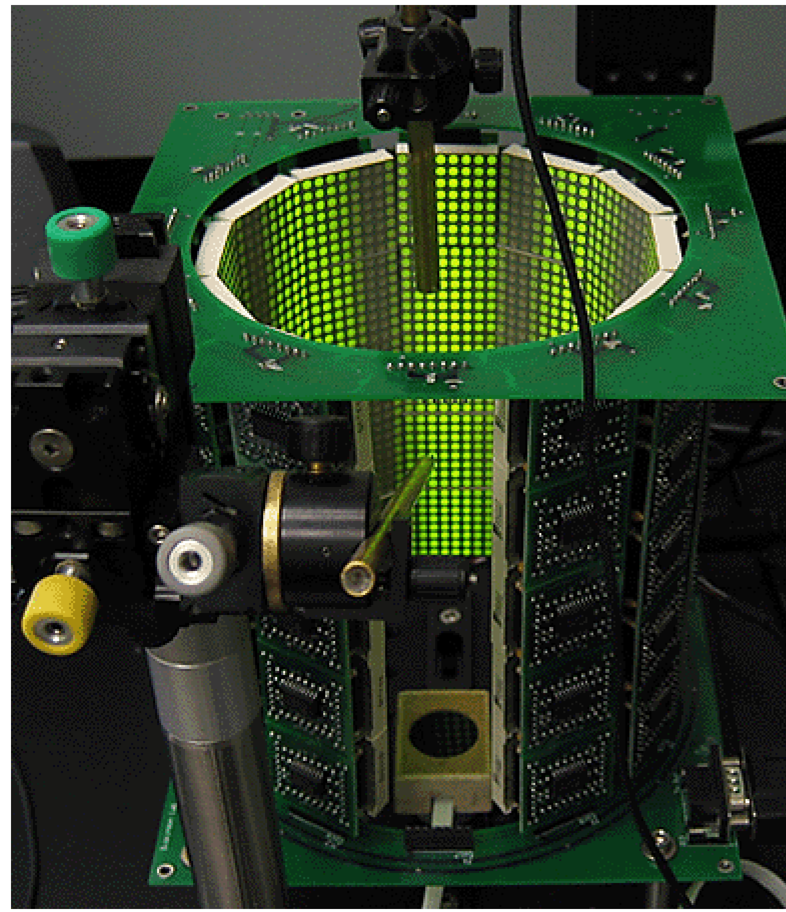
- Present various stimuli; look at response



Contributions of the 12 Neuron Classes in the Fly Lamina to Motion Vision
John C. Tuthill, Aljoscha Nern, Stephen L. Holtz, Gerald M. Rubin, and Michael B. Reiser

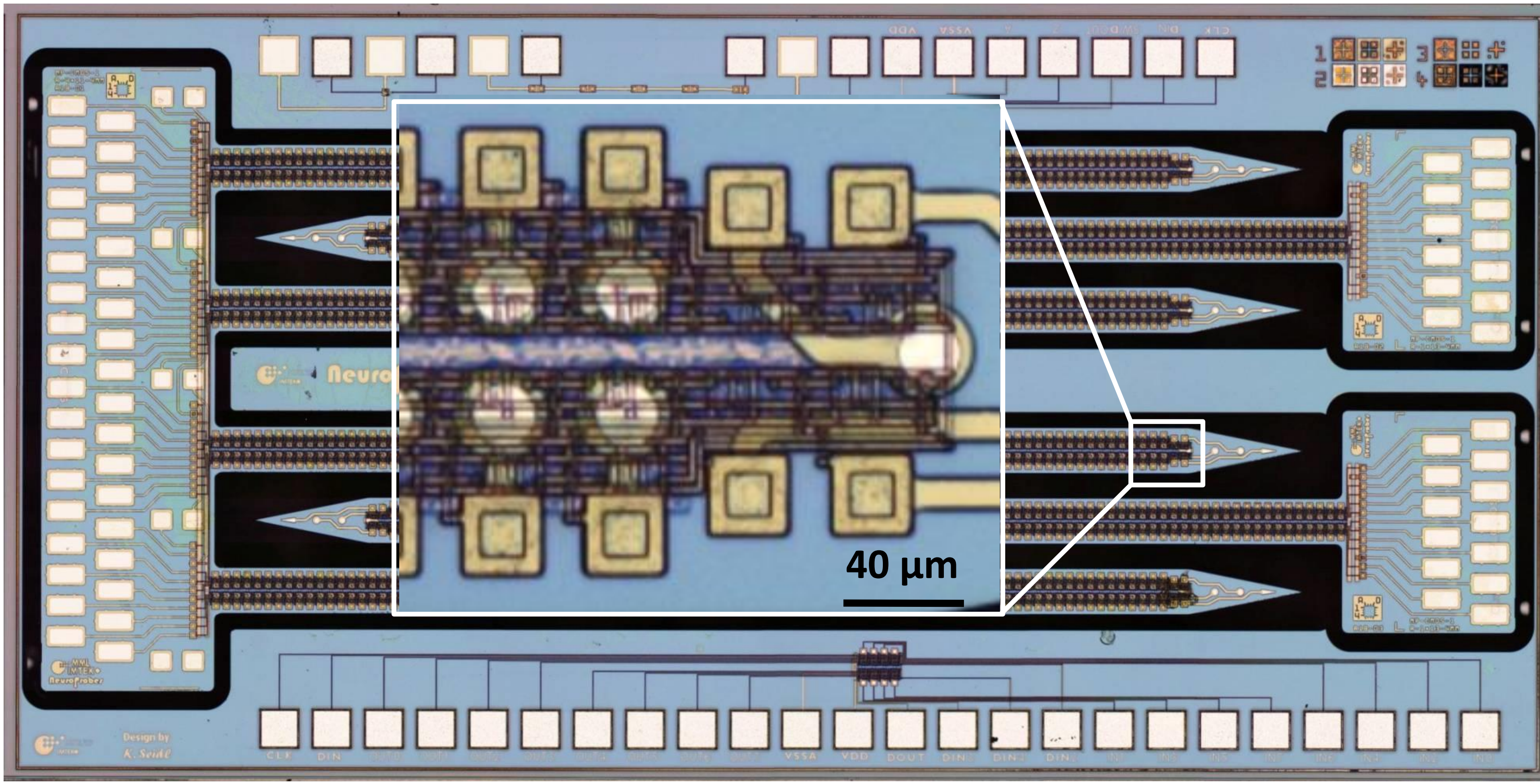
Electrophysiology

- Animals such as mice and rats can wear headgear
- Now working for flies using ‘virtual reality’



Extracellular recording (many cells)

- IMTEK probes, from CMOS technology



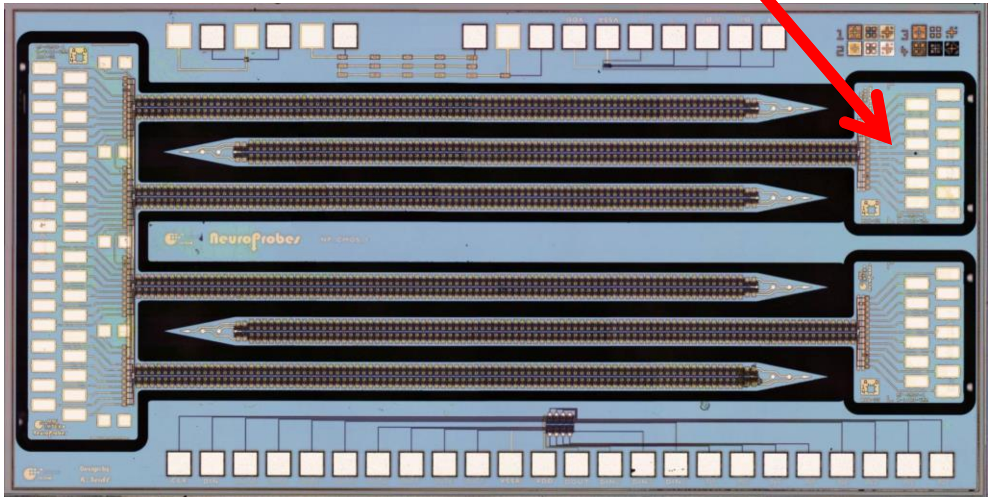
500 µm

Source: K. Seidl, et al., JMEMS 2011, vol. 20, pp. 1439 -1448

Consortium for active probes

- Readout of hundreds of channels

Replace head with LPFs, A/Ds, muxes



HHMI
HOWARD HUGHES MEDICAL INSTITUTE

ALLEN INSTITUTE for BRAIN SCIENCE
Fueling Discovery

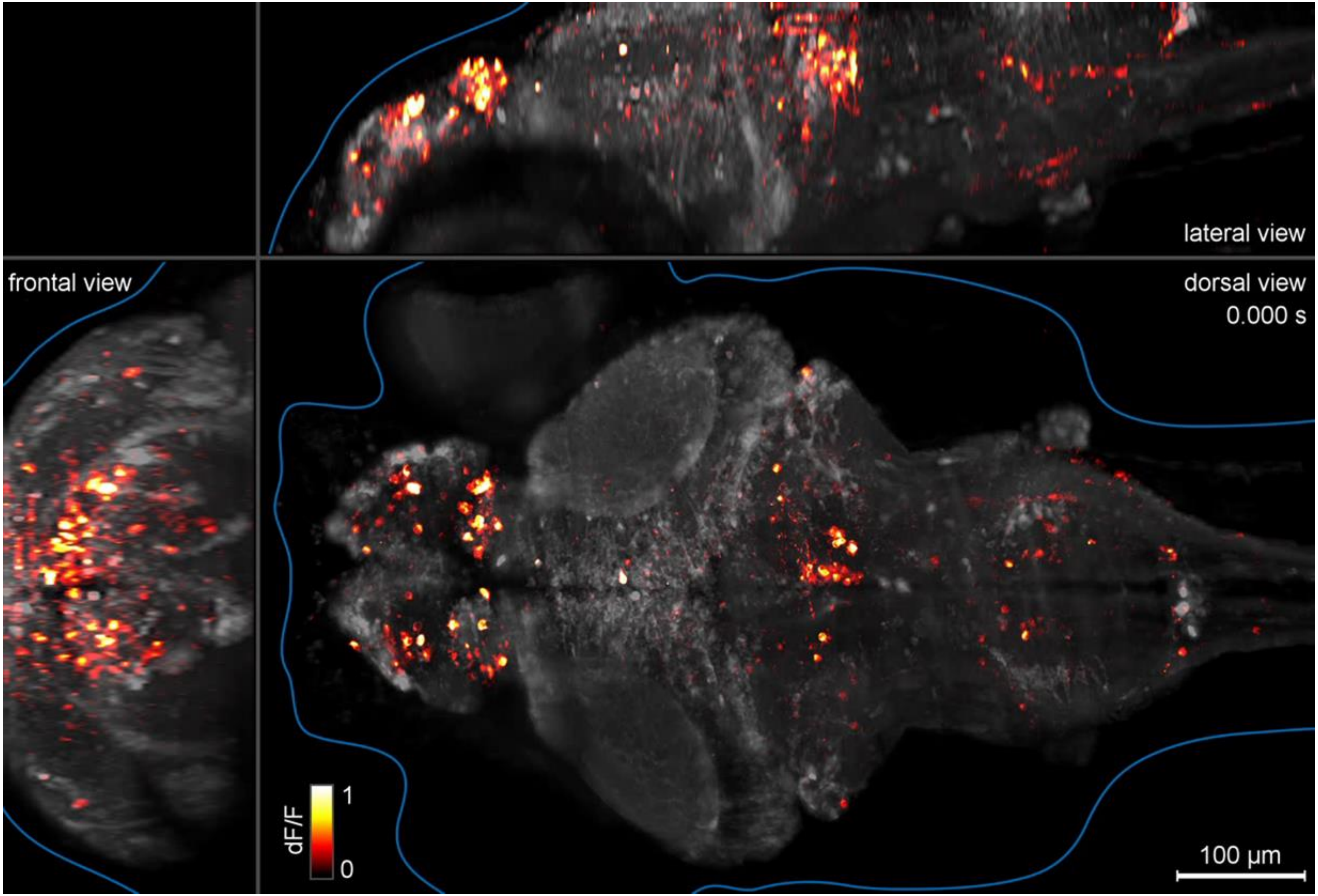
UCL

imec

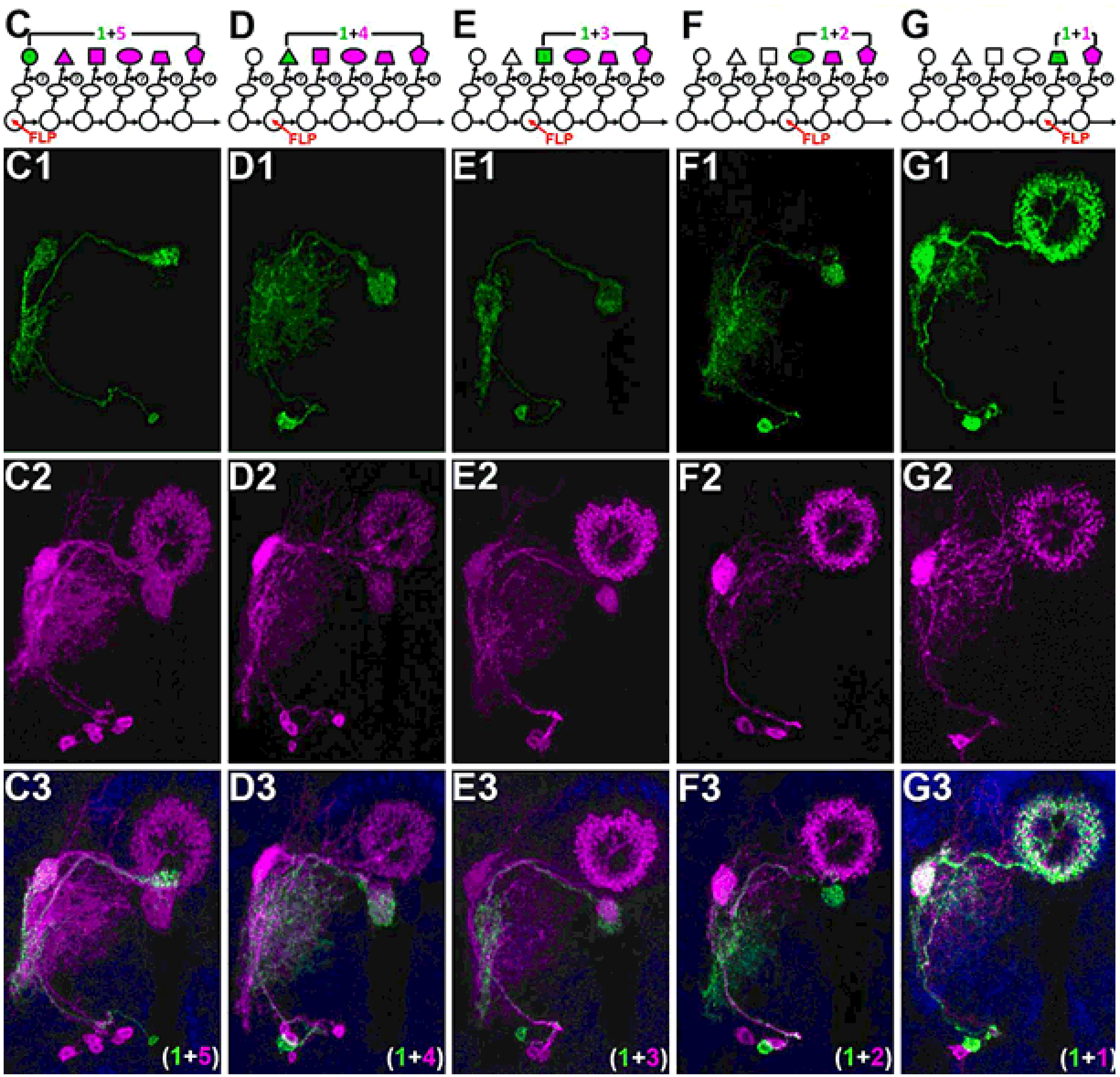
wellcome trust

The Gatsby Charitable Foundation

Brain imaging (here in zebrafish)

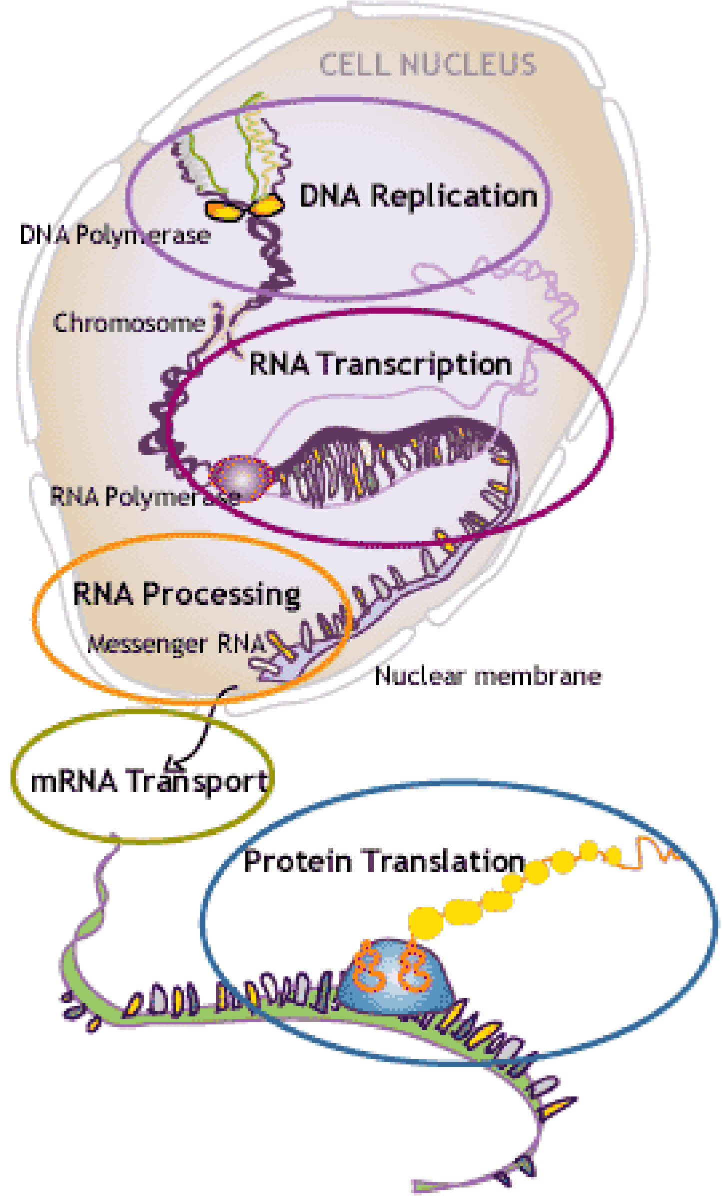


Lineage - how cells connect



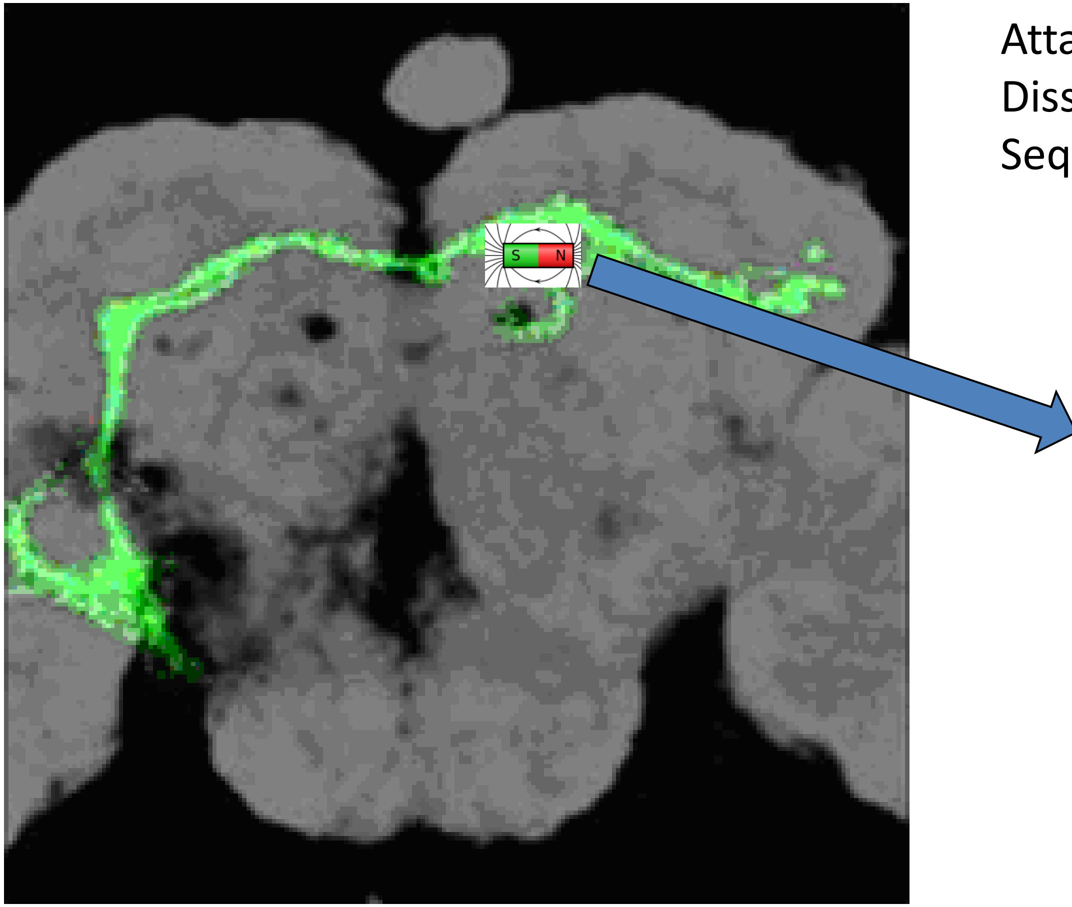
RNA-seq

- DNA for *every* protein present in *all* cells
  - Genome sequencing does not tell which are used
- Sequence RNA to see what is expressed
  - Different for every cell type
- Gives full list of expression, not just transmitters



Nobelprize.org

Attach magnet to cell types
Dissolve fly; separate out;
Sequence RNA

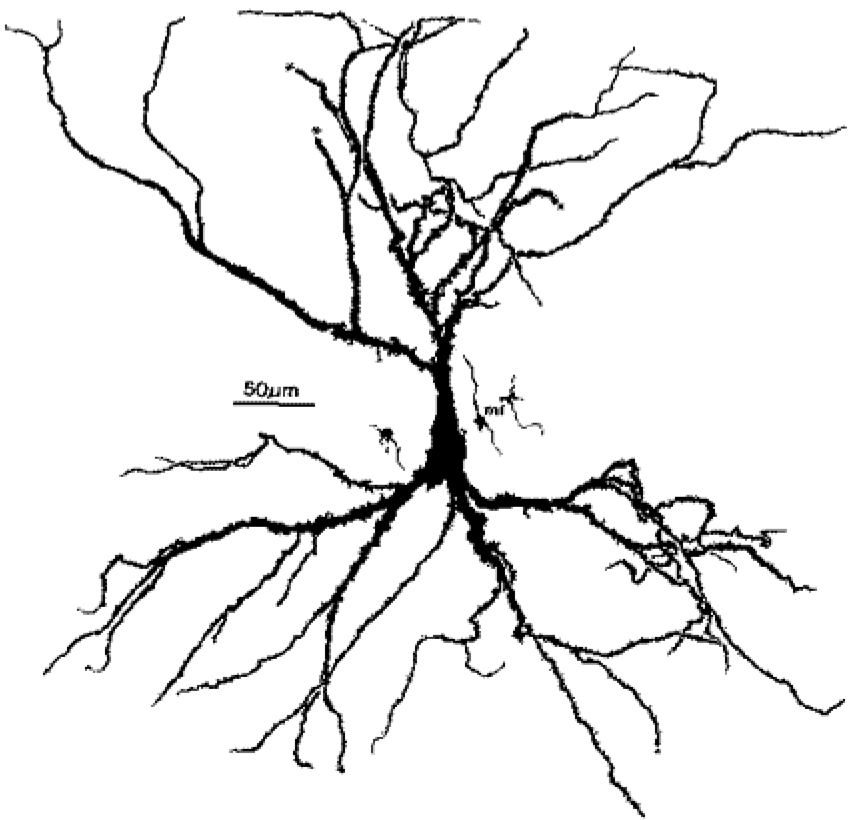


What have we learned?

- Neurons are themselves complex
- Local, non-linear feedback
- Supporting structure is active
- Neuromodulators provide non-local communication
- Time-varying connectivity

Lesson #1 - complex neurons

- Far from iso-potential



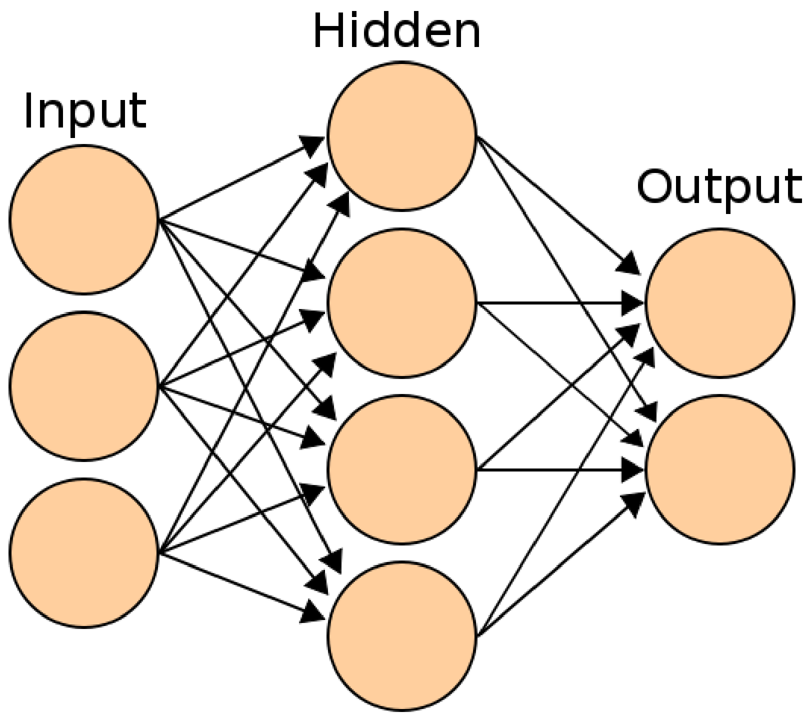
Tech	Bio 100 nm	Bio 1 um	Si 20 nm
R /mm	130G	1.3G	54K
C /mm	3.1pf	31pf	200ff
Gate delay	1ms	1ms	20ps
Break-even	71u	225 um	43u

Used in computation

- Local over-threshold causes positive feedback propagation
  - Amplification of distant inputs
  - Coincidence detection
  - Compressive non-linearities
  - Neurons within neurons - (almost) independent computation in different branches.

Lesson 2: Neural network structure

- Go to Wikipedia, look up neural net:

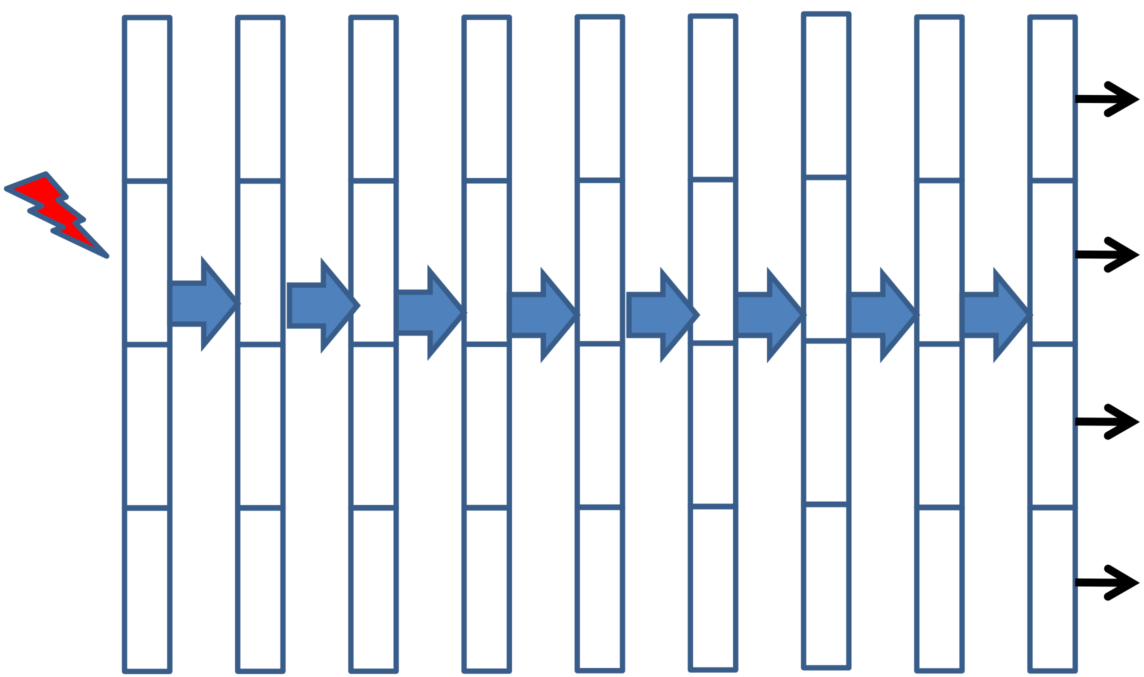


- Looks very simple

Neural Net in Practice

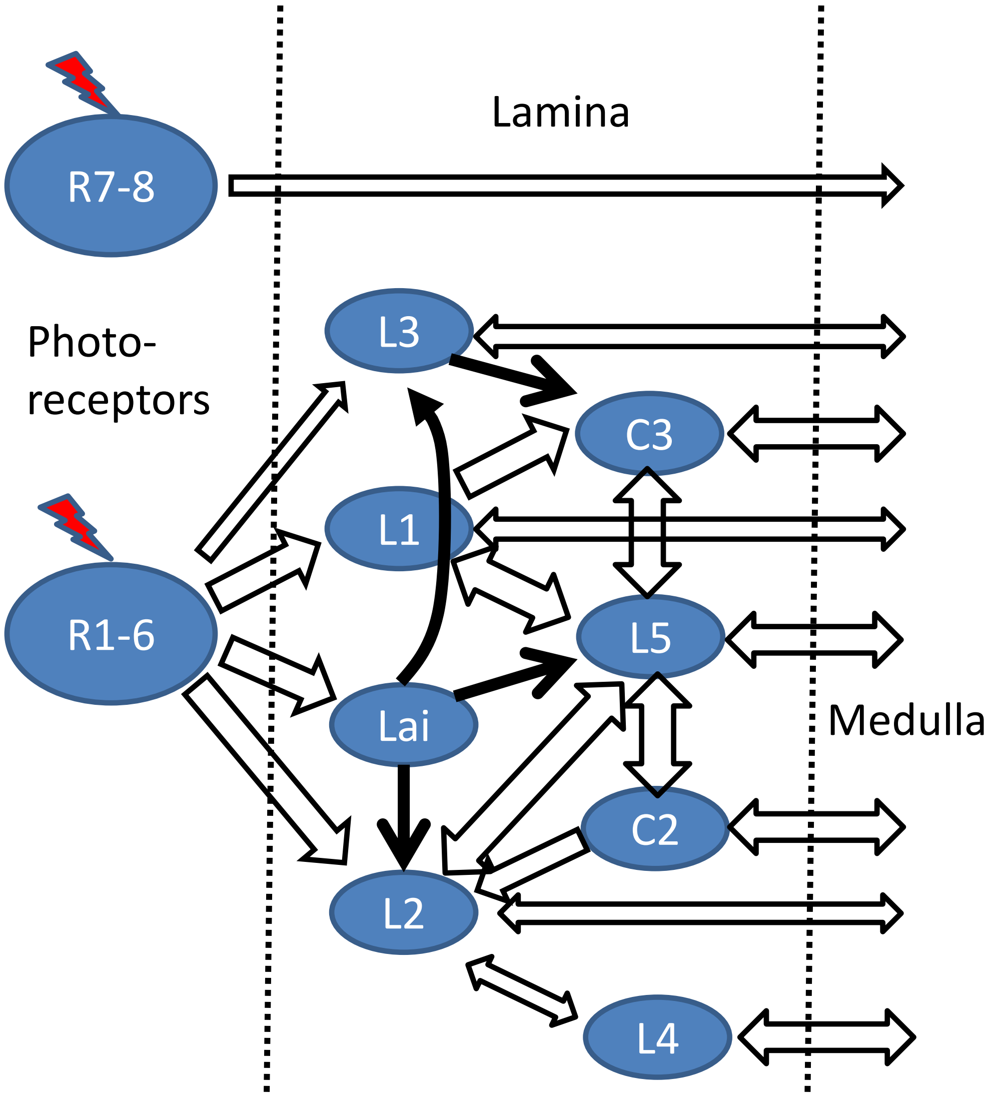
- Advanced neural nets are more complex, but conceptually similar

1	20	20	20	800	40	40	150	10	**# of units**
841	16	676	169	25	81	9	1	1	**Variables per unit**

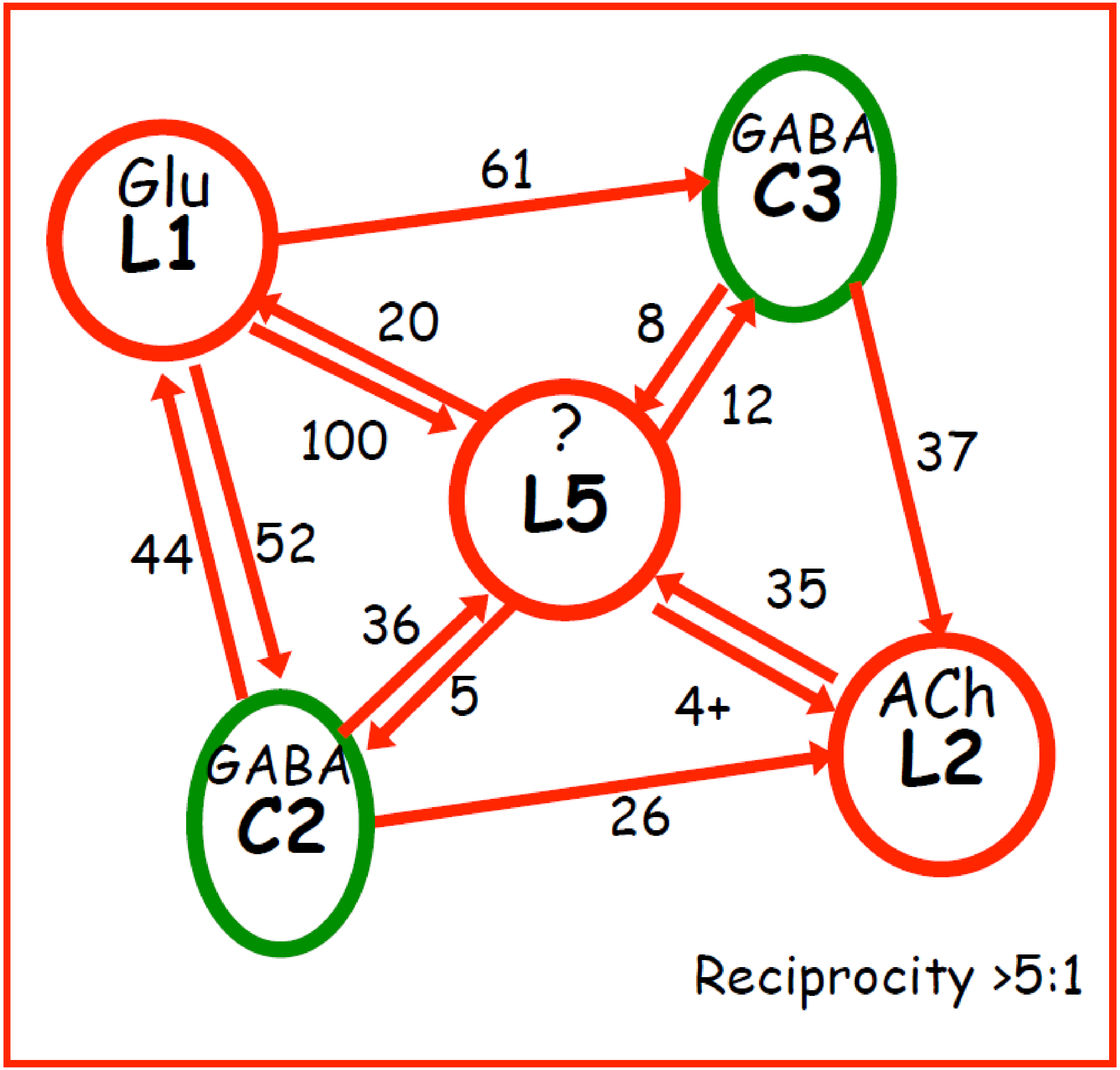


See LeCun, *et al*., Ciresan *et. al.* (2010) for many networks of this type.

Biological Neural Net



- Relatively few layers
- Not neatly organized
- Lots of lateral and feedback connections

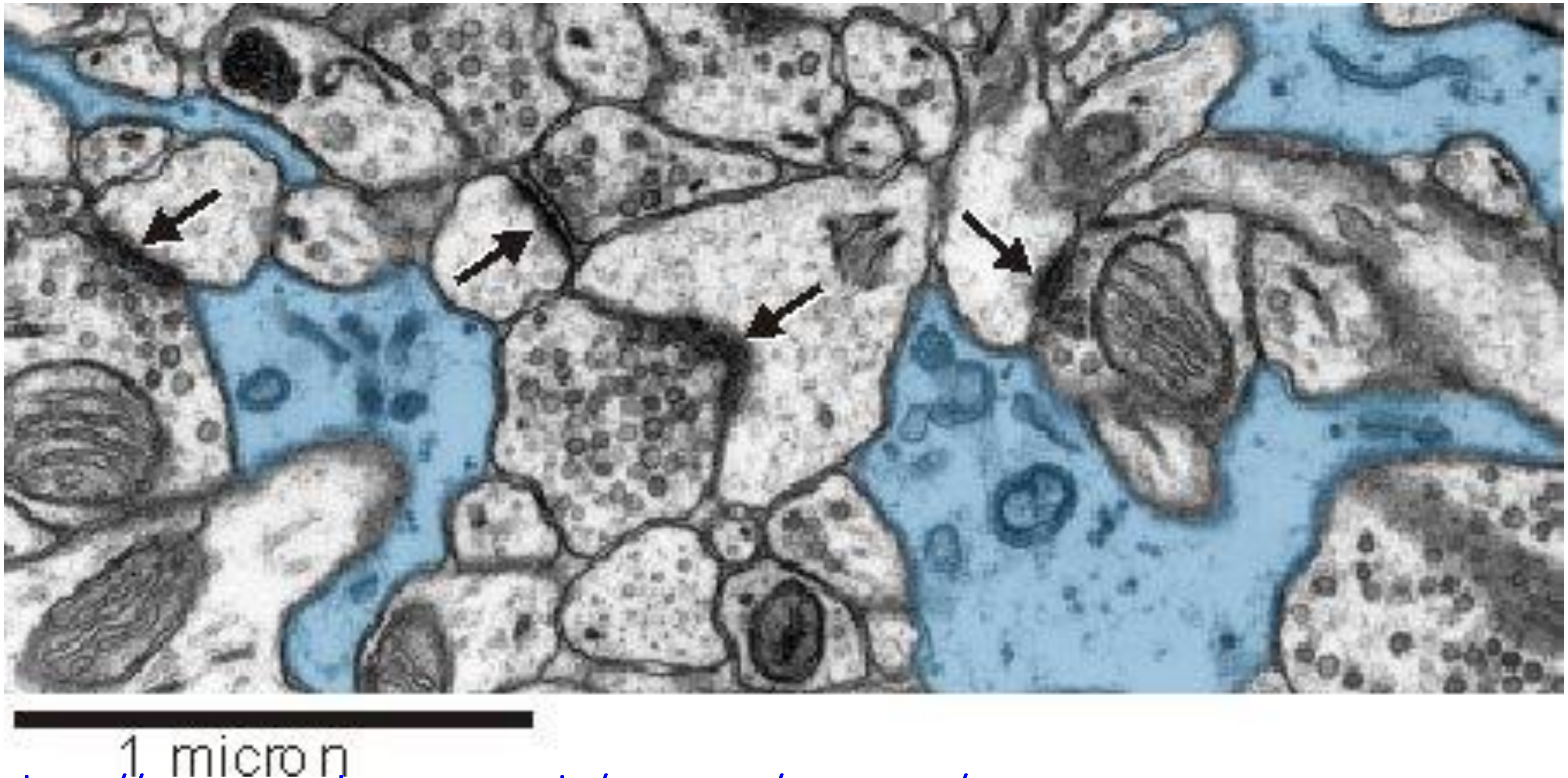


Feedback everywhere

- Lots of local feedback
- Calling all theorists!

Lesson #3: Support structure is active

- Gray is neuron, blue glia, arrow synapse
- Quick look shows a division of labor

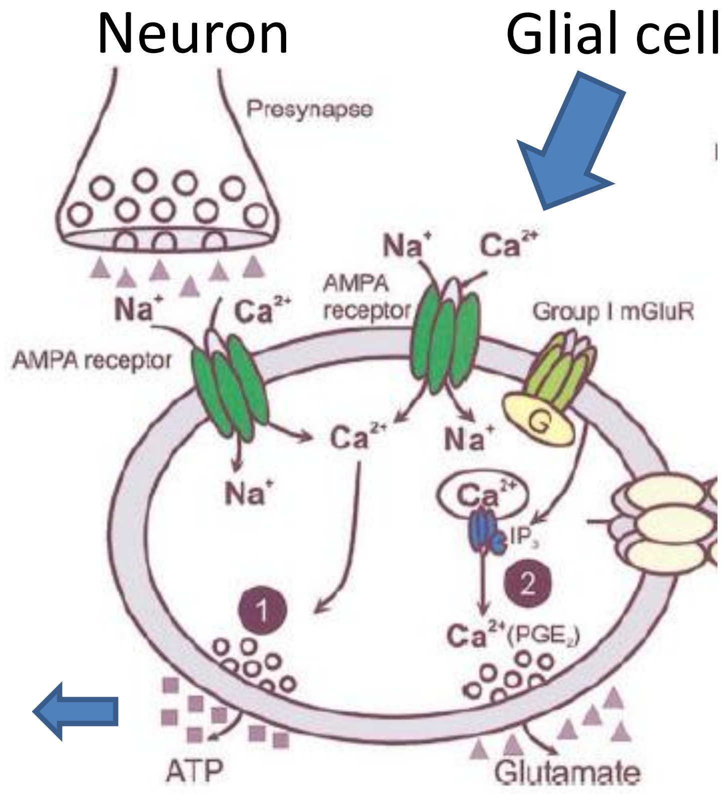


http://synapses.clm.utexas.edu/anatomy/astrocyte/astrocyte.stm

Astrocytes in the hippocampus, *Rachel E. Ventura*

But a closer look shows glia communicate

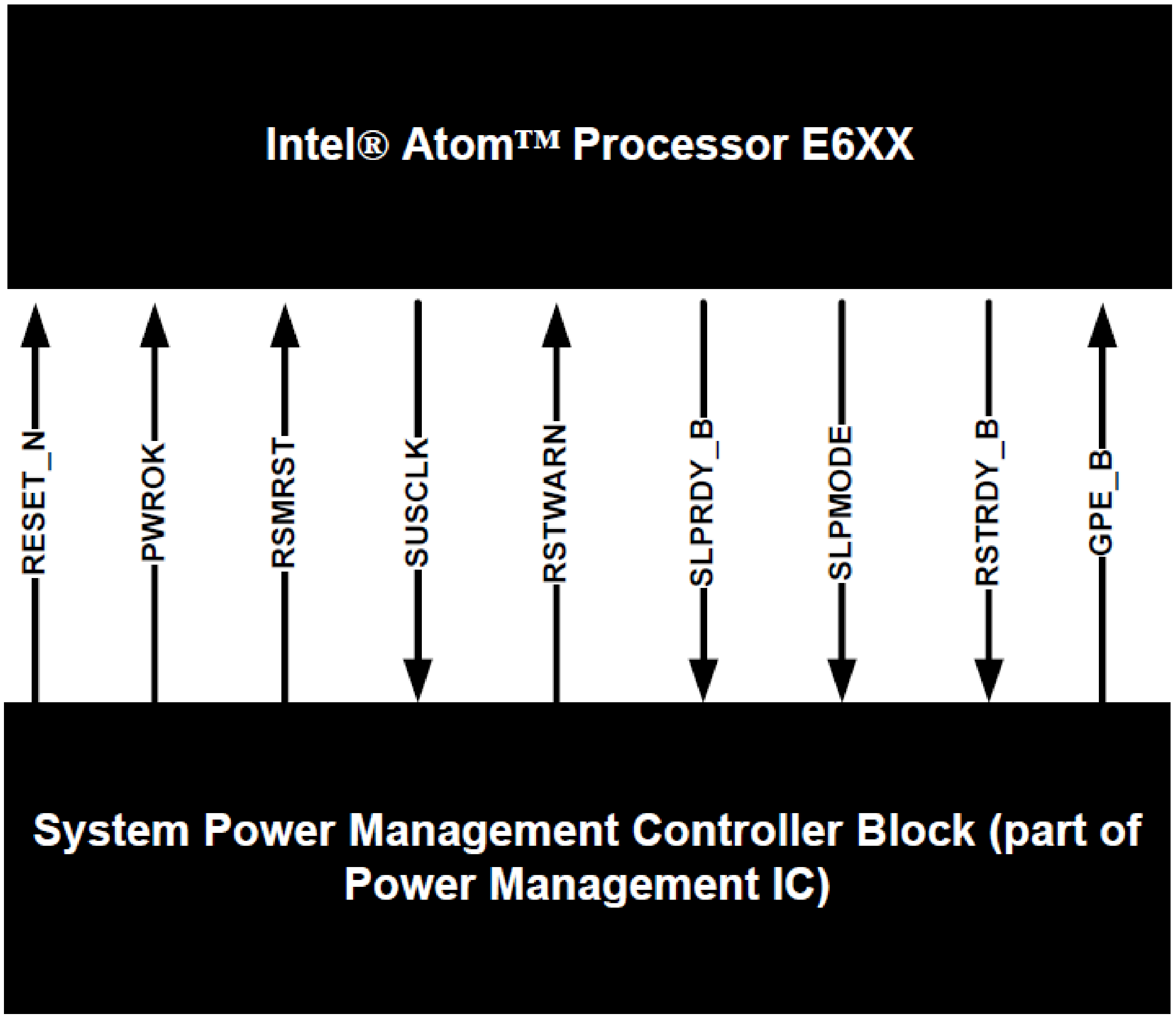
- What are are they doing?
- Perhaps modulate the energy supply?



ATP provides energy for neurons

Glial Modulation of Synaptic Transmission in the Hippocampus
Andrea Volterra and Christian Steinhauser

Modern electronics does this

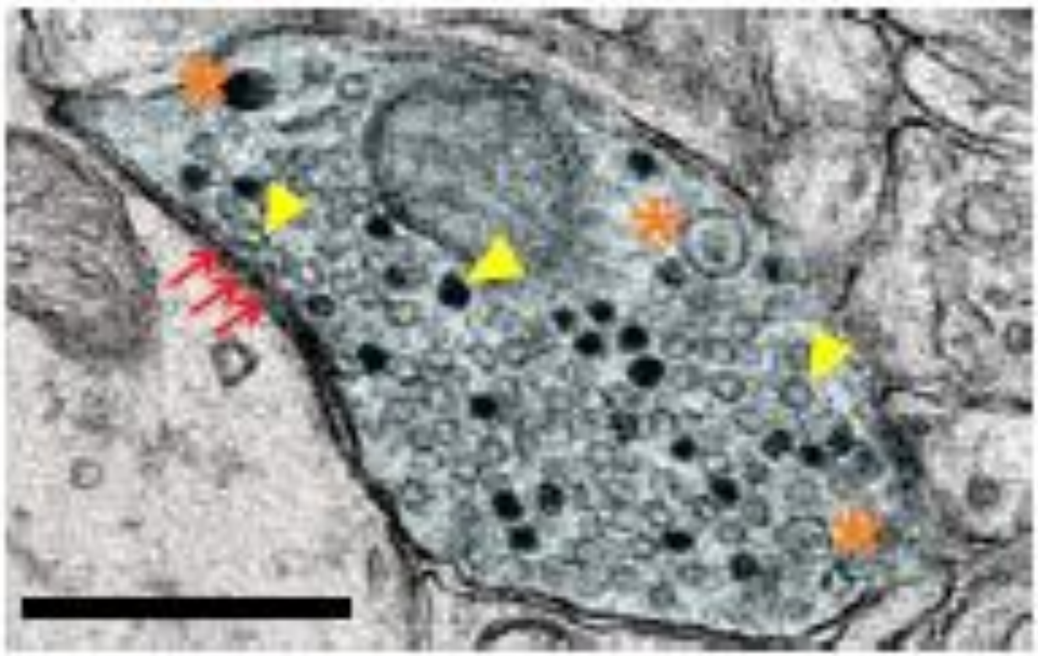


… So we should not be surprised

The Power Management IC for the Intel® Atom™ Processor E6xx Series

Lesson #4: Neuromodulators

- Cells can express two or more types of outputs
  - Neurotransmitters talk to adjacent cell
  - Neuromodulators diffuse and talk to distant cells

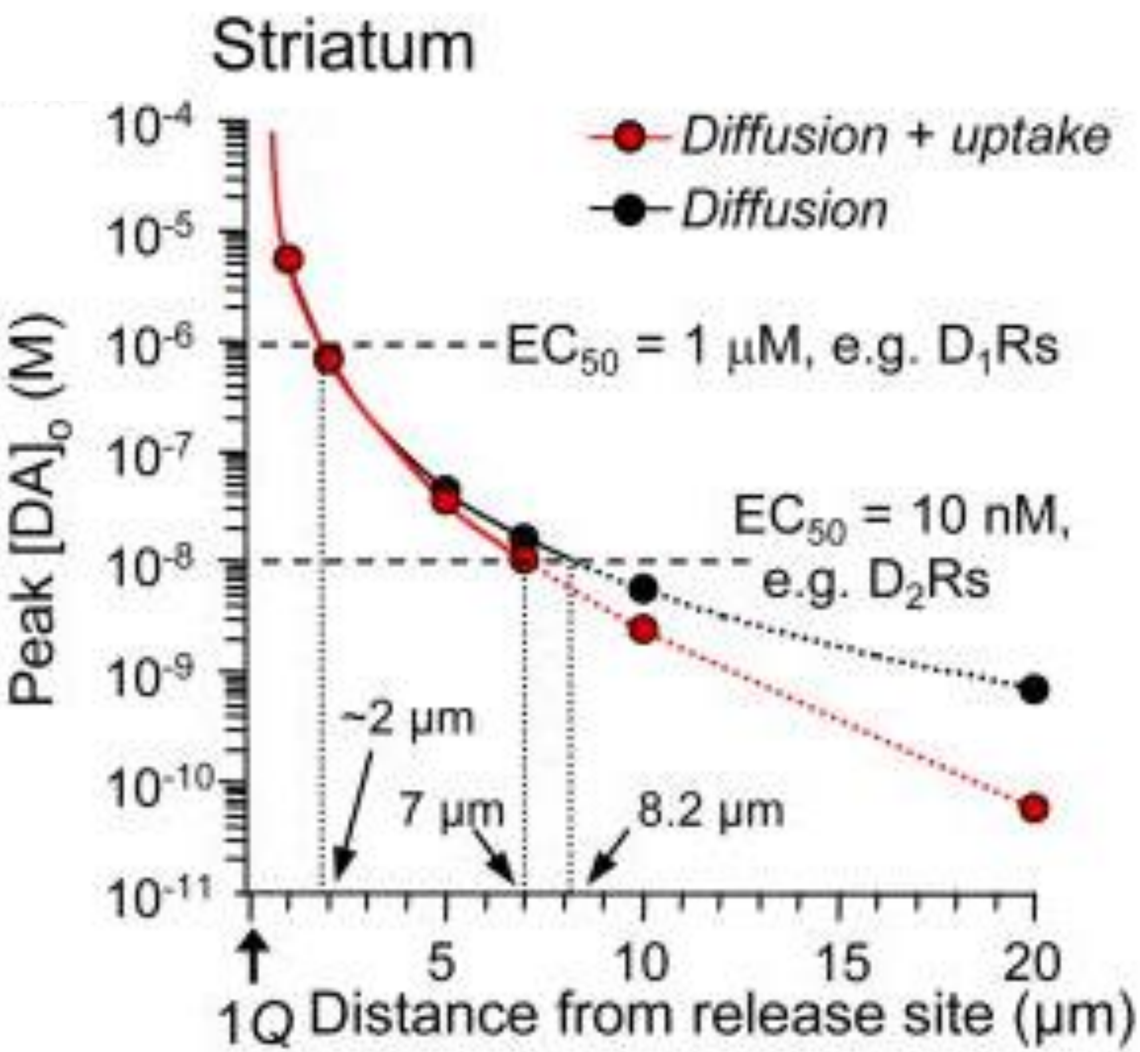


Some cells use both mechanisms

Can tell by different sizes of vesicles (yellow and orange)

Deniz Atasoy, J. Nicholas Betley, Wei-Ping Li, Helen H. Su, Louis K. Scheffer, Julie H. Simpson, Richard D. Fetter, Scott M. Sternson

Neuro-modulators behave differently



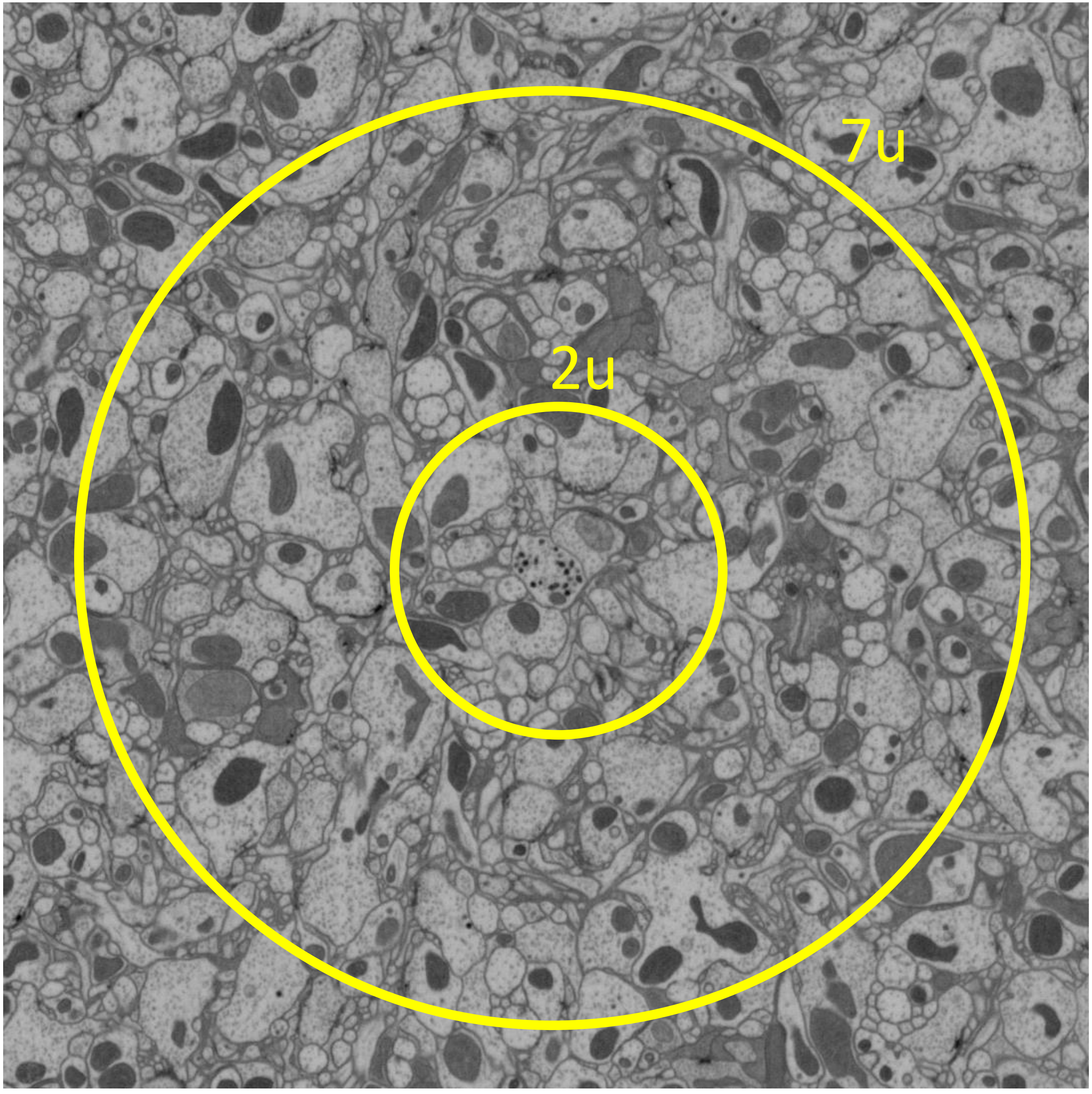
- Transmitter, uptake is rapid, only neighbor sees
- Modulator, uptake is slow
- Transport dominated by diffusion

Rice, Patel, and Cragg, Dopamine Release in the Basal Ganglia, Neuroscience 198:112-137, 2011

Neuro-modulators

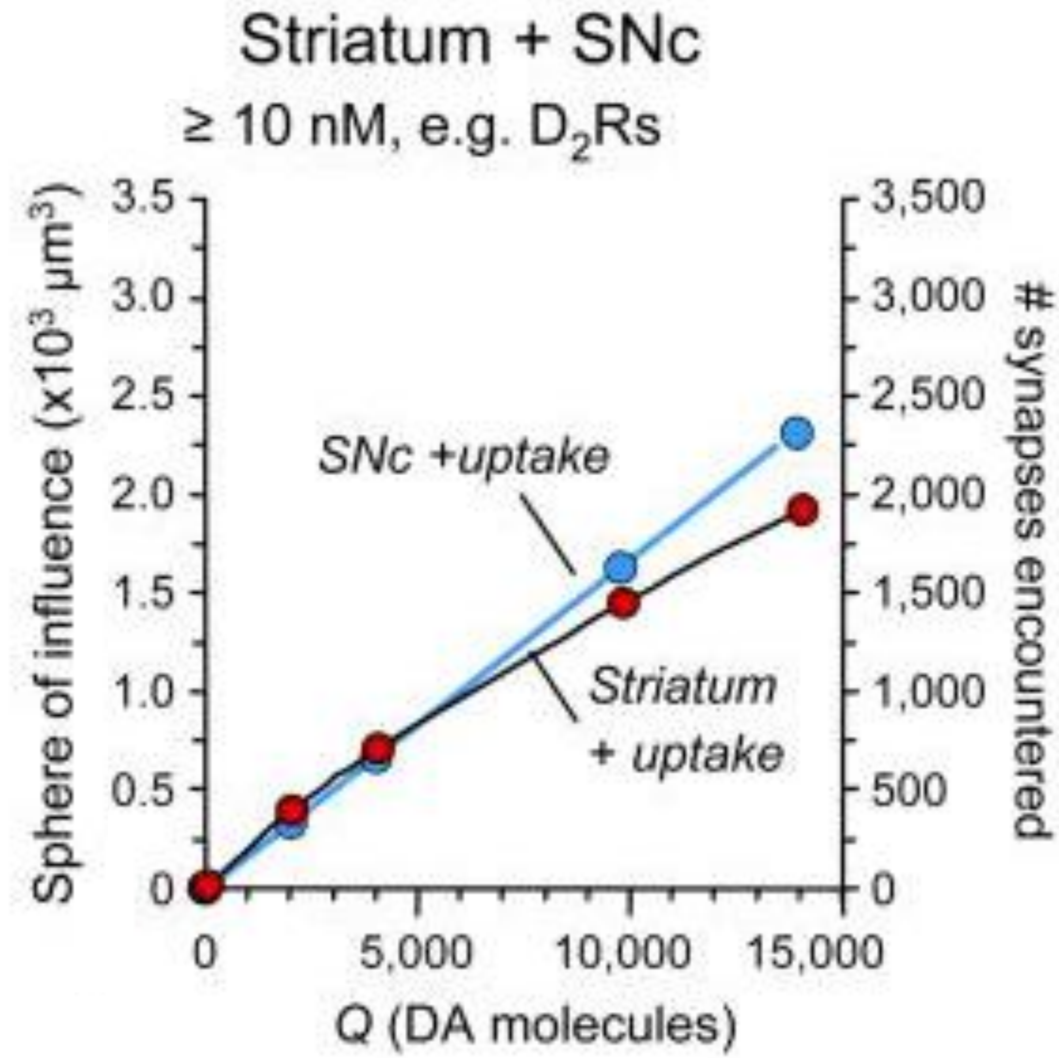
Range of influence includes hundreds of cells

Data from Zhi-Yuan Lu, Shan Xu, Harald Hess.



Influence depends on strength

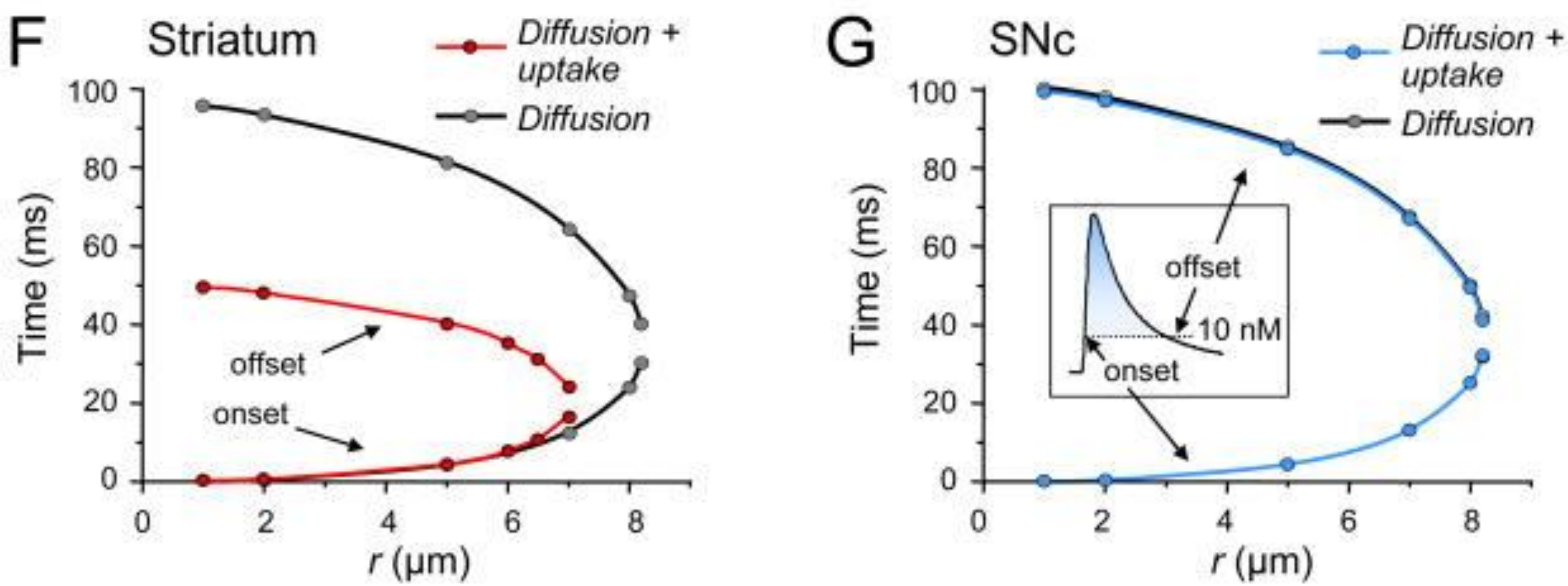
- Plot of volume (left) and number of synapses (right) vs. number of molecules released.



Rice, Patel, and Cragg, Dopamine Release in the Basal Ganglia, Neuroscience 198:112-137, 2011

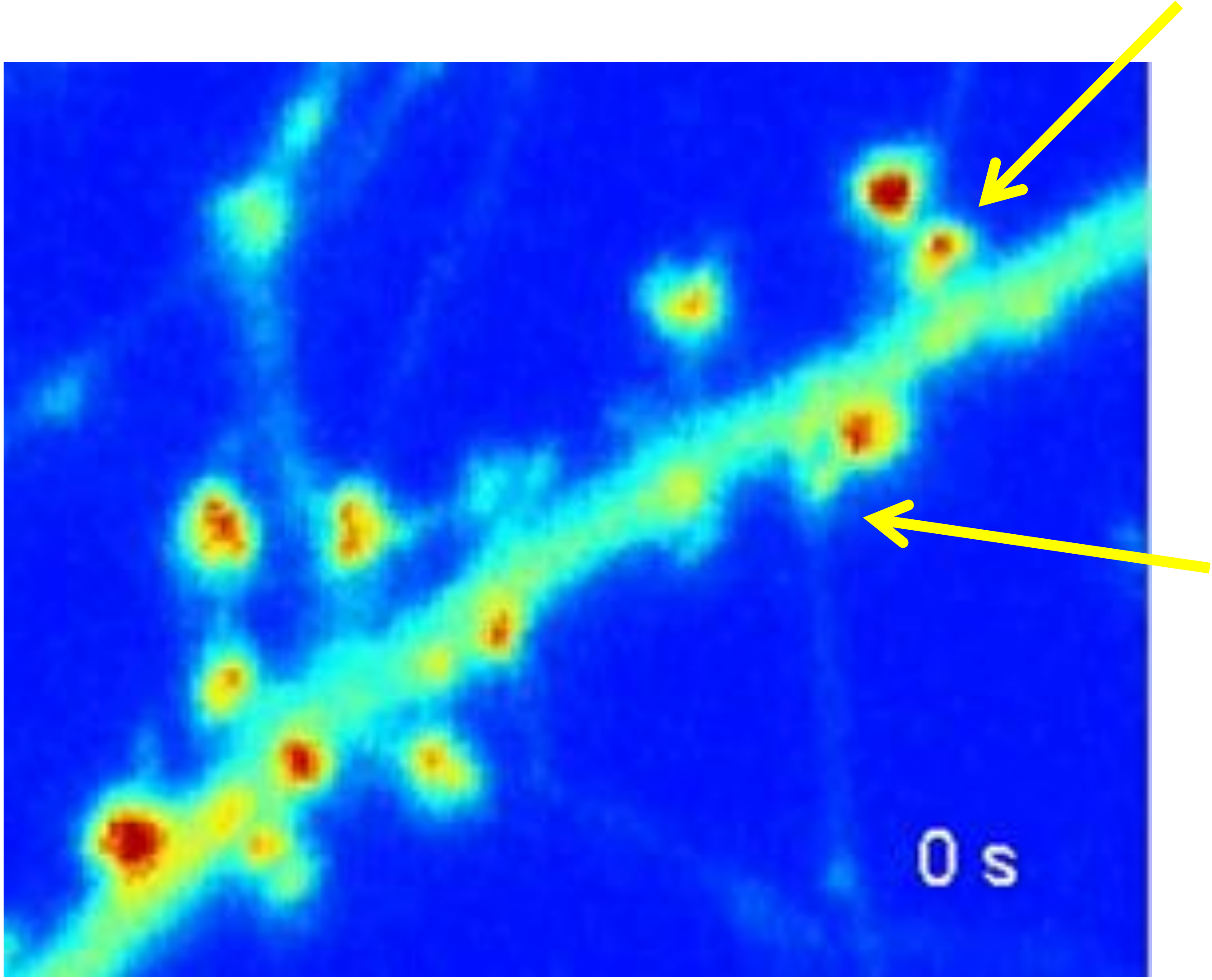
Active time depends on distance

- On and offset times vs distance away



Rice, Patel, and Cragg, Dopamine Release in the Basal Ganglia, Neuroscience 198:112-137, 2011

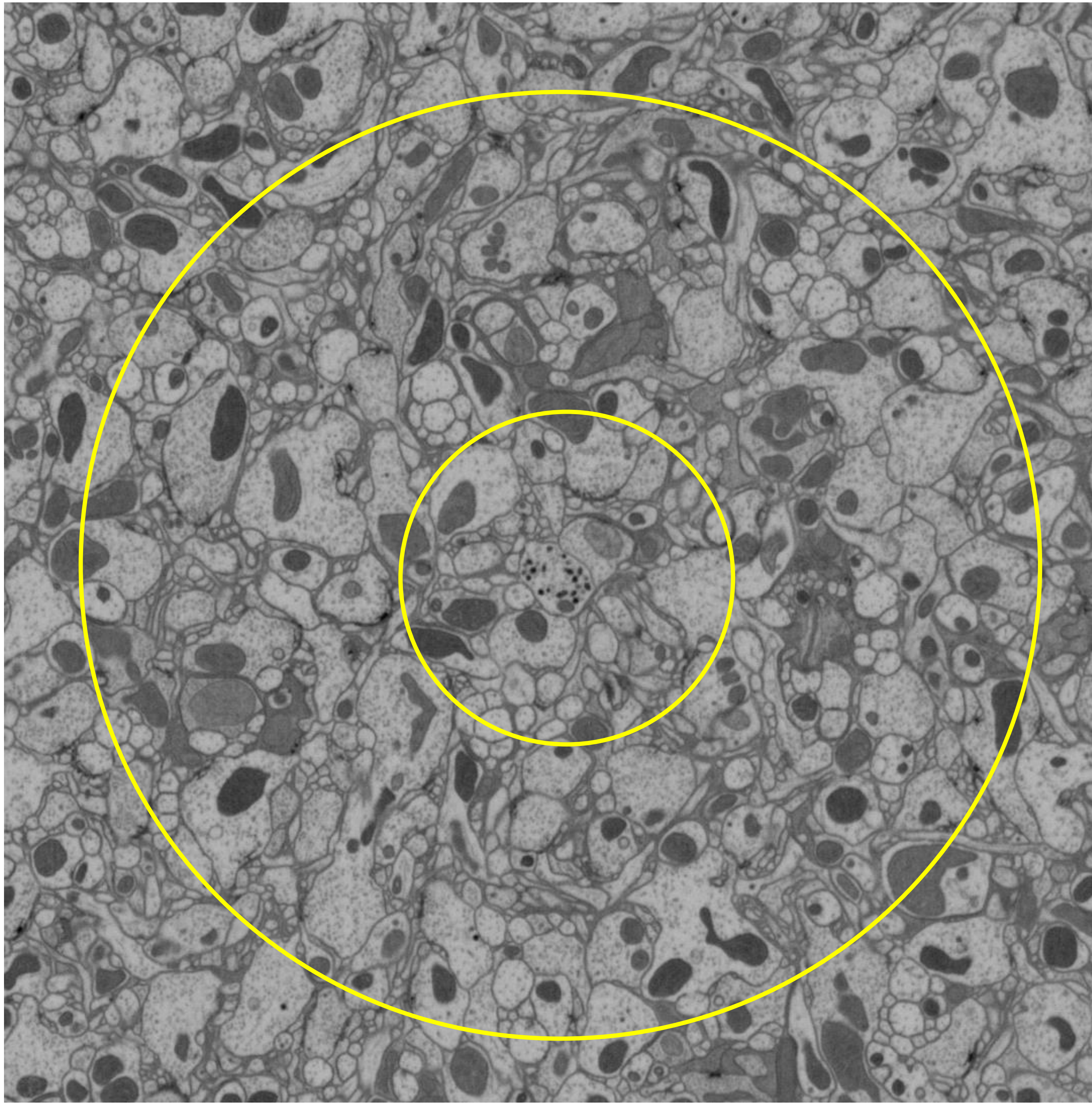
Lesson #5: Time varying circuits



Svoboda et al,
Janelia, HHMI

From how far away can a cell make new connections ??

We don't know the mechanism!



Conclusions

- Considerable progress in understanding the brain
- Biological computation uses many mechanisms
  - Computationally complex cells
  - Highly connected networks
  - Active substrates
  - Long range communication
  - Time varying circuits
- These tricks may be needed, or may be artifacts,
- But neuromorphics needs to understand them

The end

Circuit types and status

- Hardwired circuits (vision system)
  - Same from animal to animal
  - Making good progress
- PLA like systems (olfactory)
  - Every animal different, but in standard ways
  - Harder, but technical advances should suffice
- Fully programmable and time varying (cortex)
  - New ideas are needed