EDA and Biology of the nervous system

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Our Goal: Understanding the Brain

- Many approaches are possible; almost all are being tried
  - Study the behavior of the organism and deduce brain function
  - Perturb the genetics and see how the function differs
  - Look at activity in areas of the brain
  - Statistical methods – look at large numbers of examples
- Each has limitations in terms of detailed understanding of function

Alternative: take it apart to see how it works

- Idea is as old as engineering
  - Children are known for this approach
  - Patent system is a result of this method's success
  - Lots of historical examples

- Used in biology for more than 400 years
  - Starting with circulation of blood in the middle ages

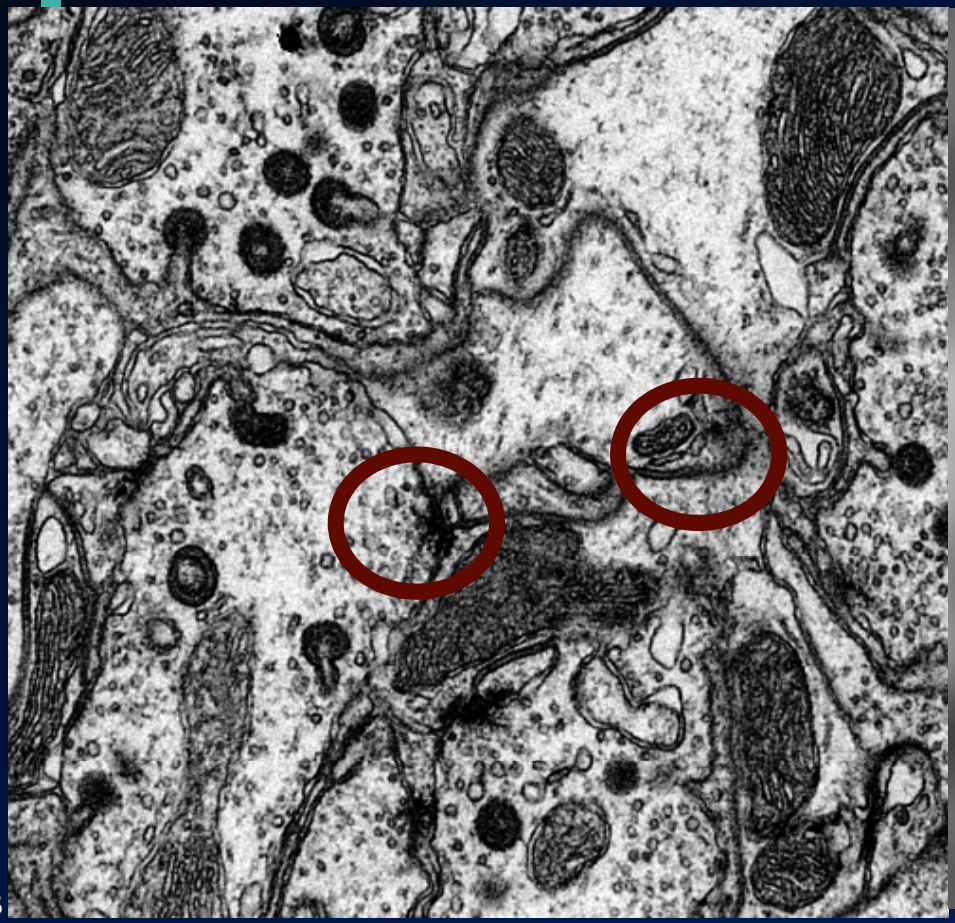
But looking at brain structure is hard

- Two main problems
  - Structures are very small
  - Network is very complex
- Until recently, only possible for very small animals with easy to resolve structure
  - C. Elegans, 302 brain cells, ~2K synapses
  - Took two decades and 10s of person-years

- Needed technical developments to make this feasible

Electron Microscopes make it possible

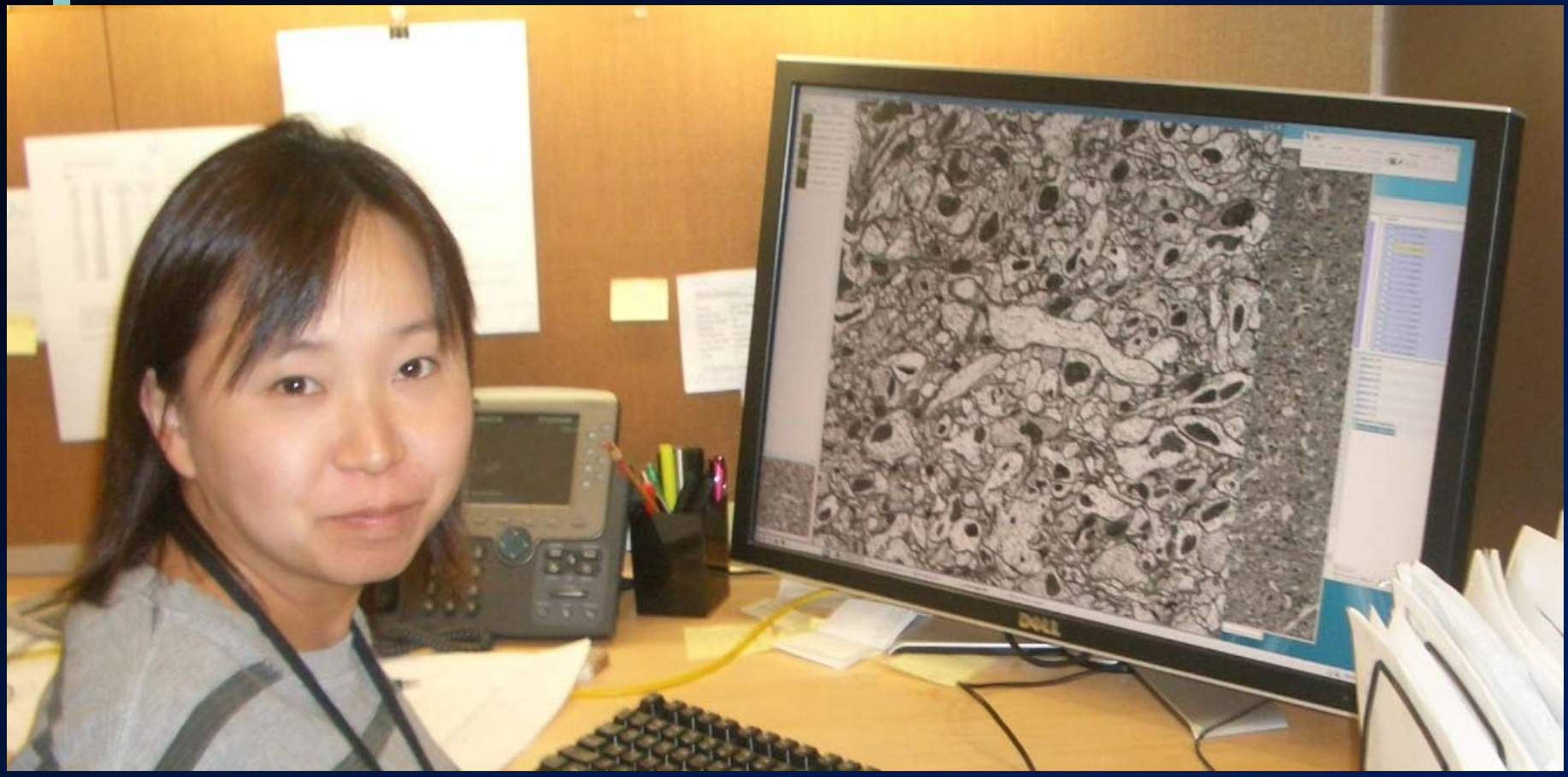
Electron microscope



Optical microscope

… But possible does not mean easy

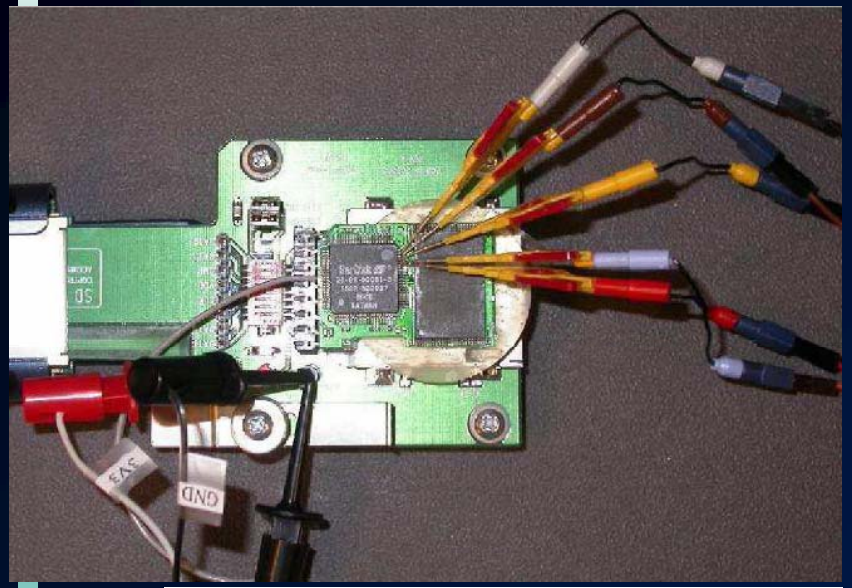
- Can do this manually now

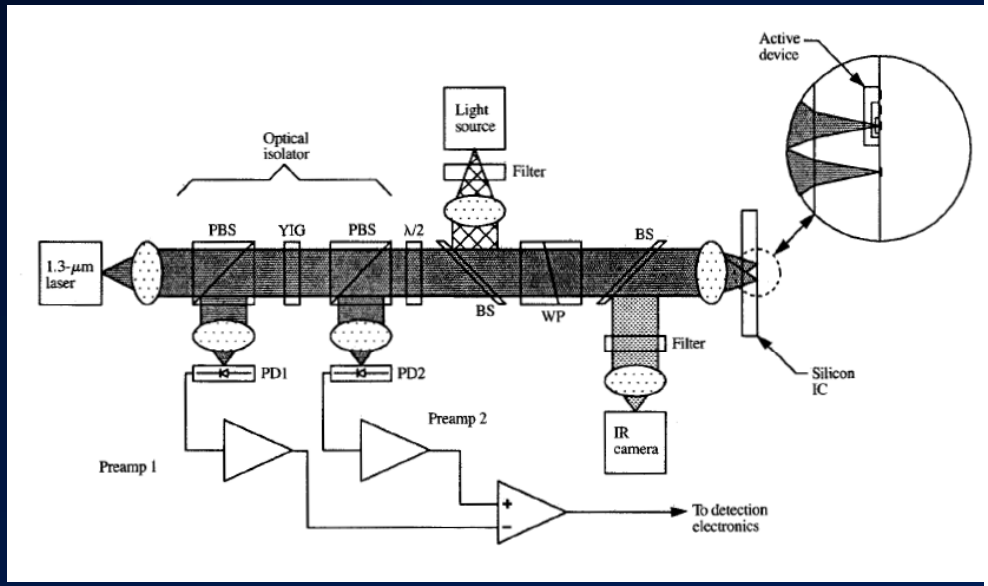


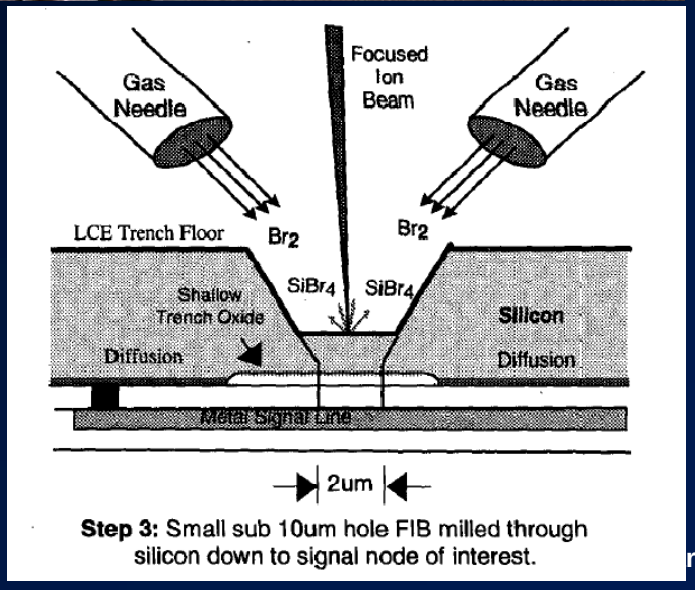
There is another field with almost exactly the same problems

- Finding out exactly how a chip works from a physical example
- Needed because
  - Chip is out of production and need a replacement
  - Military intelligence
  - Competitive analysis
  - Legal enforcements of patents
- Similar technical problems of feature size and complexity

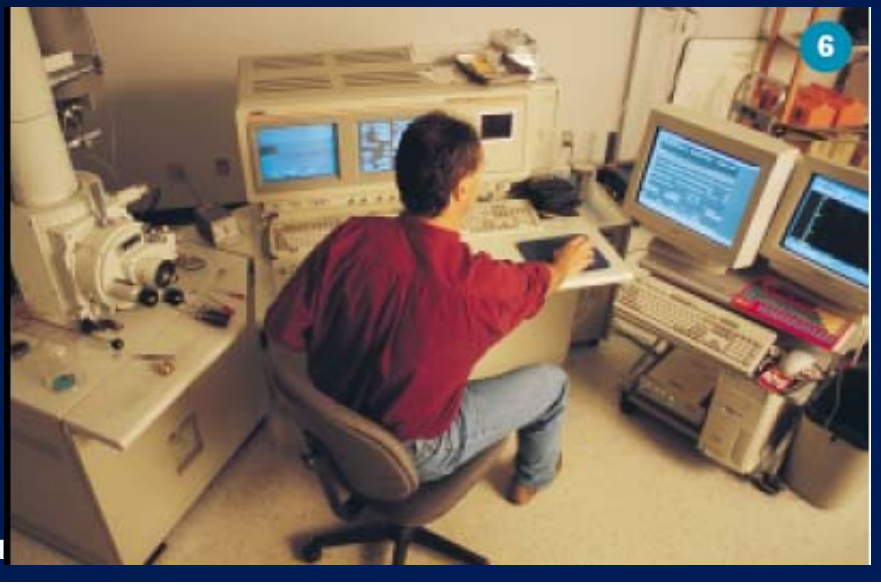
Equivalent techniques in both fields





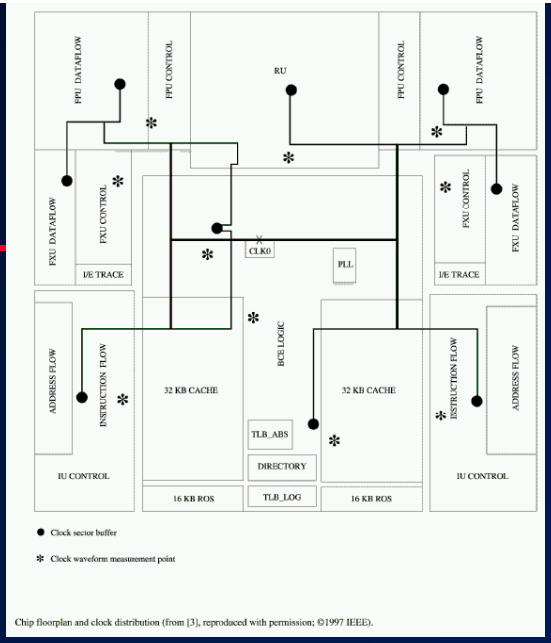


Step 3: Small sub 10um hole FIB milled through silicon down to signal node of interest.

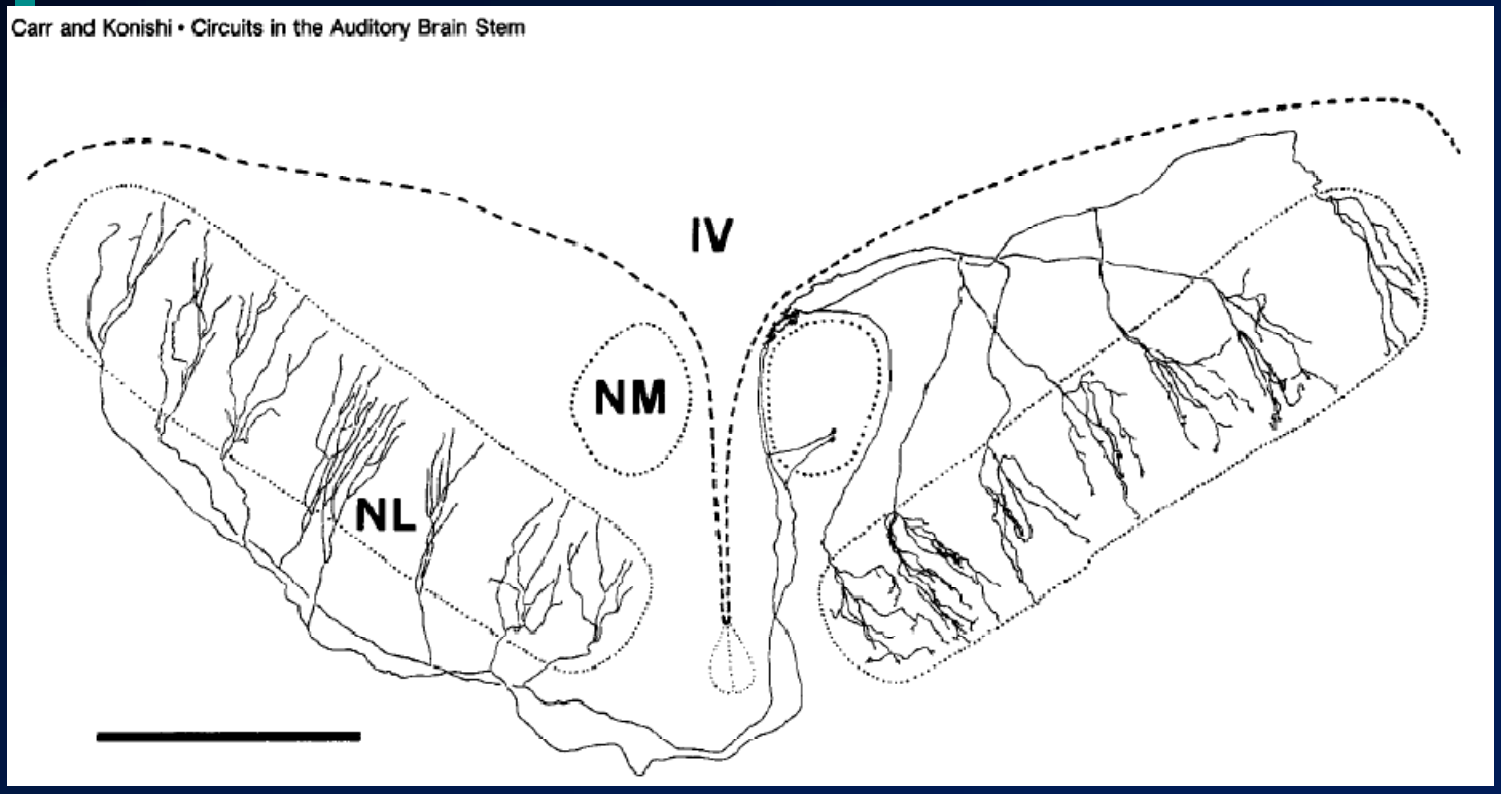


Equivalent structures in both

- Clock tree on chip (IBM)
- Auditory circuits of barn owl.



Chip floorplan and clock distribution (from [3], reproduced with permission; ©1997 IEEE).



Look at two problems analogous to EDA

- Simulation of network operations
  - Detailed simulation is ‘gold standard’
  - But most work happens at higher levels
    - Logic simulation
    - Macromodels
    - Timing analysis
  - Need similar ideas for biology
- Reconstruction of networks from library of parts
  - Both for correctness checking and understanding function

Detailed simulation is the gold standard in both fields, but not what you want for many problems

- SPICE and similar in EDA
- In biology, divide neurons into compartments, simulate at the detailed diff-eq and non-linear local operator level.
- But for looking at ‘big picture’, this is not what you want
  - Reduced models of many kinds (eg. delay)
  - Explicit coding of important variables (eg. Phase in oscillators)

A critical biology property is that networks change with time

- Neuromodulators affect a number of neurons at the same time
  - Best analogy, changing back-gate within a tub
  - But can be several at the same time, effect diffuses away as a function of distance, etc.
  - Seems a straightforward extension
- Neural networks form/remove connections as they operate.
  - “Nearly” nodes with “correlated” signals add/remove “connections”.

EDA extended to circuits that adapt/learn

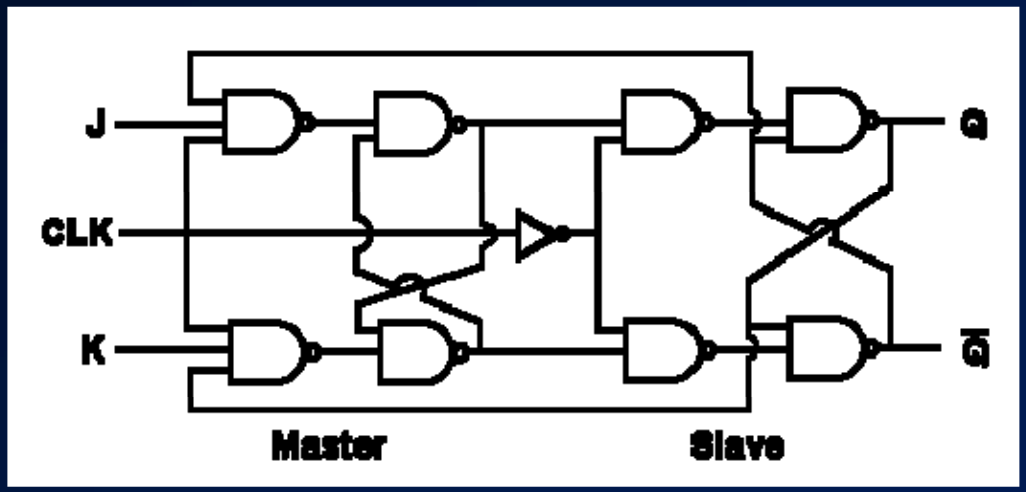
- Seems a natural extension of SPICE type technology
- Could be a huge breakthrough when figured out
- Natural area of cooperation between biology and EDA
- EDA is the best ‘base’ set of ideas for understanding this.

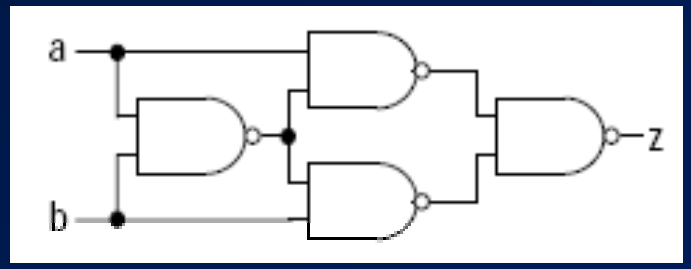
Other possible EDA/CS techniques to extend

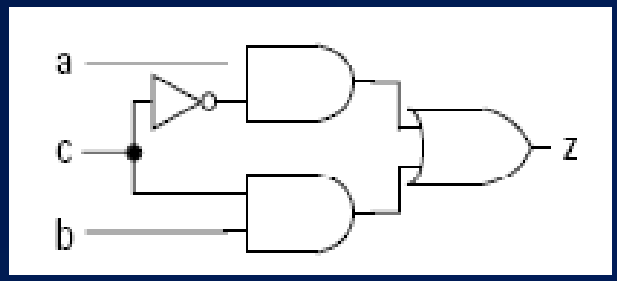
- Make automatic inferences more accurate by replacing hard decisions by probabalistic techniques
- Incorporate biological prior information in reconstruction
- Improve productivity using experience with similar graphical systems
- Attack up front the problems of a globally distributed, multi-group effort
- Plus many more speculative lines of attack

Use constraint that design uses known parts

- Chips are built from about 100 basic patterns
  - Three are shown below
- If you find something that is not one it's an error (usually) or a novel structure

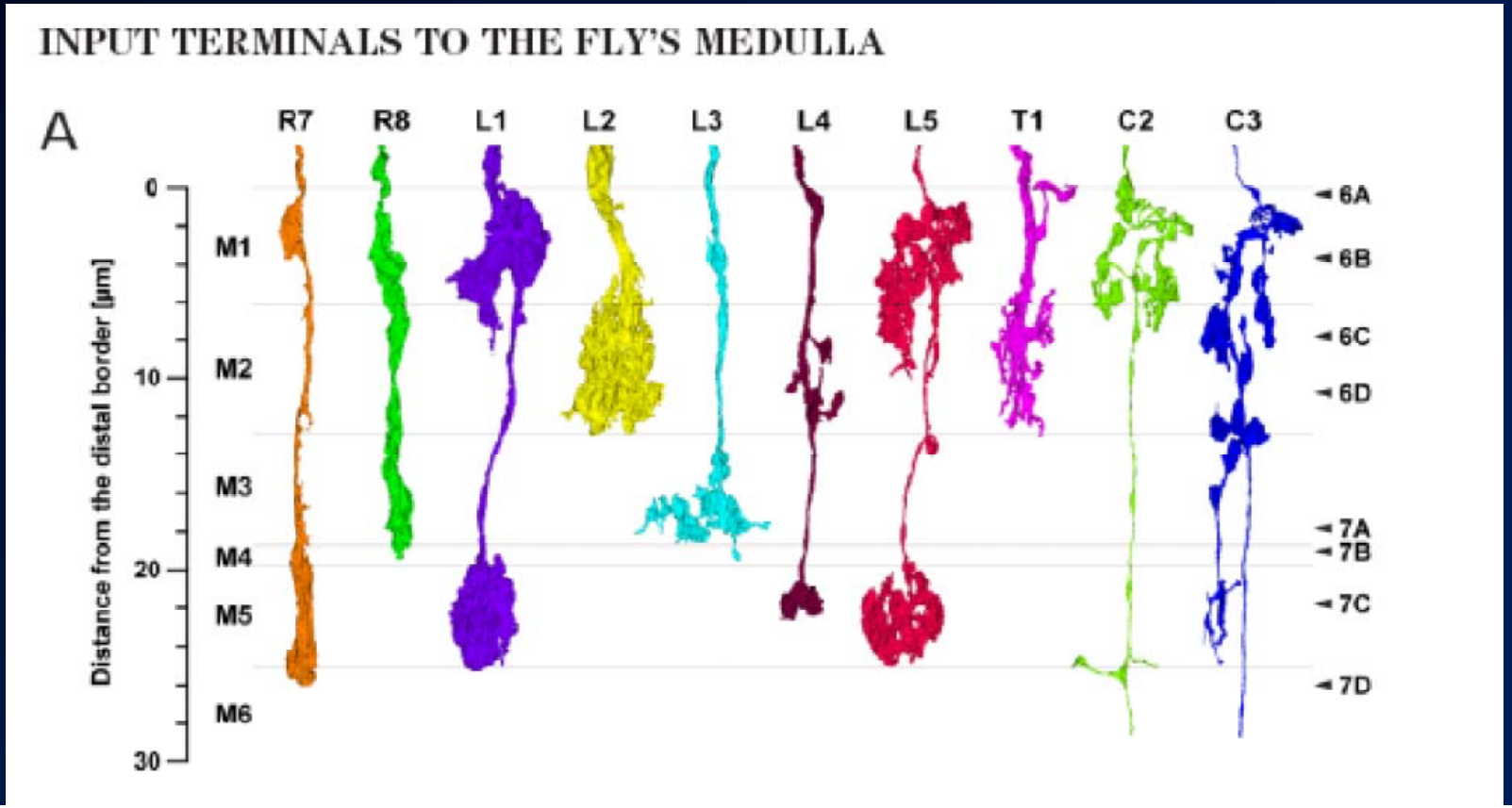






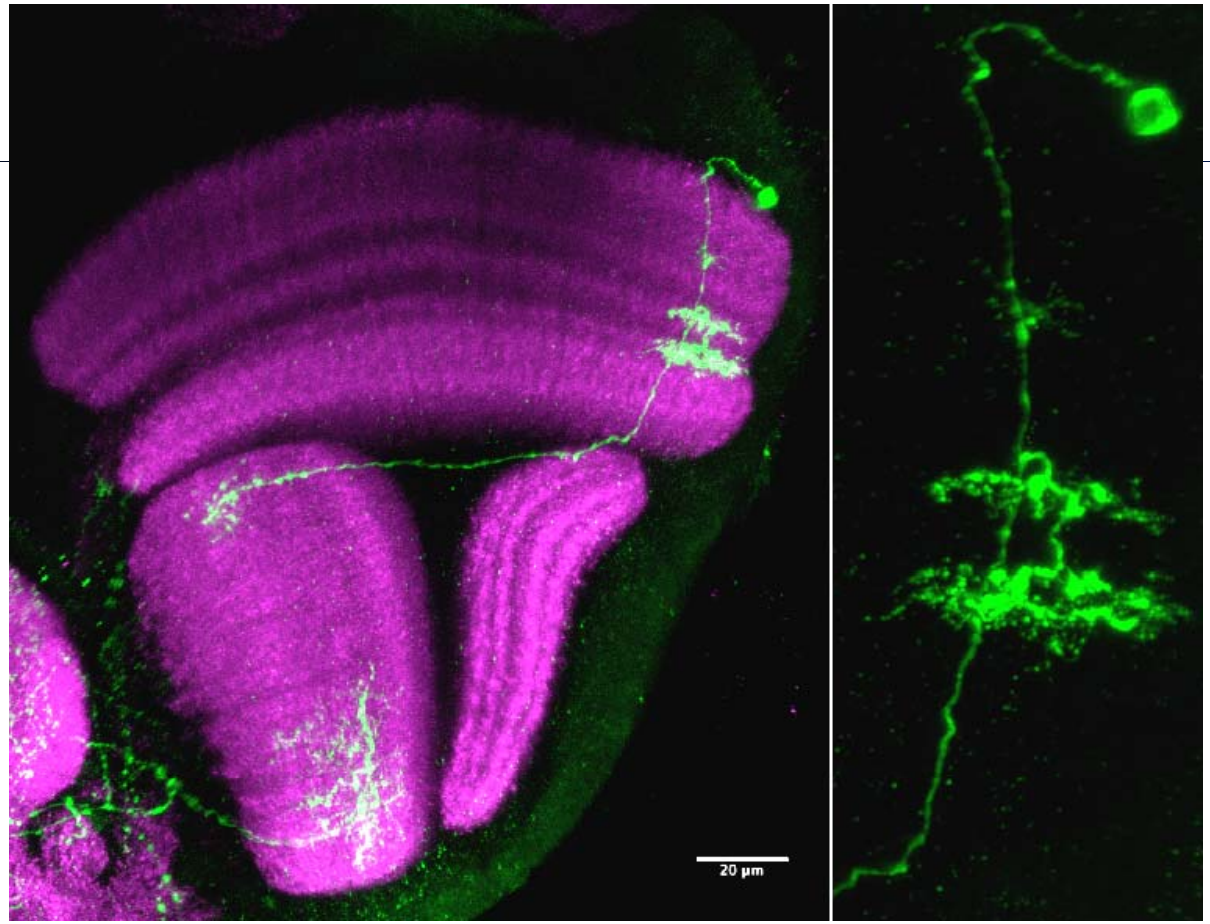
Use similar constraints from biology

- Genetics plus staining and optical techniques give us the library
  - Example – cells that go from the lamina to the medulla



Optical/genetic techniques give us the catalog

- Work of A. Nern at HHMI



- Cannot show connections, but can show each type of component.
- Like a computer, millions of parts but only hundreds of types

Conclusions

- EDA is our best ‘base’ technology for understanding biological networks
  - Changes to circuit simulation to understand biological functions
  - Circuits that ‘learn’, or even ‘adapt’, would be a huge breakthrough. (but high risk, might be premature)
- EDA and other CS fields are most natural base for reverse engineering the brain
  - Much less speculative research, though hard
  - Understanding needed for the breakthrough above