The Connectome: challenges and approaches

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Outline

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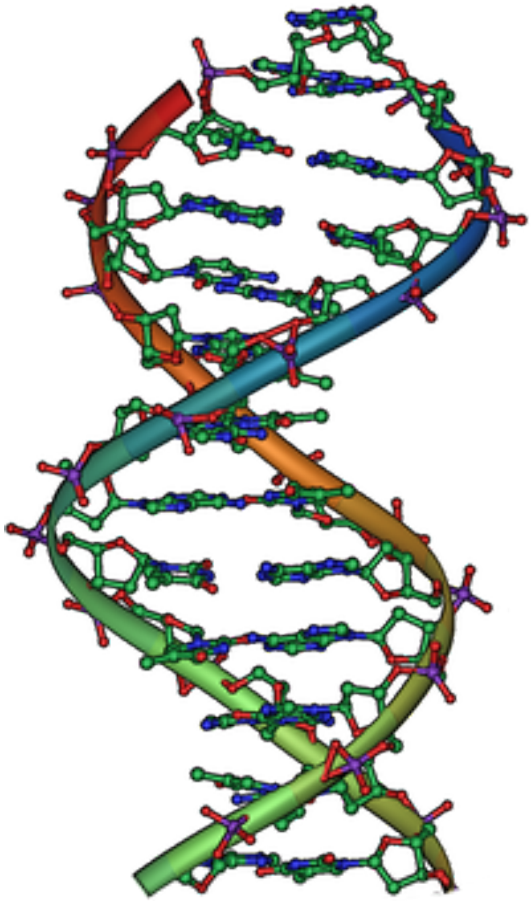
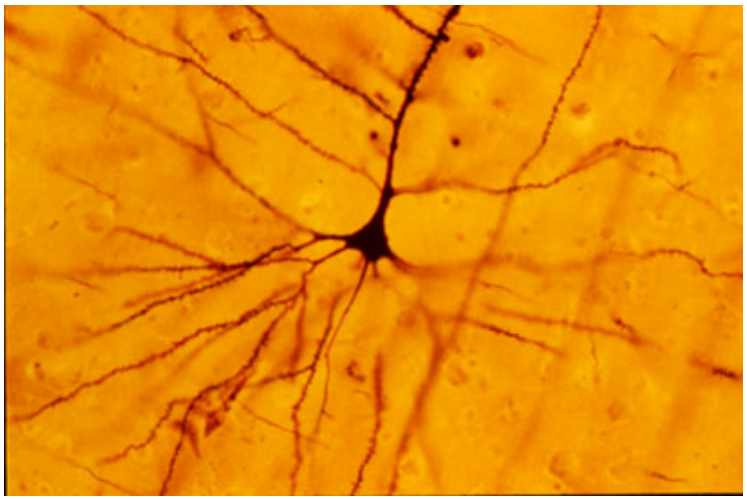
What is the connectome?



http://en.wikipedia.org/wiki/Genome

- The human genome project maps human DNA physically and functionally.

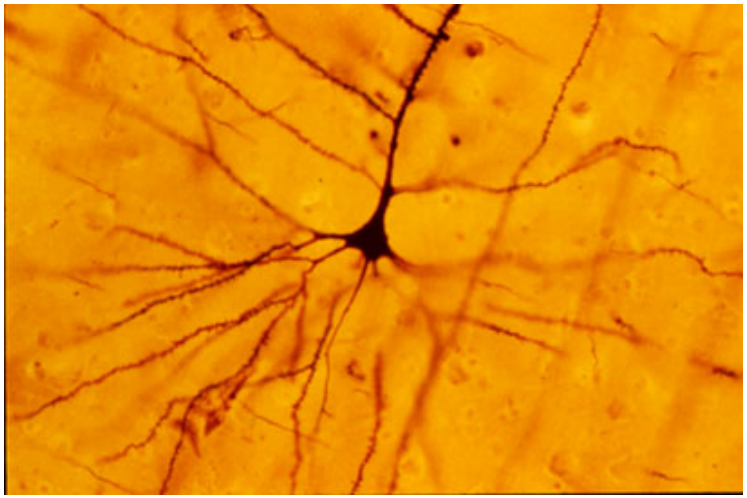
What is the connectome?



http://en.wikipedia.org/wiki/Golgi's_method

- The connectome is the "comprehensive structural description of the network of elements and connections forming the human brain." [Sporns et al., 2005]

What is the connectome?

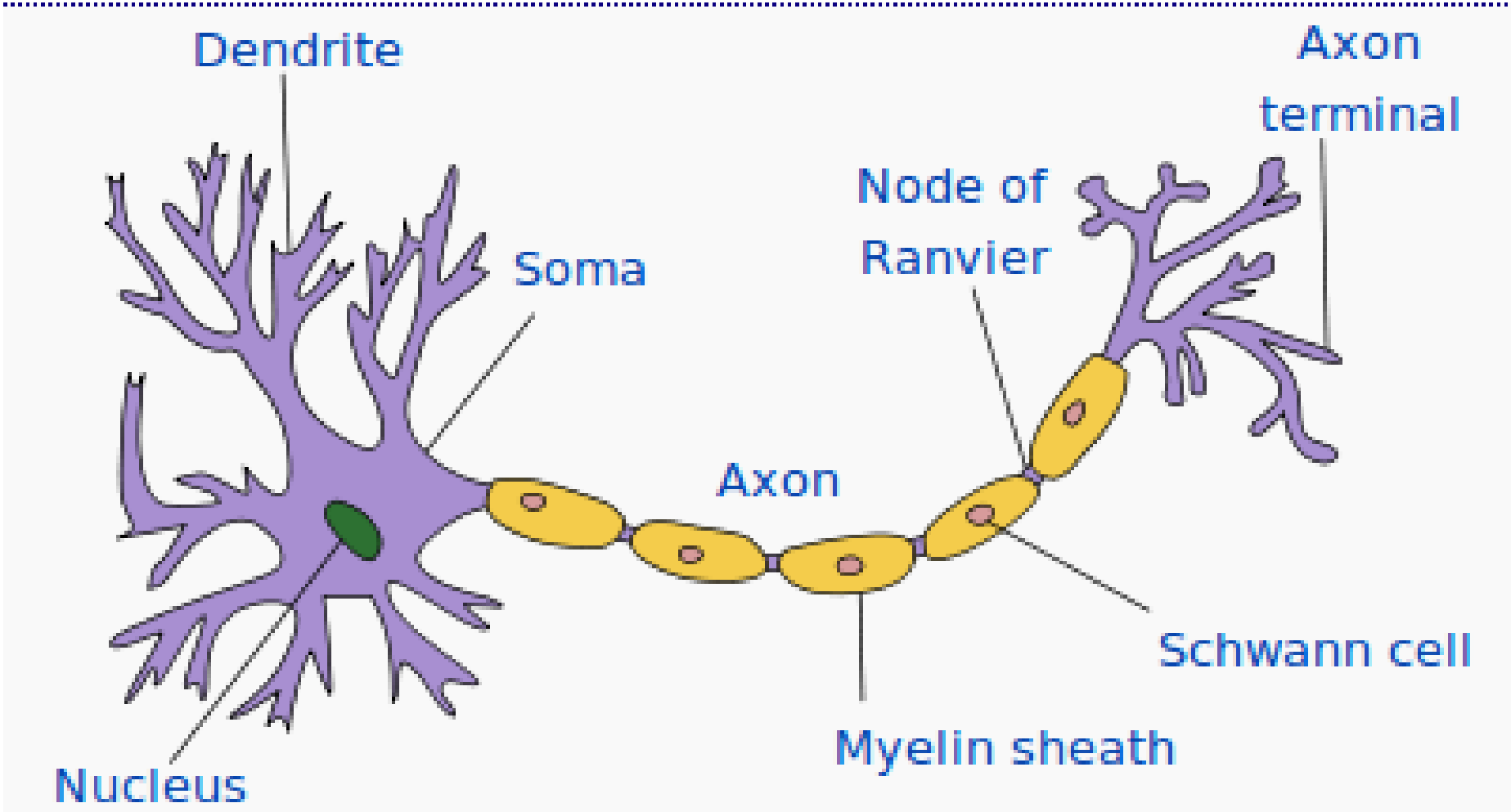


http://en.wikipedia.org/wiki/Golgi's_method

- "It is clear that, like the genome, which is much more than just a juxtaposition of genes, the set of all neuronal connections in the brain is much more than the sum of their individual components.... One could consider the brain connectome, the set of all neuronal connections, as one single entity, thus emphasizing the fact that the huge brain neuronal communication capacity and computational power critically relies on this subtle and incredibly complex connectivity architecture."
[Hagmann, 2005]

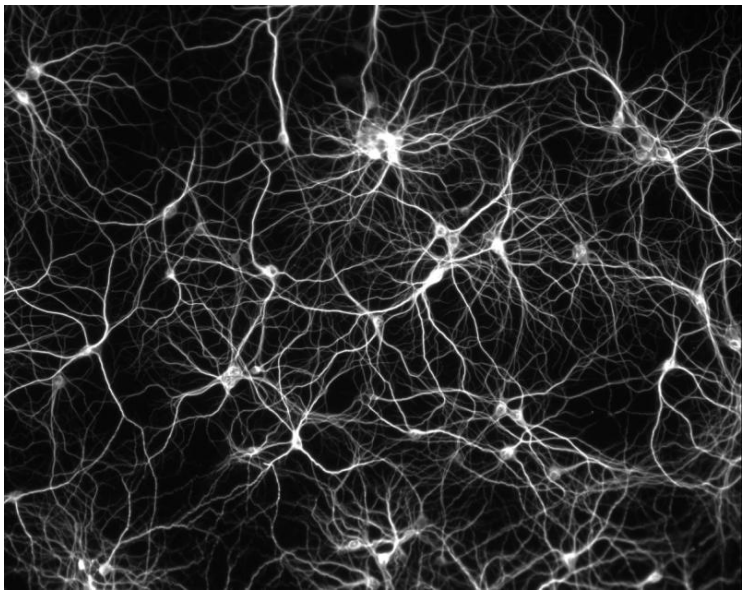
Outline

What is a neuron?



http://en.wikipedia.org/wiki/Neuron

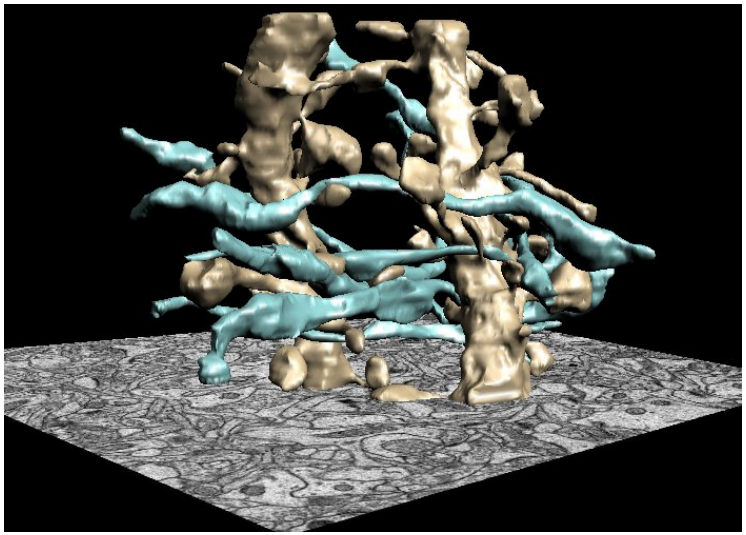
Challenges



http://www.homepages.ucl.ac.uk/~sjjgnle/

- Number of neurons in the human brain: 10^{10}
- Number of synaptic connections: 10^{14}
- Length of a typical dendrite from a pyramidal cell: several hundred microns [Megias et al., 2001]
- Total length (with branching) of an axon: many centimeters [Megias et al., 2001]

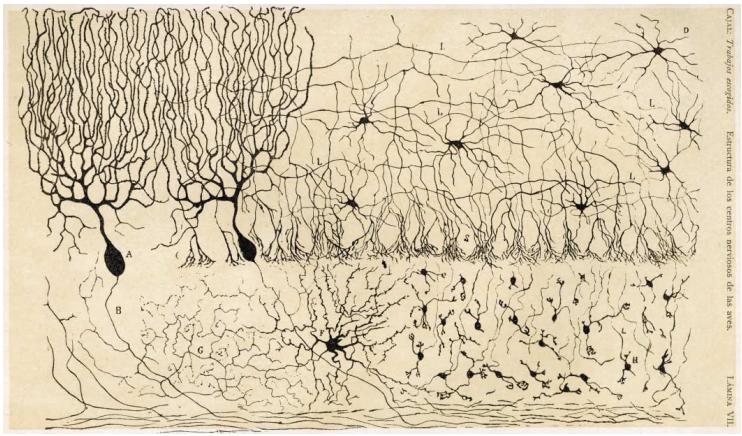
Challenges



- Diameter of axons: as low as 100 nm [Shepherd & Harris, 1998]
- Diameter of dendritic spine necks: as low as 50 nm [Fiala & Harris, 2005]
- Suppose 10 nm resolution. 1 mm^3 block requires 10^{15} voxels
- Primary issues:
  - Data collection
  - Data management
  - Data analysis

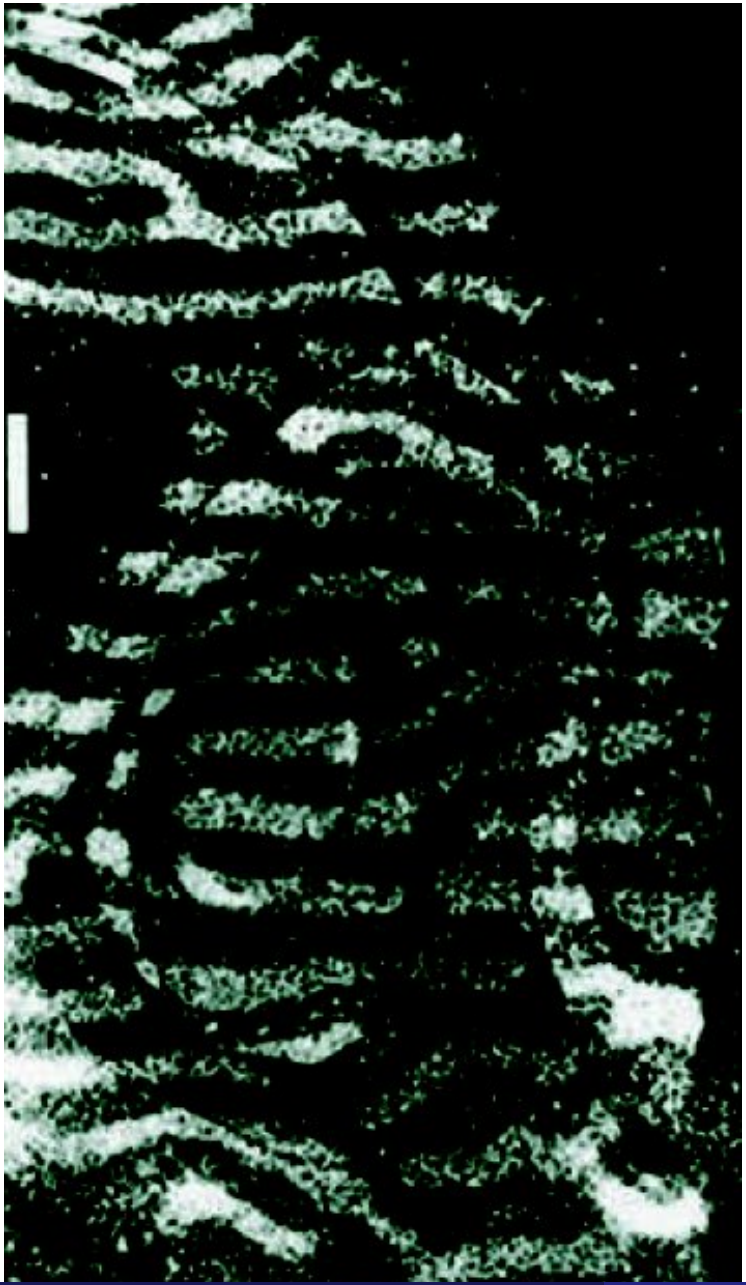
Outline

Methods - Staining



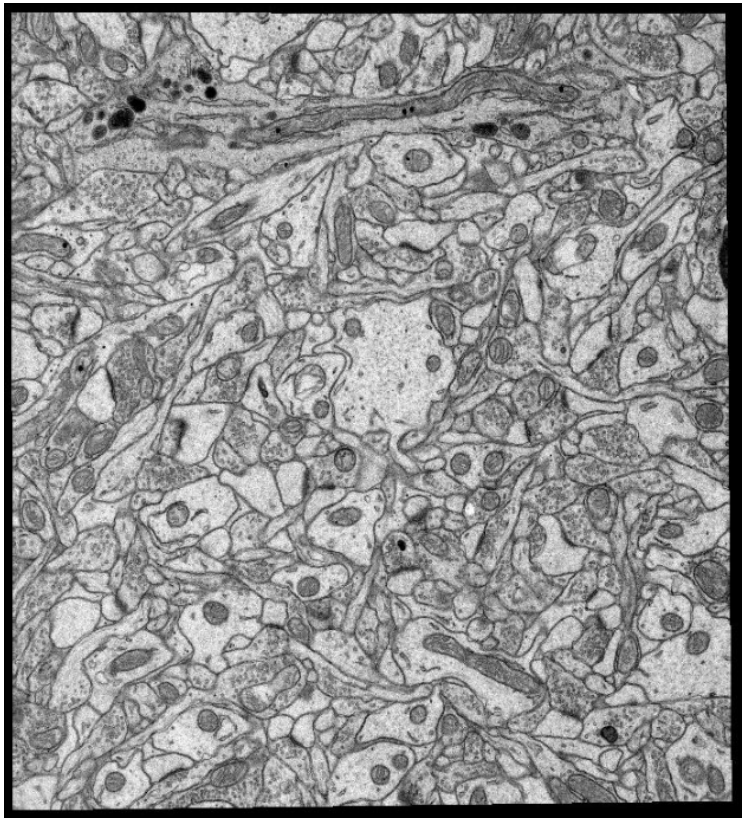
- Ramon y Cajal (1852-1934) produced excellent results from single-cell staining [Sotelo, 2003]
- This is known as the Golgi method [Golgi, 1873]
- Difficulties:
  - Can only stain a small subset of the neurons
  - Impossible to resolve between close neurons using light

Methods - Tracing



- Tracing involves introducing a labeling agent
- Agents include genetically encoded "tracers", such as flourescent proteins or viruses [Song et al., 2005]
- Markings can be permanent
- Crosses synaptic boundaries
- Can span an entire circuit
- Disadvantages:
  - May not penetrate to extremeties or to all branchings
  - Still difficult to resolve between interlaced neurons

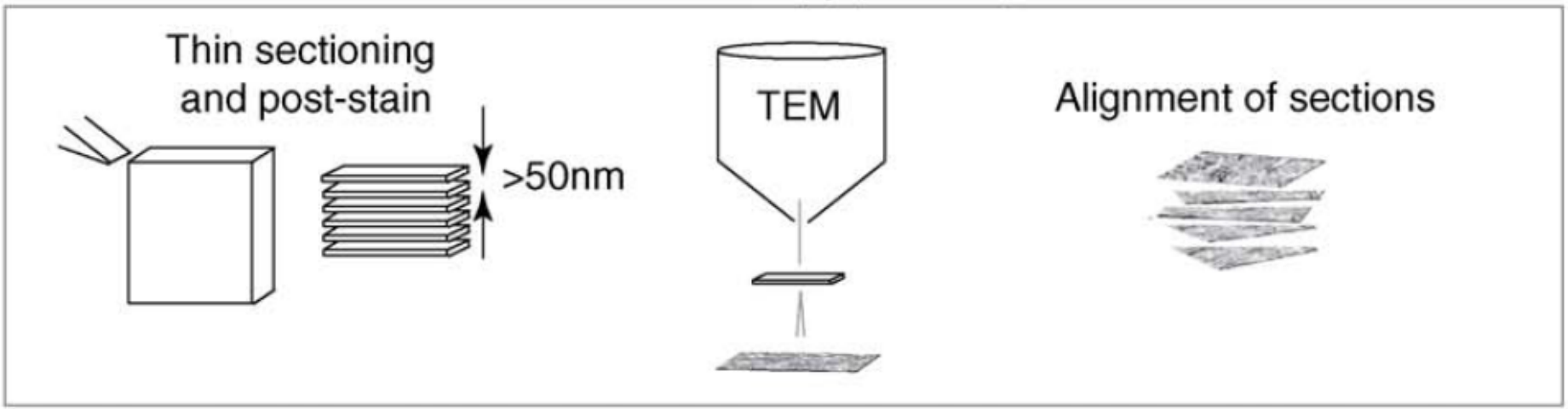
Methods - Electron Microscopy



- Gives resolution necessary to resolve neurons
- Limited viewport, compared to staining and tracing

Methods - ssTEM

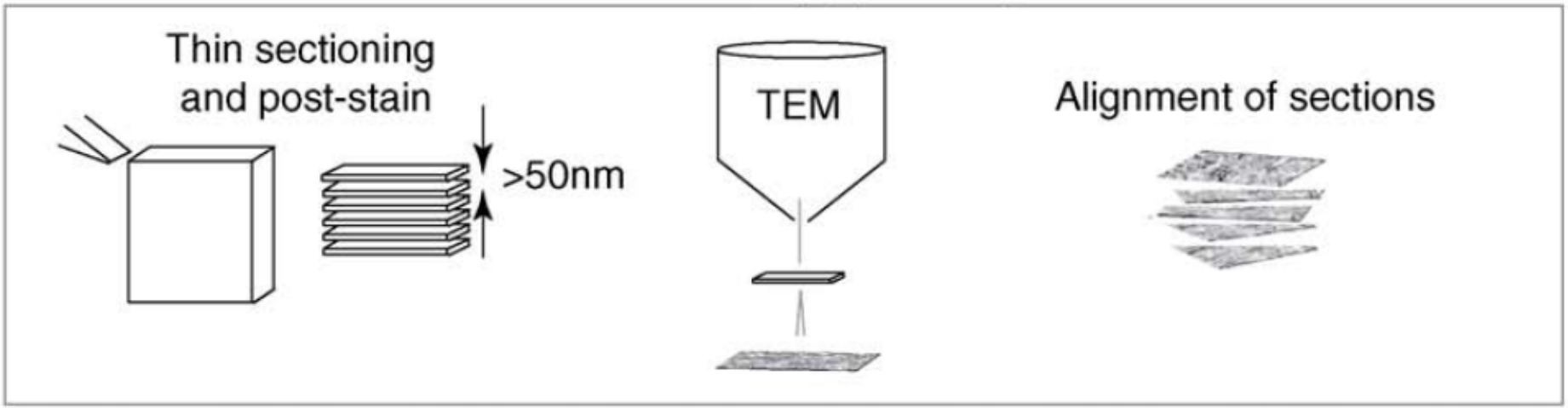
- Serial Section Transmission Electron Microscopy (ssTEM)
- Block (hundreds of microns thick) of brain tissue is "fixed" using adlehyde or by freezing
- Using diamond knife, slice block into 50 nm thick sections
- Image using a wide-footprint electron beam and capture transmitted electrons with film or CCD
- Typical datasets are 4K x 4K pixels with 2-10 nm in-plane resolution
  - Thus in-plane size is about 2 microns x 2 microns



[Briggman & Denk, 2006]

Methods - ssTEM

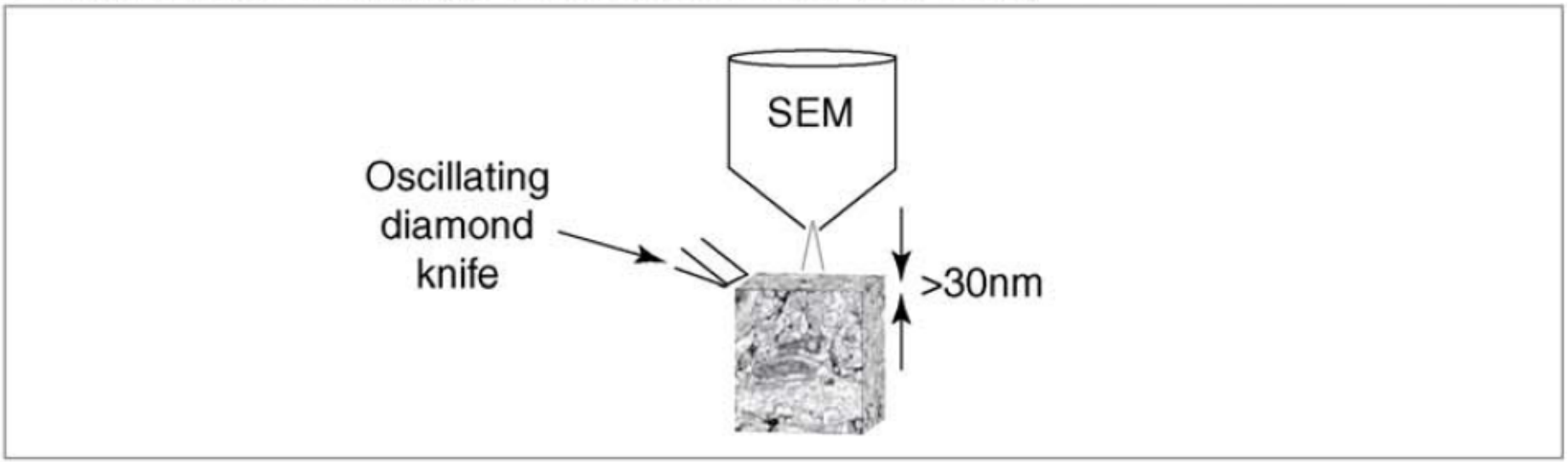
- Advantages:
  - Excellent in plane resolution
- Disadvantages:
  - Slices can tear, distort and get lost in sectioning process
  - Physical knife limits lateral (z-axis) resolution to tens of nm
  - Must montage to get larger view



[Briggman & Denk, 2006]

Methods - SBFSEM

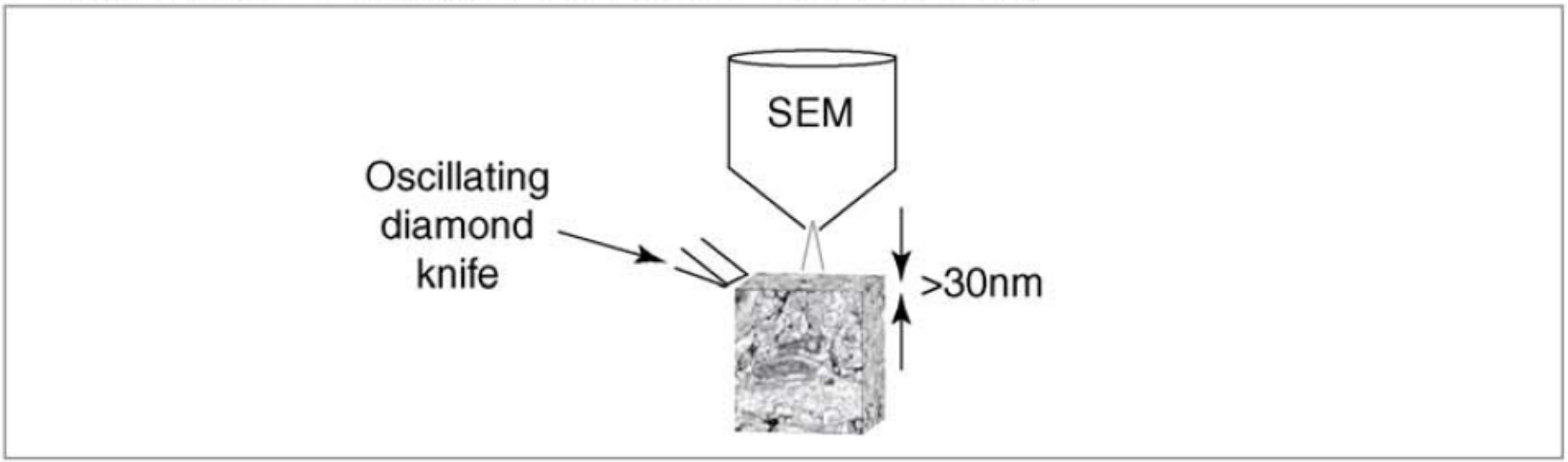
- Serial Block Face Scanning Electron Microscopy (SBFSEM)
- Block (hundreds of microns thick) of brain tissue is "fixed" using adlehyde or by freezing
- Image using a narrow scanning electron beam and capture scattered electrons with detector
- Using diamond knife, slice 30 nm top off block
  - This step can also be done using an ion beam to "mill" top off



[Briggman & Denk, 2006]

Methods - SBFSEM

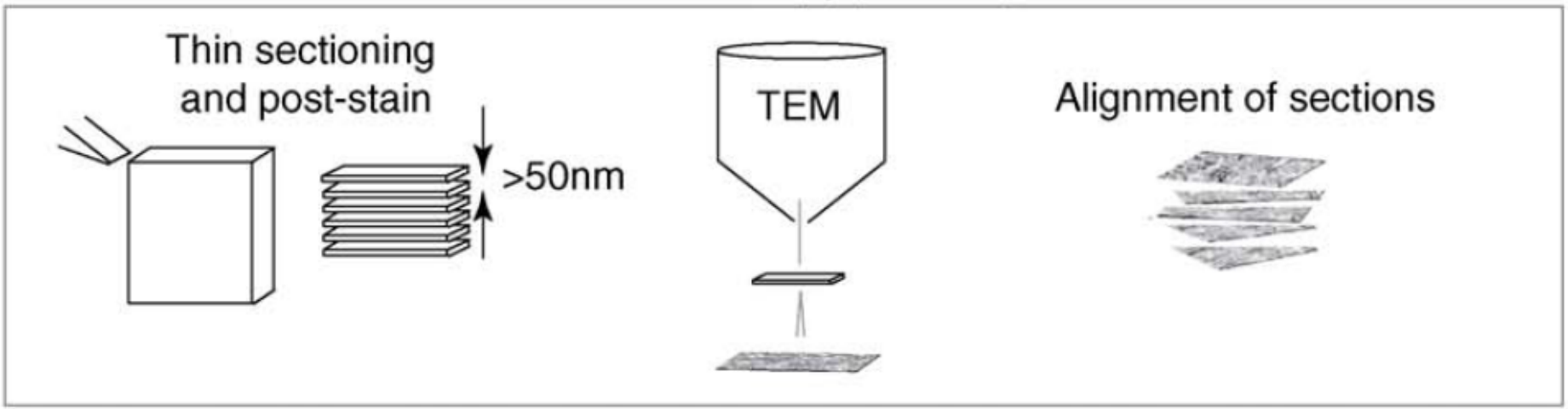
- Advantages:
  - The claim is that no registration (alignment of images) is necessary
  - Typical datasets have comparable resolution to ssTEM
- Disadvantages:
  - Physical knife limits lateral (z-axis) resolution to tens of nm
  - Must montage to get larger view
  - Some registration needed during montage



[Briggman & Denk, 2006]

Methods - ssSTEM

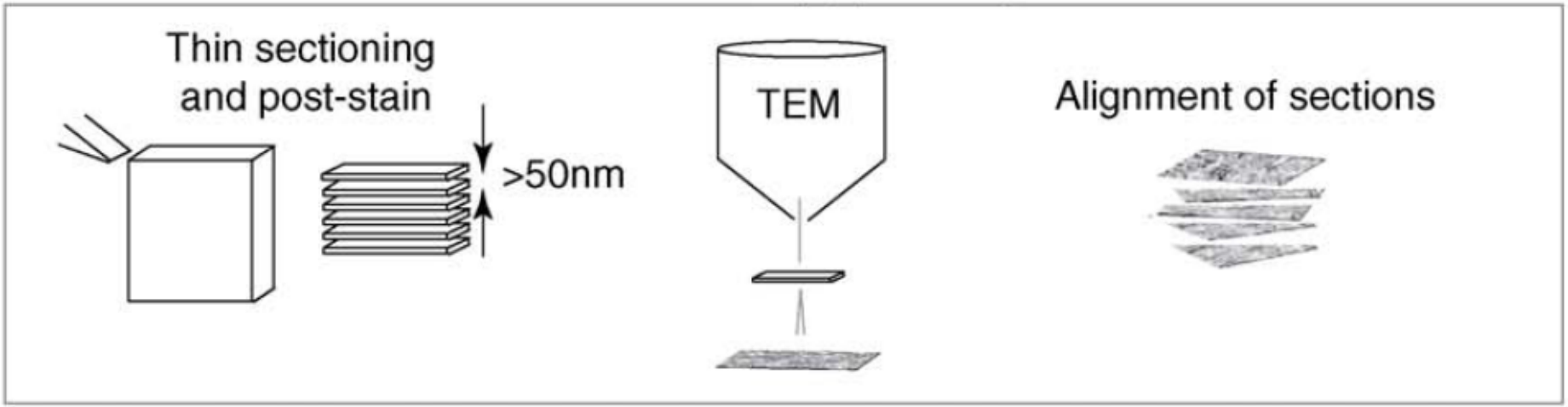
- Serial Section Scanning Transmission Electron Microscopy (ssSTEM)
- Block (hundreds of microns thick) of brain tissue is "fixed" using adlehyde or by freezing
- Using diamond knife, slice block into 50 nm thick sections
- Image using a narrow scanning electron beam and capture transmitted electrons with detector
- Typical datasets are 24K x 24K pixels with 2-10 nm resolution
  - Thus in-plane size is about 50 microns x 50 microns



[Briggman & Denk, 2006]

Methods - ssSTEM

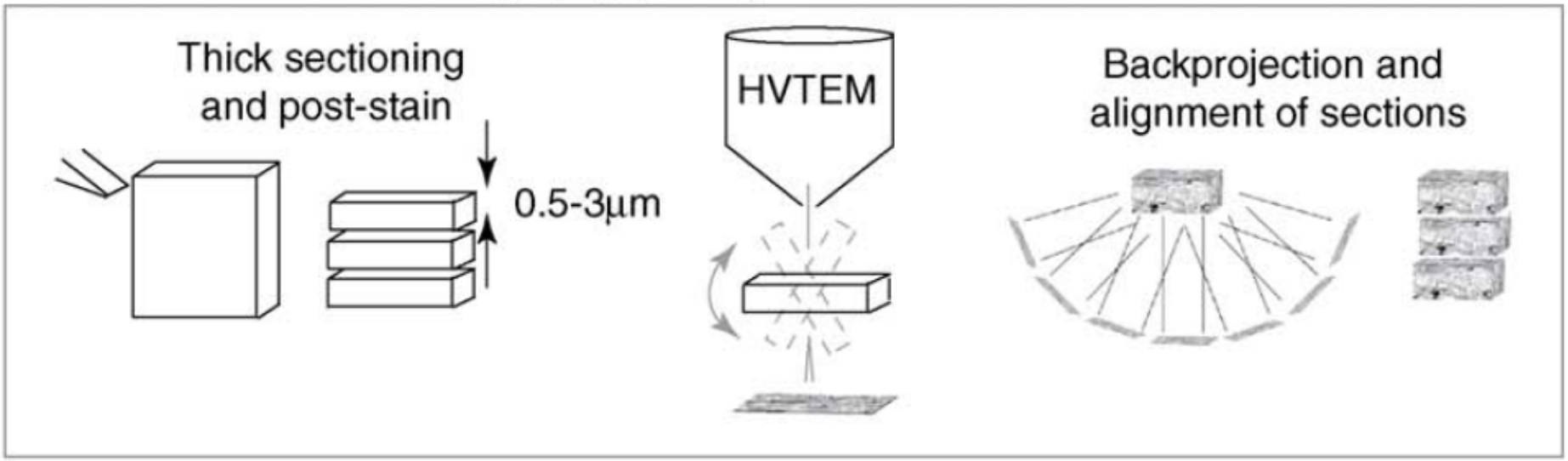
- Advantages:
  - Larger view than ssTEM or SBFSEM without stitching with comparable resolution
- Disadvantages:
  - Slices can tear, distort and get lost in sectioning process
  - Physical knife limits lateral (z-axis) resolution to tens of nm



[Briggman & Denk, 2006]

Methods - SSET

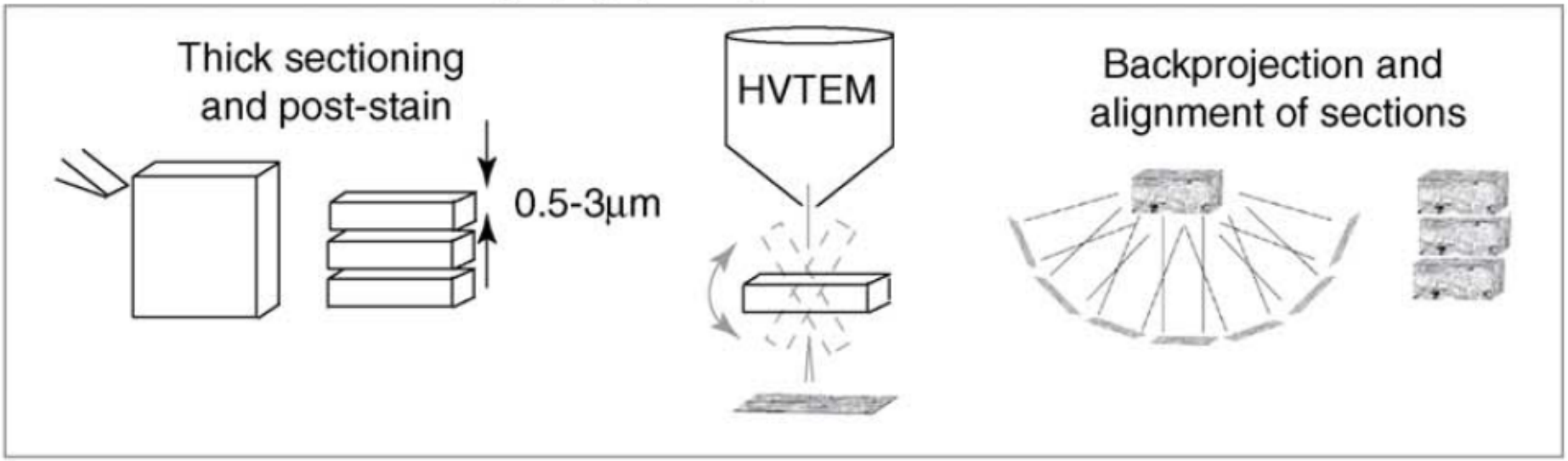
- Serial Section Electron Tomography (SSET)
- Improves lateral resolution by reconstructing from varying angles



[Briggman & Denk, 2006]

Methods - SSET

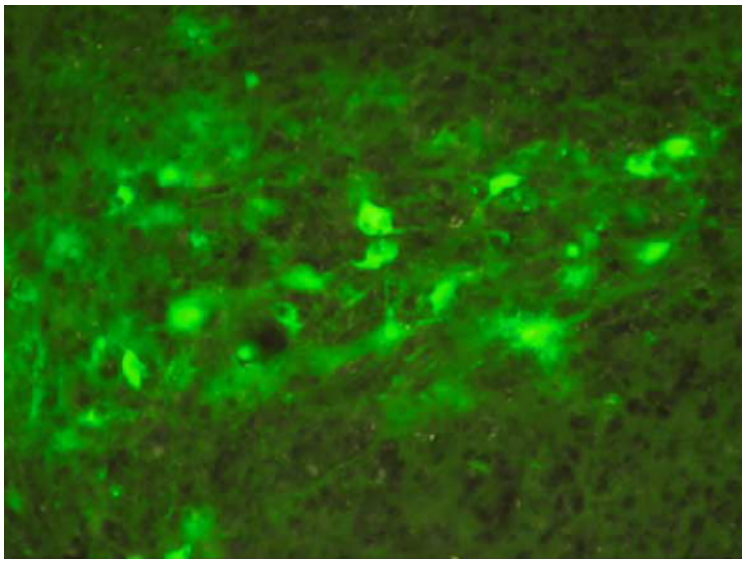
- Advantages:
  - Lateral resolution not limited by physical slice thickness - slices are usually 0.5-3 microns thick
- Disadvantages:
  - Shrinkage and distortion occur in sample from large electron doses



[Briggman & Denk, 2006]

Outline

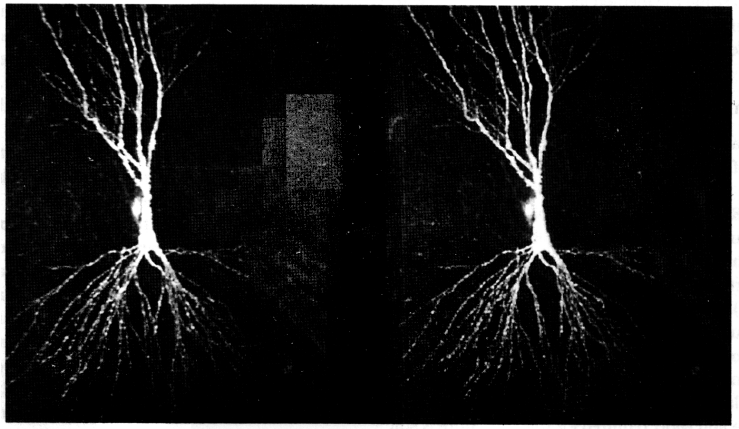
Stained/traced data



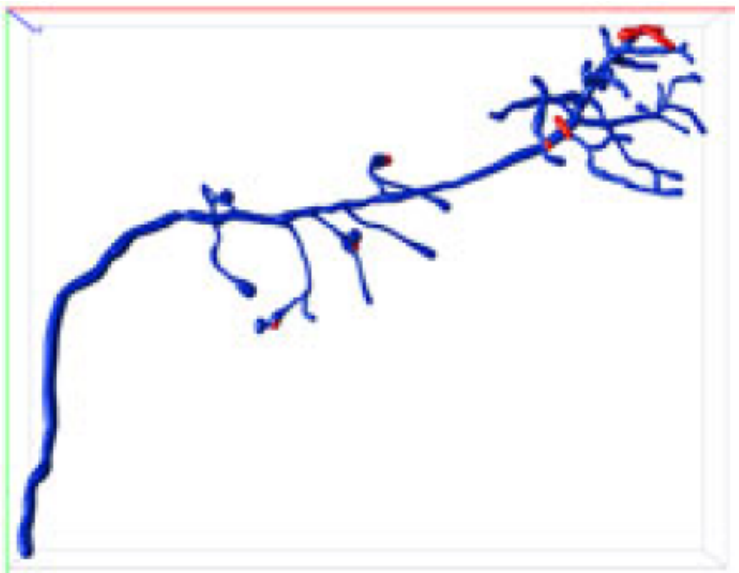
[Song et al., 2005]

- Stained and traced data is well-suited to topological reconstruction of neurons
- Largely an image processing problem
- Find tree structures and which neurons connect to which
- The recent Diadem challenge (`diademchallenge.org/`) focused on this problem

Stained/traced data



[Cohen et al., 1994]

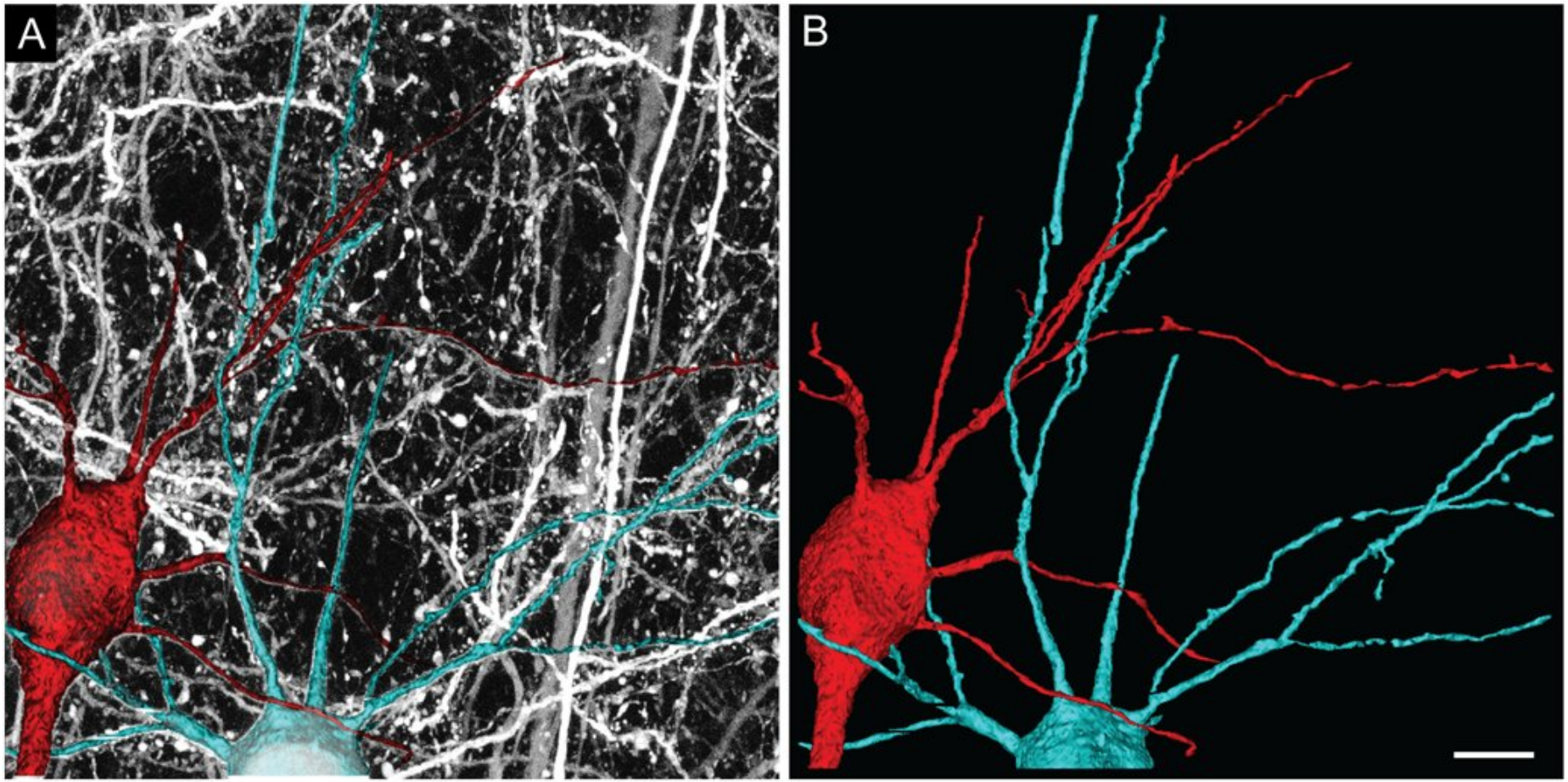


[Xie et al., 2010]

- First step in automatic tracing was [Cohen et al., 1994].
- A series of papers has followed, with [Xie et al., 2010] appearing as a result of the Diadem challenge.
- What is the state of the art?
  - The Diadem challenge grand prize was for any team that could speed up neuron tracing to 20 times faster than experts could trace by hand.
  - No team accomplished this goal. The best was 10-fold speedup.
  - For serious brain automation, we need 20,000-fold speedup.

Stained/traced data vs. EM

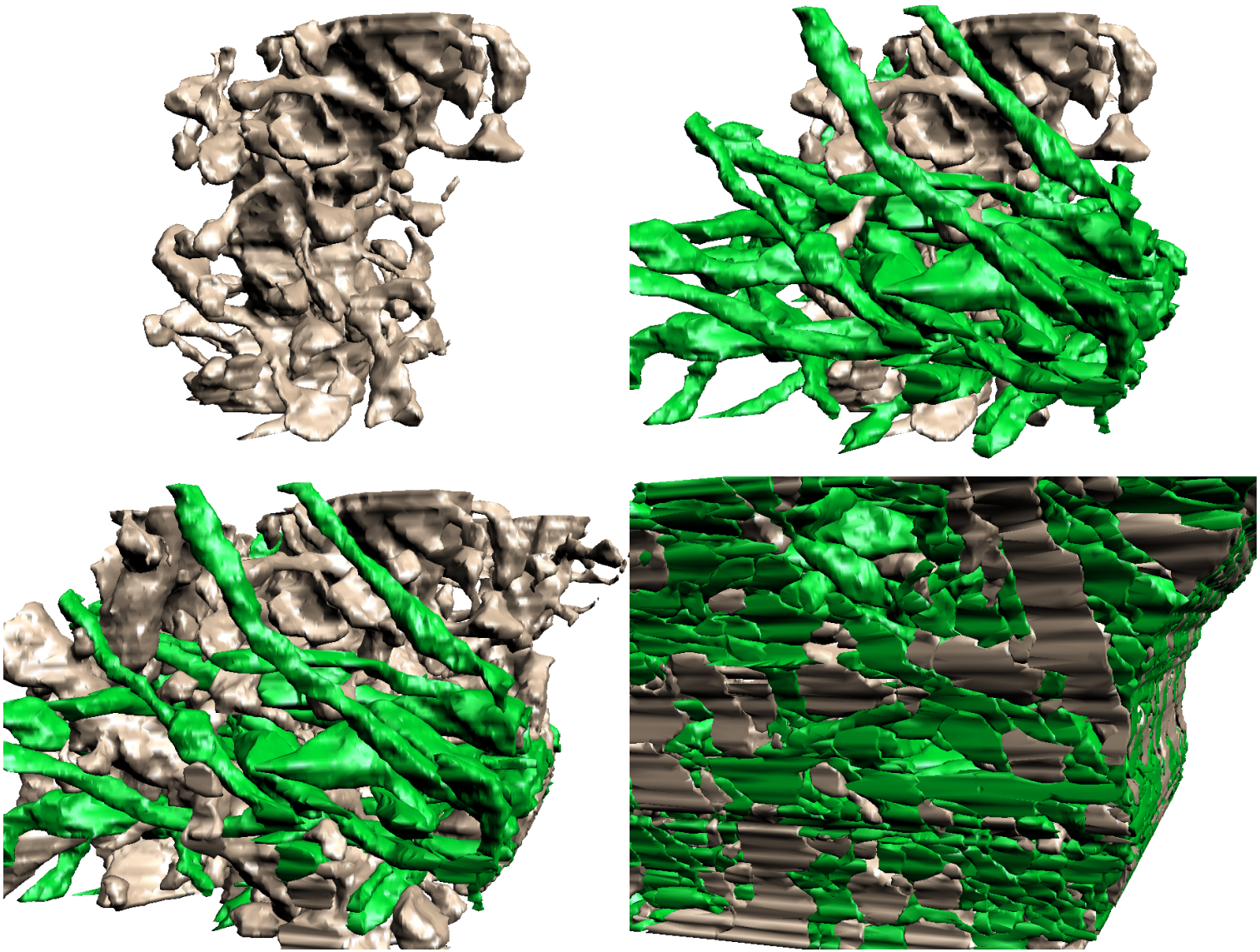
This data gives nice results! Why do we need to bother with EM?



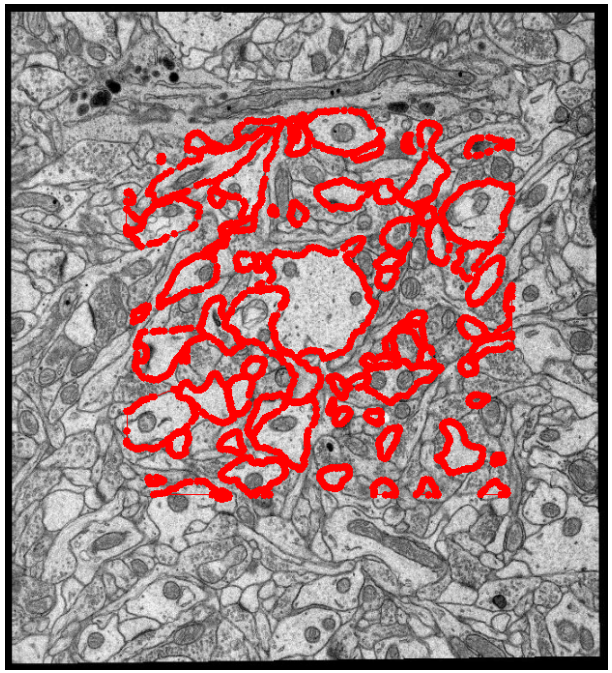
[Lu et al., 2009]

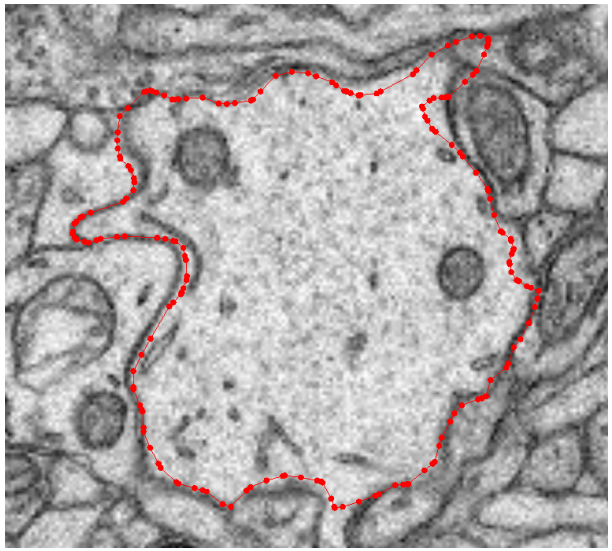
Stained/traced data vs. EM

Why EM? Tight packing is a compelling reason.



EM data

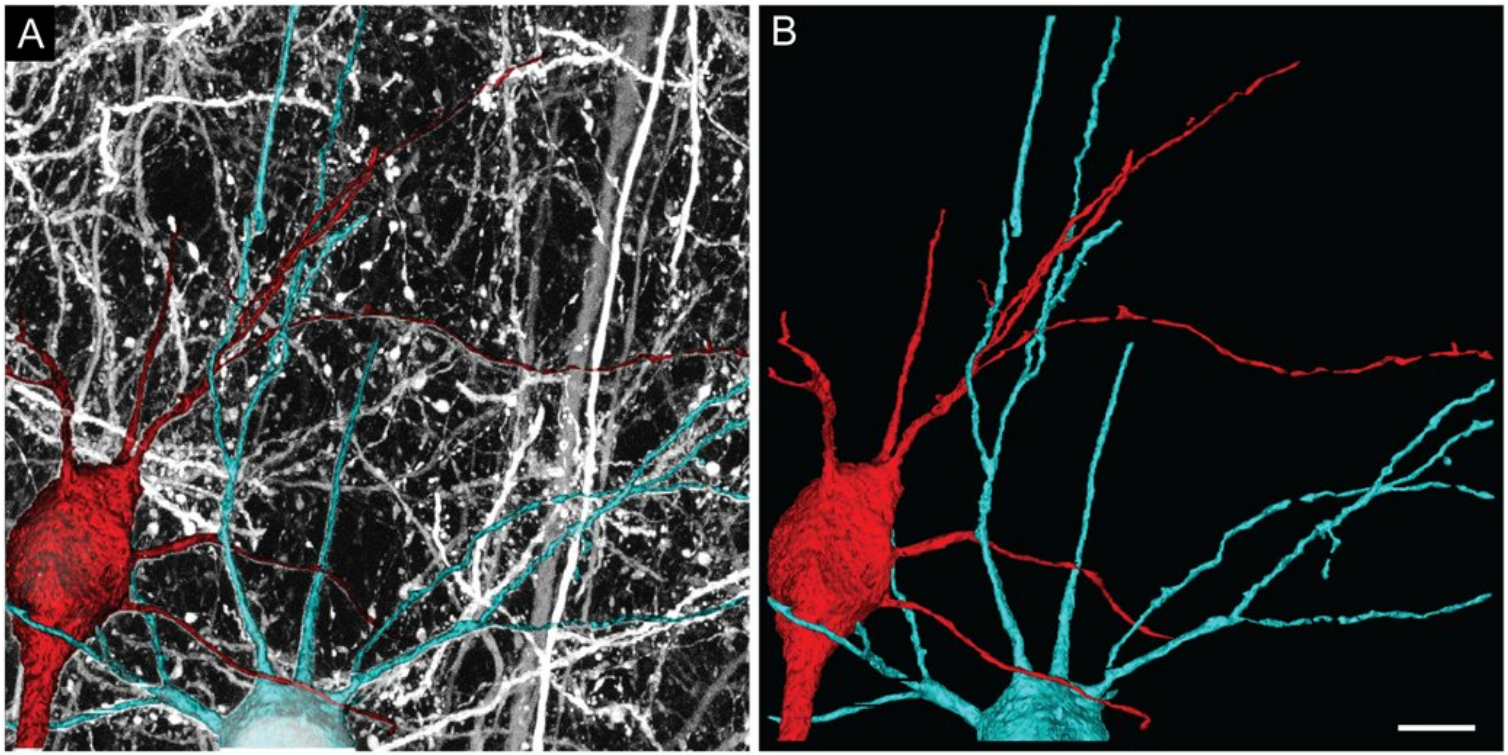




- Before working with EM data it must be segmented into contours representing neuronal processes
- The most-used software to do this is Reconstruct [Fiala, 2005] (both EM and optical).
- Reconstruct allows the user to trace contours slice-by-slice.
- Tracing contours is simple "Paint"-like drawing.

EM data

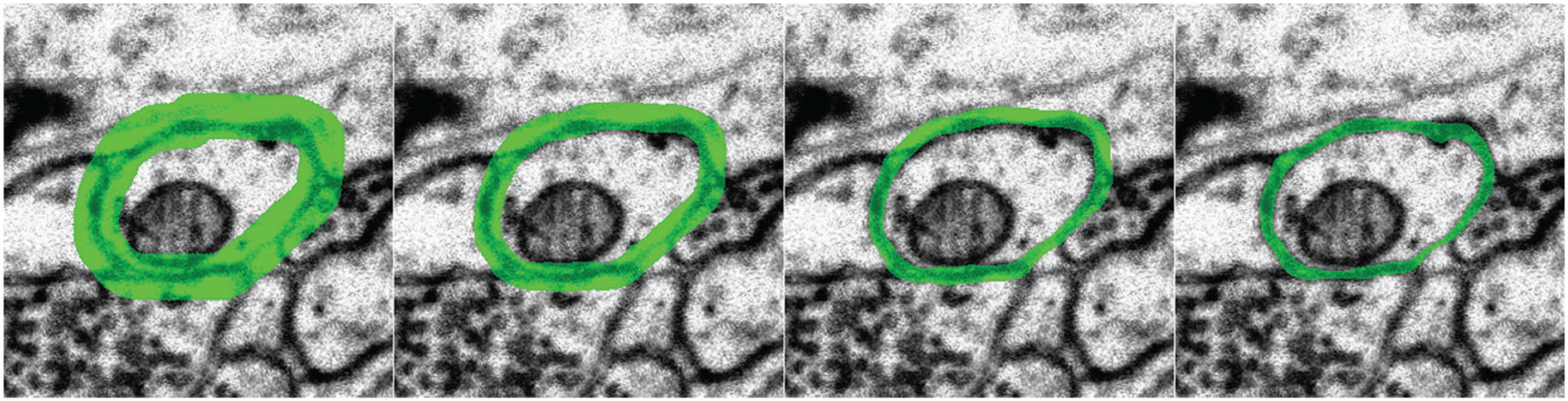
- An improvement to Reconstruct uses region growing [Lu et al., 2009] (both EM and optical)
- Average reconstruction speed improves to about 0.5mm per hour



[Lu et al., 2009]

EM data

- Recent software have semi-automatic tools to assist users
- NeuroTrace [Jeong et al., 2010] uses "ActiveRibbons," a variant of active contours (both EM and optical).
- This is geared toward interactive renderings and not so much toward high quality.

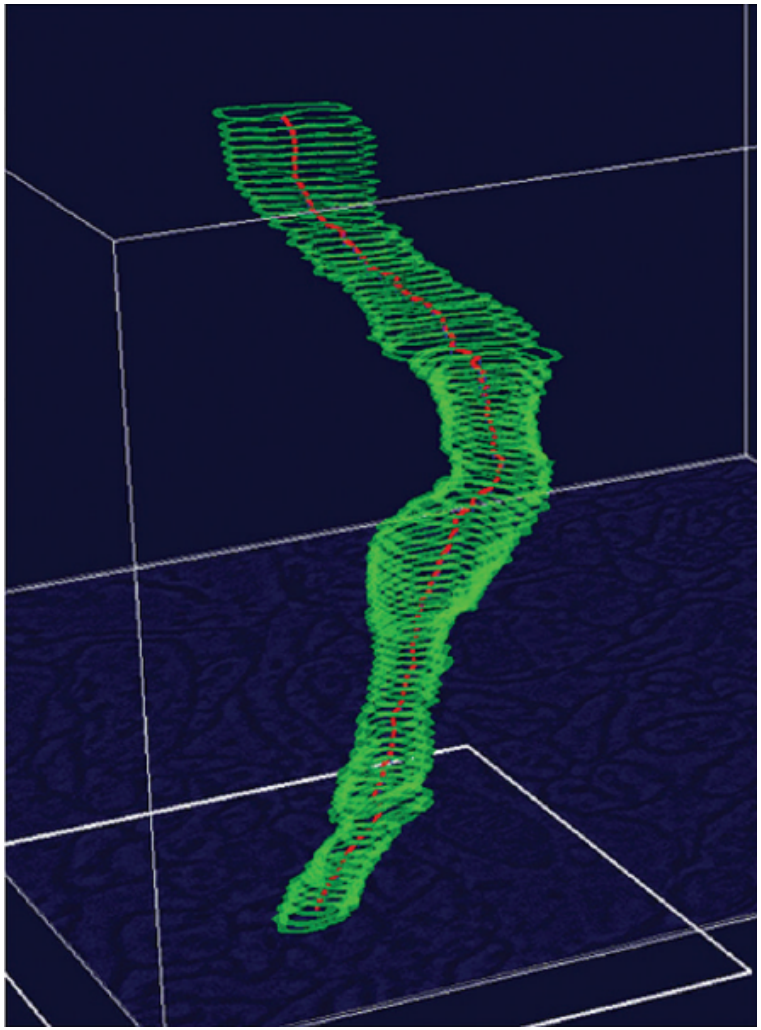


- [Mishchenko, 2009] uses machine learning to segment contours (both EM and optical).
- [Jurrus et al., 2009, Macke et al., 2008] use algorithms that track axons through slices (EM images only).

EM data

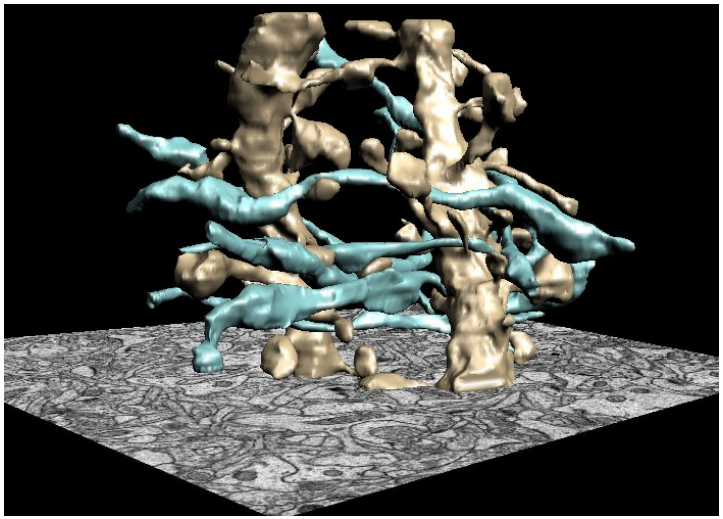
- Output from software such as Reconstruct and NeuroTrace is a series of contours

[Fiala, 2005]



[Jeong et al., 2010]

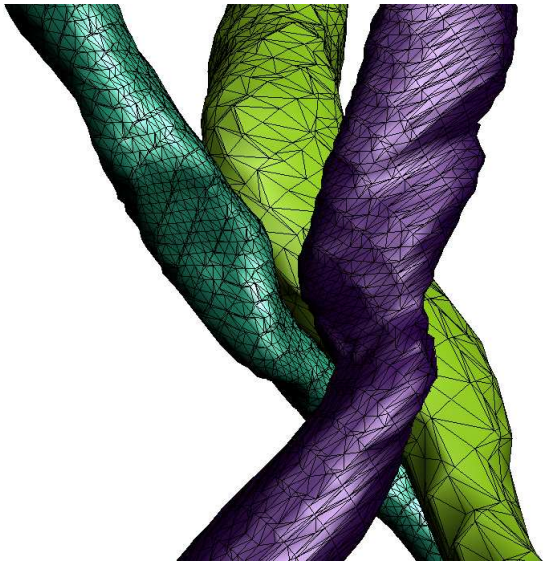
EM data



- The benefit of these contours of EM imagery is that we now have geometry of the neuronal processes
- Geometry can assist in topology reconstruction
  [Mishchenko et al., 2010]
- Geometry can provide for very high-resolution electrophysiological simulations using the finite element method

Outline

Reconstruction

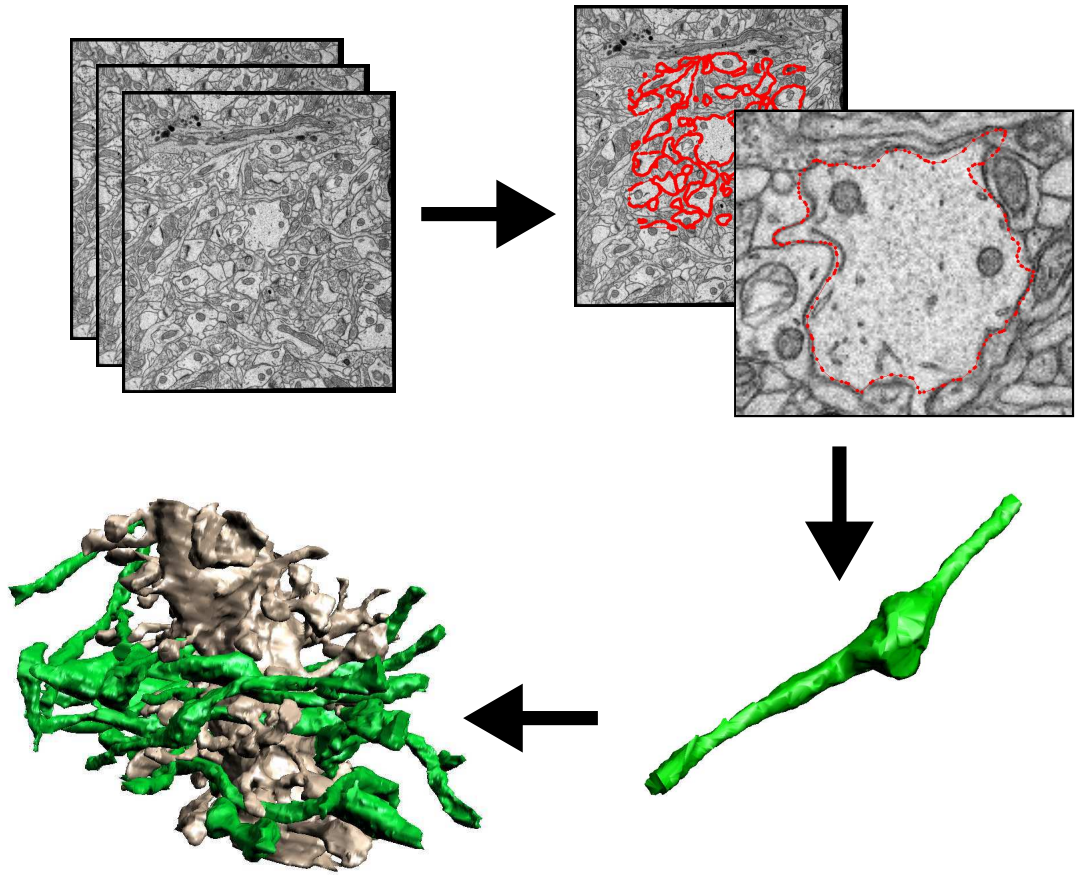


- Our work deals with high-fidelity 3D neuronal reconstructions
- Assists in connectome generation in that interpolated geometry characteristics (e.g. dendritic shaft diameter, area of axo-dendritic touch) can be accurately calculated
- Can use these geometries also to run simulations

Reconstruction

Our approach:

- Begin with series of ssTEM or ssSTEM images
- Generate contours around components of interest (axons, dendrites, etc in our case) using Reconstruct
- Use method from [Bajaj et al., 1996] to reconstruct 3D objects from 2D contours
- Combine 3D objects into a forest of structures [Edwards & Bajaj, 2010]



Thanks!

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