# Multiscale Imaging, Analysis, and Integration of Brain Networks

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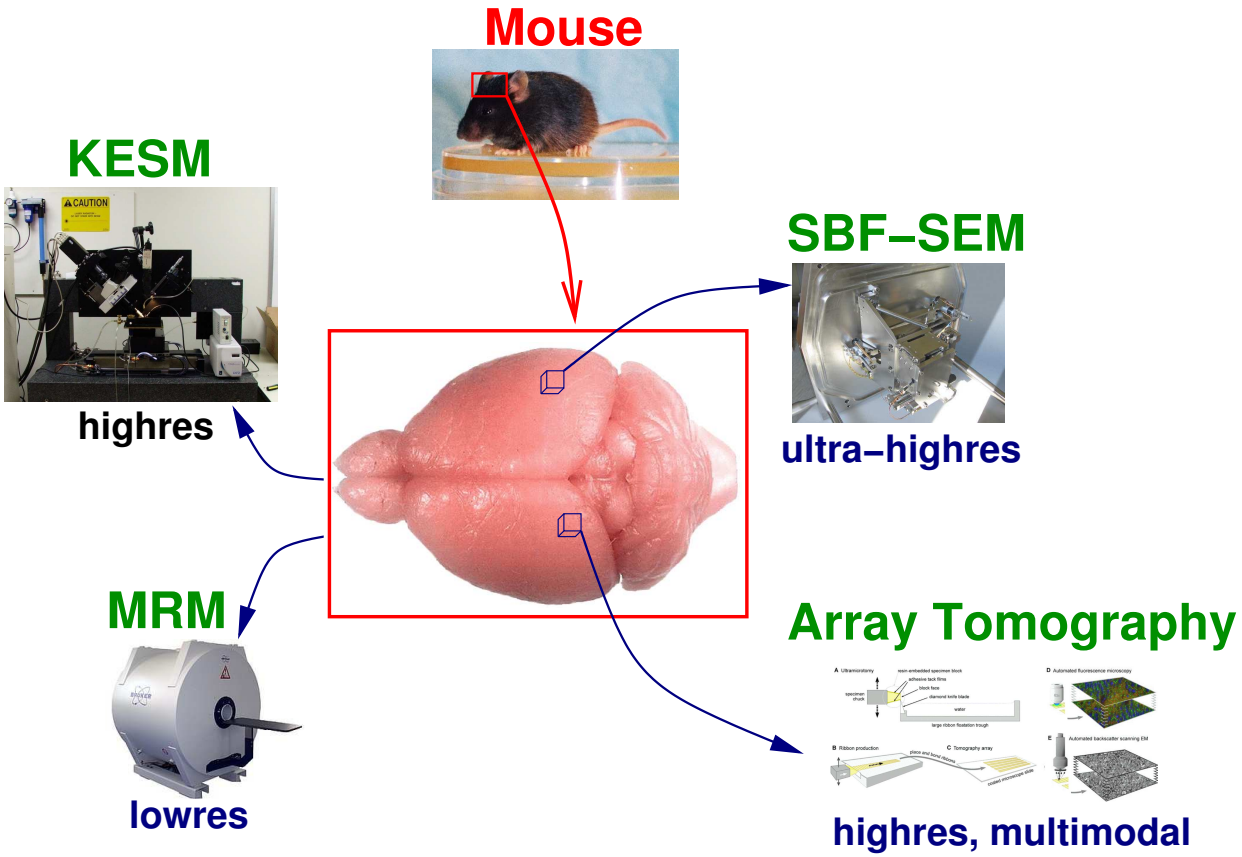
Yoonsuck Choe
Brain Networks Laboratory
Department of Computer Science
Texas A&M University
choe@tamu.edu, http://research.cs.tamu.edu/bnl

Collaborators: Bruce H. McCormick, Louise C. Abbott, John Keyser, (**Texas A&M**); Stephen J. Smith, Kristina Micheva (**Stanford**); Arthur Toga (**UCLA**)

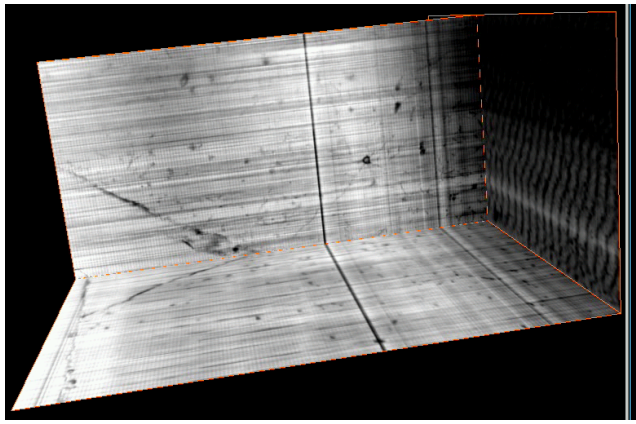
# Introduction

# Imaging: Exploring the Mouse Brain Network

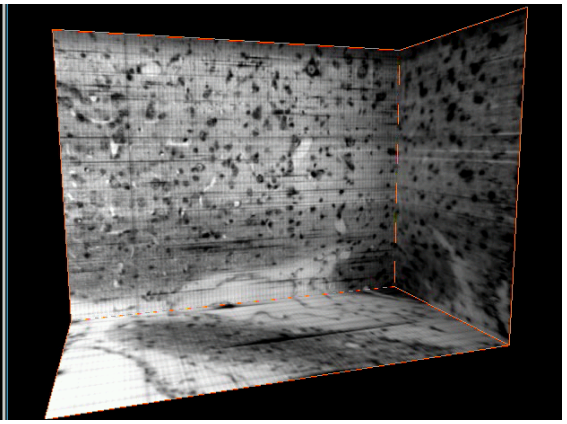



- Imaging: Knife-Edge Scanning Microscope (KESM, Mayerich et al. 2008), Serial Block-Face Scanning Electron Microscope (SBF-SEM, Denk and Horstmann 2004), and Array Tomography (Micheva and Smith 2007).
- Magnetic Resonance Microscopy (MRM) data: from UCLA.

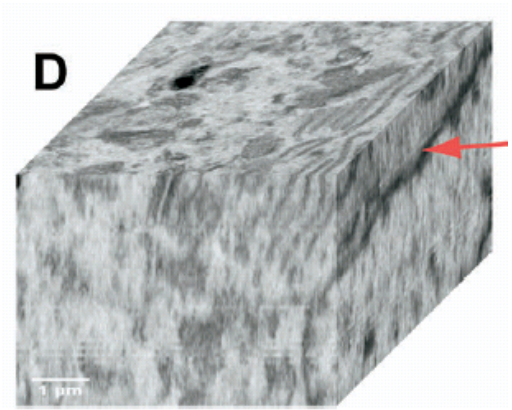
# Analysis: From Raw Image Stack to Geometric Reconstruction



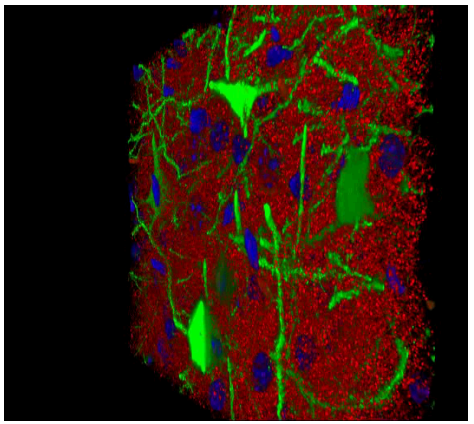
KESM Golgi



KESM Nissl




SBF-SEM (Denk and Horstmann 2004)

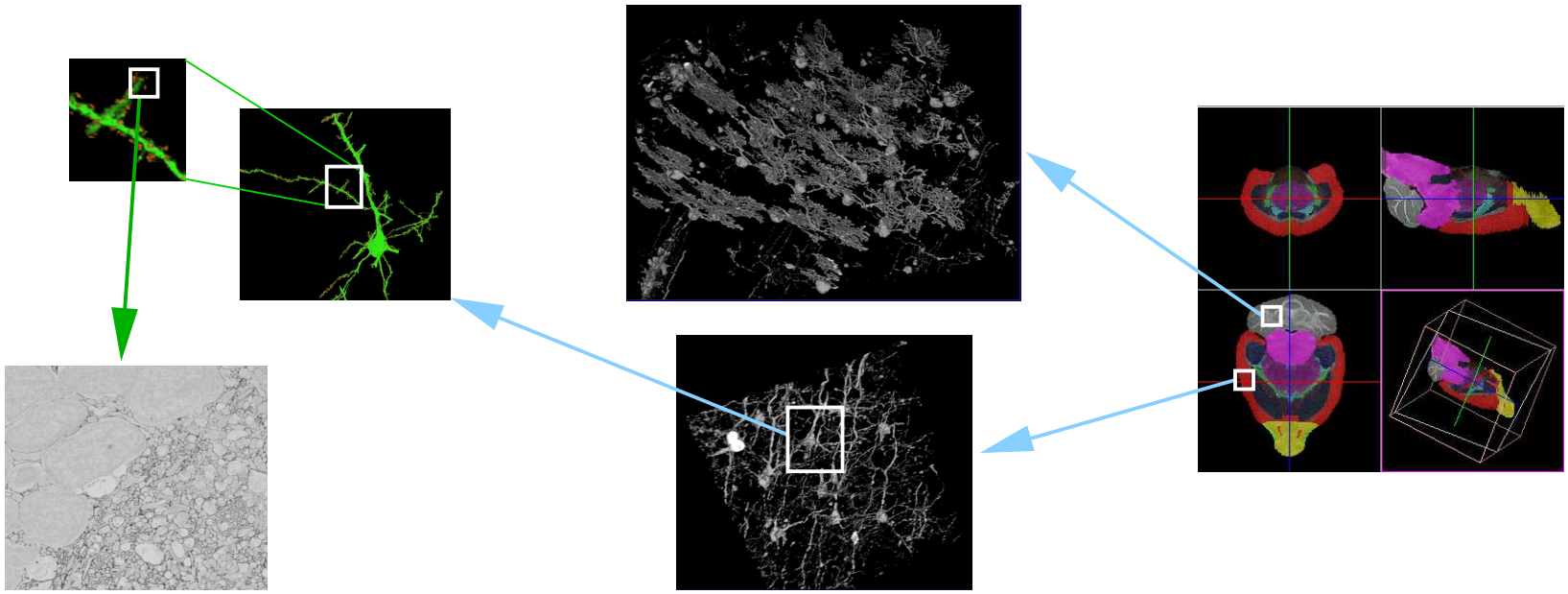


Array Tomography

- A stack of images needs to be turned into geometric information (*reconstruction*) before it can be analyzed further.

# Integration: Synapses to Circuits to Brain Networks

## Synapse Level  Circuit Level  System Level



**Array Tomography**
**SBF–SEM**

**KESM**
**Array Tomography**

**MRM, KESM**

Once the reconstruction is complete, we need to infer how the functions link:

- **Nanoscale**: Synapses
- **Microscale**: Local circuits and modules
- **Macroscale**: Cortical maps and major nuclei

# Imaging

# Physical Sectioning Microscopy

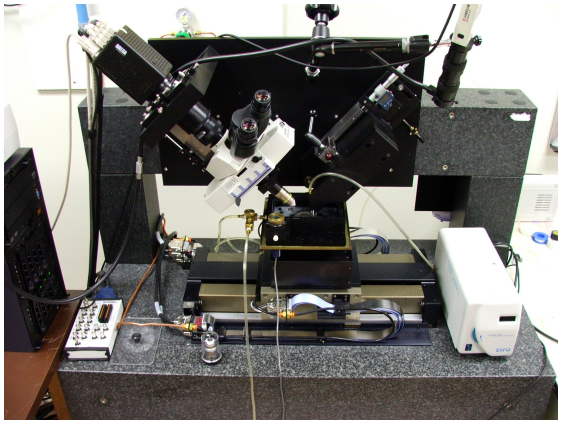
A need to go beyond hundreds of micrometers in volume (limit in confocal and multi-photon microscopy): **Physical sectioning**

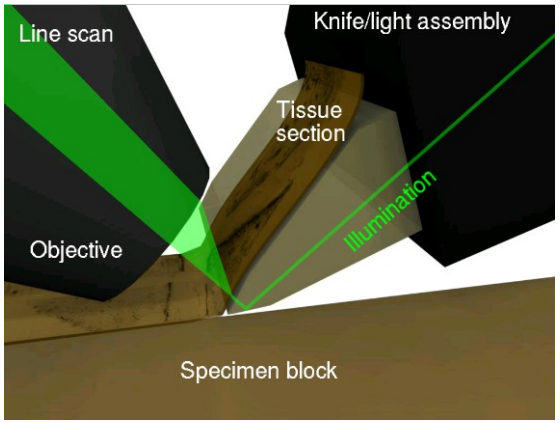
| Method | Resol. (x/y) | Resol. (z) | Volume | Modality | Time |
|---|---|---|---|---|---|
| All-Optical Hist. | 0.5 $\mu$m | 1 $\mu$m | 1 cm$^3$ | Fluorescence | $\sim$900 hours |
| KESM | 0.3–0.6 $\mu$m | 0.5–1 $\mu$m | 1 cm$^3$ | Bright field, Fluorescence$^*$ | $\sim$100 hours |
| Array Tomography | $\sim$0.2 $\mu$m | 0.05–0.2 $\mu$m | $\sim$100$^3$ $\mu$m$^3$ | Fluorescence, EM | N/A |
| SBF-SEM | $\sim$0.01 $\mu$m | $\sim$0.03 $\mu$m | $\sim$500$^3$ $\mu$m$^3$ | EM | N/A |
| ATLUM | $\sim$0.01 $\mu$m | 0.05 $\mu$m | $\sim$2.15$^3$ mm$^3$ | EM | N/A |

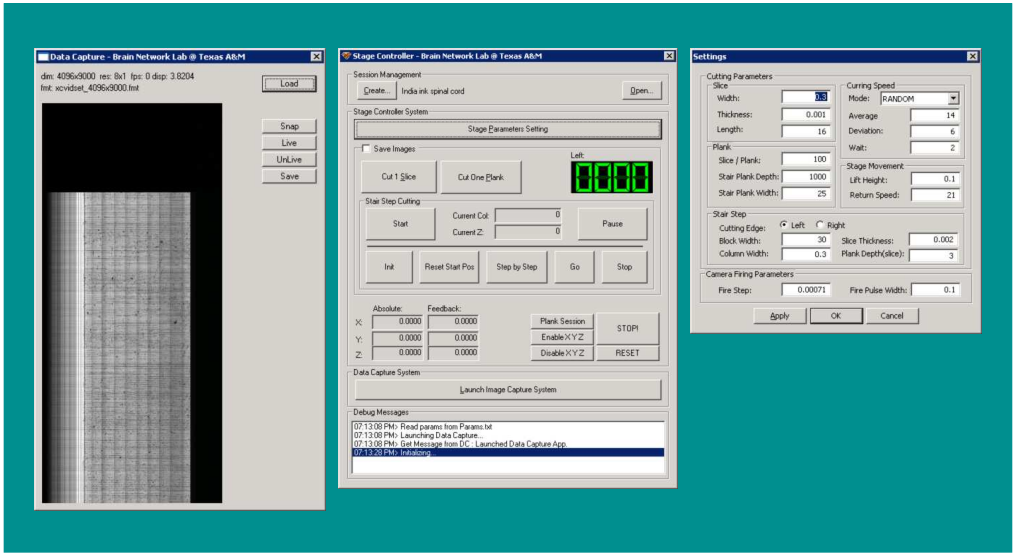
$^*$ Expected in the near future.

ATLUM (Hayworth and Lichtman 2007); All-Optical Histology (Tsai et al. 2003)

# Knife-Edge Scanning Microscopy

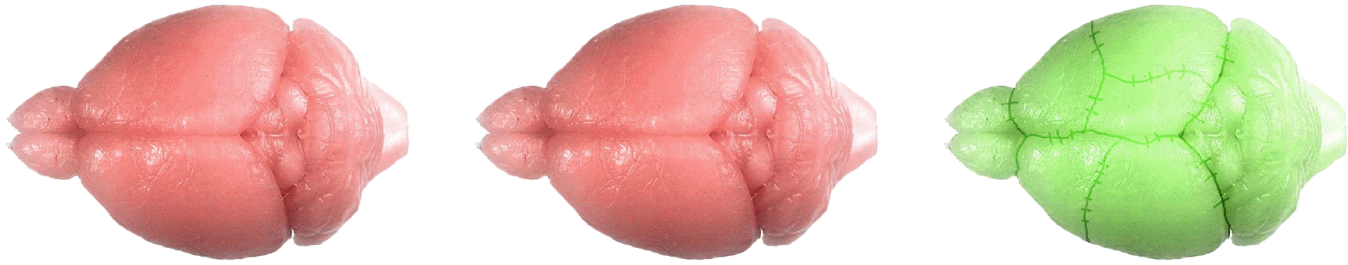




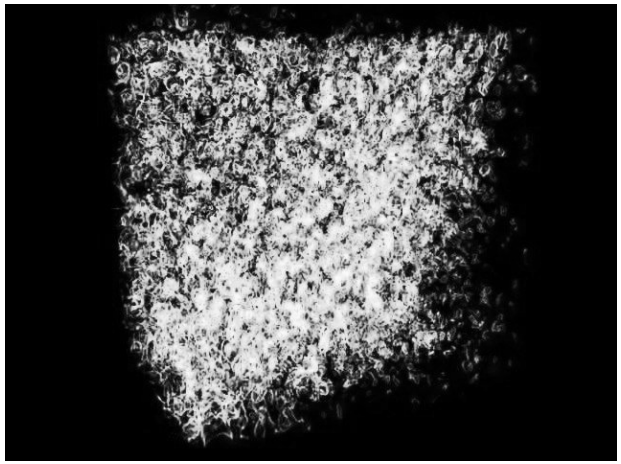

- Stair-step cutting algorithm allows sectioning and imaging of whole mouse brains at submicrometer resolution.
- Fully automated control software developed in-house.

# Progress in Sectioning and Imaging with KESM

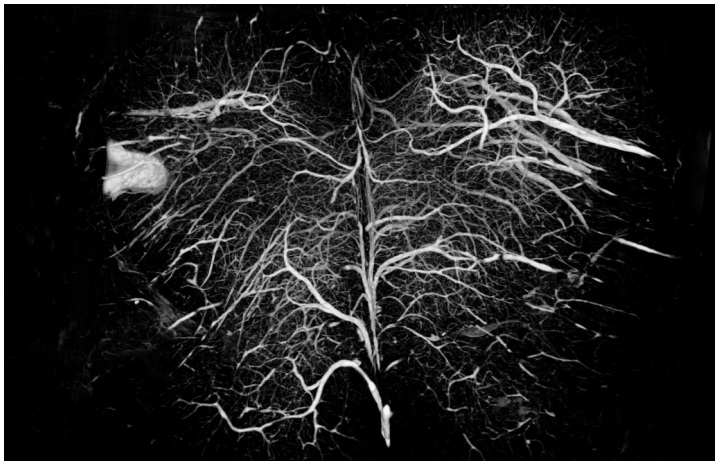


- One whole India-ink-stained mouse brain.
- One whole Golgi-stained mouse brain (almost complete).
- Nissl-stained mouse brain: olfactory bulb, cortex (selective), cerebellum, brainstem and spinal cord,

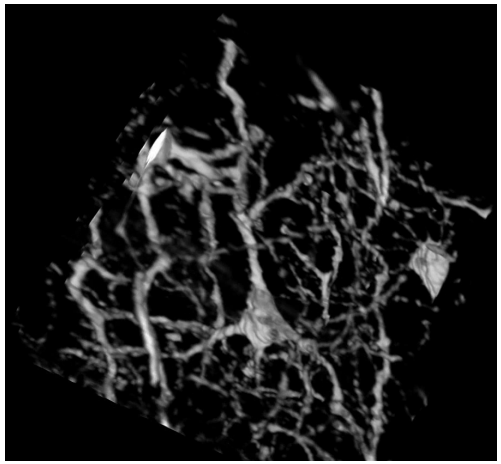
# Imaging Results



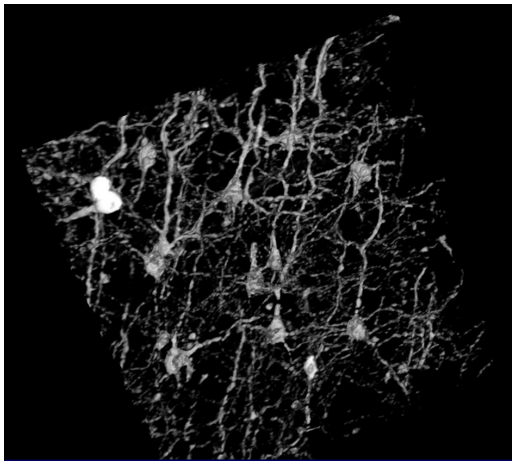
Nissl (Cortex)



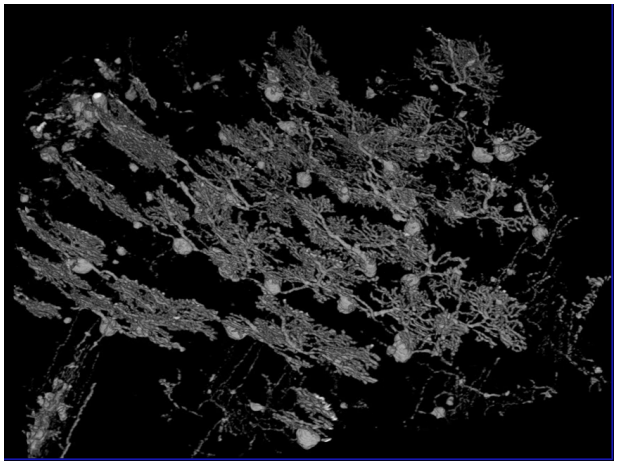
India ink (Spinal cord)



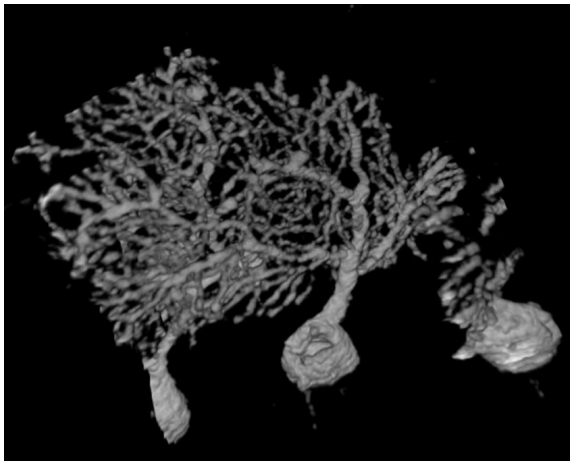
Golgi (Pyramidal cell)



Golgi (Cortex)

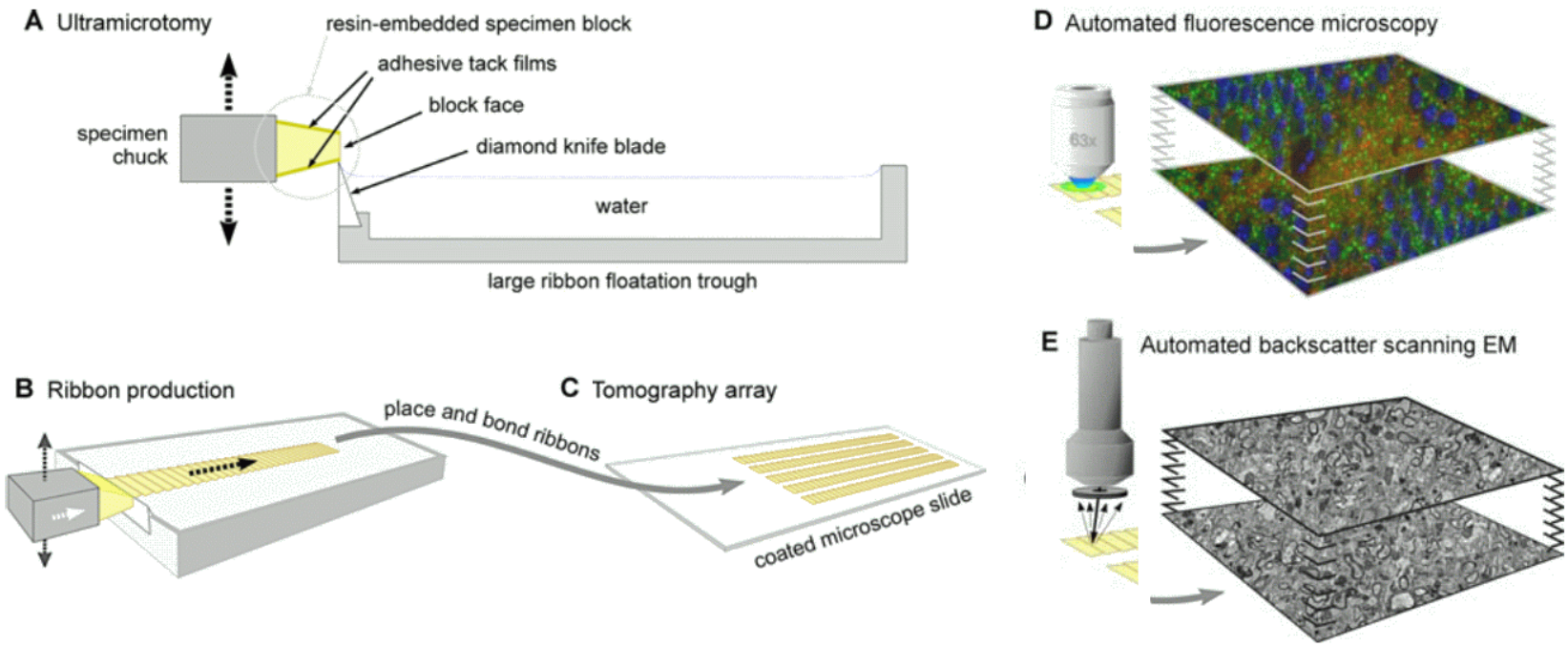


Golgi (Cerebellum)



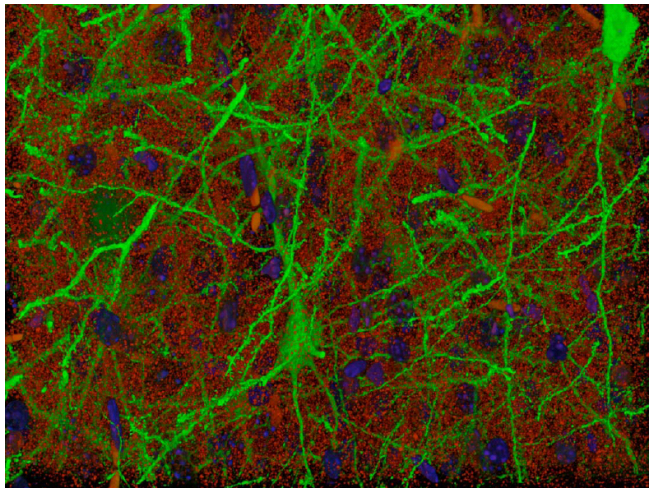
Golgi (Purkinje cell)

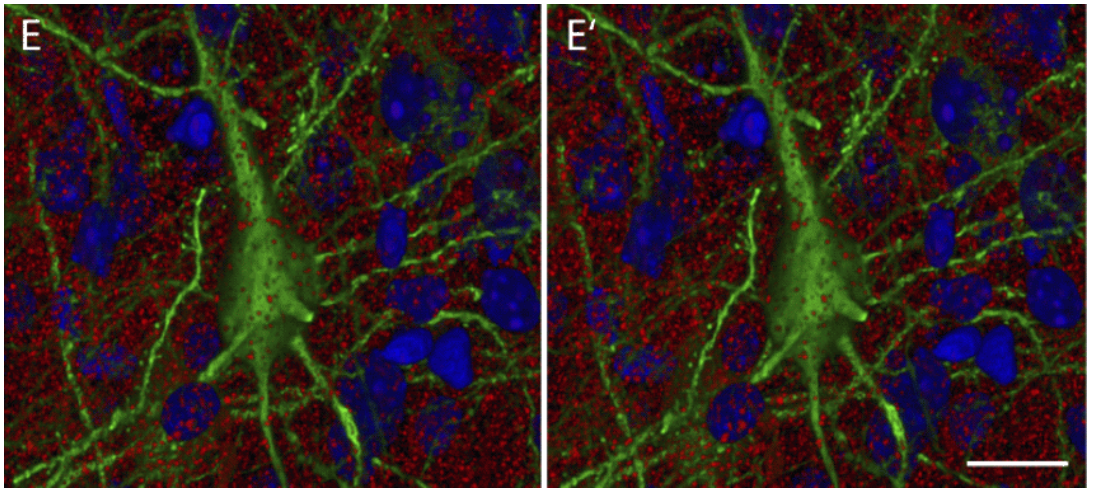
# Array Tomography

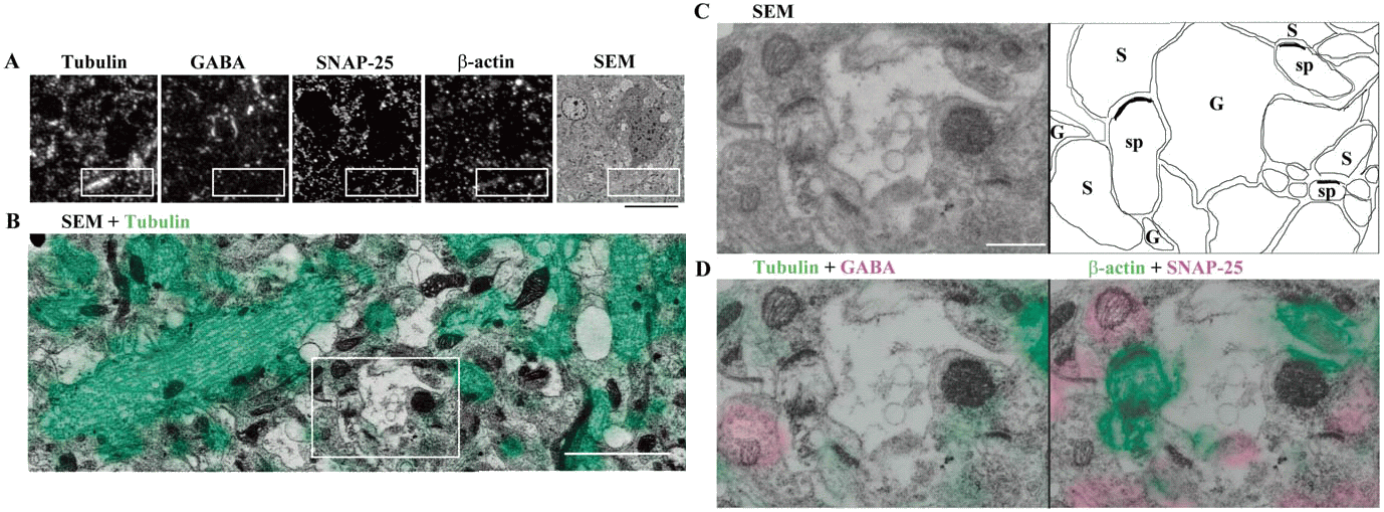



- Repeated washing and staining allows perfectly registered volume data from multiple staining modalities.
- Progress: sectioned and imaged selected mouse, zebra fish, and human brain tissue samples.

# Imaging Results



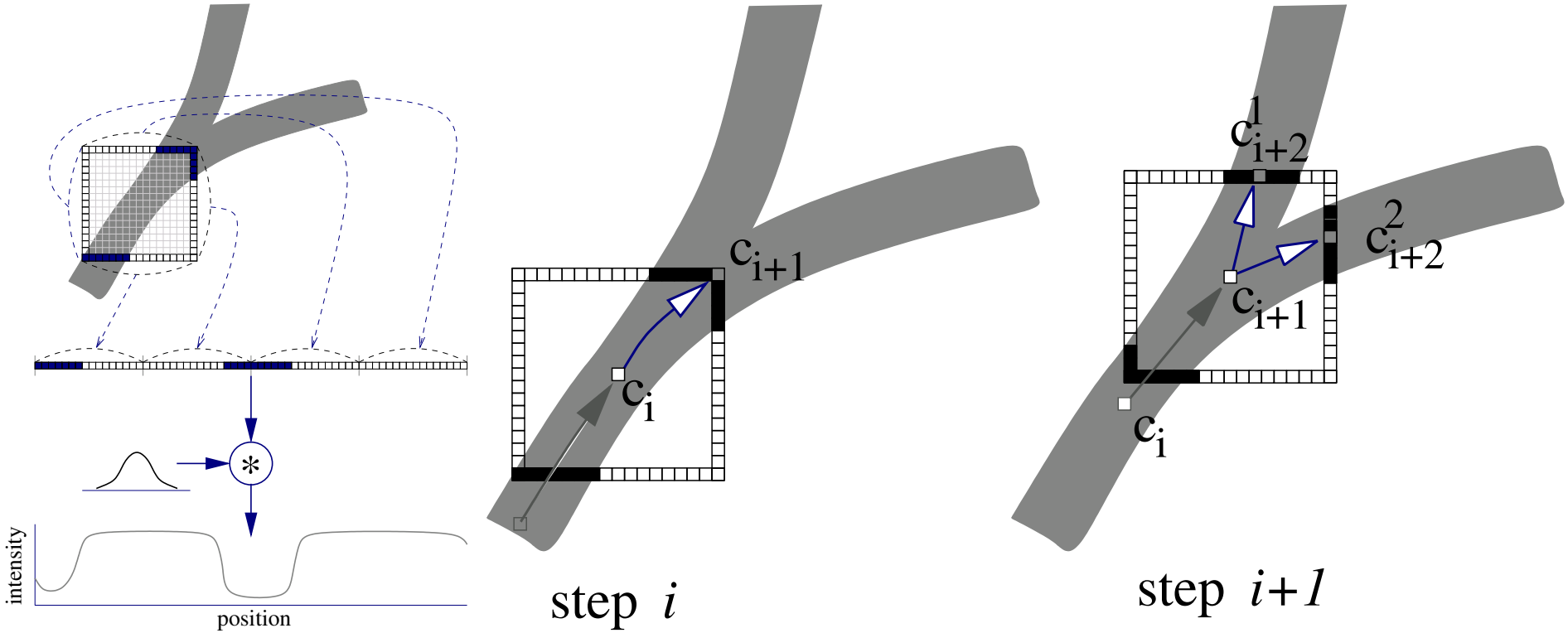



- Rhodamine anti-synapsin I (red), showing putative synapses; DAPI-DNA (blue), showing DNA; and FITC anti-GFP (green) showing detailed structure of the soma, dendrites and its spines, and axons.

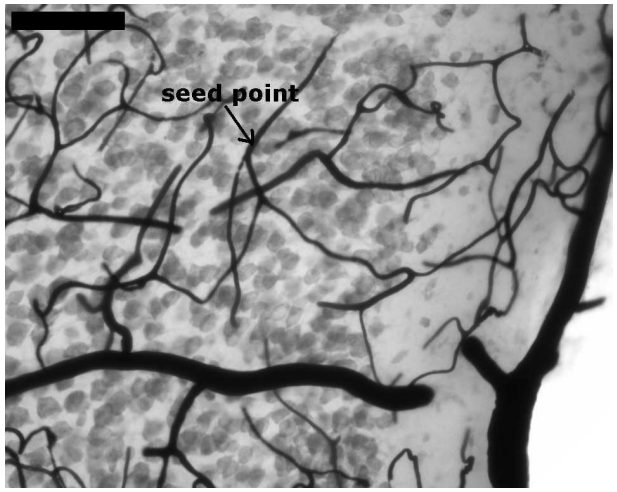
# Analysis

# Reconstruction: Tracing in 2D

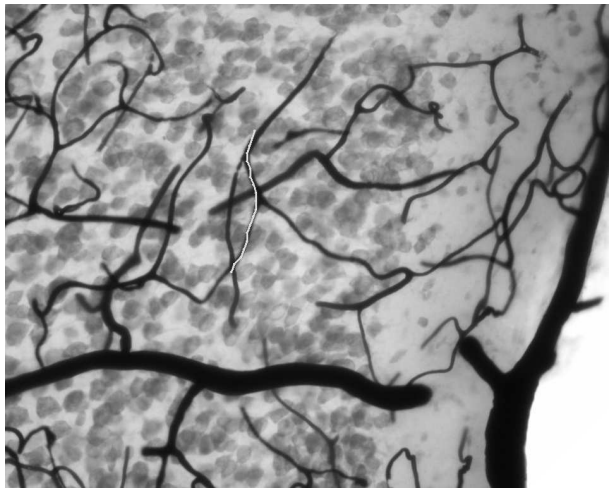



- Moving window with cubic tangential trace spline method.
- Investigates pixels only on the moving window border and on the interpolated splines for fast processing.

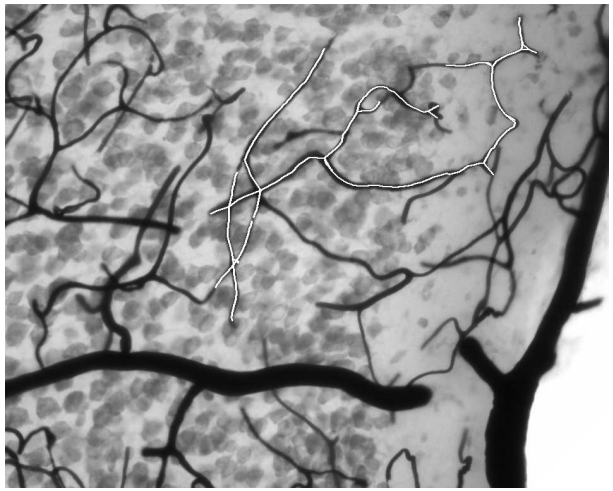
# Tracing Results



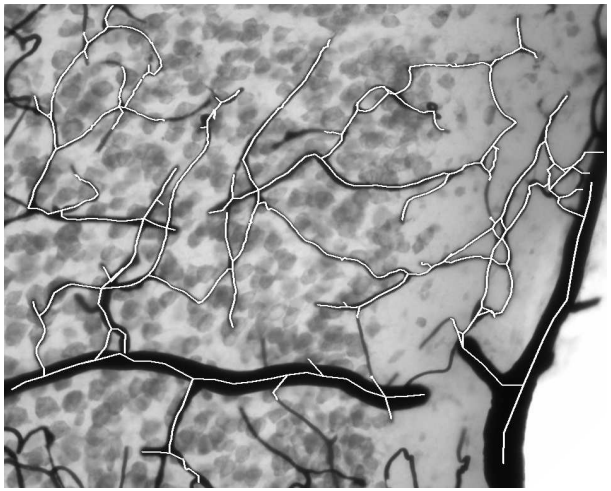

Seed



Can et al. (1999)

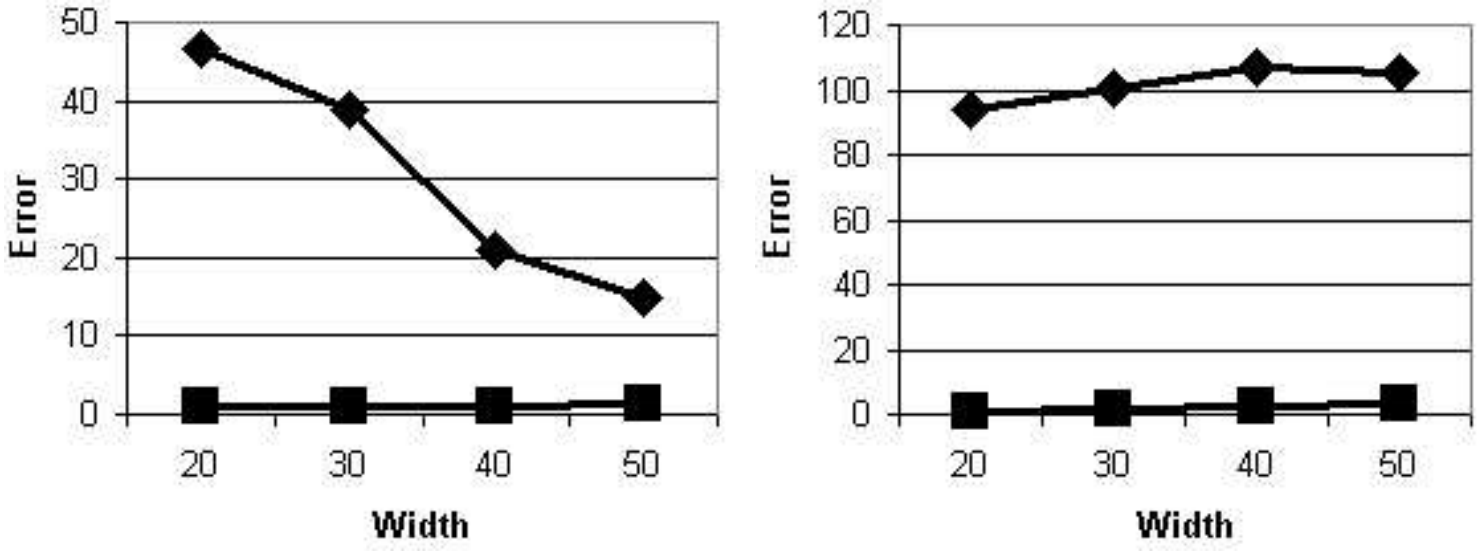


Haris et al. (1999)



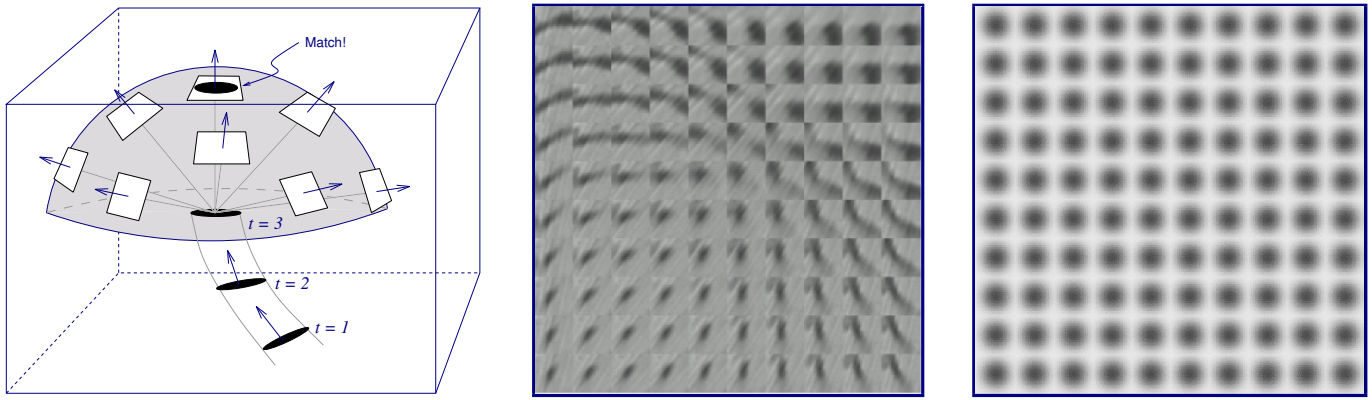
Our method

# Performance




- Accuracy tested based on synthetic data (by varying fiber width).
- Much more accurate compared toe competing approaches such as Can et al. (1999).

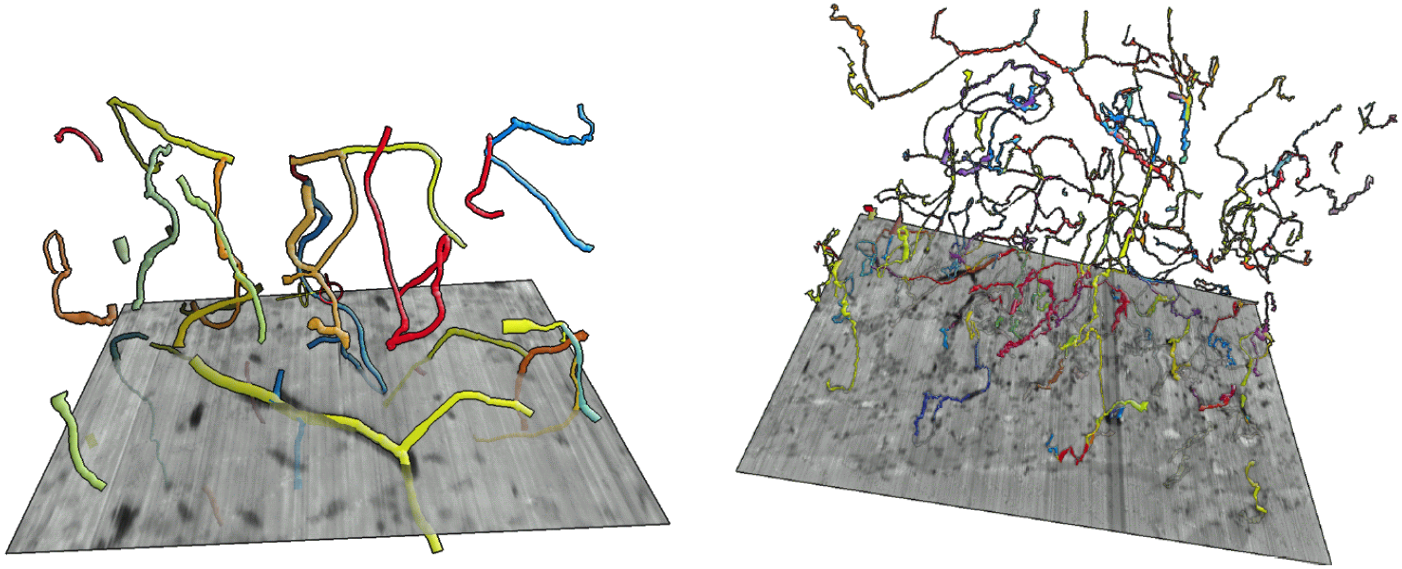
# Reconstruction: Tracing in 3D



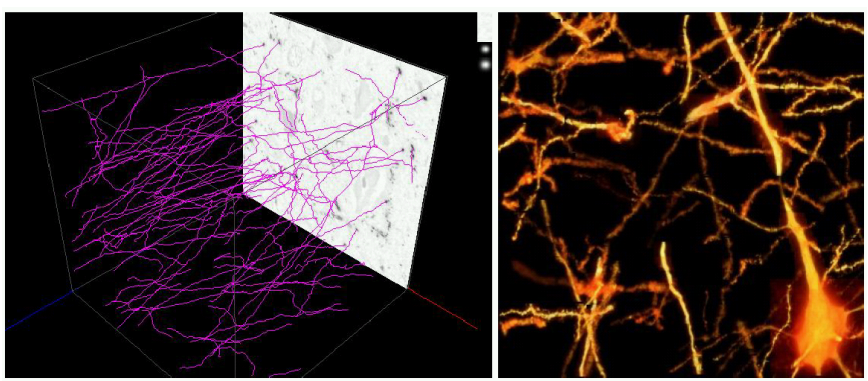

Template matching  Tangential slices  Templates

- Generalization of the moving window approach to 3D.
- Use a moving sphere and trace along points on the surface of the sphere.
- Use graphics hardware (GPU) for fast matrix operations to find slices that have the optimal fiber cross-section shape.

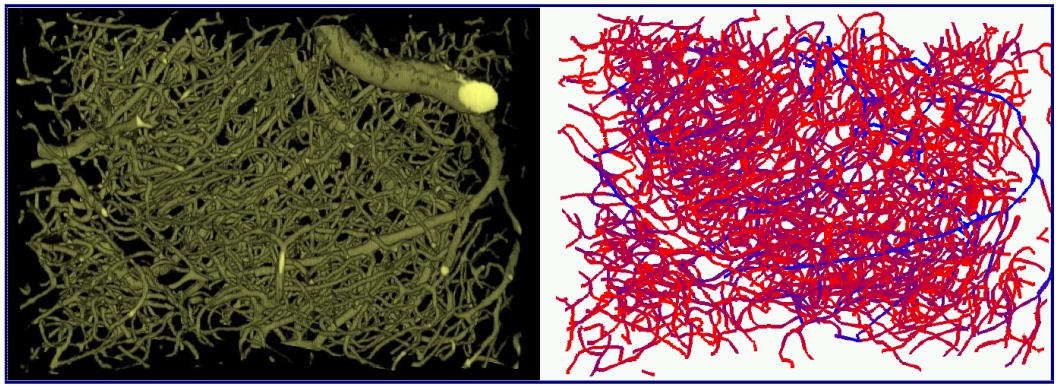
# Tracing Results



Spinal cord vasculature (KESM)

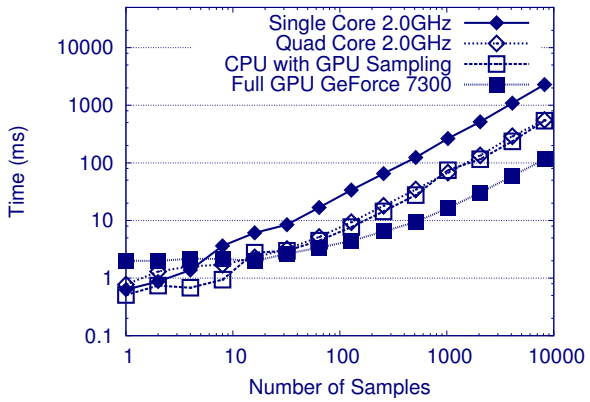


Neuron (Array Tomography, tectum)

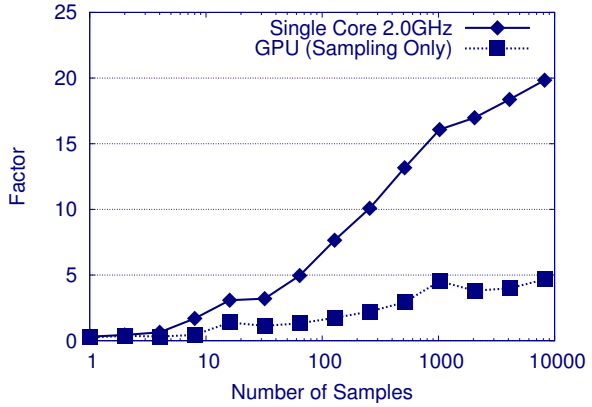


Vasculature (KESM, cerebellum)

# Performance




Run time




Speedup

Performance figures demonstrate the speedup obtained by using GPU computation.

- The use of GPU gives an order-of-magnitude reduction in computation time.
- Speedup achieved by using the full capacity of GPUs show an almost 20-fold speedup compared to single-core CPU-based runs.

# Preliminary Branching Statistics (vasculature)

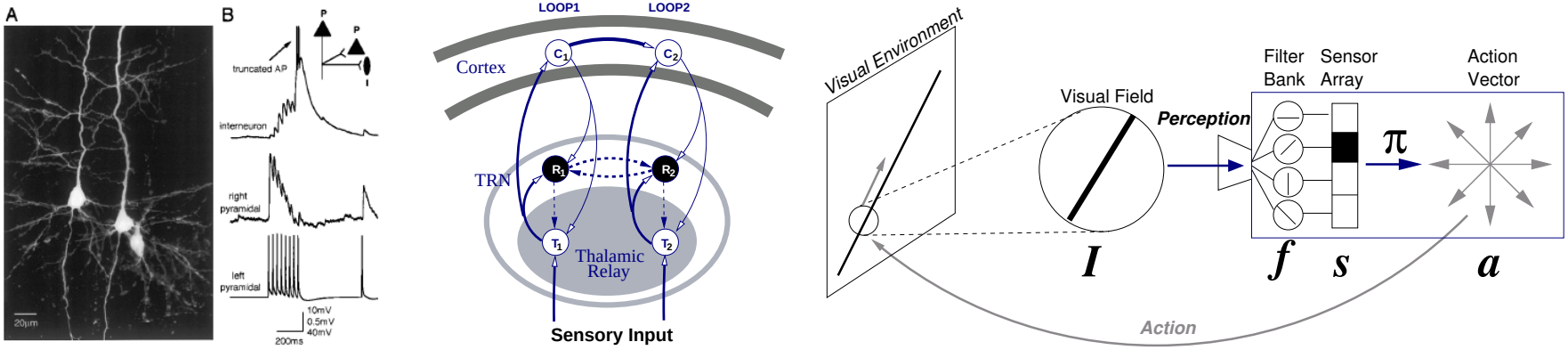
Sample Statistics from Reconstructed KESM Brain Vasculature Data (1 $mm^3$ volume)

| Region 5 | Segments 5 | Length (mm) | Branches | Surface ($mm^2$) | Volume ($mm^3$) | Volume (% of total) |
|---|---|---|---|---|---|---|
| Neocortex | 11459.7 | 758.5 | 9100.0 | 10.40 | 0.0140 | 1.4% |
| Cerebellum | 34911.3 | 1676.4 | 19034.4 | 20.0 | 0.0252 | 2.5% |
| Spinal Cord | 36791.7 | 1927.6 | 26449.1 | 22.2 | 0.0236 | 2.4% |

- Geometric structures extracted using the automated reconstruction algorithms allow us to conduct quantitative investigation of the structural properties of brain microstructures.

# Integration

# Integrating Theme: Time and Prediction



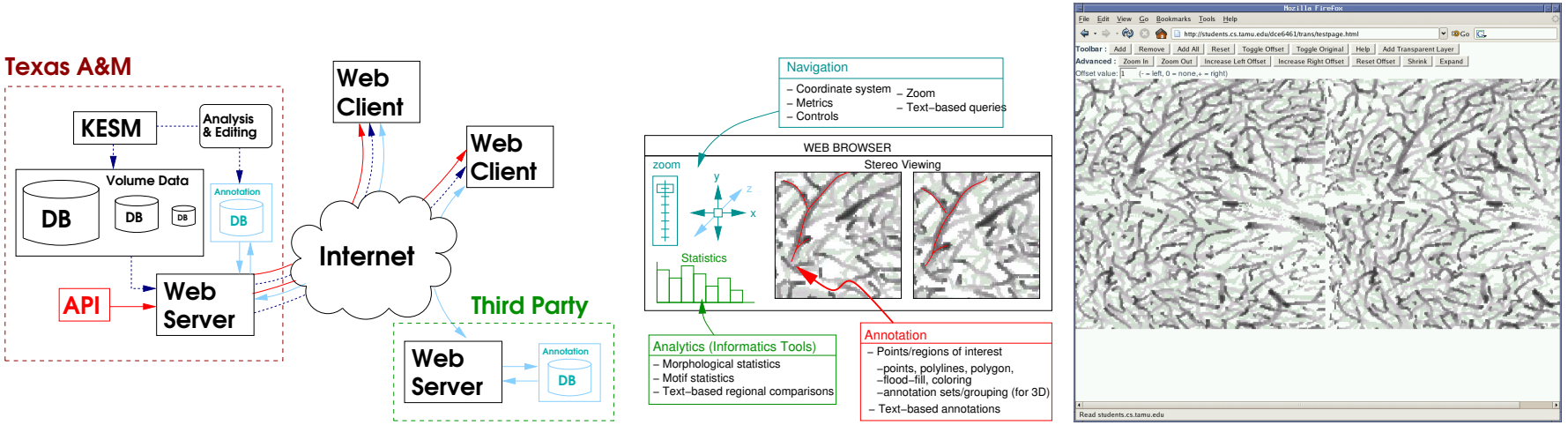

- **Synapse level:** facilitating synapses for delay compensation (Lim and Choe 2008).
- **Circuit level:** propagation of predictive preactivations (Choe 2004; Yu and Choe 2005).
- **System level:** sensorimotor integration for internal understanding (Choe et al. 2007), evolutionary advantage of more predictable internal dynamics (Kwon and Choe 2008).

# Integrating Theme (cont'd)

Even though the above are about dynamical properties of brain function, accurate system-level anatomy can provide good insights:

- **Synapse level:** Array Tomography can be used to investigate distribution of certain molecular markers involved in facilitating synapses.
- **Circuit level:** Axonal length and diameter can be used to estimate dynamical parameters such as latency.
- **System level:** Connectivity between sensory and motor maps can be investigated at the system level.

# Multi-scale Data Integration Environment




- Multi-scale investigation requires a data browsing and annotation environment that integrates multiple scales and informations sources seamlessly.
- A cohesive framework is under development for integrating multi-scale data into a single informatics platform.
- The platform can also facilitate data and model sharing.

# Wrap-Up

# Conclusion

- Understanding brain function requires a multi-scale approach.
- Innovative microscopy technologies are enabling a data-driven multi-scale investigation linking the microstructure to system
- The massive data can only be effectively understood through automated computational algorithms.
- Integrating the multiple scales depend on models based on plausible theories and the ability to explore the data in an integrative environment.

# Acknowledgments


- People:
  - Texas A&M: Y. Choe, B. McCormick, J. Keyser, L. C. Abbott, D. Mayerich, D. Han, J. Kwon, Y. H. Bai, D. C.-Y. Eng, H.-F. Yang, G. Kazama, K. Manavi, W. Koh, Z. Melek, J. S. Guntupalli, P.-S. Huang, A. Aluri, H. S. Muddana
  - Stanford: S. J. Smith, K. Micheva, J. Buchanan, B. Busse
  - UCLA: A. Toga
  - Others: T. Huffman (Arizona State U), R. Koene (Boston U), Bernard Mesa (Micro Star Technologies)
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- In memory of Bruce H. McCormick (1928–2007).

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