Multiscale Imaging, Analysis, and Integration of Brain Networks

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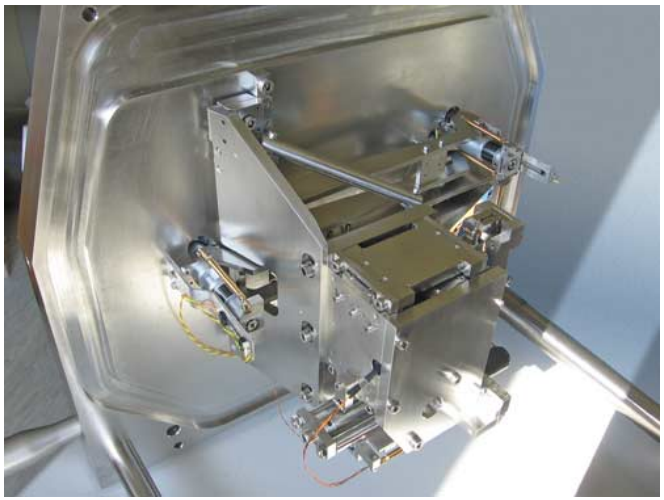
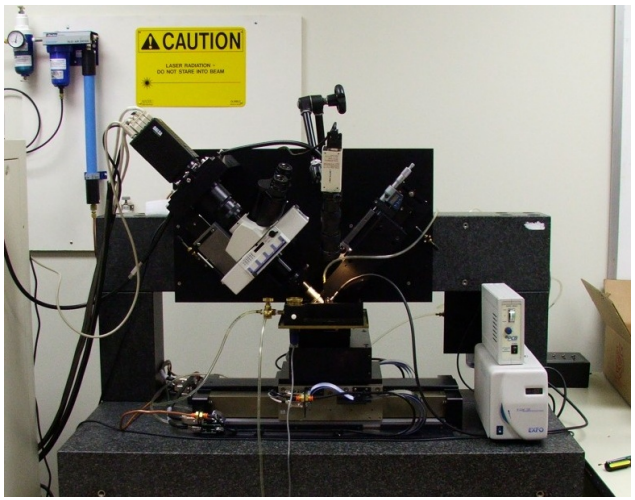
Project Overview: Multiscale Mouse Brain Microstructure

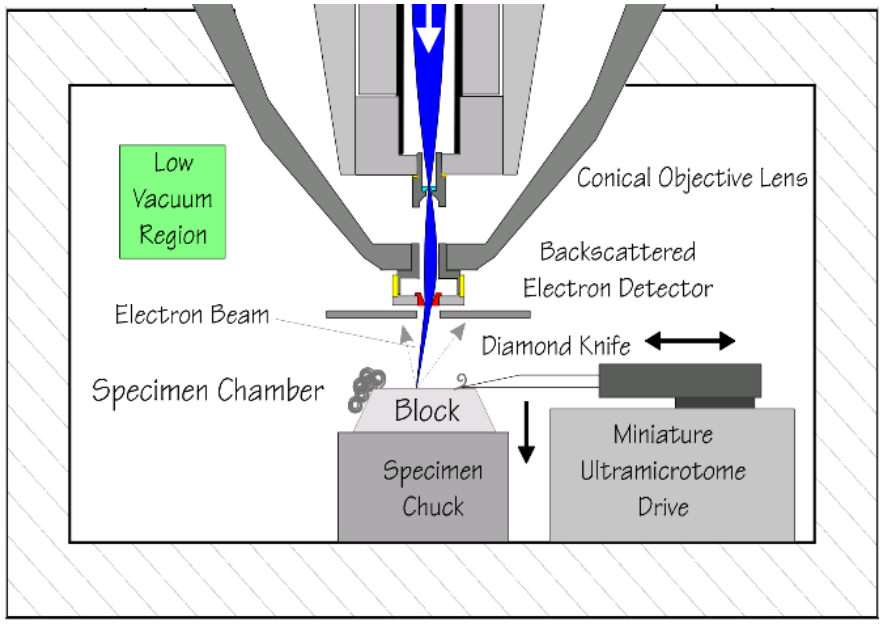
Nano	Micro	Macro
		
* SBF-SEM, EM, 20–30 nm Stanford	KESM, Optical, 0.3–0.6 μm Texas A&M	† MRM, MR, ∼60 μm UCLA

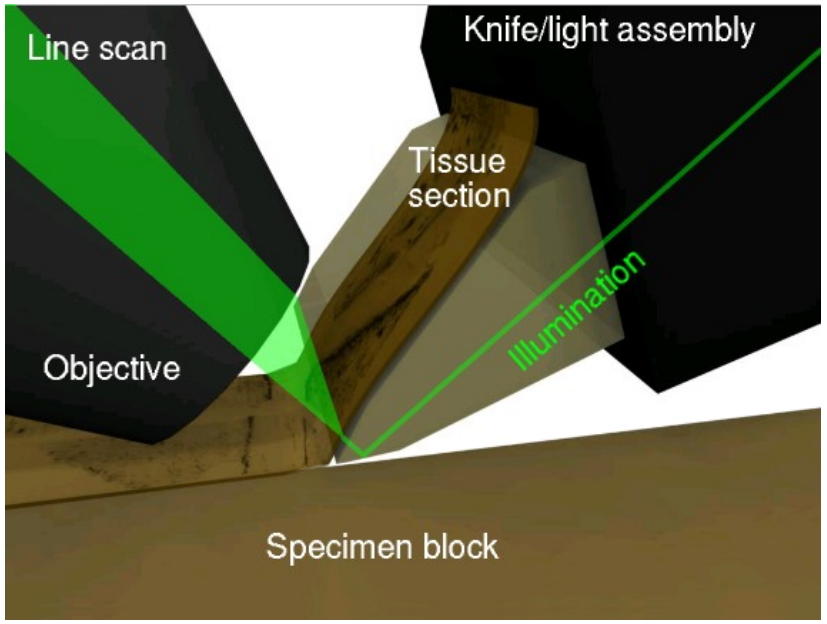
- Surveying mouse brain microstructures.
- Three imaging modalities, three scales, one hard problem.
- Effort focused on KESM and SBF-SEM (and Array Tomography).

* SBF-SEM image source: Gatan http://www.gatan.com/sem/3view.php

† MRM image source: Bruker http://www.bruker-biospin.com/biospec_117_16_usr.html?&L=0

KESM and SBF-SEM: Serial-Sectioning Imaging

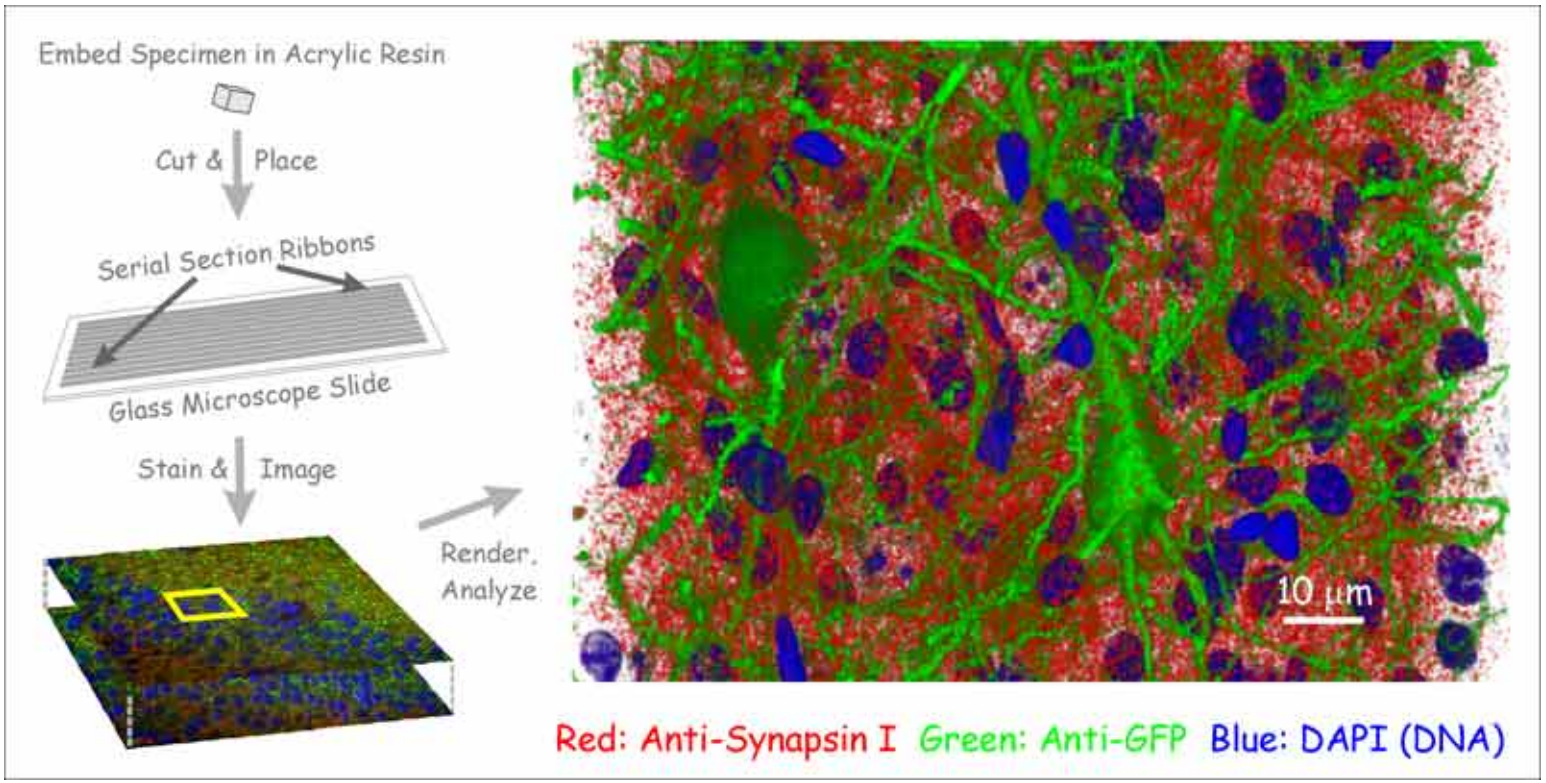




SBF-SEM KESM

- Serial, physical sectioning for high z-axis resolution.
- Deeper imaging possible compared to optical sectioning such as confocal microscopy or multiphoton microscopy.
- KESM (McCormick 2004, 2003, 2006; McCormick and Mayerich 2004; McCormick et al. 2007); SBF-SEM (Denk and Horstmann 2004)

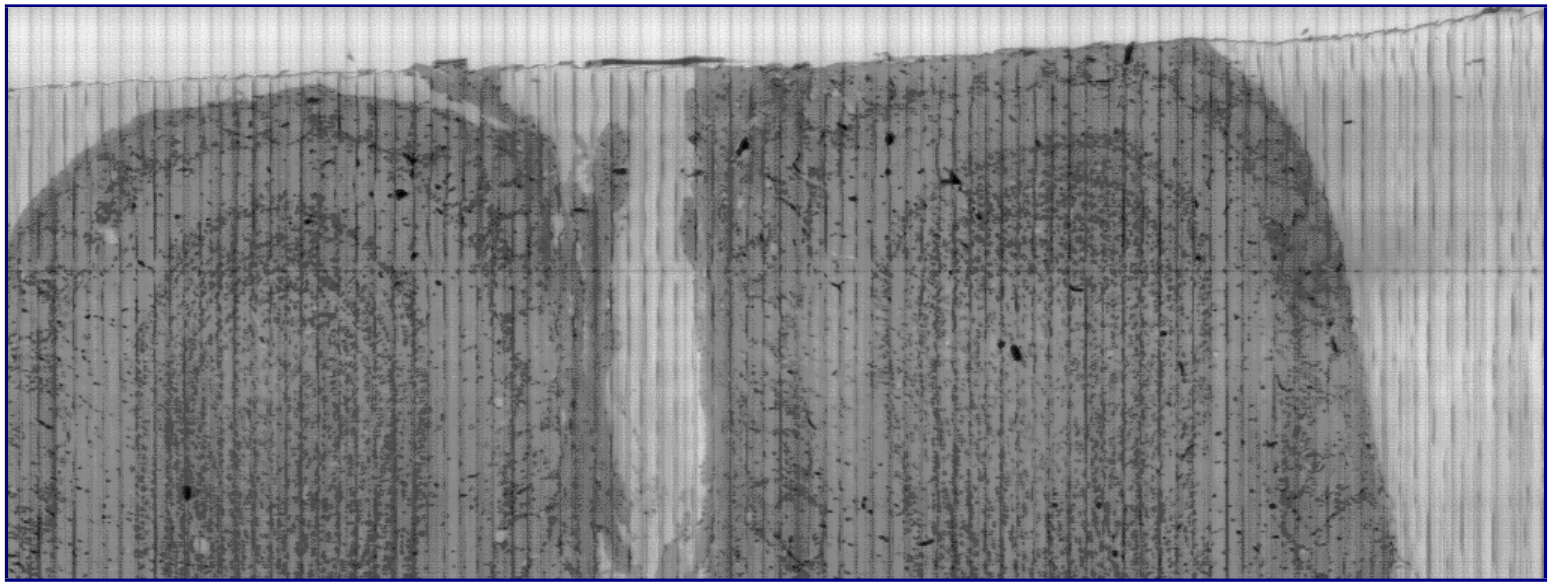
New: Array Tomography



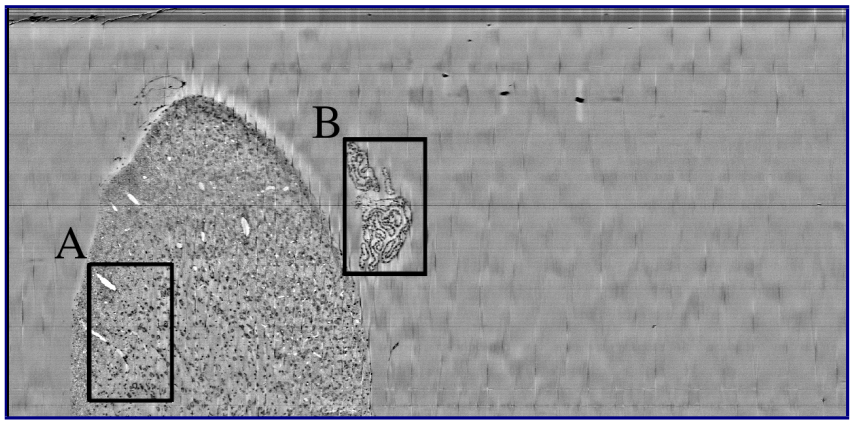
Stanford: Micheva and Smith

- Ultrathin sections (50nm–200nm).
- Repeated staining and imaging of same tissue arrya with molecularly specific stains, plus SEM imaging.

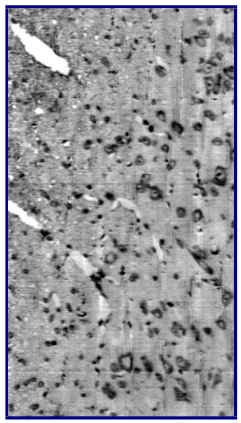
Typical Data: Nissl Stain, KESM



Olfactory bulb



(a) Brain stem (Nissl)

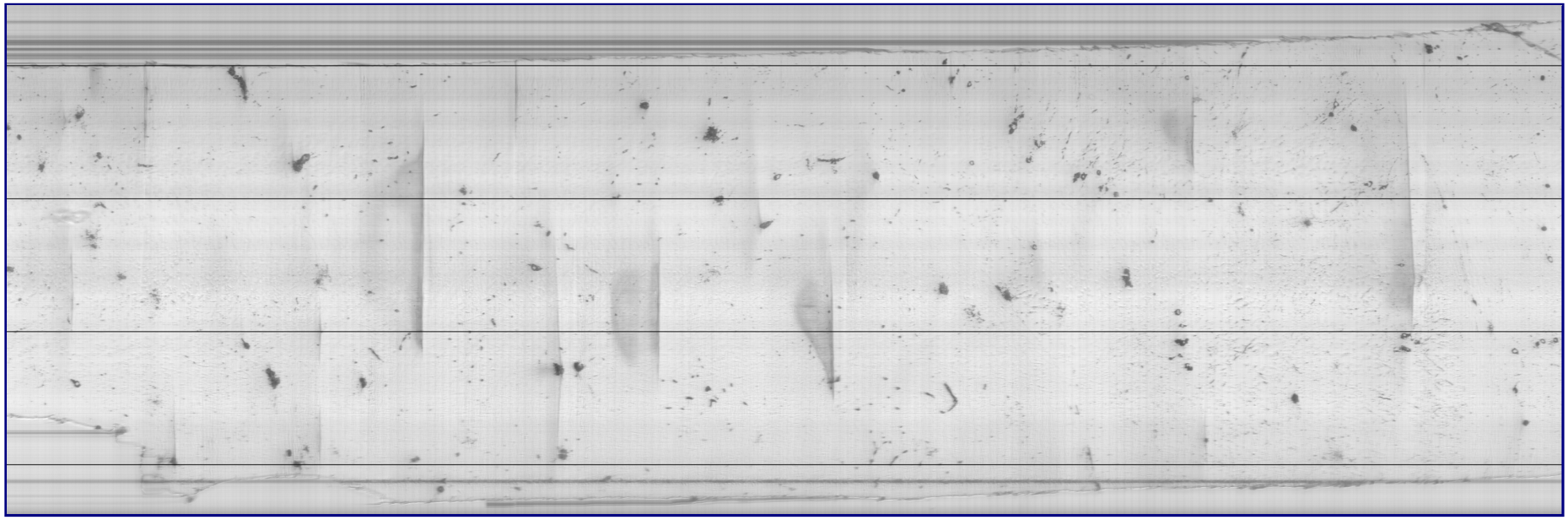


(b) Close-up A

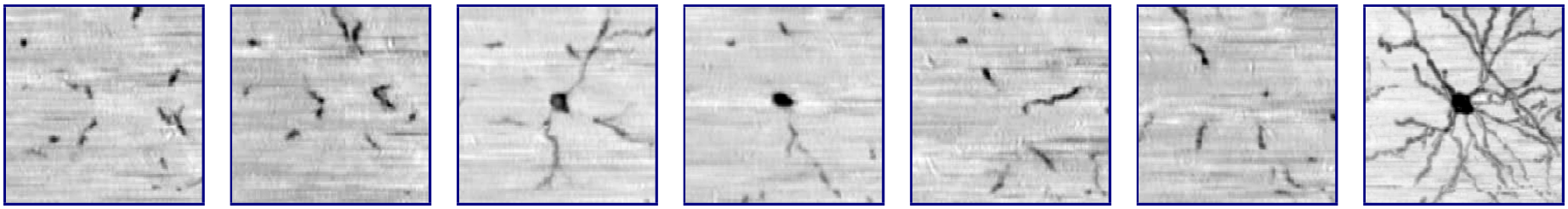
(c) Close-up B

- Typically, somata of cells are stained.

Typical Data: Golgi Stain, KESM



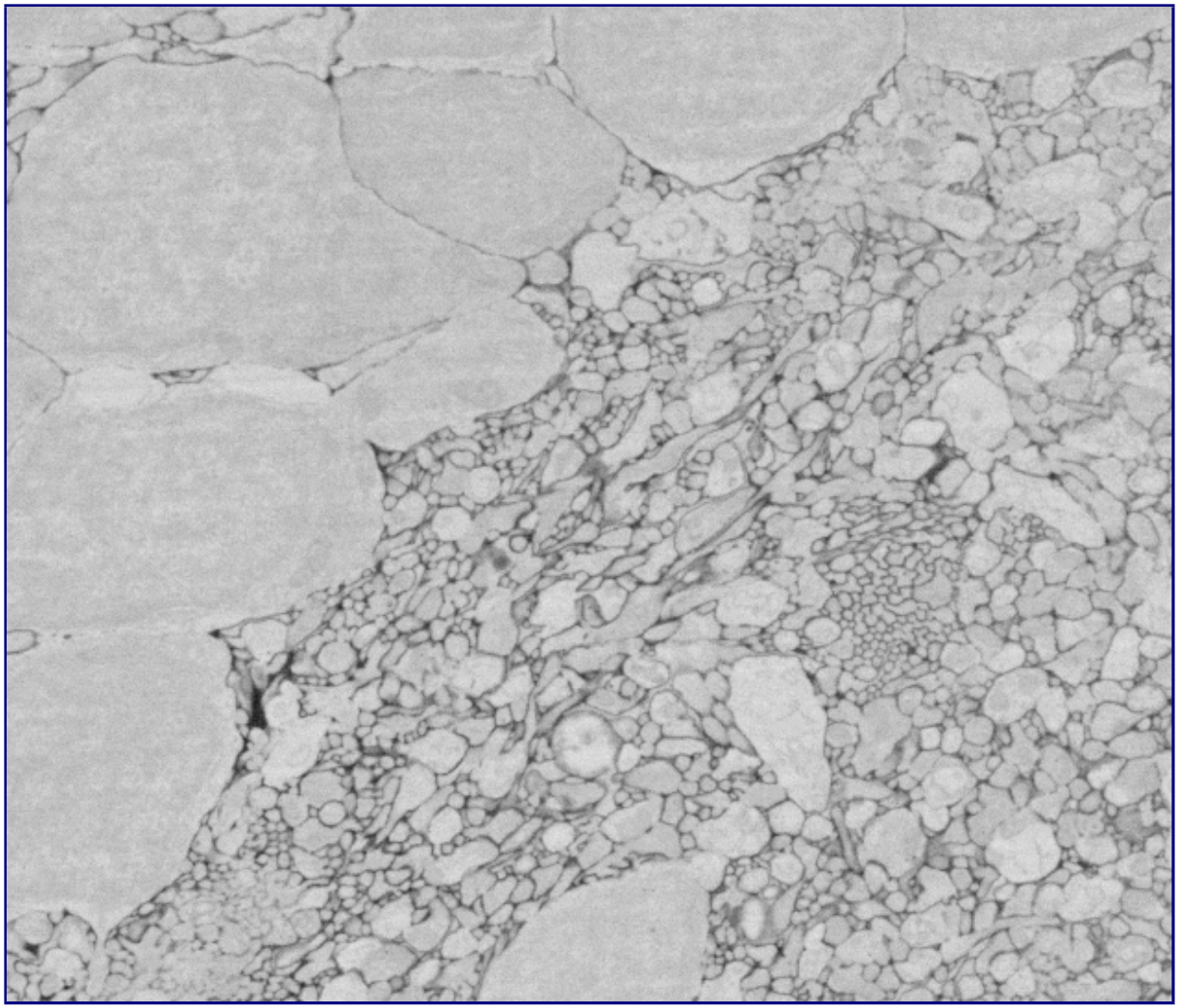
Mouse cortex



Slice 360 Slice 400 Slice 480 Slice 520 Slice 560 Slice 600 Overlay

- Full neuronal morphology is observable. Only $\sim$1% of all neurons stained.

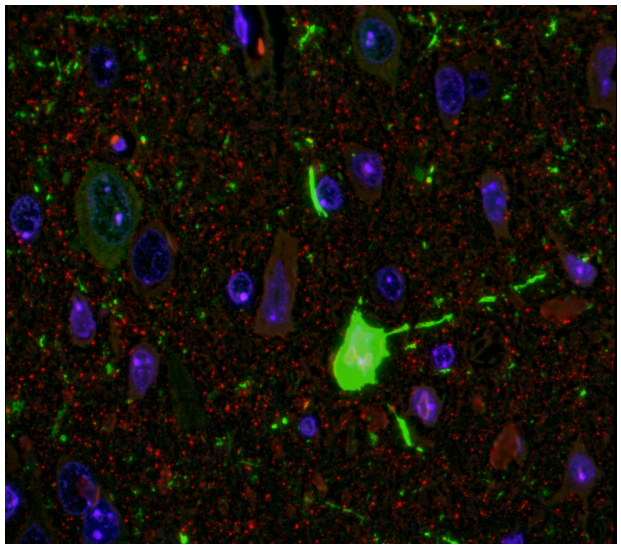
Typical Data: Heavy-element Stain, SBF-SEM



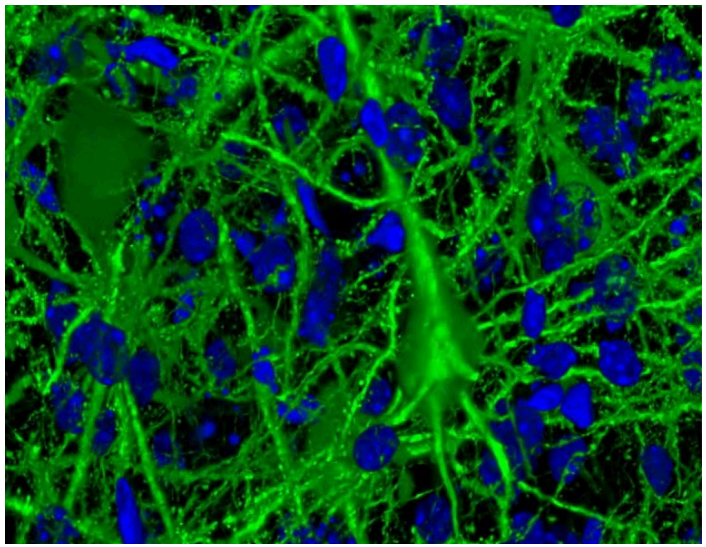
Zebra fish tectum

- Heavy-element staining of extracellular matrix.

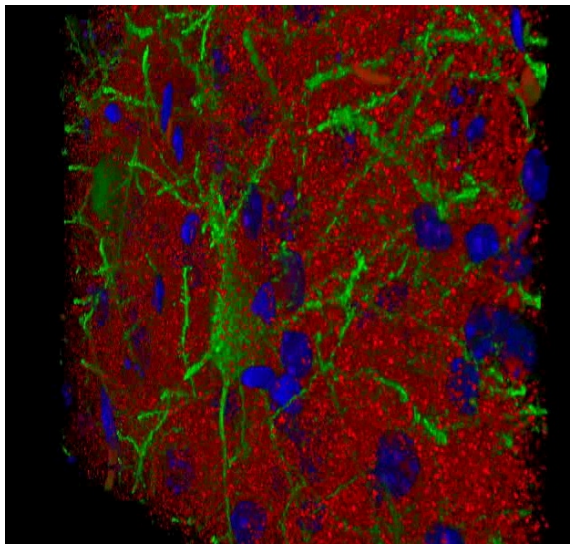
Typical Data: Array Tomography



(a) Single image plane



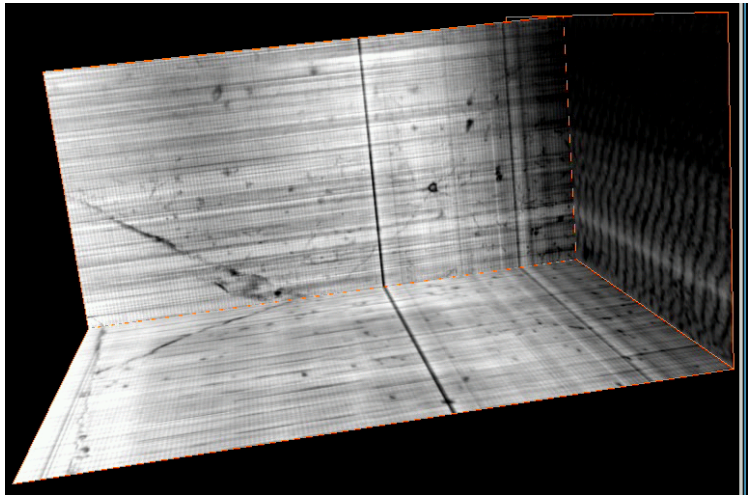
(b) Volume closeup



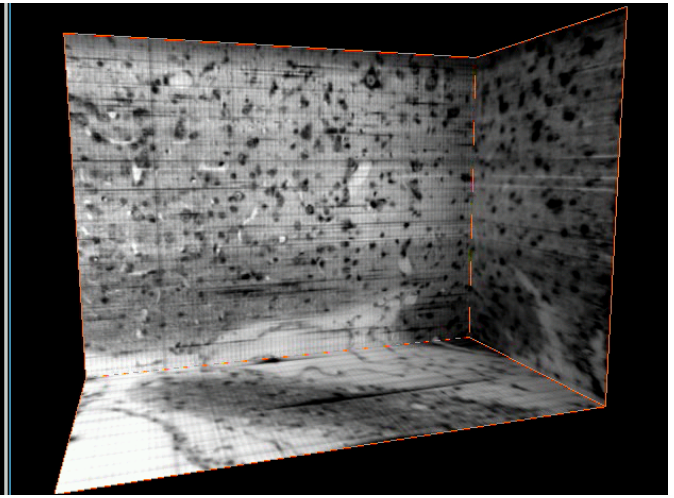
(c) Volume

- Multiple molecular stains: YFP (green), synapsin1 (red), DAPI (blue).
- $120 \times 110 \times 34$ μm^3 volume shown.

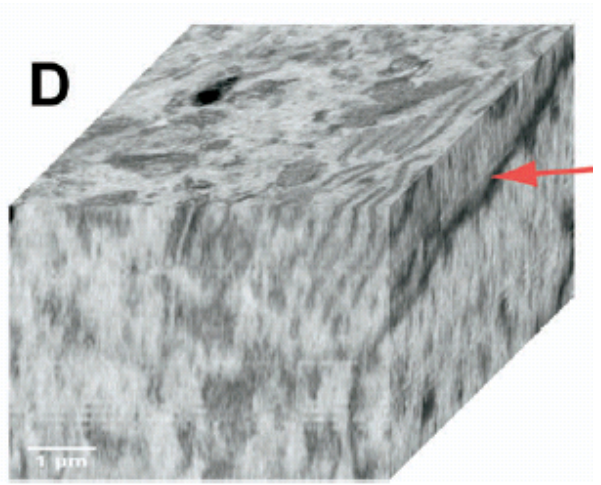
Typical Data Volumes



KESM Golgi (Mayerich et al. 2007a)



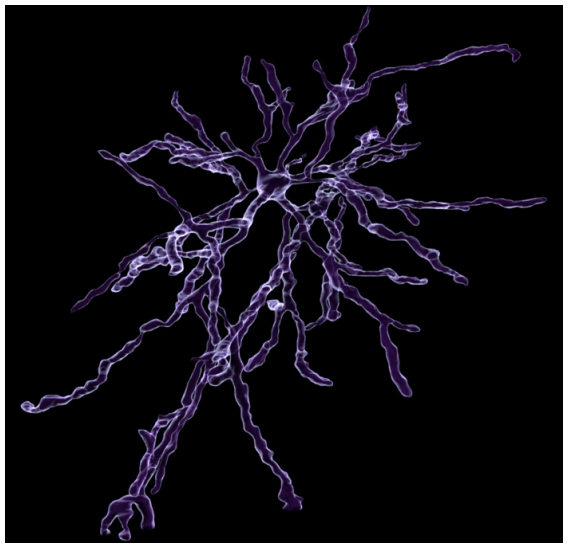
KESM Nissl (Mayerich et al. 2007a)



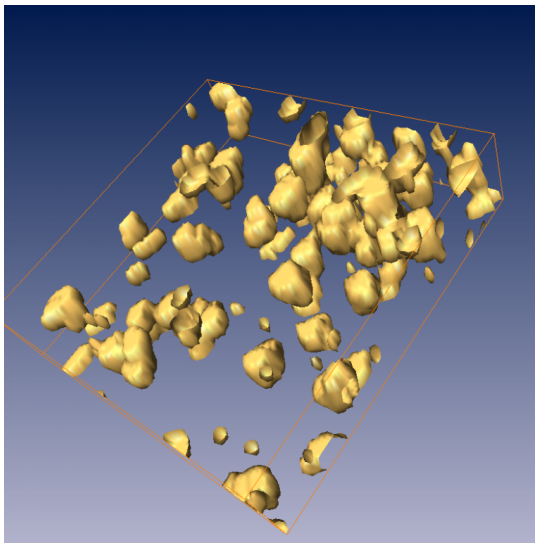
SBF-SEM (Denk and Horstmann 2004)

- A stack of images is obtained, representing a volume of brain tissue.

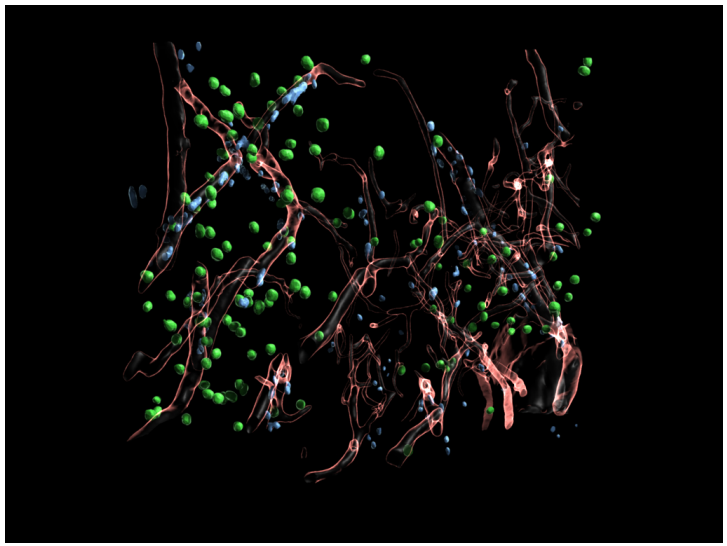
3D Reconstruction



Golgi (Neuron)



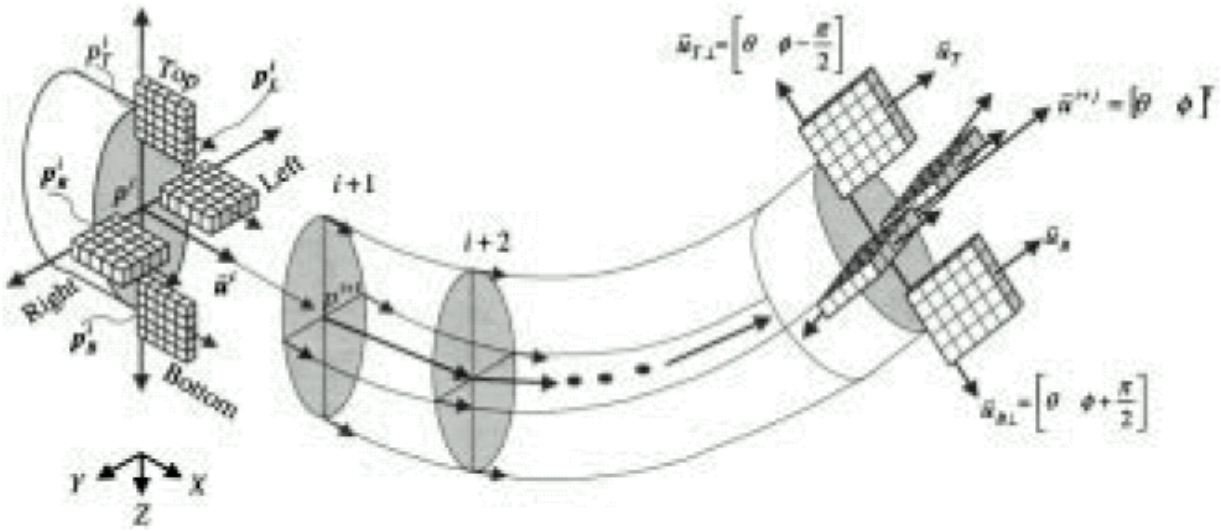
Nissl (Soma)



Nissl (Vasculature)

- Thresholding and iso-surface reconstruction can be used for sparse data.
- This approach does not work well for densely packed objects (EM).
- This approach does not result in morphological models.

3D Reconstruction: Vector Tracing

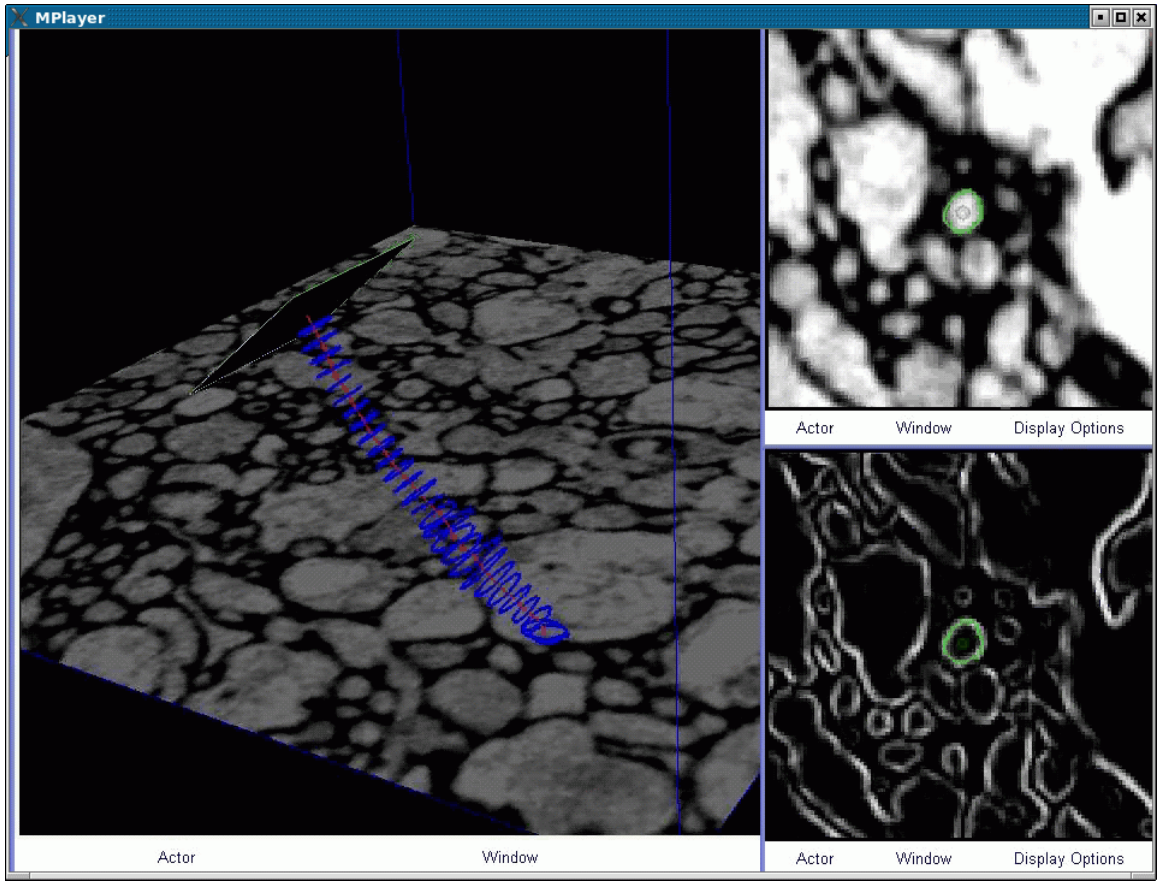


(a)

(Al-Kofahi et al. 2002)

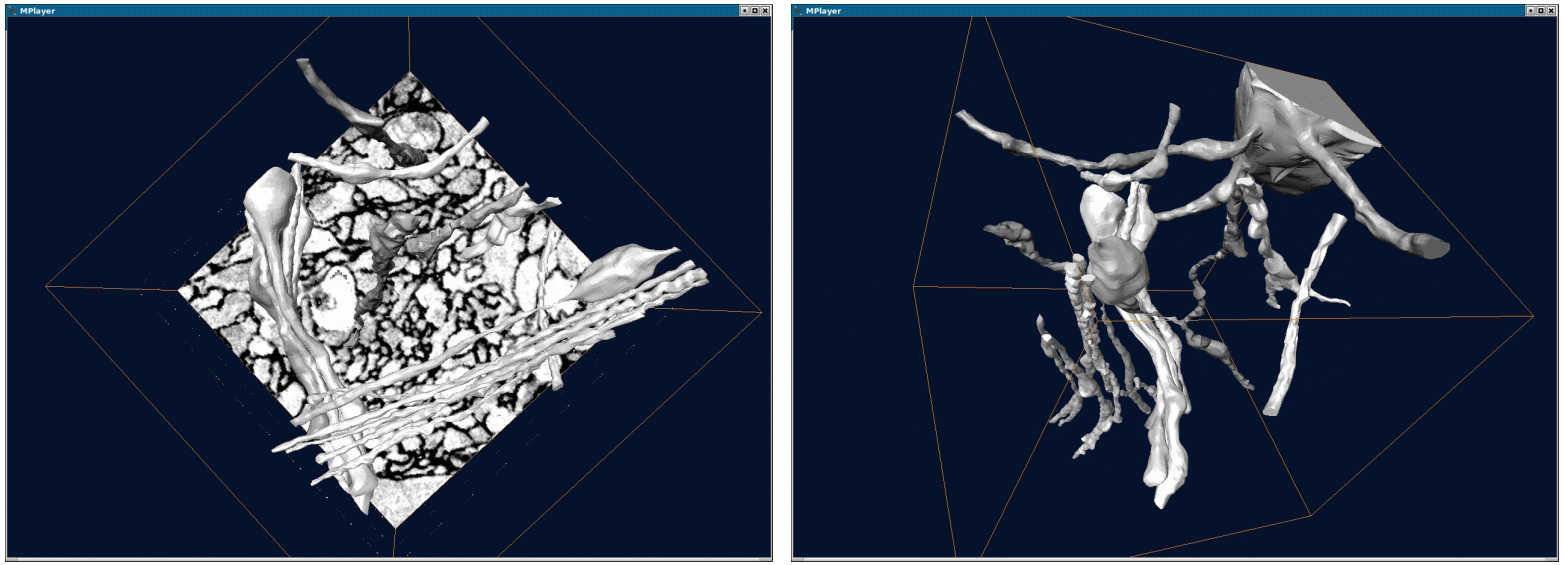
- Template-based vector tracing algorithm: computationally efficient.
- Templates are like orientable paddles (yaw, pitch, roll, translation, and distance from central axis).

3D Reconstruction: Vector Tracing



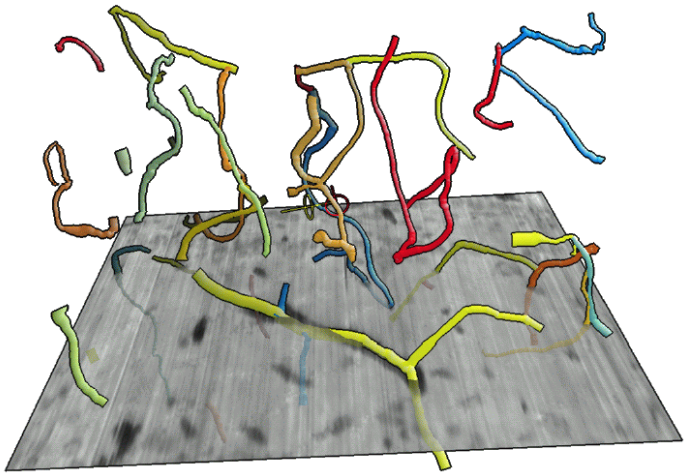
- Many densely packed fibers.
- Virtual sectioning along plane perpendicular to fiber path (local coordinate system), used with vector tracing algorithm (Busse et al. 2006).

3D Reconstruction: Vector Tracing Results (SEM)

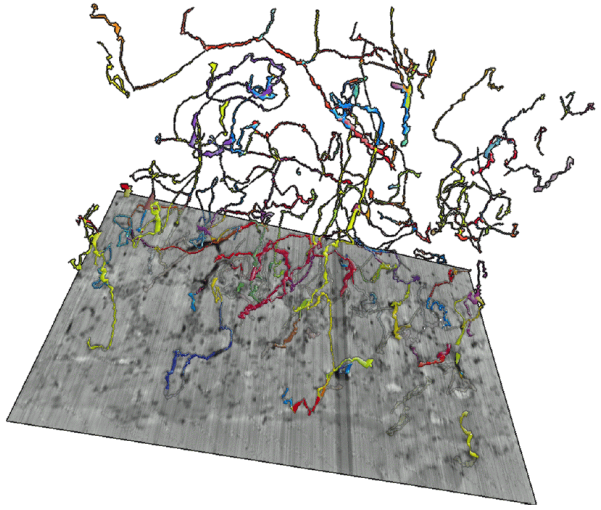


- Vector tracing combined with level set methods for segmentation (Busse et al. 2006).

3D Reconstruction: Vector Tracing (KESM)



(a) India Ink: Vasculature



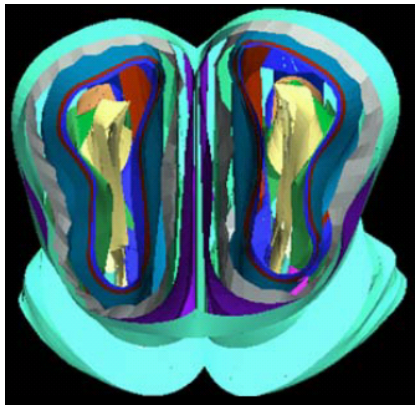
(b) India Ink: Vasculature

(c) Vector tracing process

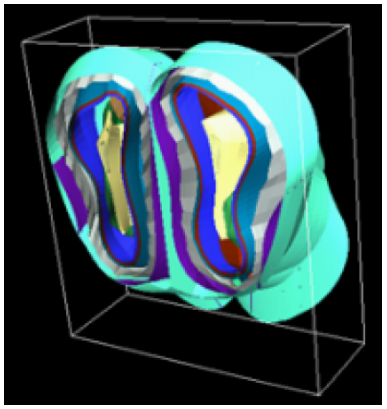
- Use of Graphical Processing Unit (GPU) for fast tracing (Mayerich et al. submitted, 2007). (Also see Han and Choe (2007).)

Mapping KESM to Brain Atlas

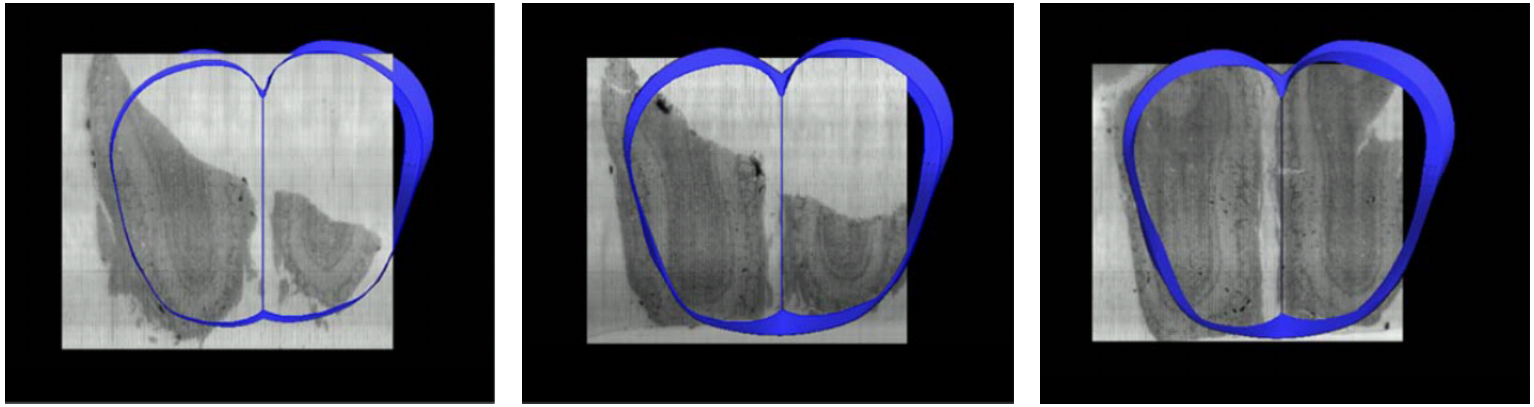
(a) 2D contour-based atlas



(b) 3D surface-based atlas



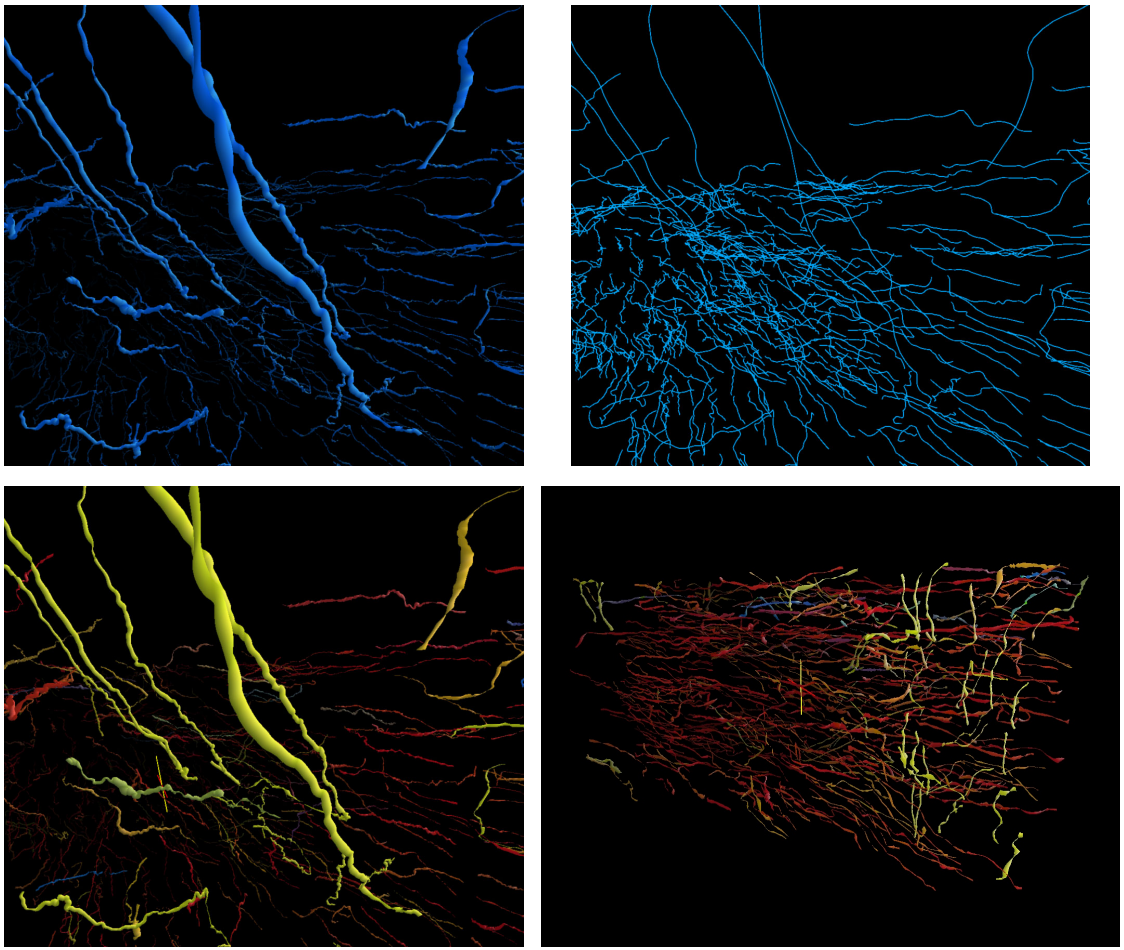
(c) 3D surface-based atlas



(e) Aligning KESM data to surface-based atlas

- From 2D contour-based atlas (Paxinos and Franklin 2001) to 3D surface-based atlas (Koh 2007).
- Map KESM data to 3D surface-based atlas (Koh 2007).

Interactive Visualization of Dense Fibers



- Use of self-orienting surfaces and GPU for fast interactive visualization of dense fibers (Melek et al. 2006).
- Orientation filtering for selective visualization (Melek et al. 2006).

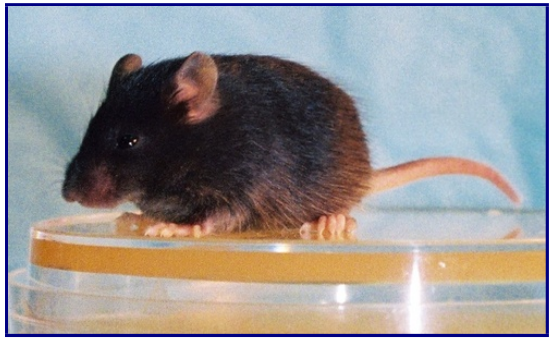
Collaborative Opportunities: Beyond the Brain

- Serial sectioning and imaging of cellular microstructure (300nm to 500nm resolution).
- Not restricted to brain tissue: Other small animal organs or small tissue volumes can be sectioned and imaged.

On-going Work and Future Directions

- Improved *en bloc* staining methods.
- Array tomography for high-resolution molecular imaging (Smith and Micheva 2007).
- Design, construction and commissioning of modified KESM (KESM 1.5).
- Superresolution methods to link SBF-SEM and KESM.
- Image processing and cutting artifact removal (Mayerich et al. 2007b).
- Texture segmentation of Nissl KESM data to link KESM and MRM-based mouse brain atlas.
- Morphological model and model fitting.
- Databasing reconstructed data and statistical querying.
- Integrated software environment and processing pipeline.
- Interactive, selective visualization using self-orienting surfaces.
- Multiscale integration: connectivity inference, neural density mapping, inferring scaling laws.

Acknowledgments



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- Project Personnel:
  - Texas A&M: Bruce H. McCormick, Louise C. Abbott, John Keyser, David Mayerich, Jaerock Kwon, Zeki Melek, Donghyeop Han, Yoon H. Bai, Jyothi S. Guntupalli, Pei-San Huang.
  - Stanford: Stephen J. Smith, Kristina Micheva, Brad Busse
- Contributors: Charles A. Taylor, R. Y. Arakaki (Stanford); Arthur Toga (UCLA); Winfried Denk (Max Planck)

Image source: http://www.mouseatlas.org/data/mouse/stages/t47/view

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