Multiscale Integration of Brain Data: New insights into glial architecture in health and disease

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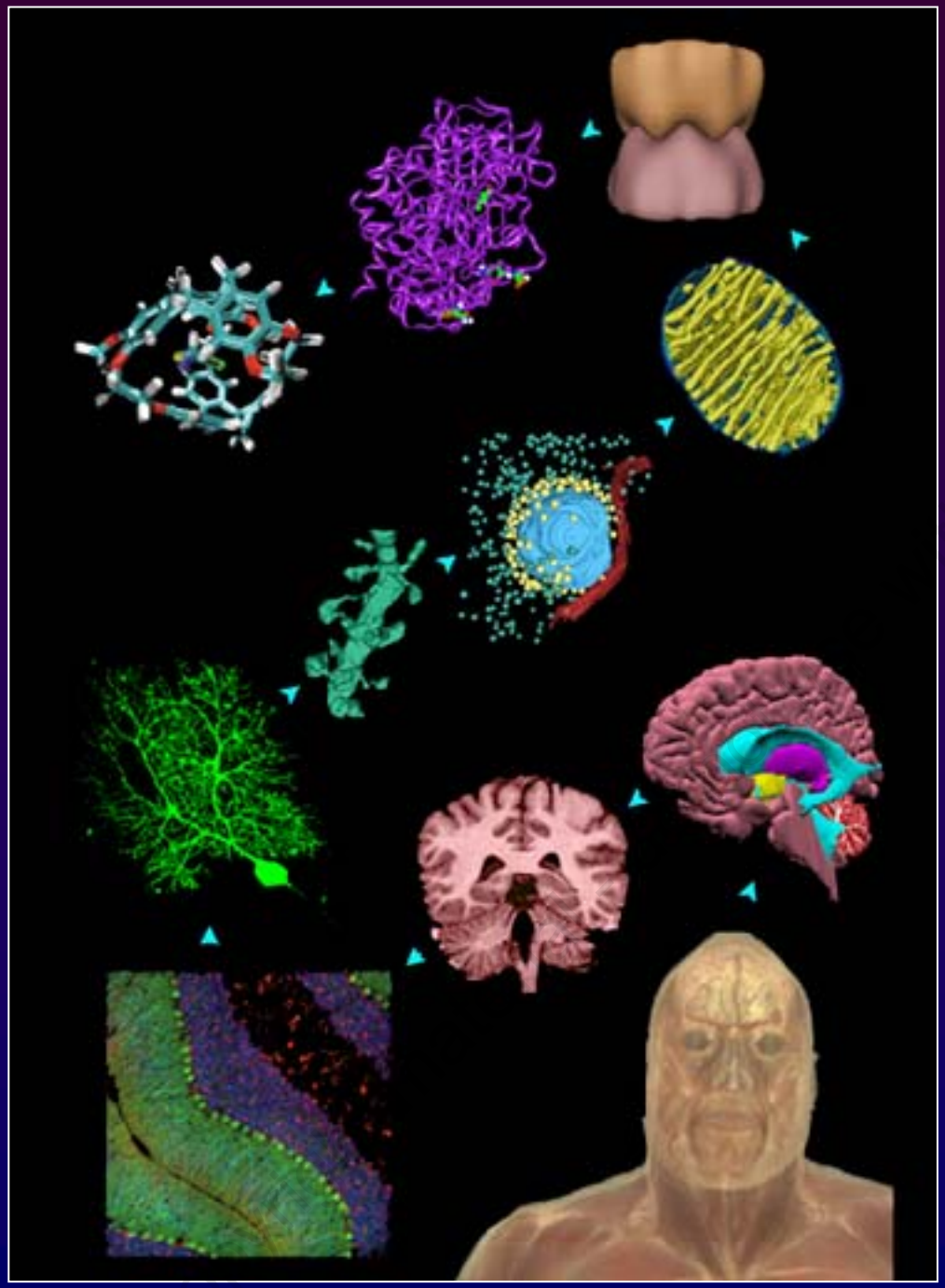
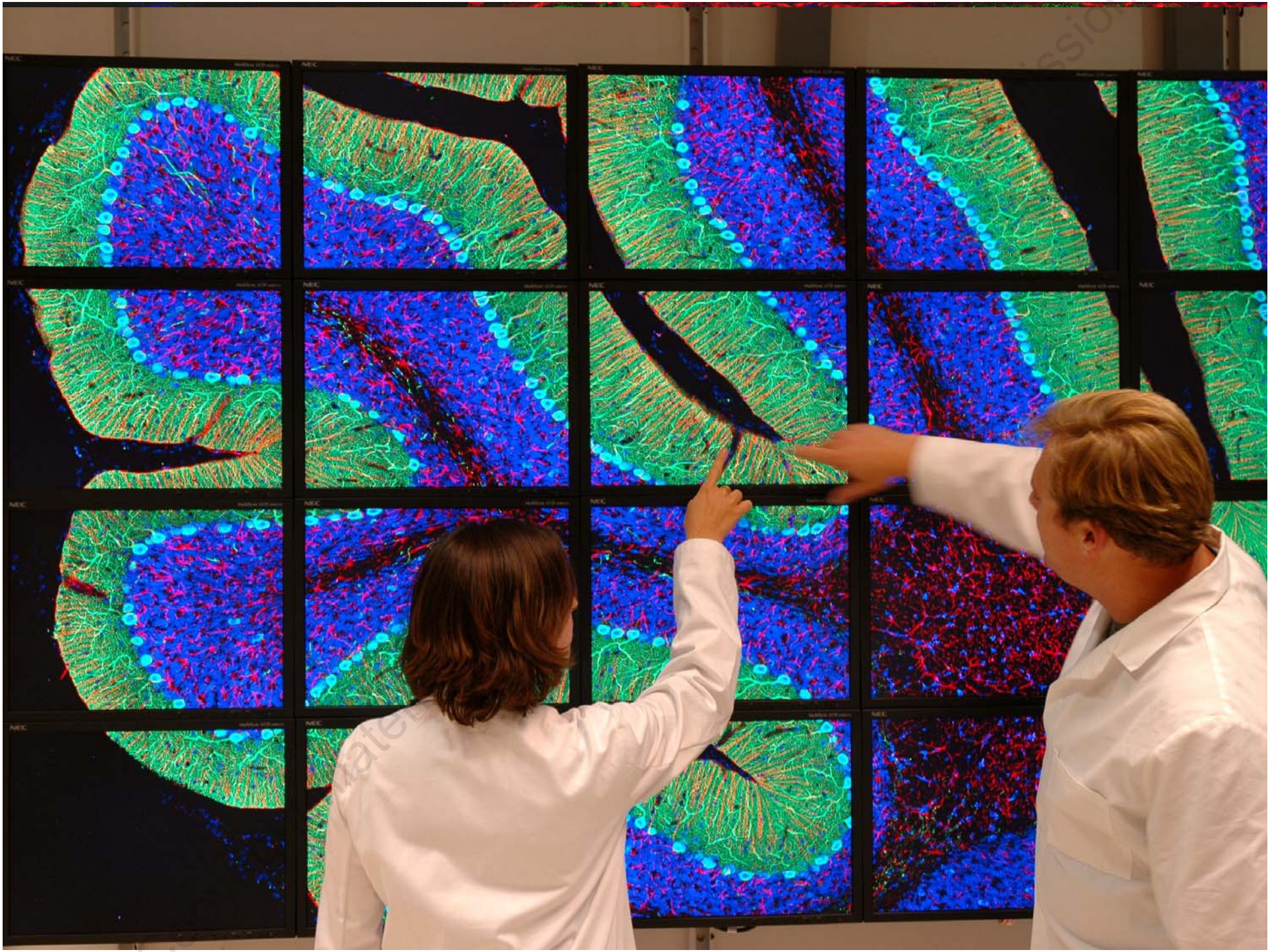


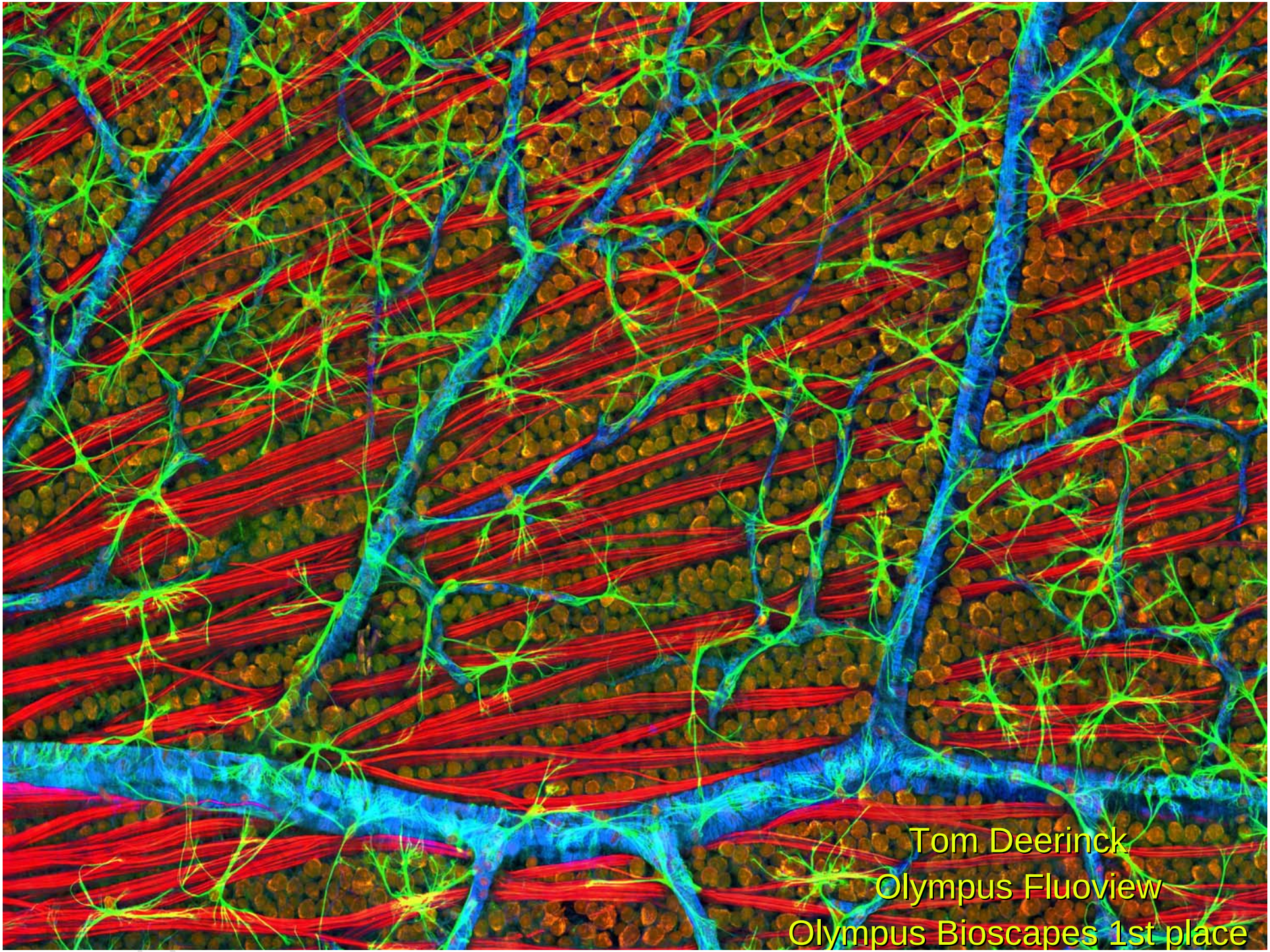
"We now have unprecedented ability to collect data about nature…but there is now a crisis developing in biology, in that completely unstructured information does not enhance understanding" - Sydney Brenner, 2003, BISTI conference

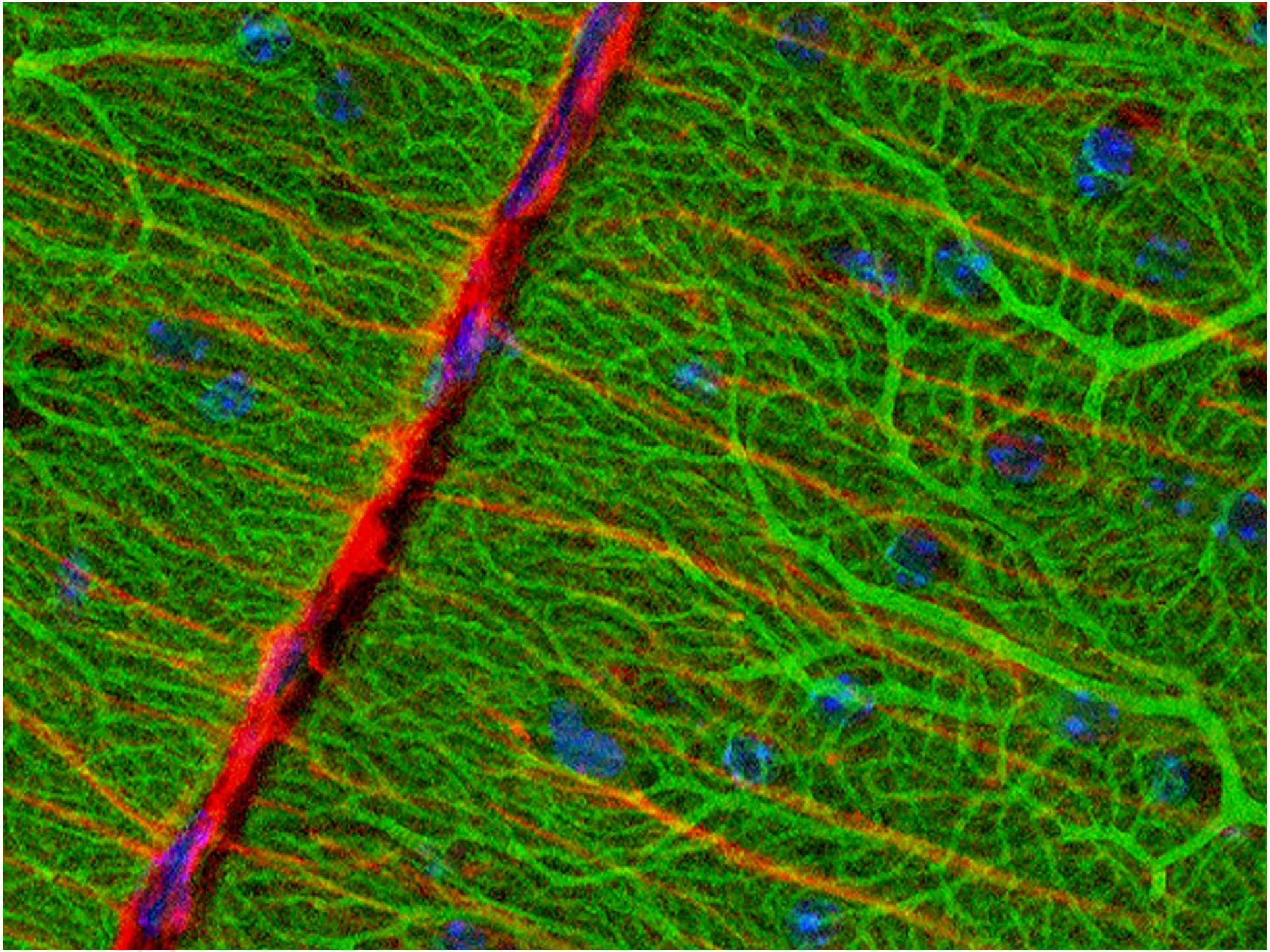
•No single technique reveals all of the molecular and structural complexity of the nervous system

•No single instrument can image the nervous system with sufficient scope and resolution

•Multiscale integration requires Imaging (staining and instrumentation), analysis and informatics

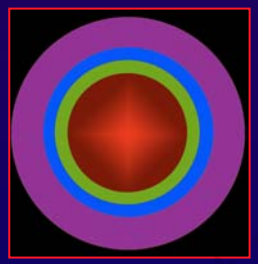


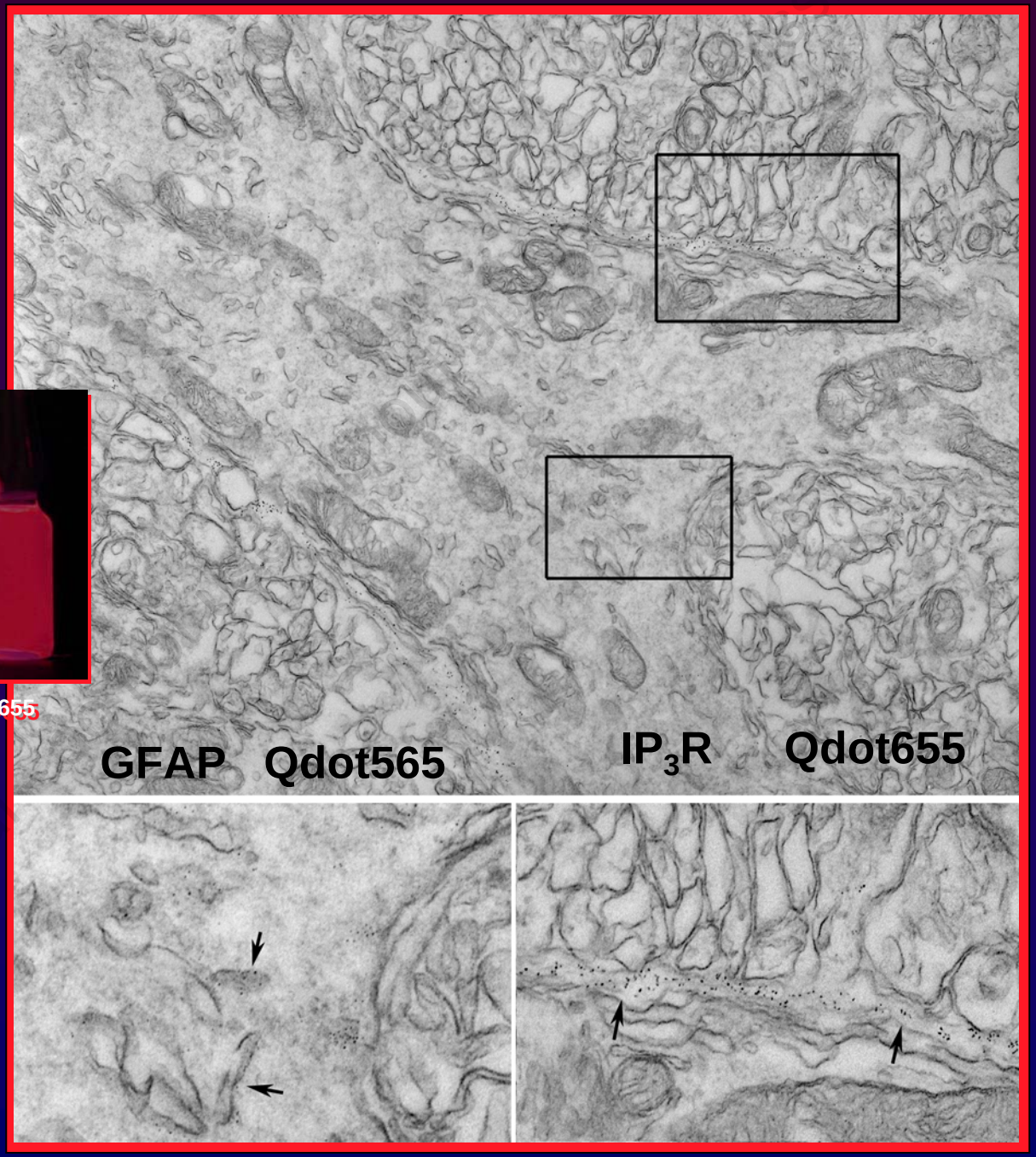

Tom Deerinck
Olympus Fluoview
Olympus Bioscapes 1st place



One step further…

Multiple labeling at EM level with QD's



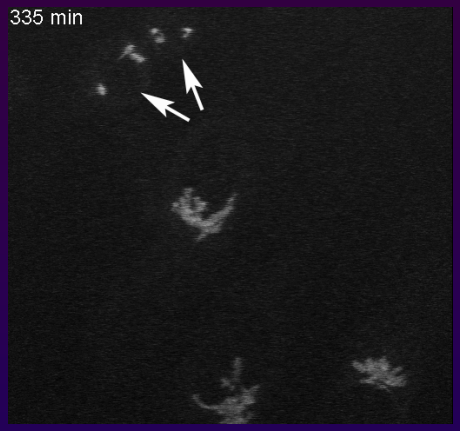


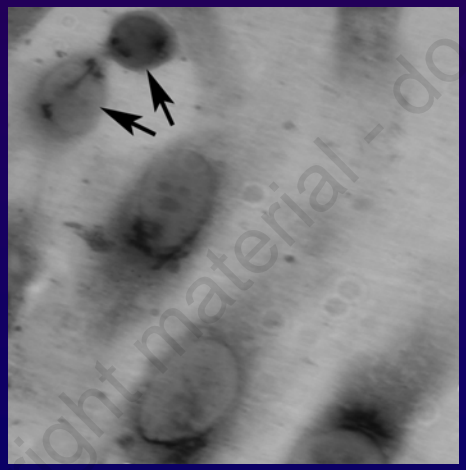
Tom Deerinck, Benjy Smarr, Ben Giepmans, Ying Jones

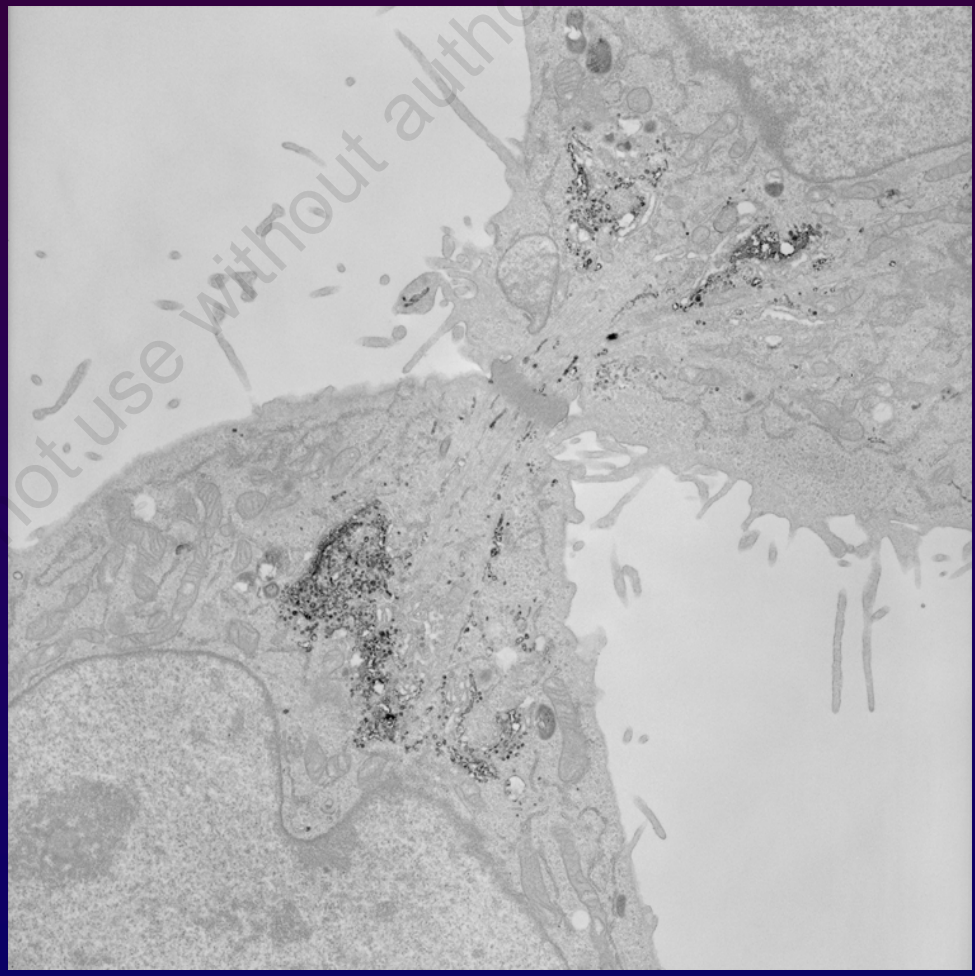
Labeling Technologies to Propel Correlated Multi-Scale Imaging of Cells and Tissues:

Tetracysteine tags as tools for correlated LM/EM

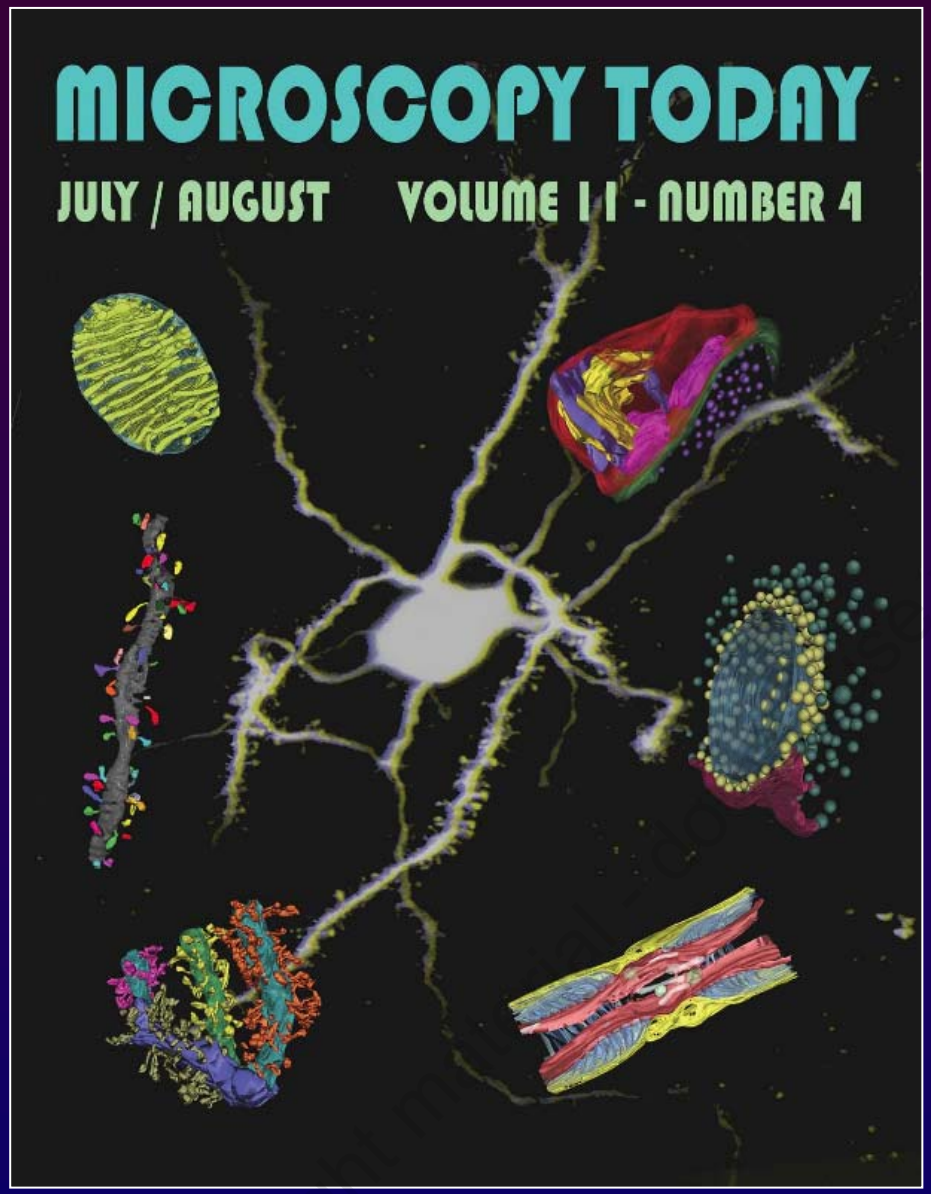
Time-lapse imaging of Golgi







Gaietta, Giepmans et al. "Golgi twins in late mitosis revealed by genetically encoded tags for live cell imaging and correlated electron microscopy." PNAS Nov. 2006



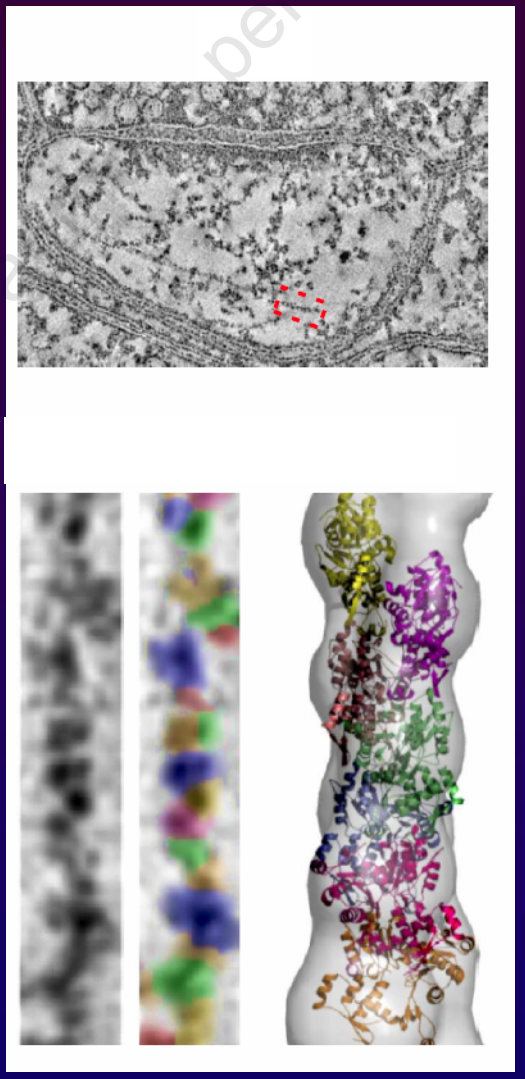
Gina Sosinsky and Maryann Martone

Electron tomography has become an indispensable tool for filling in the resolution gap between light and electron microscopy and between cell and molecule

- Derivation of 3D structure from a series of 2D projections
- Capable of resolving molecular structure in situ
- When used in conjunction with HVEM, provides detailed 3D structure in 0.5-5 µm thick sections

Cell → Subcellular Structure → Macromolecule

QuickTime™ and a Quicktime for Linux decompressor are needed to see this picture.



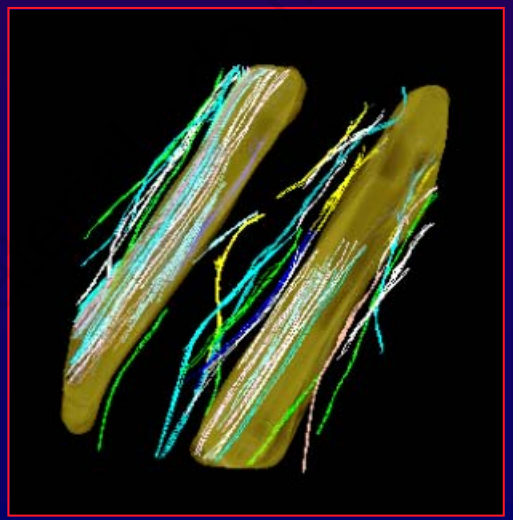
4 µm thick section of spiny dendrite imaged on the UHVEM at Osaka University

Richard Weinberg, Alain Burette, John Crum

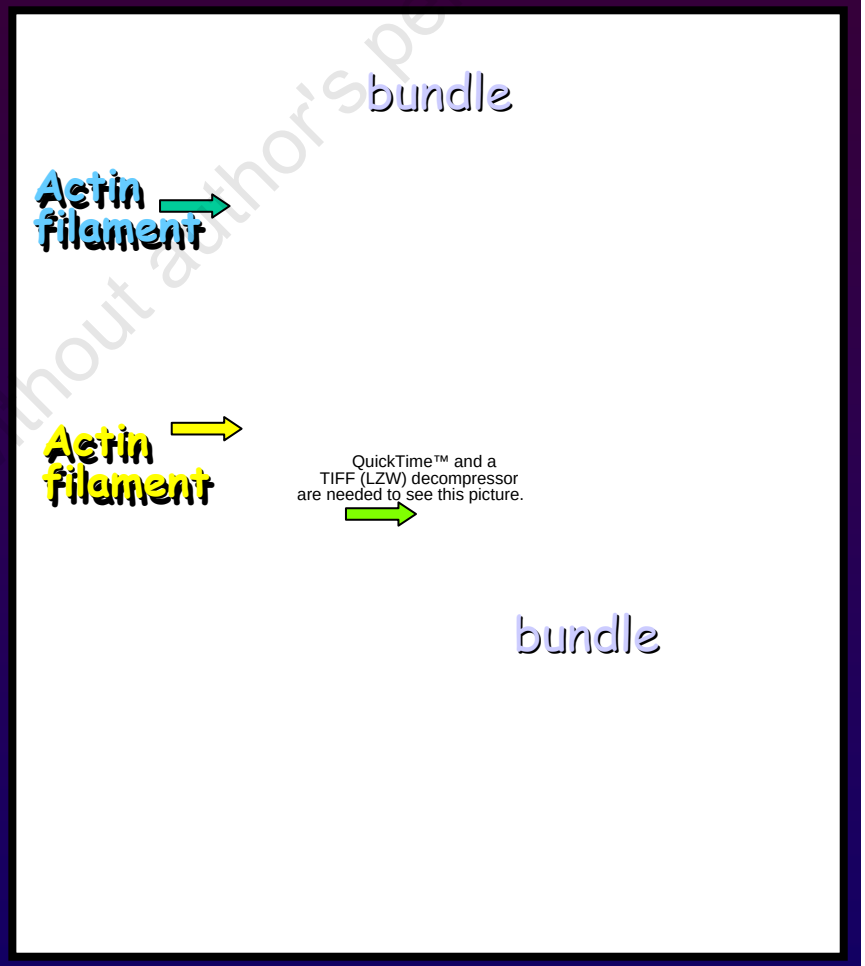
From Live Cells to Macromolecular Distributions

QuickTime™ and a
decompressor
are needed to see this picture.

Ben Giepmans,
actin-FlAsH



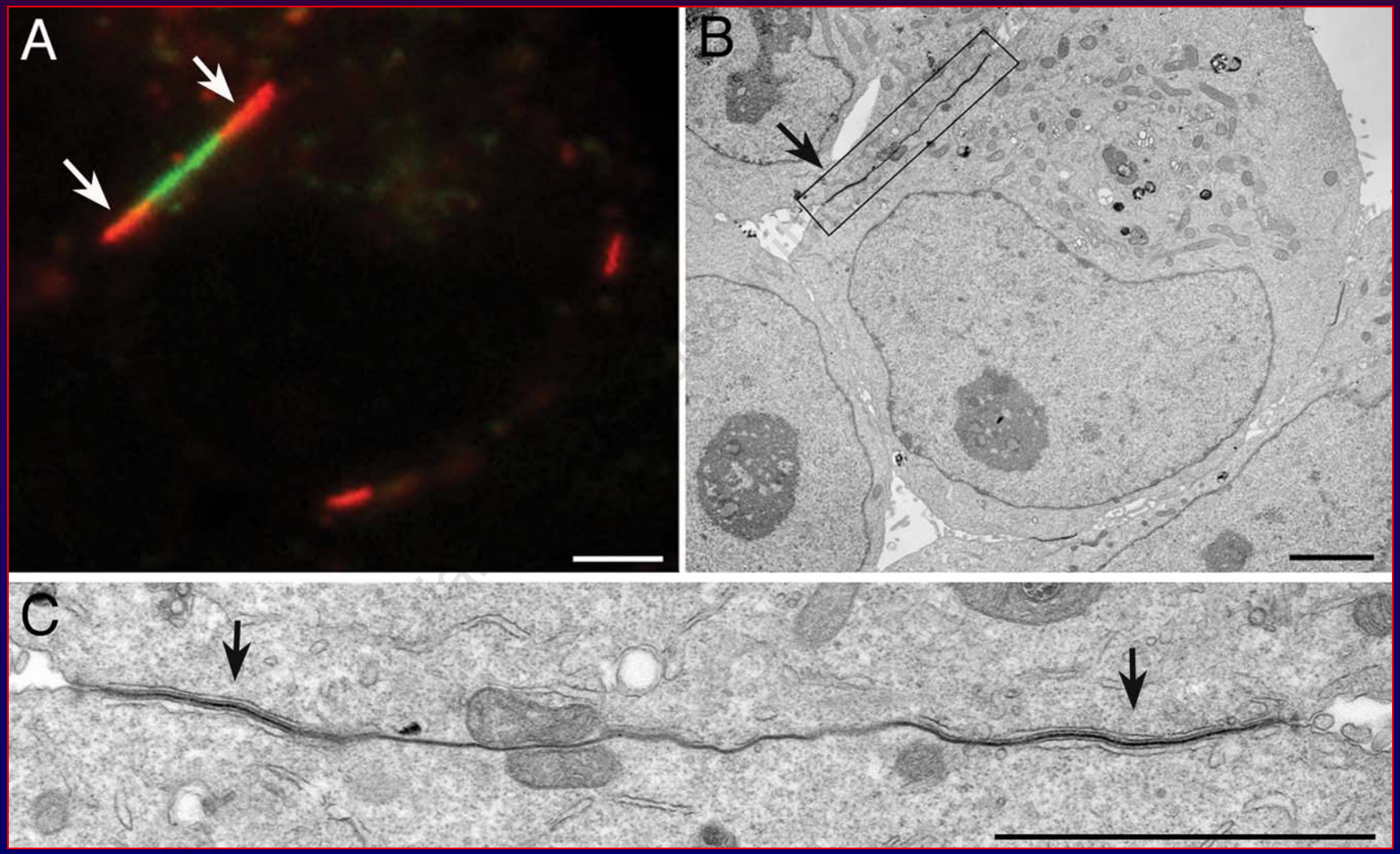
Individual filaments are resolved inside and outside the bundles



Single tilt tomography, energy filtered, ReAsH actin-photooxidation

Gina Sosinsky, Mason Mackey, Masako Terada, Rick Lawrence

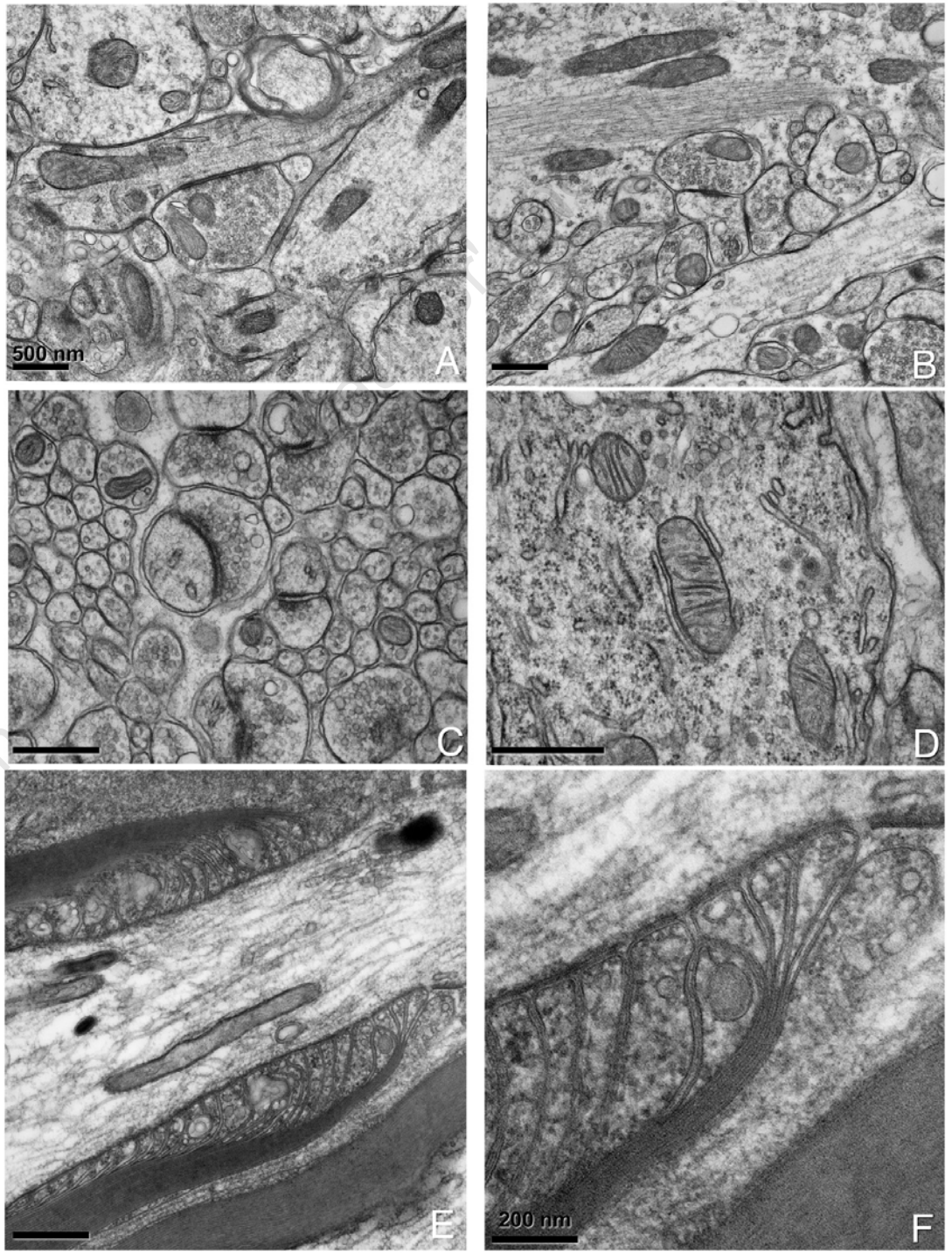
Optical Pulse Chase with FlAsH and ReAsH: correlated time-lapse microscopy



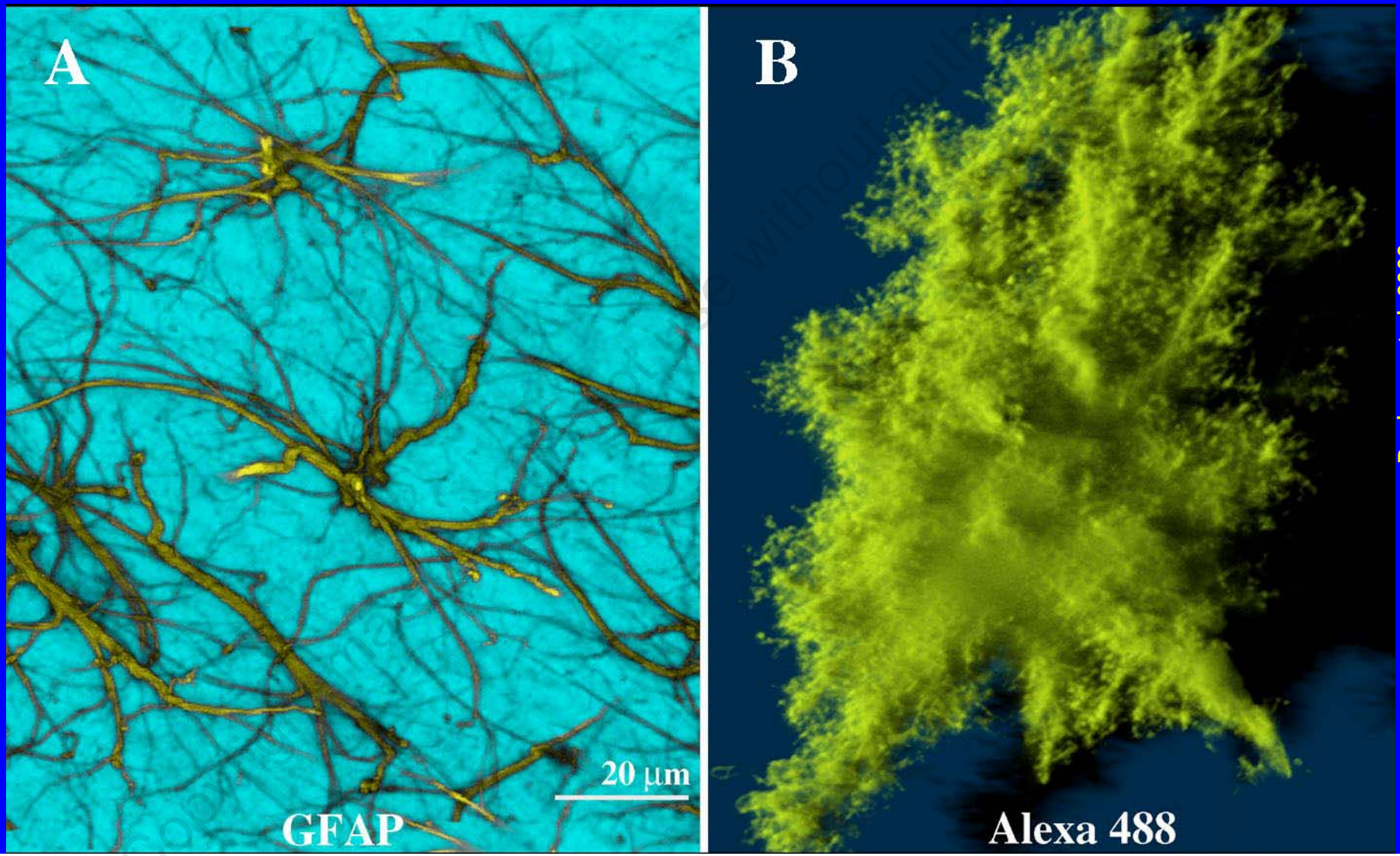
Chemical Fixation + High Pressure Freezing

- Light chemical fixation with aldehydes
  - Labeling/staining
- HPF freezing
- Freeze substitution

Gina Sosinsky, Ying Jones, Mark Ellisman

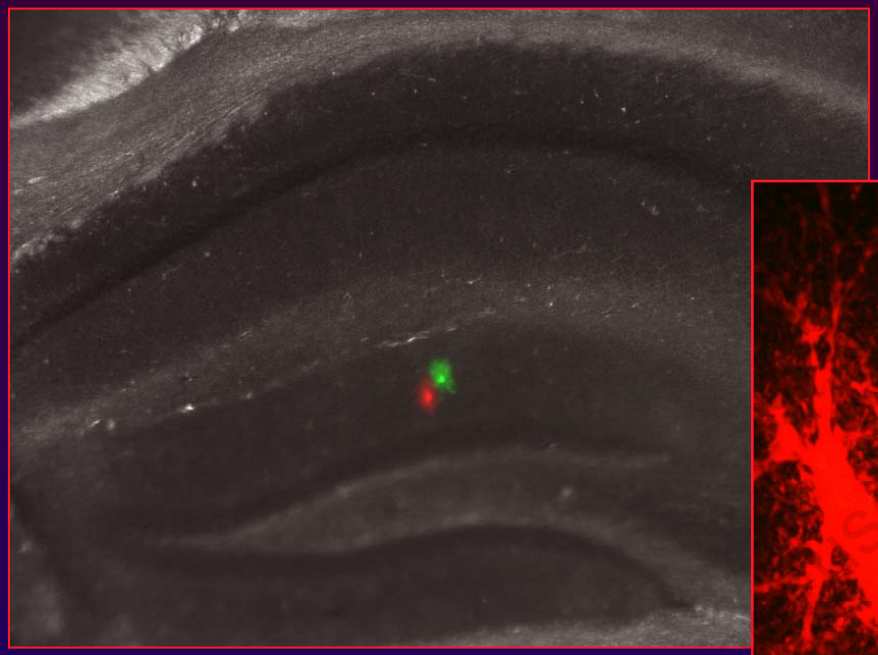


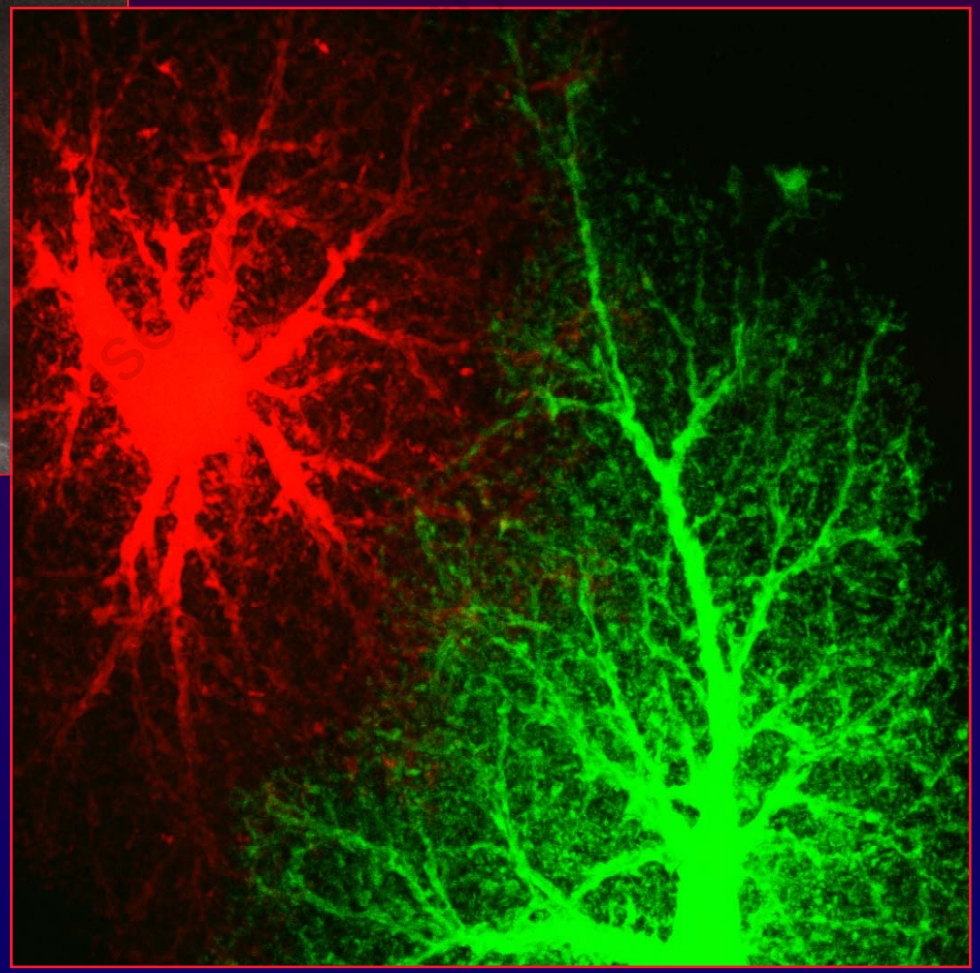
GFAP Grossly Underestimates Astrocyte Extent and Volume



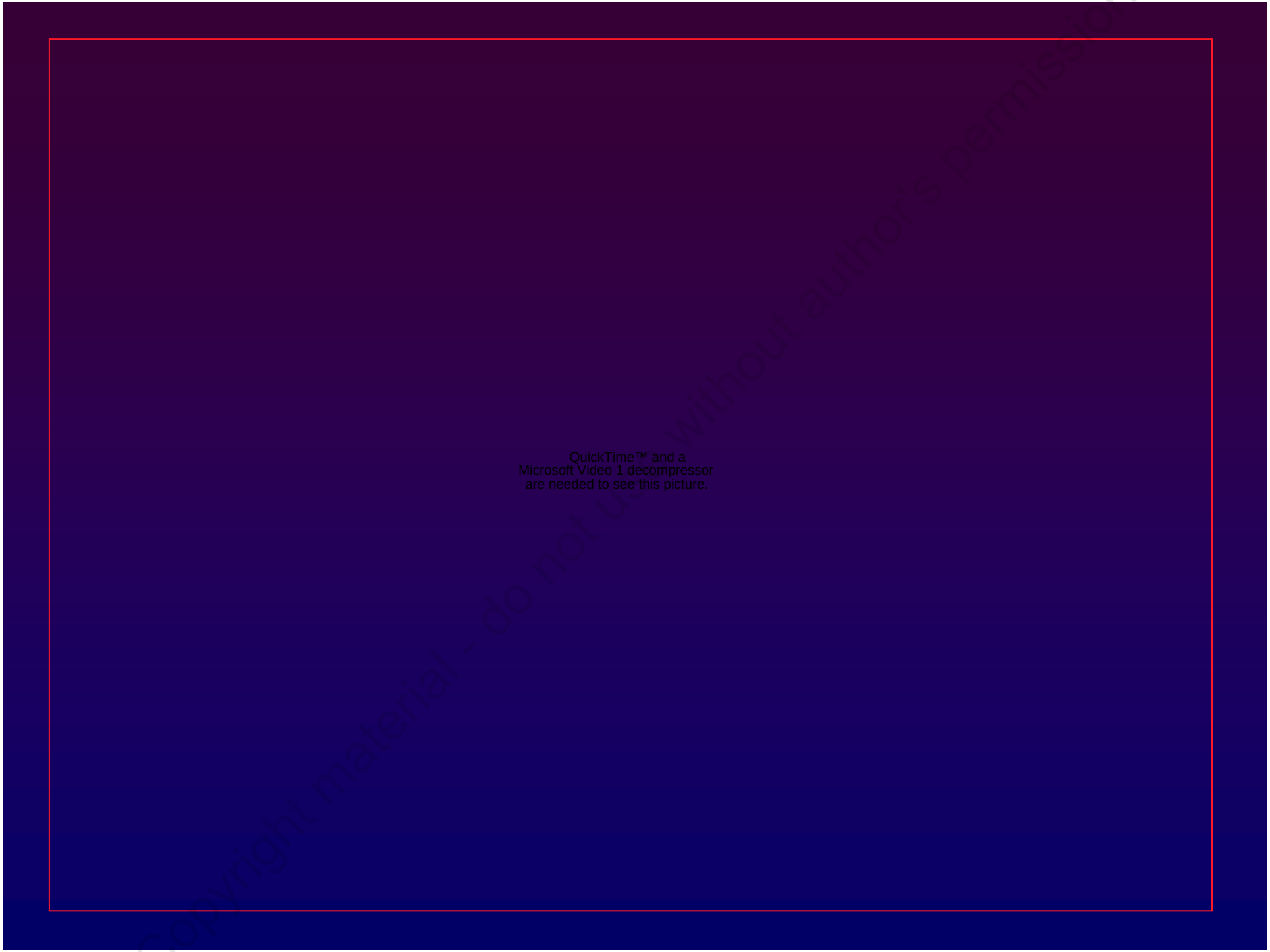
Bushong et al. 2002

Relationship between Neighboring Astrocytes

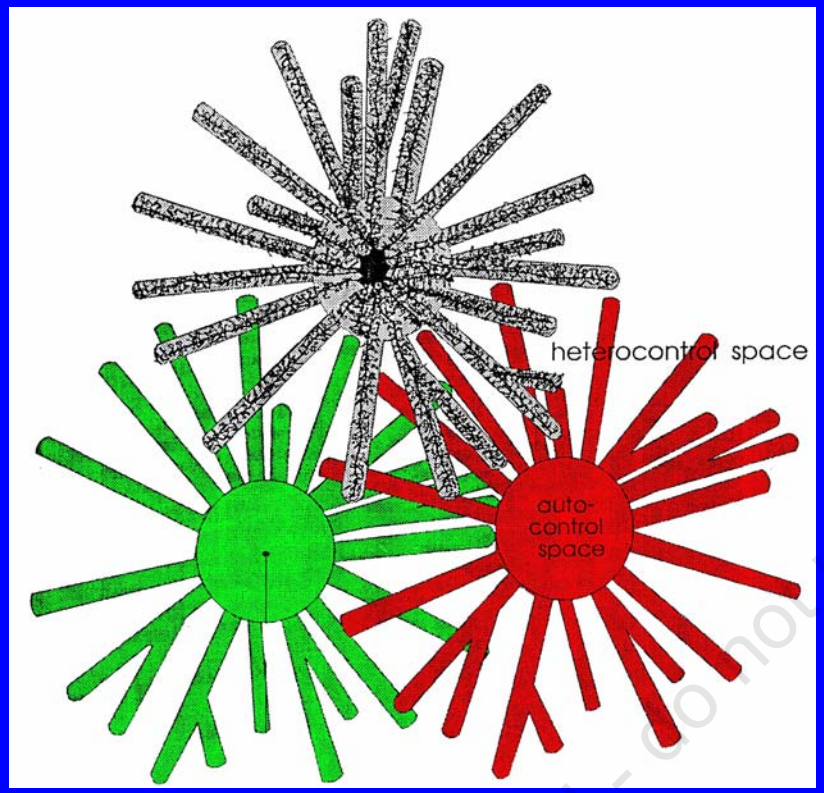


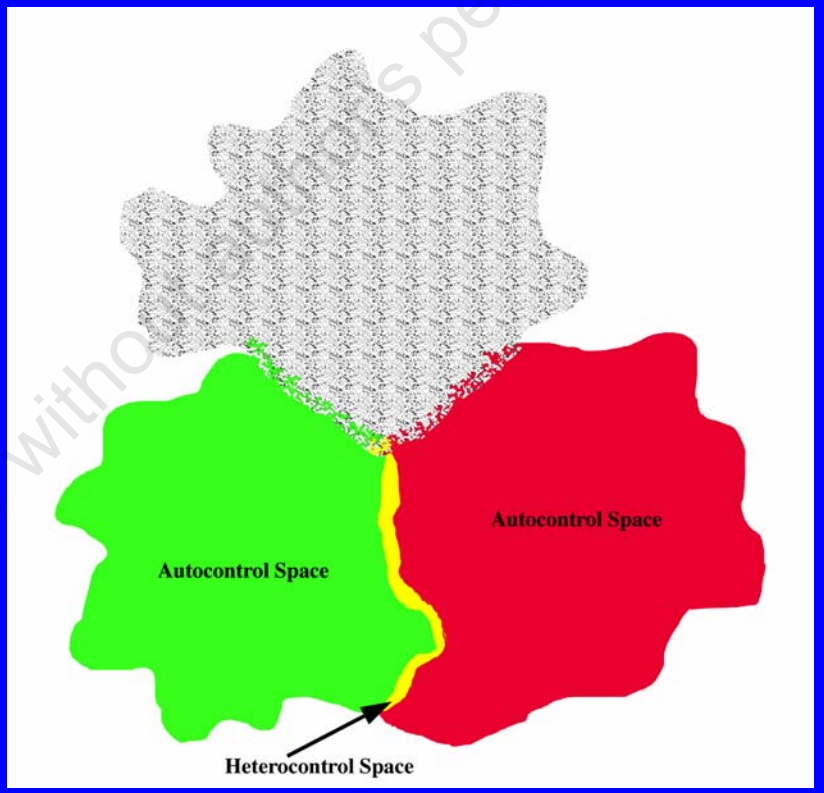


Bushong et al., 2002



Astrocytes Establish Domains





- Protoplasmic astrocytes establish large autocontrol spaces with their spongiform processes.
- Each astrocyte domain is about 65,000 cubic microns.
- There are approximately 120,000 synapses in each domain.

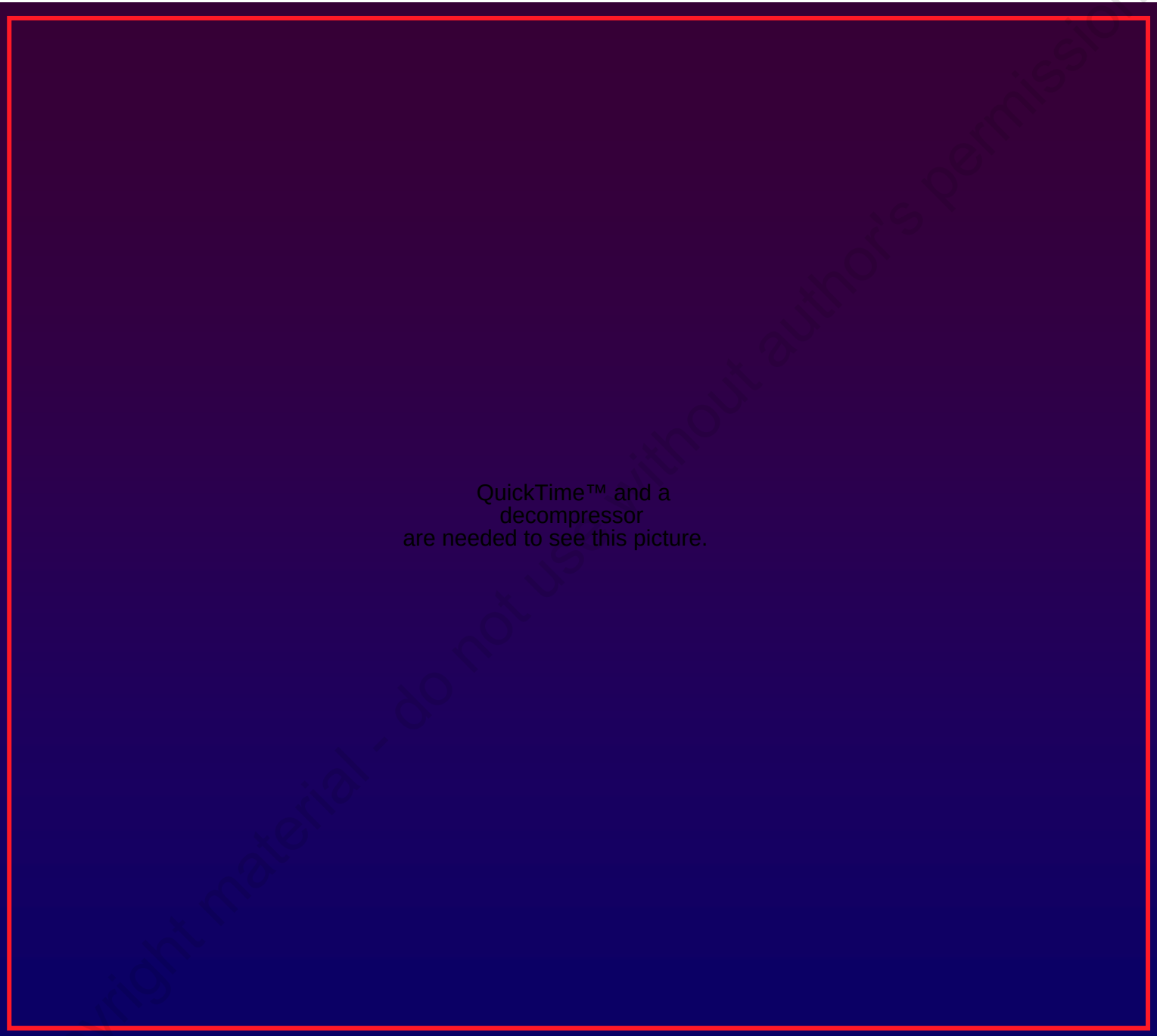
Bushong et al. 2002

Electron tomography:
connexin 43 +
quantum dots

Astrocyte-astrocyte
gap junction

QuickTime™ and a
H.264 decompressor
are needed to see this picture.

Tom Deerinck

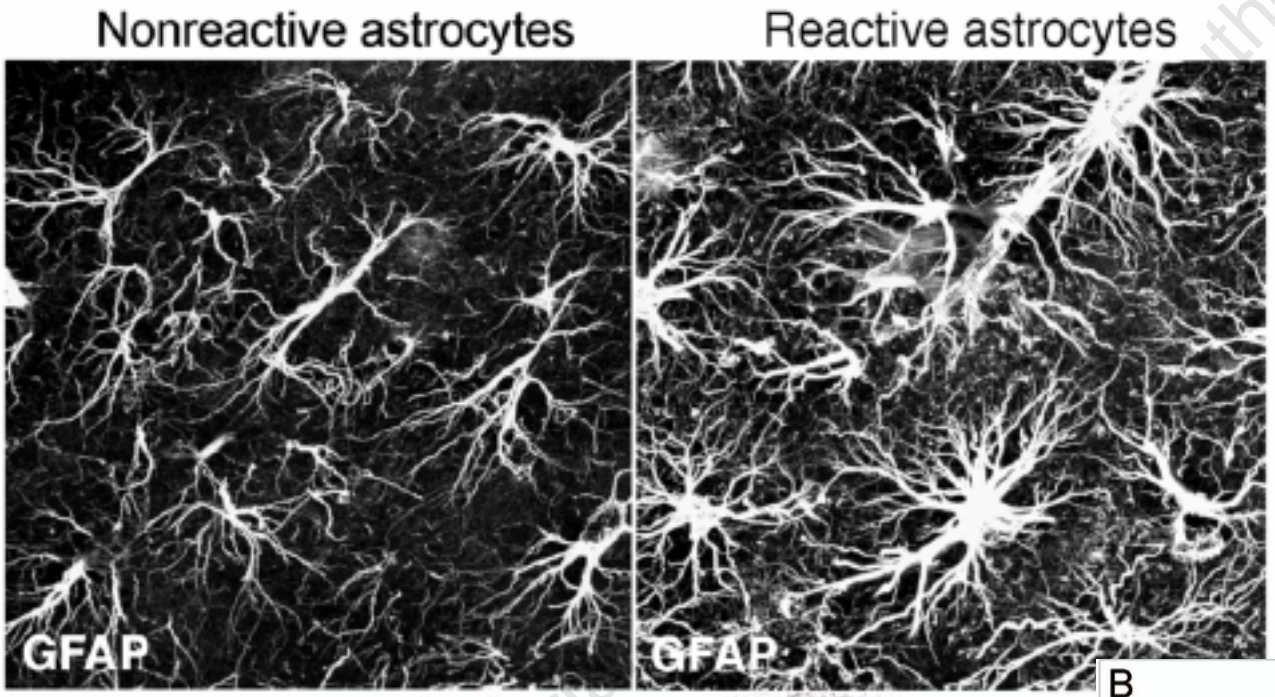


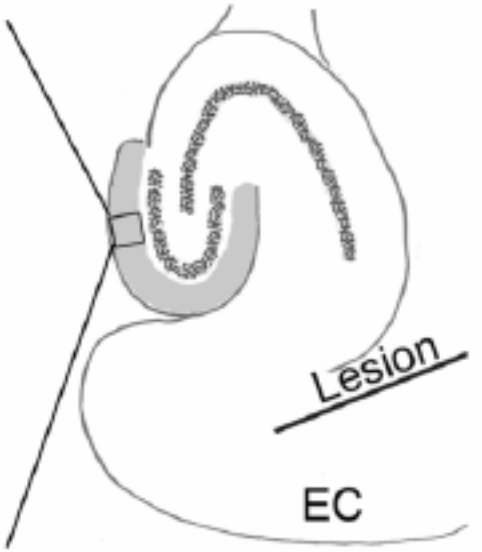
Bryan Smith, Benjy Smarr, Mark Ellisman

Redefining the Concept of Reactive Astrocytes:

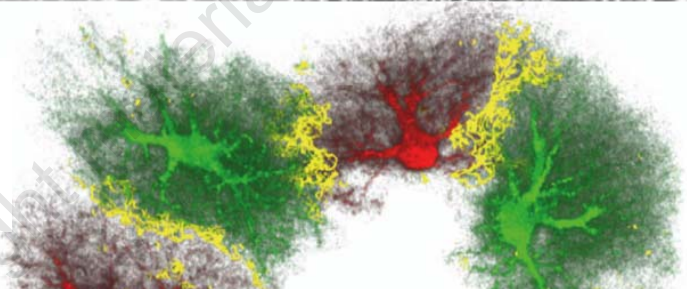
- ***Astrocytes reacting to injury remain within their unique domains***
- ***The increase in thickness of GFAP processes found in reactive astrocytes is not associated with an increased size of the astrocytes domain.***

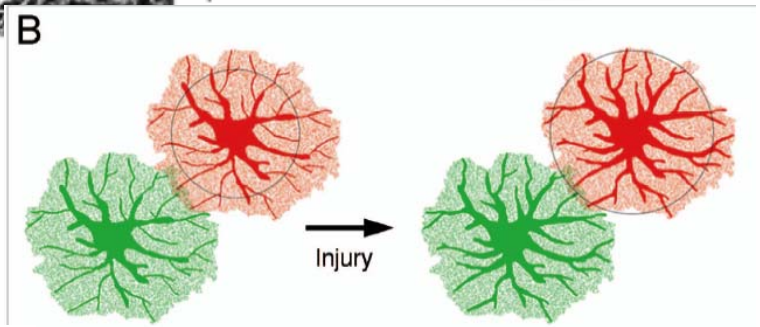
True for the deafferented dentate gyrus of the hippocampus and in the electrically lesioned cortex.





Filled and GFAP Stained





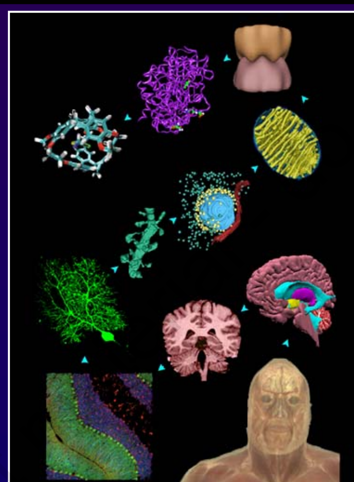
Ulrika Wilhelmsson, Eric A Bushong, Diana L Price, Benjamin L Smarr, Van Phung, Masako Terada, Mark H Ellisman, and Milos Pekny *(In Press) PNAS*

Informatics: Multiscale and Multi-investigator Integration

BIRN
Biomedical Informatics Research Network

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.

*Will no longer matter where data, instruments and computational resources are located physically"



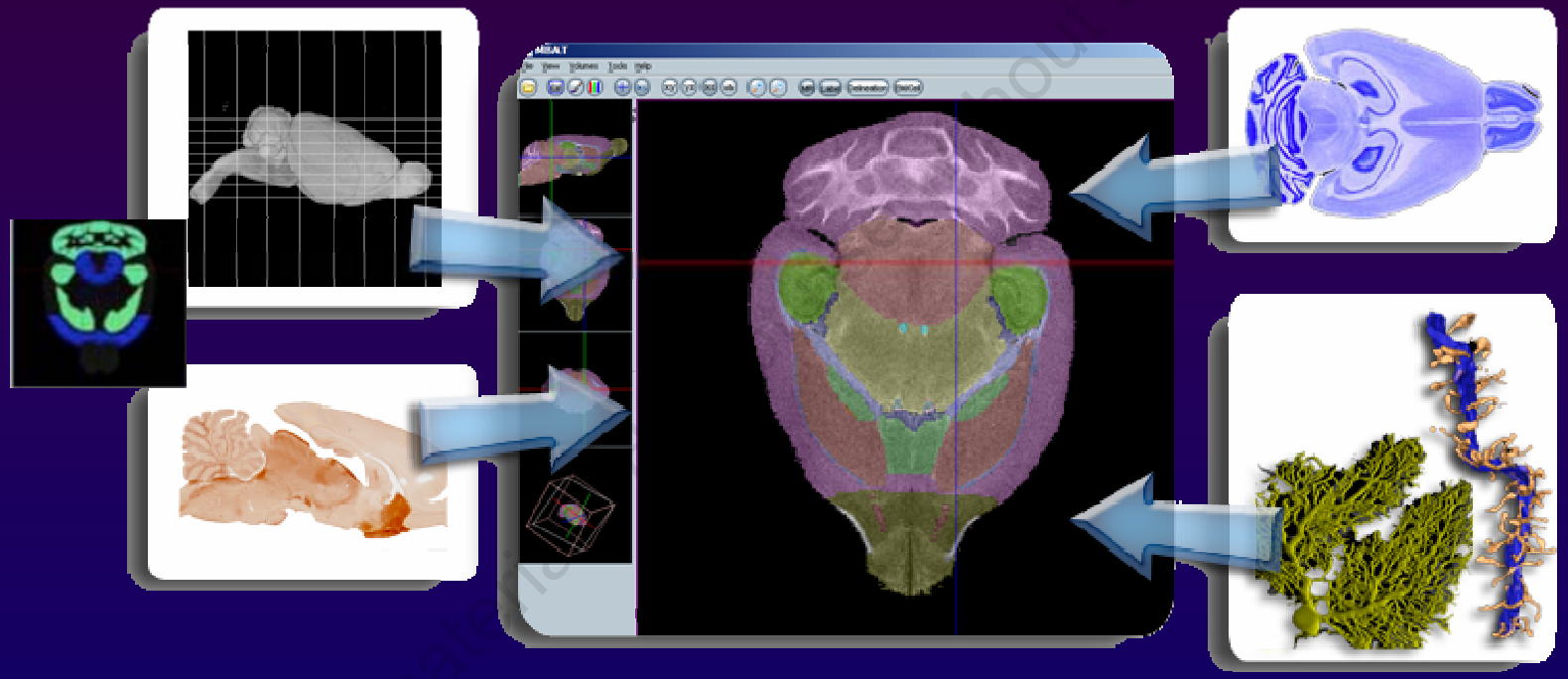
- National Center for Research Resources
- Establish cyberinfrastructure for storing, manipulating and sharing data and resources
  - High speed, robust connectivity via Internet2
  - Data and computational resources
  - Data integration over distributed databases
- Current test beds focused on neuroimaging
  - Human MRI
  - Human fMRI
  - Mouse models of neurological disease
- Test beds are developing methods for combining data across sites and across scales
  - Creating imaging databases
  - Calibration for multisite studies

http://nbirn.net

Multiscale Data Mediation

1. Create multimodal databases: standard set of metadata

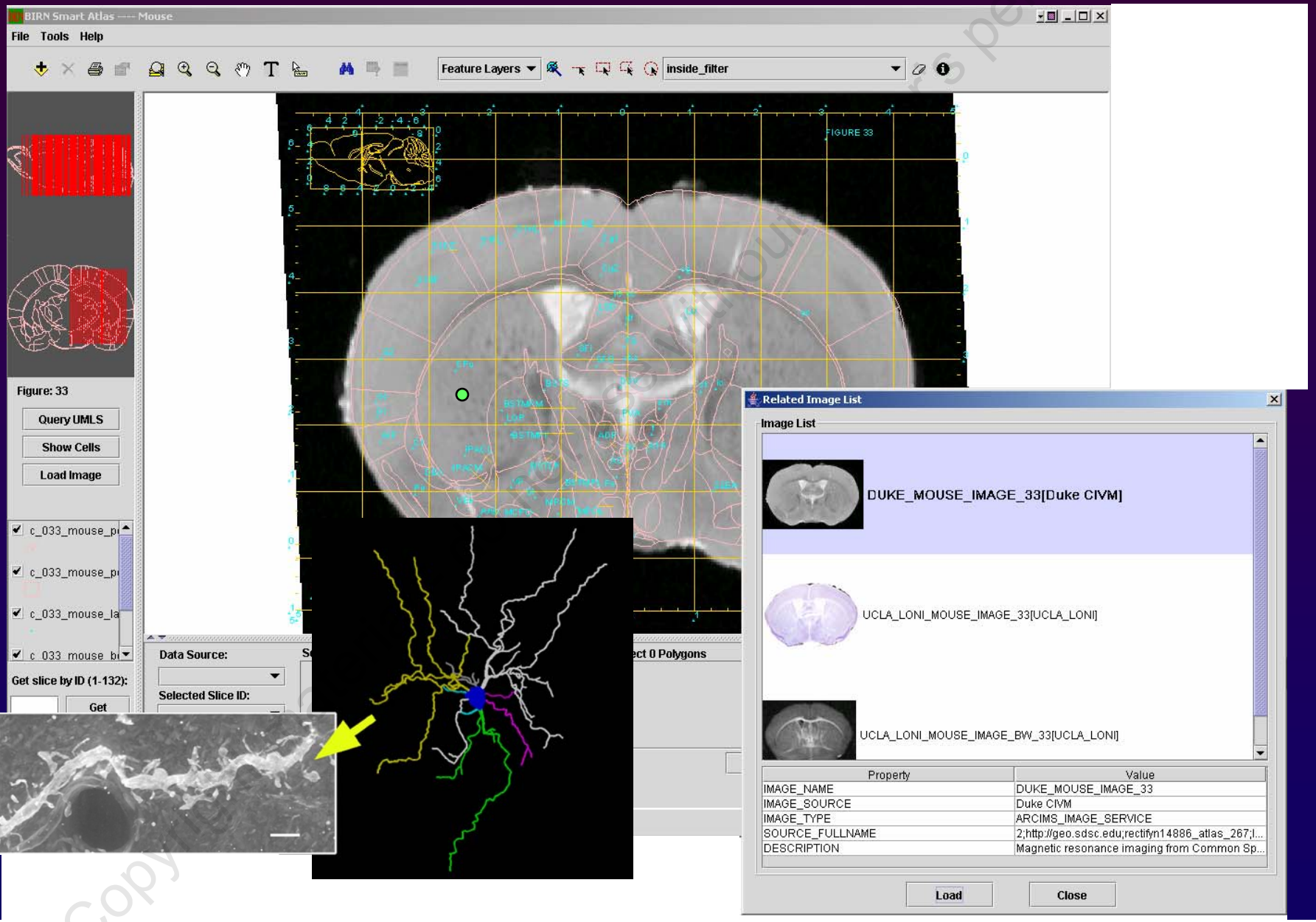
4. Use mediator to navigate and query across data sources



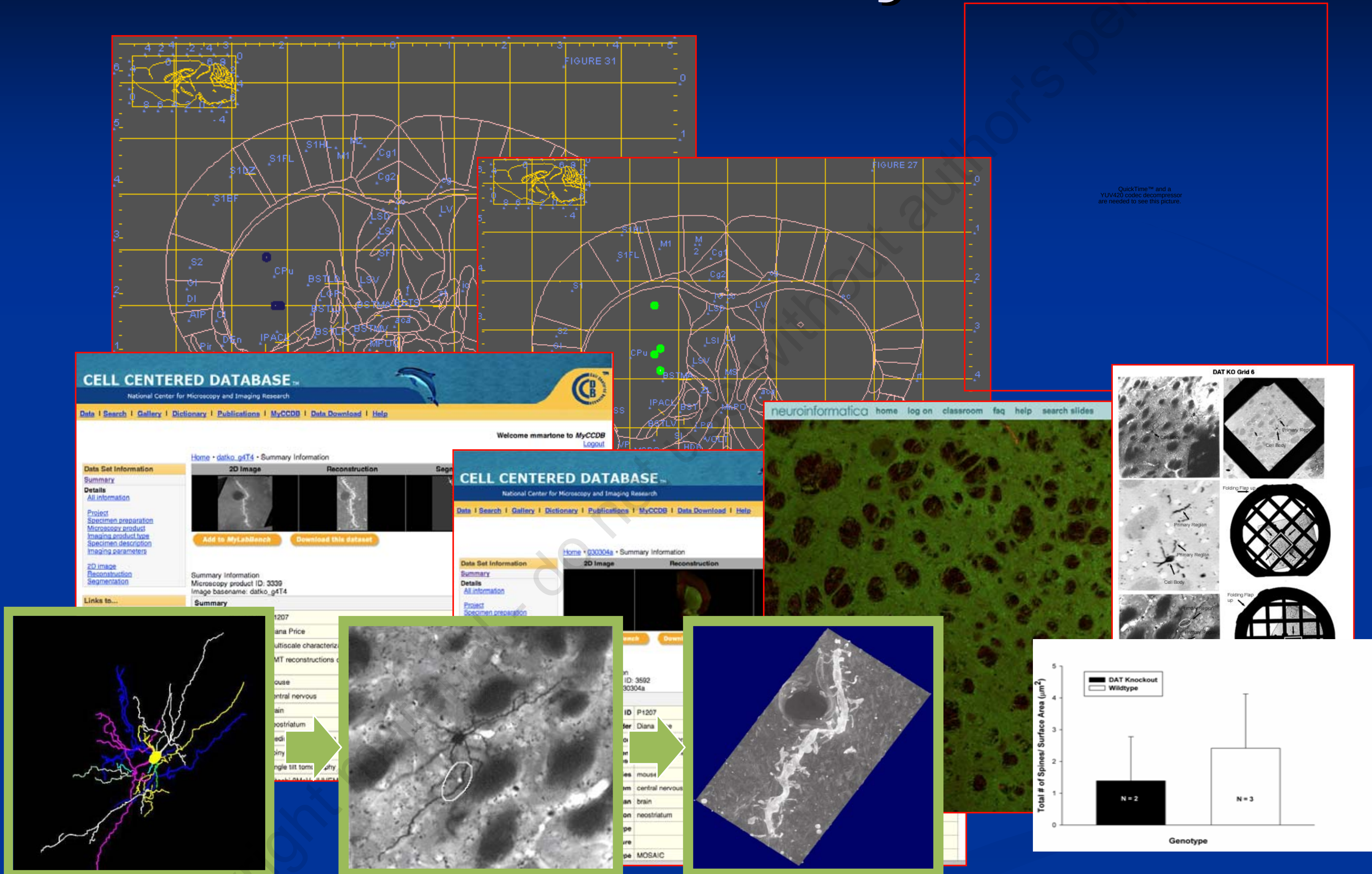
2. Create conceptual links to a shared ontology

3. Situate the data in a common spatial framework

The Smart Atlas: A Grid-based GIS tool for spatial integration of multiscale distributed brain data

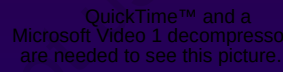


DATKO Analysis

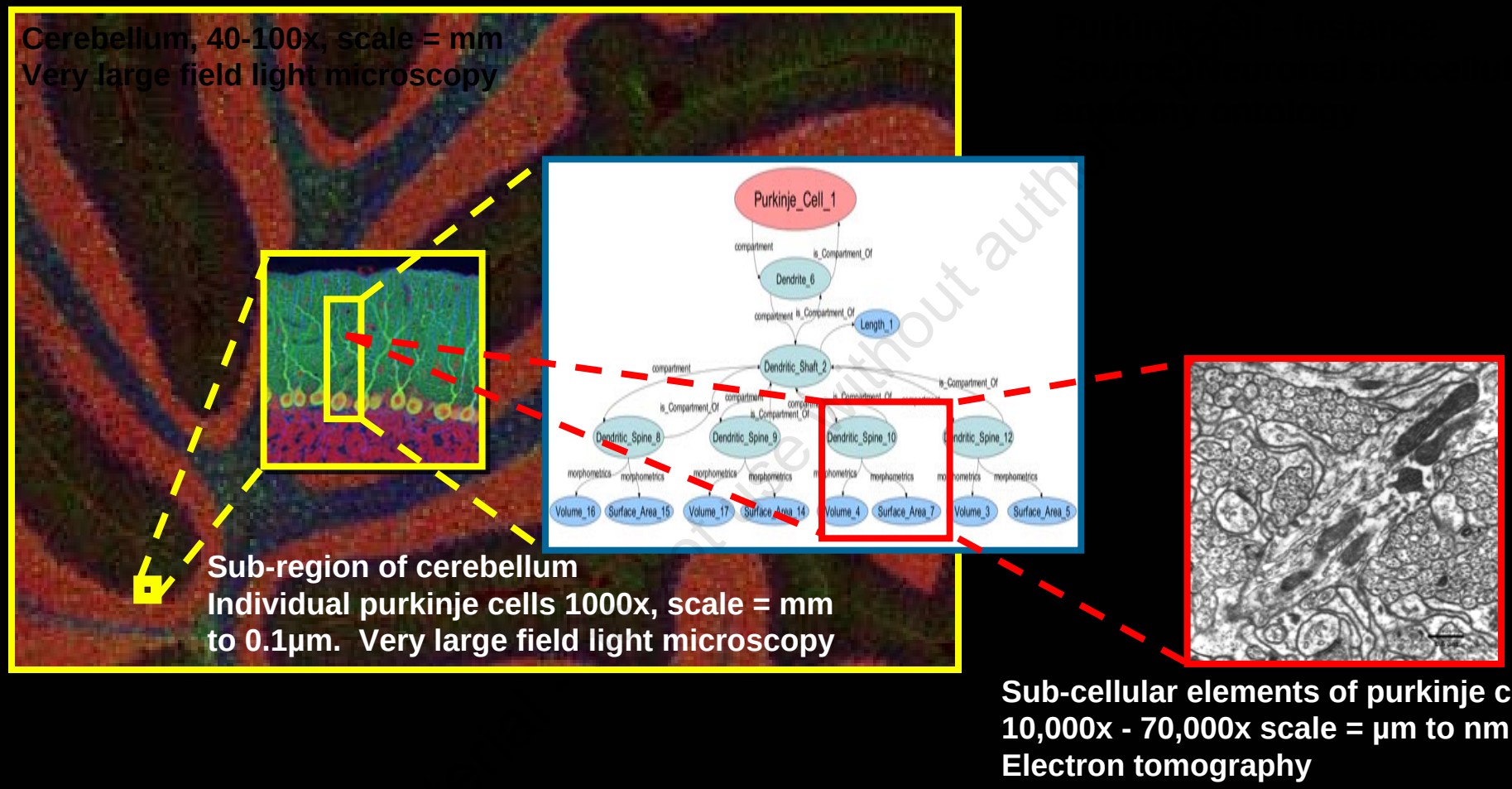


Diana Price, Van Phung, Monica Berlanga, Andrea Thor, Masako Terada, James Obayashi, Asif Memon

Google Brains

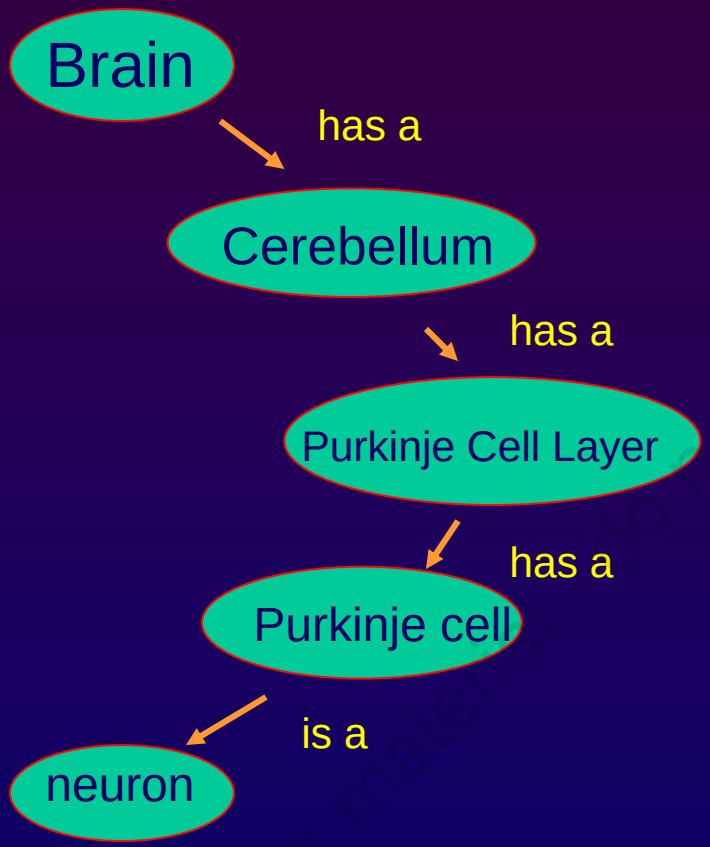


BRIDGING SCALES: Ontologies/Graphs



Use ontologies to link anatomy (data/geometry) at multiple scales (space/time) to enable *intuitive* exploration of relationships (structure/function, connectivity/networks etc.) to derive insight and/or knowledge

What is an Ontology?



- Way to communicate a shared understanding of a field
- concept hierarchy (“is-a”)
- further semantic relationships between concepts (“is part of”, “causes” etc.)

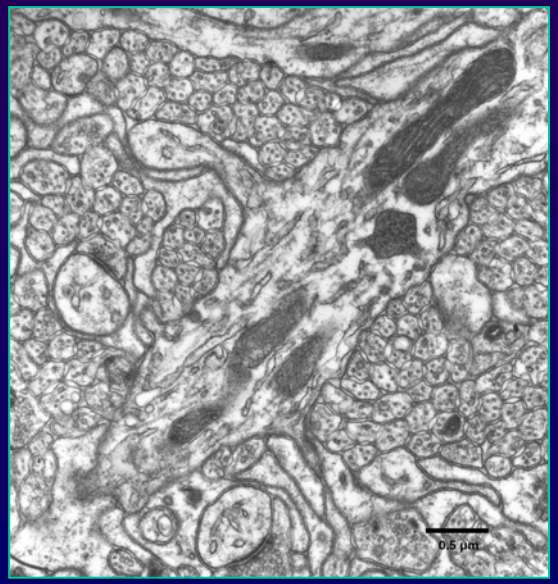
Examples:

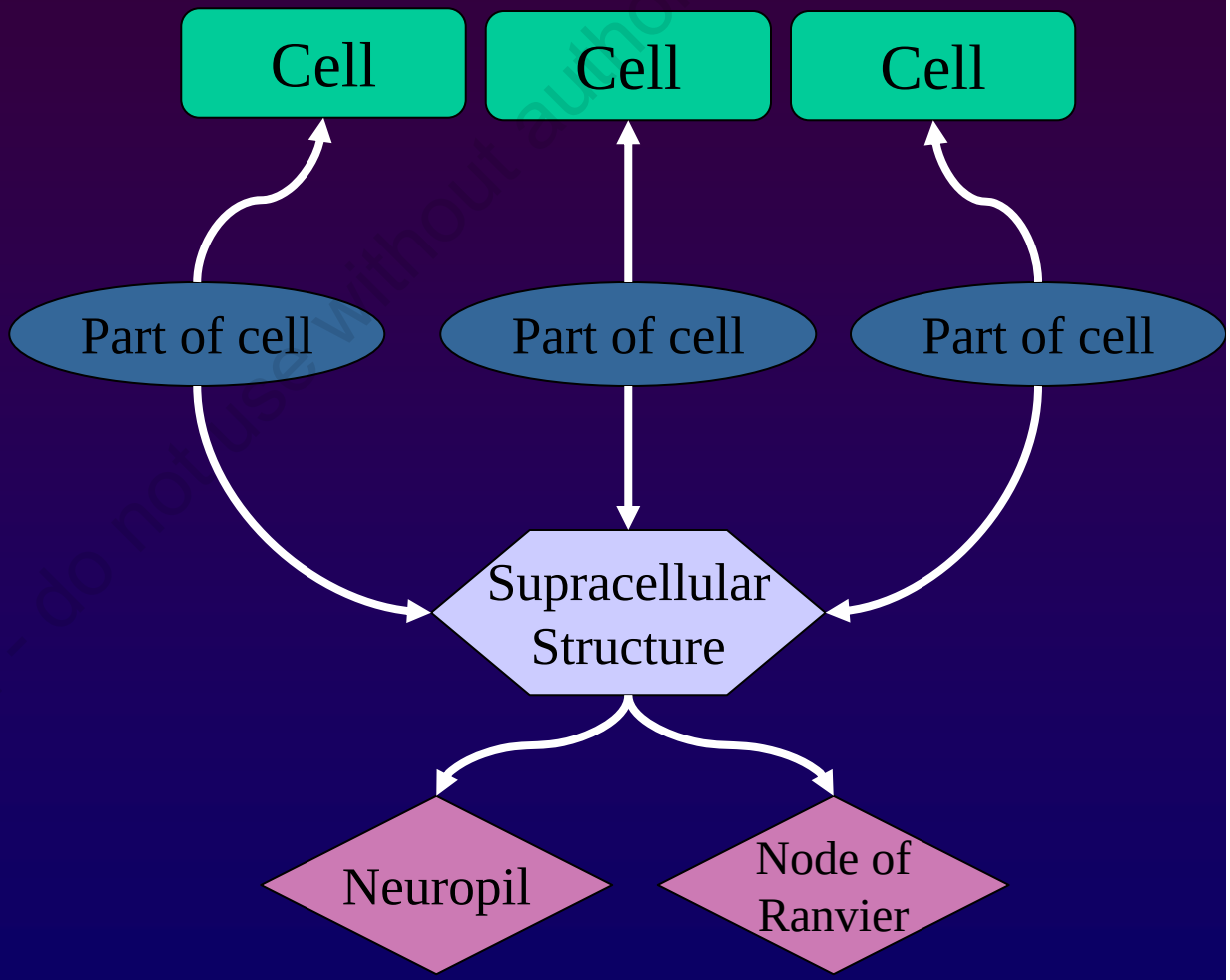
- GO (Gene Ontology)
- NeuroNames
- Foundational model of anatomy
- Mouse Anatomy (Edinburgh)

- Goal: represent terminological knowledge in a machine processable form

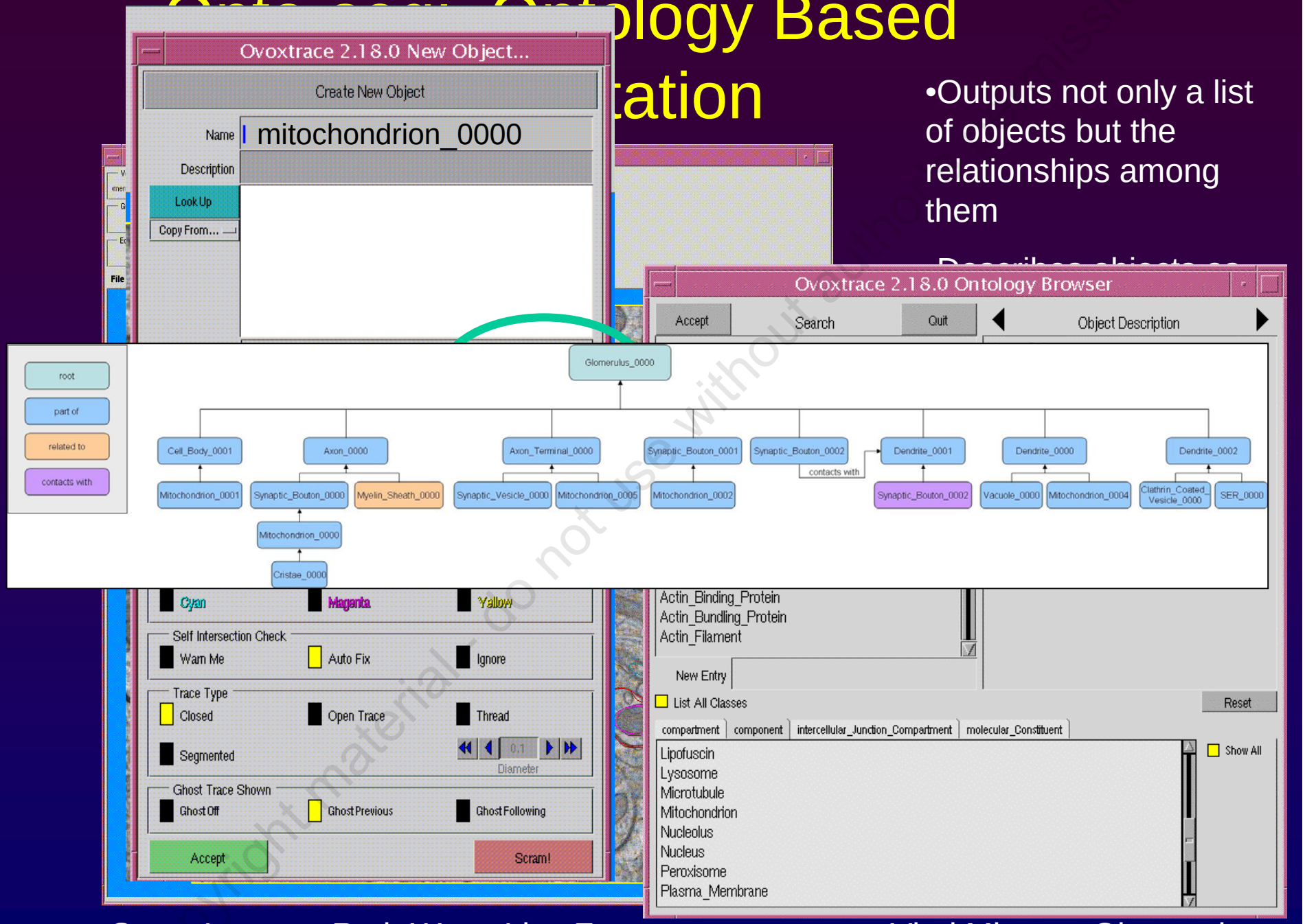
Building an Ontology for the Subcellular Anatomy of Nervous System

- Ontologies exist for cell types, cell components, macroscopic neuroanatomy
- Need ontology for subcellular anatomy: how parts of cells form supracellular domains
- Designed to bridge between gross anatomy and macromolecular scales
- V1.0 just released: http://ccdb.ucsd.edu/SAO/1.0/SAO.owl





Ontology Based



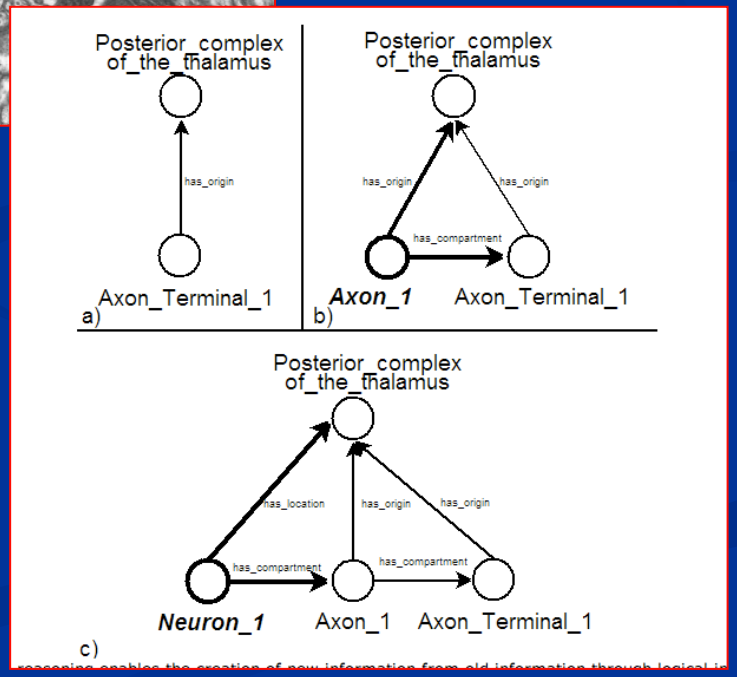
- Outputs not only a list of objects but the relationships among them

Steve Lamont, Ruth West, Lisa Fong

Vlad Mitsner, Glomerulus

Inferring the Mesoscale

- The SAO is expressed in OWL (Web Ontology Language)
  - Supports reasoning and inference
- Through integration with other ontologies covering gross anatomy and molecular entities, we are working to create inferences across scales
- Analyze locally; infer globally



Stephen Larson

Larson and Martone, 2007

Many Thanks To:

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- Hiro Hakozaki
- Lisa Fong
- Masako Terada
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- Ying Jones
- Andrea Thor
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- Stephen Larson
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- Gina Sosinsky
- Guido Gaietta
- Steven Peltier
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- Lily Chen
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- Tomas Molina
- Chris Condit
- Benjamin Smarr
- Ben Giepmanns
- Josh Tran
- Willy Wong
- Heather Jiles
- Cem Mangir

Bringing electron microscopy to life: Moleclar interactions at the synapse

J. Coggan, T. Bartol, E. Esquenazi, D. Berg, M. Martone, M. Ellisman & T. Sejnowski

Science, July 2005

Integrates observations from anatomy, physiology, molecular biology