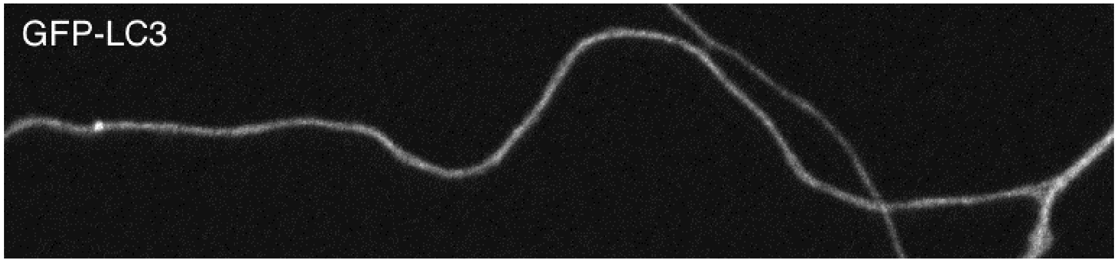
Bioimage Informatics

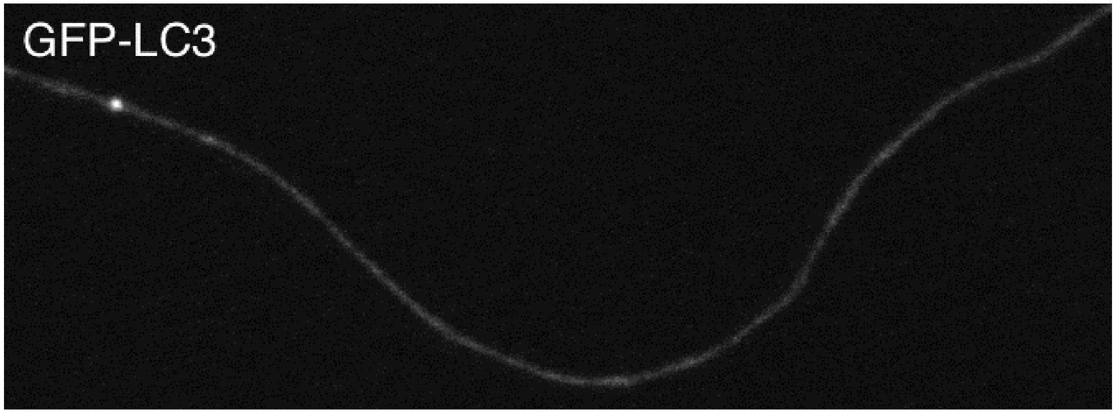
Lecture 19, Spring 2012

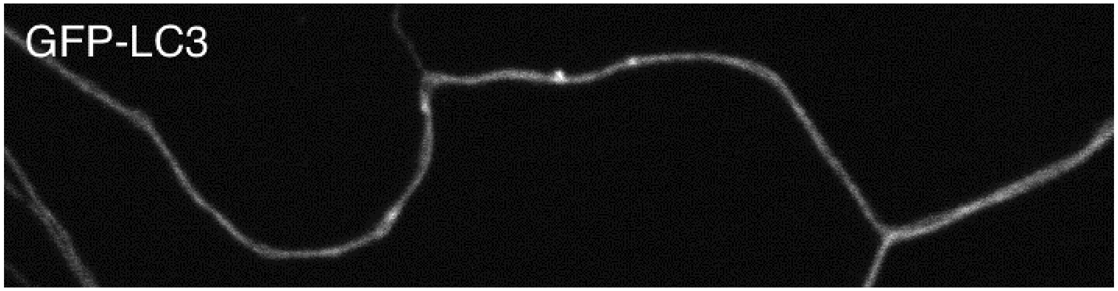
Biological Applications (I)

Experimental and Computational Analysis of Axonal Cargo Transport

Images for Curvilinear Feature Detection







Outline

- Course review
- Introduction to axonal transport
- Nanometer resolution single particle tracking of axonal transport
- Some biological findings
- Basic diffusion theory

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Course Review

- Two main topics have been covered so far.
  - Biological imaging techniques
  - Biological image analysis
- Biological imaging techniques
  - Contrast generation; Imaging resolution
  - Different imaging modalities
- Biological image analysis
  - Feature detection; Image segmentation
  - Feature tracking
  - Image alignment (registration)

- The rest of the course will focus on biological applications and informatics techniques.

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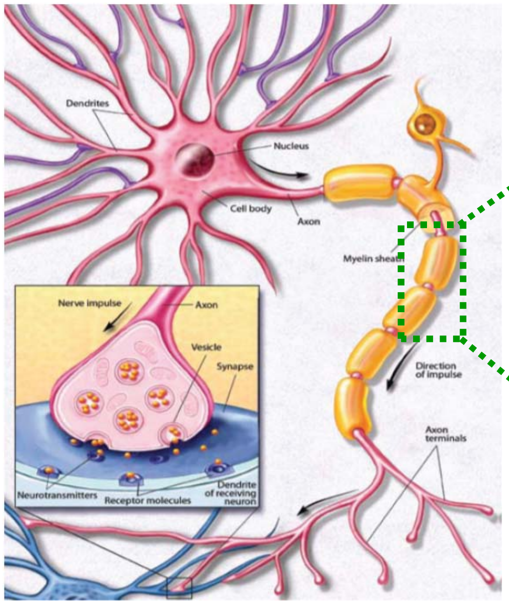
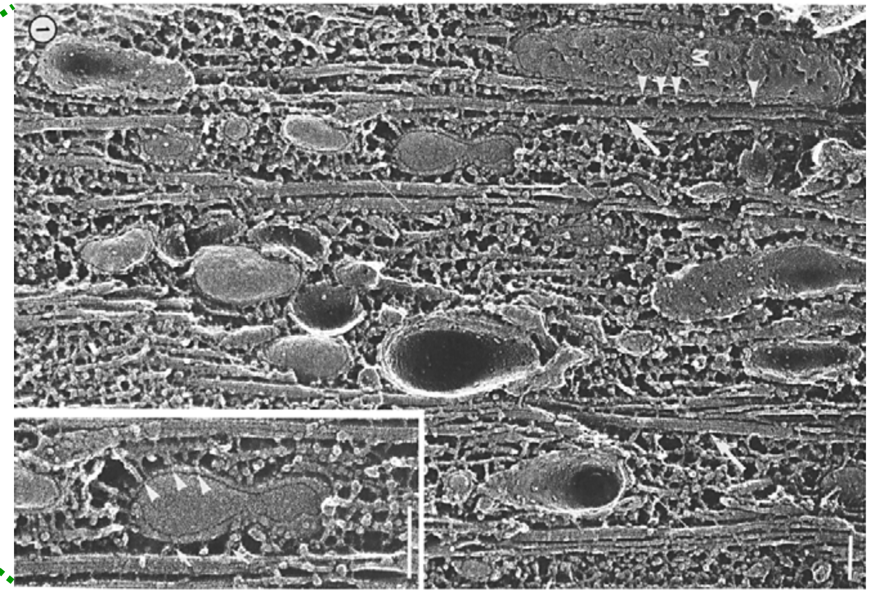
Axonal Cargo Transport (I)



From *Brain Facts*, Society for Neuroscience



Hirokawa, 1982

Bars: 0.1μm

- Axonal transport is critical to survival and function of neurons.
- Axonal transport provides a powerful model of intracellular transport.

Axonal Cargo Transport (I)

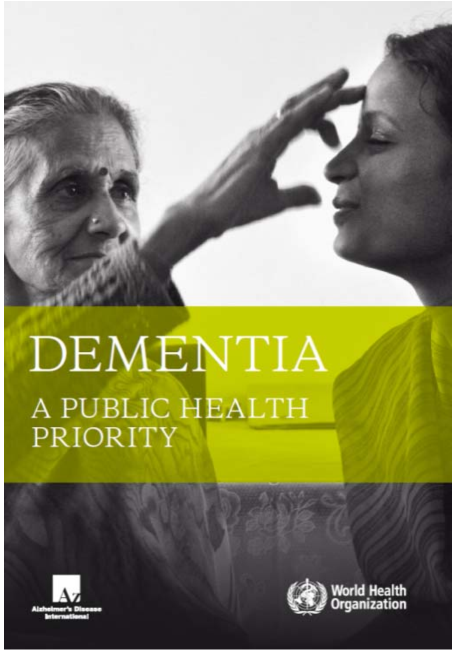
Table 1 | **The moving structures of axonal transport***

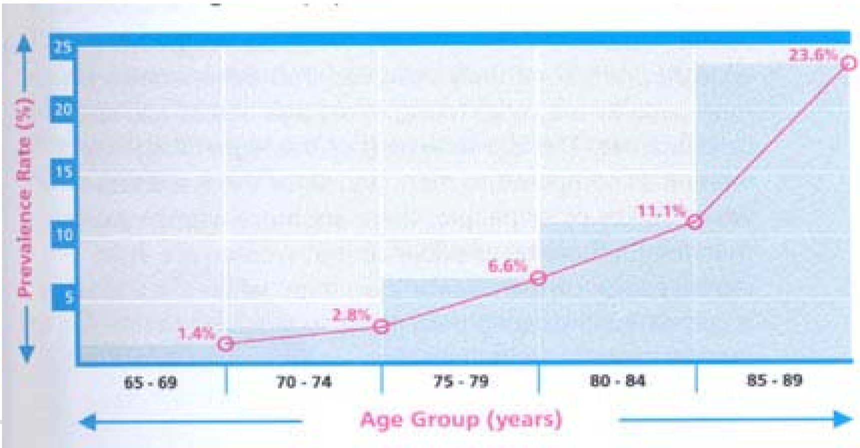
Rate class	Average rate	Moving structures	Composition (selected examples)
Fast components			
Fast anterograde	200–400 mm day^{-1} (≈2–5 μm s^{-1})	Golgi-derived vesicles and tubules (secretory pathway)	Synaptic vesicle proteins, kinesin, enzymes of neurotransmitter metabolism
Bi-directional	50–100 mm day^{-1} (≈0.5–1 $μms^{-1}$)	Mitochondria	Cytochromes, enzymes of oxidative phosphorylation
Fast retrograde	200–400 mm day^{-1} (≈2–5 μm s^{-1})	Endosomes, lysosomes (endocytic pathway)	Internalized membrane receptors, neurotrophins, active lysosomal hydrolases
Slow components			
Slow component 'a'	0.3–3 mm day^{-1}	Neurofilaments, microtubules‡	Neurofilament proteins, tubulin, spectrin, tau proteins
Slow component 'b'	2–8 mm day^{-1} (≈0.02–0.09 μm s^{-1})	Microfilaments, supramolecular complexes of the cytosolic matrix	Actin, clathrin, dynein, dynactin, glycolytic enzymes

Brown, Nat. Rev. Mol. Cell Biol., 2000

Axonal Transport Dysfunction Implicated in Neurodegenerative Disease

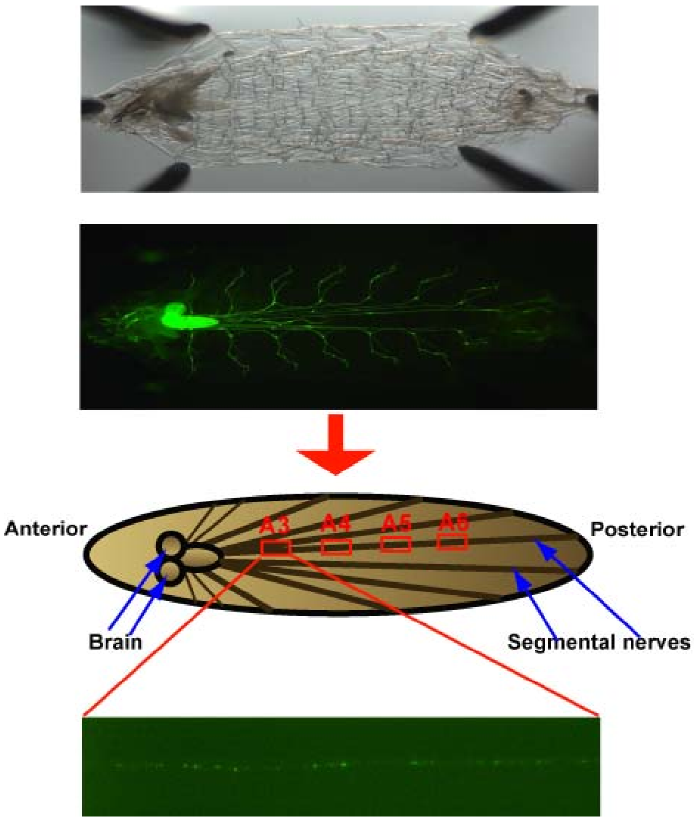
- Dementia is a loss of brain function that occurs with certain diseases.
- It is estimated that today 35.6 million people worldwide live with dementia
- The number is expected to increase significantly by 2050.
- Axonal transport defects have been strongly implicated in many neurodegenerative diseases.

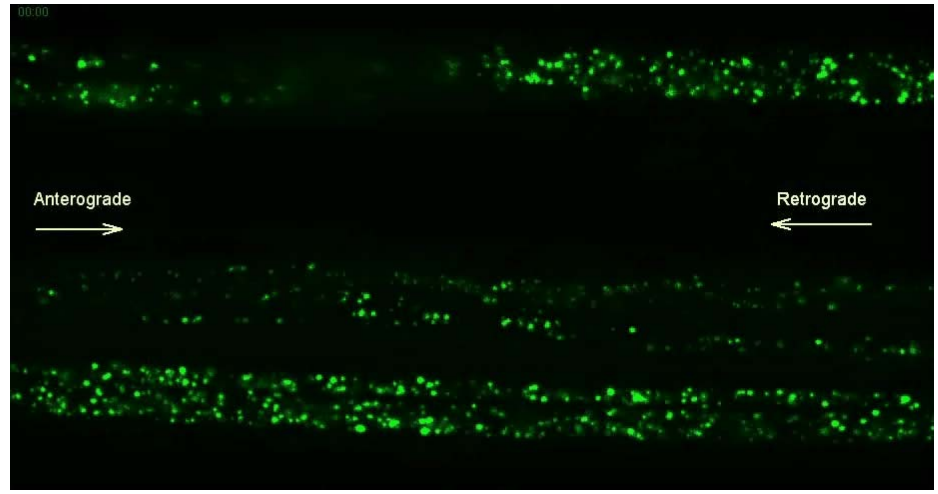


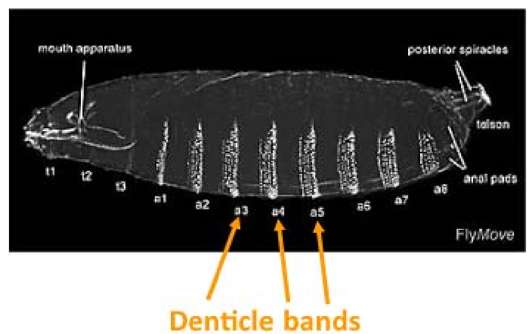


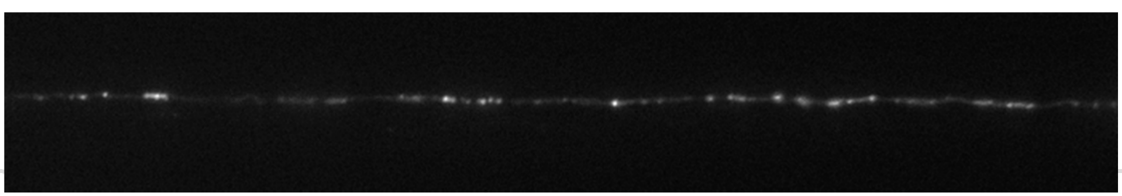
http://www.searo.who.int/en/Section1174/Section1199/Section1567/Section1823_8066.htm

Imaging Axonal Transport

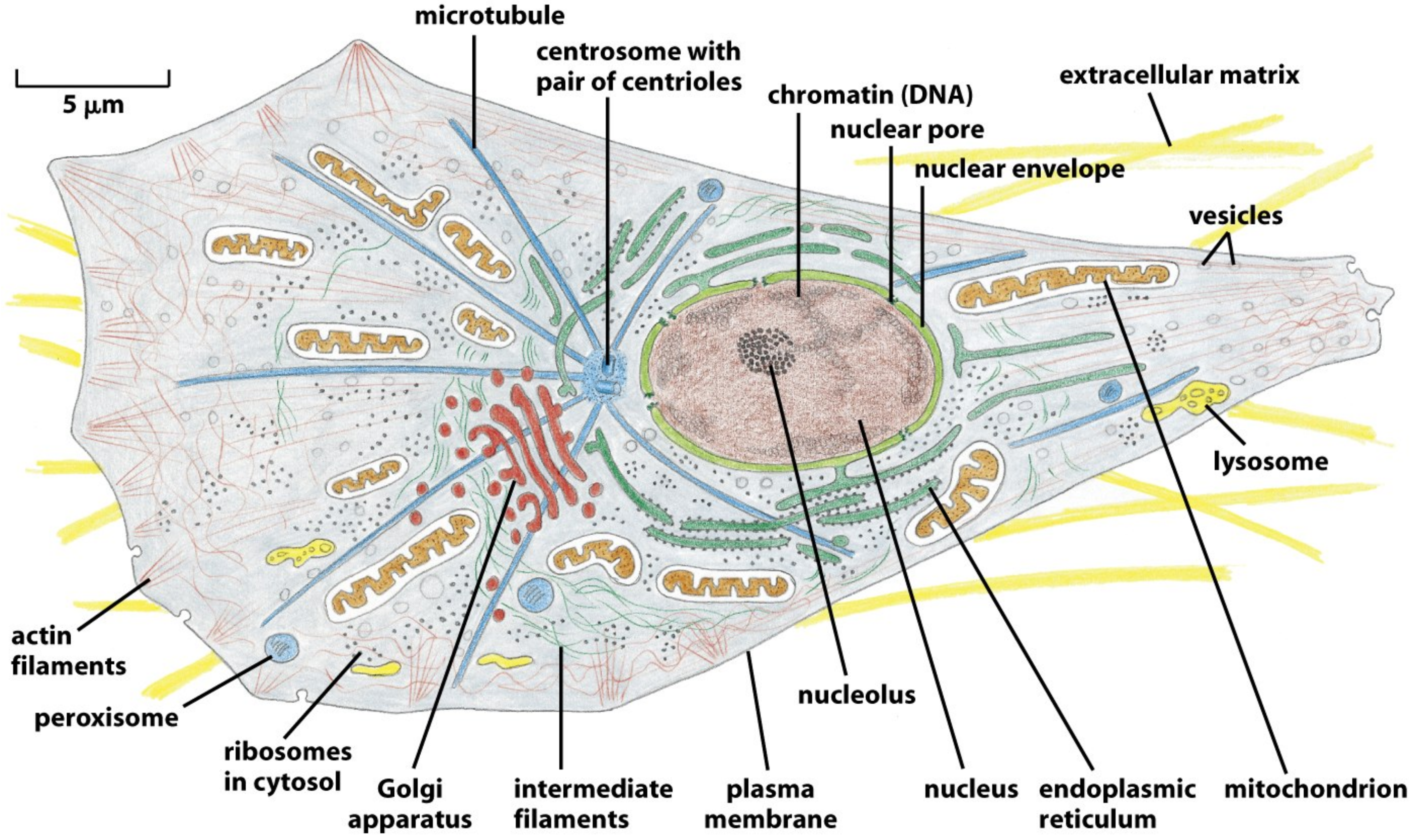




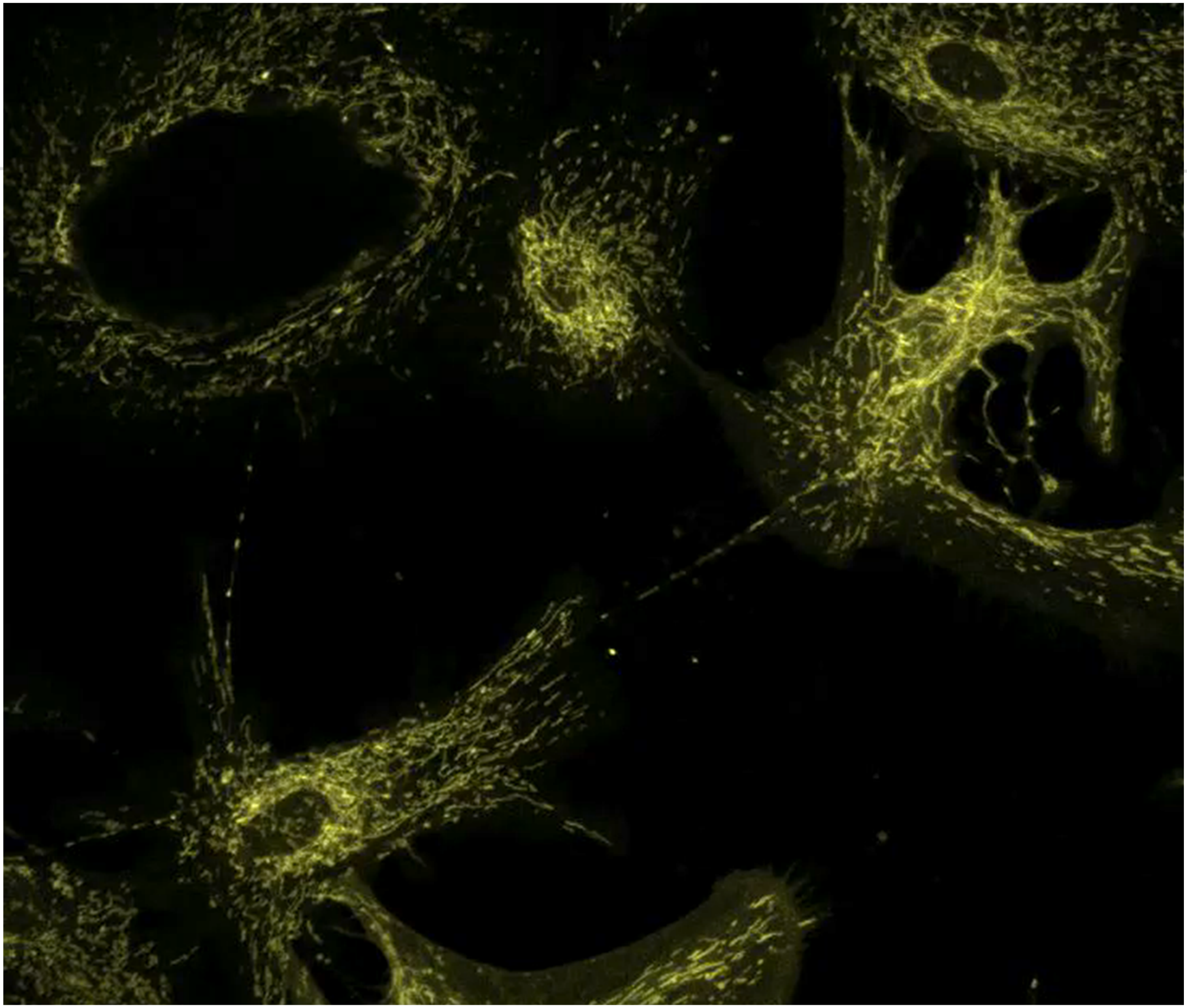




The Eukaryotic Cell

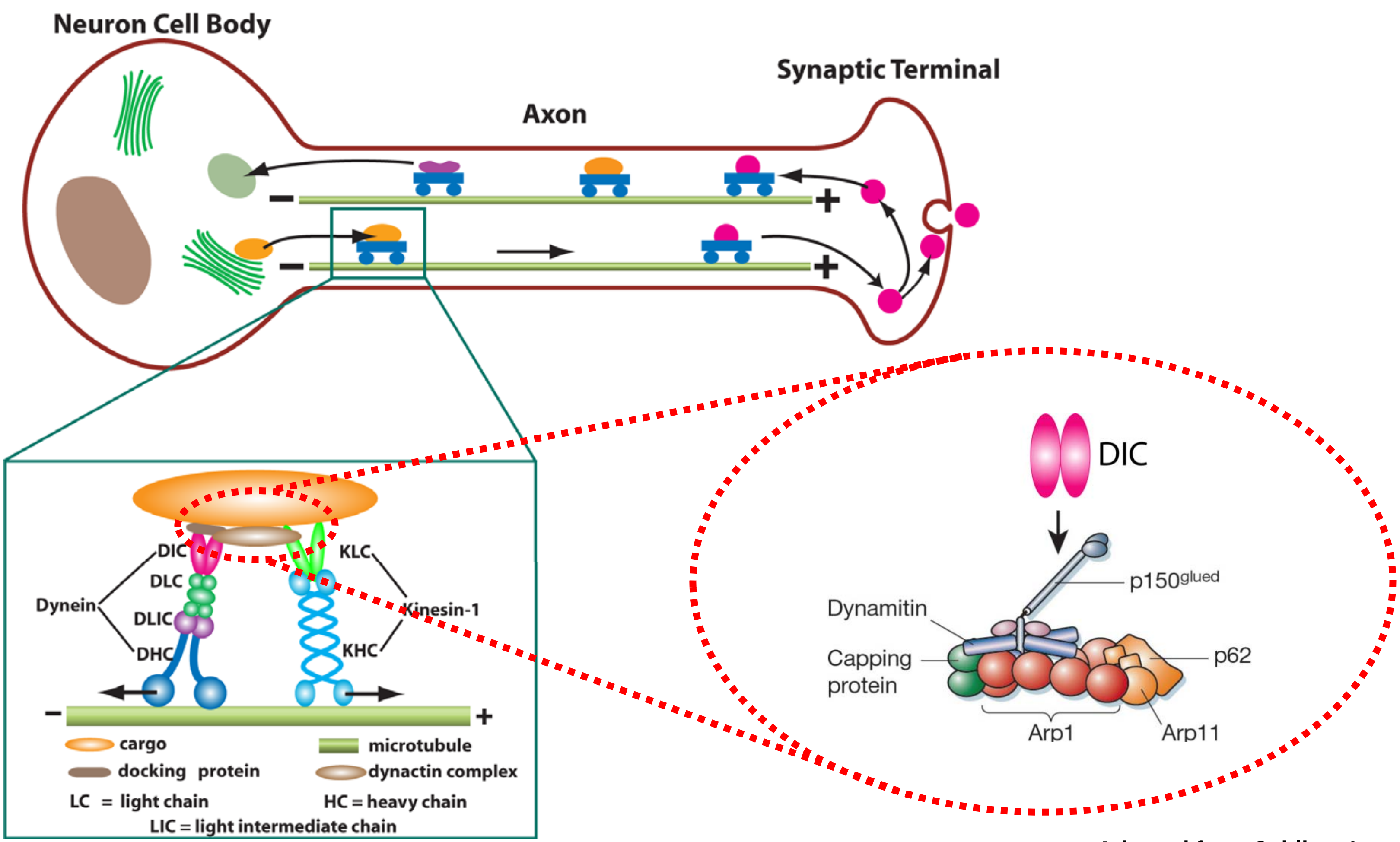


Alberts et al, MBoC, 5/e



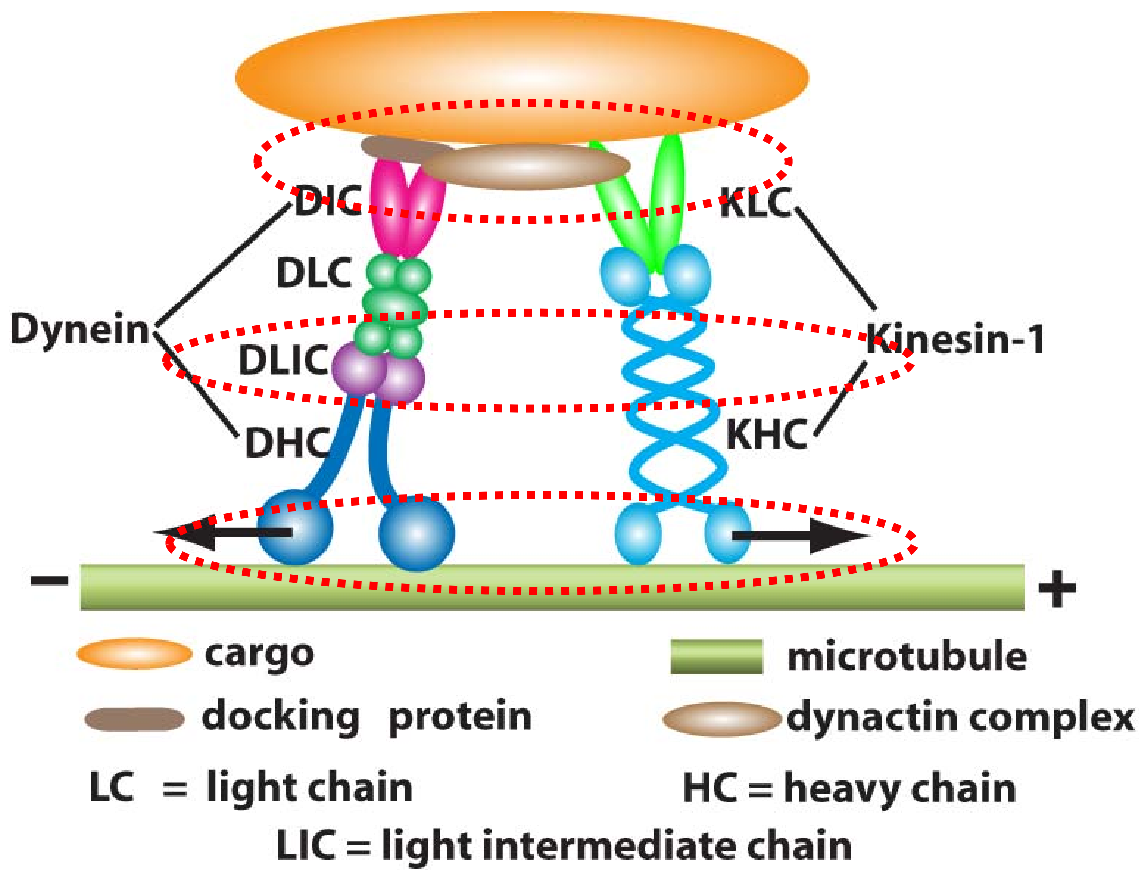
Mitochondrial transport, Courtesy of James Lim, LBNL

Molecular Motor Machinery of Axonal Transport

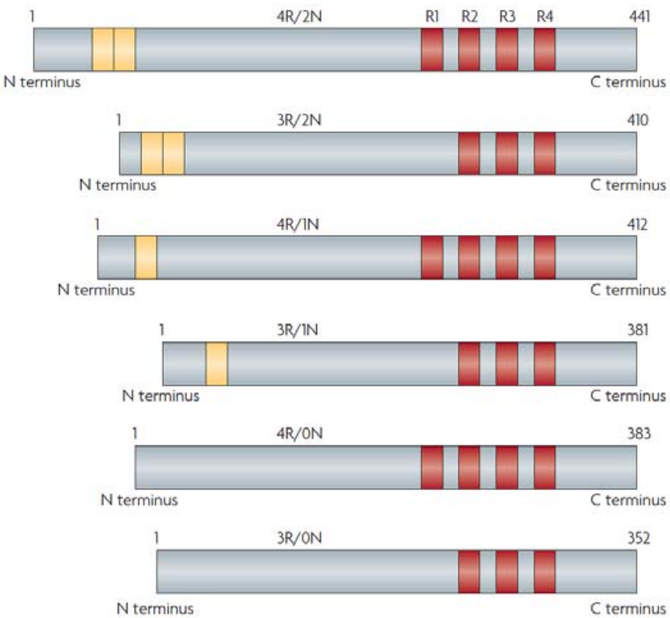


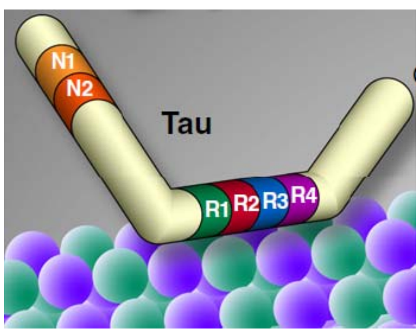
Adapted from Schliwa & Woehlke, *Nature*, 422:759, 2003

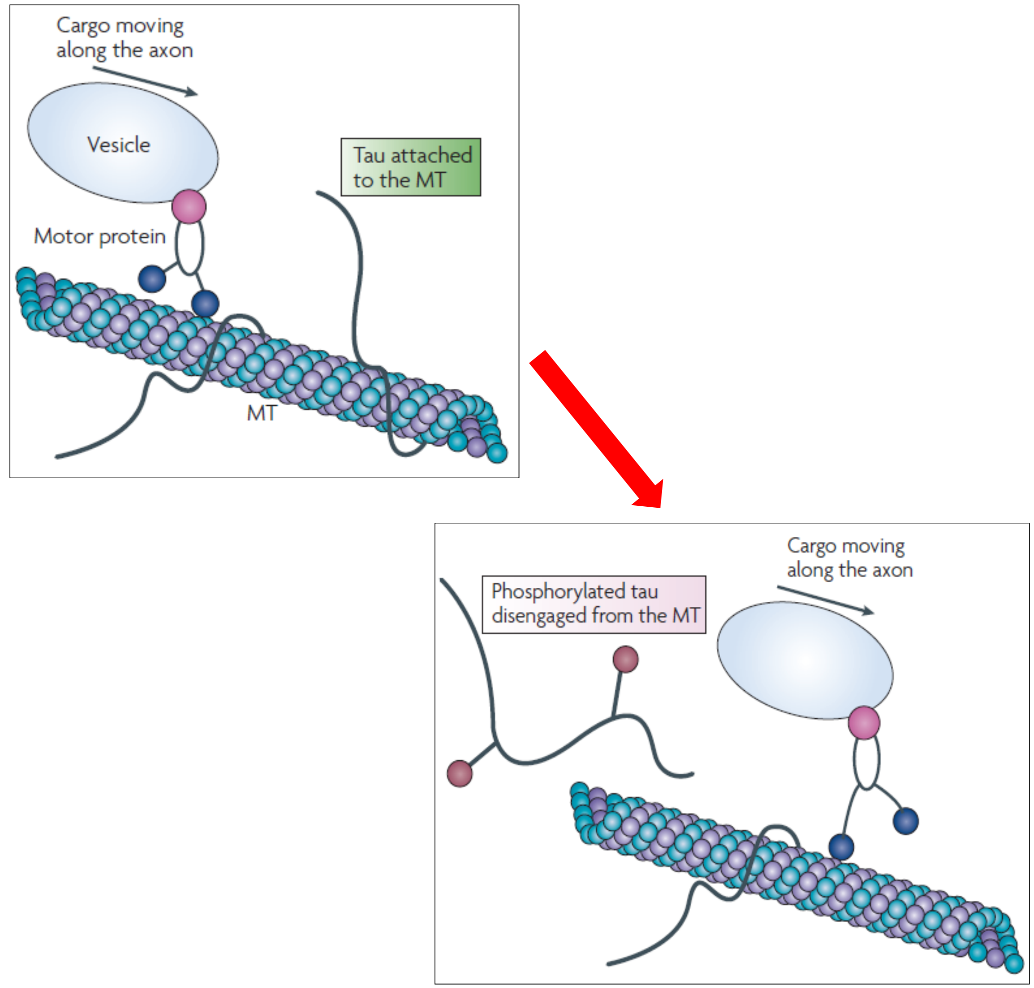
Potential Mechanisms of Axonal Transport Defects



Microtubule Associated Protein Tau in Axonal Transport

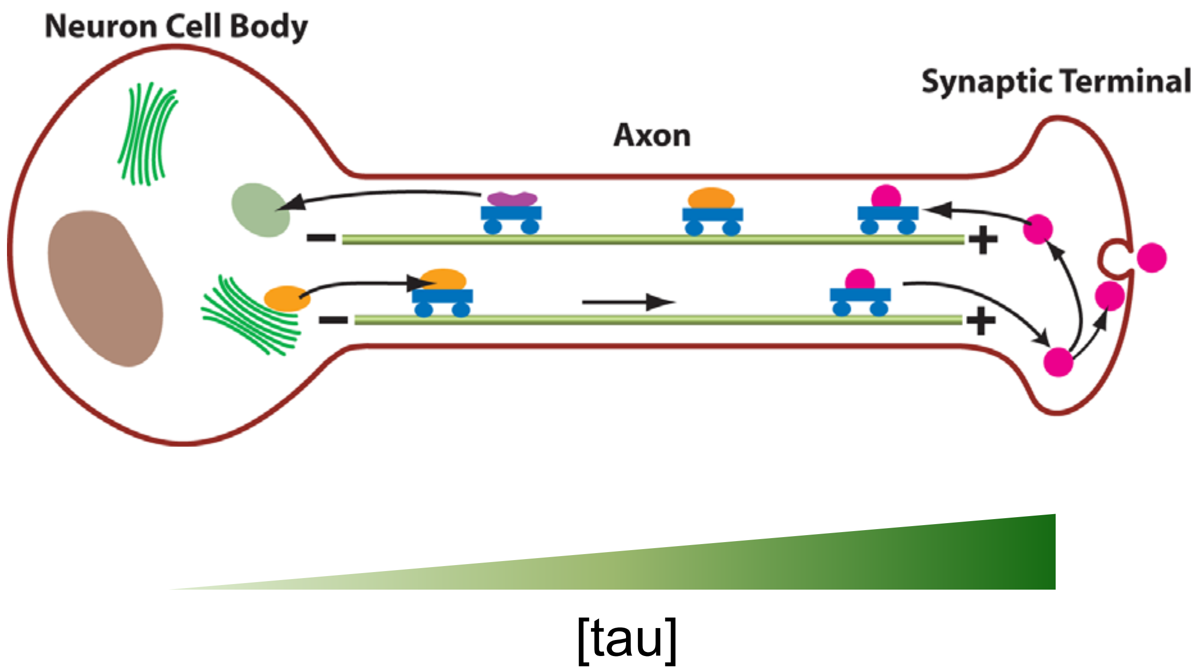






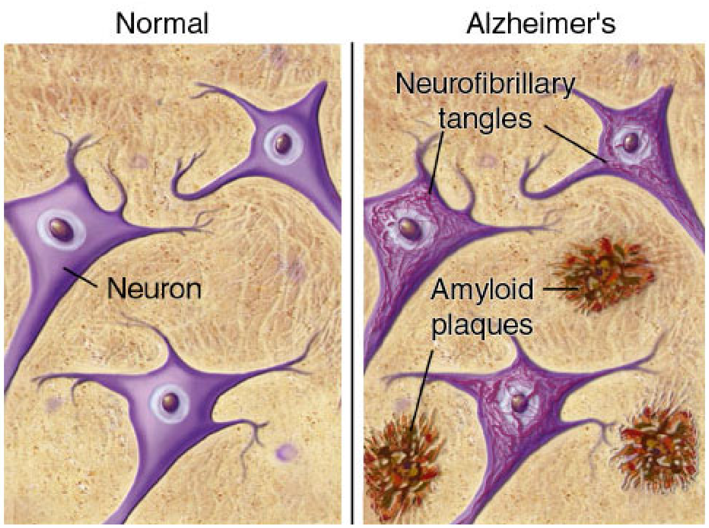
Ballatore et al, *Nat. Rev. Neurosci.* 2007
Morris et al, *Neuron*, 2011

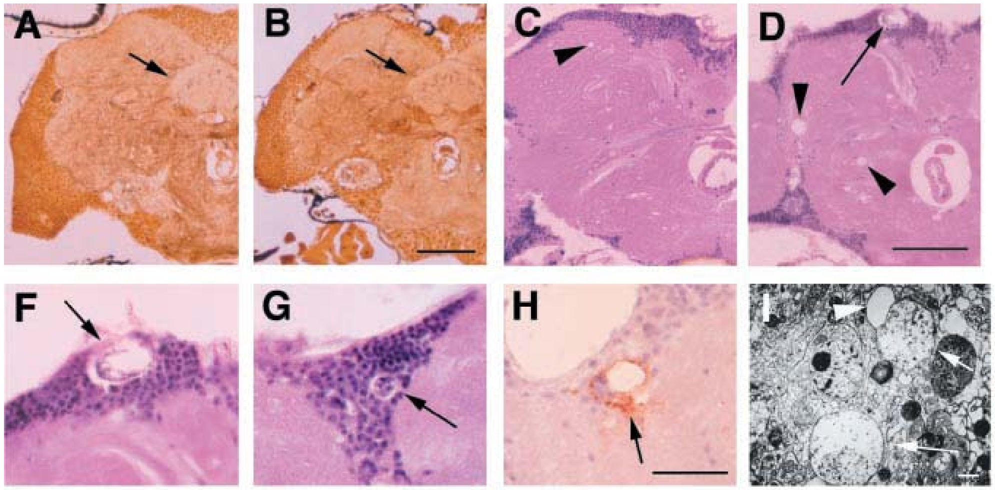
How does tau modulate axonal transport?



A Drosophila Model of Alzheimer's Disease

- Two pathological hallmarks of AD: Aβ plaques & tau tangles
- Control:
  - *SG26.1 GAL4/+; UAS-APPYFP/+* ← transport is driven by kinesin-1
  - *SG26.1 GAL4/+; UAS-SynGFP* ← transport is driven by kinesin-3
- Mutants:
  - *SG26.1 GAL4/+; UAS-APPYFP/+; UAS-wt hTau/+*
  - *SG26.1 GAL4/+; UAS-APPYFP/+; UAS-R406W hTau/+*





Wittmann et al, *Science*, 2001

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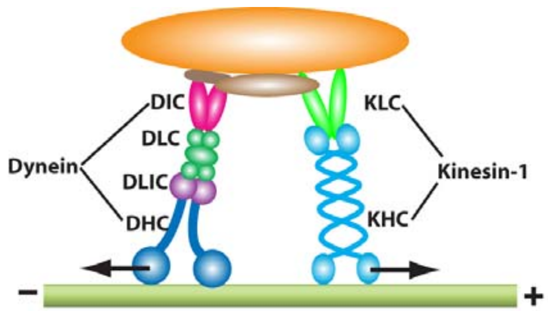
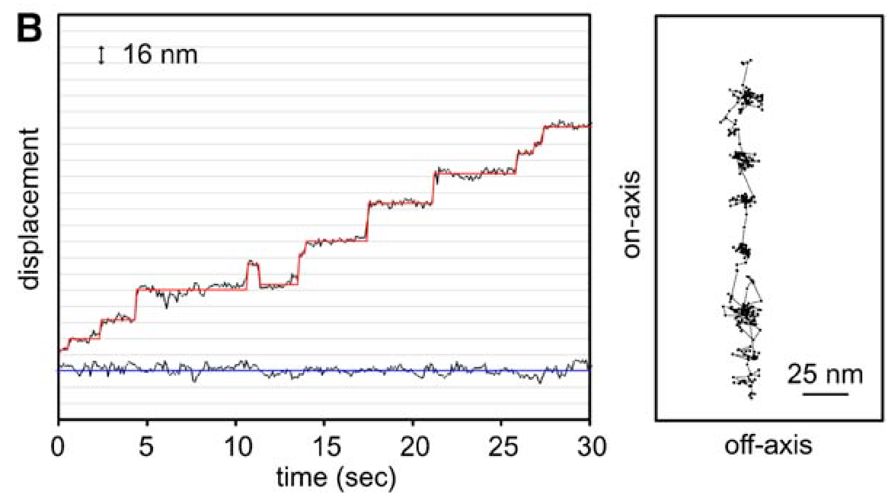
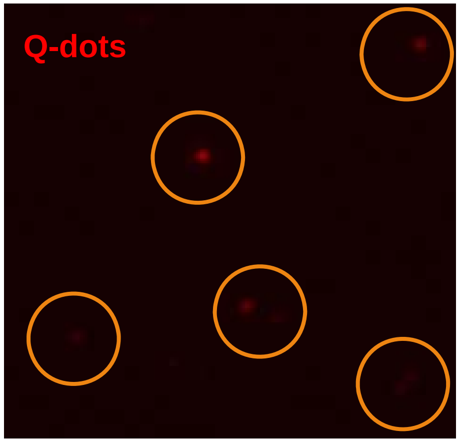
Why Nanometer Resolution?

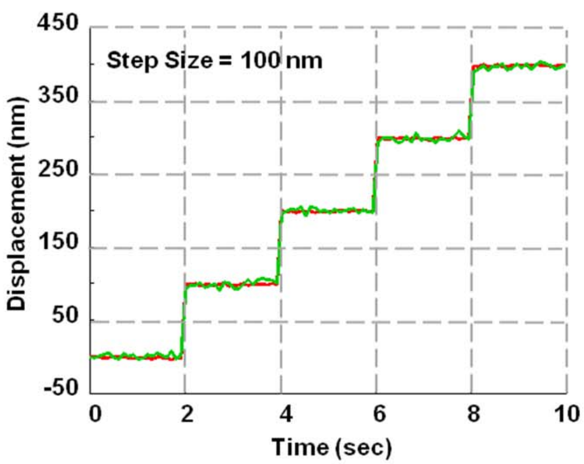
- Nanometer resolution is essential to axonal transport characterization.

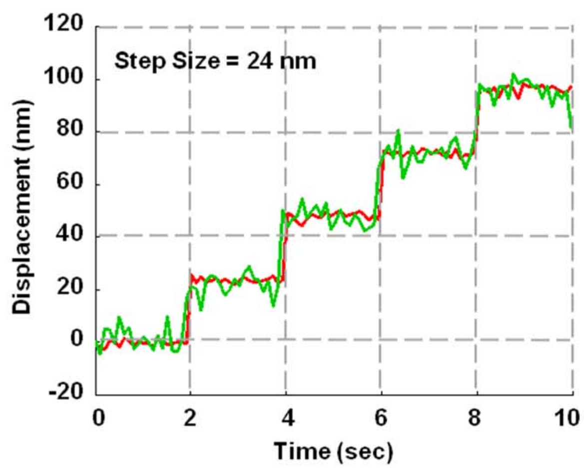


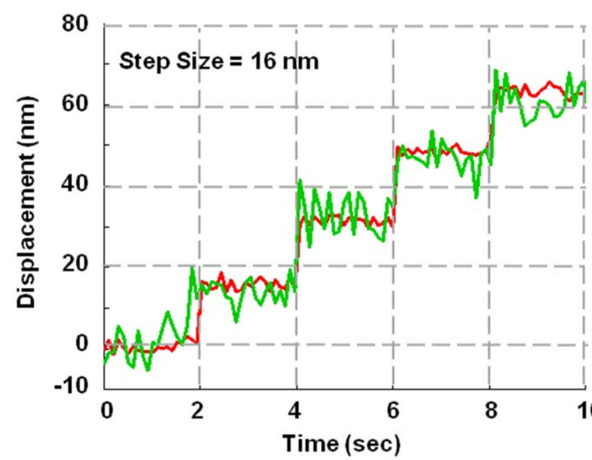


Detection Resolution Validation



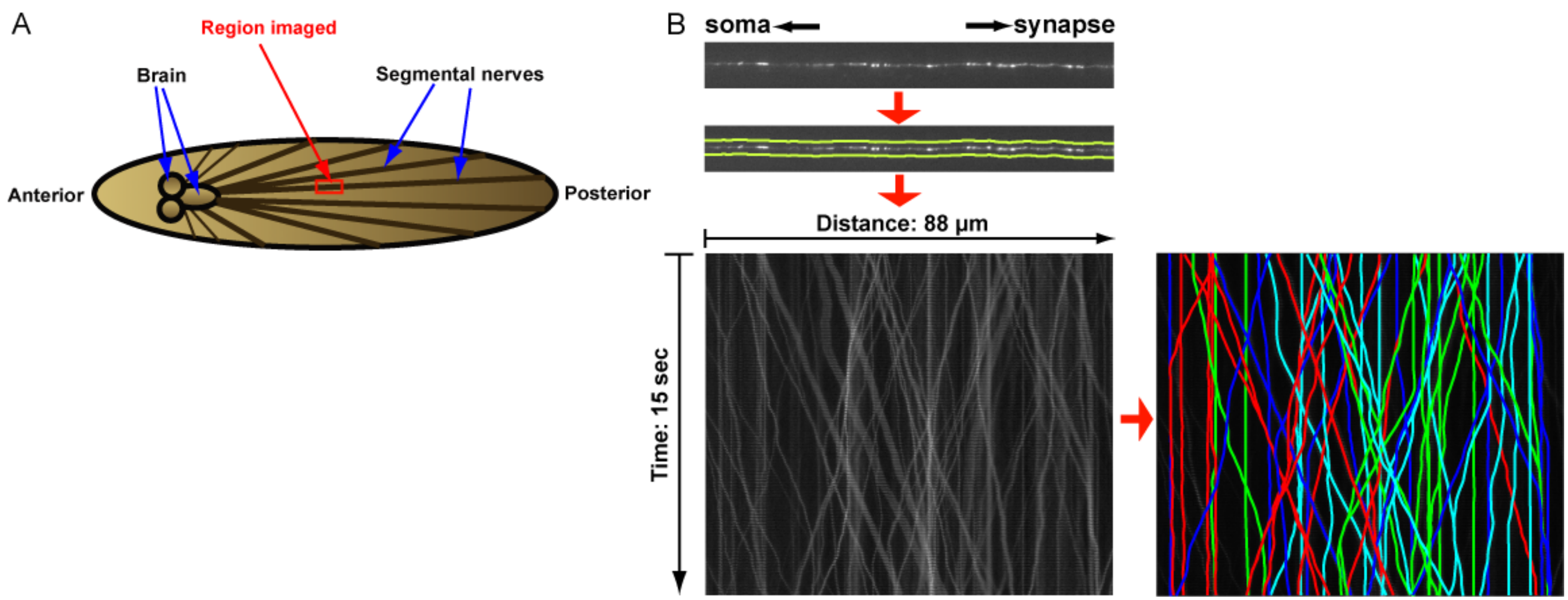


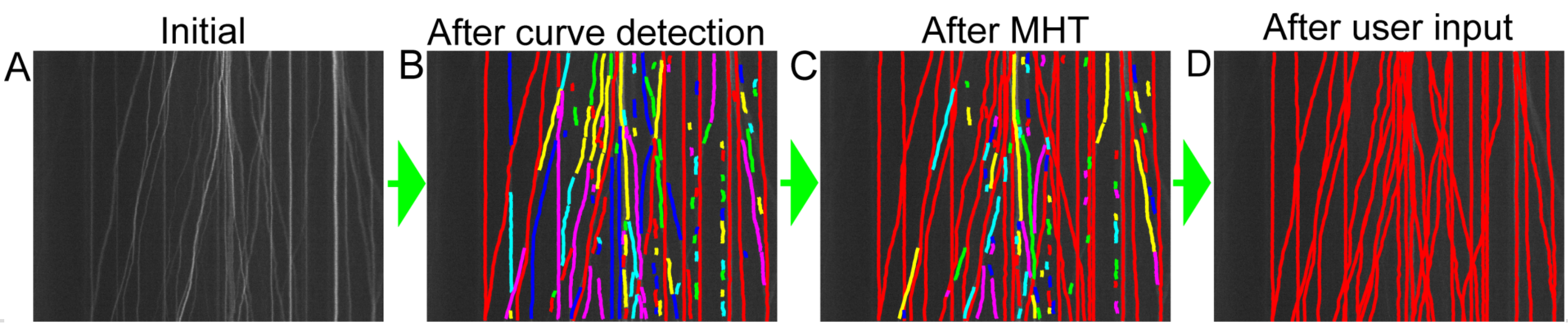




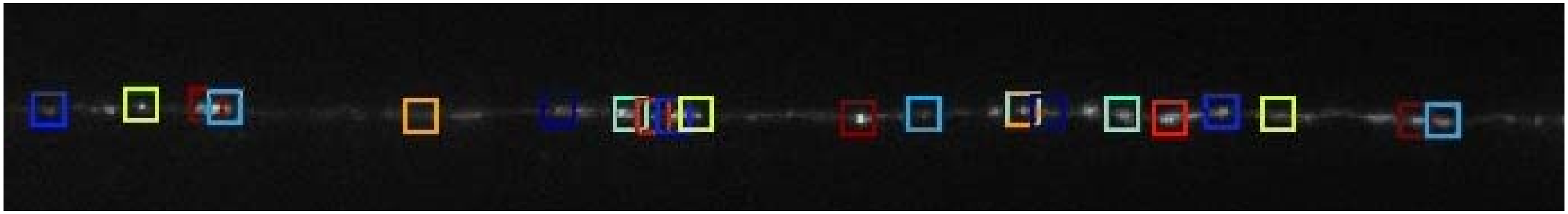
QStorm

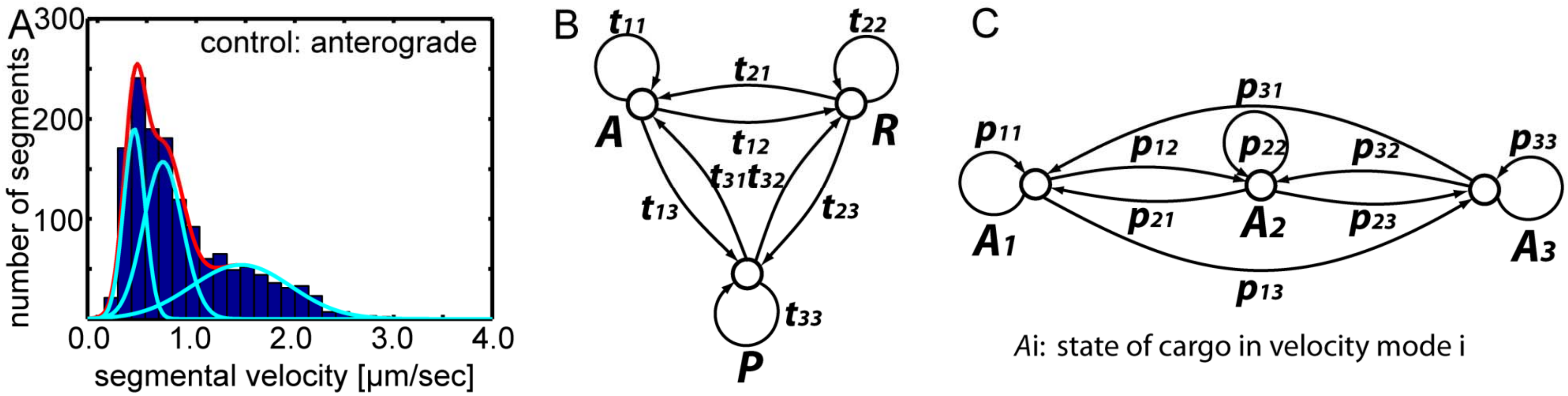
Tracking Vesicle Movement Using Computer Vision Techniques (I)





Tracking Vesicle Movement Using Computer Vision Techniques (II)





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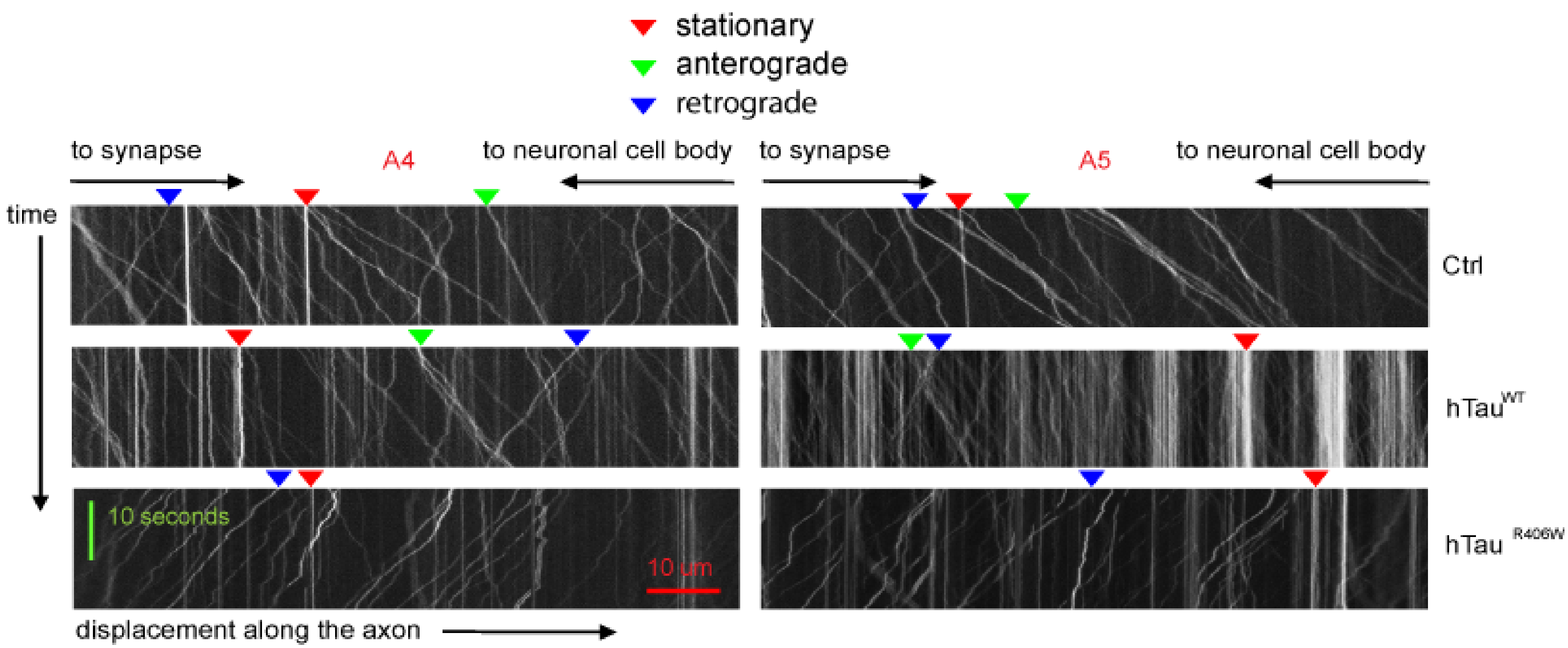
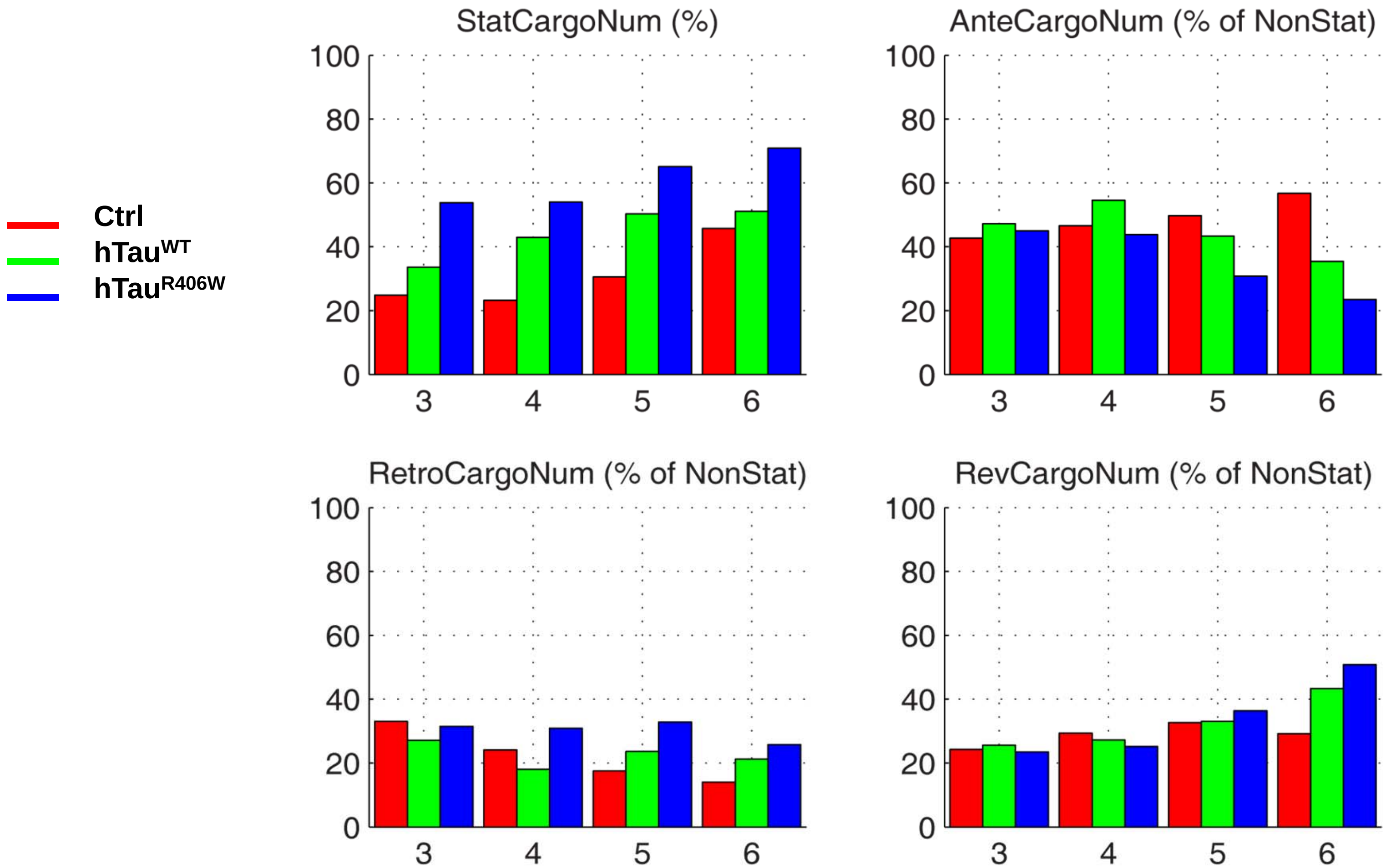
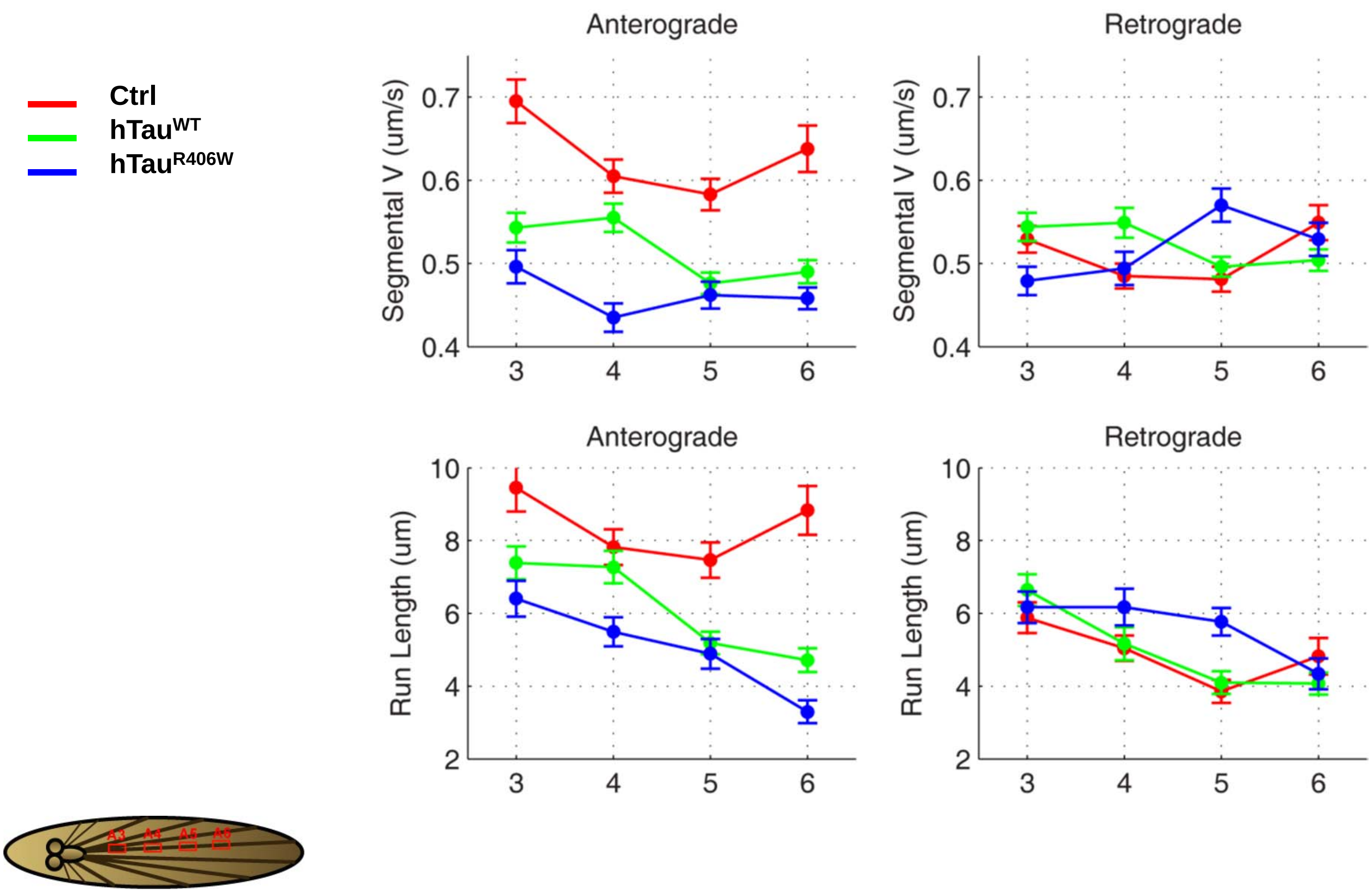
Tau Overexpression Differentially Affects Axonal Transport



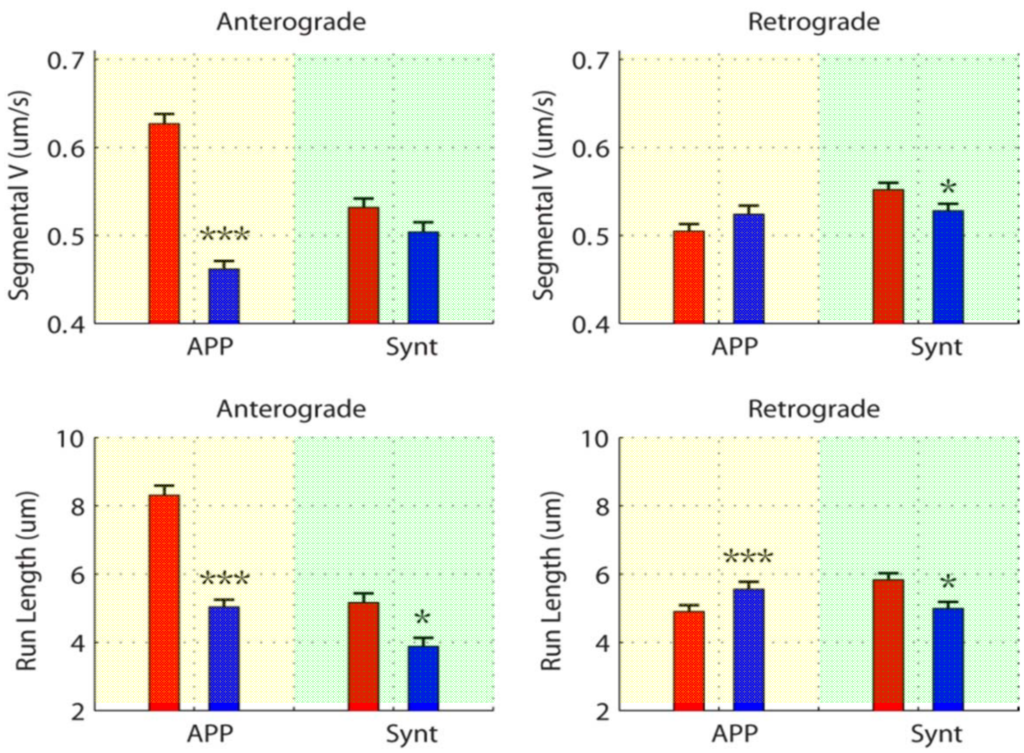
Quantification of Cargo Population



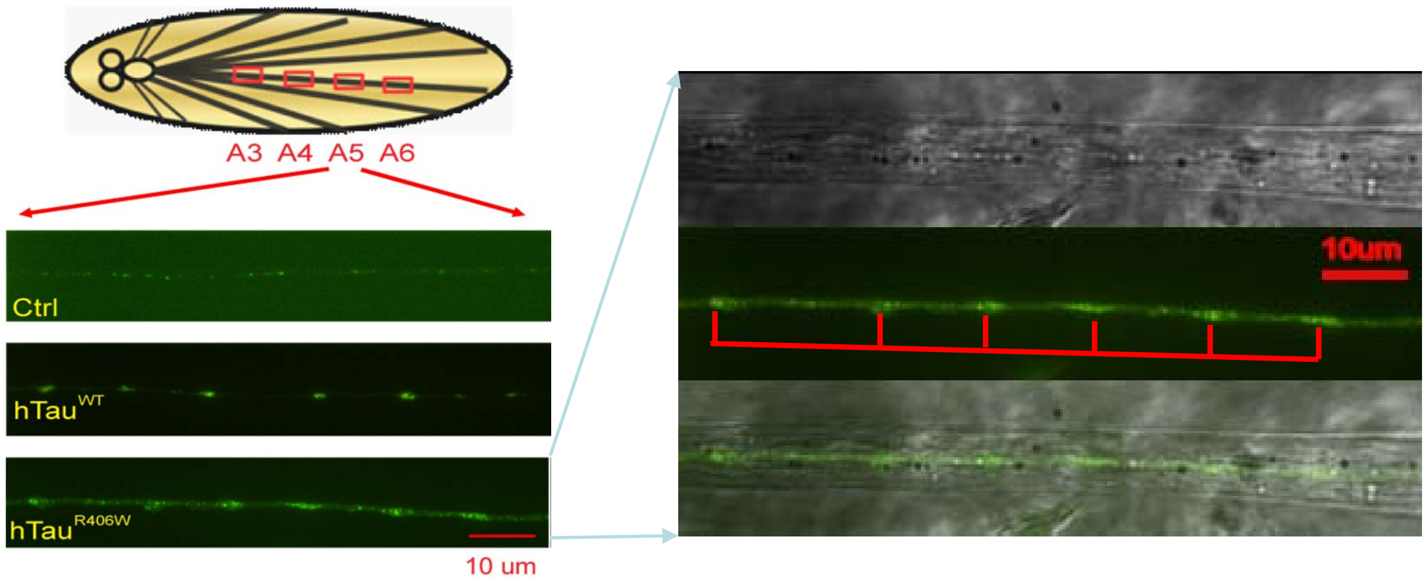
APP Vesicle Transport and its Impairment is Region-Specific



Transport Impairment is Cargo-Specific



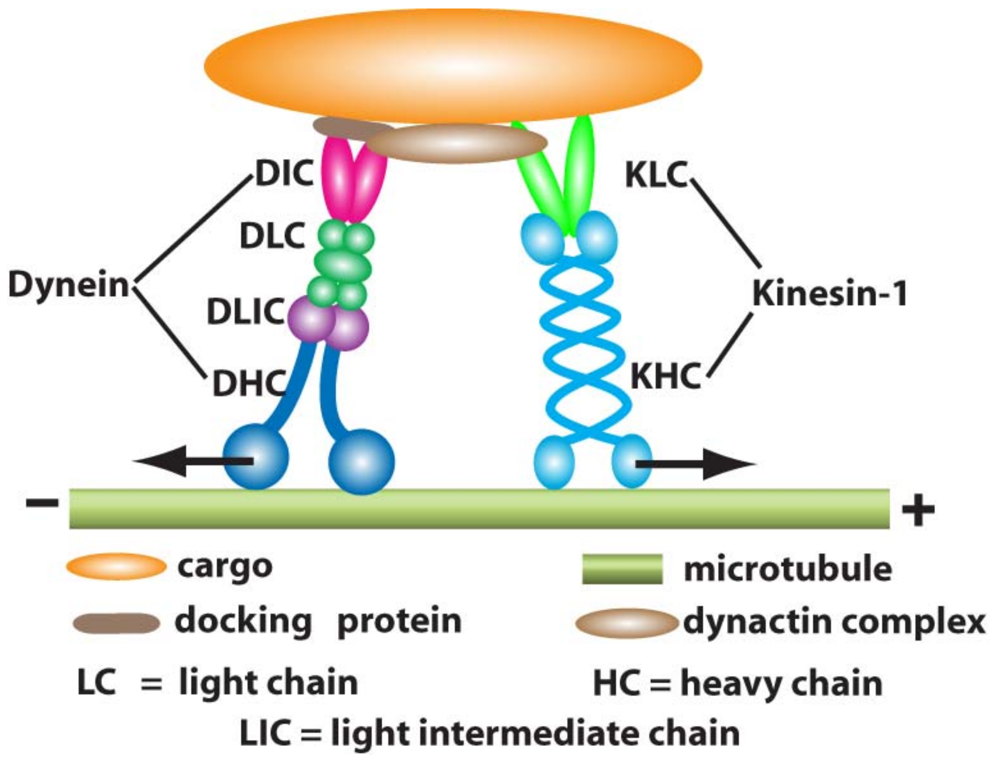
Axon Swelling and Vesicles Accumulation

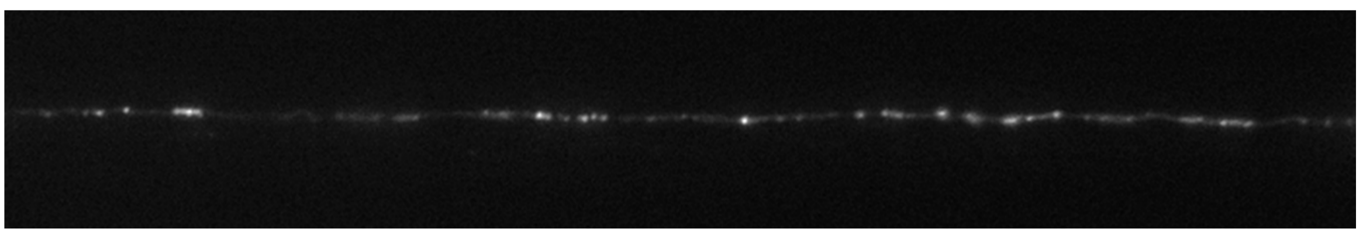


Summary

- Computational analysis of biological imaging data is crucial to understanding the underlying biological processes.
- The biological questions to be addressed usually define how the images should be analyzed.
- To obtain quantitative measurements is often the first step.
- Statistical analysis and data mining techniques are often used to understand the measurement data.
- <u>The fundamental challenge: to infer the underlying molecular mechanisms from measurements.</u>

Challenge: To Infer Mechanisms from Behaviors





Questions?