Bioimage Informatics

Lecture 20, Spring 2012

Basic Diffusion Theory

Biological Applications (II)

Experimental and Computational Analysis of Spindle Microtubule Flux

Outline

- Review: computational analysis of axonal transport
- Basic diffusion theory
- Computational analysis of Spindle Microtubule Flux

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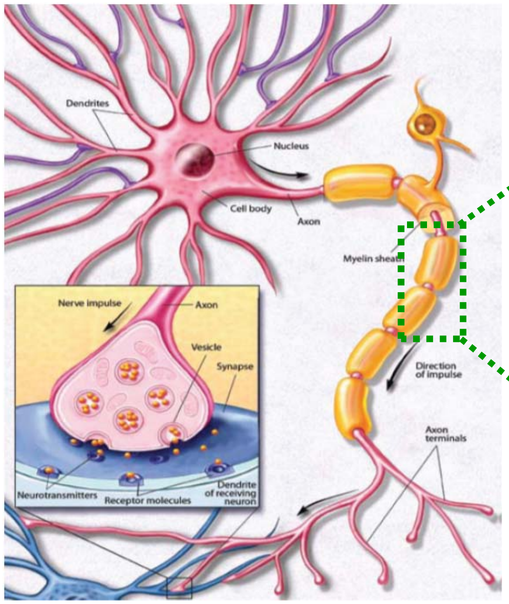
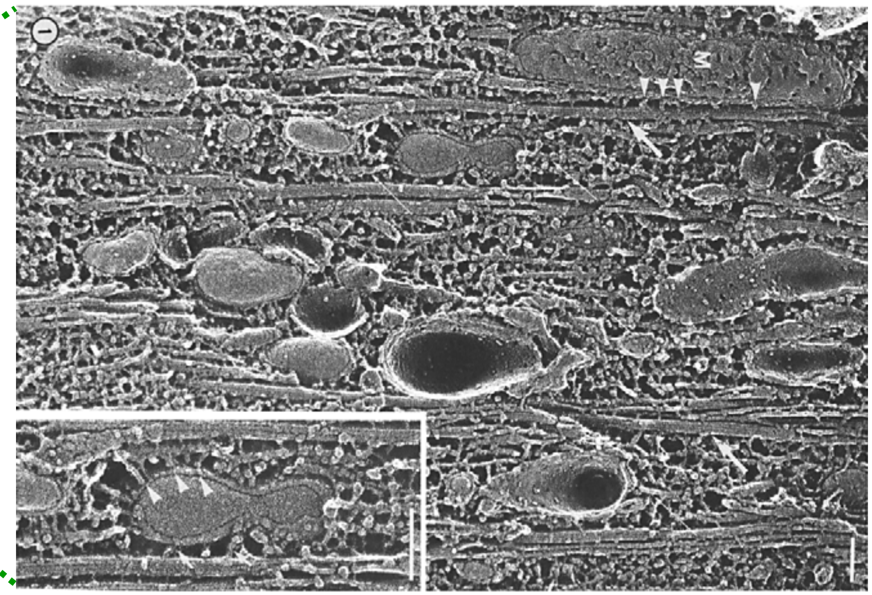
- Basic diffusion theory
- Computational analysis of spindle microtubule flux

Axonal Cargo Transport (I)

From *Brain Facts*, Society for Neuroscience





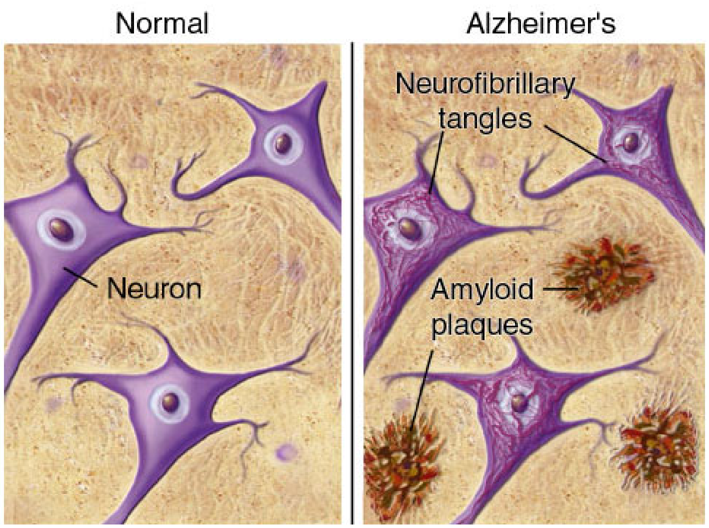
Hirokawa, 1982

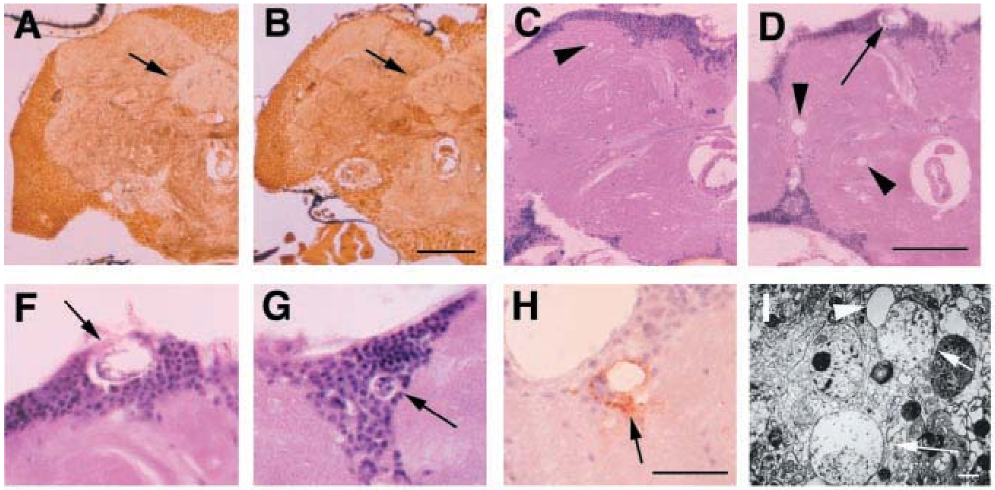
Bars: 0.1μm

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

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/+*





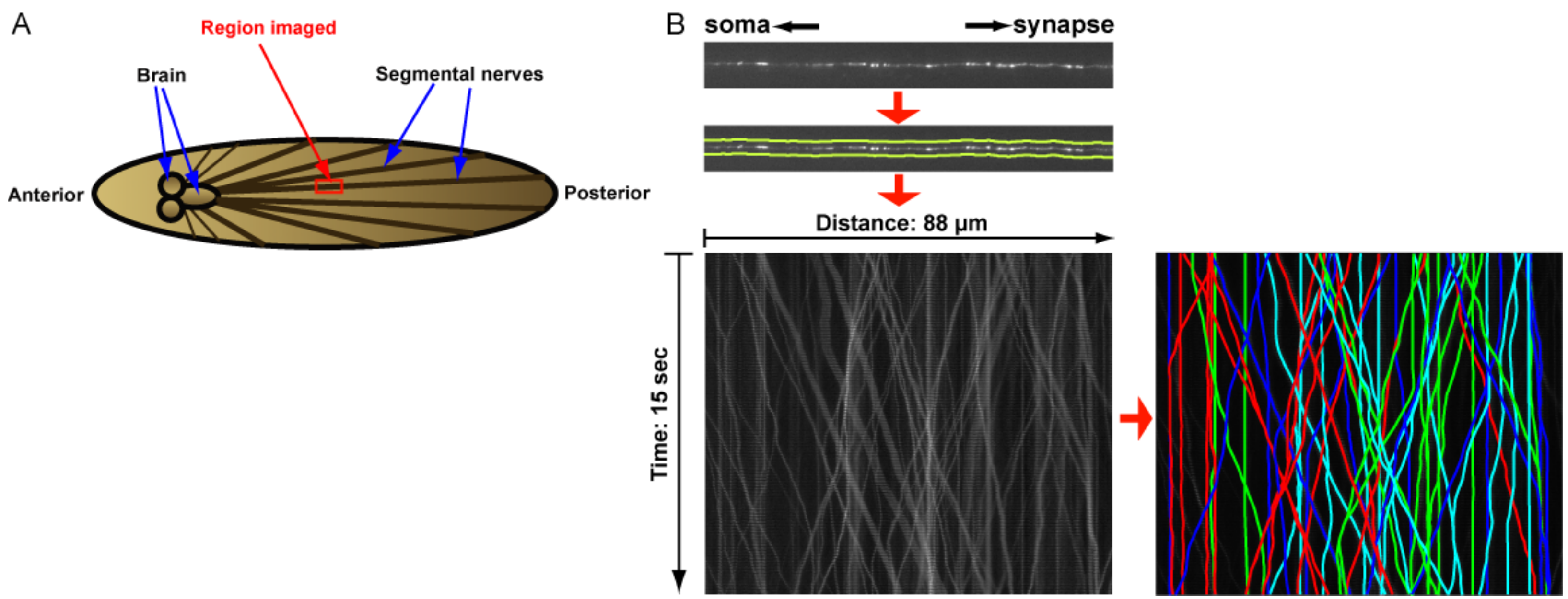
Wittmann et al, *Science*, 2001

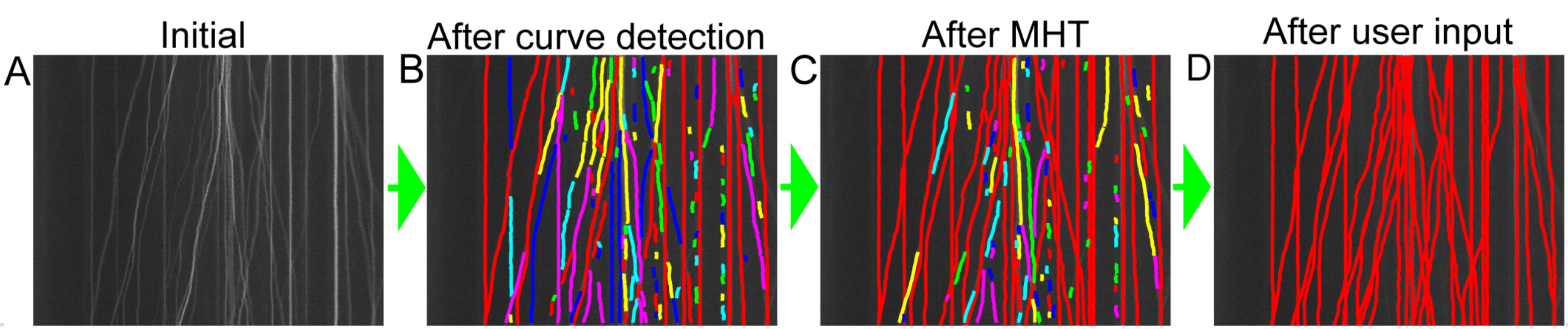
The questions:

1) What are the differences between normal and degenerative neurons in their axonal transport behaviors?

2) What causes transport defects in degenerative neurons?

Tracking Vesicle Movement Using Computer Vision Techniques (I)



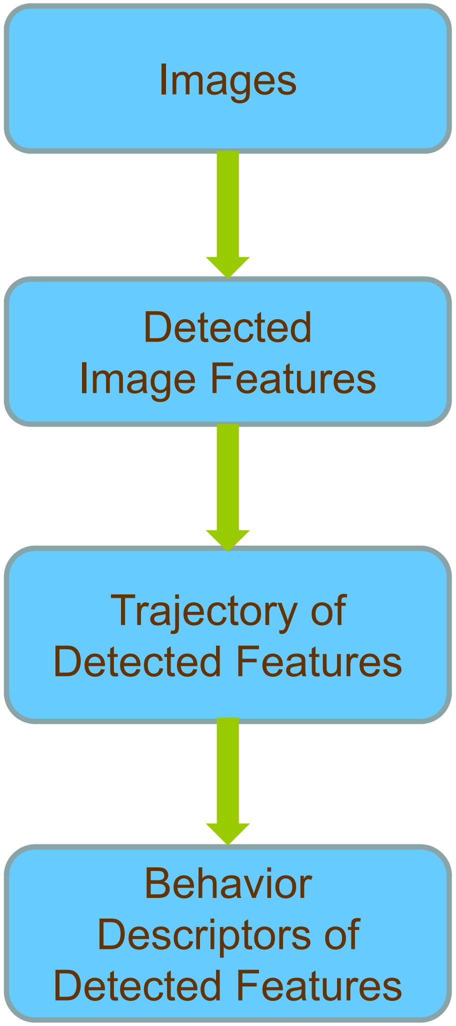


Some General Comments (I)

- To select or build effective visualization tools is very important to the development of biological image analysis algorithms.

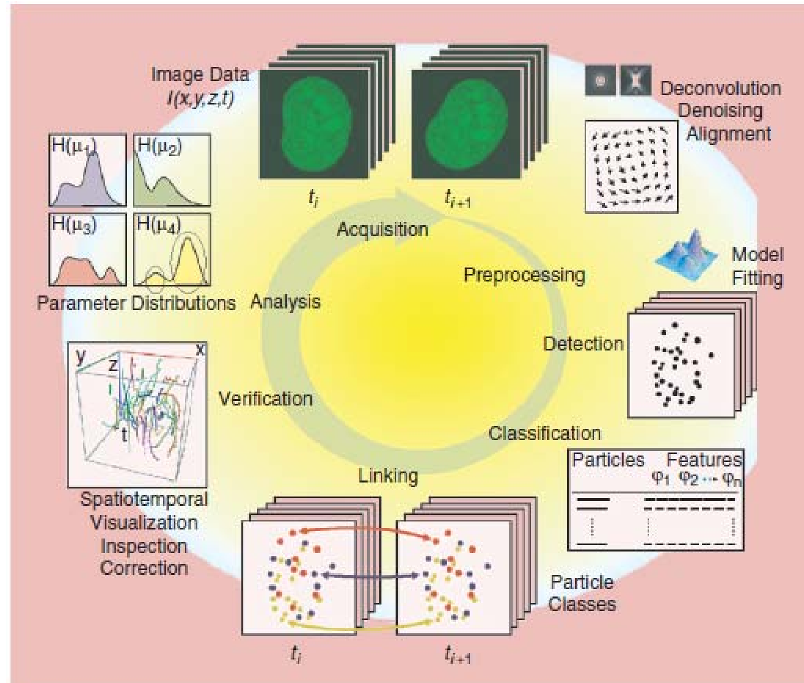
- It is critical to recognize and prevent potential information loss in the analysis work flow.

- Because of the small number of features, it is feasible to use algorithms with high computational complexity.



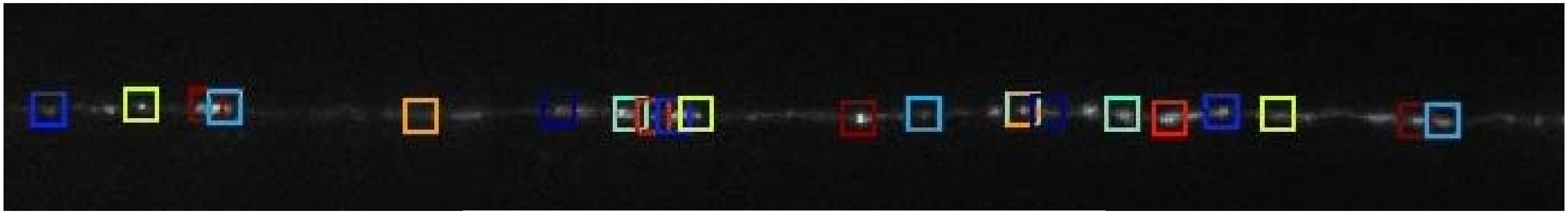
Some General Comments (II)

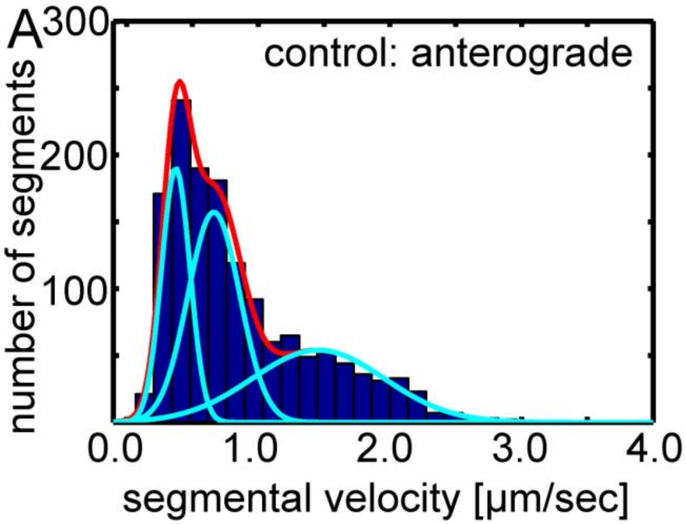
- A more comprehensive description of the work flow of particle tracking.
- What problems do you see in this picture?



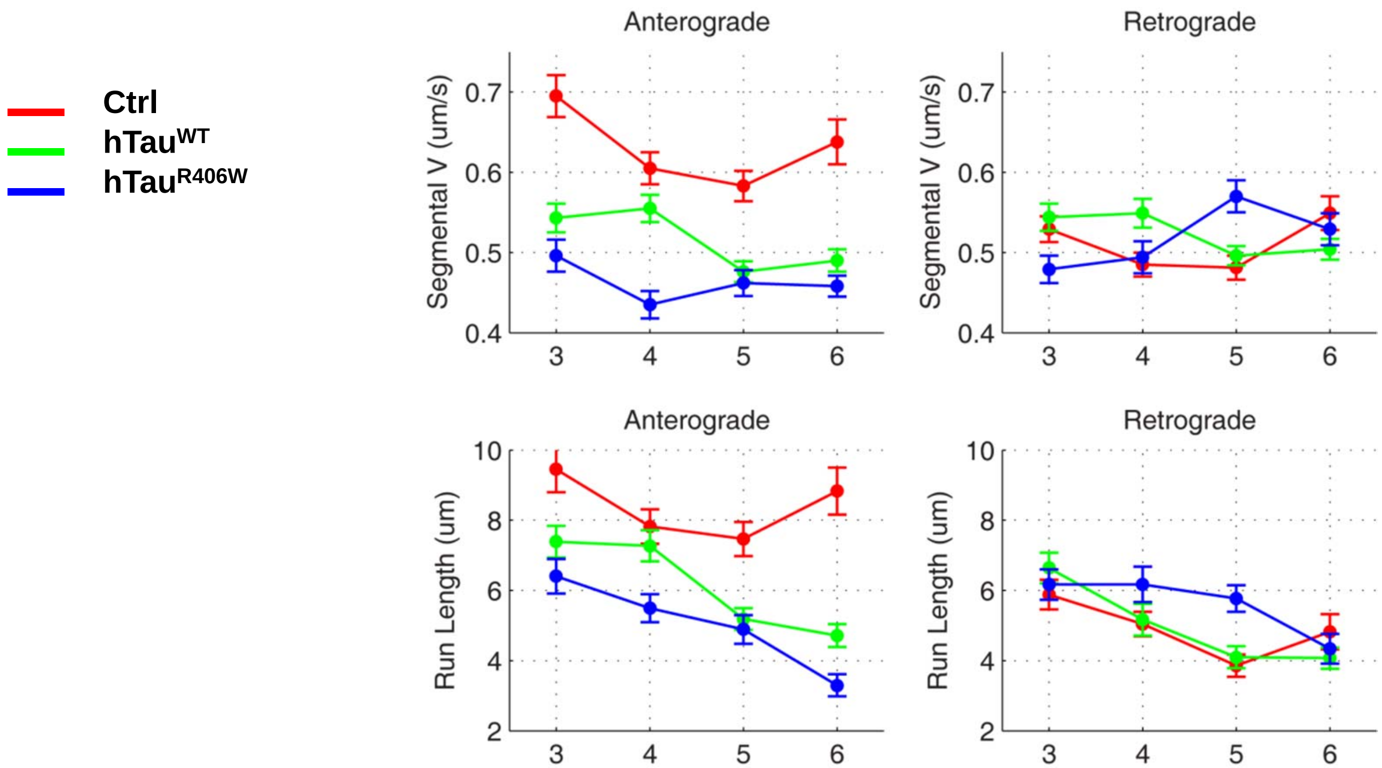
Meijering et al, _Tracking in Molecular Bioimaging_, IEEE Signal Processing Magazine, 2006.

Tracking Vesicle Movement Using Computer Vision Techniques (II)





APP Vesicle Transport and its Impairment is Region-Specific



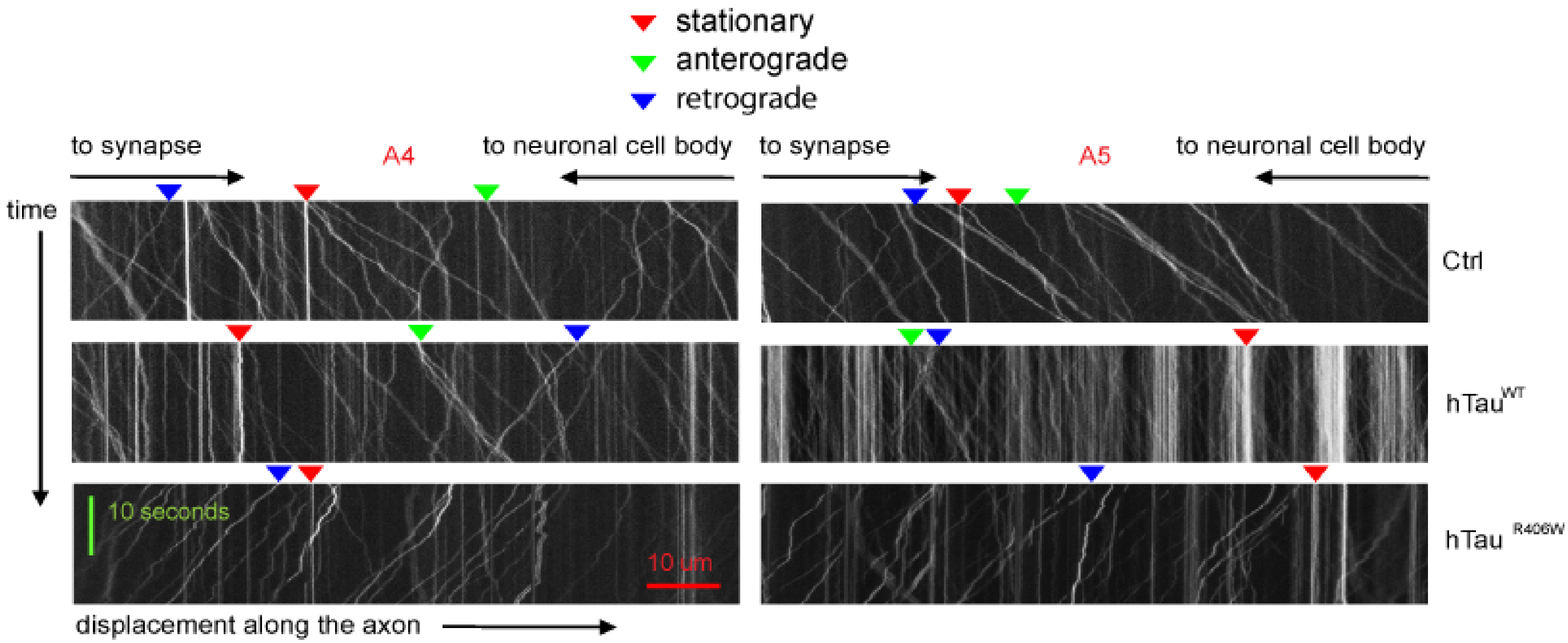
How can we make sure that information loss is minimized?

Questions for identifying potential information loss

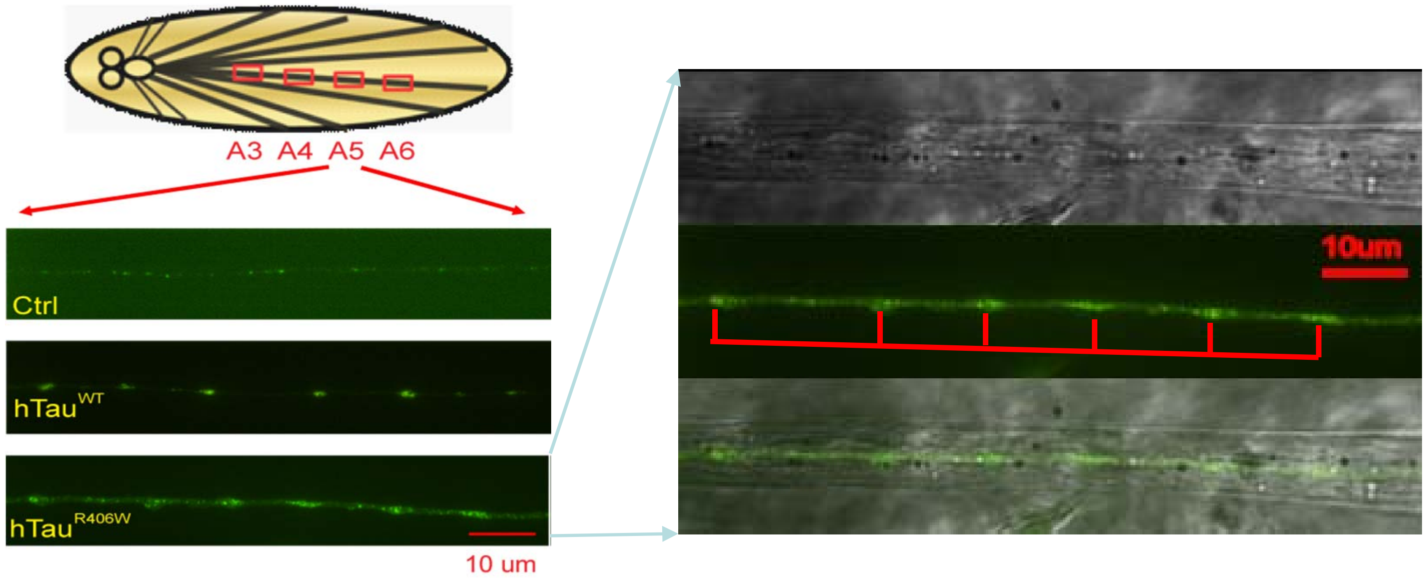
1) **Does each vesicle change its velocity over time? If so, how?**

2) **How are the vesicles spatially distributed?**

Tau Overexpression Differentially Affects Axonal Transport



Axon Swelling and Vesicles Accumulation

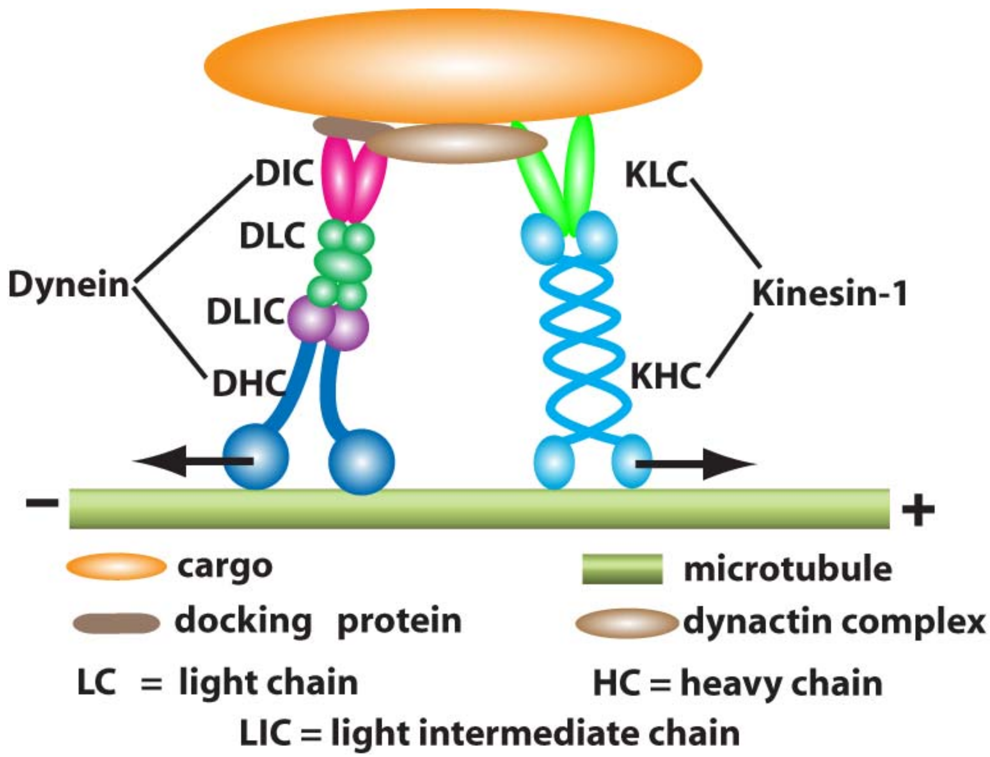


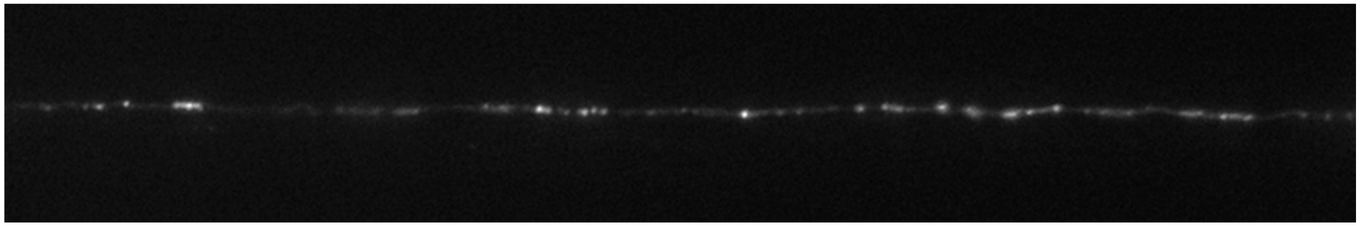
What can we learn from this?

1) How the images should be analyzed is strongly dependent on the biological questions to be addressed.

2) It is important to identify research questions from applications.

Challenge: To Infer Mechanisms from Behaviors





- Review: computational analysis of axonal transport
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Thermal Movement of a Free Molecule

- The average kinetic energy of a particle of mass *m* and velocity v_x is

$$\left\langle \frac{1}{2} m v_x^2 \right\rangle = \frac{kT}{2}$$

Boltzmann constant=1.381×10^{-23} J/K

1 Joule = 1 N·m $t_K = t_C + 273.15$

where k is Boltzmann's constant and T is absolute temperature (Einstein 1905).

- Molecular mass of GFP is 27 kDa. One atomic mass unit (Da) is 1.6606×10^{-24}g. So the mass of one GFP molecule is 4.4836×10^{-20}g.

At 27 degree C, kT is 4.1451×10^{-14}g·cm^2/sec^2.

$$\sqrt{\left\langle v_x^2 \right\rangle} = \sqrt{\frac{kT}{m}} = 961.51 \text{ cm/sec}$$

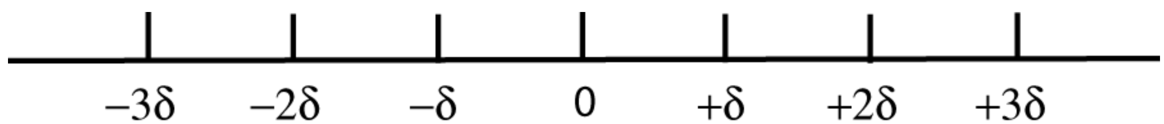
Howard Berg, Random walks in biology, Princeton University Press, 1993

1D Random Walk in Solution (I)

- Assumptions: *consider an ensemble of N particles*,

(1) A particle *i* has equal probabilities to walk to the left and to the right.
(2) Particle movement at consecutive time points are independent.
(3) Movement of different particles are independent.
(4) Each particle moves at a average step size of $\delta = v_x \cdot \tau$

$$x_i(n) = x_i(n-1) \pm \delta$$



$$\langle x(n) \rangle = \frac{1}{N}\sum_{i=1}^{N} x_i(n) = \frac{1}{N}\sum_{i=1}^{N}\left[x_i(n-1) \pm \delta\right]$$

$$= \frac{1}{N}\sum_{i=1}^{N} x_i(n-1) = \langle x(n-1) \rangle$$

- Property 1: The mean position of an ensemble of particles undergoing random walk remains unchanged.

Howard Berg, Random walks in biology, Princeton University Press, 1993

1D Random Walk in Solution (II)

- Property 2: The mean square displacement of a particle undergoing random walk increases linearly w.r.t. time.

$$\left\langle x^2(n)\right\rangle = \frac{1}{N}\sum_{i=1}^{N} x_i^2(n) = \frac{1}{N}\sum_{i=1}^{N}\left[x_i^2(n-1) \pm 2\delta x_i(n-1) + \delta^2\right]$$
$$= \left\langle x^2(n-1)\right\rangle + \delta^2$$

$$\left\langle x^2(n)\right\rangle = n\delta^2 = \frac{t}{\tau}\delta^2 = 2Dt$$

Howard Berg, *Random walks in biology*, Princeton University Press, 1993

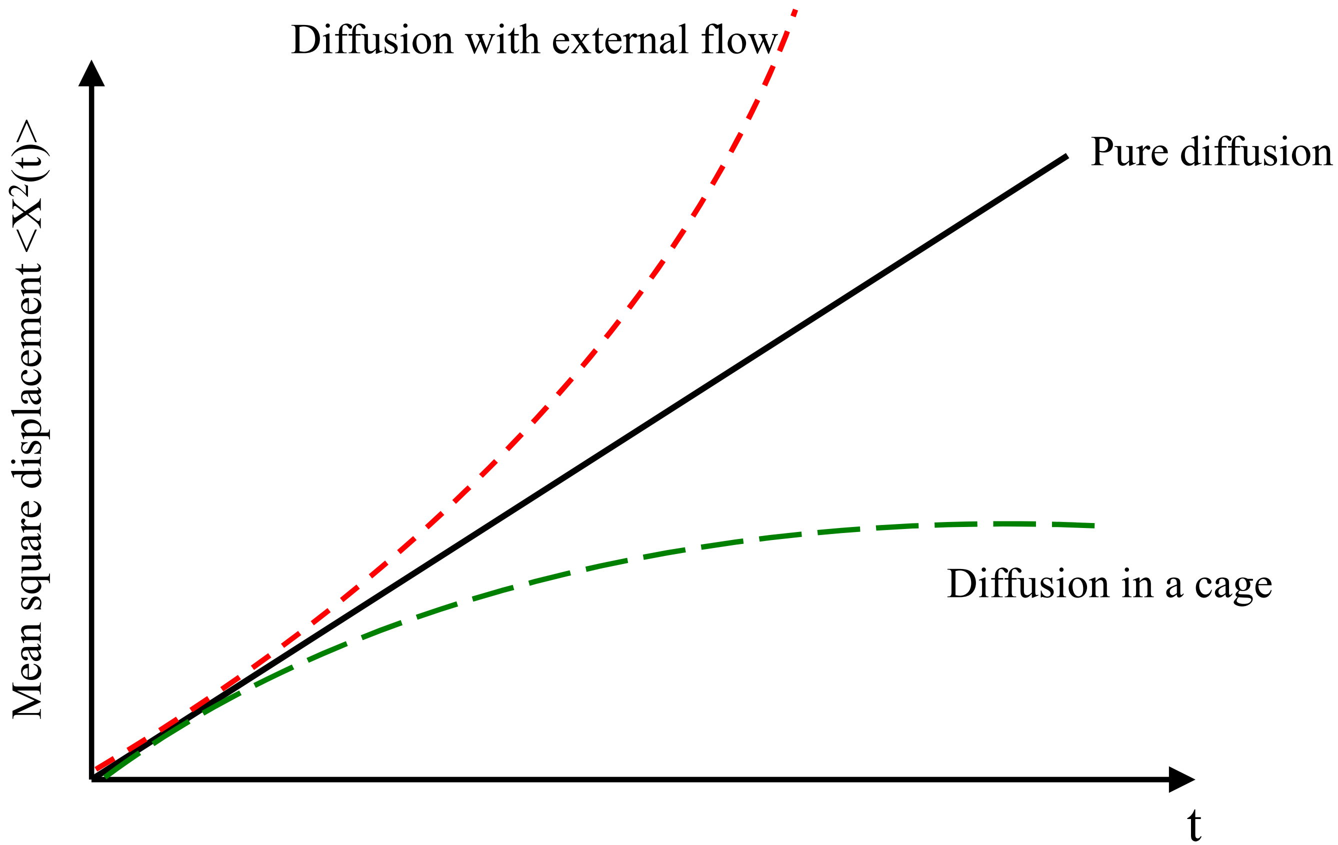
Application of the Microscopic Theory (I)

Object	**Distance diffused**			
	1 µm	**100 µm**	**1 cm**	**1 m**
K^+	0.25ms	2.5s	2.5×10^4s (7 hrs)	2.5×10^8s (8 yrs)
Protein	5ms	50s	5.0×10^5s (6 days)	5.0×10^9s (150 yrs)
Organelle	1s	10^4s (3 hrs)	10^8s (3 yrs)	10^{12}s (31710 yers)

K+: Radius = 0.1nm, viscosity = 1mPa·s^{-1}; T = 25°C; D=2000 µm^2/sec
Protein: Radius = 3nm, viscosity = 0.6915mPa·s^{-1}; T = 37; D = 100 µm^2/sec
Organelle: Radis = 500nm, viscosity = 0.8904mPa·s^{-1}; T = 25°C; D = 0.5 µm^2/sec

Jonathon Howard, *Mechanics of motor proteins and the cytoskeleton*, Sinauer, 2001

Application of the Microscopic Theory (II)



H. Qian, M. P. Sheetz, E. L. Elson, *Single particle tracking: analysis of diffusion and flow in two-dimensional systems*, Biophysical Journal, 60(4):910-921, 1991.

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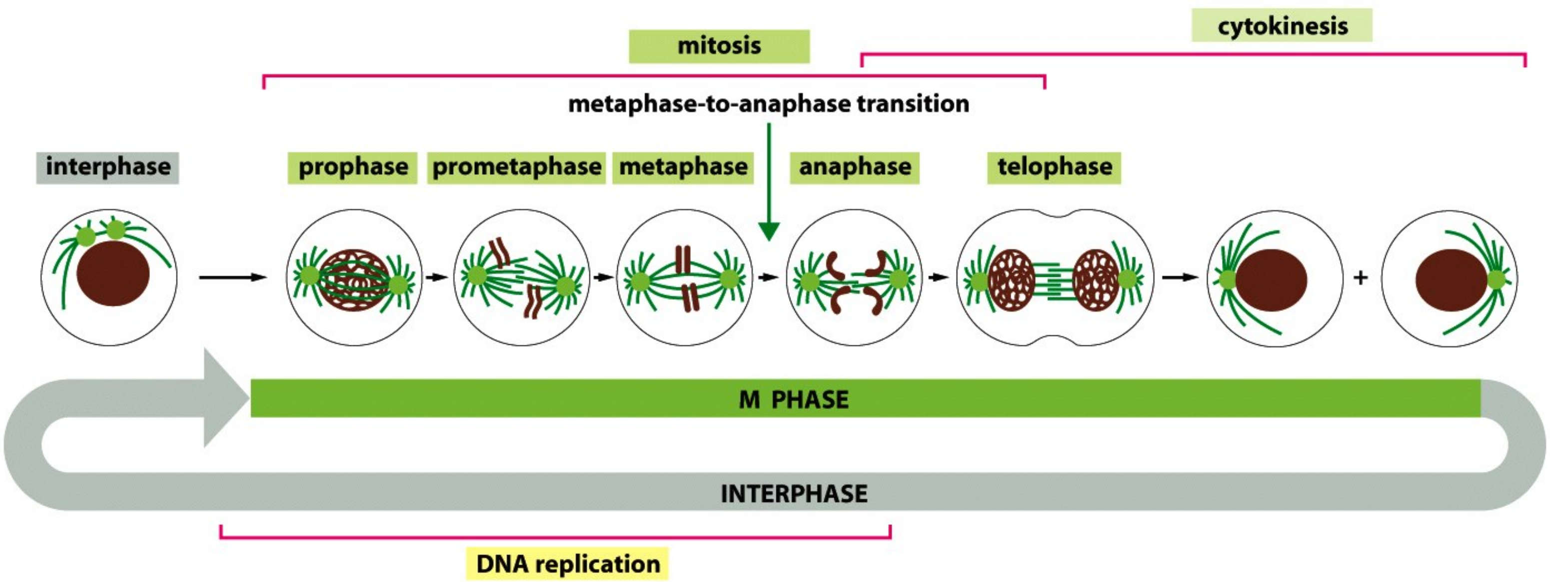
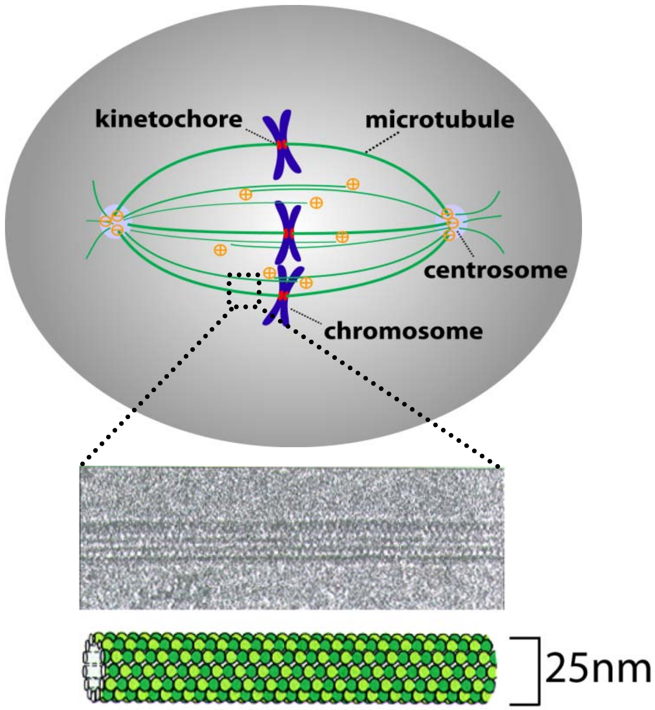
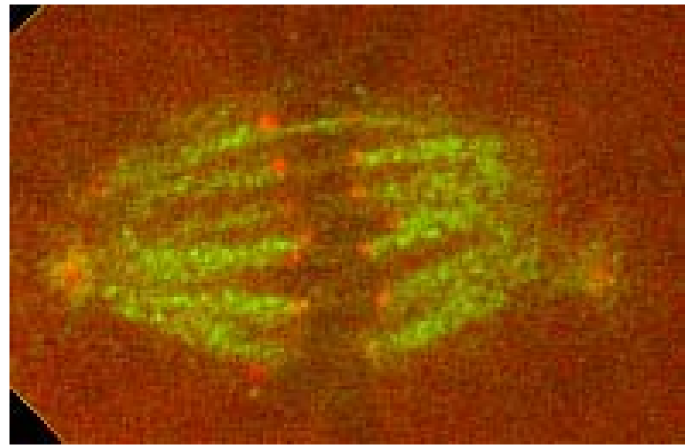
Overview of Cell Cycle



Dynamic Microtubules in the Mitotic Spindle



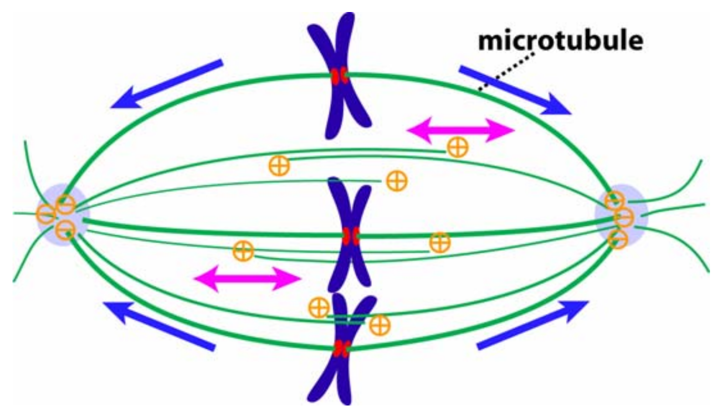
Alberts et al., MBoC5



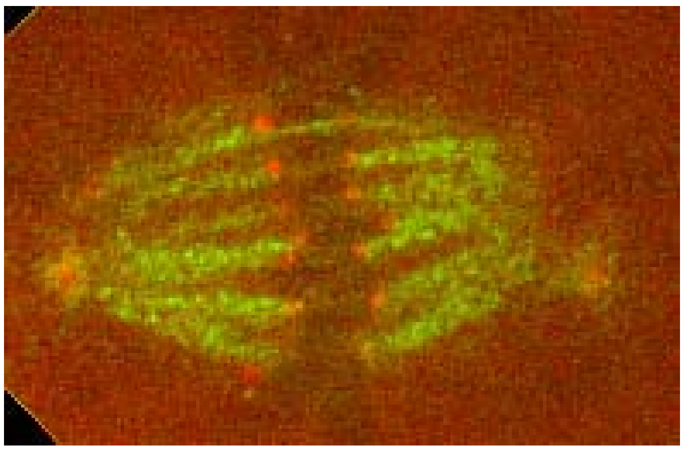
Green: microtubule

Red: kinetochore

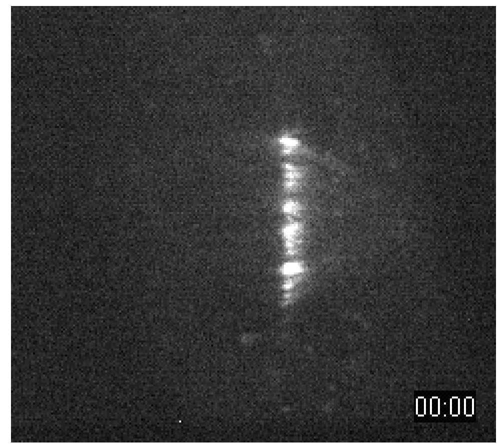
5 µm



Confirmation of Poleward Flow of Spindle Microtubules

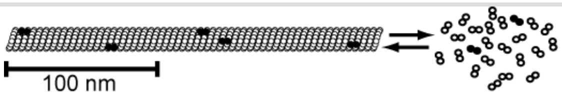


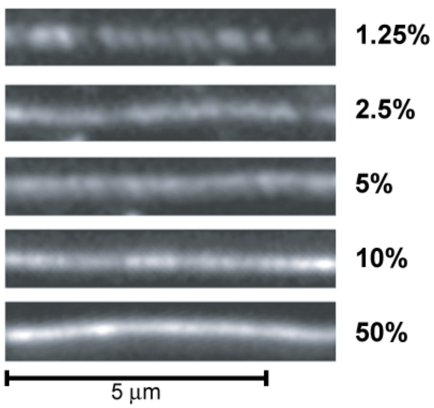
5 μm

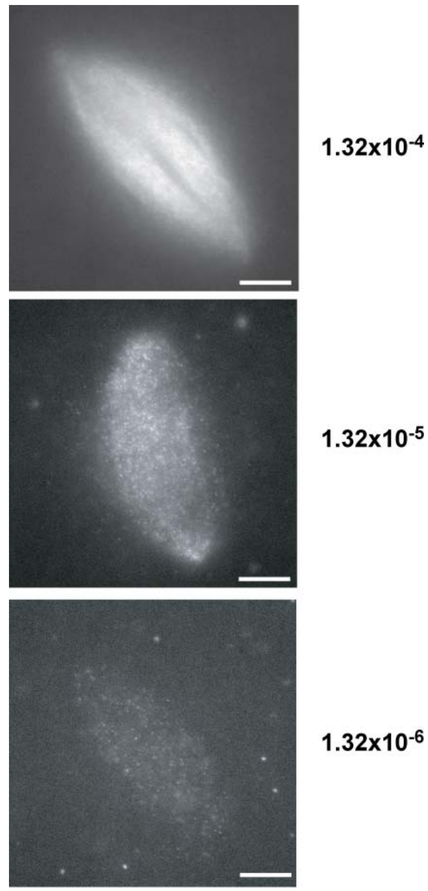


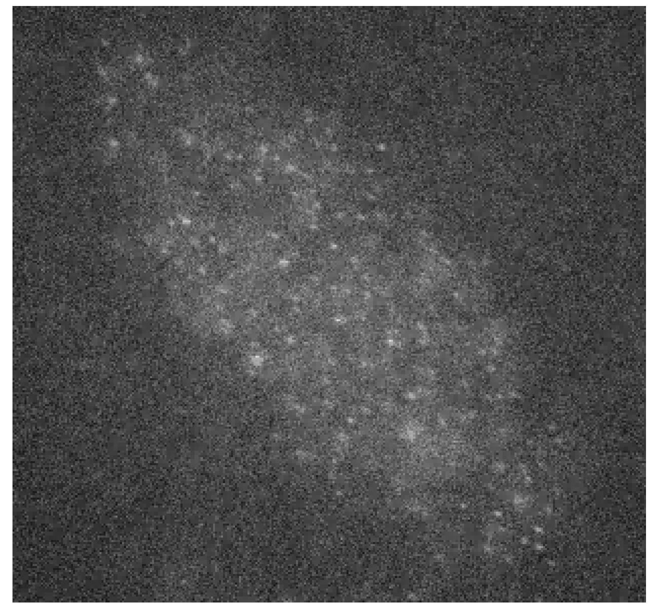
Cameron et al, *JCB*, 173:173-179,2006

Fluorescent Speckle Microscopy (FSM)

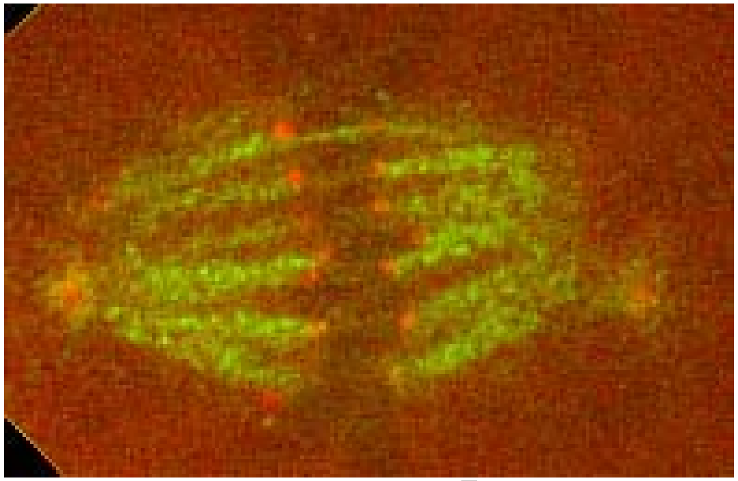






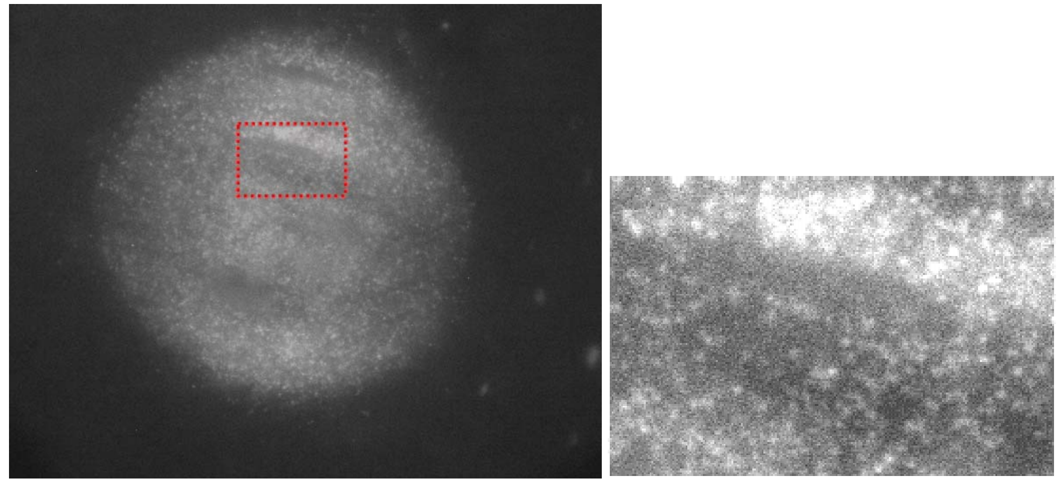


FSM of Dynamic Spindle Architecture



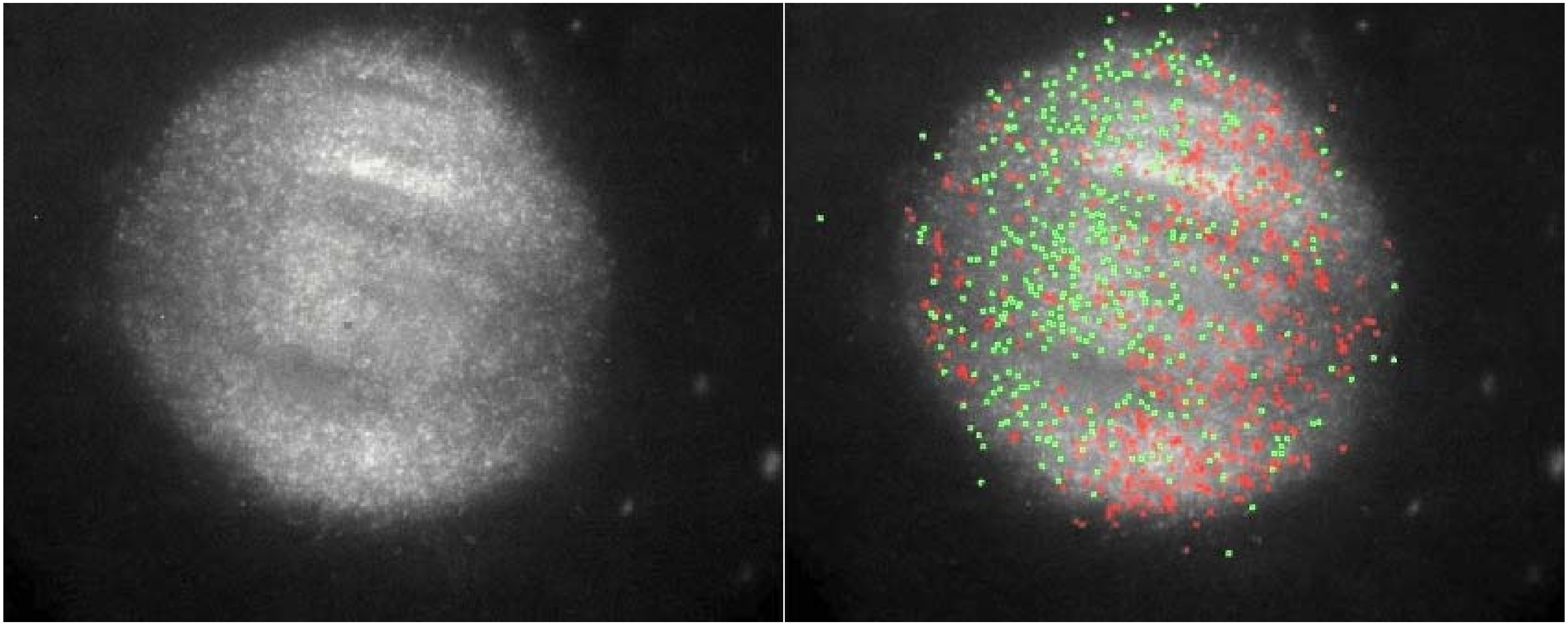
5 µm

Fluorescent speckle microscopy



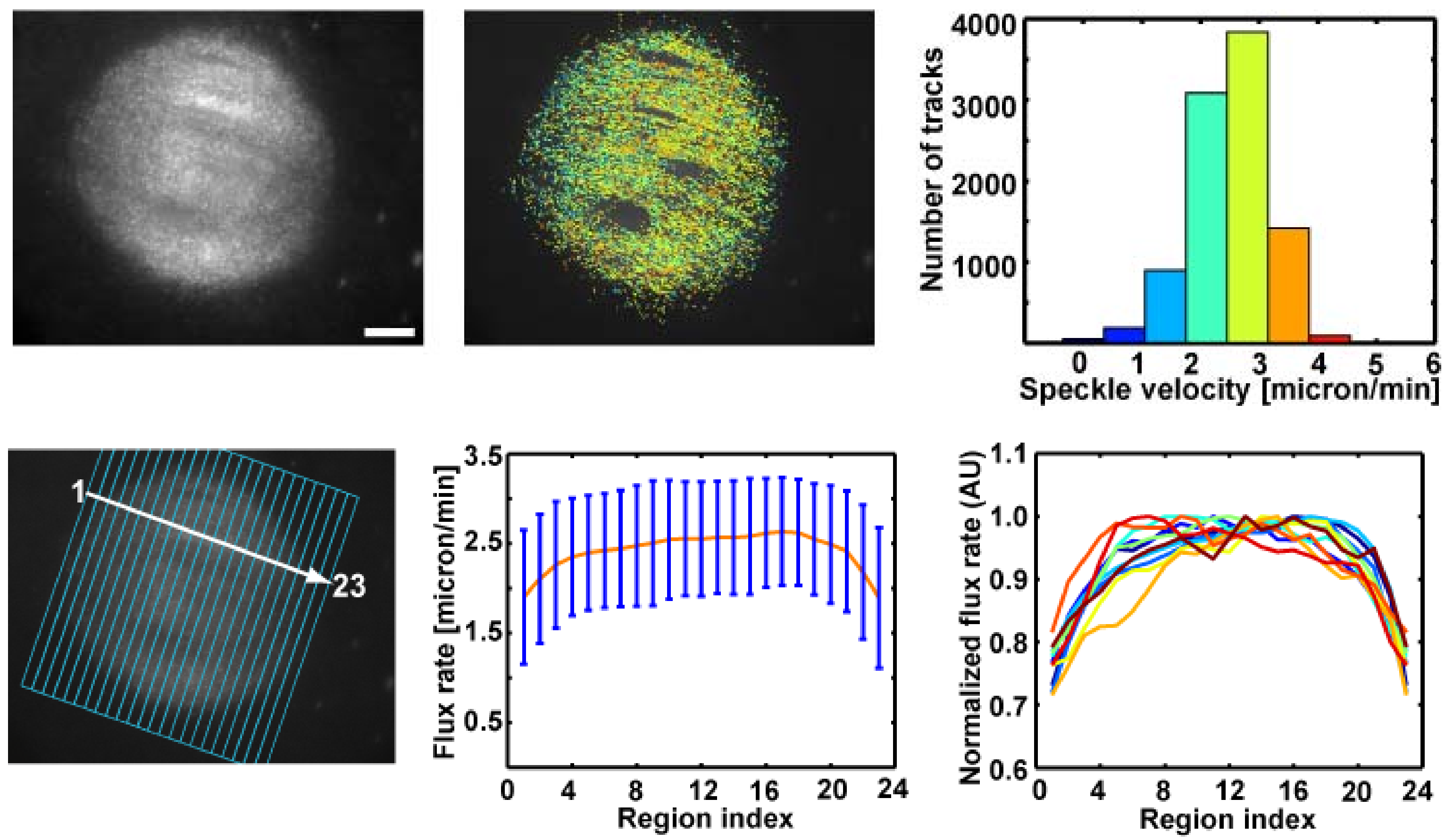
10 µm

Quantitative Mapping of Spatial-Temporal Spindle Dynamics



Yang et al., *J. Cell Biol.,* 182:631-639, 2008

Regional Variations of Microtubule Flux



Yang et al., *J. Cell Biol.,* 182:631-639, 2008

Questions?