Bioimage Informatics

Lecture 19, Spring 2012

Biological Applications (I)

Experimental and Computational Analysis of

Axonal Cargo Transport
Images for Curvilinear Feature Detection

GFP-LC3

GFP-LC3

GFP-LC3
Outline

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

• Introduction to axonal transport

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• Basic diffusion theory
Axonal Cargo Transport (I)

- 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

<table>
<thead>
<tr>
<th>Rate class</th>
<th>Average rate</th>
<th>Moving structures</th>
<th>Composition (selected examples)</th>
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</thead>
<tbody>
<tr>
<td><strong>Fast components</strong></td>
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<tr>
<td>Fast anterograde</td>
<td>200–400 mm day(^{-1})</td>
<td>Golgi-derived vesicles and tubules (secretory pathway)</td>
<td>Synaptic vesicle proteins, kinesin, enzymes of neurotransmitter metabolism</td>
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<td></td>
<td>(≈2–5 μm s(^{-1}))</td>
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<tr>
<td>Bi-directional</td>
<td>50–100 mm day(^{-1})</td>
<td>Mitochondria</td>
<td>Cytochromes, enzymes of oxidative phosphorylation</td>
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<td>(≈0.5–1 μm s(^{-1}))</td>
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</tr>
<tr>
<td>Fast retrograde</td>
<td>200–400 mm day(^{-1})</td>
<td>Endosomes, lysosomes (endocytic pathway)</td>
<td>Internalized membrane receptors, neurotrophins, active lysosomal hydrolases</td>
</tr>
<tr>
<td></td>
<td>(≈2–5 μm s(^{-1}))</td>
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<tr>
<td><strong>Slow components</strong></td>
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<td></td>
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</tr>
<tr>
<td>Slow component ‘a’</td>
<td>0.3–3 mm day(^{-1})</td>
<td>Neurofilaments, microtubules(^{\dagger})</td>
<td>Neurofilament proteins, tubulin, spectrin, tau proteins</td>
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<tr>
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<tr>
<td>Slow component ‘b’</td>
<td>2–8 mm day(^{-1})</td>
<td>Microfilaments, supramolecular complexes of the cytosolic matrix</td>
<td>Actin, clathrin, dynein, dynactin, glycolytic enzymes</td>
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<tr>
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<td>(≈0.02–0.09 μm s(^{-1}))</td>
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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
Molecular Motor Machinery of Axonal Transport

Potential Mechanisms of Axonal Transport Defects

Diagram illustrating the interactions between various components involved in axonal transport, including dynein, kinesin-1, dynactin complex, and microtubules. The diagram highlights the role of light chains (LC), heavy chains (HC), and light intermediate chains (LIC) in the transport process.

Key terms:
- Cargo
- Docking protein
- Microtubule
- Dynactin complex
- LC = light chain
- HC = heavy chain
- LIC = light intermediate chain
Microtubule Associated Protein Tau in Axonal Transport

How does tau modulate axonal transport?
A Drosophila Model of Alzheimer’s Disease

• Two pathological hallmarks of AD: Aβ plaques & tau tangles

• Control:
  
  \[
  \text{SG26.1 GAL4/+; UAS-APP-YFP/+} \quad \text{transport is driven by kinesin-1} \\
  \text{SG26.1 GAL4/+; UAS-Syn-GFP} \quad \text{transport is driven by kinesin-3}
  \]

• Mutants:
  
  \[
  \text{SG26.1 GAL4/+; UAS-APP-YFP/+; UAS-wt hTau/+} \\
  \text{SG26.1 GAL4/+; UAS-APP-YFP/+; UAS-R406W hTau/+}
  \]

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Why Nanometer Resolution?

- Nanometer resolution is essential to axonal transport characterization.
Detection Resolution Validation

Q-dots

F-beads

Graphs showing displacement over time for different step sizes:
- Step Size = 100 nm
- Step Size = 24 nm
- Step Size = 16 nm

Graphs depict the movement of particles over time with varying step sizes.
Tracking Vesicle Movement Using Computer Vision Techniques (I)
Tracking Vesicle Movement Using Computer Vision Techniques (II)
• Course review

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Tau Overexpression Differentially Affects Axonal Transport
Quantification of Cargo Population

**StatCargoNum (%)**

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**AnteCargoNum (% of NonStat)**

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**RetroCargoNum (% of NonStat)**

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**RevCargoNum (% of NonStat)**

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APP Vesicle Transport and its Impairment is Region-Specific

Ctrl
hTau^{WT}
hTau^{R406W}
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.

• The fundamental challenge: to infer the underlying molecular mechanisms from measurements.
Challenge: To Infer Mechanisms from Behaviors
Questions?