Active Transport in Microtubules Networks

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An idealized animal cell
Microtubules are directional: 
(-) ends originate from the centrosome (MTOC)
Motor proteins

- Kinesin moves toward (+) end, Dynein toward (-) end.
- Low processivity, $\sim 1$ s in bound state (step time $\sim 6$ ms).
- Velocity $\sim 1 \mu$m/s.
Microtubules

Global order vs. local disorder
Questions:

• What is the purpose of the finite motor processivity?

• What is the effect of local disorder of the microtubule network on the active transport in the cell?
In vitro experiment: 3-D with orientational order
**In vitro study**

- Fluorescently labeled ssDNA-protein complex including a nuclear localization signal (NLS) peptide. **Motor protein assisted transport.**
- Particle tracking assays using a camera & designated software.

Results

- pl – labeled complex without NLS
- an – labeled complex with NLS
- an+Noc – labeled complex with NLS without microtubules (destroyed by Nocodazole)

**Question:**
Why does the active transport appear as simple diffusion?

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Random velocity model in 1+1 dimensions
Random velocity model in 1+1 dimensions

Exact result, Super-diffusion:

\[ \langle y^2(t) \rangle \sim t^{3/2} \]

Scaling argument:

\[ \langle y^2(t) \rangle \approx P_{0,x}(t) v^2 t^2 \quad \text{where} \quad P_{0,x}(t) \sim t^{-1/2} \]

The probability of return to the origin in 1-D

Simulation results:

- Balanced tracks (% up=% down) – fits the theory of ZKB.
  
- **diffusion with drift** – a crossover from short-time super-diffusion
  
  \[ \langle y^2(t) \rangle \sim t^{3/2} \quad \text{to long-time diffusion} \quad \langle y^2(t) \rangle \sim t \]

explained by a scaling argument

G. Zumofen, J. Klafter, A. Blumen, PRA (1990)
S. Redner, PRE (1997)
**RVM – Unbalanced diffusion**

**MSD**
\[
\langle (\Delta x)^2 \rangle^{1/2} = 2 \sqrt{pq} \cdot \sqrt{t / \tau_0}
\]

**Drift**
\[
\langle x \rangle = (p - q) \frac{t}{\tau_0}
\]

**define:**
\[
\delta \equiv \frac{\langle (\Delta x)^2 \rangle^{1/2}}{\langle x \rangle} = \frac{2 \sqrt{pq}}{(p - q) \sqrt{t / \tau_0}} \cdot \frac{1}{\sqrt{t / \tau_0}}
\]

When \(\delta \gg 1 \rightarrow \text{RVM, when } \delta \ll 1 \rightarrow \text{Diffusion}

For \(p=0.51 \& q=0.49\): \(\delta=1 \quad \text{at} \quad t=2500\)
2-D network model

Scaling argument:

\[ \langle x^2(t) \rangle \approx P_{0,y}(t) v^2 t^2 \]

where

\[ P_{0,y}(t) \approx \frac{1}{\sqrt{\langle y^2(t) \rangle}} \]

The probability of return to the origin along the y axis, assuming Gaussian PDF

By symmetry

\[ \langle x^2(t) \rangle = \langle y^2(t) \rangle = \frac{\langle \rho^2(t) \rangle}{2} \]

\[ \langle \rho^2(t) \rangle \sim t^{4/3} \]
More accurate self-consistent calculation:

\[
\frac{d^2}{dt^2} \langle y^2(t) \rangle = 2v^2 P_{o,x}(t)
\]
\[
\frac{d^2}{dt^2} \langle x^2(t) \rangle = 2v^2 P_{o,y}(t)
\]

From symmetry  \( \langle x^2 \rangle = \langle y^2 \rangle \)

Assuming Gaussian PDFs

\[
\langle \rho^2 \rangle = \langle x^2 \rangle + \langle y^2 \rangle = \left( \frac{9^{2/3}}{\pi^{1/3}} v^{4/3} \xi^{2/3} \right) t^{4/3}
\]
PDF along $x$-axis at time $t = 10^5 \tau_v$

$\tau_v = \xi / v$
2-D network model

**Self-consistent theory:**

\[
\langle x^2 \rangle = \langle y^2 \rangle \sim t^{4/3}
\]

**Simulation results:**

- Balanced network – fits theory
  
- Unbalanced network, long times:
  
  unbalanced direction $\rightarrow$ RVM with drift
  \[
  \langle x \rangle = (p - q)vt
  \]
  
  perpendicular direction $\rightarrow$ Long-time diffusion
  \[
  \langle y^2 \rangle \sim t
  \]
\[ \langle y^2 \rangle / \xi^2 \]

Slope = 1.25 \ (4/3)

Slope = 1.02

\[ t^* \approx \frac{\xi}{v|p-q|^3} \]

\[ \langle y^2 \rangle \approx \begin{cases} 
(9C/2)^{2/3} (v^2 \xi)^{2/3} t^{4/3} & \text{for } t \ll t^*; \\
\frac{v\xi}{|p-q|} t & \text{for } t \gg t^*. 
\end{cases} \]
\[ \langle (x - \langle x \rangle)^2 \rangle \approx \begin{cases} 
(9C/2)^{2/3} (v^2 \xi)^{2/3} t^{4/3} & \text{for } t \ll t^*; \\
\frac{4\sqrt{2}}{3\sqrt{\pi}} |p - q|^{1/2} v^{3/2} \xi t^{3/2} & \text{for } t \gg t^*. 
\end{cases} \]
Processivity dependence

\[ \frac{\langle \rho^2 \rangle}{\xi^2} \]

Slope = 1.33

Processivities - \( f \)

- \( f = 0.5 \)
- \( f = 0.6 \)
- \( f = 0.75 \)
- \( f = 0.8 \)
- \( f = 0.9 \)
3-D network model
Scaling argument:
\[
\left\langle x^2(t) \right\rangle \approx P_{0, yz}(t) v^2 t^2
\]
where
\[
P_{0, yz}(t) = P_{0, y}(t) P_{0, z}(t) \approx \frac{1}{\sqrt{\left\langle y^2(t) \right\rangle}} \times \frac{1}{\sqrt{\left\langle z^2(t) \right\rangle}}
\]
The probability of return to the origin in the y-z plane

By symmetry
\[
\left\langle x^2(t) \right\rangle = \left\langle y^2(t) \right\rangle = \left\langle z^2(t) \right\rangle = \frac{\left\langle r^2(t) \right\rangle}{3}
\]

Diffusion-like, but active (non-thermal)

More accurate self-consistent calculation:
\[
\left\langle \vec{r}^2(t) \right\rangle \approx A \xi v t \left[ \ln \left( \frac{t}{\tau_v} \right) \right]^{1/2}
\]
where
\[
\tau_v = \frac{\xi}{v}
\]
\[
A \approx 2.4
\]
is the mesh size.
In vitro experiment: 3-D with orientational order
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**Question:**
Why does the active transport appear as simple diffusion?
Scaling argument:

\[ \langle x^2(t) \rangle \approx P_{0,\text{yz}}(t) v^2 t^2 \]

where

\[ P_{0,\text{yz}}(t) = P_{0,y}(t) P_{0,z}(t) \approx \frac{1}{\sqrt{\langle y^2(t) \rangle}} \times \frac{1}{\sqrt{Dt}} \]

The probability of return to the origin in the y-z plane

By symmetry \[ P_{0,\text{yz}}(t) = P_{0,xz}(t) \] and

\[ \langle x^2(t) \rangle = \langle y^2(t) \rangle = \frac{\langle \rho^2(t) \rangle}{2} \]

Diffusion-like, but active (non-thermal)

More accurate self-consistent calculation:

\[ \langle \rho^2(t) \rangle \approx A \frac{(\xi v)^{4/3}}{D^{1/3}} t \left[ \ln \left( \frac{t}{\tau_\nu} \right) \right]^{2/3} \]

where \[ \tau_\nu = \frac{\xi}{v} \]

\[ \xi \] is the mesh size

\[ A \approx 1.2 \]
Slope = 0.63

\[ t / \tau_v [\ln (t / \tau_v)]^{2/3} \]
3-D animal cell model
Simulations of “First Exit” problem:

• Kinesin mediated transport:
  
  (i) Probability to arrive from the nucleus to the membrane until time $t$.

  (ii) Probability to arrive from the nucleus to a localized target in the cell (e.g., ribosome) until time $t$.

• Dynein mediated transport: Probability to arrive from the membrane to the nucleus until time $t$. 
Kinesin mediated transport: From nucleus to membrane

Many cells averaging
Dynein mediated transport: From membrane to nucleus
Many cells averaging
Kinesin mediated transport:

*From nucleus to a localized target (e.g. ribosome)*

**Radiative** boundary conditions at the membrane

*Many cells averaging*
Kinesin mediated transport:

*From nucleus to a localized target (e.g. ribosome)*

**Reflective** boundary conditions at the membrane

Many cells averaging
Short times
What else?

Unusual Response to Force (?)

Assumption –
Linear-like response of a single motor walking on a single MT:

\[ \vec{v} = \vec{v}_0 + \mu \vec{f} \]

or

\[ v = v_0 \pm \mu f \]

i.e. stall force is

\[ f_{\text{stall}} = \frac{v_0}{\mu} \]
Along the force:

\[ \langle x \rangle = \mu f t \quad \text{linear response} \]

\[ \langle (x - \langle x \rangle)^2 \rangle \sim \begin{cases} t^{4/3} & \text{for } t \ll t^* \\ t^{3/2} & \text{for } t \ll t^* \end{cases} \]

Perpendicular to the force:

\[ \langle y^2 \rangle \sim \begin{cases} t^{4/3} & \text{for } t \ll t^* \\ t & \text{for } t \gg t^* \end{cases} \]

\[ t^* = \frac{v_0^2 \xi}{\mu^3 f^3} \]
Conclusions:

• Increase of polarity (velocity) field and Euclidean dimensions leads to a decrease of the anomalous diffusion exponent.

• In 3-D disordered networks active transport may appear diffusive-like (with minor logarithmic factors hinting to its origin) consistent with experiments.

• The finite, intermediate, processivity of the microtubule associated motor proteins appears “optimize” the efficiency of transport between the different network tasks: transport from nucleus to the membrane and vice-versa, and between localized cell compartments.

• The local disorder of the microtubule network in the cell also appears to enhance the efficiency of transport between different locations.
Thank you
\[
\langle y^2(t) \rangle \sim \begin{cases}
\frac{4v^2 \xi}{3(\pi D)^{1/2}} t^{3/2} & \text{for } t \ll t^*; \\
\frac{v^2 \xi^2}{2D|p-q|} t & \text{for } t \gg t^*.
\end{cases}
\]
Slope = 1.333