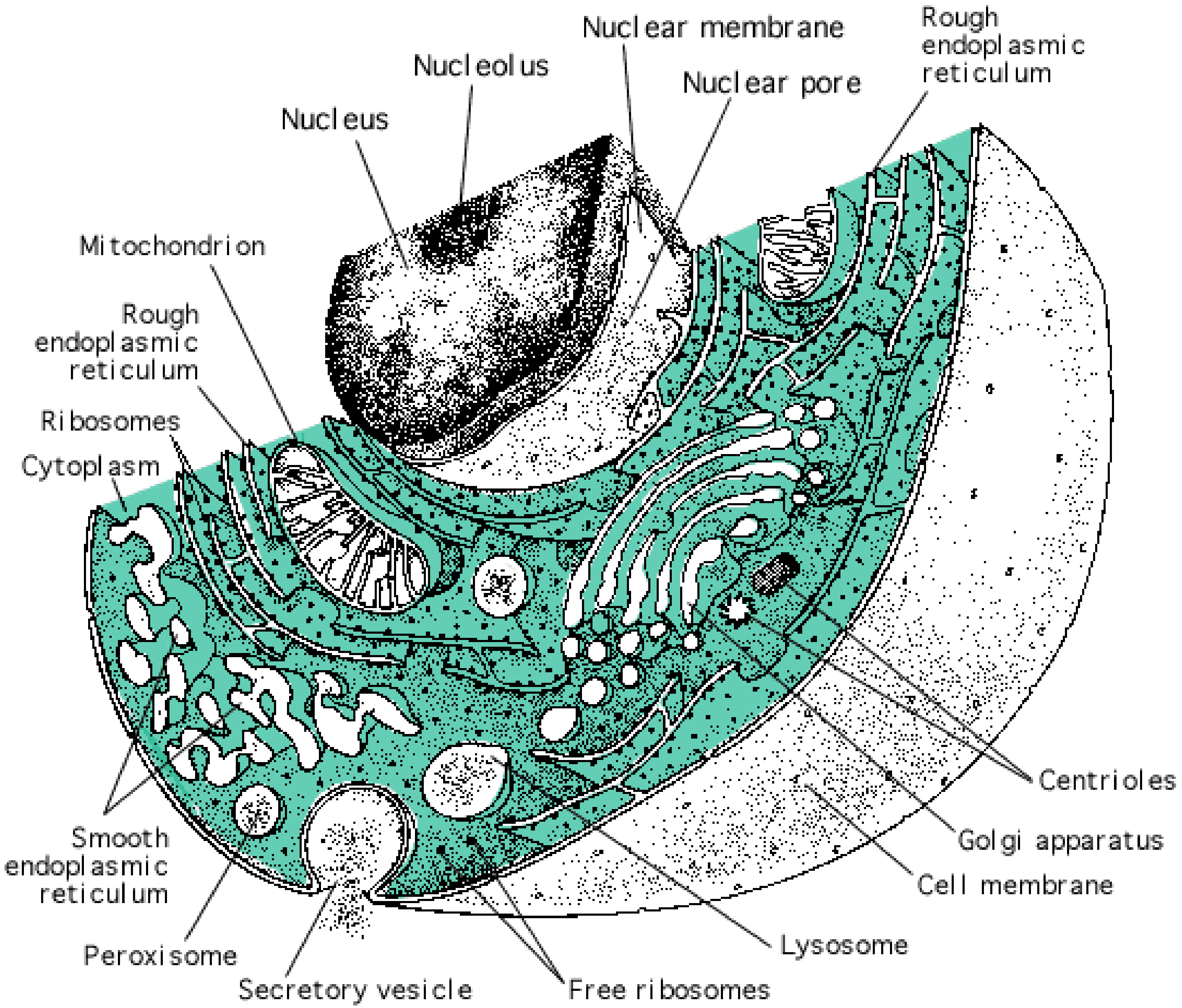
אוניברסיטת בן-גוריון בנגב
Ben-Gurion University of the Negev

Active Transport in Microtubules Networks

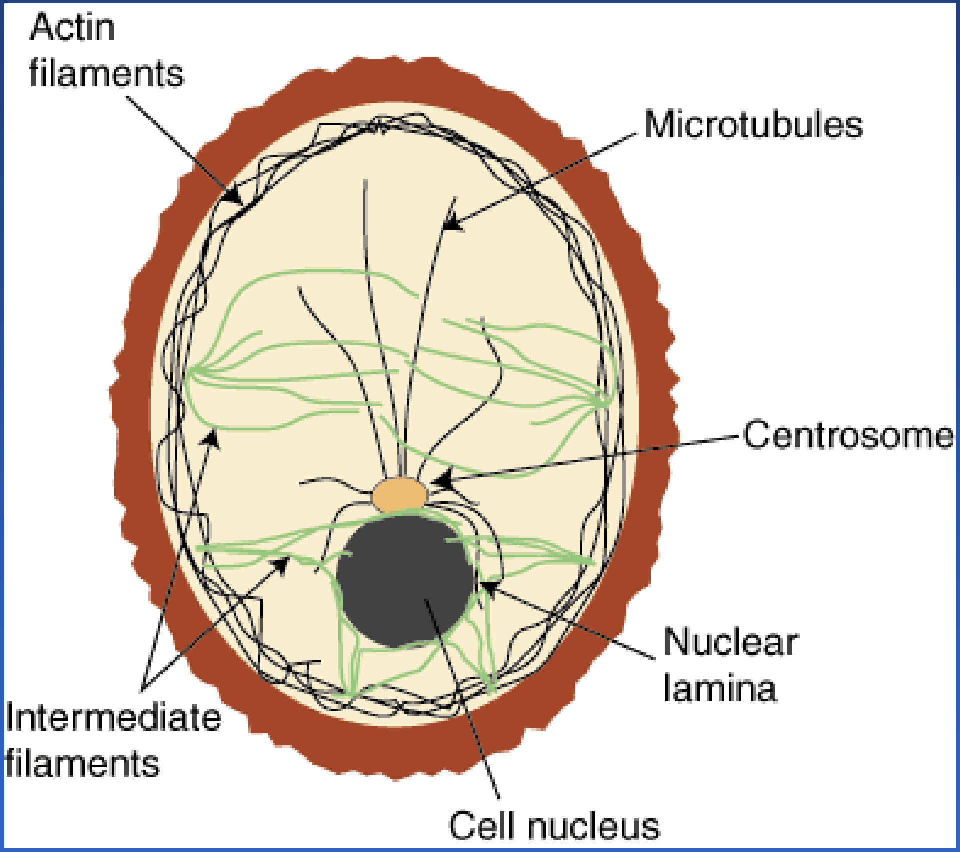
Rony Granek
Biotechnology Engineering, BGU

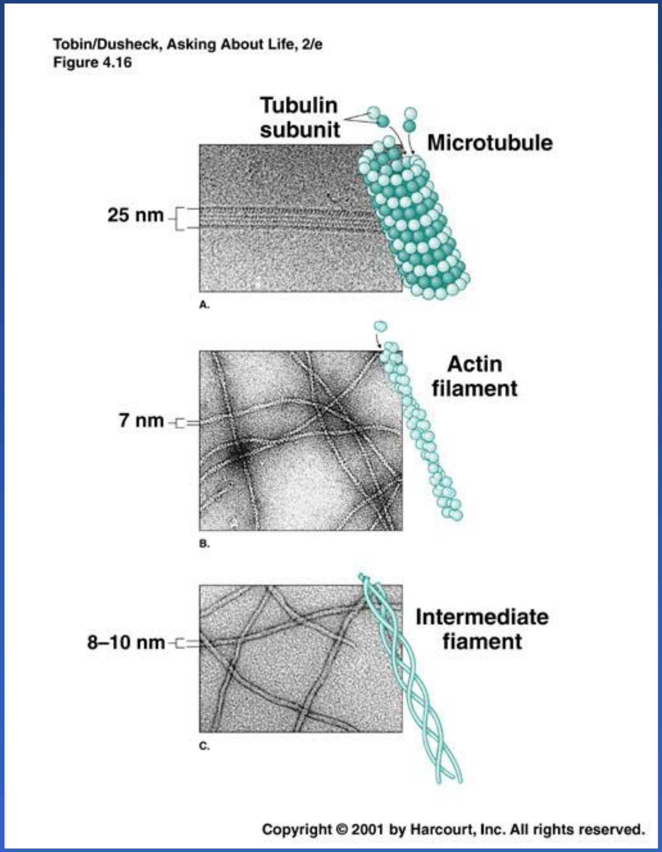
Coworkers: **Aviv Kahana, Gilad Kenan, Mario Feingold**
BGU
Michael Elbaum
WIS

An idealized animal cell



The cytoskeleton



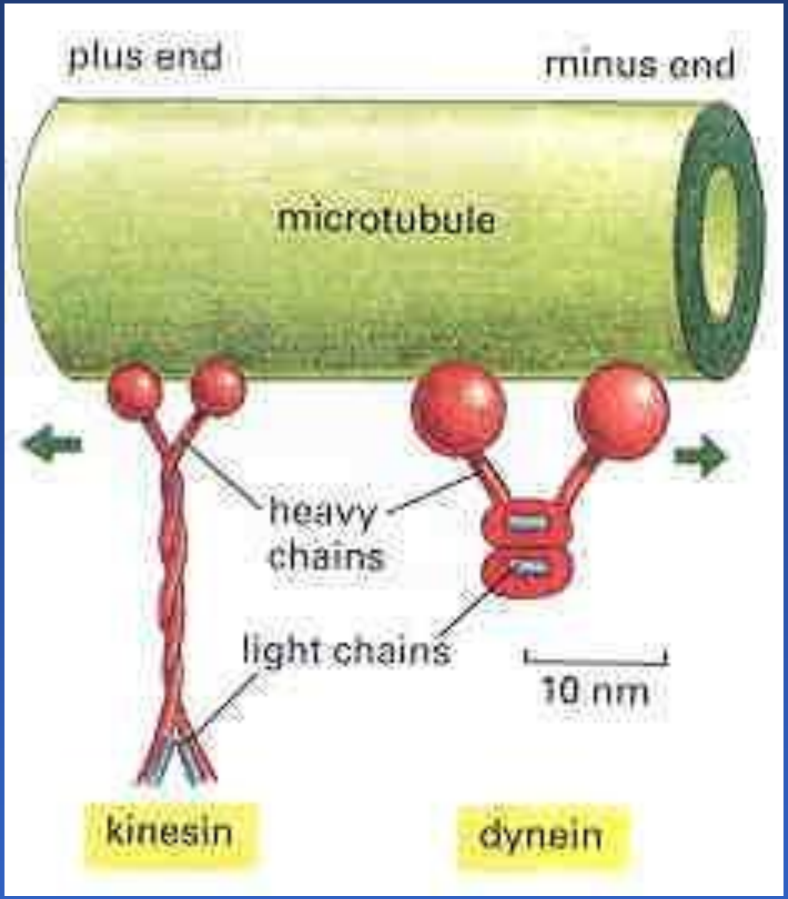


http://img.sparknotes.com/figures/D/d479f5da672c08a54f986ae699069d7a/cytoskeleton.gif

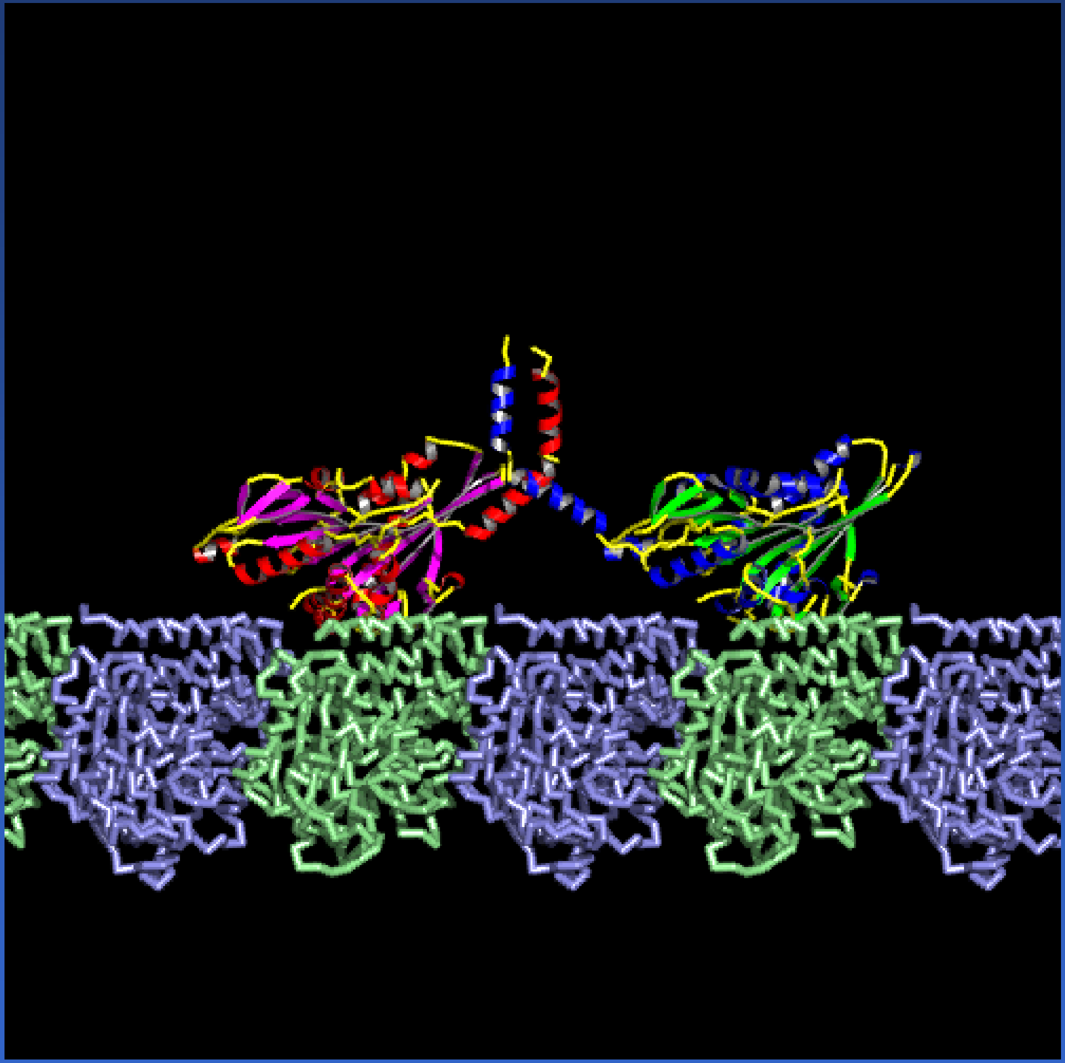
http://campus.queens.edu/faculty/jannr/cells/cell/pics/cytoskeleton.jpg%20

Microtubules are directional:
(-) ends originate from the centrosome (MTOC)

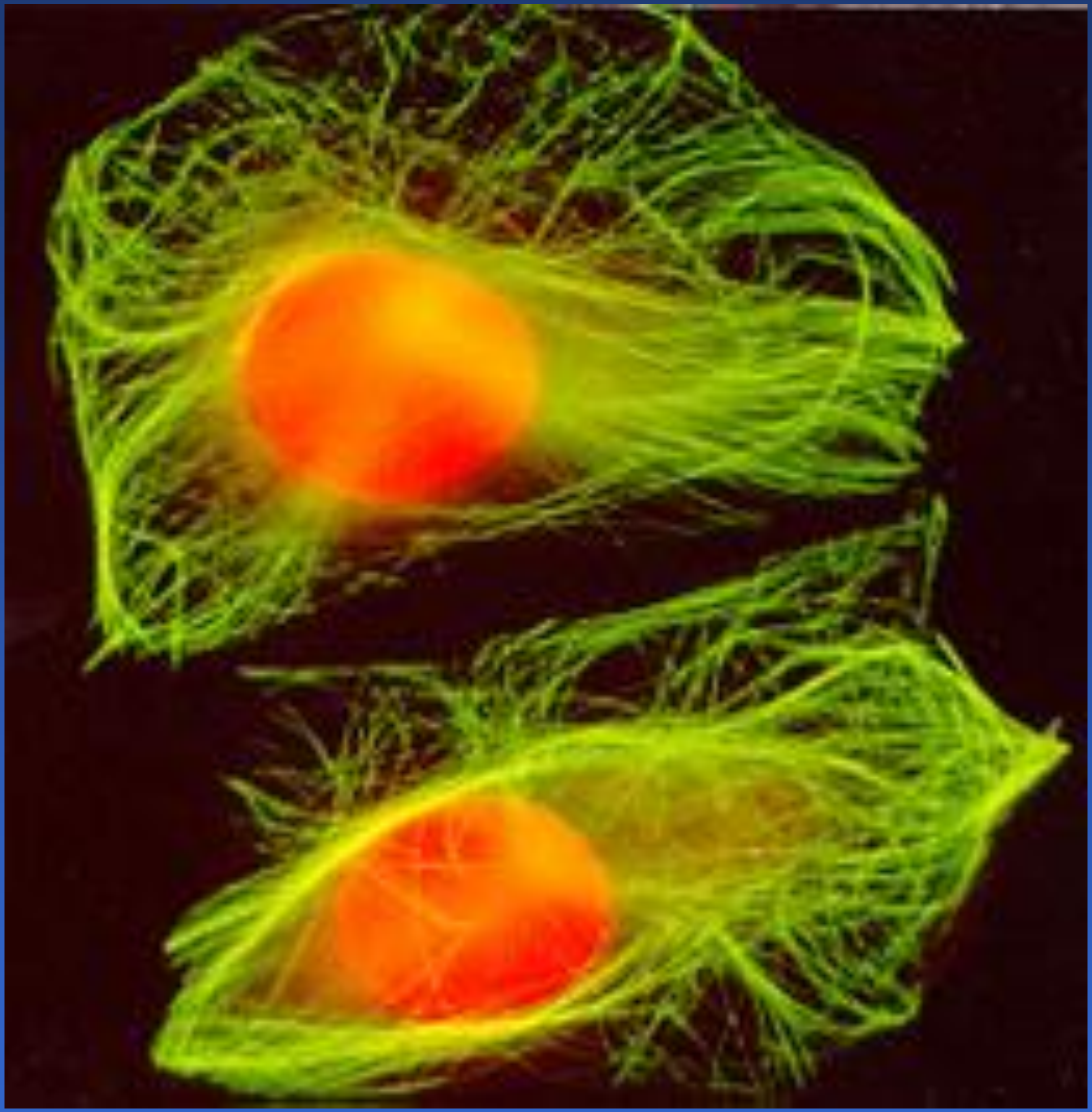
Motor proteins



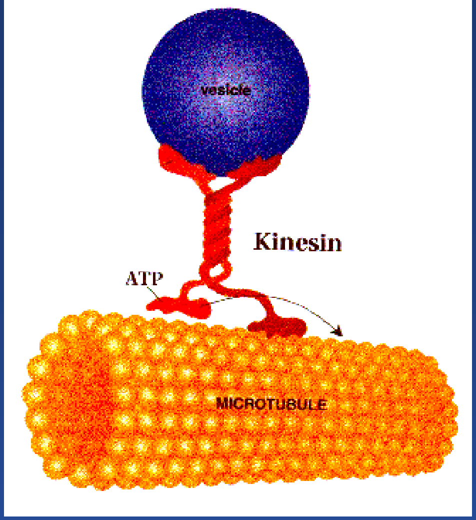
- Kinesin moves toward (+) end, Dynein toward (-) end.
- Low processivity, ~1 s in bound state (step time ~6ms).
- Velocity ~1μm/s.



Microtubules



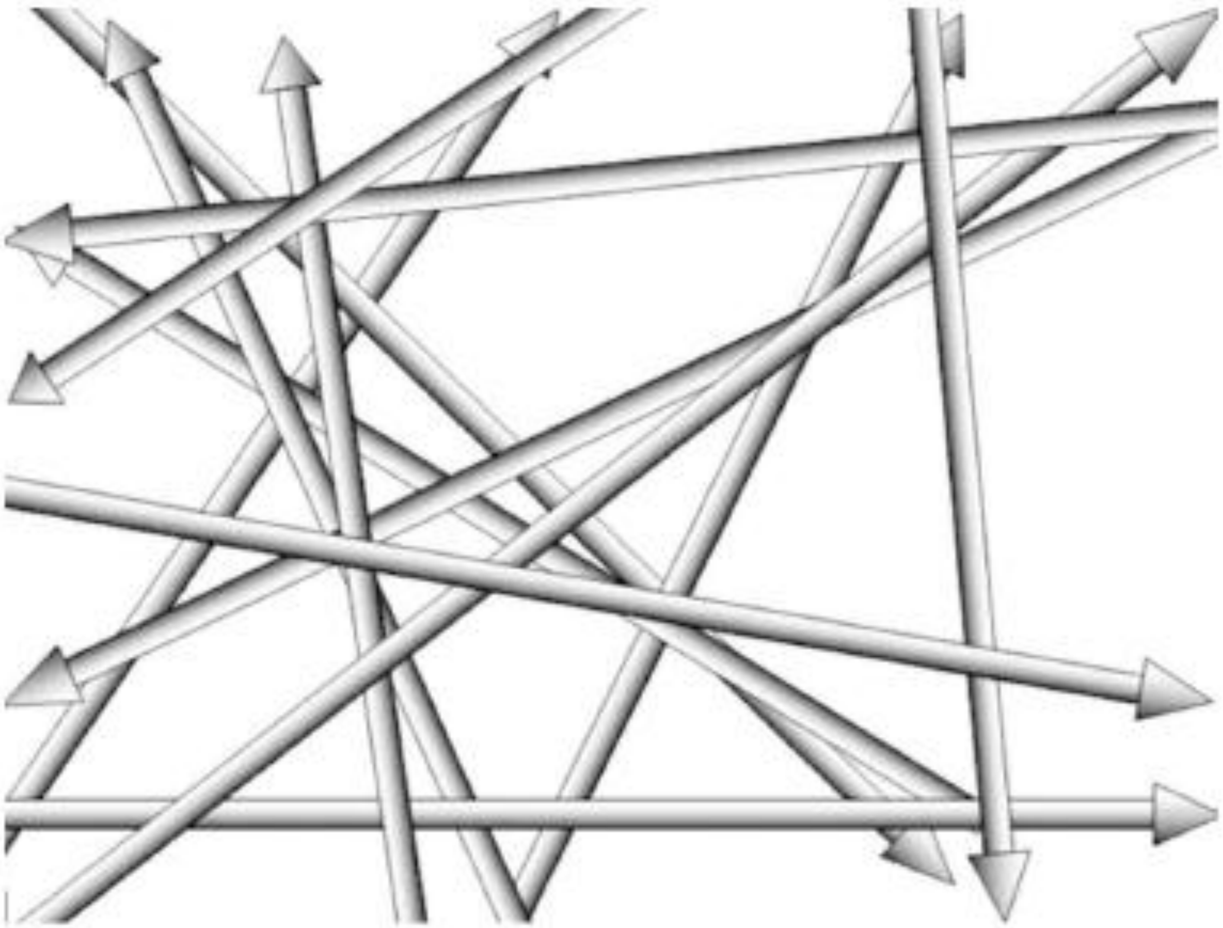
Global order *vs.* local disorder



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

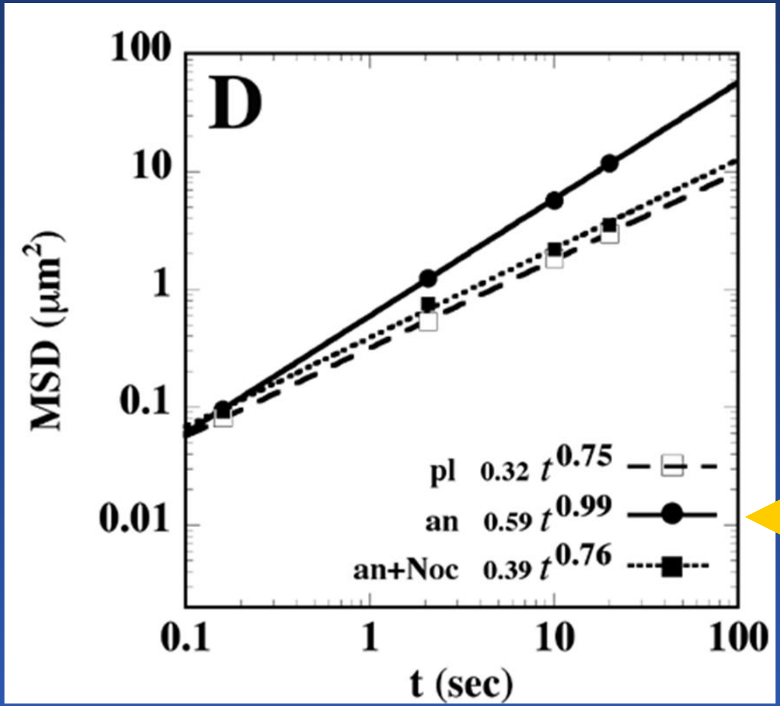

(a)

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.

H. Salman, A. Abu-Arish, S. Oliel, A. Loyter, J. Klafter, R. Granek, and M. Elbaum,
Biophys. J. (2005)

Results



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

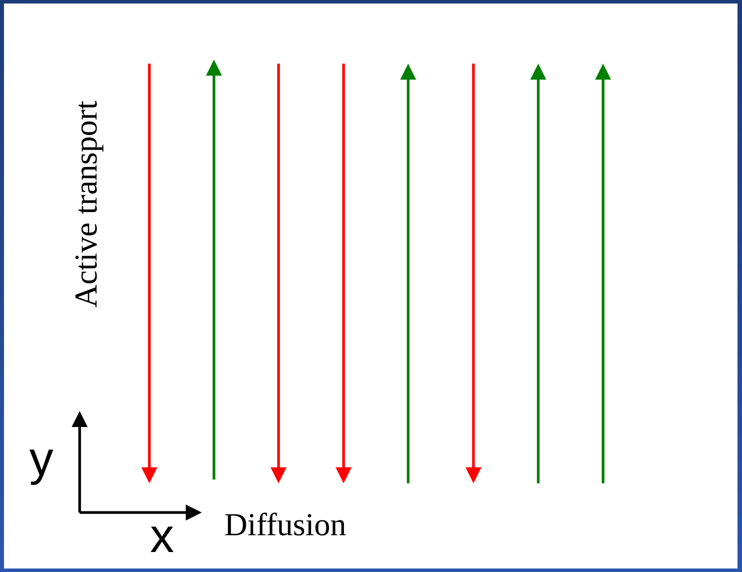
Question:

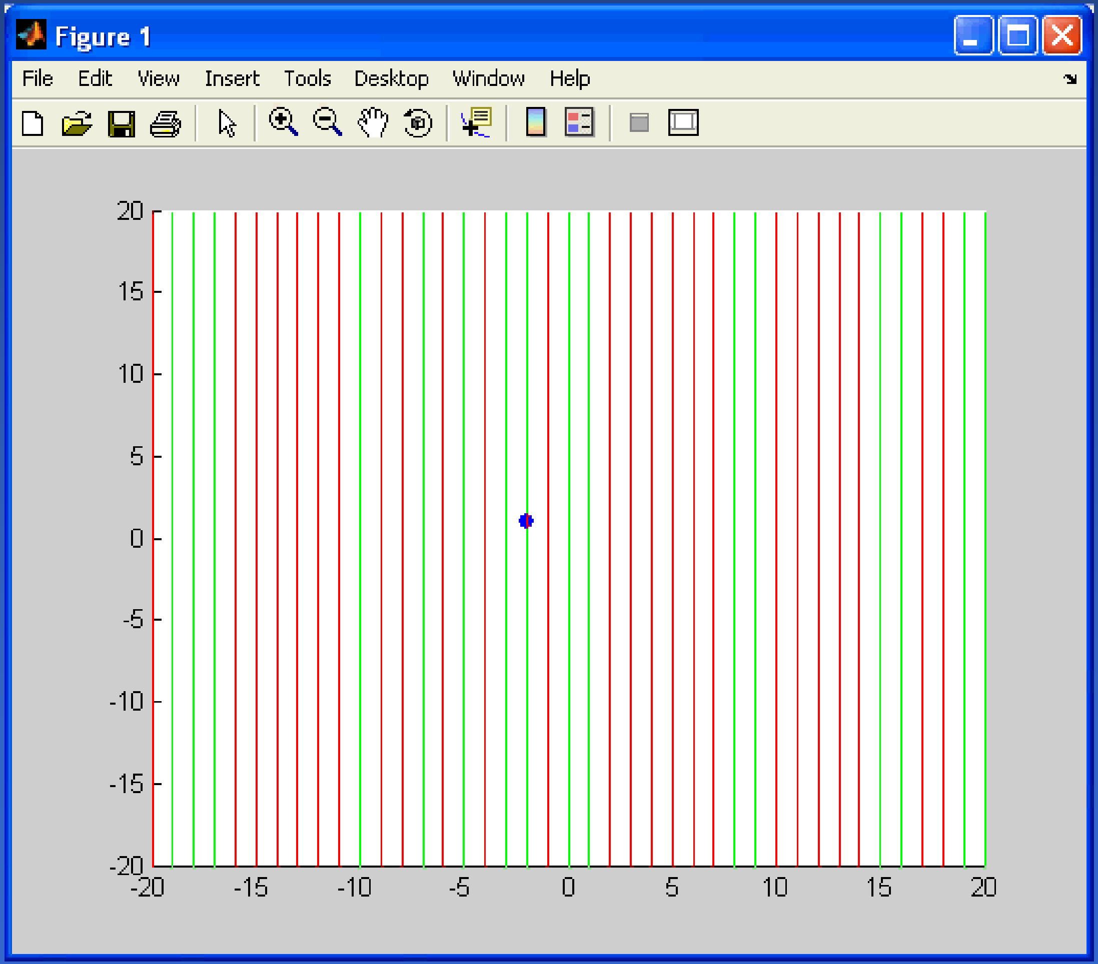
Why does the active transport appear as simple diffusion?

Aviv Kahana,[1,2] Gilad Kenan,[1] Mario Feingold,[2] Michael Elbaum,[3] and Rony Granek[1,4,*]

PHYSICAL REVIEW E **78**, 051912 (2008)

Random velocity model in 1+1 dimensions





Random velocity model in 1+1 dimensions

Exact result, Super-diffusion:

$$\left\langle y^2(t) \right\rangle \sim t^{3/2}$$

G. Zumofen, J. Klafter, A. Blumen, PRA (1990)
S. Redner, PRE (1997)
J.-P. Bouchaud, A. Georges, P. Le Doussal, J. Physique (1987)

Scaling argument:

$\left\langle y^2(t) \right\rangle \approx P_{0,x}(t) v^2 t^2$ **where** $P_{0,x}(t) \sim t^{-1/2}$ **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**

$\left\langle y^2(t) \right\rangle \sim t^{3/2}$ **to long-time diffusion** $\left\langle y^2(t) \right\rangle \sim t$

explained by a scaling argument

RVM – Unbalanced diffusion

MSD $$\left\langle (\Delta x)^2 \right\rangle^{1/2} = 2\sqrt{pq} \cdot \sqrt{t/\tau_0}$$

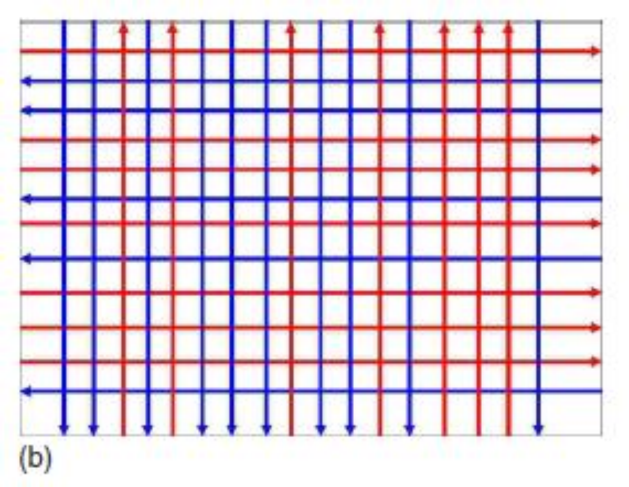
Drift $$\left\langle x \right\rangle = (p-q)\frac{t}{\tau_0}$$

define: $$\delta \equiv \frac{\left\langle (\Delta x)^2 \right\rangle^{1/2}}{\left\langle x \right\rangle} = \frac{2\sqrt{pq}}{(p-q)} \frac{1}{\sqrt{t/\tau_0}}$$

When δ>>1 → RVM, when δ<<1 → Diffusion

For *p*=0.51 & *q*=0.49: δ=1 at t=2500

2-D network model



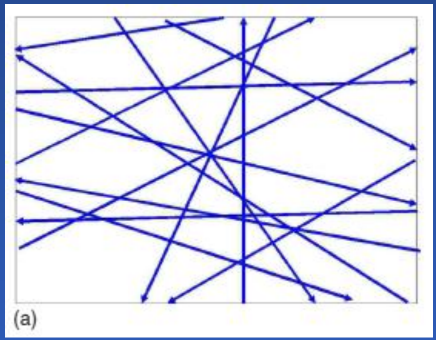
Scaling argument:

$$\left\langle x^2(t)\right\rangle \approx P_{0,y}(t)\, v^2 t^2$$

where

$$P_{0,y}(t) \approx \frac{1}{\sqrt{\left\langle y^2(t)\right\rangle}}$$

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



By symmetry

$$\left\langle x^2(t)\right\rangle = \left\langle y^2(t)\right\rangle = \frac{\left\langle \rho^2(t)\right\rangle}{2}$$

$$\left\langle \rho^2(t)\right\rangle \sim t^{4/3}$$

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 $\left\langle x^2 \right\rangle = \left\langle y^2 \right\rangle$

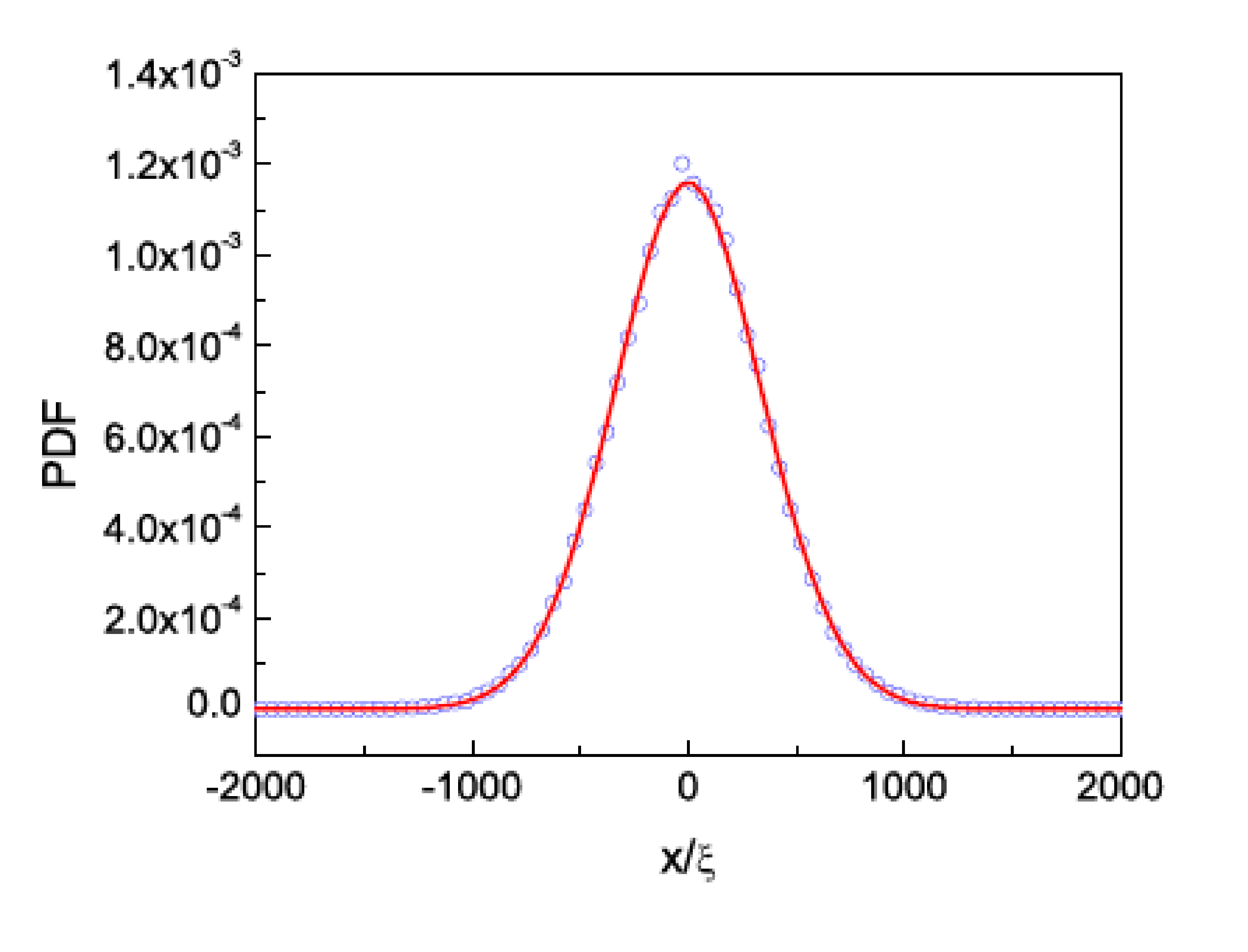
$$\Rightarrow \quad \frac{d^2}{dt^2}\langle x^2(t)\rangle = 2v^2 P_{o,x}(t)$$

Assuming Gaussian PDFs

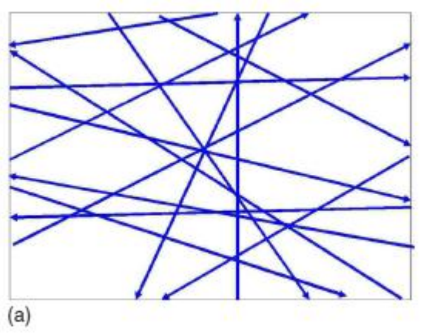
$$\left\langle \rho^2 \right\rangle = \left\langle x^2 \right\rangle + \left\langle y^2 \right\rangle = \left(\frac{9^{2/3}}{\pi^{1/3}} v^{4/3} \xi^{2/3} \right) t^{4/3}$$

PDF along x-axis at time $t = 10^5 \tau_v$

$\tau_v = \xi / v$

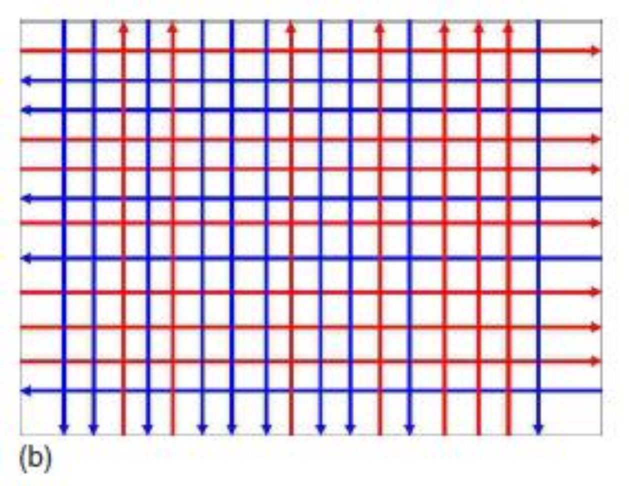


2-D network model



Self-consistent theory:

$$\left\langle x^2 \right\rangle = \left\langle y^2 \right\rangle \sim t^{4/3}$$



Simulation results:

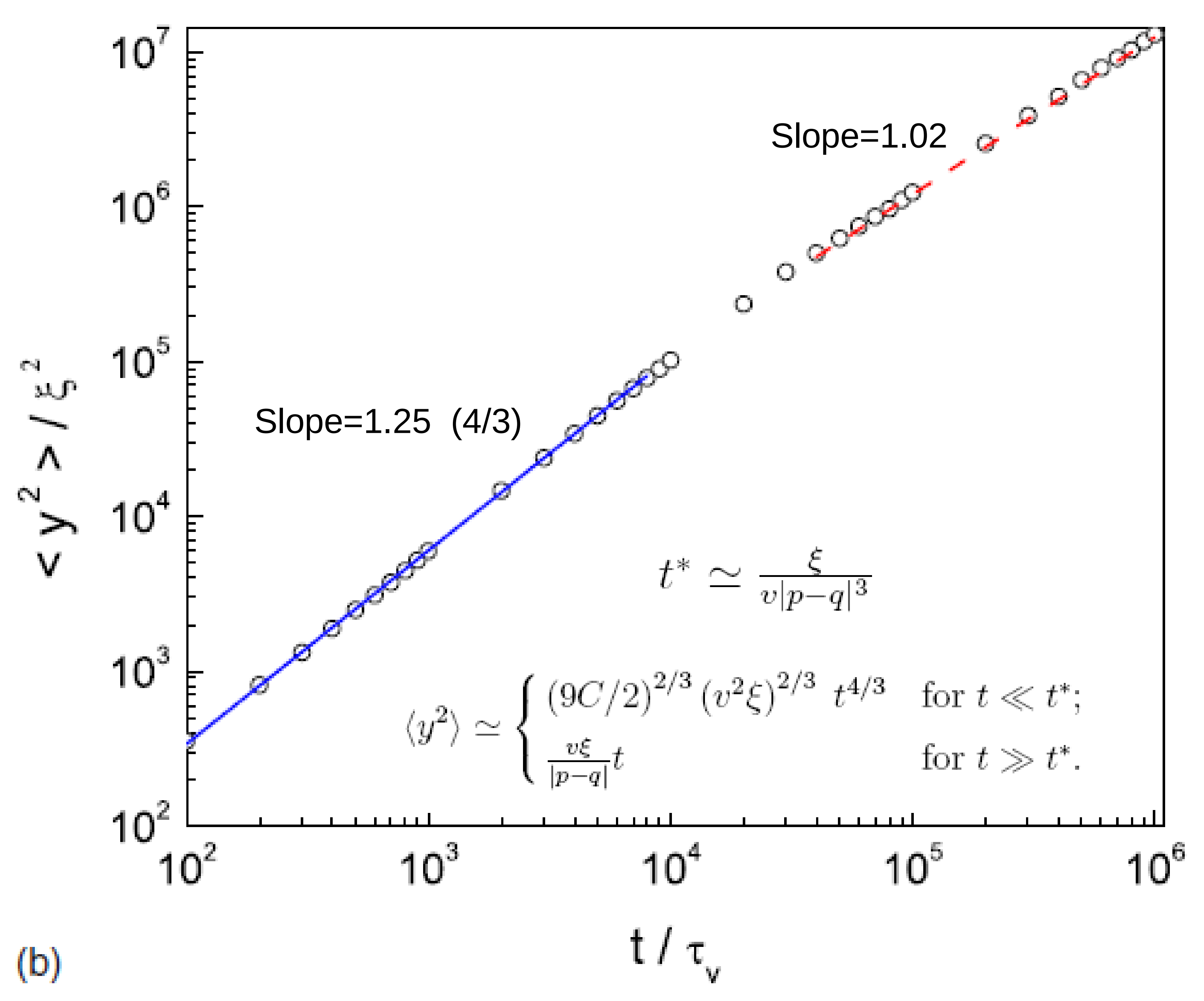
- **Balanced network – fits theory**

•Unbalanced network, long times:

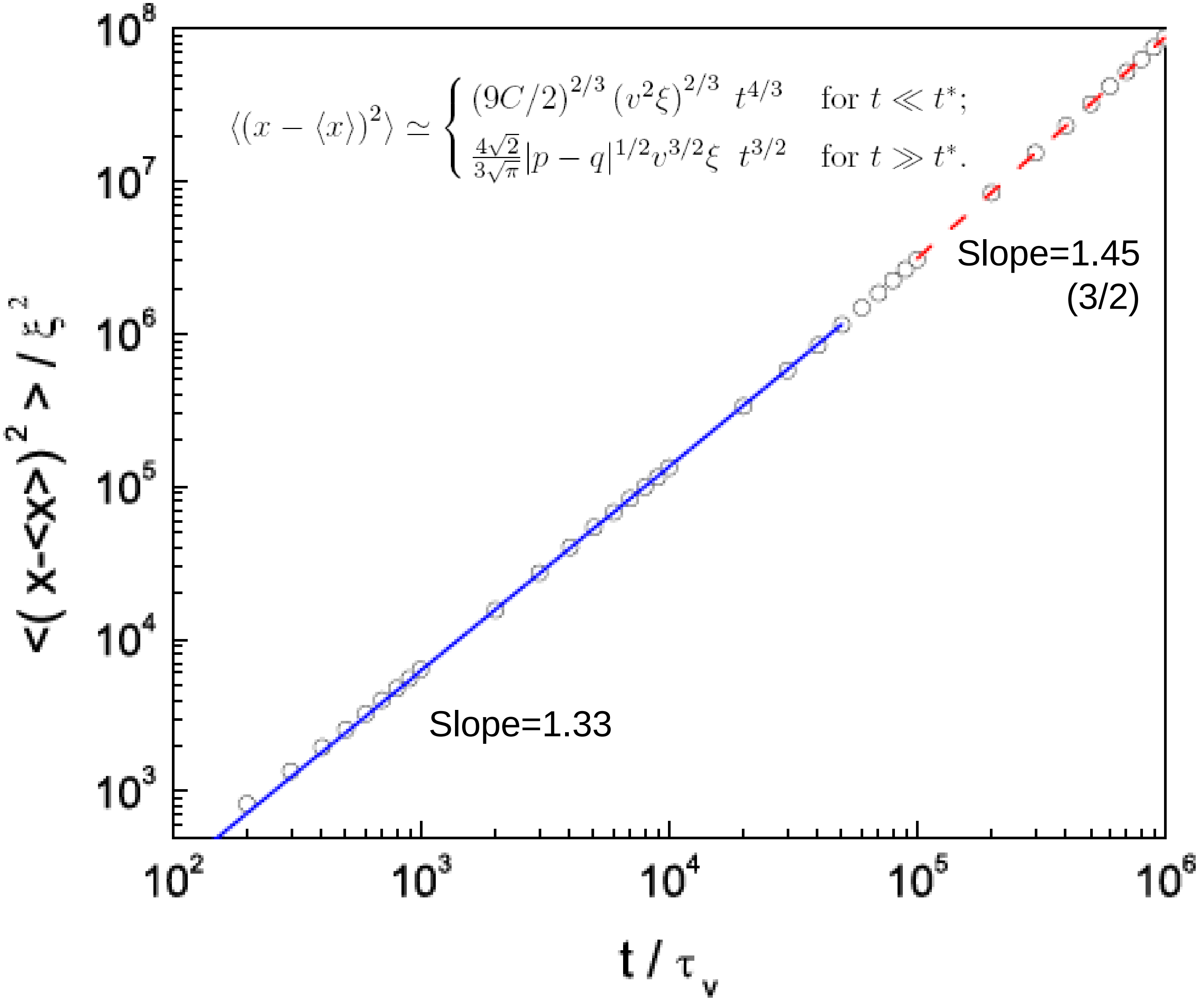
unbalanced direction → RVM with drift $\left\langle x \right\rangle = (p-q)vt$

perpendicular direction → Long-time diffusion

$$\left\langle y^2 \right\rangle \sim t$$

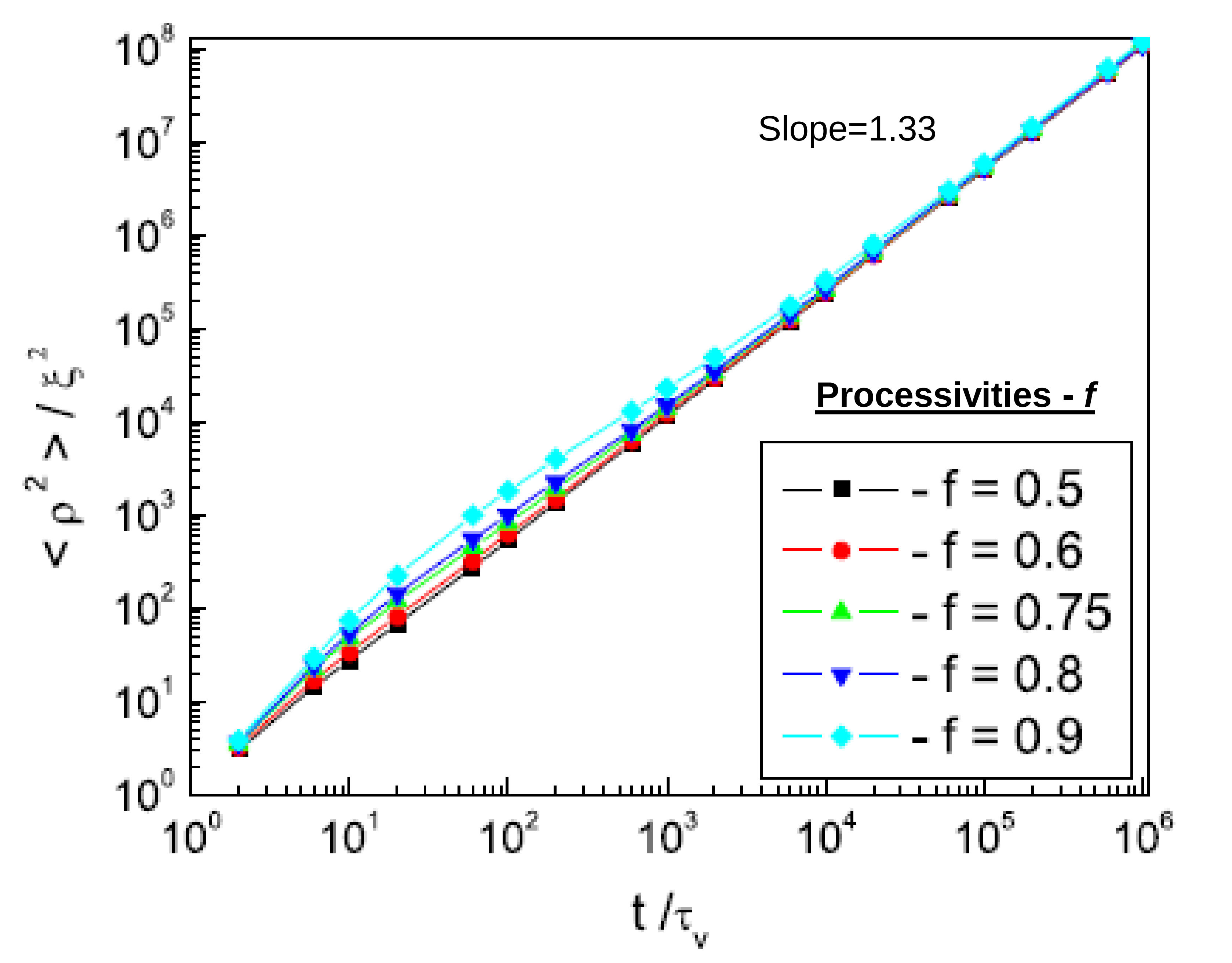


Slope=1.02
Slope=1.25 (4/3)
$t^* \simeq \frac{\xi}{v|p-q|^3}$
$\langle y^2 \rangle \simeq \begin{cases} (9C/2)^{2/3} (v^2\xi)^{2/3} \; t^{4/3} & \text{for } t \ll t^*; \\ \frac{v\xi}{|p-q|} t & \text{for } t \gg t^*. \end{cases}$
$< y^2 > / \xi^2$
t / τ_v
(b)

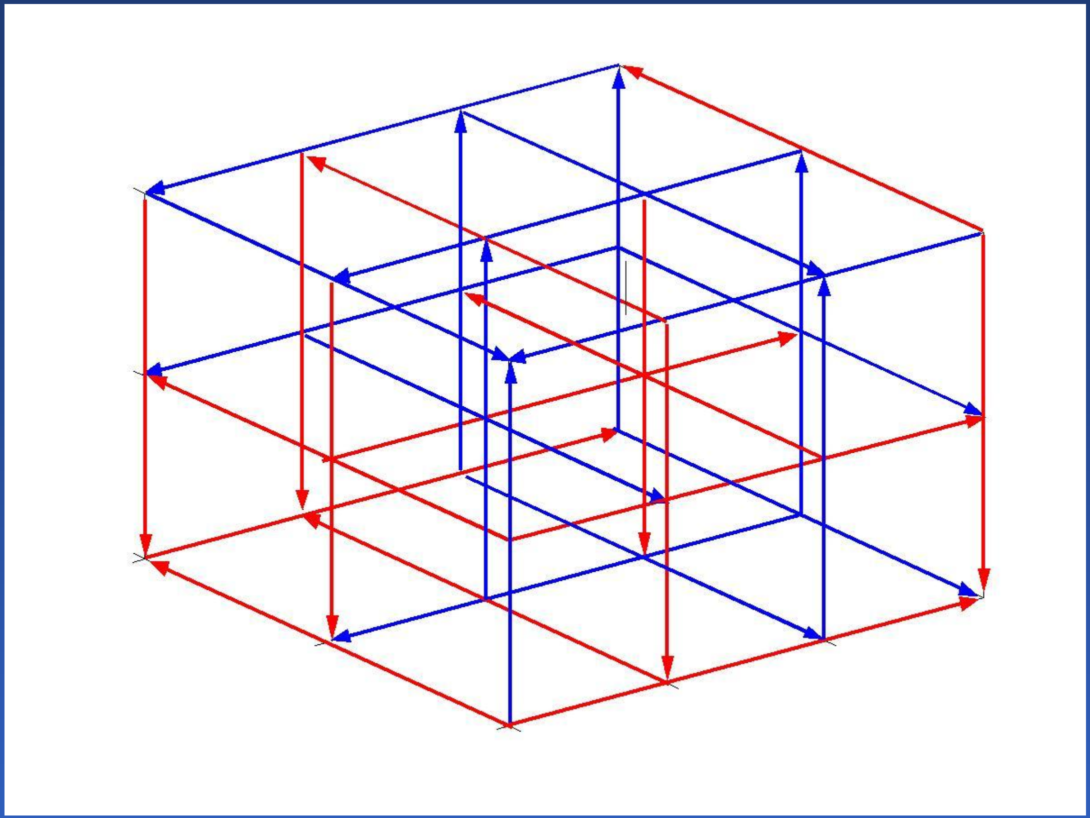


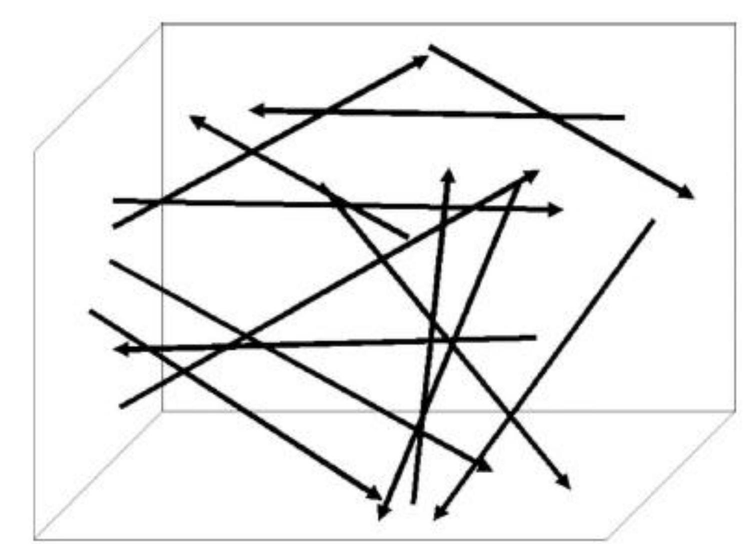
$\langle (x - \langle x \rangle)^2 \rangle \simeq \begin{cases} (9C/2)^{2/3} (v^2\xi)^{2/3} \; t^{4/3} & \text{for } t \ll t^*; \\ \frac{4\sqrt{2}}{3\sqrt{\pi}} |p-q|^{1/2} v^{3/2} \xi \; t^{3/2} & \text{for } t \gg t^*. \end{cases}$
Slope=1.45
(3/2)
Slope=1.33
$<(x-<x>)^2> / \xi^2$
t / τ_v
10^2
10^3
10^4
10^5
10^6
10^7
10^8

Processivity dependence



3-D network model





(a)

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 probablity of return to the origin in the y-z plane

By symmetry

$$\left\langle x^2(t) \right\rangle = \left\langle y^2(t) \right\rangle = \left\langle z^2(t) \right\rangle = \frac{\left\langle r^2(t) \right\rangle}{3}$$

$$\Rightarrow \quad \left\langle r^2(t) \right\rangle \sim t$$

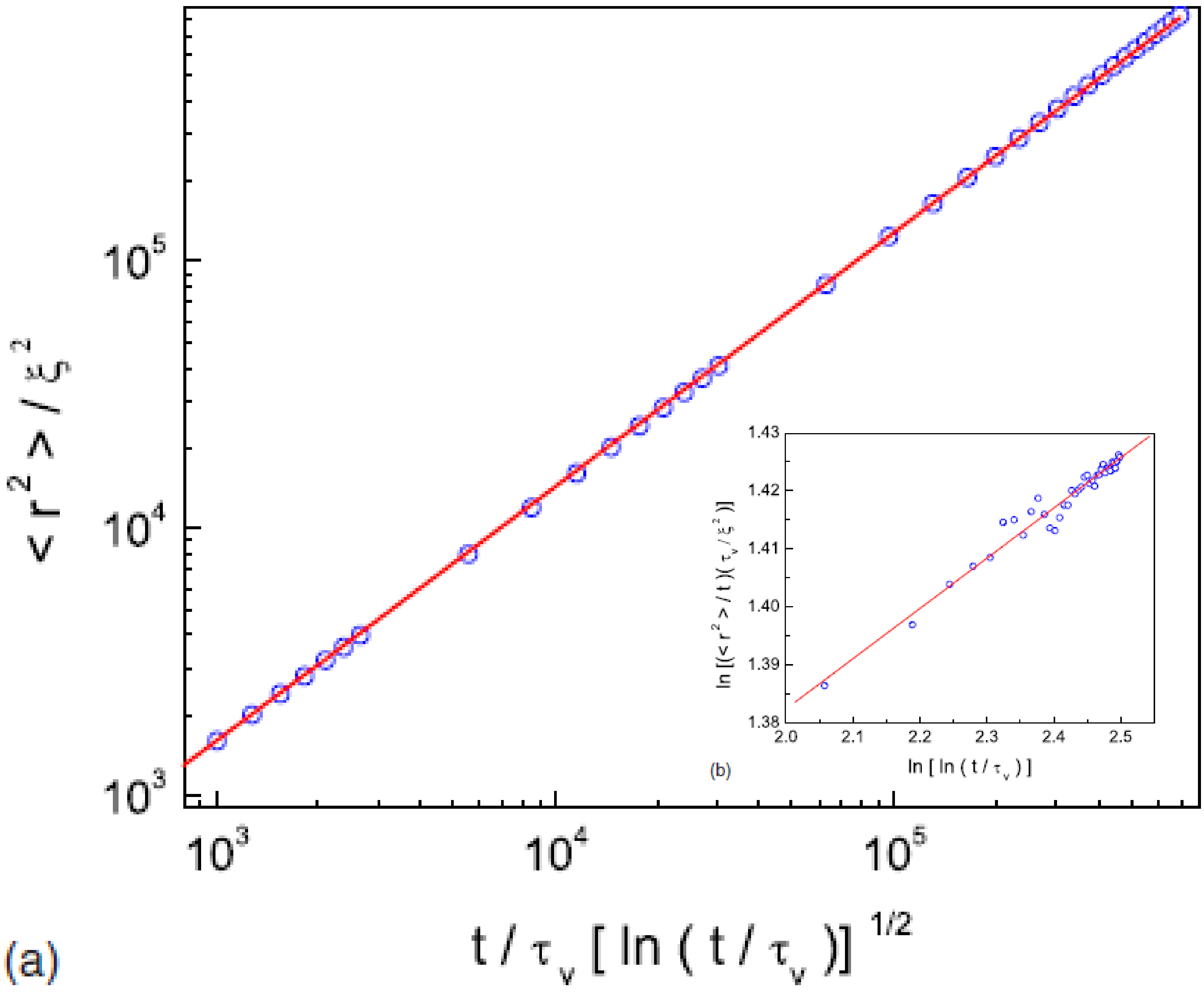
Diffusion-like, but active (non-thermal)

More accurate self-consistent calculation:

$$\left\langle \vec{r}^{\,2}(t) \right\rangle \approx A\, \xi\, v\, t \left[\ln\left(\frac{t}{\tau_v} \right) \right]^{1/2}$$

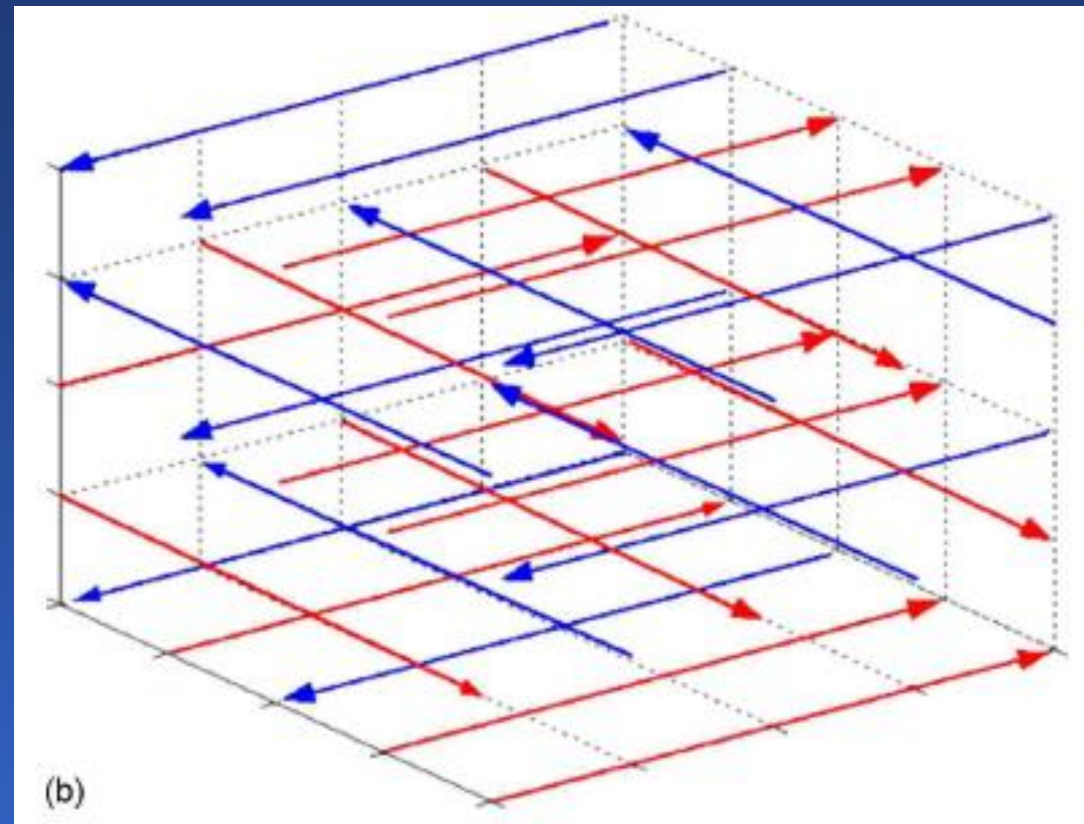
where $\tau_v = \dfrac{\xi}{v}$, ξ **is the mesh size**

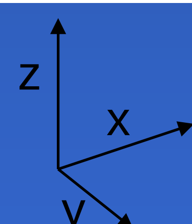
$$A \cong 2.4$$

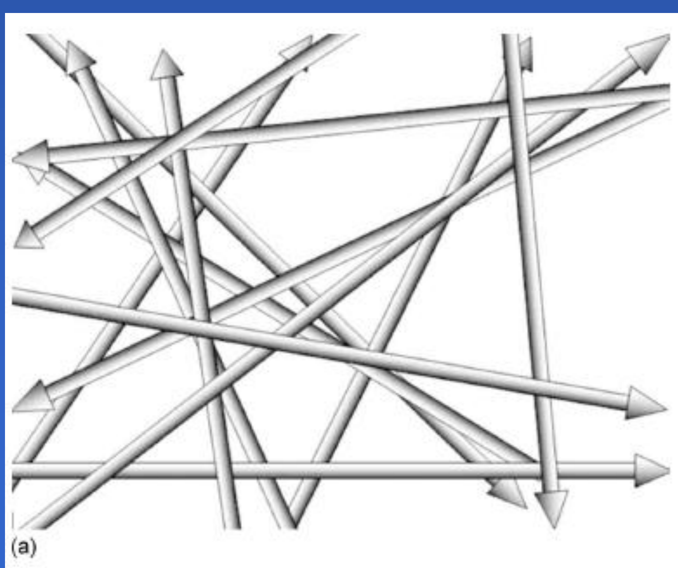


< r^2 > / ξ^2
10^5
10^4
10^3
10^3
10^4
10^5
t / τ$_v$ [ln (t / τ$_v$)] $^{1/2}$
(a)
1.43
1.42
1.41
1.40
1.39
1.38
2.0
2.1
2.2
2.3
2.4
2.5
ln [(< r^2 > / t)(τ$_v$ / ξ^2)]
ln [ln (t / τ$_v$)]
(b)

In vitro experiment: 3-D with orientational order







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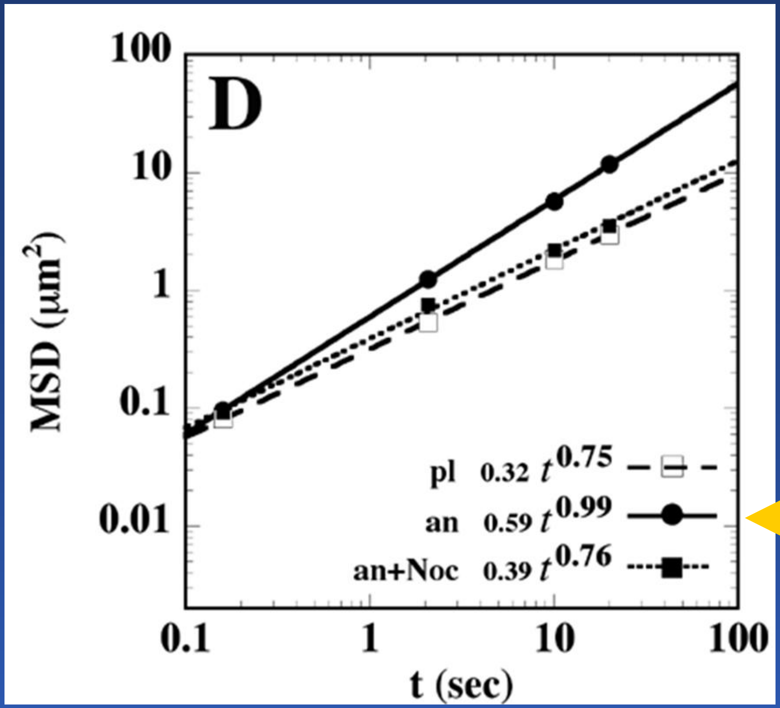

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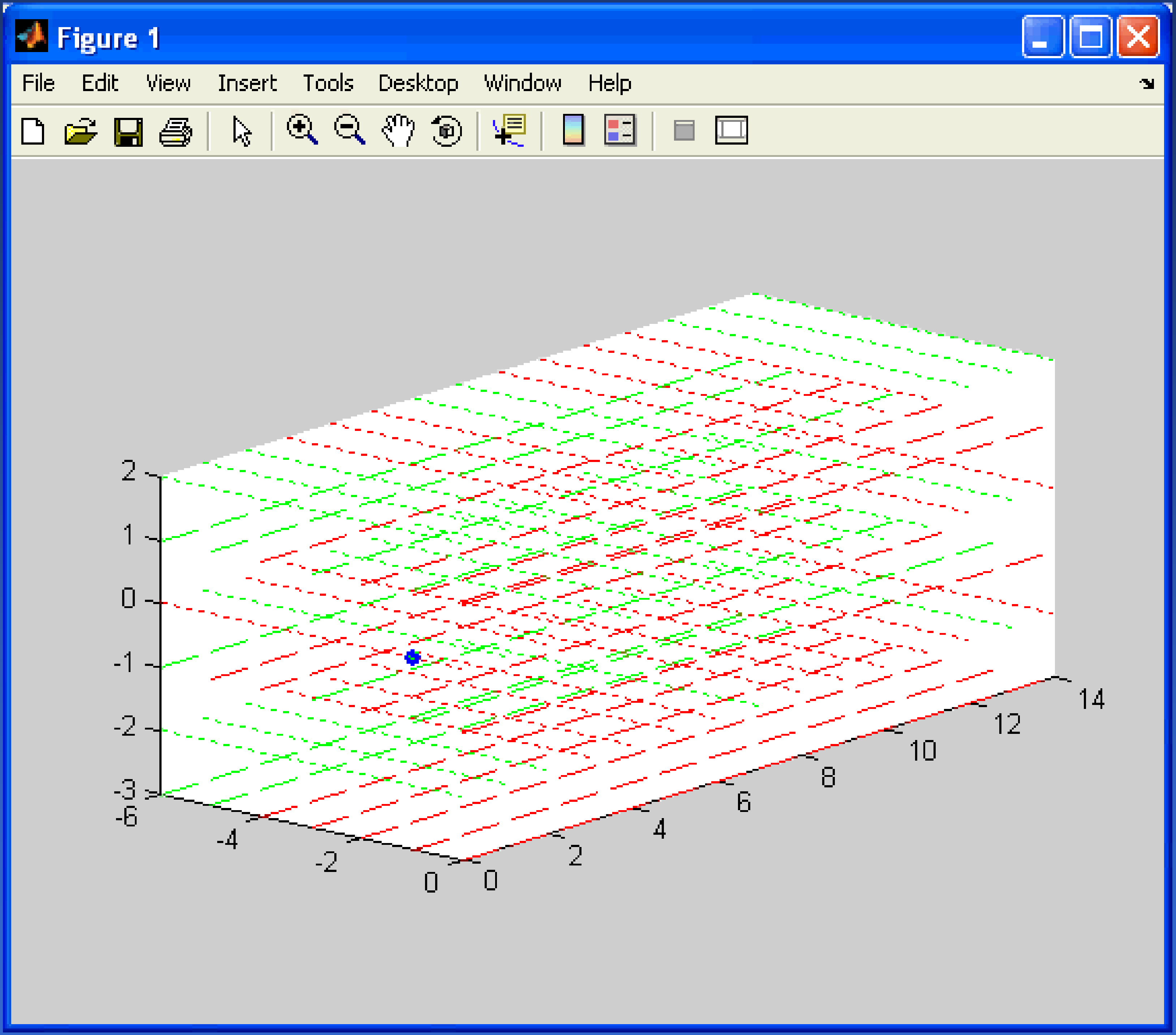


Figure 1
File Edit View Insert Tools Desktop Window Help
2
1
0
-1
-2
-3
-6
-4
-2
0
0
2
4
6
8
10
12
14

Scaling argument:

$$\left\langle x^2(t)\right\rangle \approx P_{0,yz}(t)\, v^2 t^2$$

where

$$P_{0,yz}(t) = P_{0,y}(t)\,P_{0,z}(t) \approx \frac{1}{\sqrt{\left\langle y^2(t)\right\rangle}} \times \frac{1}{\sqrt{Dt}}$$

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

By symmetry $P_{0,yz}(t) = P_{0,xz}(t)$ and $\left\langle x^2(t)\right\rangle = \left\langle y^2(t)\right\rangle = \frac{\left\langle \rho^2(t)\right\rangle}{2}$

$$\Rightarrow \left\langle \rho^2(t)\right\rangle \sim t$$

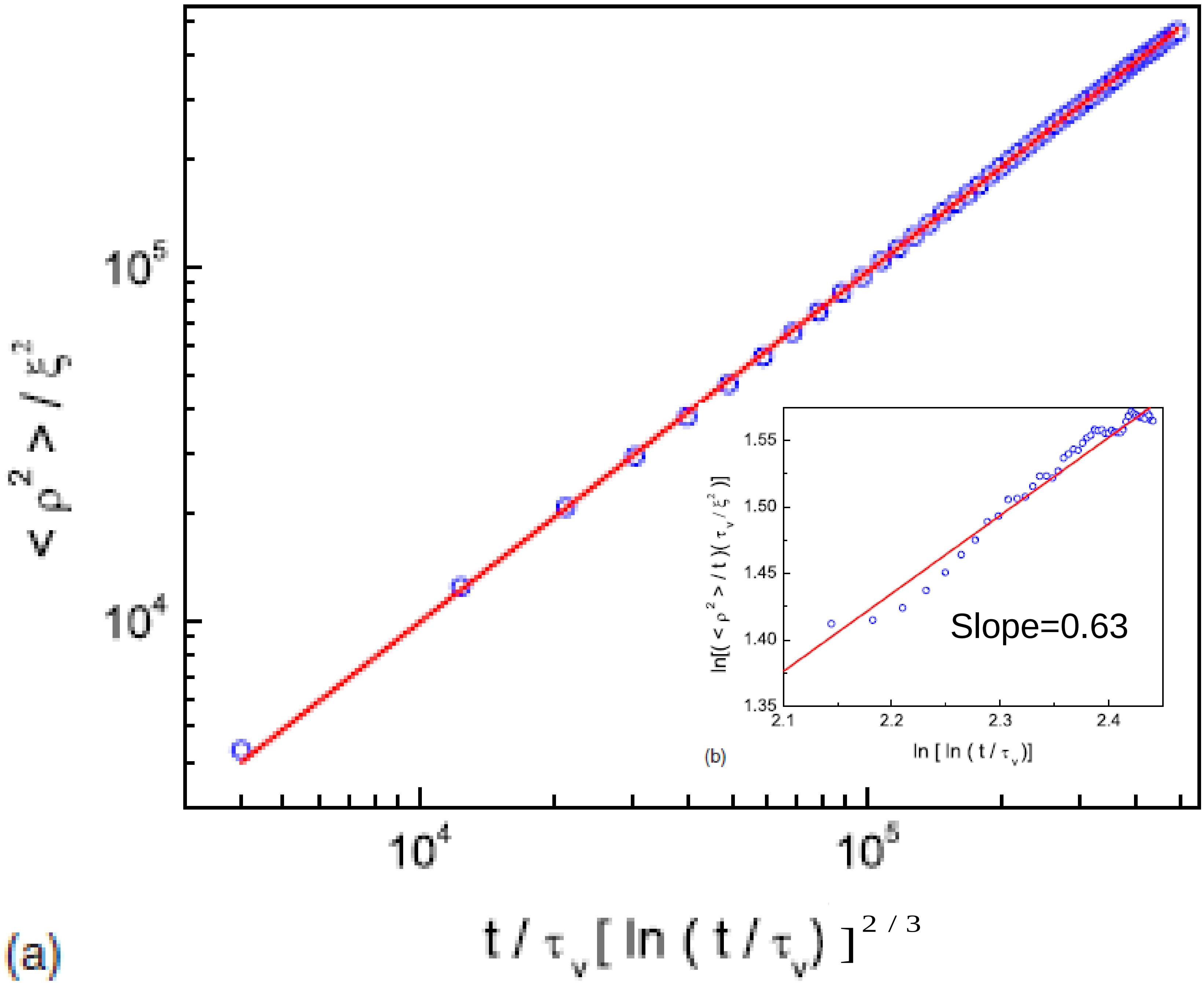
Diffusion-like, but active (non-thermal)

More accurate self-consistent calculation:

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

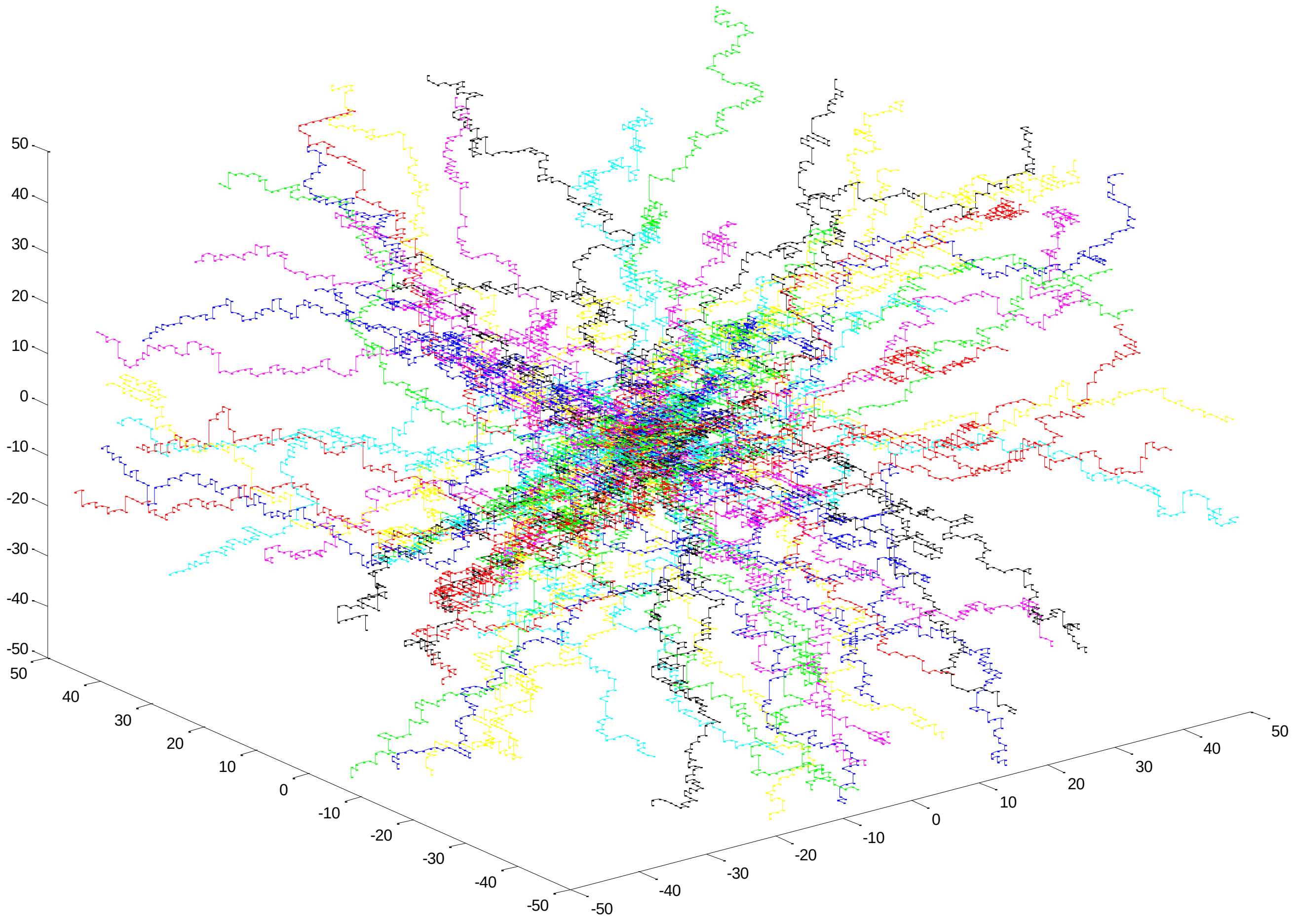
where $\tau_v = \frac{\xi}{v}$, ξ is the mesh size

$A \cong 1.2$



10^5
10^4
$< \rho^2 > / \xi^2$
$t / \tau_v [\ln(t/\tau_v)]^{2/3}$
(a)
1.55
1.50
1.45
1.40
1.35
2.1
2.2
2.3
2.4
$\ln[(<\rho^2>/t)(\tau_v/\xi^2)]$
$\ln[\ln(t/\tau_v)]$
Slope=0.63
(b)

3-D animal cell model



Simulations of "First Exit" problem:

- Kinesin mediated transport:

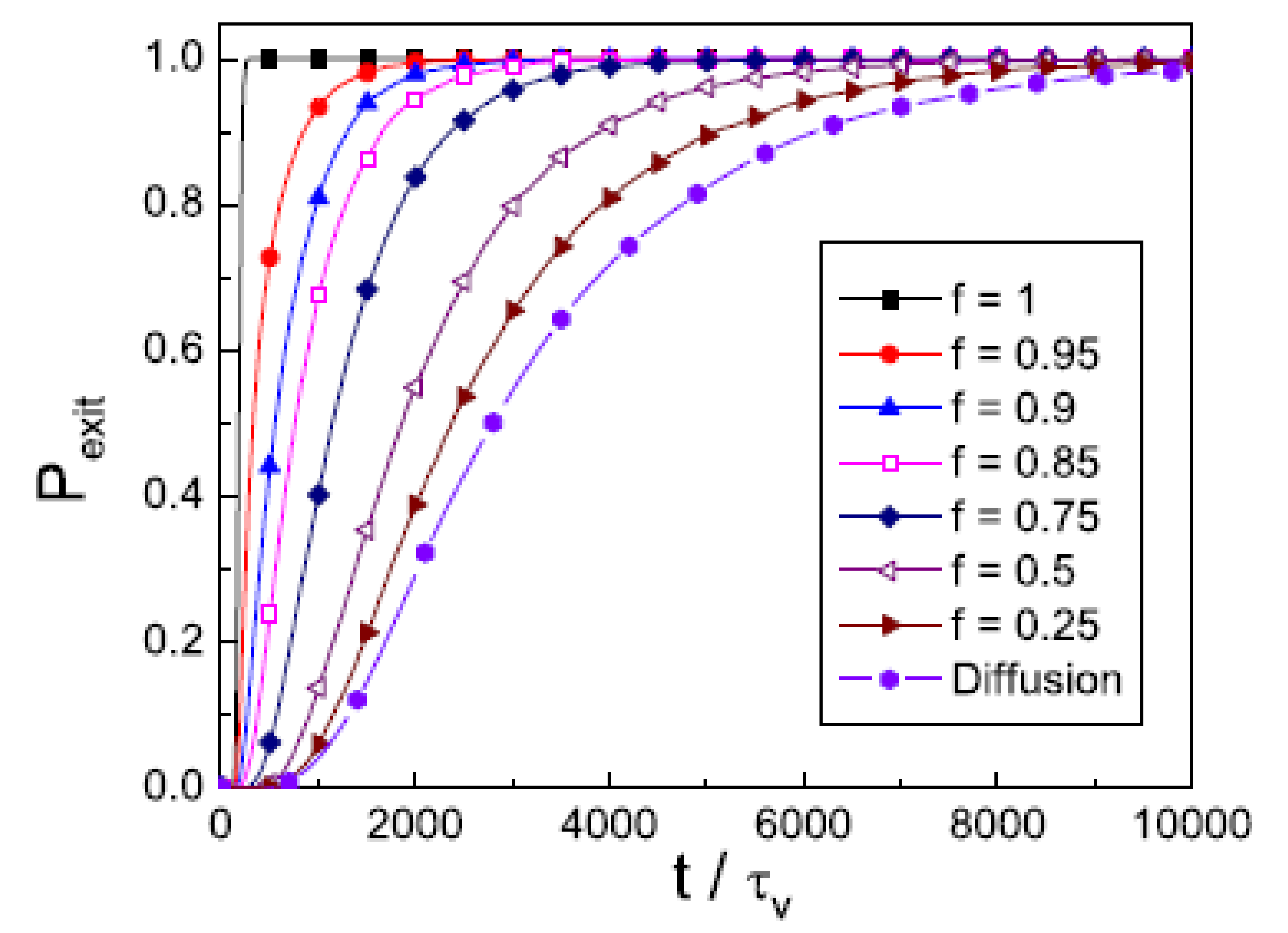
  (i) Probability to arrive from the nucleus to the membrane until time t.

  (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.

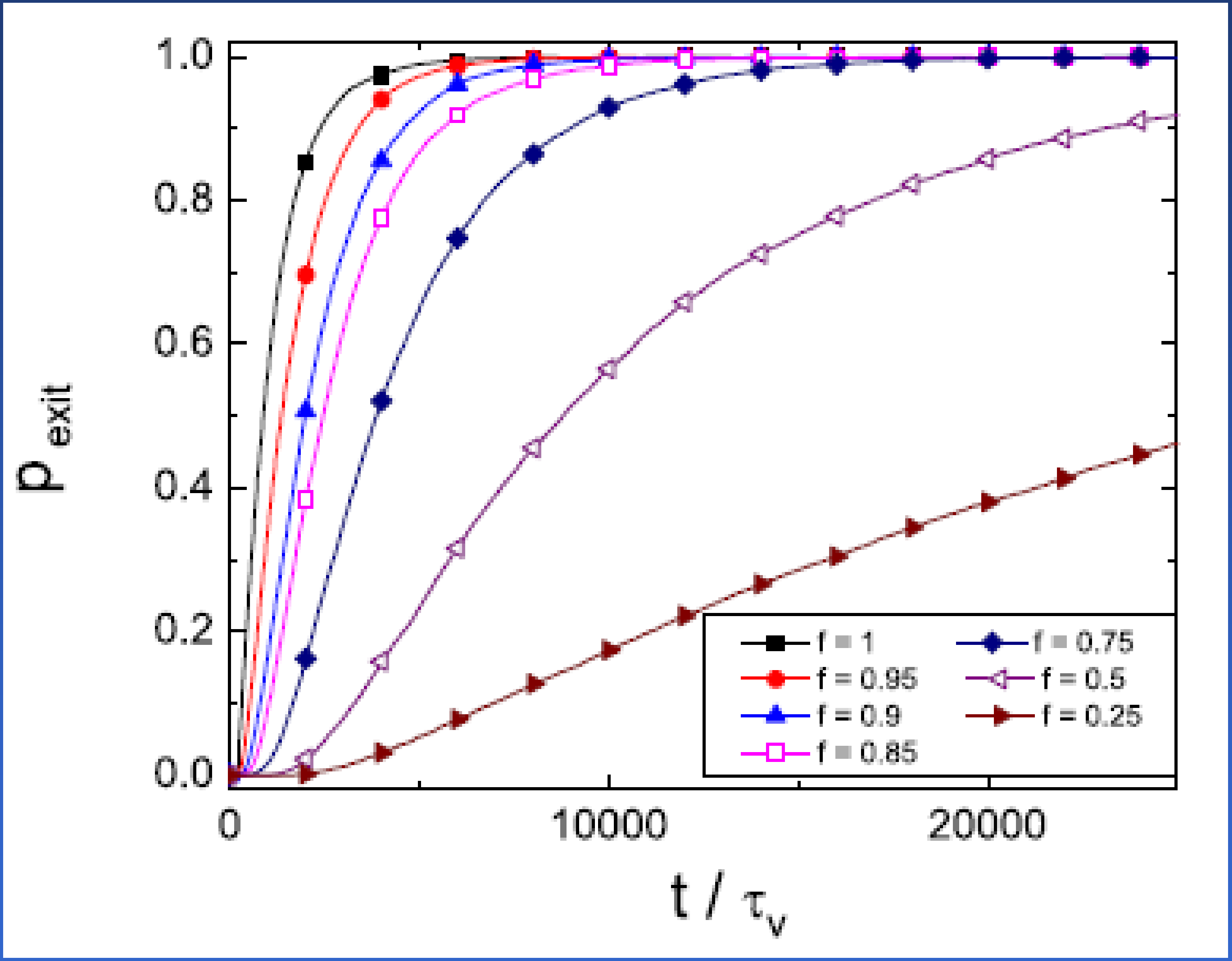
Kinesin mediated transport: From nucleus to membrane

Many cells averaging



Dynein mediated transport: From membrane to nucleus

Many cells averaging

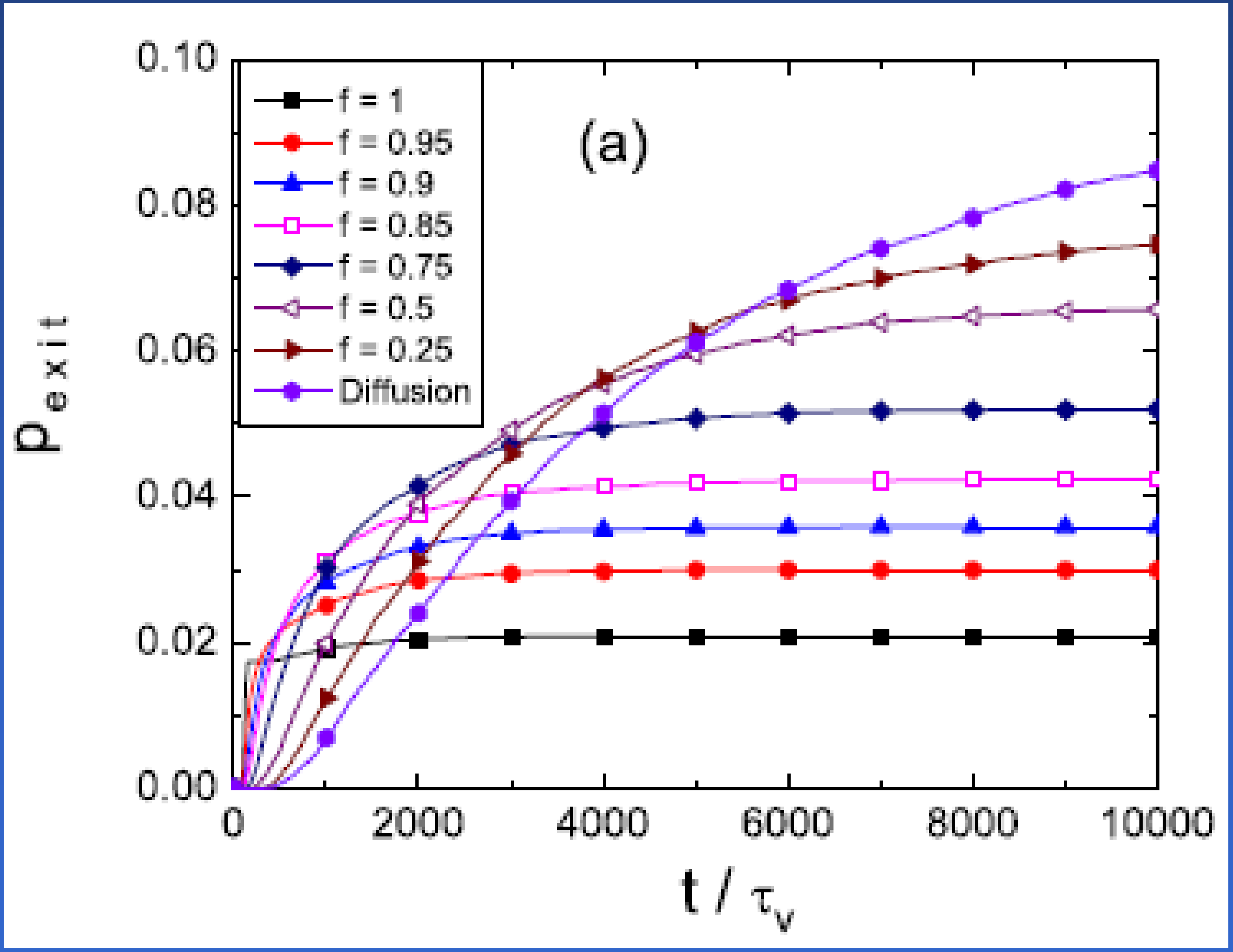


Kinesin mediated transport:

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

Radiative boundary conditions at the membrane

Many cells averaging

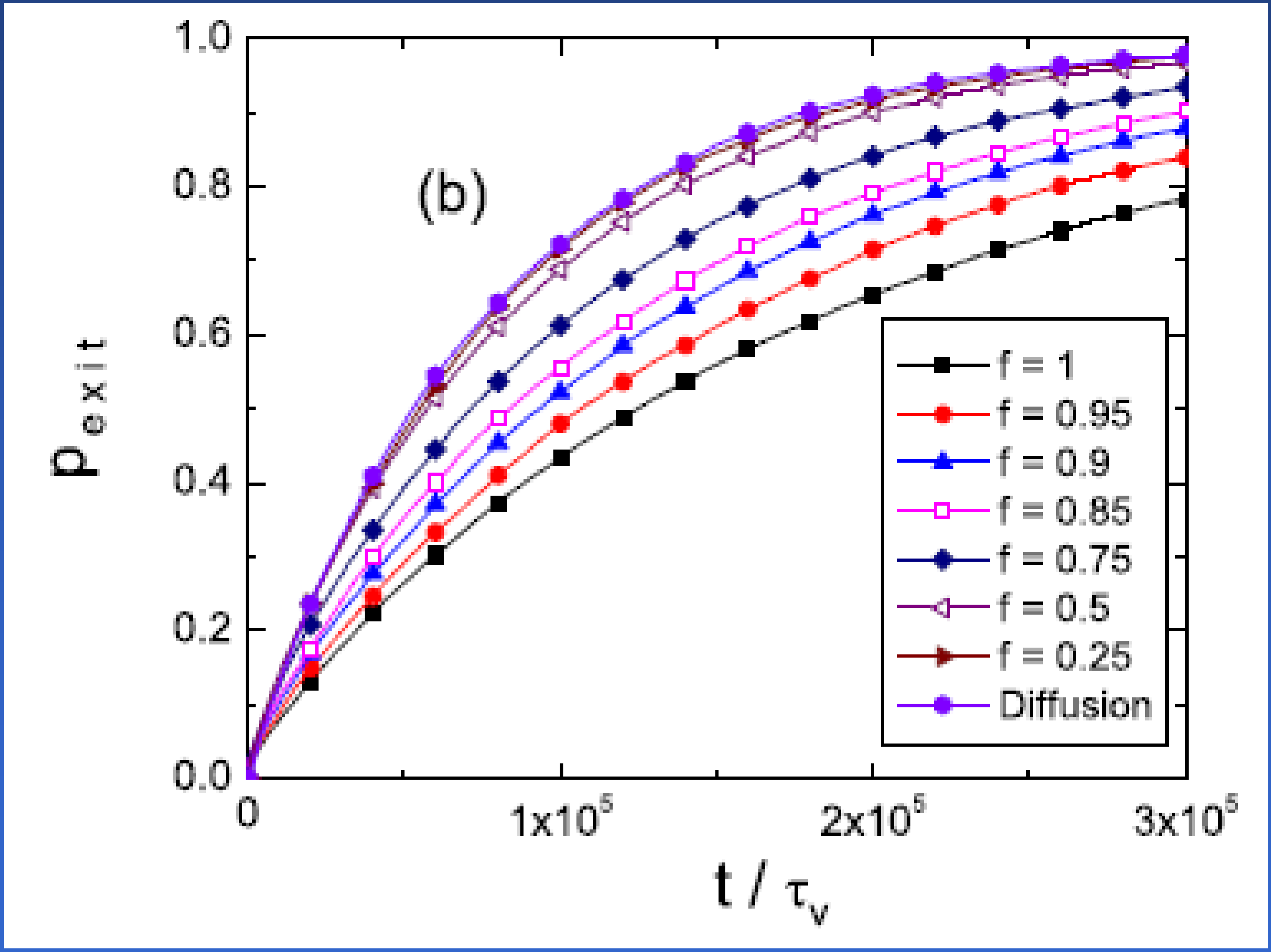


Kinesin mediated transport:

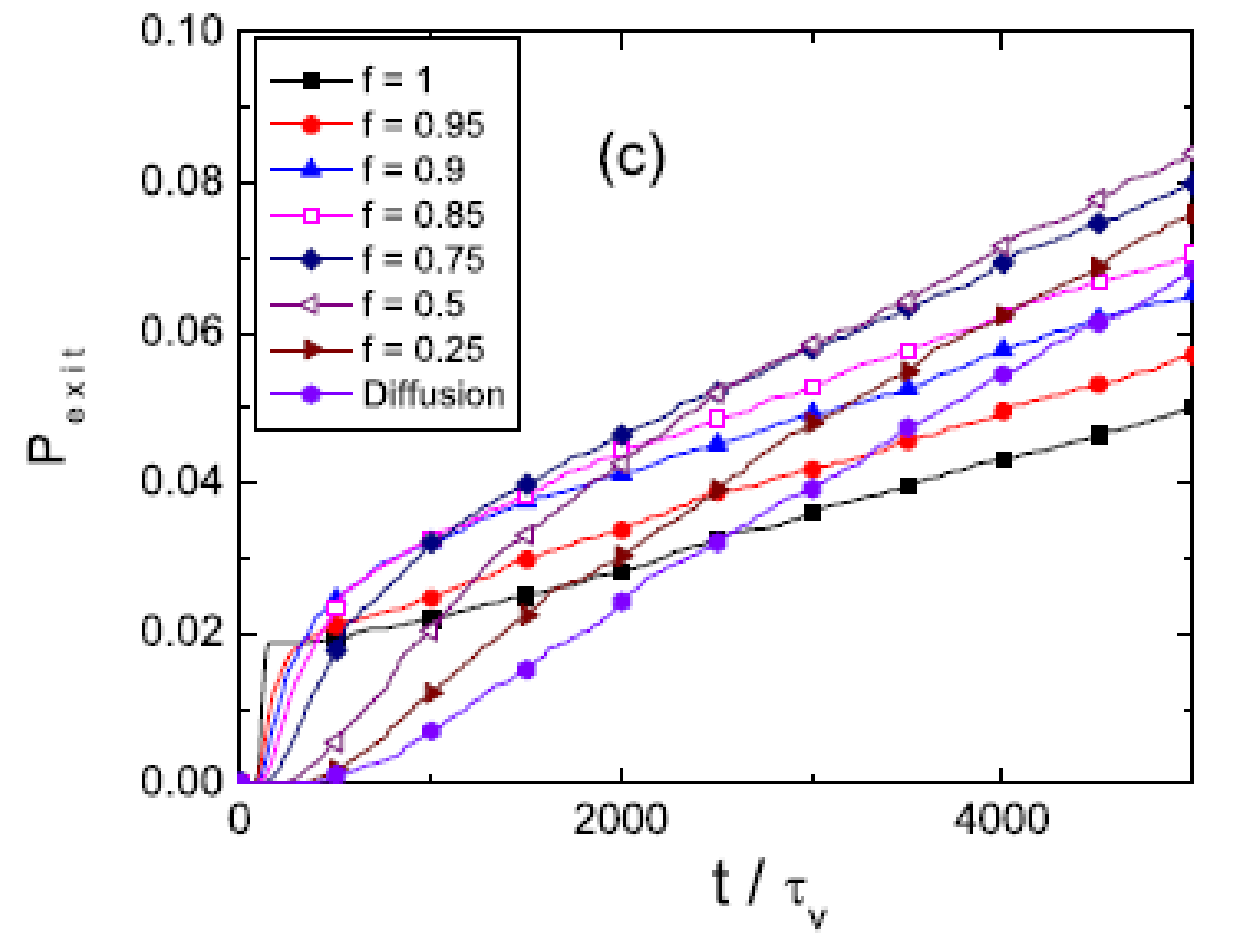
From nucleus to a localized target (e.g. ribosome)

Reflective boundary conditions at the membrane

Many cells averaging



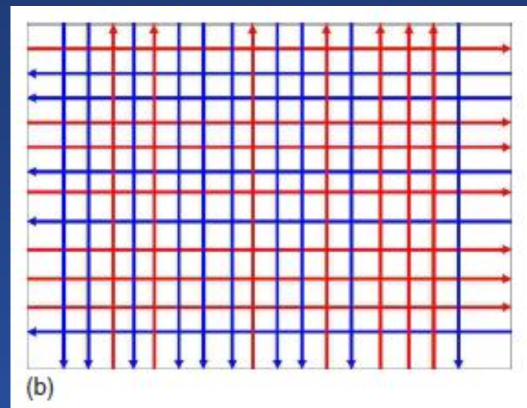
Short times



0.10
0.08
0.06
0.04
0.02
0.00
0
2000
4000
P_{exit}
t / τ_v
(c)
f = 1
f = 0.95
f = 0.9
f = 0.85
f = 0.75
f = 0.5
f = 0.25
Diffusion

What else?

Unusual Response to Force (?)



$\vec{f}$

Assumption –

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

$$\vec{v} = \vec{v}_0 + \mu \, \vec{f}$$

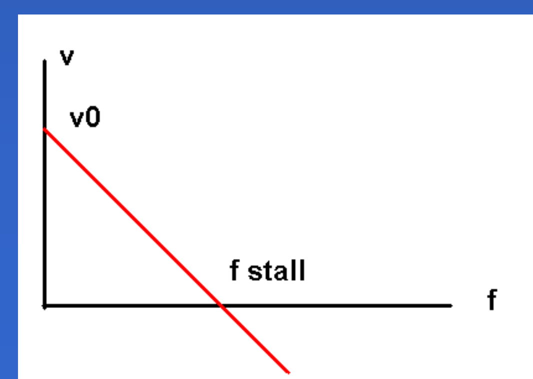
μ - mobility

or

$$v = v_0 \pm \mu \, f$$

i.e. stall force is

$$f_{\text{stall}} = v_0 / \mu$$



Along the force:

$$\langle x \rangle = \mu f t$$

linear response

$$\left\langle \left(x - \langle x \rangle\right)^2 \right\rangle \sim \begin{cases} t^{4/3} & \text{for} \quad t << t^* \\ t^{3/2} & \text{for} \quad t << t^* \end{cases}$$

$$t^* = \frac{v_0^{\,2}\,\xi}{\mu^3 f^3}$$

Perpendicular to the force:

$$\left\langle y^2 \right\rangle \sim \begin{cases} t^{4/3} & \text{for} \quad t << t^* \\ t & \text{for} \quad t >> t^* \end{cases}$$

Conclusions:

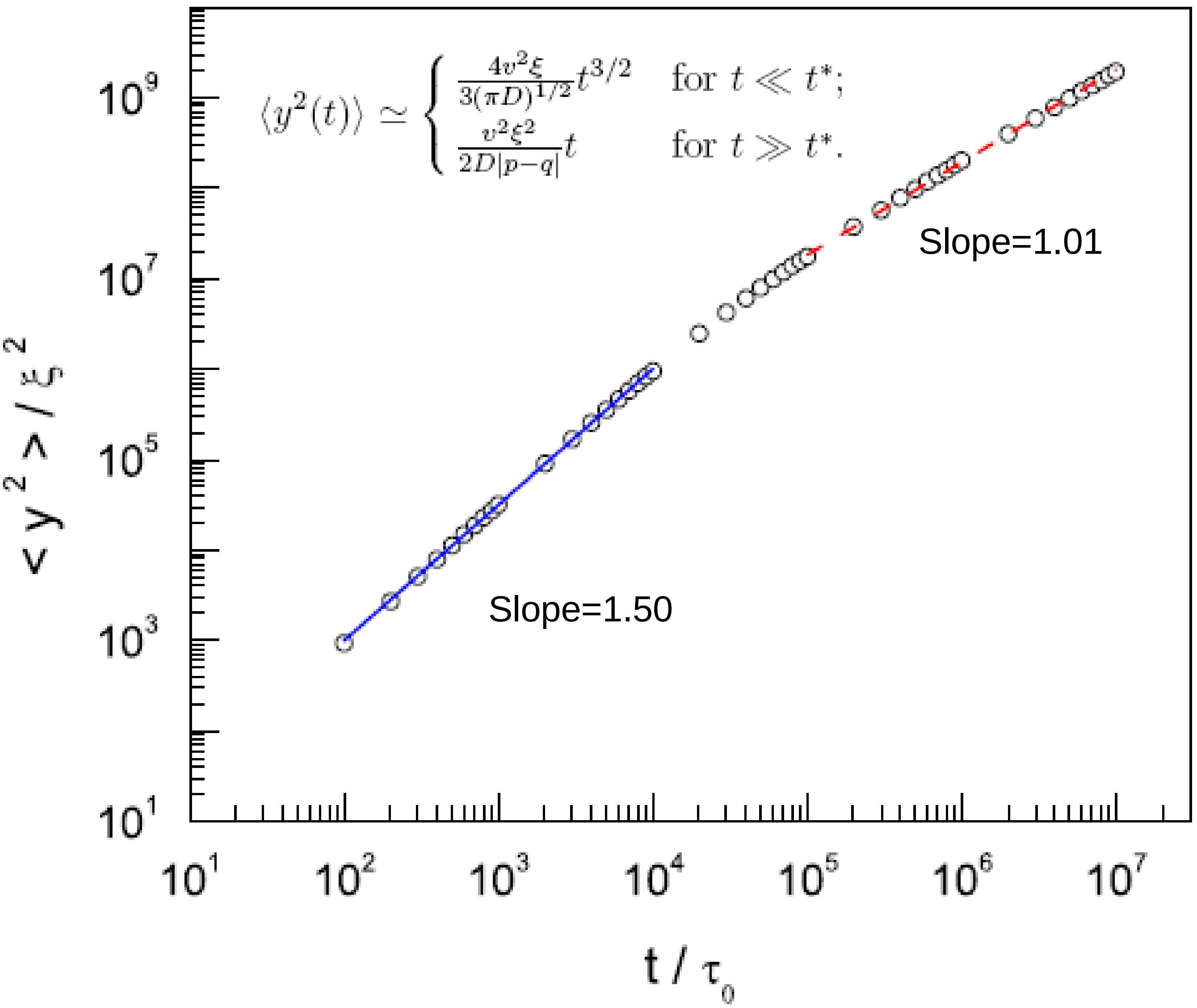
•Increase of polarity (velocity) field and Euclidean dimensions leads to a decrease of the anomalous diffusion exponent.

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

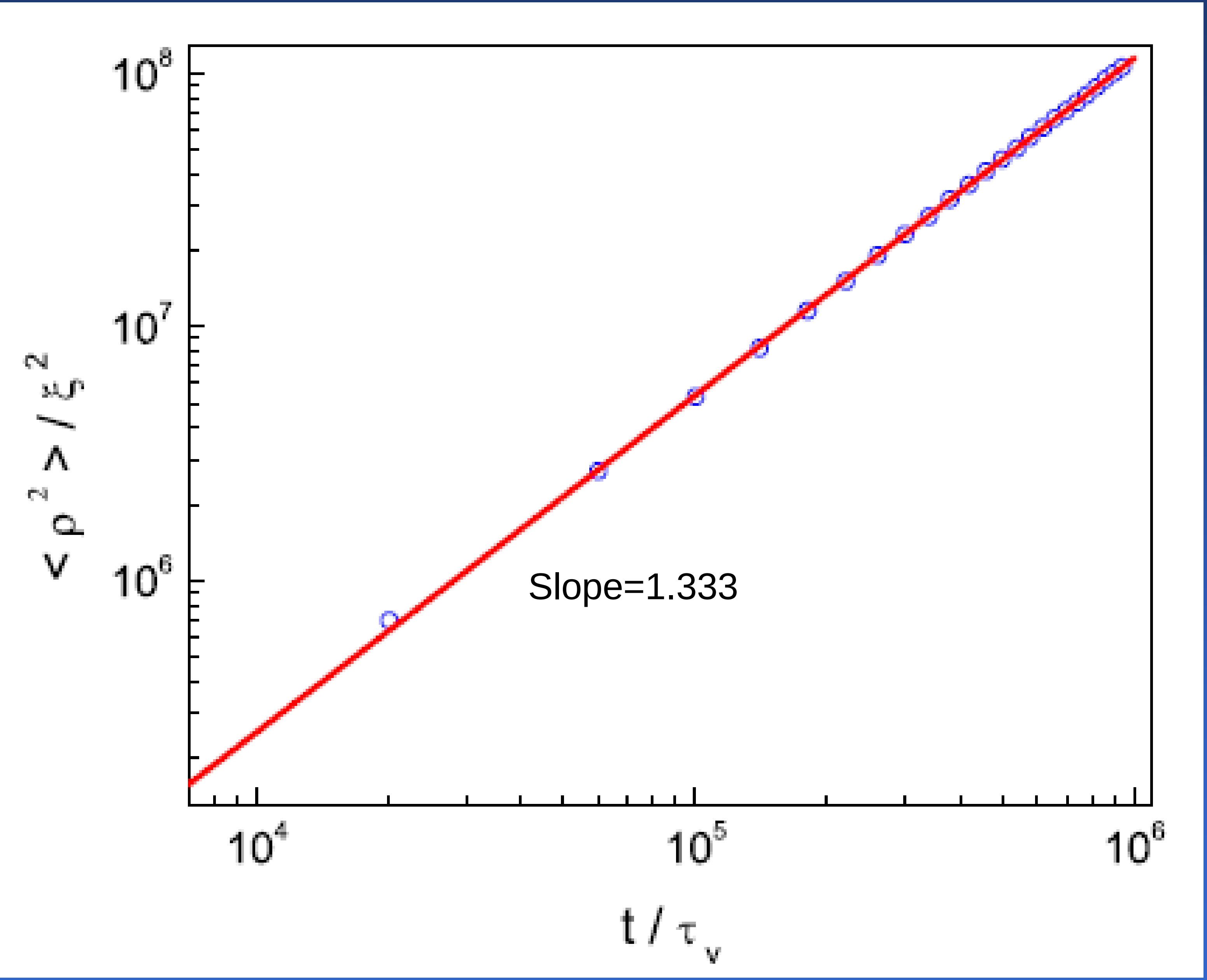
• The finite, intermediate, processivity of the microtubule associated motor proteins appears "optimize" the efficiency of transport between the different network tasks: transport from nucleus to the membrane and *vice-versa,* and between localized cell compartments.

• The local disorder of the microtubule network in the cell also appears to enhance the efficiency of transport between different locations.

Thank you



$\langle y^2(t)\rangle \simeq \begin{cases} \frac{4v^2\xi}{3(\pi D)^{1/2}}t^{3/2} & \text{for } t \ll t^*; \\ \frac{v^2\xi^2}{2D|p-q|}t & \text{for } t \gg t^*. \end{cases}$
Slope=1.01
Slope=1.50
10^9
10^7
10^5
10^3
10^1
10^1 10^2 10^3 10^4 10^5 10^6 10^7
$< y^2 > / \xi^2$
t / τ_0



10^8
10^7
10^6
$< \rho^2 > / \xi^2$
Slope=1.333
10^4
10^5
10^6
t / τ_v