Intracellular transport of cargos: tug-of-war, anomalous diffusion, and lattice deformation

Cécile Appert-Rolland

Laboratoire de Physique Théorique
CNRS / University Paris-Sud / University Paris-Saclay

Collaboration

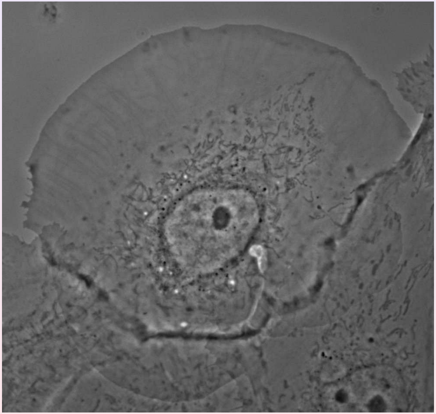
+ Inès Weber

Plan - Intra-cellular Transport

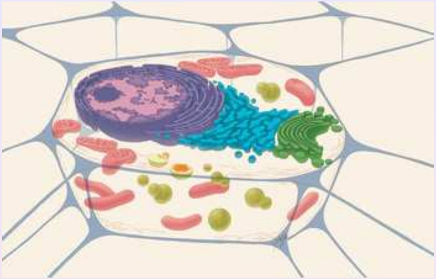
- Dynamics of cargo-motors complexes
  - Tug-of-war: Mean-Field model
  - Explicit Position Based model
  - Anomalous diffusion
  - External control
- Interplay between transport and lattice dynamics
  - Impact of lattice dynamics on collective cargo transport
  - Lattice deformation driven by active cross-linkers

Intra-cellular transport

- Need for transport



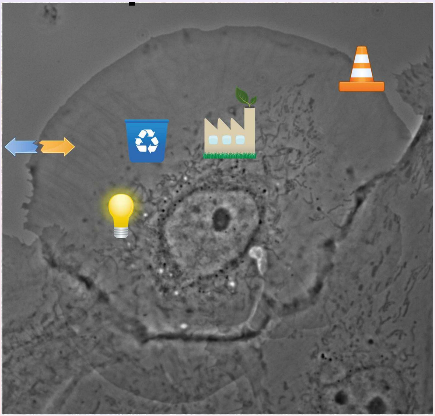
From [Wittmann et al, J. Cell Biol. 161:845 (2003)]



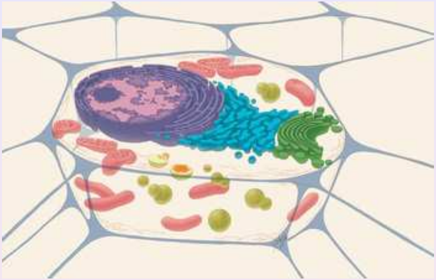
From [Judith Stoffer, NIGMS]

Intra-cellular transport

- Need for transport



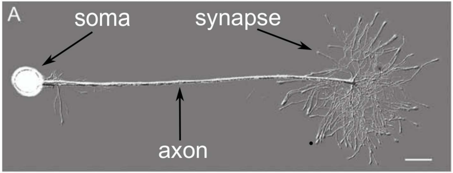
From [Wittmann et al, J. Cell Biol. 161:845 (2003)]



From [Judith Stoffer, NIGMS]

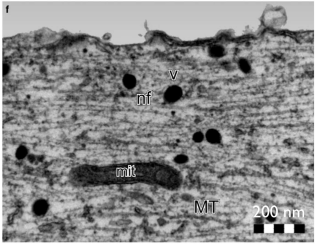
Intra-cellular transport

Shemesh et al., Traffic **9**, 458 (2008)



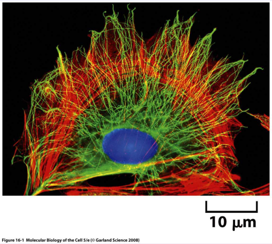
- Particular case: the axon
  - up to 1 m in human beings, a few microns for the diameter
  - crowded environment
- Link with neurodegenerative diseases

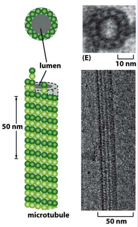
v: vesicle
nf: neurofilament
mit: mitochondrion
MT: microtubule



Shemesh & Spira, Acta Neuropathol **120**, 209 (2010)

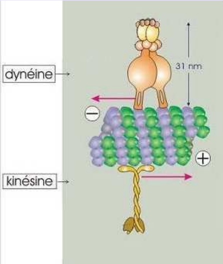
Intracellular transport



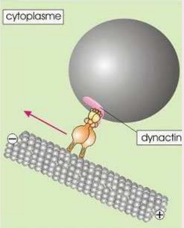


From [Alberts et al, *Molecular Biology of the Cell*, 5th ed. (2008)]

[Modified from www.ulysse.u-bordeaux.fr/atelier/ikramer/biocell_diffusion]

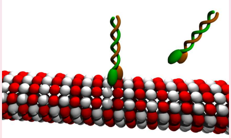


Microtubules are polarized



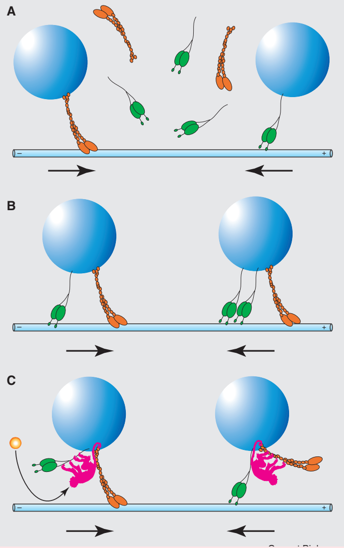
[From www.ulysse.u-bordeaux.fr/atelier/ikramer/biocell_diffusion]

[Modified from a wikipedia image by Kebes]



Motors can attach and detach

Cargo-motor complexes

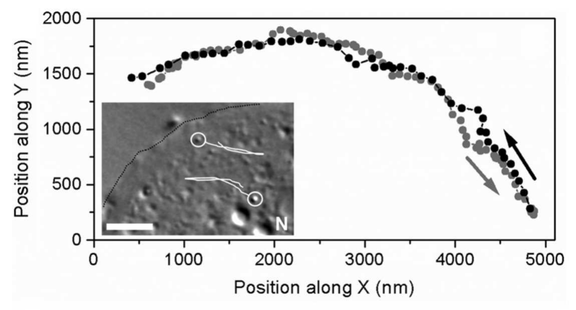


Teams of motors

- Can apply stronger forces
- Increases processivity

[Welte (2004) Curr. Biol.]

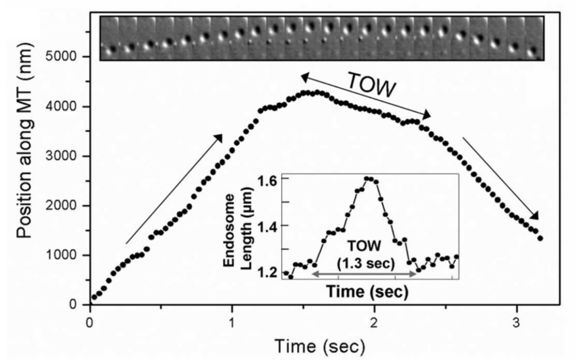
Tug-of-war



Endosome inside Dictyostelium cells.

[Soppina et al (2009) PNAS]

Tug-of-war



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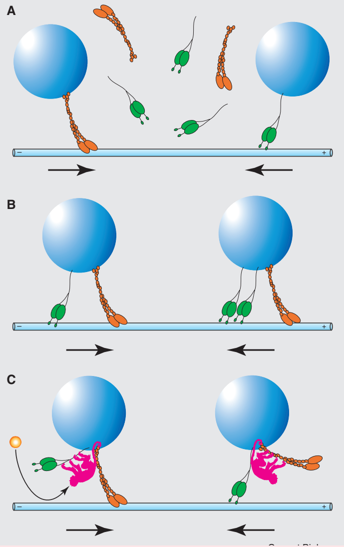
Cargo-motor complexes



Teams of motors

- Dynamics of cargo-motors complexes
- Comparison with experimental data
- Consequences in terms of transport properties

[Welte (2004) Curr. Biol.]

Plan - Intra-cellular Transport

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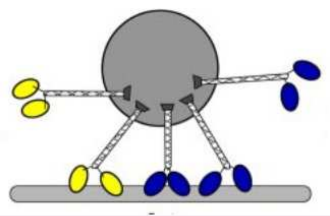
Tug-of-war, symmetric motors

[Müller, Klumpp, and Lipovsky (2008) PNAS]



Variables

Number of attached motors of each type

Mean field model

➥ Equal sharing of the force among attached motors of one given type

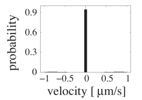
Motor Dynamics:

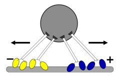
-detachment rate $\omega = \omega(F_i)$

-motor velocity $v = v(F_i)$

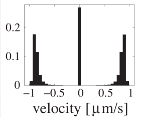
Tug-of-war, symmetric motors

- If motors stop walking before detaching

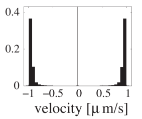


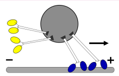


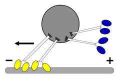
- Intermediate case



- If motors detach before stall







MF prediction

Symmetric bimodal/trimodal distributions of the velocity

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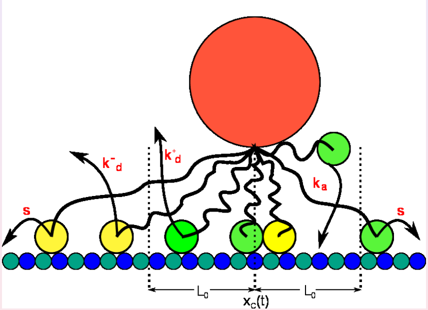
Explicit Position Based Model

EPB-model

- Motor positions are explicitely taken into account
- Motors are linked by springs to the cargo



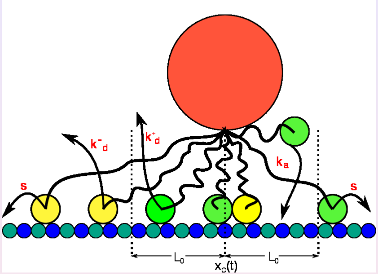
See Kunwar et al;
Bouzat et al;

Variables

Position of each attached motor

Position $\Longrightarrow$ Force

Explicit Position Based Model



Stochastic Motor Dynamics:

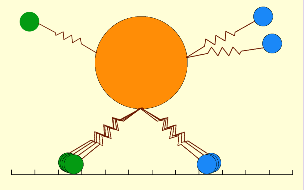
- attachment rate $\tilde{\omega}$
- stepping rate $p = p(F_i)$
- detachment rate $\omega = \omega(F_i)$

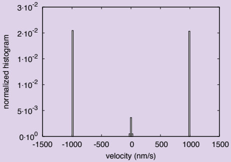
Cargo dynamics

$$m\frac{\partial^2 x_C(t)}{\partial t^2} = -\beta\frac{\partial x_C(t)}{\partial t} + F(x_C, \{x_i\})$$

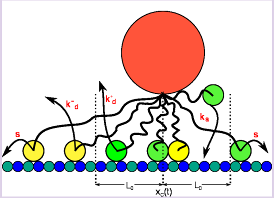
Tug-of-war, symmetric motors

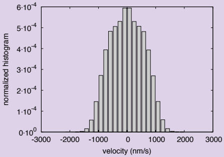
Mean field model





Non mean field model

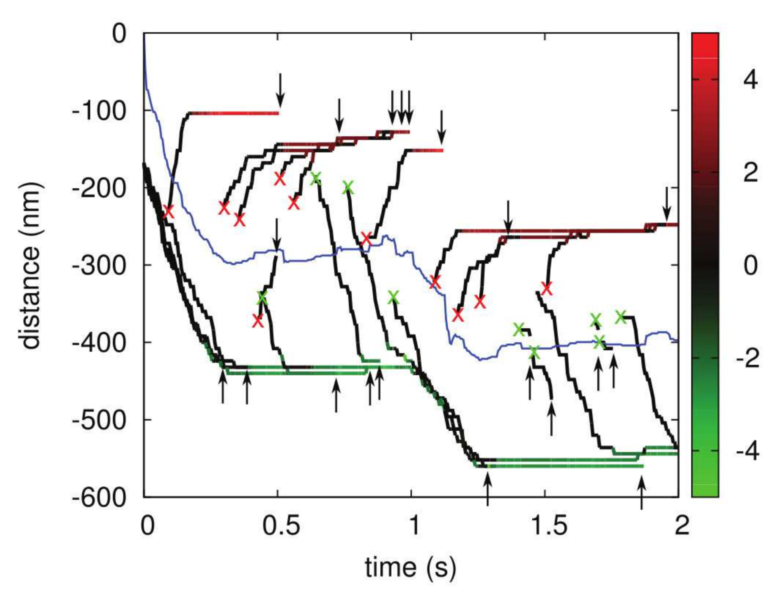




For the same motors

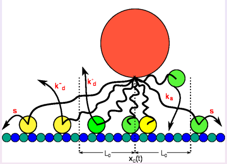
[S. Klein et al, Eur. Phys. J. Special Topics, 223 (2014) 3215]

Tug-of-war, symmetric motors



Tug-of-war, asymmetric motors

N_+, N_- motors attached to the cargo, among which n_+, n_- attached to the filament



Asymmetric teams

Kinesins and dyneins behave differently

Tug-of-war, asymmetric motors

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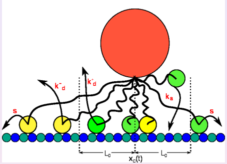
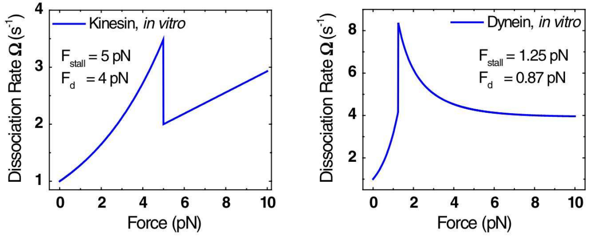


Stochastic motor dynamics

Detachment rate



From [Kunwar et al (2011) PNAS]

Tug-of-war, asymmetric motors

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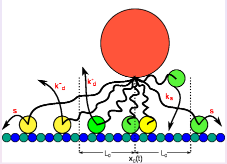

Stochastic motor dynamics

- Stepping rate (for F_i below stall force) :

$$s(|F_i|, [ATP]) = \frac{k_{cat}(|F_i|)[ATP]}{[ATP] + k_{cat}(|F_i|) k_b(|F_i|)^{-1}},$$

Michaelis-Menten kinetics

From [Schnitzer et al (2000) Nat. Cell Biol.]

- Stepping rate (for F_i above stall force) :
  backward stepping $s_b = v_b/d$

Tug-of-war, asymmetric motors

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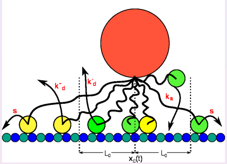
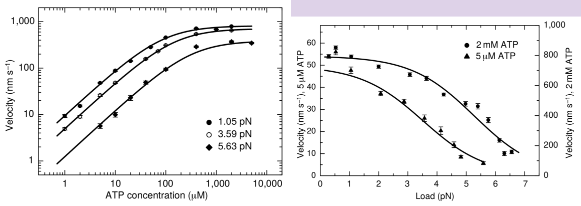


Stochastic motor dynamics

[ATP] and force dependence



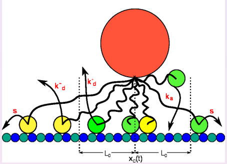
Comparison for kinesin

From [Schnitzer et al (2000) Nat. Cell Biol.]

From [Visscher et al (1999) Nature]

Tug-of-war, asymmetric motors

N_+, N_- motors attached to the cargo, among which n_+, n_- attached to the filament



How does this cargo-motors complex behave?

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Anomalous diffusion

Preliminary remarks:

Mean Square Displacement

$$\text{MSD} \equiv \langle (X(t+\Delta t) - X(t))^2 \rangle$$

- Ballistic : MSD $\sim \Delta t^2$
- Purely diffusive without bias : MSD $\sim \Delta t$
- Anomalous diffusion:

  MSD $\sim \Delta t^\gamma$ with $\gamma < 1$ or $1 < \gamma < 2$.

$\langle \rangle$ = average over t.

Anomalous diffusion

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At finite time:

Apparent superdiffusion ($\gamma > 1$)

➥ biased but uncorrelated motion ?

➥ positive temporal correlations of the displacements ?

Anomalous diffusion

Preliminary remarks:

Mean Square Displacement

$$\text{MSD} \equiv \langle (X(t+\Delta t) - X(t))^2 \rangle$$

Variance

$$\begin{aligned} \text{Var} &= \langle (X(t+\Delta t) - X(t))^2 \rangle \\ &- \langle (X(t+\Delta t) - X(t)) \rangle^2 . \end{aligned}$$

$\langle\rangle$ = average over t.

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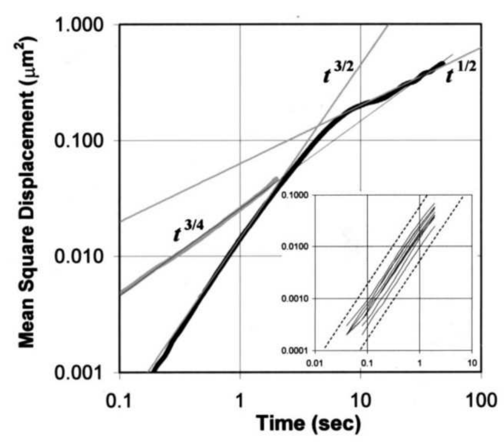
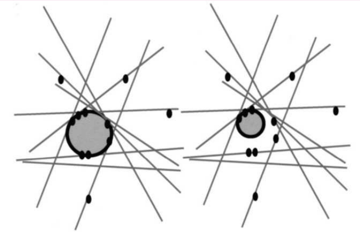
Anomalous diffusion

[Caspi et al, PRE (2002) 22, 011916]
Engulfed 2 and 3 μm beads, in living cells, driven by microtubule-associated motors



black line: 3 μm beads

- Enhanced diffusion scaling as $t^{3/2}$ at short times
- Ordinary (small spheres) or subdiffusive (large) scaling at long times



Anomalous diffusion

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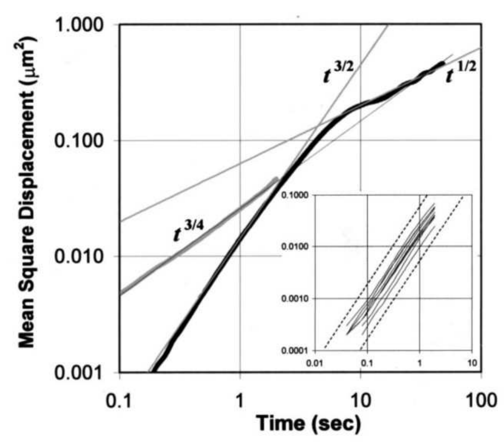

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- Enhanced diffusion scaling as $t^{3/2}$ at short times
- Ordinary (small spheres) or subdiffusive (large) scaling at long times

(see also in grey: subdiffusive motion of nondriven lipid spheres granules naturally appearing in these cells)

Anomalous diffusion

[Salman et al, Chem. Phys. (2002) 284, 389]

In vitro experiment with egg extract;
3 μm beads coated with motors and moving along MTs

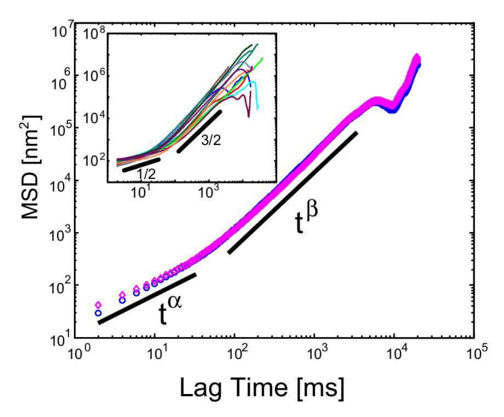
$$MSD \sim \Delta t^{\gamma}$$

Type of filament	γ	
MT + actin	$\gamma \simeq 3/2$	superdiffusive
MT (no actin)	$\gamma \simeq 3/2$	superdiffusive
Actin (no MT)	$\gamma \simeq 3/4$	subdiffusive
no MT, no actin	$\gamma \simeq 1$	diffusive

"the $t^{3/2}$ behavior comes about due to a hindrance to ballistic motion"

Anomalous diffusion

[Kulic et al (2008) PNAS **105**, 10011]
Peroxisome trajectories in Drosophila S2 cells



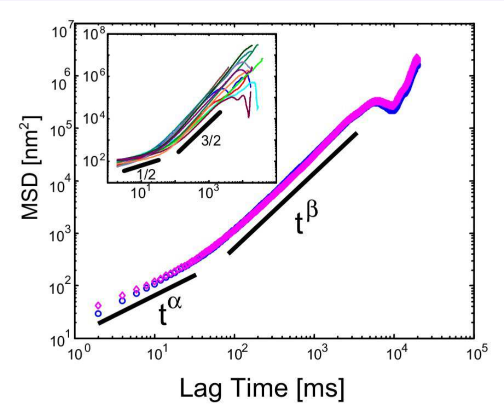
- At short time scales (below 30ms): subdiffusion
- At intermediate times: superdiffusion
- At longer time scales: diffusion or subdiffusion.

$\alpha = 0.59 \pm 0.28$ and $\beta = 1.62 \pm 0.29$

Anomalous diffusion

[Kulic et al (2008) PNAS **105**, 10011]

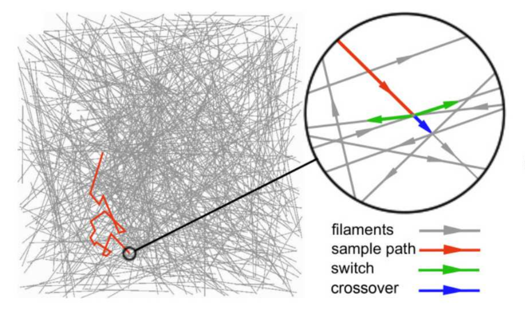
Peroxisome trajectories in Drosophila S2 cells



"an exponent close to 1.5, an observation challenging the simple motor-hauling-a-cargo and random motor switching model and indicating the movements of microtubules"

$\alpha = 0.59 \pm 0.28$ and $\beta = 1.62 \pm 0.29$

Network Effects

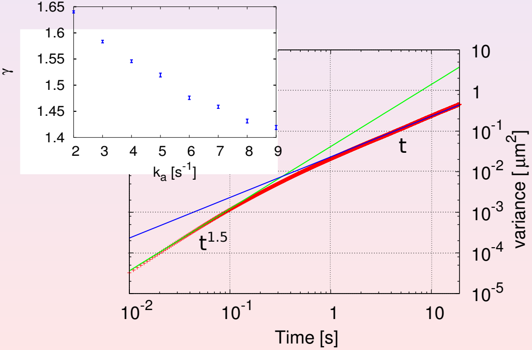


• On a branched network, purely ballistic motion also shows
Var[X] $\sim \Delta t^{\gamma}$ with $1 < \gamma < 2$
depending on the turning angle distribution

[Shaebani et al (2014) PRE 90, 030701(R)]

Cargo dynamics

$$m\frac{\partial^2 x_C(t)}{\partial t^2} = -\beta\frac{\partial x_C(t)}{\partial t} + F(x_C(t), \{x_i\})$$



[Klein et al, EPL (2014)]

Anomalous diffusion

Cargo dynamics

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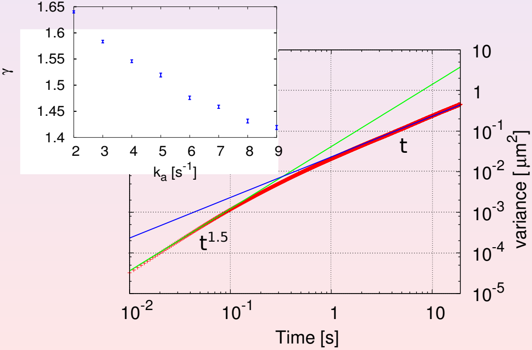


[Klein et al, EPL (2014)]

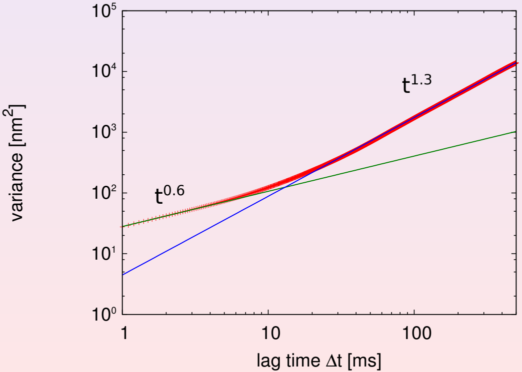
No need for further ingredient

Superdiffusion can be explained by cargo-motors dynamics

Anomalous diffusion

Cargo dynamics with thermal noise

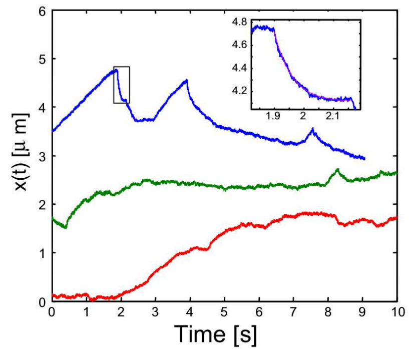
$$m\frac{\partial^2 x_C(t)}{\partial t^2} = -\beta\frac{\partial x_C(t)}{\partial t} + F(x_C(t), \{x_i\}) + \sqrt{2k_BT\beta}\,\xi(t)$$



[Klein et al, EPJST (2014)]

$v_f = 1000$ nm/s
$d = 8$ nm
Crossover time $\simeq$ delay between steps

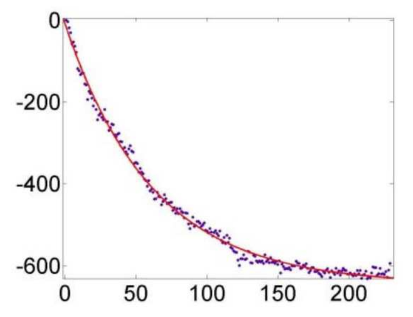
Relaxation phenomenon



[Kulic et al (2008) PNAS **105**, 10011]

"These velocity relaxation events indicated the presence of an elastic component in the system and suggested that bent and buckled microtubules could influence peroxisome transport"

Relaxation phenomenon

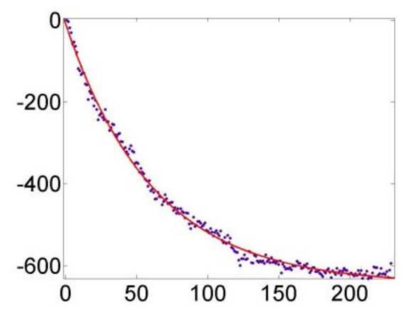


Time (ms)

[Kulic et al (2008) PNAS **105**, 10011]

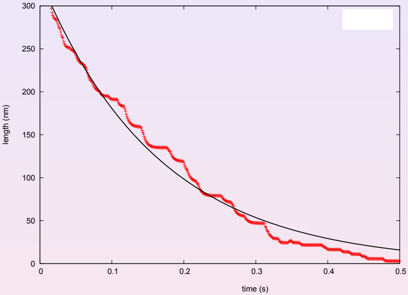
"These velocity relaxation events indicated the presence of an elastic component in the system and suggested that bent and buckled microtubules could influence peroxisome transport"

Relaxation phenomenon



Time (ms)

[Kulic et al (2008) PNAS **105**, 10011]



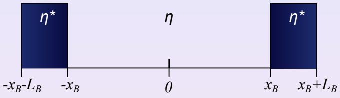
EPB Model

Elastic energy can be stored and released when a motor detaches

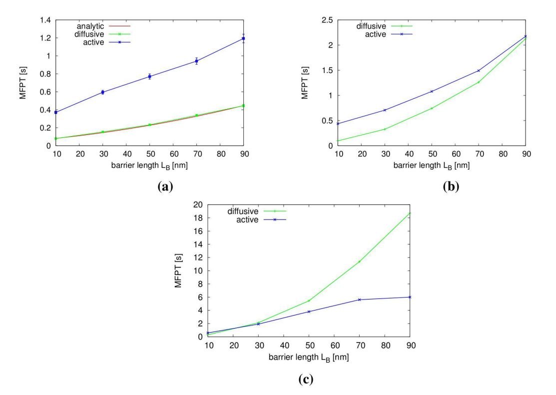
Dynamics of cargo-motors complexes along a single filament

- The EPB model allows to reproduce some experimental observations:
  - anomalous diffusion
  - elastic relaxation events
- Why is it interesting for the cell to have these cargo-motors complexes?

Active transport versus diffusion



(a) $\eta^* = \eta$,
(b) $\eta^* = 10\eta$,
(c) $\eta^* = 100\eta$



[Klein et al, EPJST (2014)]

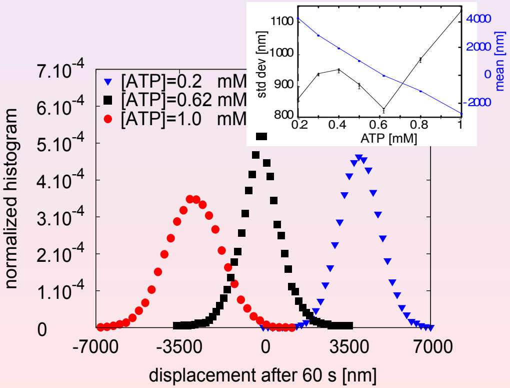
Plan - Intra-cellular Transport

- Dynamics of cargo-motors complexes
  - Tug-of-war: Mean-Field model
  - Explicit Position Based model
  - Anomalous diffusion
  - External control
- Interplay between transport and lattice dynamics
  - Impact of lattice dynamics on transport
  - Lattice deformation driven by active cross-linkers

Control by fuel supply

Stall force ATP dependence

- Kinesin: constant $F_s = 2.6$ pN
- Dynein: F_s varies linearly from 0.3 pN at vanishing [ATP] to 1.2 pN for saturating [ATP]



$N_+ = N_- = 5$

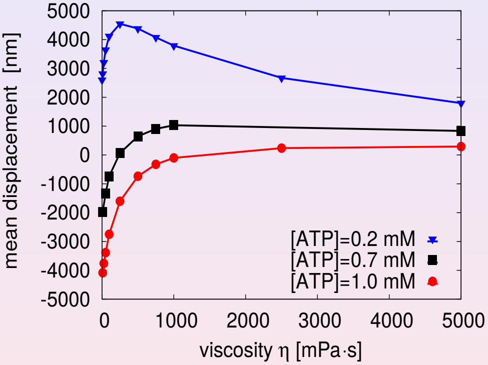
From [Klein et al (2014) EPL]

ATP dependence

- More energy (ATP) can slow down the cargo
- It can also reverse cargo velocity

Control by External Force

Effective viscosity dependence



$N_+ = N_- = 5$

From [Klein et al (2014) EPL]

Viscosity dependence

- Increase of viscosity can speed up the cargo
- It can also reverse cargo velocity

Advantage

Easy control of the cargo-motors complex by a single external parameter

Conclusion

- Many experimental observations can already be explained by the stochastic motion of cargo-motors complexes along a single microtubule.
- Highly controlable system.
- Our predictions for [ATP] dependence or external force control could be tested experimentally.

Challenges

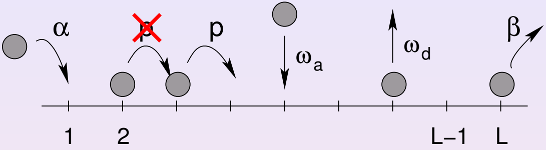
- Need of well controlled experiments to check tug-of-war scenarios
- In vitro / in vivo differences?

Plan - Intra-cellular Transport

- Dynamics of cargo-motors complexes
  - Tug-of-war: Mean-Field model
  - Explicit Position Based model
  - Anomalous diffusion
  - External control
- Interplay between transport and lattice dynamics
  - Impact of lattice dynamics on transport
  - Lattice deformation driven by active cross-linkers

Collective effects

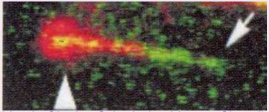
Cellular automata models with one type of motors



[Lipowsky, Klumpp, & Nieuwenhuizen, P.R.L. (2001)]
[Parmeggiani, Franosch, & Frey, P.R.L. (2003)]
[J. Tailleur, M. Evans, & Y. Kafri, P.R.L. (2009)]

In vitro

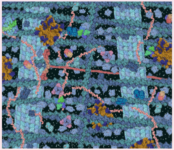
- well suited for motility assays, predicts the experimentally observed bulk localization of high and low density domains



[Nishinari, Okada, Schadschneider, & Chowdhury, P.R.L. (2005)]

In vivo

- Crowded environment
- No infinite diffusion

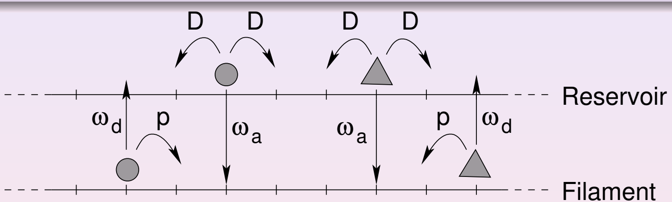


[by Tim Vickers]

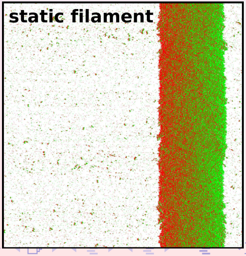
Collective effects in bidirectional intracellular transport

Ingredients

- Two types of complexes going in opposite directions
- Confined diffusion in the surrounding cytoplasm



[M. Ebbinghaus and L. Santen, J. Stat. Mech. (2009)]



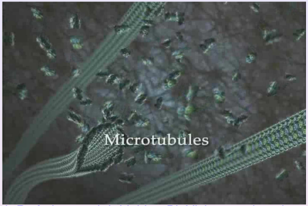
Jamming

➥ No transport in thermodynamic limit

➥ Offering multiple filaments enhances cluster formation.

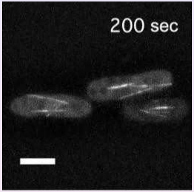
Intra-cellular traffic - Dynamic instability

MTs exhibit stochastic switching between a shrinking and a growing state



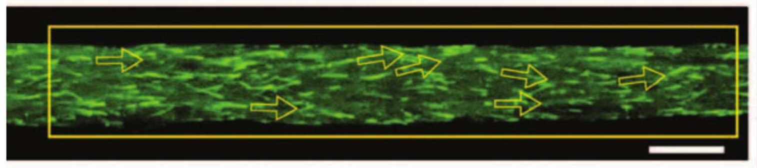
[A. Viel, R. A. Lue and J. Liebler, BioVisions project, http://multimedia.mcb.harvard.edu]

Microtubules seen by fluorescence in S. pombe (yeast)



Scale bar = 5 μm

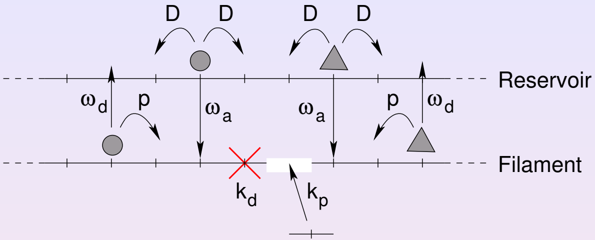
[M. Erent, D.R. Drummond, R.A. Cross (2012) PLoS ONE 7(2): e30738]

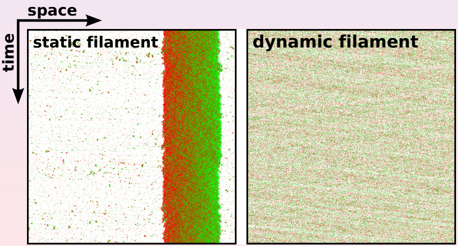


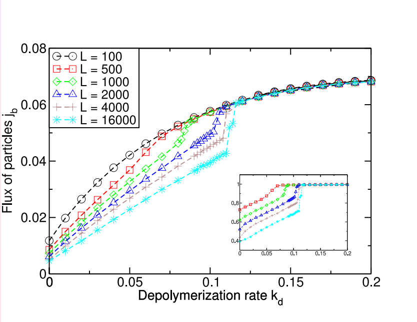
[*Shemesh, Erez, Ginzburg, Spira. Traffic (2008)*]

1s (video) = 120s (real time)
Scale bar = 10 μm

Dynamics of the lattice







[Ebbinghaus, Appert, Santen, PRE 82 (2010) 040901]

Bidirectional intracellular traffic

☞ Drugs modifying the dynamics of the microtubules induce jams

- video 1: microtubule dynamics with and without drugs (Paclitaxel)

[*Shemesh and Spira, Acta Neuropathol (2010) 119:235*]

Bidirectional intracellular traffic

☞ Drugs modifying the dynamics of the microtubules induce jams

- video 2: microtubule dynamics and pinocytotic vesicles transport without drugs

[*Shemesh and Spira, Acta Neuropathol (2010) 119:235*]

☞ Drugs modifying the dynamics of the microtubules induce jams

- video 3: microtubule dynamics and pinocytotic vesicles transport with drugs

[*Shemesh and Spira, Acta Neuropathol (2010) 119:235*]

Challenges

- A full picture of the axonal MT network is still missing
- Understanding the mechanisms of transport breakdown in neurodegenerative diseases

Plan - Intra-cellular Transport

- Dynamics of cargo-motors complexes
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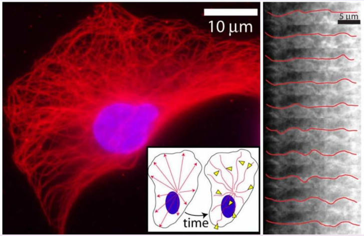
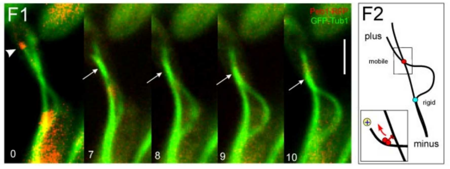
  - Lattice deformation driven by active cross-linkers

MT deformation: Observations

In vivo



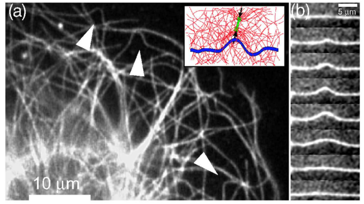
[Brangwynne et al, PNAS (2007)]



[Straube et al, Molec. Biol. of the Cell (2006)]

MT-MT interactions mediated by conventional kinesin (fungus Ustilago maydis)

In vitro



[Brangwynne et al, PRL (2008)]

MT embedded in acto-myosin gel

In vitro measurements

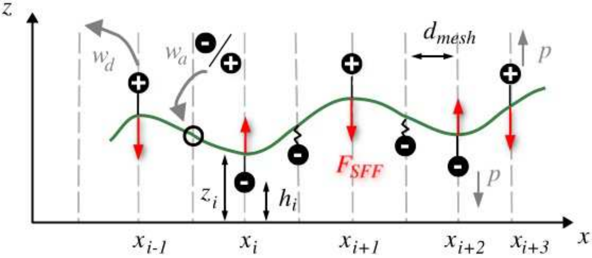
Persistence length of a free MT = a few mm

In vivo measurements

Persistence length of MTs = 30 μm

Model definition

[Ines Weber, Cécile Appert-Rolland, Grégory Schehr, and Ludger Santen, "Non-equilibrium fluctuations of a semi-flexible filament driven by active cross-linkers" (2017) submitted]

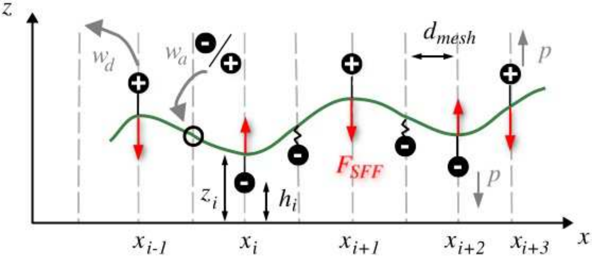


Model

- Semi-flexible filament $E = k \int_0^L \left(\frac{\partial \theta}{\partial s}\right)^2 ds$
- Connected to a background network by active cross-linkers
- Stochastic dynamics for the cross-linkers
- Cross-linkers feel a force F_{SFF} only for elongated chain

k = bending rigidity

Model definition

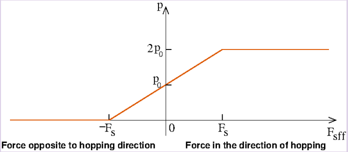


Active Cross-linkers

- bind at available sites with rate ω_a
- ➥ Polarity of the background filament chosen at each attachment event
- unbind with rate

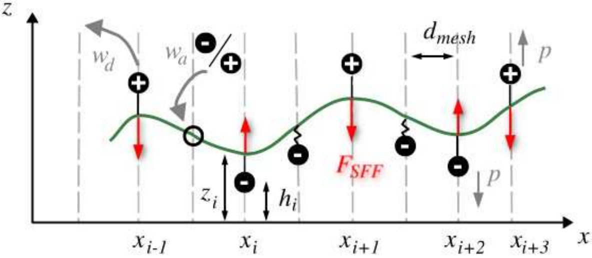
$$\omega_d = \omega_{d_0} \exp\left(\frac{|F_{SFF}|}{F_d}\right)$$

- step with rate $p(F_{SFF})$



F_s = stall force.

Model definition



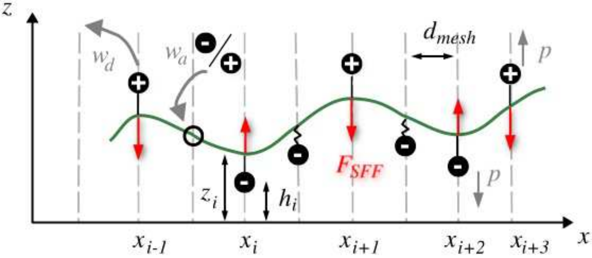
Coupling SFF / linkers

- $\{x_i\}$ = positions of pulling linkers (elongated chains)
- Between x_i and x_{i+1}: F = Force / unit length

  $E_i = k \int_{x_i}^{x_{i+1}} \left[\partial_x^2 u_i(x)\right]^2 dx$ and $F \sim \partial_x^4 u_i(x)$
- Equilibrium shape

  $F = 0 \Rightarrow u_i(x) = a_i(x - x_i)^3 + b_i(x - x_i)^2 + c_i(x - x_i) + d_i$

Model definition



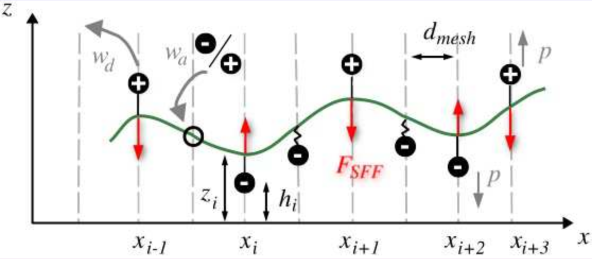
Coupling SFF / linkers

- We put end-to-end these segments with boundary conditions :

$$u_i(x_i) = z_i, \qquad u_i(x_{i+1}) = z_{i+1}$$
$$\partial_x u_i(x_i) = v_i, \qquad \partial_x u_i(x_{i+1}) = v_{i+1}$$

- z_i = vertical displacement of the SFF imposed at position x_i
- v_i = the local slope ➥ differentiability of the global polynomial

Model definition



Coupling SFF / linkers

- For each set of positions $\{x_i\}$, we find
- ➥ the global equilibrium shape of the SFF
- ➥ the local force exerted at each attachment point:

$$F_k = \frac{\partial E}{\partial z_k} = 24k\left(\frac{\Delta z_{k-1}}{\Delta x_{k-1}^3} - \frac{\Delta z_k}{\Delta x_k^3}\right) - 12k\left\{v_k\left(\frac{1}{\Delta x_{k-1}^2} - \frac{1}{\Delta x_k^2}\right)\right\} - 12k\left\{\frac{v_{k-1}}{\Delta x_{k-1}^2} - \frac{v_{k+1}}{\Delta x_k^2}\right\}$$

Coupling between SFF and linkers

Update scheme

- We update the system of linkers with a tower sampling algorithm and perform stochastic events until the occurrence of an event that modifies the force exerted on the SFF
- Then the new equilibrium shape of the SFF is calculated
- The new forces exerted on the linkers are obtained and the value of force-dependent rates is calculated for each linker.

➥ Can model cascades of detachment

➥ Understanding how deformations originate from microscopic discrete forcing

Non-equilibrium fluctuations of a SFF driven by active cross-linkers

Results

- ➥ Obtain deformation spectrum
- ➥ Obtain persistance length
- ➥ Investigate the role of parameters (rigidity, mesh size, etc)
- ➥ Compare thermal and active linkers to identify geometrical effects

Deformation spectrum

Decomposition into cosine modes

$$\theta(s) = \sqrt{2/L} \sum_{n=0}^{\infty} a(q) \cos(qs)$$

with the wavenumber $q = (n\pi/L)$

Thermal fluctuations in 2D

The variance of cosine modes' amplitudes is known to vary with q as

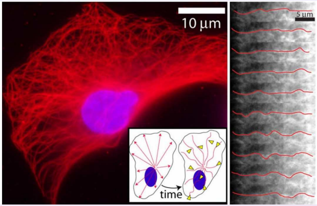
$$\mathrm{Var}(a(q)) \equiv \langle a(q)^2 \rangle = \frac{1}{L_p} \frac{1}{q^2} \quad \text{with} \quad L_p^{thermal} = \frac{2k}{k_B T} \,.$$

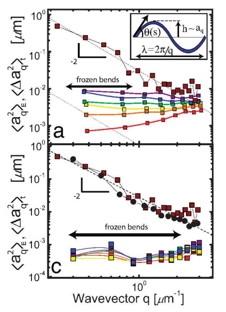
Non-thermal fluctuations

No reason to have q^{-2} dependence

Deformation spectrum

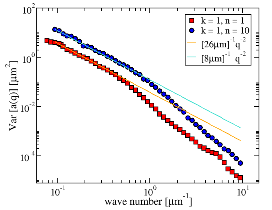
In vivo





[Brangwynne et al, PNAS (2007)]

In silico



[I. Weber et al, submitted (2017)]

Red squares: parameters inspired by biological system. The q^{-2} behavior (orange line) for small q can be associated with a persistence length of 26μm.

Generic: no clear q^{-2} behavior.

Persistence length

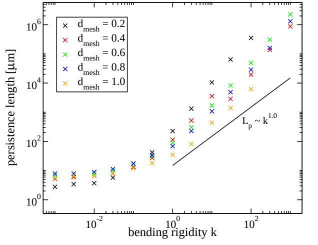
For two dimensional fluctuations

Auto-correlation of the tangent angle θ

$$\langle \cos\left(\theta(s) - \theta(s')\right)\rangle = \exp\left(-|s - s'|/(2L_p)\right)$$

$$L_p^{thermal} = \frac{2k}{k_B T}$$

Persistence length



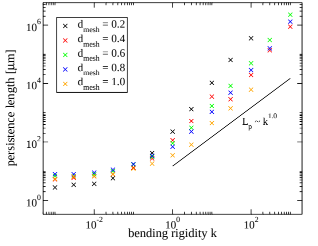
$k = 1$ for MTs

Straight line = the linear increase expected for purely thermal fluctuations

Rigidity dependence

- For small k, deformations are limited by the mesh size.
- For $k \geq 1$, super-linear increase of the persistence length up to, and beyond the SFF length.

Persistence length



$k = 1$ for MTs

Straight line = the linear increase expected for purely thermal fluctuations

Mesh size dependence (fixed number of linkers)

- For small k, the persistence length slightly decreases with d_{mesh} (This dependence is linear in d_{mesh})
- For large k, it is the contrary! When d_{mesh} decreases, the curvature induced by a single linker step is more pronounced. At high k, this results into strong load forces, which most likely the linker will not be able to sustain. Therefore, it is difficult to deform the stiff SFF at all, if the density of cross-linkers is too high.

Non-equilibrium fluctuations of a SFF driven by active cross-linkers

- Model allowing to couple the dynamics of a SFF with the stochastic dynamics of active linkers.
  - Deformation spectrum
  - investigate the role of parameters (rigidity, mesh size, etc)
- Can be generalized to other types of cross-linkers.
- We could have expected that one type of motors could pull off the other. This is not the case.
  - ➥ cf Tug-of-war

Challenges

- In vitro experiments in simplified geometry?

For more details:
http://www.th.u-psud.fr/page_perso/Appert/

Thank-you