Fluctuation relations for molecular motors

D. Lacoste

Laboratoire Physico-Chimie Théorique,

UMR Gulliver, ESPCI, Paris

ESPCI ParisTech

Outline of the talk

I. Energetics and fluctuation relations of a single molecular motor

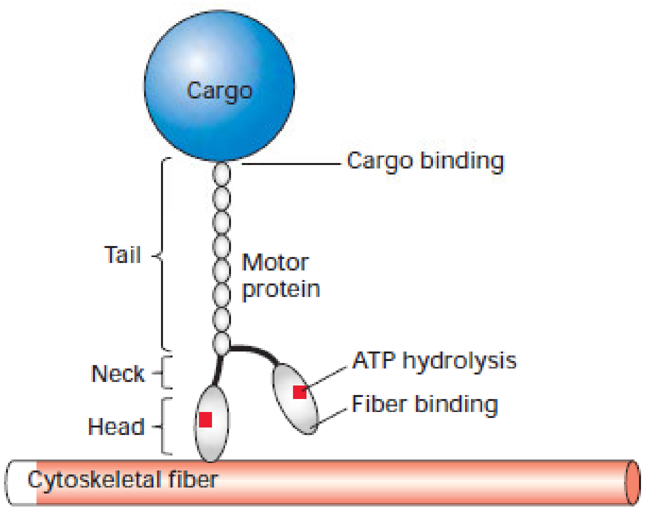
II. Dynamics of a single filament coupled to ATP/GTP hydrolysis

Acknowlegments:

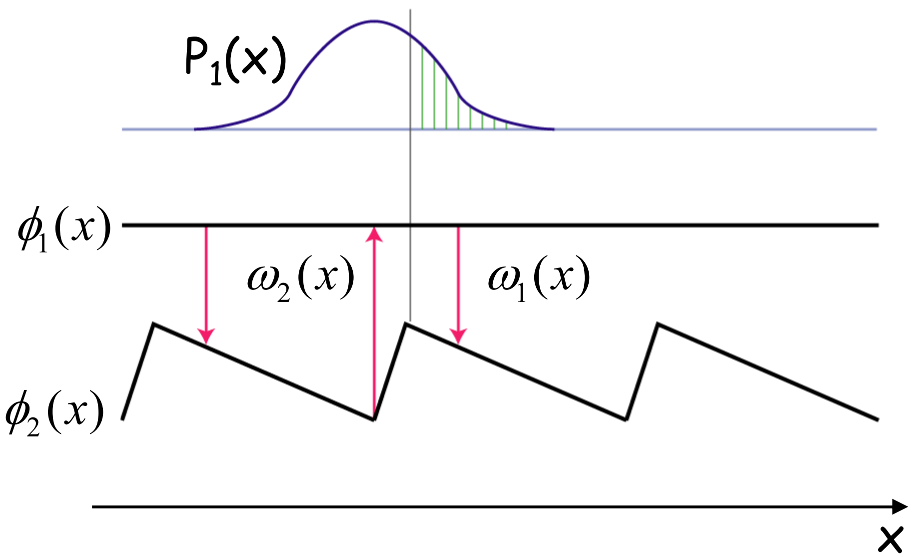
Part I: K. Mallick, CEA Saclay, France
A. Lau, Atlantic University, USA

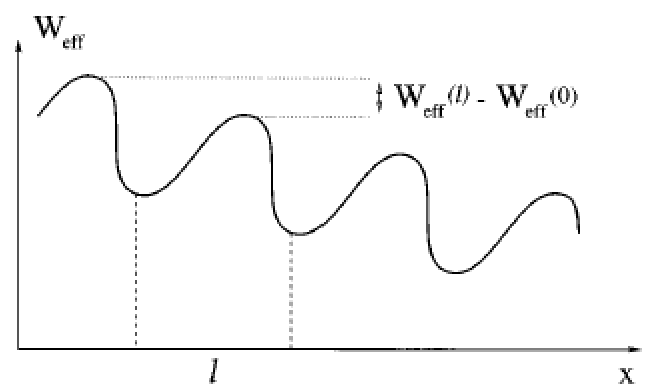
Part II: R. Padinhatteeri, now IIT Mumbai
JF. Joanny, Institut Curie, France

I. Energetics and fluctuation relations of a single molecular motor



Flashing ratchet model





<u>Conditions for directed motion in the absence of applied force:</u>

- Asymmetric potentials (spatial symmetry)
- Breaking of detailed balance (time-reversal symmetry)

A.Ajdari et al., Rev. Mod. Physics **69**, 1269 (1997)

Two coupled Fokker-Plank equations:

$$\begin{cases} \partial_t P_1 + \partial_x J_1 = -\omega_1(x) P_1 + \omega_2(x) P_2 \\ \partial_t P_2 + \partial_x J_2 = \omega_1(x) P_1 - \omega_2(x) P_2 \end{cases}$$

with particle currents (kT=1) $J_i = -D\left(\partial_x P_i + P_i \partial_x \phi_i - P_i f\right)$

Coupling to chemical reactions

$ATP + M_1 \rightleftarrows M_2 + ADP + P$ or $M_1 \rightleftarrows M_2$

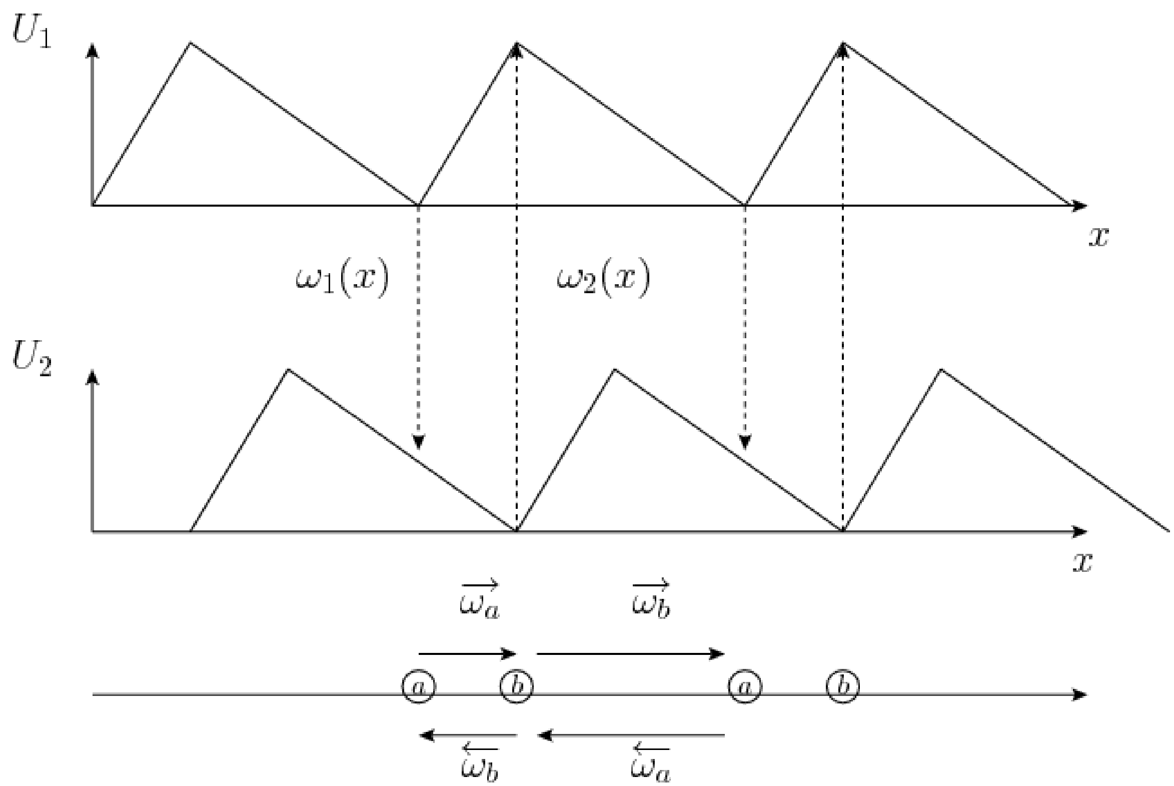
Transitions rates

$$\omega_1(x) = \left(\psi(x) e^{\Delta\mu} + \omega(x)\right) e^{(U_1(x) - fx)/k_B T}$$

$$\omega_2(x) = (\psi(x) + \omega(x)) e^{(U_2(x) - fx)/k_B T}$$

$$\Delta\mu = k_B T \ln\left(\frac{[ATP]}{[ADP][P]} \frac{[ADP]_{eq}[P]_{eq}}{[ATP]_{eq}} \right)$$

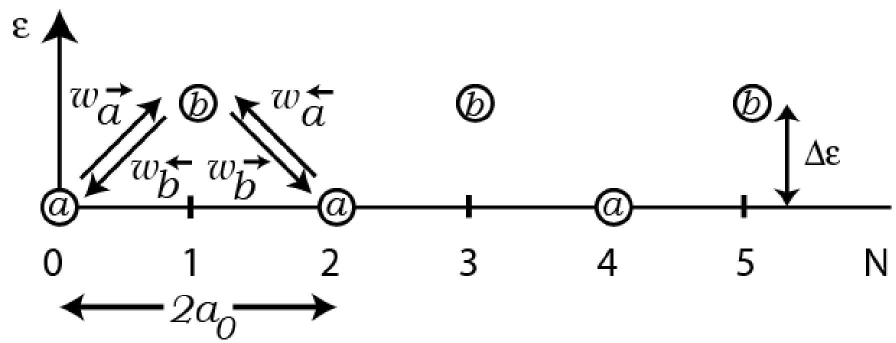
Construction of a minimal ratchet model



B. Widom et al., J. Stat. Phys. **93**, 663 (1998)
M. E. Fisher et al., PNAS **96**, 6597 (1999)

Minimal ratchet model: dynamics

Binding energy



Transition rates (at f=0)

$$
\begin{aligned}
w_a^{\rightarrow} &= (\alpha e^{\Delta\mu/T} + \omega) e^{-\Delta\varepsilon/T} \\
w_b^{\leftarrow} &= (\alpha + \omega) \\
w_a^{\leftarrow} &= (\alpha' e^{\Delta\mu/T} + \omega') e^{-\Delta\varepsilon/T} \\
w_b^{\rightarrow} &= (\alpha' + \omega') \, .
\end{aligned}
$$

Conditions for directed motion

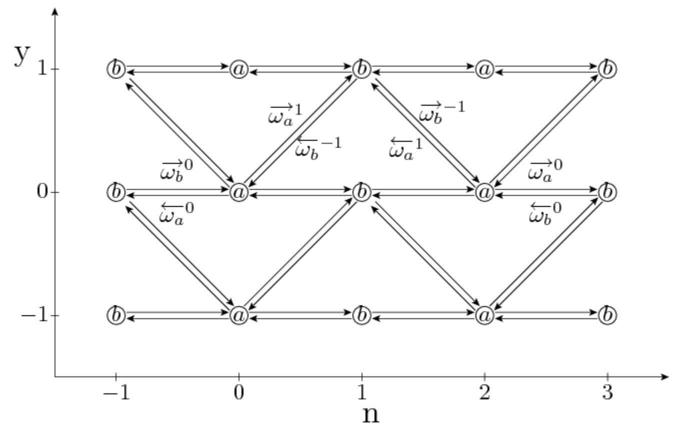
$\alpha \neq \alpha'$ or $\omega \neq \omega'$ *asymmetric potentials*

$\Delta\mu \neq 0$ or $f \neq 0$ *breaking of detailed balance*

Y. Kafri et al., Biophys. J. **86**, 3373 (2004)

Minimal ratchet model: thermodynamics

number of ATP molecules consumed: y(t)



Oblique transitions:
Active (ATP consumed)

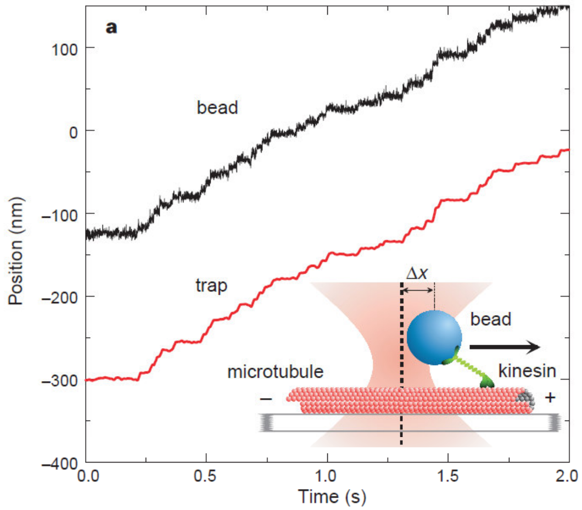
$$\overleftarrow{\omega_b}^{-1} = \alpha\, e^{-\theta_b^- f},$$
$$\overrightarrow{\omega_a}^{1} = \alpha\, e^{-\epsilon+\Delta\mu+\theta_a^+ f},$$
$$\overleftarrow{\omega_a}^{1} = \alpha' e^{-\epsilon+\Delta\mu-\theta_a^- f},$$
$$\overrightarrow{\omega_b}^{-1} = \alpha' e^{\theta_b^+ f},$$

Horizontal transitions:
passive or thermal

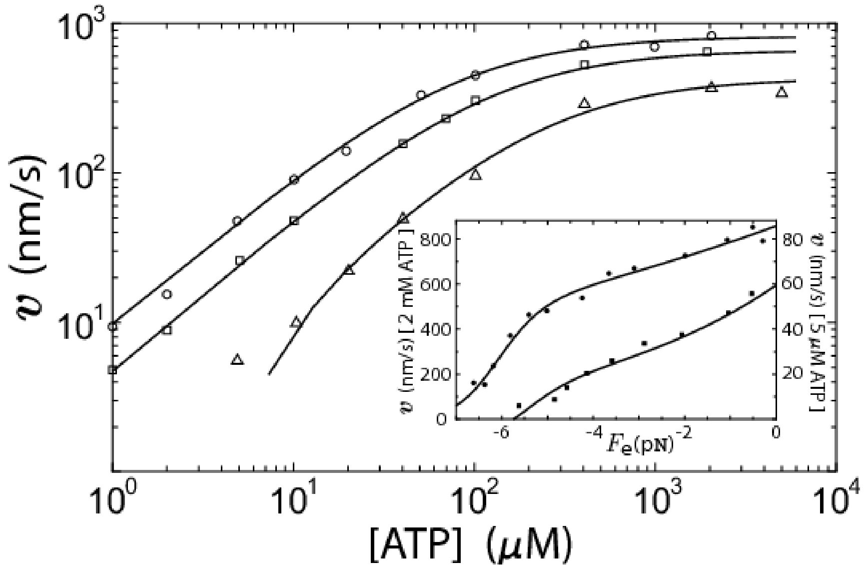
$$\overleftarrow{\omega_b}^{0} = \omega\, e^{-\theta_b^- f},$$
$$\overrightarrow{\omega_a}^{0} = \omega\, e^{-\epsilon+\theta_a^+ f},$$
$$\overleftarrow{\omega_a}^{0} = \omega'\, e^{-\epsilon-\theta_a^- f},$$
$$\overrightarrow{\omega_b}^{0} = \omega'\, e^{\theta_b^+ f},$$

Normalized variables $\widetilde{\Delta\mu} = k_B T \Delta\mu$ $\quad f = \dfrac{Fd}{k_B T}$ $\quad \varepsilon = \dfrac{\Delta E}{k_B T}$

Fitting the model to kinesin experiments



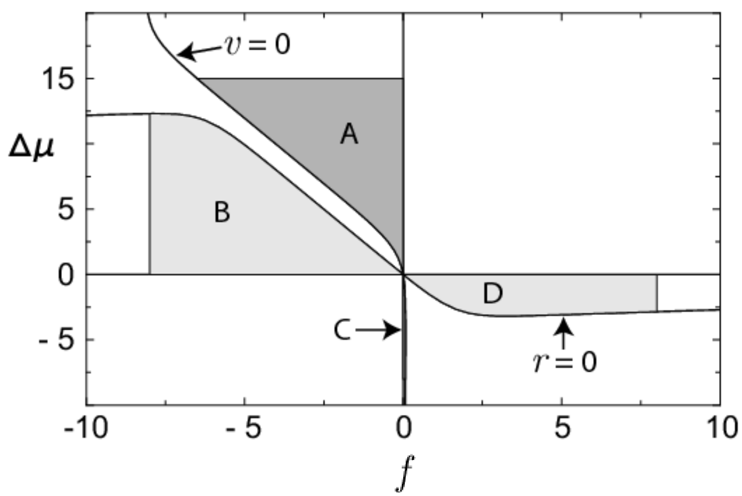
K. Visshar, M. J. Schnitzer, S. M. Block
Nature **400**, 184 (1999)



- Global ATP consumption $r = 111 s^{-1}$ (ATPase assays)
- Coupling parameter $\ell = \dfrac{v}{r} \simeq 0.97$ close to one (tightly coupled motors)

A.W.C. Lau et al., PRL **99**, 158102 (2007)

Operational diagram of kinesin



Normalized variables

$$\widetilde{\Delta\mu} = k_B T \Delta\mu \qquad f = \frac{Fd}{k_B T}$$

<u>4 regions of mechano-transduction :</u>

A: excess ATP -> mechanical work $f\,\overline{v} < 0$ and $r\Delta\mu > 0$

B: mechanical work -> ATP $f\,\overline{v} > 0$ and $r\Delta\mu < 0$

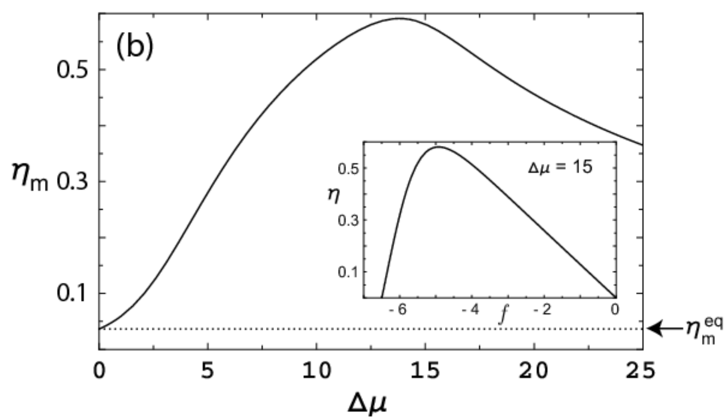
C: excess ADP-> mechanical work $f\,\overline{v} < 0$ and $r\Delta\mu > 0$

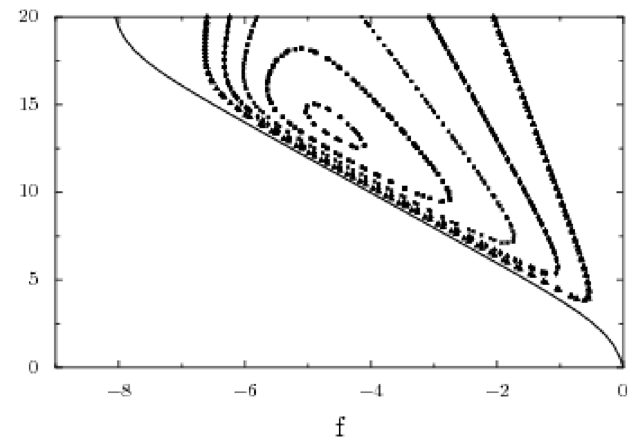
D: mechanical work -> ADP $f\,\overline{v} < 0$ and $r\Delta\mu < 0$

Thermodynamic efficiency

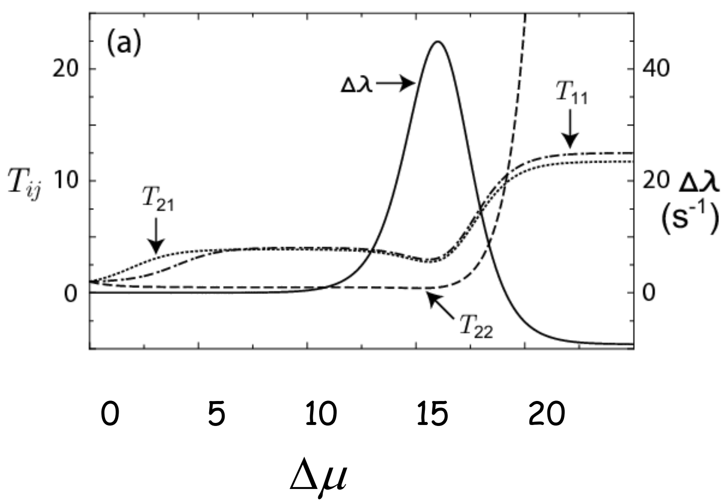
Definition:

$$\eta = -\frac{f\,\overline{v}}{r\Delta\mu}$$





Violation of Einstein-Onsager relations



Breaking of Onsager relation

$$\Delta\lambda = \lambda_{12} - \lambda_{21},$$

Breaking of Einstein relation

$$T_{ij} = \frac{D_{ij}}{\lambda_{ij}}$$

Fluctuation relations

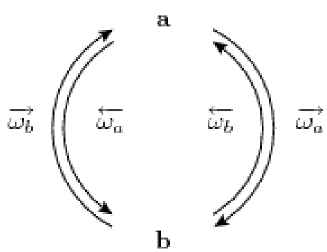
- Linear response theory
  - For systems close to equilibrium
    (Onsager-Einstein-FDT)

- Fluctuation relations
  - Beyond linear response
  - Arbitrarily far from equilibrium
    (Jarzynski, Crooks, Evans, Cohen, Galavotti, Kurchan, Lebowitz & Spohn, Sasa, Seifert, Gaspard)

- Applications to enzymes or nanomachines
  - Small size, small number of molecules involved, large fluctuations
  - Thermodynamic constraints
    (Seifert, Gaspard, Lipowsky)

General construction of cycles associated to currents for NESS

Case of a single cycle associated with the position variable n only



Thermodynamic force (affinity)

$$\frac{\Pi^+}{\Pi^-} = \frac{\overrightarrow{\omega}_a \overrightarrow{\omega}_b}{\overleftarrow{\omega}_a \overleftarrow{\omega}_b} = \frac{J^+}{J^-} = e^{-\Psi/2} \Leftrightarrow \Psi = \tfrac{1}{2} \ln\left(\frac{\overleftarrow{\omega}_a \overleftarrow{\omega}_b}{\overrightarrow{\omega}_a \overrightarrow{\omega}_b} \right)$$

$$\bar{v} = 2(J^+ - J^-) = 2\,\frac{\overrightarrow{\omega}_a \overrightarrow{\omega}_b - \overleftarrow{\omega}_a \overleftarrow{\omega}_b}{\overrightarrow{\omega}_a + \overrightarrow{\omega}_b + \overleftarrow{\omega}_a + \overleftarrow{\omega}_b}$$

with previous rates : $\Psi = -f + f_{st}(\Delta\mu)$

T. Hill, J. Schnakenberger (1976),
D. Andrieux et al. (2004), U. Seifert (2005)

Gallavotti-Cohen symmetry

Generating function of the currents $$F_n(\lambda,t) \equiv \sum_n e^{-\lambda n} P_i(n,t)$$

evolves according to $$\partial_t F_i(\lambda,t) \equiv M_{ij} F_j(\lambda,t)$$

$$M(\lambda) = \begin{pmatrix} -\overrightarrow{\omega_a} - \overleftarrow{\omega_a} & e^{\lambda}\overleftarrow{\omega_b}(\gamma) + e^{-\lambda}\overrightarrow{\omega_b}(\gamma) \\ e^{\lambda}\overleftarrow{\omega_a}(\gamma) + e^{-\lambda}\overrightarrow{\omega_a}(\gamma) & -\overrightarrow{\omega_b} - \overleftarrow{\omega_b} \end{pmatrix}$$

$$\left\langle e^{-\lambda n} \right\rangle = \sum_i F_i(\lambda,t) \sim \exp\left[\theta(\lambda)t\right] \quad \text{as} \quad t \to \infty$$

$$\bar{v} = \frac{\langle n \rangle}{t} = -\left.\frac{\partial \theta}{\partial \lambda}\right|_{\lambda=0,\gamma=0} \quad \text{and} \quad D = \frac{1}{2}\left.\frac{\partial^2 \theta}{\partial^2 \lambda}\right|_{\lambda=0}$$

Gallavotti-Cohen (GC) symmetry : $$\theta(-\Psi - \lambda) = \theta(\lambda)$$

Large-deviation function of the current

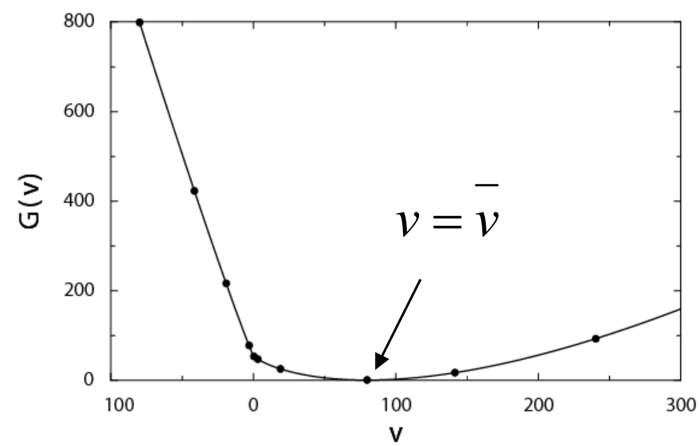
$$P(\frac{n}{t} = v) \sim \exp[-G(v)t]$$

(for large time t)

$$\theta(\lambda) = \max_v[-G(v) - \lambda v]$$

Legendre transform of the maximal eigenvalue

Exact analytical expression for G(v)



One remarkable fact :

$$G(v) - G(-v) = \Psi v$$

Fluctuation relations for currents (on long times)

1) $$\theta(\lambda) = \theta(-\Psi - \lambda)$$

2) $$\frac{P(\frac{n}{t} = v)}{P(\frac{n}{t} = -v)} = e^{-\Psi v t}$$

3) $$G(v) - G(-v) = \Psi v$$

Average entropy production rate $\Pi_S = -\Psi \bar{v}$

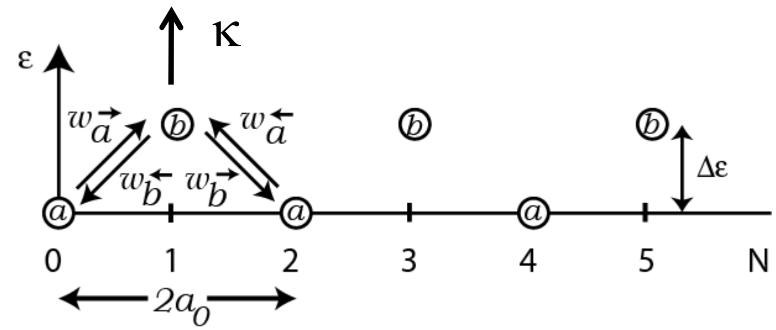
→ The GC symmetry is a macroscopic consequence of the reversibility of the microscopic dynamics of the physical model

D. L., A. Lau, K. Mallick, PRE **78**, 011915 (2008)

Modelling processivity

- With an absorbing state (*C*)

$$F(\lambda,t) = Ae^{\mu_1 t}\left|\mu_1\right\rangle + Be^{\mu_2 t}\left|\mu_2\right\rangle + C\left|c\right\rangle$$

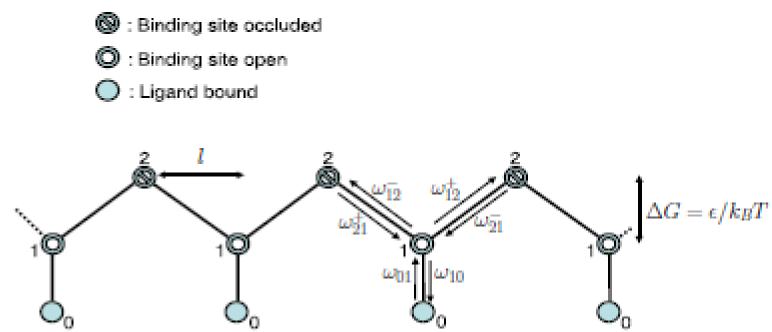


$$\left\langle n\right\rangle = -\frac{\partial C}{\partial \lambda}\bigg|_{\lambda=0} = 2\,\frac{\overrightarrow{\omega_a}\,\overrightarrow{\omega_b} - \overleftarrow{\omega_a}\,\overleftarrow{\omega_b}}{\kappa(\overrightarrow{\omega_a} + \overrightarrow{\omega_a})} = \frac{\bar{v}}{\kappa P_b}$$

run length

- With a third state (non absorbing)

Nucleosome sliding under a force :
PRE **79**, 031922 (2009)



An absorbing state breaks the time reversal symmetry and thus the *GC* symmetry

Mechano-chemical coupling

Microscopic level :

Steady state balance condition :

$$P_b^{eq}\,\overrightarrow{\omega_b}^{-l} = P_a^{eq}\, e^{\left(\theta_a^- + \theta_b^+\right) f - l\Delta\mu}$$

$$\ln\left(\frac{\overrightarrow{\omega_b}^{-l}}{\overleftarrow{\omega_a}^{-l}}\right) = \varepsilon - l\Delta\mu + \left(\theta_a^- + \theta_b^+\right) f$$

Heat exchanged

Internal energy

Mechanical work

Macroscopic level

GC symmetry

$$\Lambda(f-\lambda, \Delta\mu - \gamma) = \Lambda(\lambda, \gamma)$$

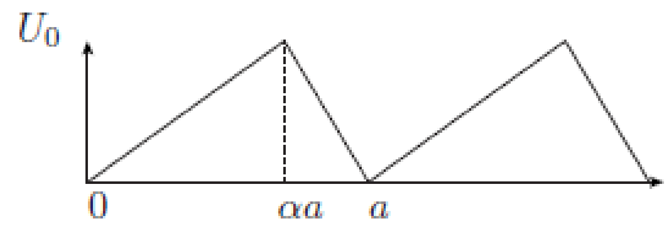
Stochastic thermodynamics : → GC symmetry

First law at the level of single trajectory

The purely mechanical ratchet

Random walker in a periodic potential U(x)

$$\frac{\partial P}{\partial t} = D_0 \frac{\partial}{\partial x}\left[\frac{\partial P}{\partial x} + \frac{U'(x) - F}{k_B T} P\right]$$



Generating function

$$F_\lambda(\xi, t) = \sum_n \exp(\lambda(\xi + n)) P((\xi + n)a, t) \quad \text{obeys} \quad \frac{\partial F_\lambda(\xi, t)}{\partial t} = L(\lambda) F_\lambda(\xi, t)$$

Conjugation property

$$e^{U(x)/k_B T} L(\lambda)\left(e^{-U(x)/k_B T}\phi\right) = L^\dagger(-f - \lambda)\phi \quad \text{with} \quad f = \frac{Fa}{k_B T}$$

Gallavotti-Cohen symmetry $\theta(\lambda) = \theta(-f - \lambda)$

J. Kurchan, J. Phys. A **31**, 3719 (1998),
J. L. Lebowitz and H. Spohn, J. Stat. Phys. **95**, 333 (1999)

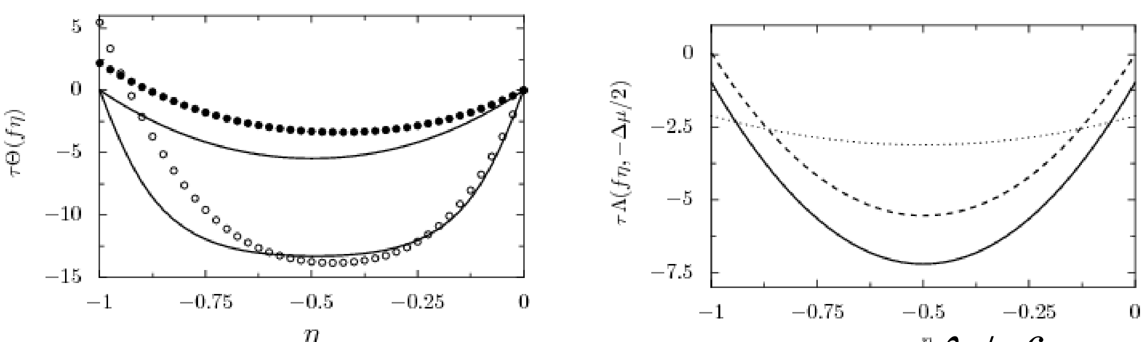
The flashing ratchet

Generating function $$F_{i,\lambda,\gamma}(\xi,t) = \sum_q e^{\gamma q} e^{\lambda(\xi+n)} P_i(a(\xi+n,q,t)$$

evolves according to $$\partial_t F_{i,\lambda,\gamma}(t) \equiv M_{ij}(\lambda,\gamma)\, F_{j,\lambda,\gamma}(t)$$

$$QM^\dagger(f-\lambda,\Delta\mu-\gamma)Q^{-1} = M(\lambda,\gamma)$$ with $$Q = \begin{pmatrix} e^{-\phi_1} & 0 \\ 0 & e^{-\phi_2} \end{pmatrix}$$

GC symmetry $\Lambda(f-\lambda,\Delta\mu-\gamma) = \Lambda(\lambda,\gamma)$ but in general $\theta(f-\lambda) \neq \theta(\lambda)$



$$\eta = \lambda / f$$

D. L. et al., PRE **80**, 021923 (2009)

Conclusion of Part I

• Dynamics of a molecular motor can be described by an effective potential $U_{eff}(x,y)$ (egg-carton like)

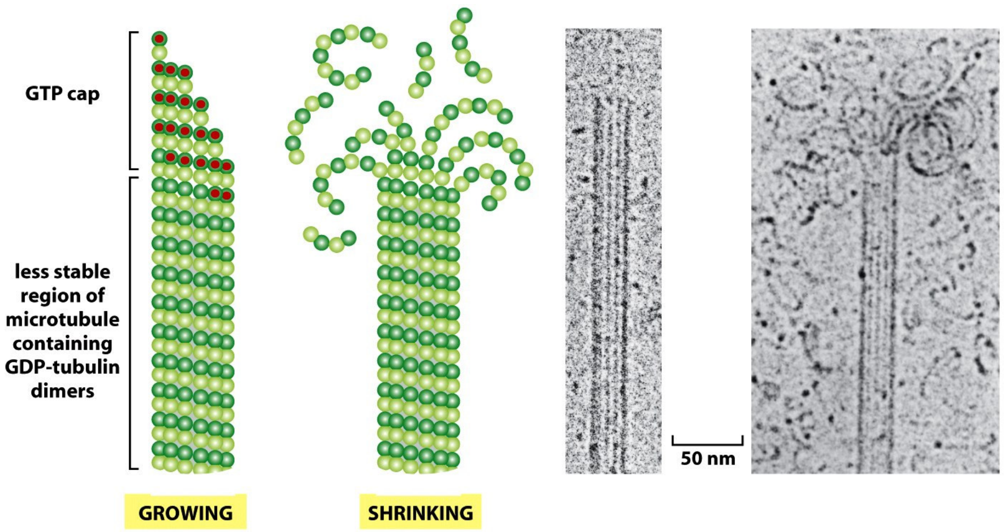
• Flashing ratchet model satisfies the *GC* symmetry provided all degrees of freedom are included.

• Fluctuations relations for molecular motors need to be tested experimentally !

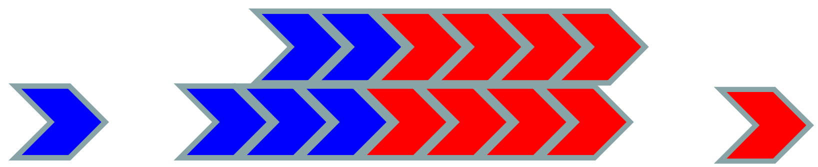
References

D. L. et al., to appear in Poincaré seminar (2010)
http://arxiv.org/abs/0912.0391

II. Non-equilibrium self-assembly of a single filament coupled to ATP/GTP hydrolysis

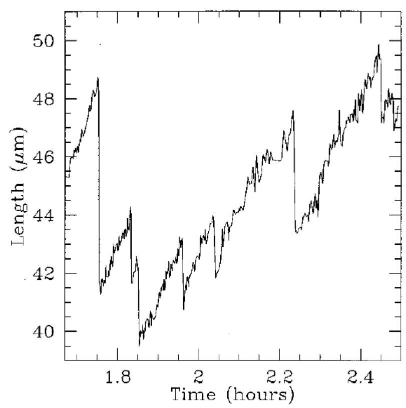


Thread-milling of actin

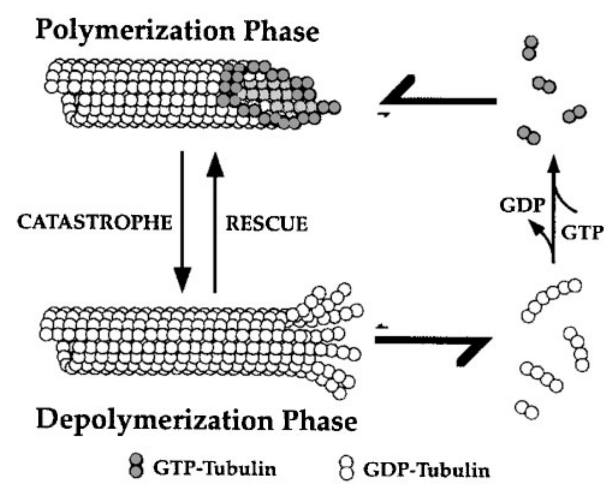


Barbed end pointed end

Dynamic instability of microtubules



D. Fygenson et al. (1994)



A. Desai et al. (1997)

A single filament of actin or microtubule coupled to ATP/GTP hydrolysis

- Protofilament structure is neglected
- Assume a reservoir of ATP-actin monomers
- Growth occurs from one end only (the barbed end for actin)
- Neglect some reaction intermediates (ex: ADP-Pi-actin)

- Vectorial model of hydrolysis

D	D	D	D	D	D	D	T	T

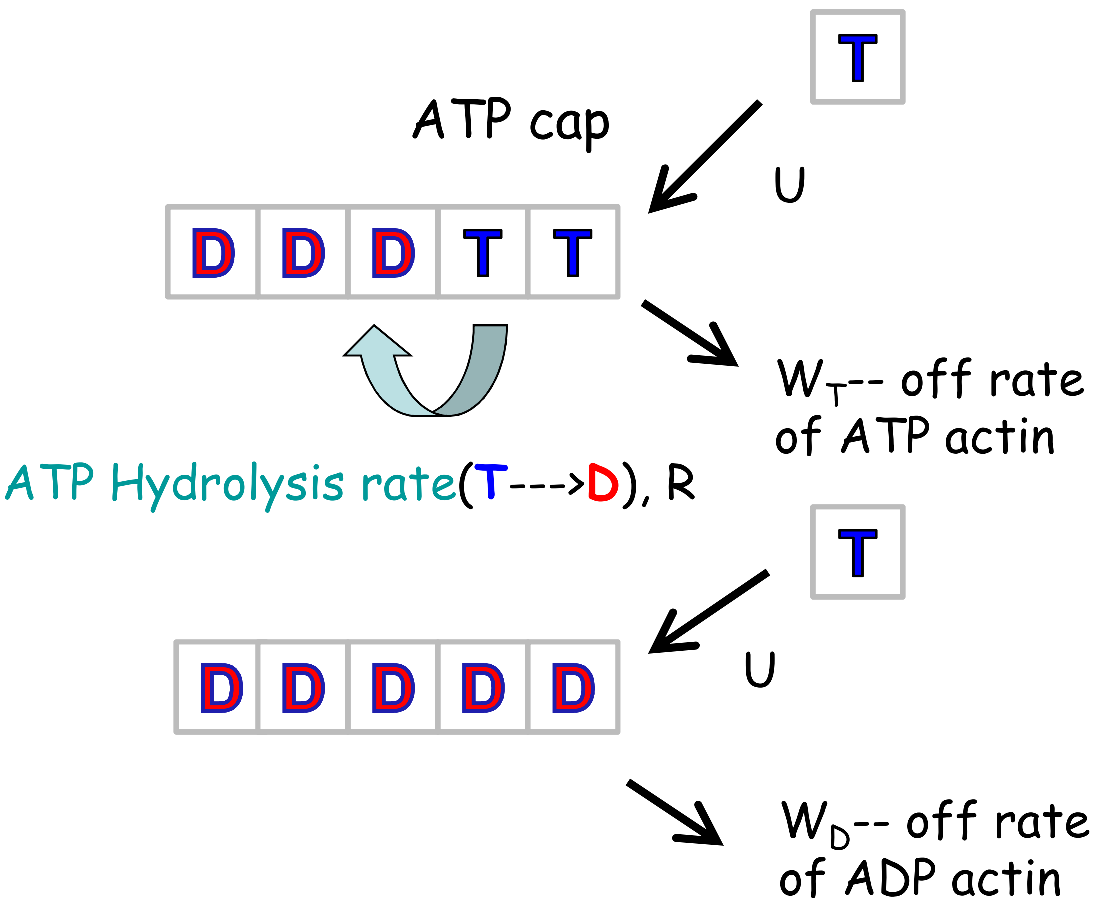
Stukalin et al. (2006)
Hill et al. (1985)

- Random model of hydrolysis

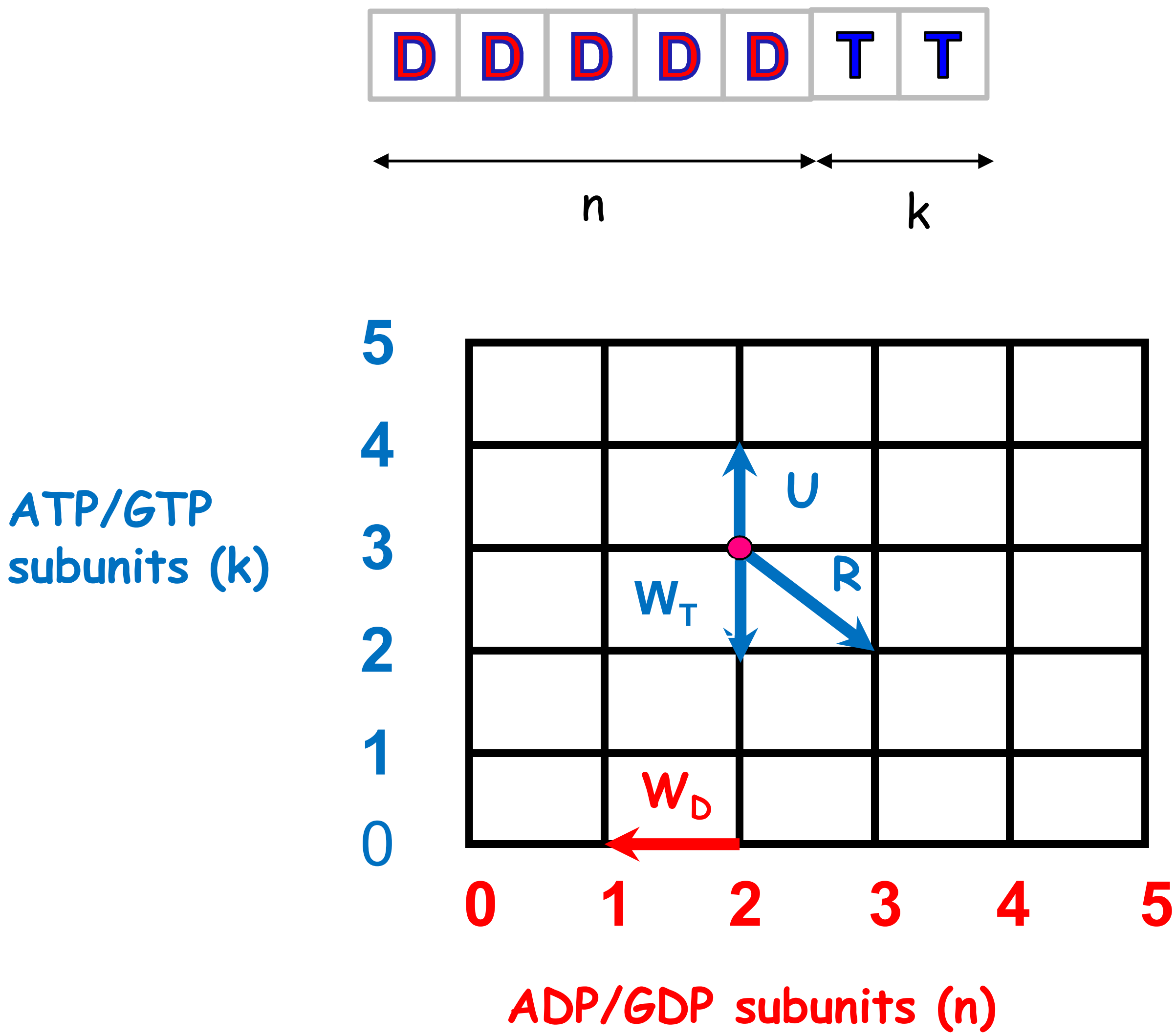
D	D	T	D	T	D	D	T	T

T. Antal et al. (2007)
H. Flyvberg et al. (1996)

A simple 4 parameters model



A 2D biaised random walk



Dynamics of the model

For k>0

$$\frac{dP(n,k)}{dt} = UP(n,k-1) + W_T P(n,k+1) + RP(n-1,k+1) - (U + W_T + R)P(n,k)$$

For k=0 and n>0

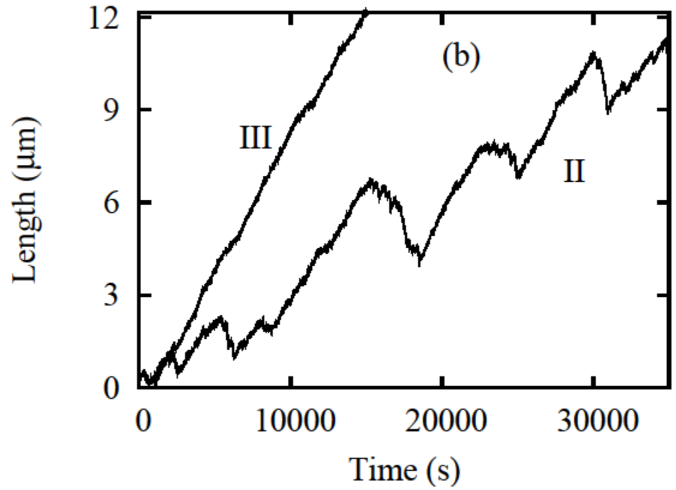
$$\frac{dP(n,0)}{dt} = W_D P(n+1,0) + W_T P(n,1) + RP(n-1,1) - (U + W_D)P(n,0)$$

For n=0 and k=0

$$\frac{dP(0,0)}{dt} = W_T P(0,1) + W_D P(1,0) - UP(0,0)$$

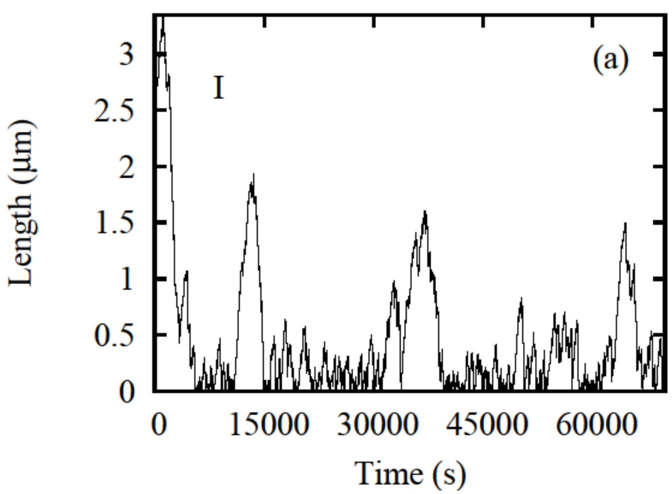
Filament $\quad v = \lim_{t\to\infty} \frac{d\langle l \rangle}{dt}, \quad D = \lim_{t\to\infty} \frac{1}{2}\frac{d}{dt}\left(\langle l^2 \rangle - \langle l \rangle^2\right), \quad l = n + k,$

Cap $\quad J = \lim_{t\to\infty} \frac{d\langle k \rangle}{dt}, \quad D_C = \lim_{t\to\infty} \frac{1}{2}\frac{d}{dt}\left(\langle k^2 \rangle - \langle k \rangle^2\right),$

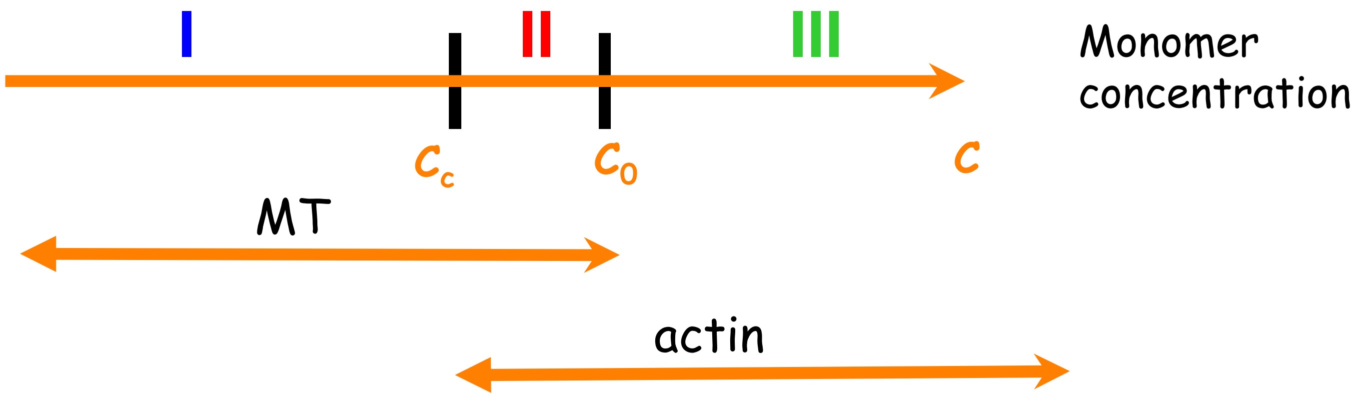


II: Phase of unbounded growth with a bounded cap

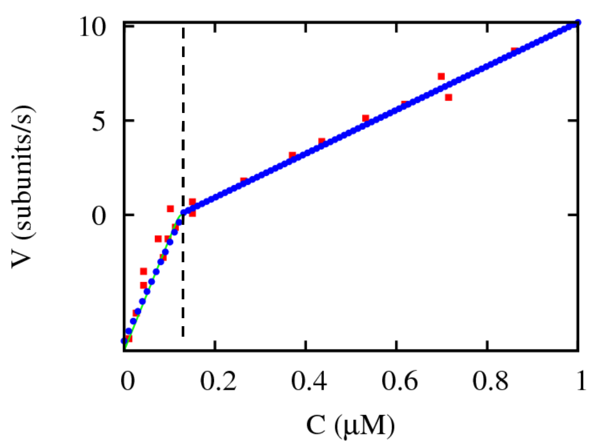
III: phase of unbounded growth with an unbounded cap



I: phase of bounded growth (both for the filament and the cap)

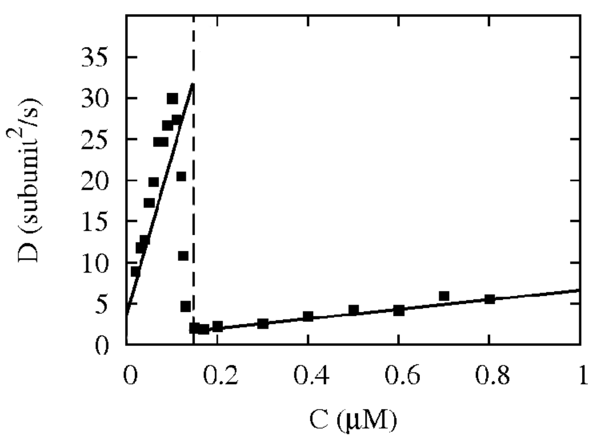


Filament velocity



MF. Carlier et al. (1986)

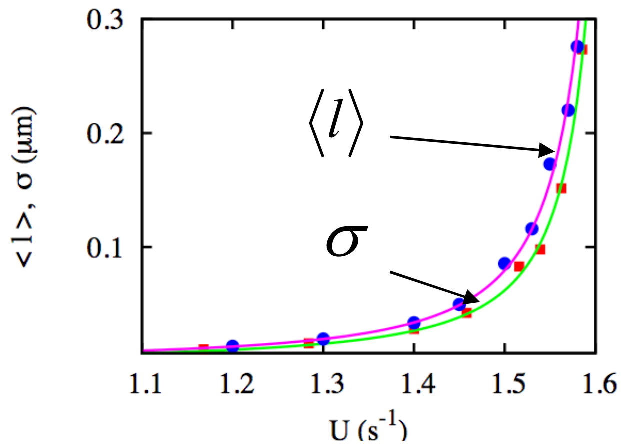
Length Fluctuations

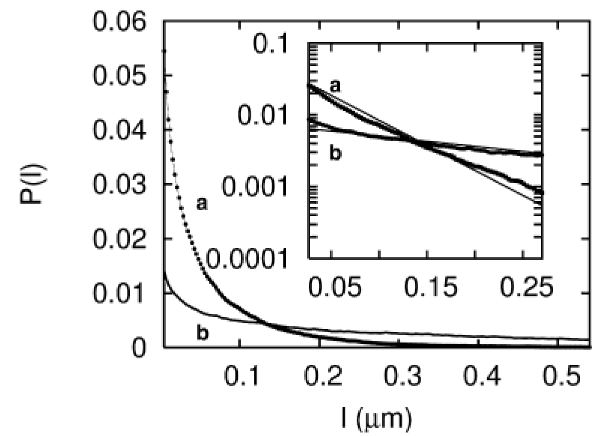


Fujiwara et al. (2002), Pollard et al. (2005)

$$D(c \simeq c_c) \simeq 30\,\text{monomers}^2\text{s}^{-1}$$

Large fluctuations of phase I : $\langle l \rangle \approx \sigma = \sqrt{\langle l^2 \rangle - \langle l \rangle^2}$





• Average length $\langle l \rangle = -\dfrac{A(R, W_T, W_D, U)}{v} d^2$ with $v < 0$

The distribution of l is known and is quasi-exponential

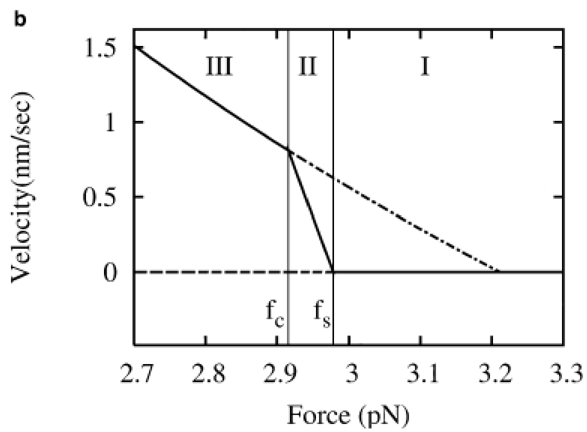
• Near transition to phase II, $\langle l \rangle = -\dfrac{D}{v} = \dfrac{Ud}{W_T - U}$ diverges.

• Phase I is stationnary : $v_I = D_I = 0$

Effect of an applied force on polymerization

$$U = k_0 C \exp\left(-\frac{fd}{k_B T} \right)$$

Reduction of stalling force due to hydrolysis

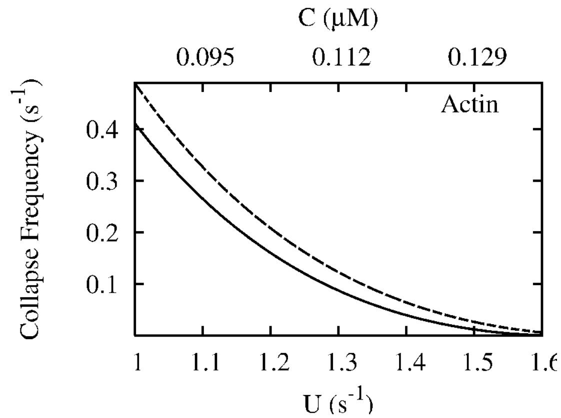


Characteristic times of dynamic instability

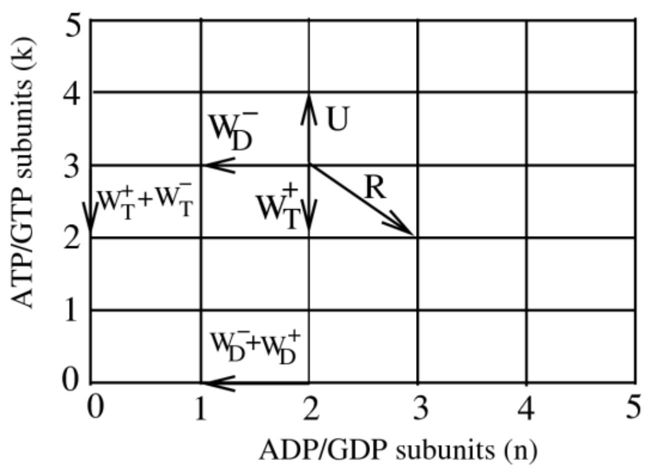
First passage time for

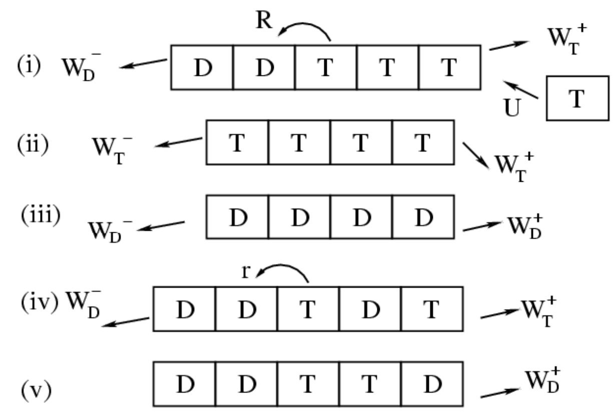
-disparition of the cap

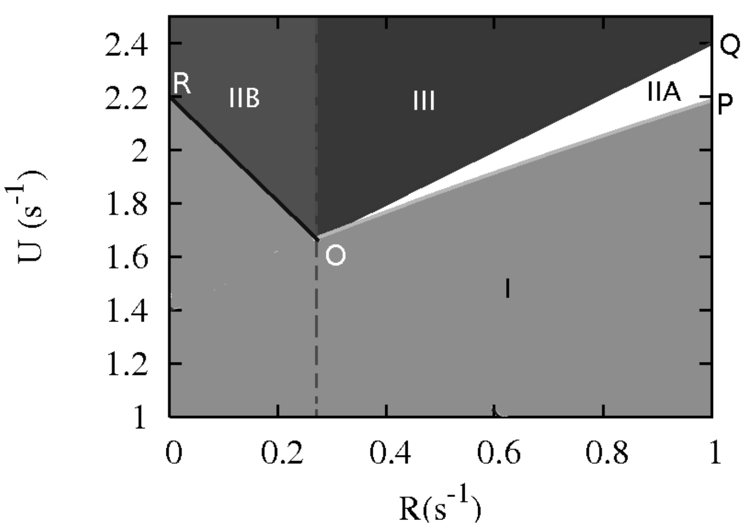
-complete depolymerization



Extension of the model to include two active ends

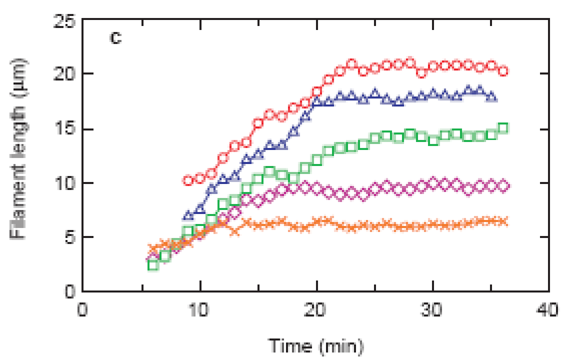




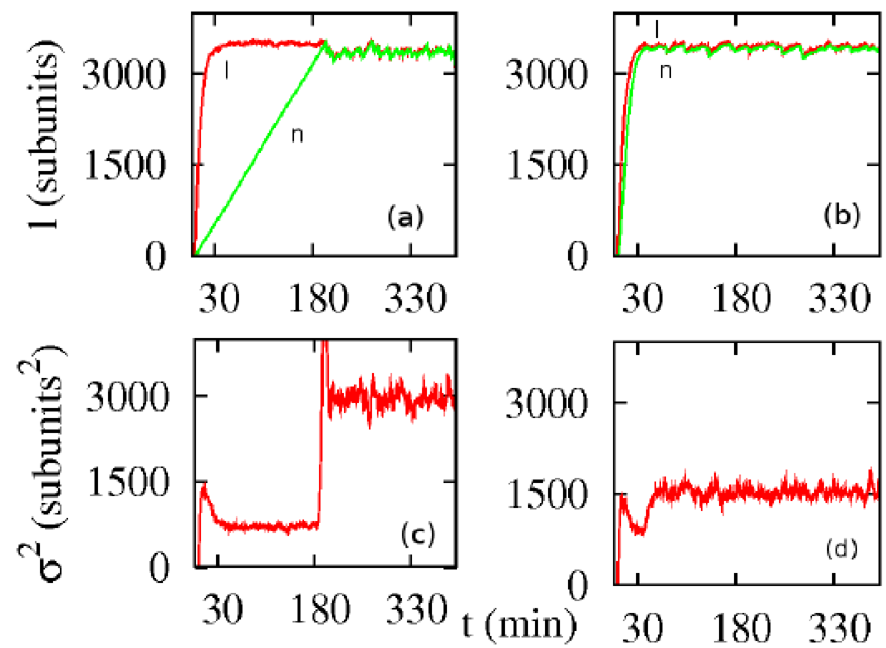


Hydrolysis rate (vectorial model)

Hydrolysis of ATP:
a vectorial or random process ?



Fujiwara et al. (2002)



vectorial

random

Conclusion of part II

- ATP/GTP hydrolysis enhances the length fluctuations of actin filaments and is responsible for the dynamic instability of microtubules.

- Steady state measurements can not distinguish the mechanism of hydrolysis but dynamic measurements can.

References

P. Ranjith et al., Biophys. J. **96,** 2146 (2009)
P. Ranjith et al., Biophys. J. in press (2010)