

OUT-OF-EQUILIBRIUM DIRECTIONALITY AND INFORMATION PROCESSING IN BIOPHYSICAL NANOSYSTEMS

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- **INTRODUCTION: OUT-OF-EQUILIBRIUM DIRECTIONALITY**
- **F₁-ATPase MOLECULAR MOTOR & FLUCTUATION THEOREM**
- **INFORMATION PROCESSING IN COPOLYMERIZATIONS**
- **CONCLUSIONS**

ICTS Program on Non-Equilibrium Statistical Physics,

Indian Institute of Technology, Kanpur

NESP2010 Plenary Lecture, 6 February 2010

FLUCTUATION THEOREM FOR THE CURRENTS

fluctuating currents: $J_\gamma = \frac{1}{t} \int_0^t j_\gamma(t') dt'$

- ex: • velocity of a molecular motor
• rate of ATP hydrolysis

De Donder affinities or thermodynamic forces: $A_\gamma = \frac{\Delta G_\gamma}{k_B T} = \frac{G_\gamma - G_\gamma^{\text{eq}}}{k_B T}$ (free energy sources)

stationary probability distribution P :

Fluctuation theorem for the currents $\{J_\gamma\}$
driven by the affinities $\{A_\gamma\}$

$$\frac{P\{+J_\gamma\}}{P\{-J_\gamma\}} \Big|_{t \rightarrow \infty} \approx \exp\left(t \sum_\gamma A_\gamma J_\gamma\right)$$

- no directionality at equilibrium $A_\gamma = 0$: the principle of detailed balancing is recovered
- directionality out of equilibrium $A_\gamma \neq 0$

thermodynamic entropy production:

$$\frac{1}{k_B} \frac{d_i S}{dt} = \sum_\gamma A_\gamma \langle J_\gamma \rangle \geq 0$$

D. Andrieux & P. Gaspard, *Fluctuation theorem and Onsager reciprocity relations*,
J. Chem. Phys. **121** (2004) 6167.

D. Andrieux & P. Gaspard, *Fluctuation theorem for currents and Schnakenberg network theory*,
J. Stat. Phys. **127** (2007) 107.

OUT-OF-EQUILIBRIUM DIRECTIONALITY

temporal disorder = decay rate h of path probabilities $P(\omega_0\omega_1\omega_2\cdots\omega_{n-1}) \underset{n \rightarrow \infty}{\approx} \exp(-n \Delta t h)$

thermodynamic entropy production = time asymmetry in temporal disorder

$$\frac{1}{k_B} \frac{d_i S}{dt} = h^R - h \geq 0$$

$$\frac{P(\omega_0\omega_1\omega_2\cdots\omega_{n-1})}{P(\omega_{n-1}\cdots\omega_2\omega_1\omega_0)} \underset{n \rightarrow \infty}{\approx} \exp[n\Delta t(h^R - h)] = \exp\left(\frac{n\Delta t}{k_B} \frac{d_i S}{dt}\right)$$

for typical paths

Theorem of temporal ordering as a corollary of the second law:

*In nonequilibrium steady states, the typical paths are more ordered **in time** relative to the corresponding time-reversed paths, in the sense that $h < h^R$.*

Nonequilibrium processes can generate dynamical order and information, which are key features of biological phenomena.

Part I.

**F_1 -ATPase MOLECULAR MOTOR
AND
FLUCTUATION THEOREM**

ROTARY AND LINEAR MOLECULAR MOTORS

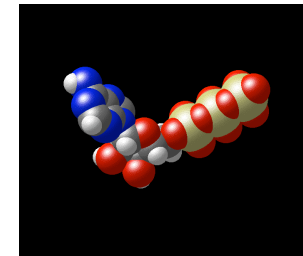
- Linear motors:
- actin-myosin II (muscles)
 - kinesin-microtubule (anterograde transport cargo)
 - dynein-microtubule (retrograde transport cargo)

- Rotary motors:
- F_1 -ATPase + actin filament or bead

Powered by chemical energy: ATP hydrolysis



ATP



difference of free energy:

$$\Delta G^0 = -30.5 \text{ kJ/mole} = -7.3 \text{ kcal/mole} = -50 \text{ pN nm} = -12.5 k_B T$$

$$\frac{[\text{ATP}]_{\text{eq}}}{[\text{ADP}]_{\text{eq}} [\text{P}_i]_{\text{eq}}} = \exp(\Delta G^0 / k_B T) \approx 4.5 \cdot 10^{-6} \text{ M}^{-1}$$

nonequilibrium thermodynamics

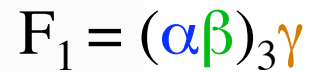
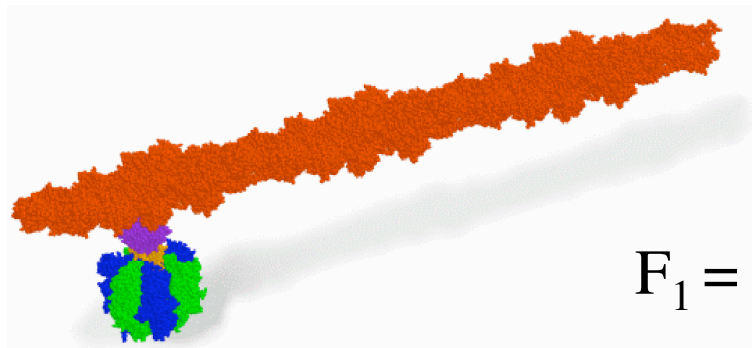
$$k_B T = 4 \text{ pN nm} = 0.026 \text{ eV} \quad (300 \text{ K})$$

*importance of the chirality of the molecular structure
for the directionality of motion under specific nonequilibrium conditions*

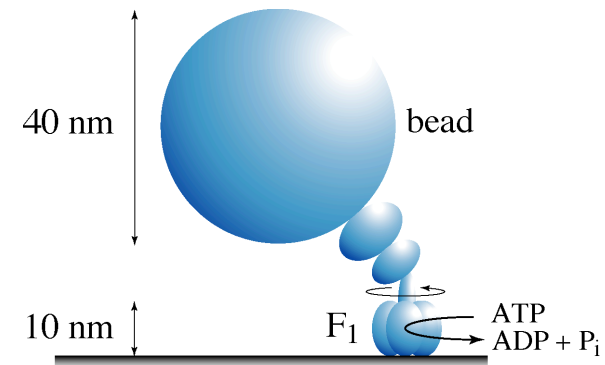
F₁-ATPase NANOMOTOR

H. Noji, R. Yasuda, M. Yoshida, & K. Kinosita Jr., Nature **386** (1997) 299

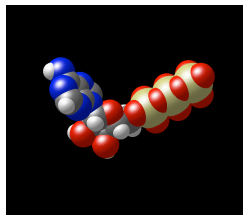
R. Yasuda, H. Noji, M. Yoshida, K. Kinosita Jr. & H. Itoh, Nature **410** (2001) 898



(Courtesy Professor K. Kinosita Jr.)



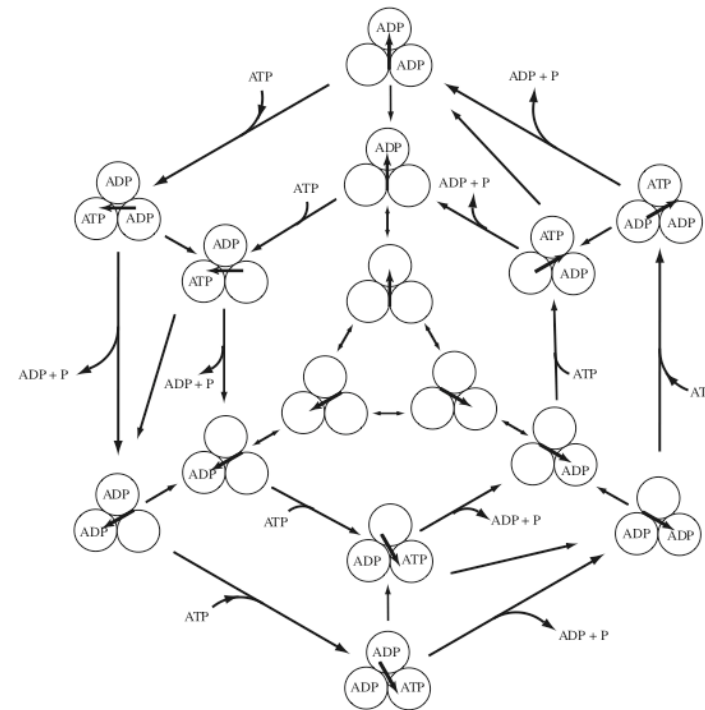
chemical fuel of F₁ : ATP



power = 10⁻¹⁸ Watt

chiral molecules

cycle:



DISCRETE-STATE STOCHASTIC PROCESSES FOR MOLECULAR MOTORS

Markovian jump process between the discrete states σ : master equation

$$\frac{d}{dt}P_{\sigma}(t) = \sum_{\rho, \sigma' (\neq \sigma)} [W_{\rho}(\sigma'|\sigma) P_{\sigma'}(t) - W_{-\rho}(\sigma|\sigma') P_{\sigma}(t)]$$

A. B. Kolomeisky & M. E. Fisher, Ann. Rev. Phys. Chem. **58** (2007) 675

R. Lipowsky & S. Liepelt, J. Stat. Phys. **130** (2008) 39

A. Garai, D. Chowdhury & M. P. Betterton, Phys. Rev. E **77** (2008) 061910

Fluctuation theorems:

U. Seifert, EPL **70** (2005) 36 (rotary motor, 3 states)

D. Andrieux & P. Gaspard, Phys. Rev. E **74** (2006) 011906 (rotary motor, F₁-ATPase, 6 states)

D. Lacoste, A. W. C. Lau & K. Mallick, Phys. Rev. E **78** (2008) 011915 (linear motor)

CONTINUOUS STOCHASTIC PROCESSES

F. Jülicher, A. Adjari & J. Prost, Rev. Mod. Phys. **69** (1997) 1269

H. Wang & G. Oster, Nature **396** (1998) 279

↓

$$1 = \{\emptyset, x, \text{ADP}\}$$

↓

$$2 = \{\text{ATP}, x, \text{ADP}\}$$

↓

$$3 = \{\text{ADP}, \emptyset, x\}$$

↓

$$4 = \{\text{ADP}, \text{ATP}, x\}$$

↓

$$5 = \{x, \text{ADP}, \emptyset\}$$

↓

$$6 = \{x, \text{ADP}, \text{ATP}\}$$

↓

$$(x = \emptyset \text{ or } \text{ADP})$$

coupled Fokker-Planck equations for the probability densities:

$$\partial_t p_1 + \partial_\theta J_1 = w_{+2}(\theta) p_6 + w_{-1}(\theta) p_2 - [w_{+1}(\theta) + w_{-2}(\theta)] p_1$$

$$\partial_t p_2 + \partial_\theta J_2 = w_{+1}(\theta) p_1 + w_{-2}(\theta - \frac{2\pi}{3}) p_3 - [w_{+2}(\theta - \frac{2\pi}{3}) + w_{-1}(\theta)] p_2$$

...

Mechanical part: probability currents: diffusion coefficient:

$$J_i = -D \partial_\theta p_i + \frac{1}{\xi} \left(-\frac{\partial U_i}{\partial \theta} + \tau_{\text{load}} \right) p_i \quad D = \frac{k_B T}{\xi} \longleftarrow \text{friction coefficient}$$

Chemical part:

transition rates of the reactions

Arrhenius' law of chemical kinetics

$$w_{+1}(\theta) = k_1^0 e^{-\beta[U_1^*(\theta) - U_1(\theta) - G_{\text{ATP}}^0]} [\text{ATP}]$$

$$w_{-1}(\theta) = k_1^0 e^{-\beta[U_1^*(\theta) - U_2(\theta)]}$$

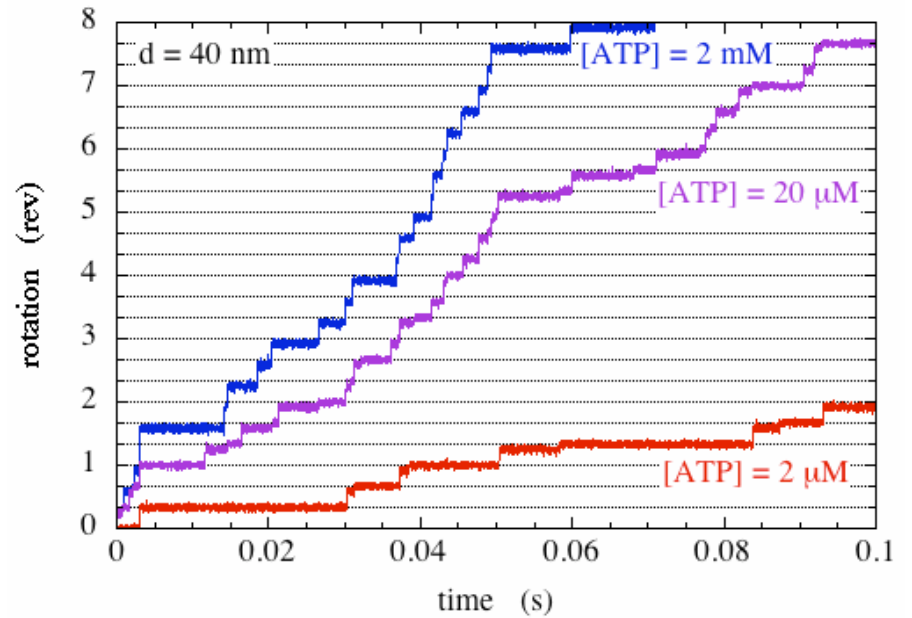
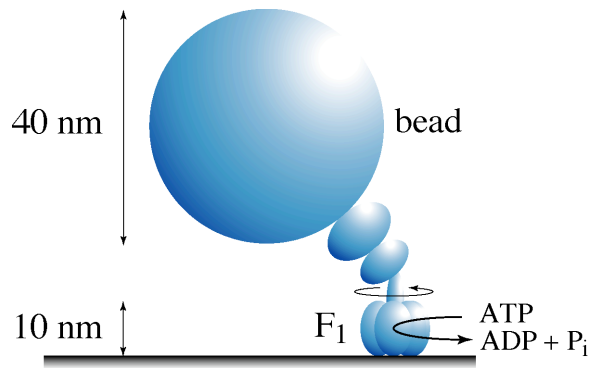
$$w_{+2}(\theta) = k_2^0 e^{-\beta[U_2^*(\theta) - U_2(\theta + 2\pi/3)]}$$

$$w_{-2}(\theta) = k_2^0 e^{-\beta[U_2^*(\theta) - U_1(\theta) - G_{\text{ADP}}^0 - G_{\text{P}_i}^0]} [\text{ADP}] [\text{P}_i]$$

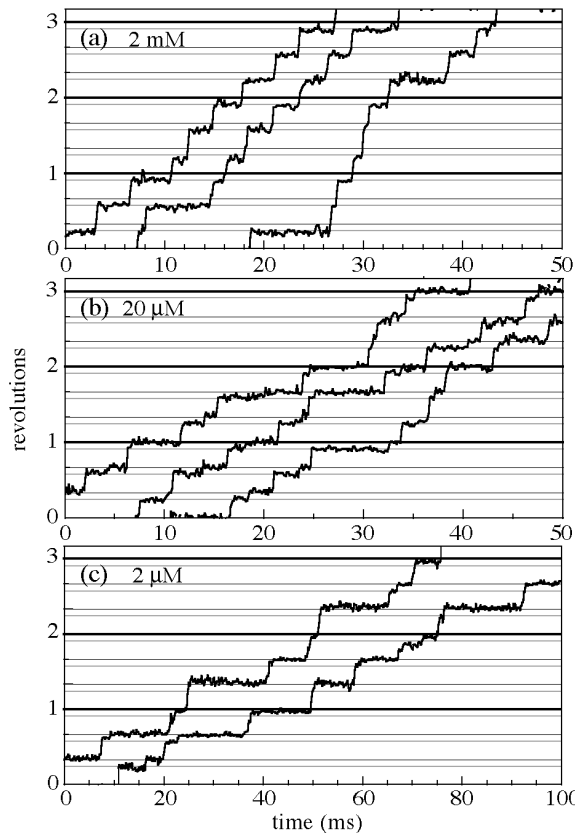
potentials for the wells: $U_i(\theta)$

potentials for the transition states: $U_i^*(\theta)$

RANDOM TRAJECTORIES OF THE F₁-ATPase MOTOR

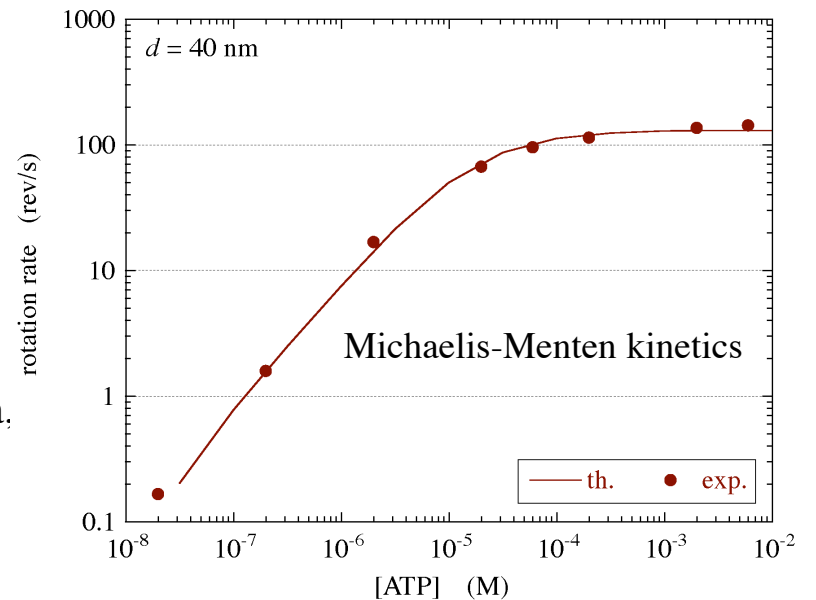


Random trajectories simulated by a model:
P. Gaspard & E. Gerritsma, *J. Theor. Biol.* **247** (2007) 672



Random trajectories
observed in experiments

R. Yasuda, H. Noji, M. Yoshida,
K. Kinosita Jr. & H. Itoh,
Nature **410** (2001) 898



EFFICIENCIES OF F₁-ATPase

F₁-ATPase under an external torque (e.g. from F₀)

number of ATP **synthesized**
or **consumed** per revolution:

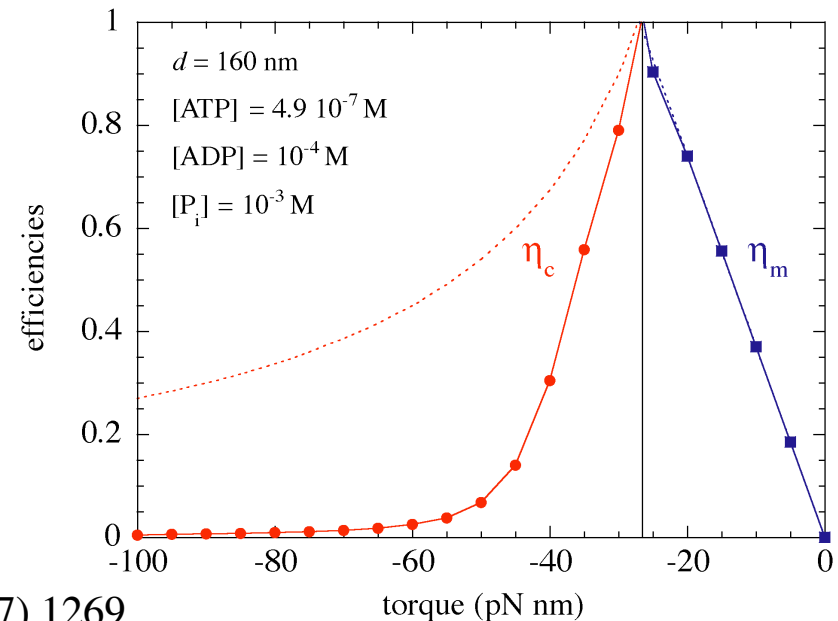
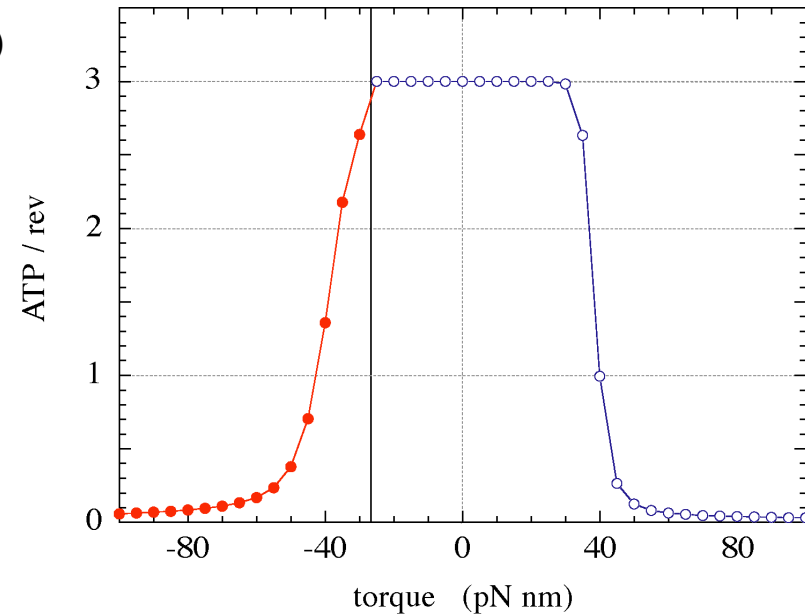
tight chemomechanical coupling for $|\tau| < 27$ pN nm

chemical efficiency in ATP synthesis:

$$\eta_c = -\frac{\Delta\mu R}{2\pi\tau V}$$

mechanical efficiency in energy transduction:

$$\eta_m = -\frac{2\pi\tau V}{\Delta\mu R}$$



TIGHT/LOOSE CHEMOMECHANICAL COUPLING

tight coupling condition:

$$R = 3V$$

entropy production:

$$\frac{1}{k_B} \frac{d_i S}{dt} = \frac{2\pi\tau}{k_B T} V + \frac{\Delta\mu}{k_B T} R = AR \geq 0$$

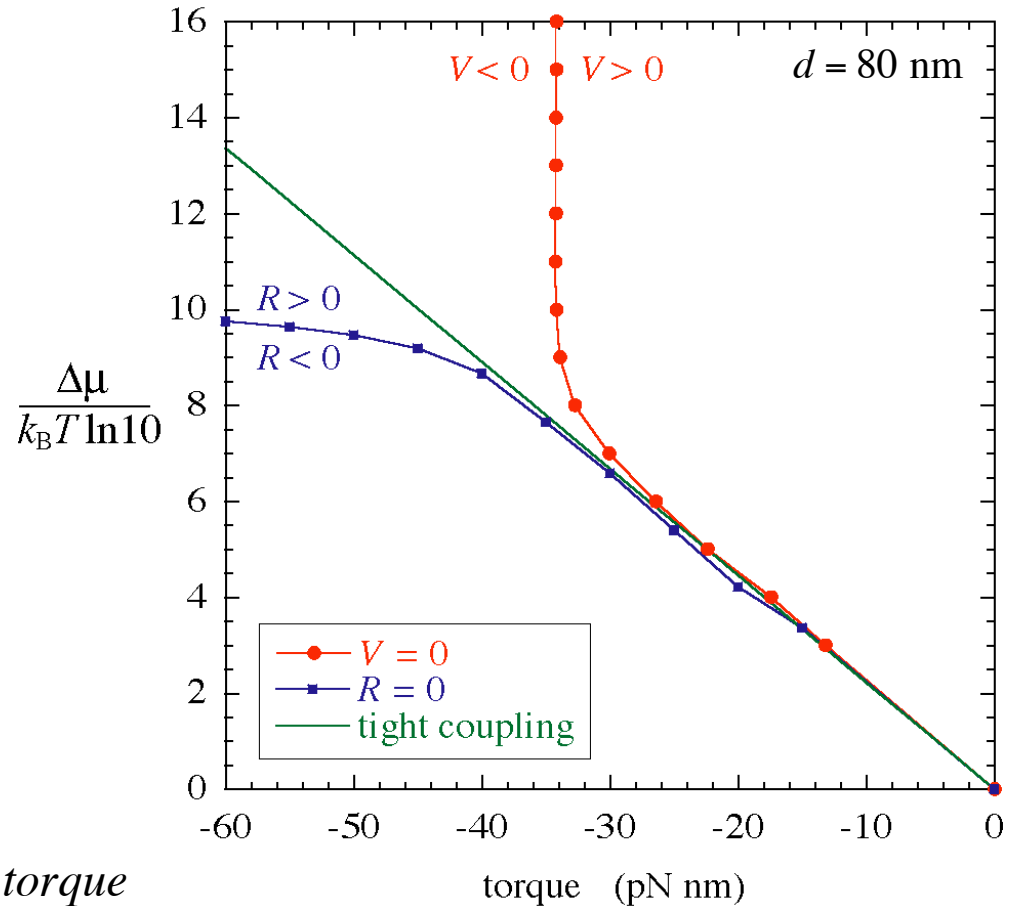
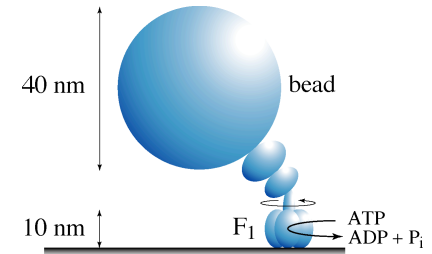
chemomechanical affinity:

$$A \equiv \frac{2\pi\tau}{3k_B T} + \frac{\Delta\mu}{k_B T}$$

$$A = \frac{2\pi\tau}{3k_B T} + \ln \frac{[\text{ATP}]}{K_{\text{eq}} [\text{ADP}][\text{P}_i]}$$

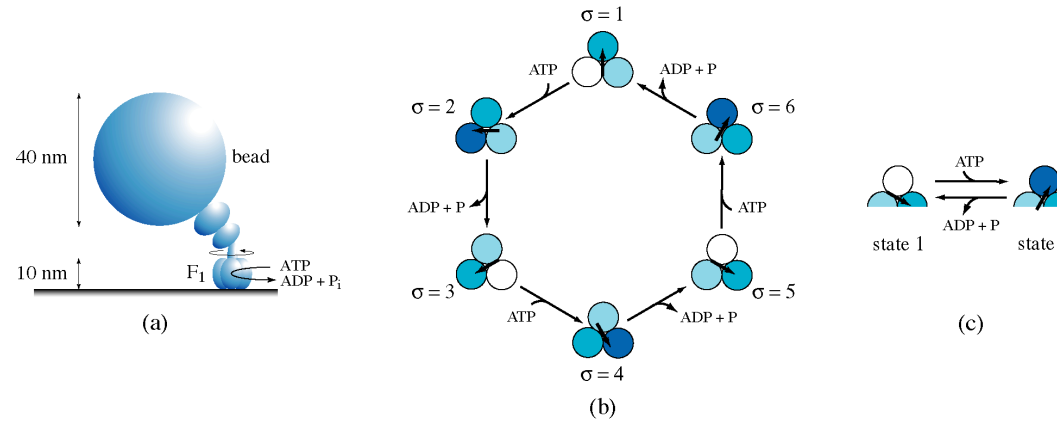
shift of effective equilibrium by the external torque

E. Gerritsma & P. Gaspard, arXiv:0904.4218



$$[\text{ATP}] = 4.9 \cdot 10^{-11} e^{0.8 \frac{\Delta\mu}{k_B T}} \quad [\text{ADP}][\text{P}_i] = 10^{-5} e^{-0.2 \frac{\Delta\mu}{k_B T}}$$

DISCRETE-STATE MODEL FOR THE F₁-ATPase MOTOR



The angle jump at each reactive event: the tight coupling condition is always fulfilled.

Markovian jump process between the discrete states σ :

$$\frac{d}{dt} P_{\sigma}(t) = \sum_{\rho, \sigma' (\neq \sigma)} [W_{\rho}(\sigma' | \sigma) P_{\sigma'}(t) - W_{-\rho}(\sigma | \sigma') P_{\sigma}(t)]$$

transition rates:

$$\text{ATP binding } +90^{\circ}: W_{+1} = k_{+1}[\text{ATP}]$$

$$\text{ATP unbinding } -90^{\circ}: W_{-1} = k_{-1}$$

$$\text{ADP - P}_i \text{ release } +30^{\circ}: W_{+2} = k_{+2}$$

$$\text{ADP - P}_i \text{ binding } -30^{\circ}: W_{-2} = k_{-2}[\text{ADP}][\text{P}_i]$$

dependence on friction ζ and torque τ :

$$k_{\rho}(\zeta, \tau) = \frac{1}{e^{a_{\rho}(\tau)} + e^{b_{\rho}(\tau)} \zeta}$$

$$a_{\rho}(\tau) = a_{\rho}^{(0)} + a_{\rho}^{(1)} \tau + a_{\rho}^{(2)} \tau^2 + O(\tau^3)$$

$$b_{\rho}(\tau) = b_{\rho}^{(0)} + b_{\rho}^{(1)} \tau + b_{\rho}^{(2)} \tau^2 + O(\tau^3)$$

F₁-ATPase ROTATION RATE VERSUS AFFINITY

dimensionless affinity or thermodynamic force:

$$\tau = 0$$

$$A \equiv \frac{\Delta\mu}{k_B T} = \ln \frac{[\text{ATP}]}{K_{\text{eq}} [\text{ADP}][\text{P}_i]}$$

mean rotation rate:

highly nonlinear dependence on A

$$V = L \frac{e^A - 1}{1 + \frac{L}{V_{\text{max}}} (e^A - 1)}$$

$$[\text{ADP}][\text{P}_i] = 10^{-7}$$

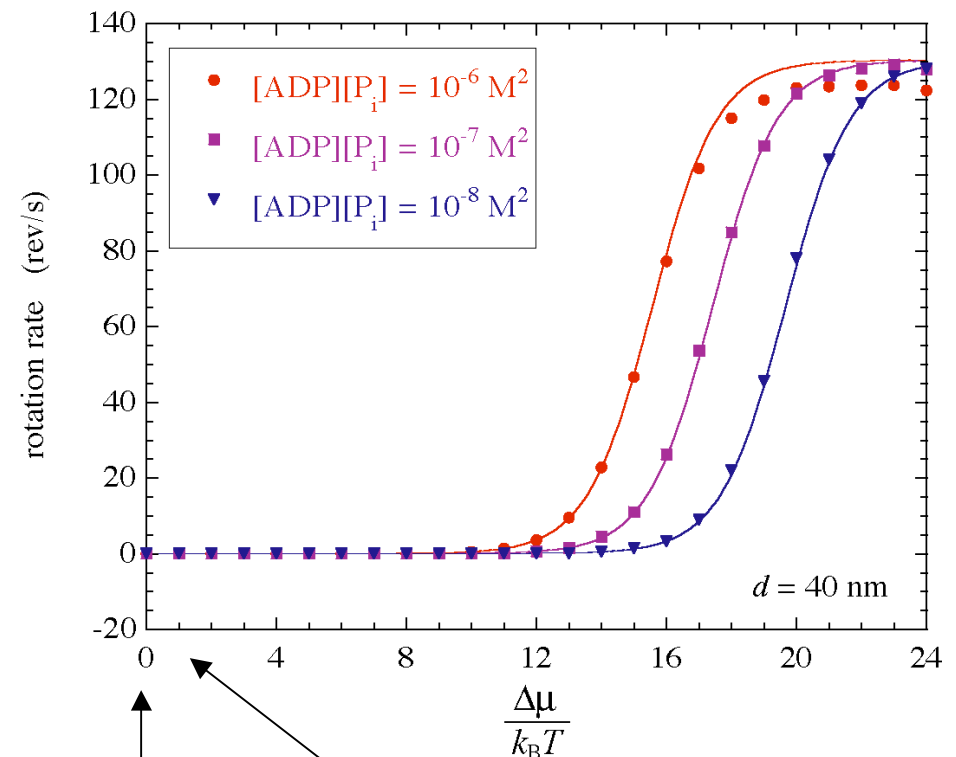
linear regime around equilibrium:

$$A \approx 0: \quad V \approx LA \quad \text{with} \quad L \approx 3.7 \cdot 10^{-6} \text{ rev/s}$$

nonlinear regime far from equilibrium:

$$A \geq 22: \quad V \approx V_{\text{max}} = 130 \text{ rev/s}$$

The F₁ molecular motor typically works in a highly nonlinear regime far from equilibrium.



equilibrium:

$$A = \frac{\Delta\mu}{k_B T} = 0$$

A = 1: 3.1 days/rev !

FULL COUNTING STATISTICS & FLUCTUATION THEOREM

discrete-state model:

generating function of the statistical cumulants of the number N_t of reactive events during the time t :

$$Q(\lambda) \equiv \lim_{t \rightarrow \infty} -\frac{1}{t} \ln \langle \exp(-\lambda N_t) \rangle$$

$$Q(\lambda) = \frac{1}{2}(W_{+1} + W_{+2} + W_{-1} + W_{-2}) - \sqrt{\frac{1}{4}(W_{+1} + W_{+2} + W_{-1} + W_{-2})^2 + W_{+1}W_{+2}(e^{-\lambda} - 1) + W_{-1}W_{-2}(e^{\lambda} - 1)}$$

1st cumulant: mean rate

$$R = \left. \frac{\partial Q}{\partial \lambda} \right|_{\lambda=0} = \lim_{t \rightarrow \infty} \frac{\langle N_t \rangle}{t} = \frac{W_{+1}W_{+2} - W_{-1}W_{-2}}{W_{+1} + W_{+2} + W_{-1} + W_{-2}} = 3V$$

2nd cumulant: diffusivity

$$D = -\left. \frac{1}{2} \frac{\partial^2 Q}{\partial \lambda^2} \right|_{\lambda=0}$$

A. B. Kolomeisky & M. E. Fisher,
Ann. Rev. Phys. Chem. **58** (2007) 675

fluctuation theorem:

$$Q(\lambda) = Q(A - \lambda)$$

chemomechanical affinity:

$$A = \frac{2\pi\tau}{3k_B T} + \ln \frac{[\text{ATP}]}{K_{\text{eq}} [\text{ADP}][\text{P}_i]}$$

D. Andrieux & P. Gaspard, Phys. Rev. E **74** (2006) 011906

E. Gerritsma & P. Gaspard, *unpublished*

FLUCTUATION THEOREM FOR THE F₁-ATPase MOTOR: NO EXTERNAL TORQUE

affinity or thermodynamic force: $A = \ln \frac{k_{+1}k_{+2}[ATP]}{k_{-1}k_{-2}[ADP][P_i]} = \frac{\Delta\mu}{k_B T} \quad \tau = 0$

Fluctuation theorem for the number S_t of substeps:

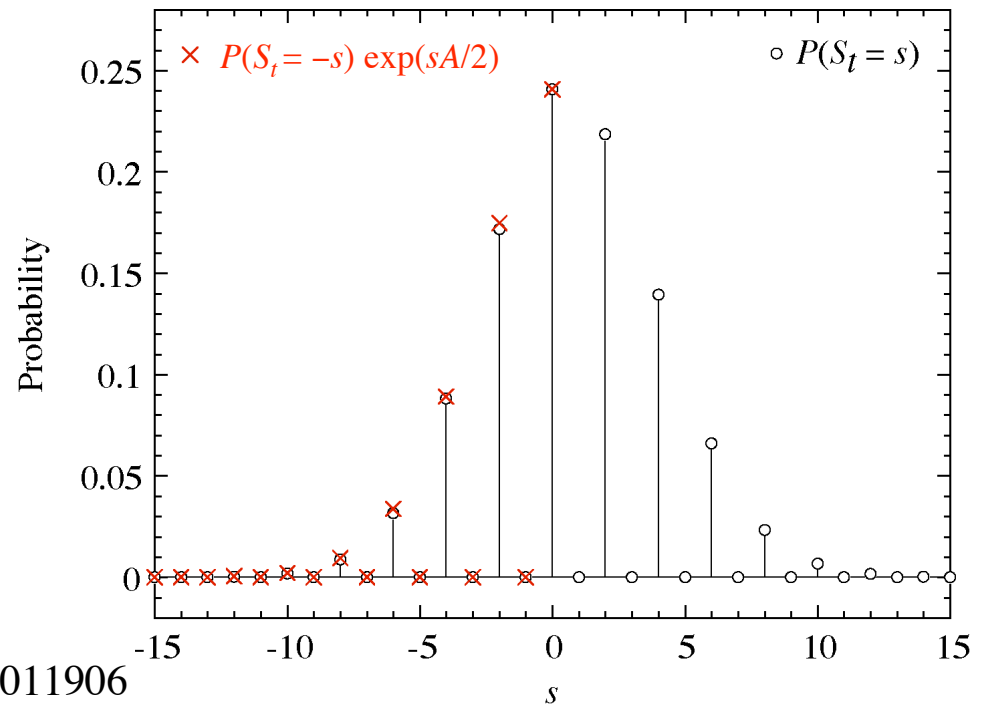
$$\frac{P(S_t = s)}{P(S_t = -s)} = \exp\left(s \frac{A}{2}\right) = \exp\left(s \frac{\Delta\mu}{2k_B T}\right)$$

$[ATP] = 6 \cdot 10^{-8} \quad [ADP][P_i] = 10^{-2}$

$d = 40 \text{ nm}$

very long time interval:

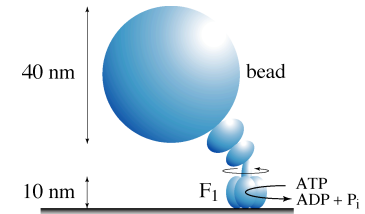
$t = 10^4 \text{ s}$



FLUCTUATION THEOREM FOR THE F₁-ATPase MOTOR: WITH EXTERNAL TORQUE

chemomechanical affinity:

$$A = \frac{2\pi\tau}{3k_B T} + \ln \frac{[\text{ATP}]}{K_{\text{eq}}[\text{ADP}][\text{P}_i]}$$



Fluctuation theorem for the number S_t of substeps:

$$\frac{P(S_t = s)}{P(S_t = -s)} = \exp\left(s \frac{A}{2}\right) = \exp\left(s \frac{\Delta\mu}{2k_B T}\right)$$

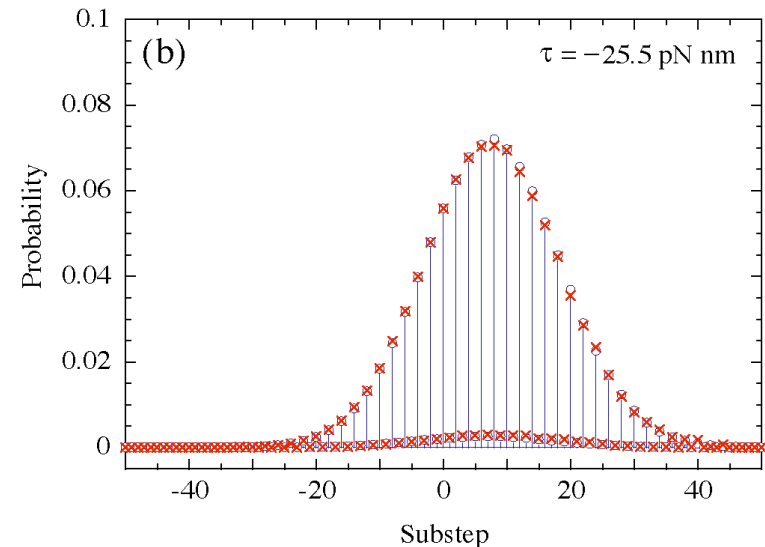
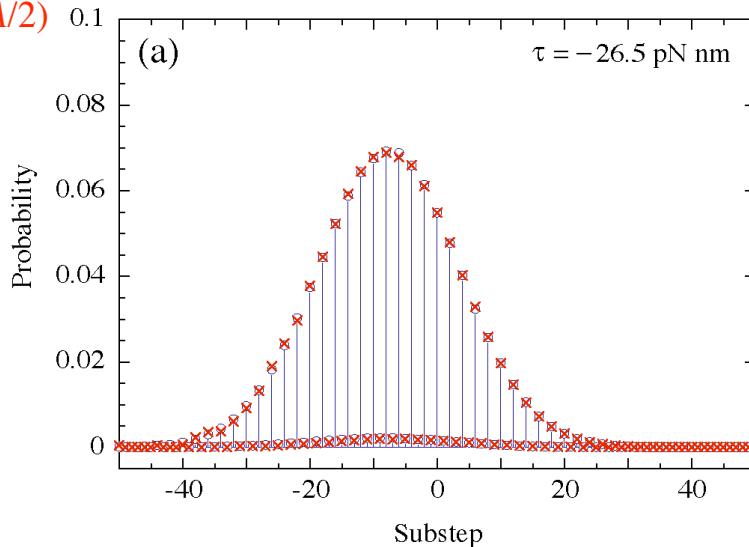
shorter time interval: $t = 10$ s

$$[\text{ATP}] = 3 \cdot 10^{-6} \quad [\text{ADP}][\text{P}_i] = 10^{-6}$$

$$\tau_{\text{stall}} = -26.0 \text{ pN nm}$$

$$d = 80 \text{ nm}$$

x $P(S_t = -s) \exp(sA/2)$
o $P(S_t = s)$



E. Gerritsma & P. Gaspard, *unpublished*

FLUCTUATION THEOREM & TIGHT CHEMOMECHANICAL COUPLING

Loose coupling: independent mechanical & chemical fluctuating currents

$$\frac{P(J_m, J_c)}{P(-J_m, -J_c)} \underset{t \rightarrow \infty}{\approx} \exp[t(A_m J_m + A_c J_c)]$$

D. Andrieux & P. Gaspard, J. Chem. Phys. **121** (2004) 6167

D. Andrieux & P. Gaspard, Phys. Rev. E **74** (2006) 011906

D. Lacoste *et al.*, Phys. Rev. E **80** (2009) 021923

E. Gerritsma & P. Gaspard, *unpublished*

Tight coupling:

$$J_m = J_c \equiv J$$

chemomechanical affinity: $A \equiv A_m + A_c$

$$\frac{\tilde{P}(J)}{\tilde{P}(-J)} \underset{t \rightarrow \infty}{\approx} \exp(t A J)$$

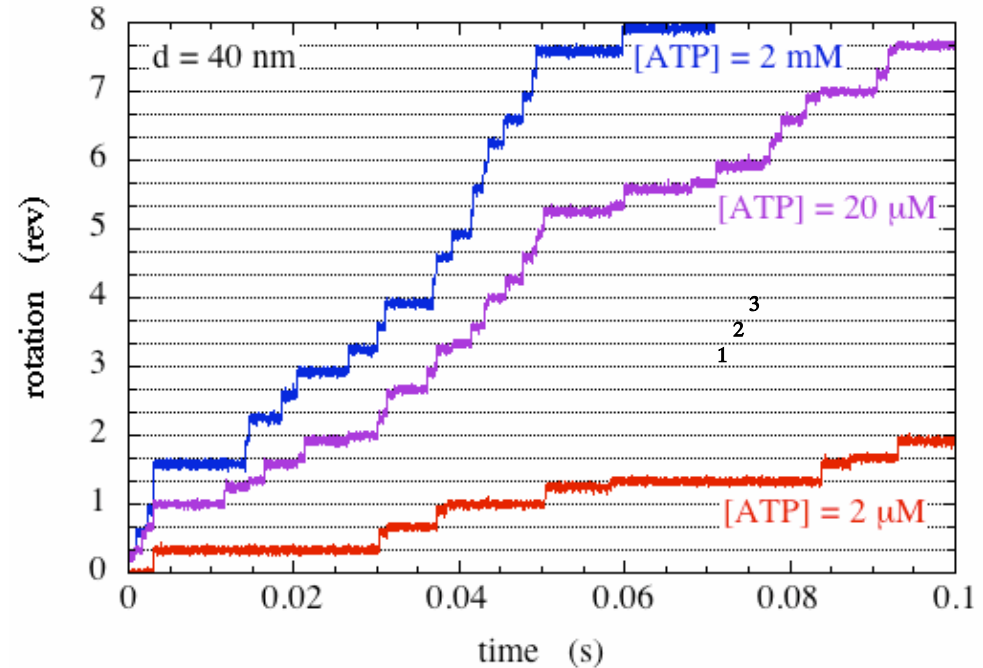
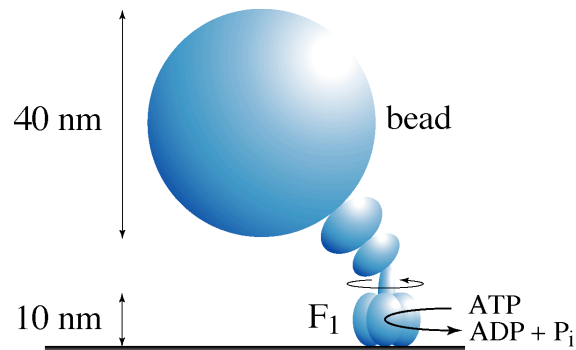
$$\tilde{P}(J) \equiv P(J, J) = P(J_m, J_c)$$

U. Seifert, EPL **70** (2005) 36 (rotary motor, 3 states)

D. Andrieux & P. Gaspard, Phys. Rev. E **74** (2006) 011906 (rotary motor, F₁-ATPase, 6 states)

D. Lacoste, A. W. C. Lau & K. Mallick, Phys. Rev. E **78** (2008) 011915 (linear motors)

OUT-OF-EQUILIBRIUM DIRECTIONALITY IN THE F_1 -ATPase NANOMOTOR



at equilibrium:
...212132131223132...
(random)

out of equilibrium:
...123123123123123...
(more regular)

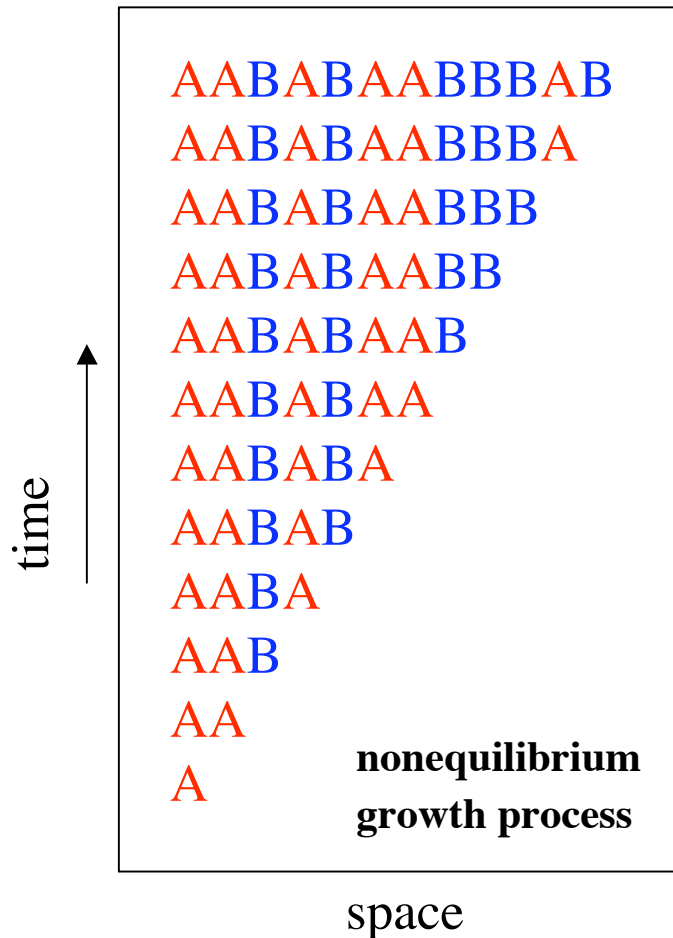
*detailed balance between
forward and backward rotations,
zero currents*

*directionality of motion:
non-zero currents,
dynamical order*

Part II.

**INFORMATION PROCESSING
IN
COPOLYMERIZATIONS**

NONEQUILIBRIUM PROCESS WITH RECORDING THE INFORMATION ON A SPATIAL SUPPORT



spatial support of information

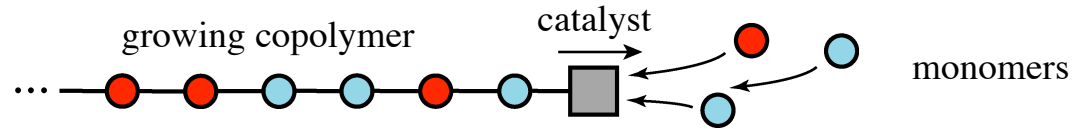
= random copolymer (covalent bonds)

= aperiodic crystal by E. Schrödinger, *What if Life?* (1944)

At equilibrium, detailed balance would prevent
the ordering of temporal fluctuations.

Out of equilibrium, the temporal ordering in the presence
of a spatial support of information may lead to
information generation or processing

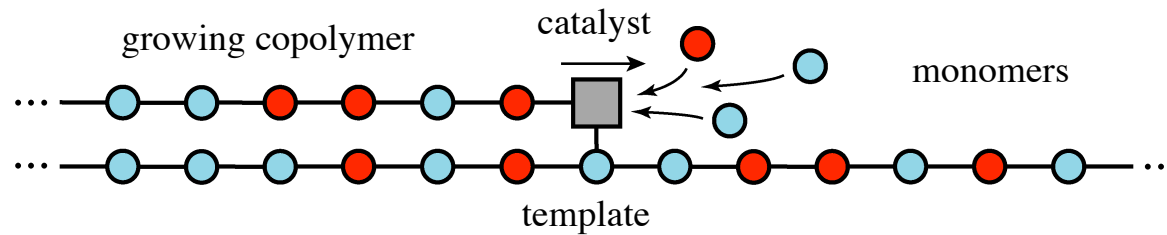
COPOLYMERIZATION PROCESSES



free copolymerization: random copolymers

ex: styrene-butadiene rubber

atactic polypropylene



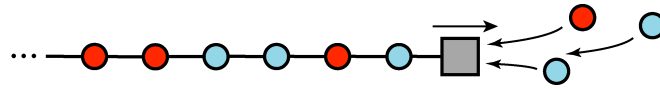
copolymerization with a template:

ex: DNA replication

DNA-mRNA transcription

mRNA-protein translation

STATISTICAL THERMODYNAMICS OF FREE COPOLYMERIZATION



Stochastic growth of a single copolymer

$$\omega = m_1 m_2 m_3 \dots m_l \rightleftharpoons \omega' = m_1 m_2 m_3 \dots m_l m_{l+1}$$

master equation for the probability $P_t(\omega)$ to find the copolymer ω of length $l = |\omega|$ at the time t :

$$\frac{d}{dt} P_t(\omega) = \sum_{\omega'} [P_t(\omega') W(\omega'|\omega) - P_t(\omega) W(\omega|\omega')]$$

$W(\omega|\omega')$ rate of the transition $\omega \rightarrow \omega'$

$$\frac{W(\omega|\omega')}{W(\omega'|\omega)} = \exp \frac{G(\omega) - G(\omega')}{k_B T}$$

Gibbs free energy or free enthalpy of the single copolymer ω : $G(\omega)$

enthalpy of the copolymer ω in its environment: $H(\omega)$

$$G(\omega) = H(\omega) - T S(\omega)$$

entropy of the copolymer ω in its environment: $S(\omega)$

total entropy:

$$S_t \equiv \sum_{\omega} P_t(\omega) S(\omega) - k_B \sum_{\omega} P_t(\omega) \ln P_t(\omega)$$

THE REGIME OF STEADY GROWTH

B. D. Coleman and T. G. Fox, J. Polym. Sci. A 1 (1963) 3183

The growth proceeds in a regime described by a stationary statistical distribution $\mu_l(\omega)$:

$$P_t(\omega) = p_t(l) \mu_l(\omega) \quad \text{with the statistical distribution of lengths } p_t(l)$$

constant mean growth velocity: $v \equiv \frac{d\langle l \rangle_t}{dt} = \frac{d}{dt} \sum_l p_t(l) \times l \quad k_B = 1$

total entropy:
$$\begin{aligned} S_t &= \sum_{\omega} P_t(\omega) S(\omega) - \sum_{\omega} P_t(\omega) \ln P_t(\omega) \\ &= \sum_{l,\omega} p_t(l) \mu_l(\omega) S(\omega) - \sum_{l,\omega} p_t(l) \mu_l(\omega) \ln \mu_l(\omega) - \sum_l p_t(l) \ln p_t(l) \\ &\approx \langle l \rangle_t \times s + \langle l \rangle_t \times D(\text{polymer}) \end{aligned}$$

mean entropy per monomer: $s \equiv \lim_{l \rightarrow \infty} \frac{1}{l} \sum_{\omega} \mu_l(\omega) S(\omega)$

spatial disorder: Shannon disorder per monomer: $D(\text{polymer}) \equiv \lim_{l \rightarrow \infty} -\frac{1}{l} \sum_{\omega} \mu_l(\omega) \ln \mu_l(\omega)$

time derivative of entropy: $\frac{dS}{dt} = v[s + D(\text{polymer})]$

THERMODYNAMIC ENTROPY PRODUCTION OF FREE COPOLYMERIZATION

time derivative of entropy: $\frac{dS}{dt} = \nu [s + D(\text{polymer})] = \frac{d_e S}{dt} + \frac{d_i S}{dt}$

entropy exchange: $\frac{d_e S}{dt} = \nu \frac{h}{T}$

mean enthalpy per monomer: $h \equiv \lim_{l \rightarrow \infty} \frac{1}{l} \sum_{\omega} \mu_l(\omega) H(\omega)$

mean Gibbs free energy or free enthalpy per monomer: $g \equiv \lim_{l \rightarrow \infty} \frac{1}{l} \sum_{\omega} \mu_l(\omega) G(\omega) = h - T s$

entropy production: $\frac{d_i S}{dt} = \nu A \geq 0$

affinity per monomer:

$$A = -\frac{g}{T} + D(\text{polymer}) = \varepsilon + D(\text{polymer})$$

spatial disorder: Shannon disorder per monomer: $D(\text{polymer}) \equiv \lim_{l \rightarrow \infty} -\frac{1}{l} \sum_{\omega} \mu_l(\omega) \ln \mu_l(\omega)$

« driving force »: $\varepsilon = -\frac{g}{T}$

THE THERMODYNAMICS OF WRITING A RANDOM POLYMER

C. Jarzynski, Proc. Natl. Acad. Sci. U.S.A. **105** (2008) 9451

entropy production: $\frac{d_i S}{dt} = \nu A \geq 0$

affinity per monomer: $A = -\frac{g}{T} + D(\text{polymer}) = \varepsilon + D(\text{polymer})$

mean Gibbs free energy or free enthalpy per monomer: $g \equiv \lim_{l \rightarrow \infty} \frac{1}{l} \sum_{\omega} \mu_l(\omega) G(\omega) = h - T s$

« driving force »: $\varepsilon = -\frac{g}{T}$

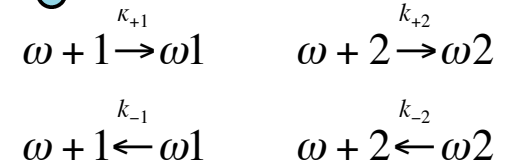
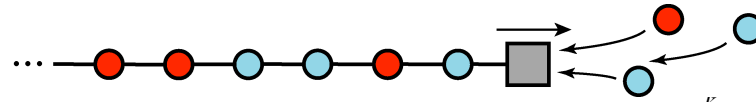
spatial disorder: Shannon disorder per monomer: $D(\text{polymer}) \equiv \lim_{l \rightarrow \infty} -\frac{1}{l} \sum_{\omega} \mu_l(\omega) \ln \mu_l(\omega)$

A copolymer can grow by the entropic effect of its disorder $D > 0$
in an adverse free-energy landscape with $\varepsilon < 0$ such that $A = \varepsilon + D > 0$.

D. Andrieux & P. Gaspard, *Nonequilibrium generation of information in copolymerization processes*
Proc. Natl. Acad. Sci. U.S.A. **105** (2008) 9516

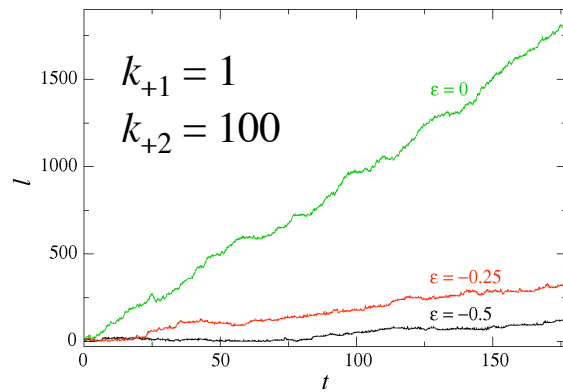
MODEL OF FREE COPOLYMERIZATION

The case of two monomers: $M = 2$



attachement/detachment of monomers 1 or 2 to the copolymer ω :

length versus time for randomly growing copolymers:

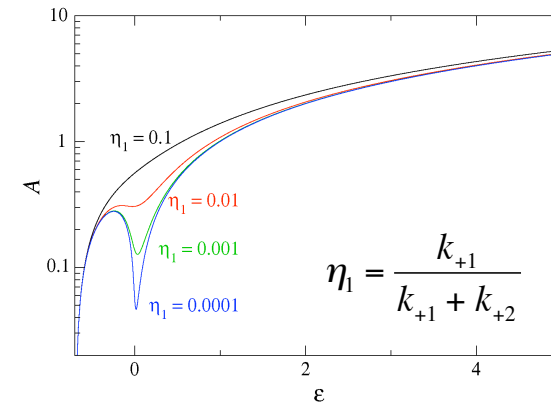


$$k_{-m} = k_{+m} \exp(-\varepsilon)$$

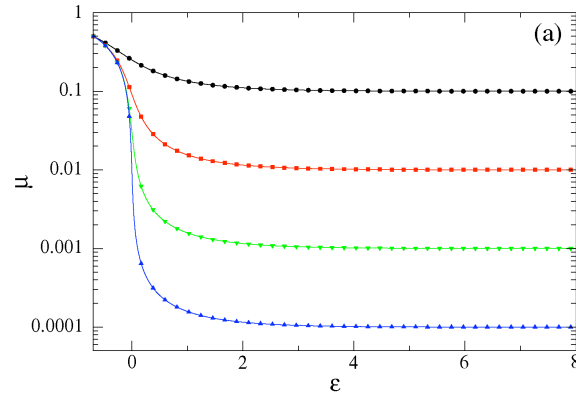
driving force: ε

equilibrium: $\varepsilon_{\text{eq}} = -\ln 2$

entropy production per monomer:



fraction of monomer 1:



$$k_{+1} = 2$$

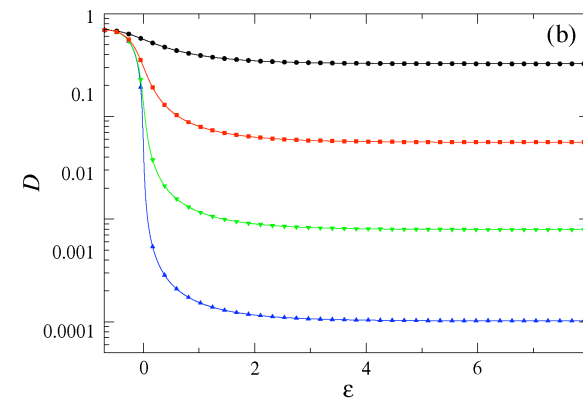
$$k_{+2} = 2 \times 9$$

$$k_{+2} = 2 \times 99$$

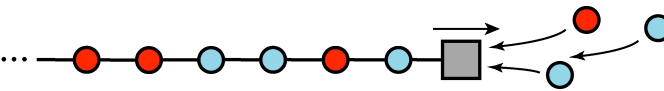
$$k_{+2} = 2 \times 999$$

$$k_{+2} = 2 \times 9999$$

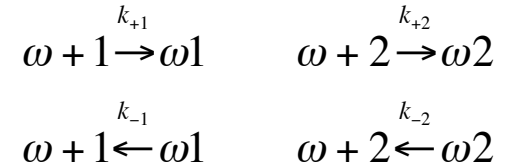
disorder D :



RESOLUTION OF LOOK-ALIKE GIBBS' PARADOX IN THE LIMIT OF IDENTICAL MONOMERS

The case of two monomers: $M = 2$ 

attachement/detachment of monomers 1 or 2 to the copolymer ω :



growth velocity:
$$v = \frac{k_{+1}}{\mu_1} - k_{-1} = \frac{k_{+2}}{\mu_2} - k_{-2}$$

μ_1 = fraction of monomers 1
 μ_2 = fraction of monomers 2

Shannon disorder:
$$D = -\mu_1 \ln \mu_1 - \mu_2 \ln \mu_2$$

$$\mu_1 + \mu_2 = 1$$

« driving force »:
$$\varepsilon = -\frac{g}{T} = \mu_1 \varepsilon_1 + \mu_2 \varepsilon_2 = \mu_1 \ln \frac{k_{+1}}{k_{-1}} + \mu_2 \ln \frac{k_{+2}}{k_{-2}}$$

affinity:
$$A = \varepsilon + D$$

Limit of identical monomers:

$$\begin{array}{lll} k_{+1} = k_{+2} = \tilde{k}_+ & \mu_1 = \mu_2 = \frac{1}{2} & D = \ln 2 \\ k_{-1} = k_{-2} = \tilde{k}_- & & \end{array}$$

$$\varepsilon = \ln \frac{\tilde{k}_+}{\tilde{k}_-}$$

$$A = \varepsilon + D = \ln \frac{2\tilde{k}_+}{\tilde{k}_-}$$

$$v = 2\tilde{k}_+ - \tilde{k}_-$$

Growth of a polymer:
$$\begin{array}{l} \omega + 0 \xrightarrow{k_+} \omega 0 \\ \omega + 0 \xleftarrow{k_-} \omega 0 \end{array}$$

$$D = 0$$

$$\varepsilon = \ln \frac{k_+}{k_-}$$

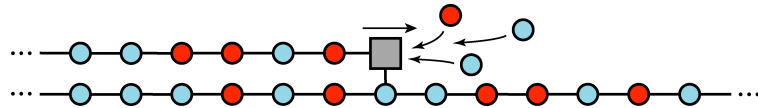
$$A = \varepsilon + D = \ln \frac{k_+}{k_-}$$

$$v = k_+ - k_-$$

Correspondence:

$$\begin{array}{l} k_+ = 2\tilde{k}_+ \\ k_- = \tilde{k}_- \end{array}$$

STATISTICAL THERMODYNAMICS OF COPOLYMERIZATION WITH A TEMPLATE



statistical distribution of length l
of template sequences α : $\nu_l(\alpha)$

entropy production:

$$\frac{d_i S}{dt} = \nu A \geq 0$$

affinity per monomer:

$$\begin{aligned} A &= \varepsilon + D(\text{polymer}|\text{template}) \\ &= \varepsilon + D(\text{polymer}) - I(\text{polymer}, \text{template}) \end{aligned}$$

« driving force »: $\varepsilon = -\frac{g}{T}$

$g =$ mean Gibbs free energy per monomer

Shannon conditional disorder of the polymer with respect to the template:

$$D(\omega|\alpha) \equiv \lim_{l \rightarrow \infty} -\frac{1}{l} \sum_{\omega, \alpha} \nu_l(\alpha) \mu_l(\omega|\alpha) \ln \mu_l(\omega|\alpha)$$

Shannon disorder of the polymer:

$$D(\omega) \equiv \lim_{l \rightarrow \infty} -\frac{1}{l} \sum_{\omega} \mu_l(\omega) \ln \mu_l(\omega) \quad \text{with} \quad \mu_l(\omega) \equiv \sum_{\alpha} \nu_l(\alpha) \mu_l(\omega|\alpha) = \sum_{\alpha} \mu_l(\omega, \alpha)$$

mutual information between the polymer and the template:

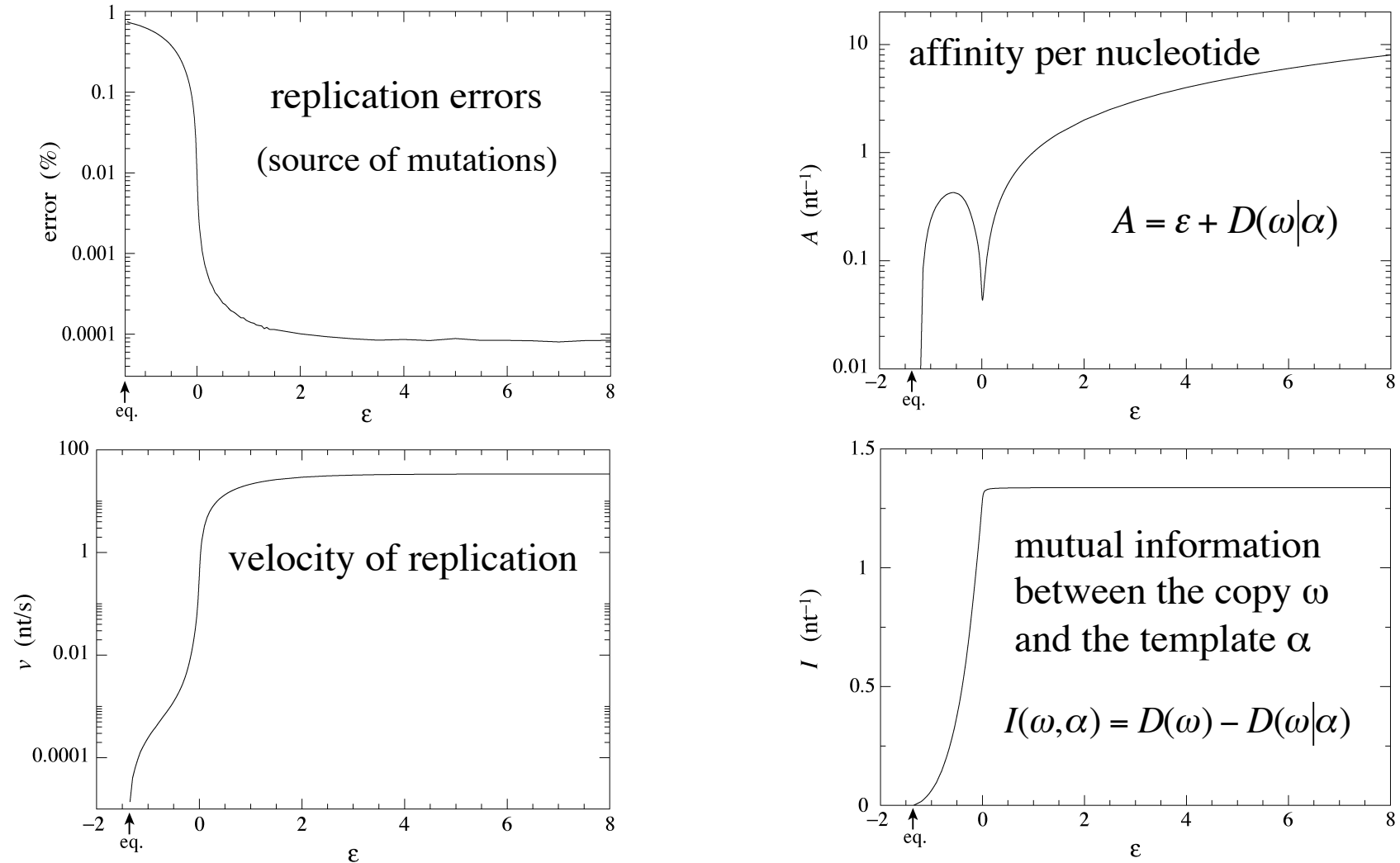
$$I(\omega, \alpha) \equiv D(\omega) - D(\omega|\alpha) = \lim_{l \rightarrow \infty} \frac{1}{l} \sum_{\omega, \alpha} \mu_l(\omega, \alpha) \ln \frac{\mu_l(\omega, \alpha)}{\nu_l(\alpha) \mu_l(\omega)} \quad \text{with} \quad \mu_l(\omega, \alpha) \equiv \nu_l(\alpha) \mu_l(\omega|\alpha)$$

THERMODYNAMICS OF DNA REPLICATION

COPOLYMERIZATION WITH A TEMPLATE

powered by 2 ATP/nucleotide

DNA-polymerase Pol γ replicating human mitochondrial DNA (A, C, G, T)



NANOPORE / SINGLE-MOLECULE SEQUENCING

possible experimental verification of the predictions
for either chemical or biological copolymerization processes

1) Standard sequencing techniques by PCR or similar amplifications

2) Forthcoming nanopore/single-molecule sequencing techniques

Nanopore with an engineered protein: detection of nucleotides by ionic current through the nanopore

Y. Astier, O. Braha, & H. Bayley, *Toward Single Molecule DNA Sequencing*, JACS **128** (2006) 1705

M. Zwolak & M. Di Ventra, *Physical approaches to DNA sequencing and detection*, Rev. Mod. Phys. **80** (2008) 141

CONCLUSIONS I

Out-of-equilibrium directionality down to the nanoscale:

- understanding in accord with the second law of thermodynamics;
- fundamental aspect of molecular motors & copolymerization processes.

F_1 -ATPase rotary motor:

Dual modeling of the experiments by Kinosita *et al.* (2001)
using fitted continuous and discrete-state stochastic processes.

Understanding of the dependences on the external torque and friction.

Identification of the regimes of tight or loose chemomechanical coupling.

The molecular motor typically works in a very nonlinear regime.

Regime of tight coupling:

The equilibrium is effectively shifted by the external torque.

The chemomechanical affinity is the sum of chemical and mechanical affinities.

The fluctuation theorem for the two currents reduces to the one for a single current.

Conditions for experimental test of the fluctuation theorem.

CONCLUSIONS II

Copolymerization processes without or with a template: *information processing*

Two contributions to the thermodynamic entropy production:

- 1) energetic contribution: free energy of attachment;
- 2) entropic contribution: disorder in the sequence of monomers.

The copolymer can grow by the entropic effect of its disorder
in an adverse free-energy landscape.

The mutual information between the copy and the template
is vanishing at equilibrium and becomes optimal away from equilibrium.

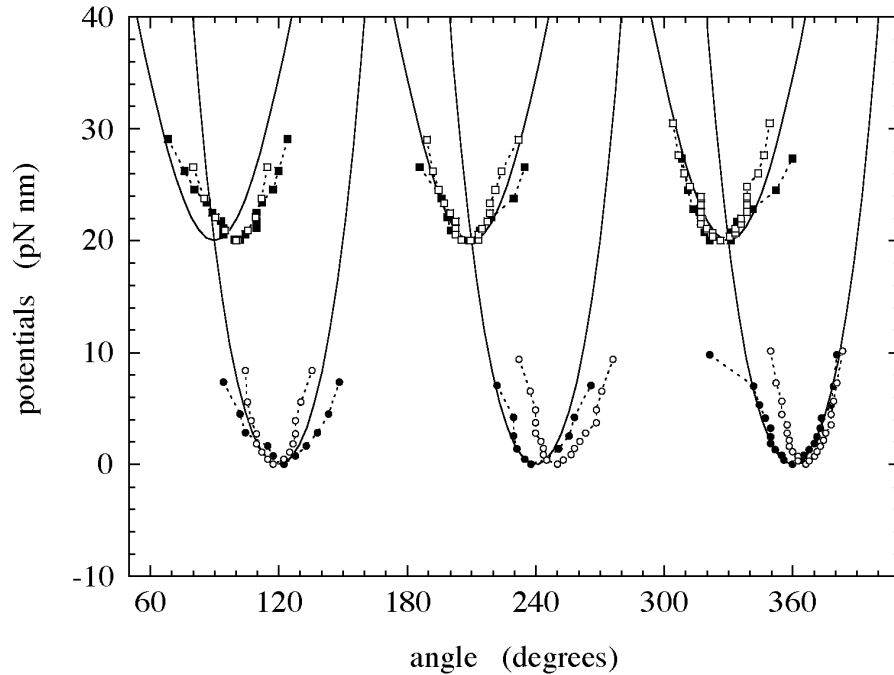
The fidelity in DNA replication requires the growth to run away from equilibrium.
Away from equilibrium, errors in replication are reduced although they persist (mutations).

Perspectives to understand the origins of dynamical order in biology:

- biological systems as physico-chemical systems
with a built-in thermodynamic arrow of time.
- Darwinian evolution performs a selection of ordered time sequences (rather than structures):
the higher the organism the longer the ordered time sequences.

**3D molecular biology + nonequilibrium statistical thermodynamics
= 4D molecular biology (3D molecular structure + dynamics)**

APPENDIX: FREE-ENERGY POTENTIALS



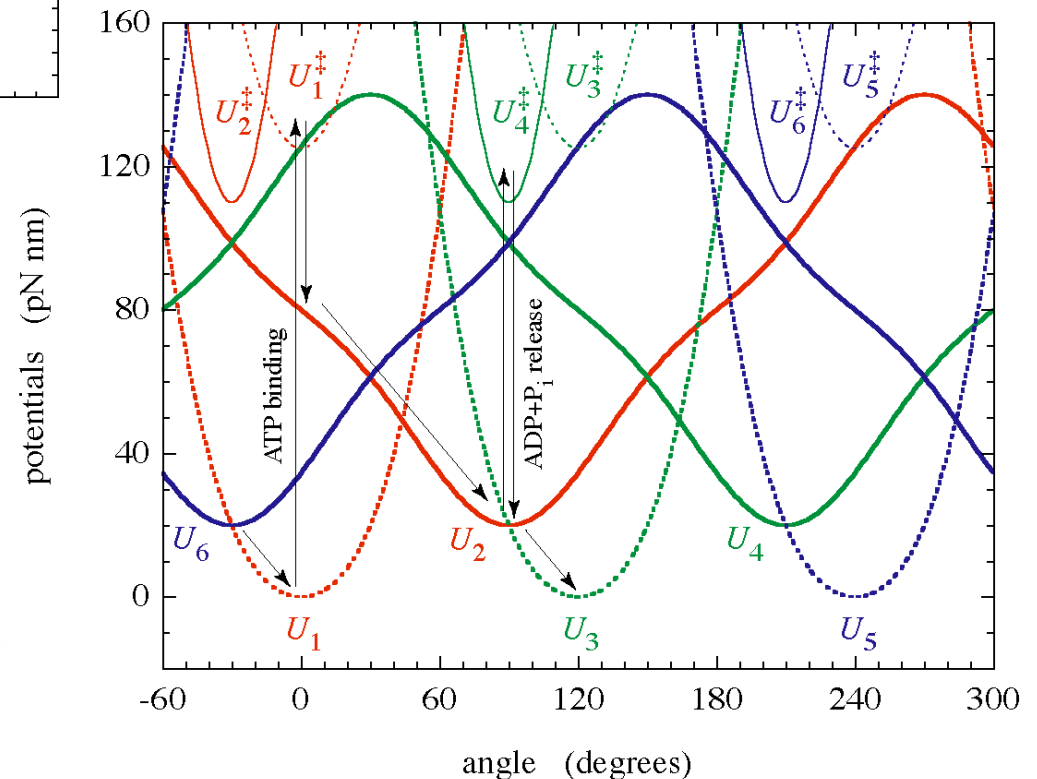
potentials for the transition states $U_i^*(\theta)$

potentials for the wells $U_i(\theta)$

- *three-fold rotation symmetry: group C_3*
- *absence of parity symmetry (chirality)*

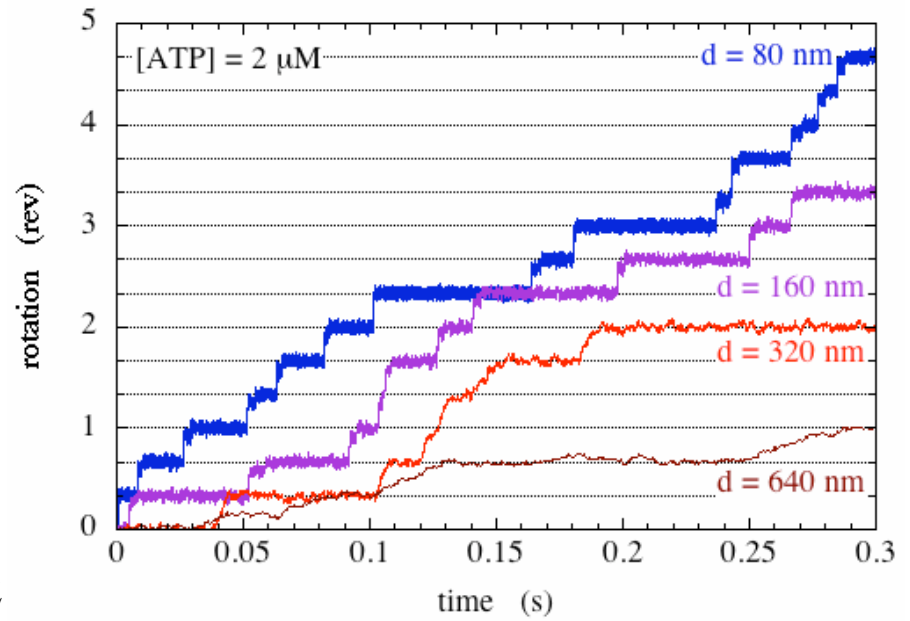
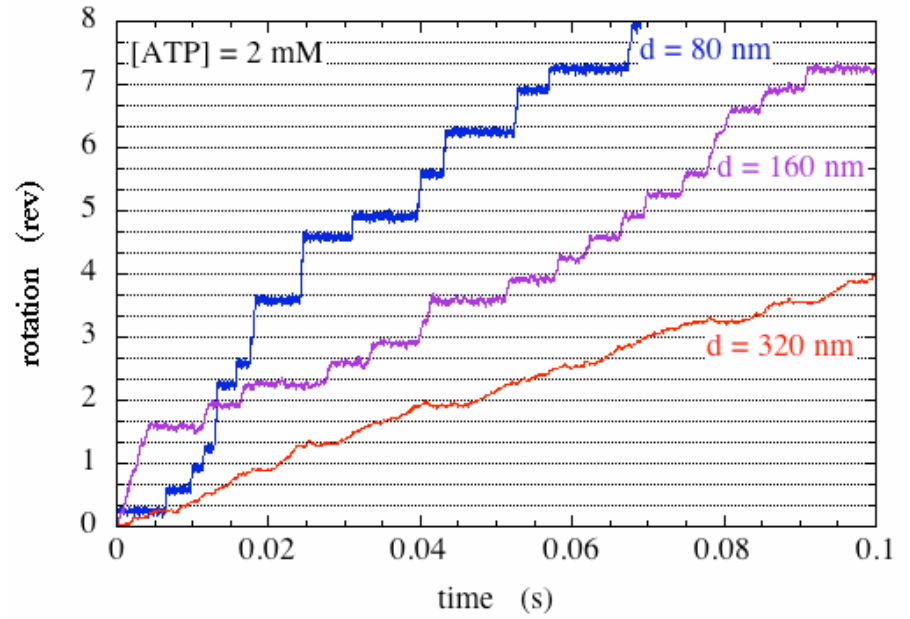
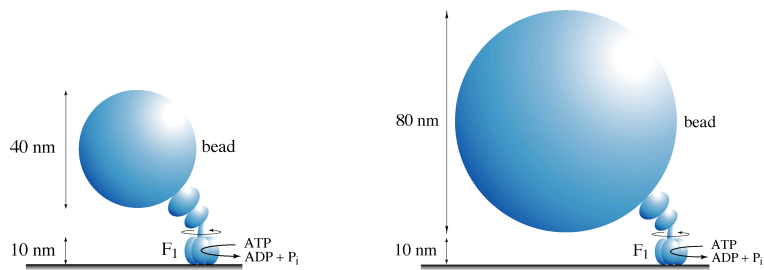
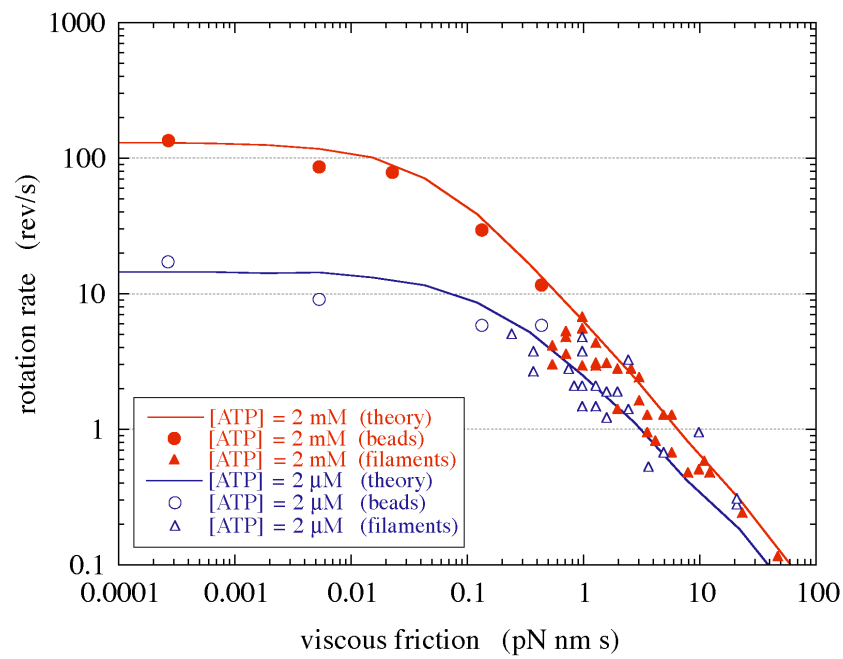
Potential wells obtained by inverting the experimental probability distributions:

R. Yasuda, H. Noji, M. Yoshida,
K. Kinosita Jr. & H. Itoh,
Nature **410** (2001) 898



APPENDIX: F₁-ATPase ROTATION RATE VERSUS FRICTION

Crossover from **reaction-limited regime** to **friction-limited regime**

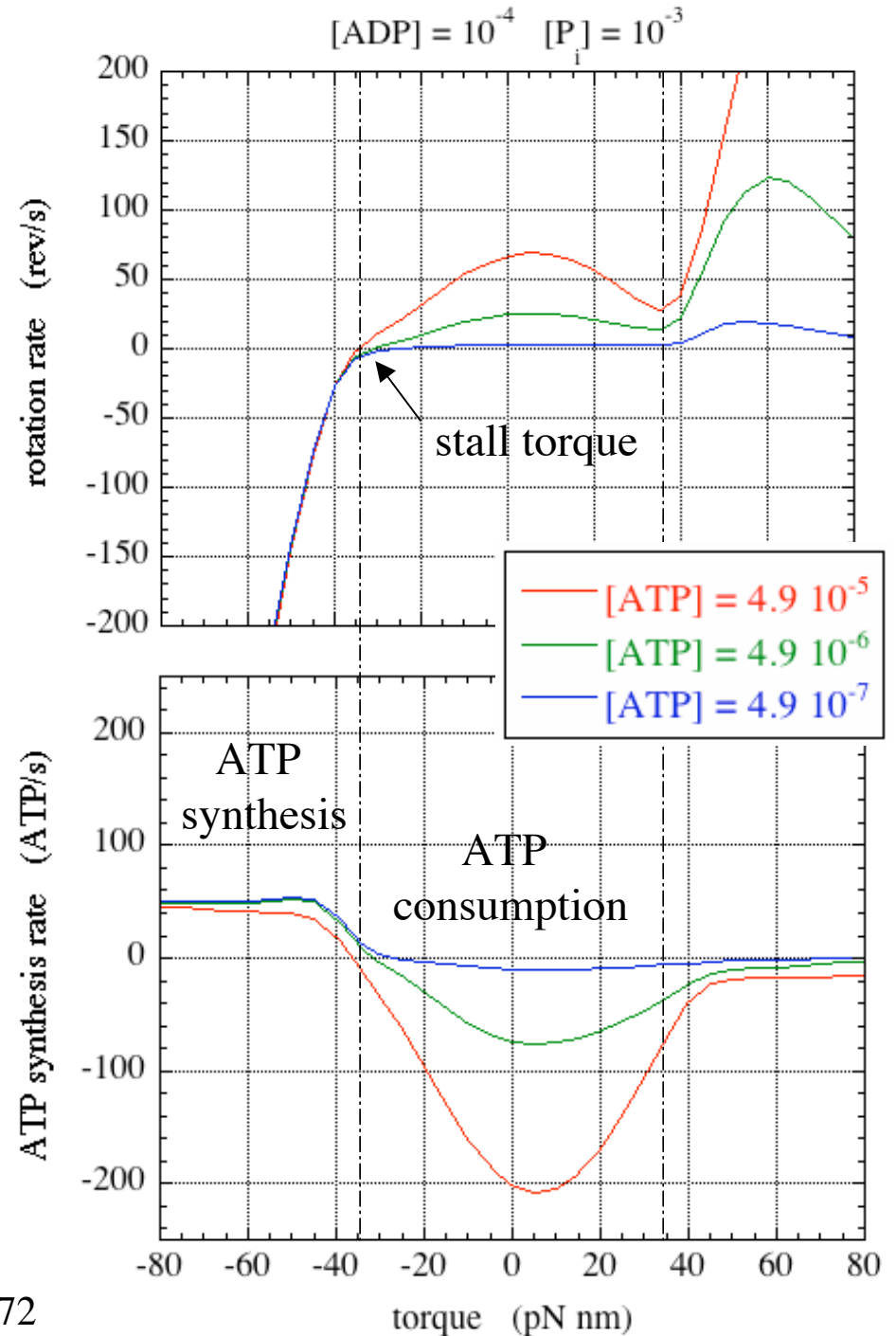


APPENDIX: F₁-ATPase UNDER AN EXTERNAL TORQUE

(e.g. from F_o)

Experimental realization:

H. Itoh , A. Takahashi, K. Adachi, H. Noji,
R. Yasuda, M. Yoshida, K. Kinosita Jr.,
Mechanically driven ATP synthesis by F₁-ATPase,
Nature **427** (2004) 465



APPENDIX: DISCRETE-STATE MODEL FOR THE F₁-ATPase MOTOR

dependence on friction ζ and torque τ :

$$k_\rho(\zeta, \tau) = \frac{1}{e^{a_\rho(\tau)} + e^{b_\rho(\tau)\zeta}}$$

$$a_\rho(\tau) = a_\rho^{(0)} + a_\rho^{(1)}\tau + a_\rho^{(2)}\tau^2 + O(\tau^3)$$

$$b_\rho(\tau) = b_\rho^{(0)} + b_\rho^{(1)}\tau + b_\rho^{(2)}\tau^2 + O(\tau^3)$$

fitted to the continuous model

$$k_{-1}(\zeta, \tau) = \frac{k_{+1}(\zeta, \tau)k_{+2}(\zeta, \tau)}{k_{-2}(\zeta, \tau)} \exp\left(\frac{1}{k_B T} \left(\Delta G^0 - \frac{2\pi}{3} \tau \right)\right)$$

$$\Delta G^0 = -50 \text{ pN nm}$$

coefficient	$k_{+1}(\zeta, \tau)$	$k_{+2}(\zeta, \tau)$	$k_{-2}(\zeta, \tau)$	units
$a_\rho^{(0)}$	-16.952	-5.973	-19.382	-
$a_\rho^{(1)}$	$9.8 \cdot 10^{-4}$	$1.7 \cdot 10^{-4}$	$1.29 \cdot 10^{-1}$	$(\text{pN nm})^{-1}$
$a_\rho^{(2)}$	$5.8 \cdot 10^{-4}$	$1.0 \cdot 10^{-3}$	$2.8 \cdot 10^{-4}$	$(\text{pN nm})^{-2}$
$b_\rho^{(0)}$	-16.352	-2.960	-18.338	-
$b_\rho^{(1)}$	$6.6 \cdot 10^{-2}$	$-2.7 \cdot 10^{-2}$	$5.9 \cdot 10^{-3}$	$(\text{pN nm})^{-1}$
$b_\rho^{(2)}$	$1.0 \cdot 10^{-3}$	$3.6 \cdot 10^{-4}$	$-2.1 \cdot 10^{-4}$	$(\text{pN nm})^{-2}$

APPENDIX: THERMODYNAMIC ENTROPY PRODUCTION

The time evolution of the probability $P_t(\omega)$ is ruled by the master equation:

$$\frac{d}{dt} P_t(\omega) = \sum_{\omega'} [P_t(\omega') W(\omega'|\omega) - P_t(\omega) W(\omega|\omega')] \quad \frac{W(\omega|\omega')}{W(\omega'|\omega)} = \exp \frac{G(\omega) - G(\omega')}{k_B T}$$

mean value: $\langle X \rangle_t = \sum_{\omega} P_t(\omega) X(\omega) \quad X = G, H \text{ or } S$

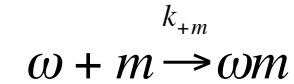
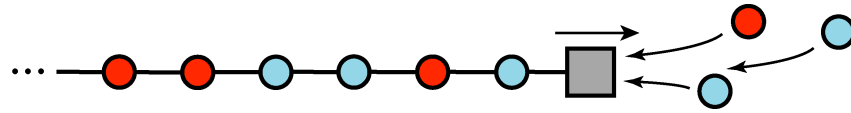
total entropy: $S_t = \langle S \rangle_t - k_B \sum_{\omega} P_t(\omega) \ln P_t(\omega)$

time variation: $\frac{dS}{dt} = \frac{d_e S}{dt} + \frac{d_i S}{dt}$

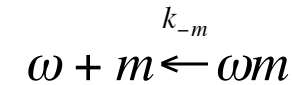
entropy exchange: $\frac{d_e S}{dt} = \frac{d \langle S \rangle_t}{dt} - k_B \sum_{\omega, \omega'} P_t(\omega) W(\omega|\omega') \ln \frac{W(\omega|\omega')}{W(\omega'|\omega)} = \frac{1}{T} \frac{d \langle H \rangle_t}{dt}$

entropy production: $\frac{d_i S}{dt} = k_B \sum_{\omega, \omega'} P_t(\omega) W(\omega|\omega') \ln \frac{P_t(\omega) W(\omega|\omega')}{P_t(\omega') W(\omega'|\omega)} \geq 0$

APPENDIX: MODEL OF FREE COPOLYMERIZATION



attachement/detachment of monomers m to the copolymer ω :



master equation:
$$\frac{d}{dt} P_t(m_1 \dots m_l) = k_{+m_l} P_t(m_1 \dots m_{l-1}) + \sum_{m_{l+1}=1}^M k_{-m_{l+1}} P_t(m_1 \dots m_{l+1}) - \left(k_{-m_l} + \sum_{m_{l+1}=1}^M k_{+m_{l+1}} \right) P_t(m_1 \dots m_l)$$

growth in a stationary statistical regime:
$$P_t(\omega) = p_t(l) \mu_l(\omega)$$

equation for the time evolution of the statistical distribution of lengths:

$$\frac{dp_t(l)}{dt} = ap_t(l-1) - (a+b)p_t(l) + bp_t(l+1) \quad a = \sum_m k_{+m} \quad b = \sum_m k_{-m} \mu_1(m)$$

mean growth velocity:
$$v = a - b$$

diffusivity:
$$D = \frac{a+b}{2}$$