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Stochastic thermodynamics*

for biomolecular and cellular processes

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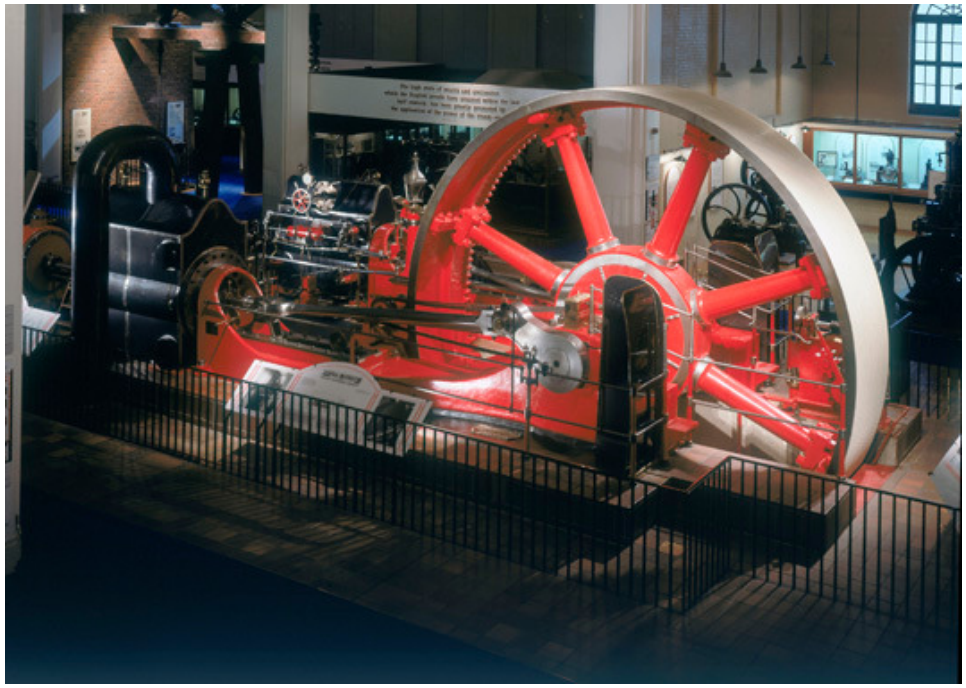
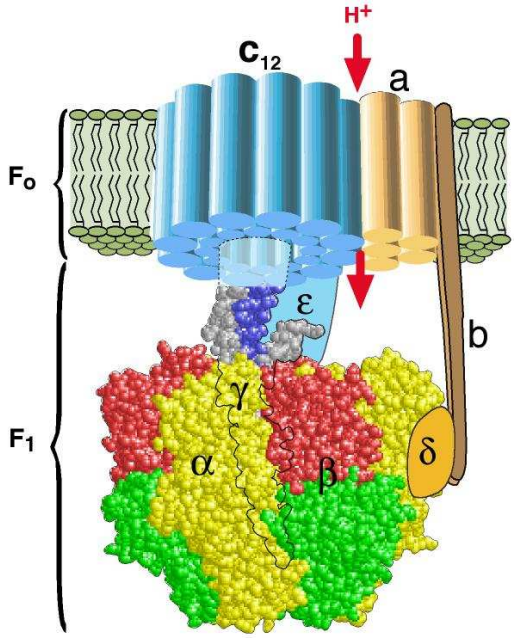
* Review: U.S., Rep. Prog. Phys. **75** 126001, 2012.

- Intro: Classical vs stochastic thermodynamics
- Equilibrium thermodynamics along a trajectory for biomolecules
- Open systems: Non-equilibrium energetics of F1-ATPase
- Thermodynamic uncertainty relation
- Cost of coherent oscillations

- From classical th'dynamics to stochastic th'dynamics



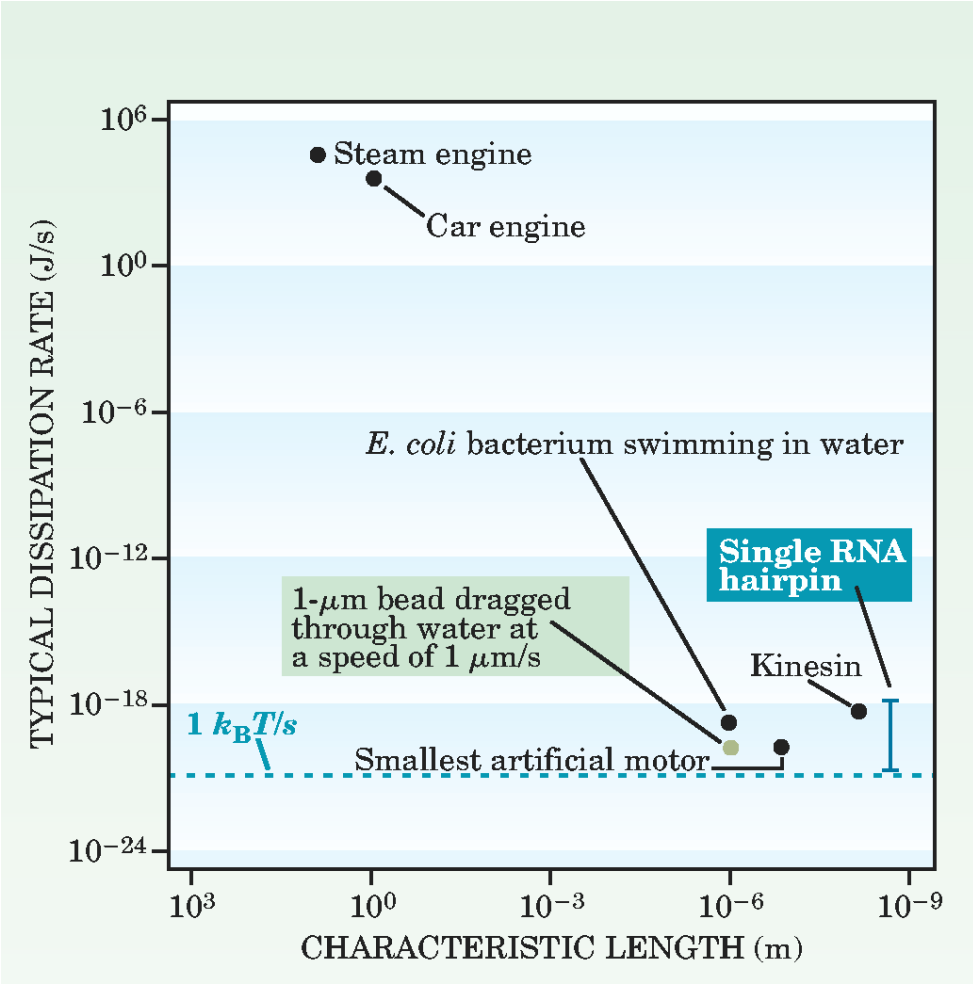
Steam engine



H. Wang and G. Oster (1998). Nature 396:279-282.

F_1ATP-ase

- Macroscopic *vs* mesoscopic *vs* molecular machines

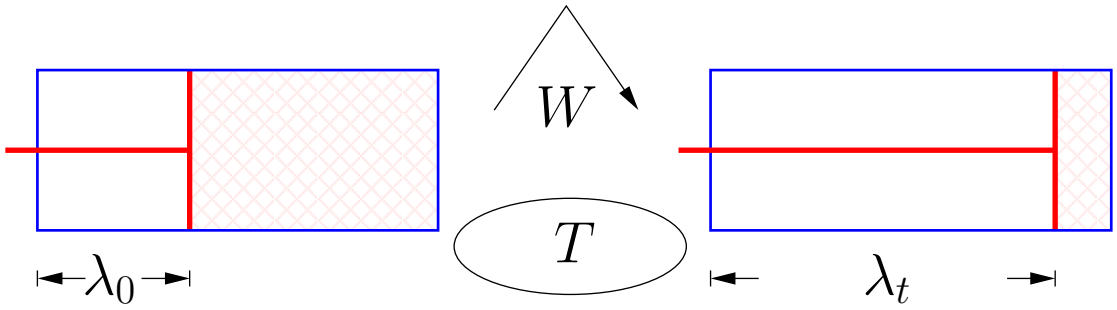


[Bustamante *et al*, Physics Today, July 2005]

- Perspective

$1820 \simeq 1850$	classical thermodynamics	$dW = dU + dQ$ $dS \geq 0$
$\simeq 1900$	eq stat phys	$p_i = \exp[-(E_i - F)/k_B T]$
$1930 \simeq 1960$	non-eq: linear response	Onsager Green-Kubo, FDT
≥ 1993	non-eq: beyond linear response stochastic thermodynamics	Fluctuation theorem Jarzynski relation
2015		thermod'dyn uncertainty rel'

- Thermodynamics of macroscopic systems



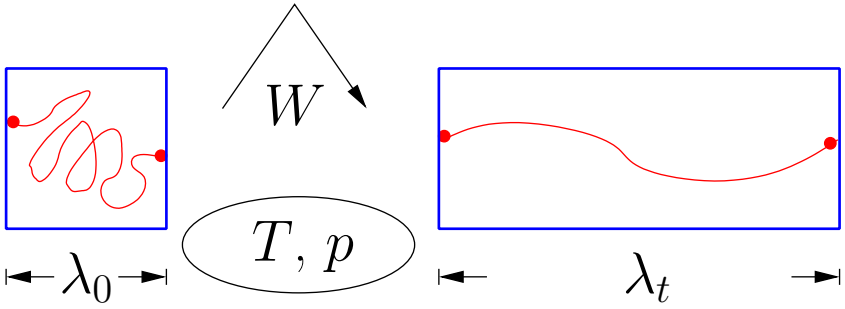
  - First law energy balance:

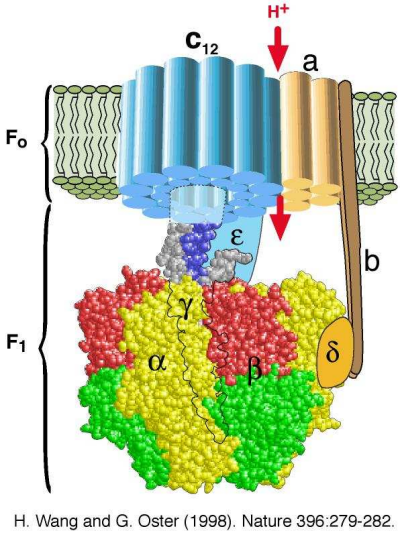
$$W = \Delta E + Q = \Delta E + T\Delta S_{\text{res}}$$

  - Second law:

$$\begin{aligned} \Delta S_{\text{tot}} &\equiv \Delta S + \Delta S_{\text{res}} > 0 \\ W &> \Delta E - T\Delta S \equiv \Delta F \\ W_{\text{diss}} &\equiv W - \Delta F > 0 \end{aligned}$$

- Stochastic thermodynamics for small systems





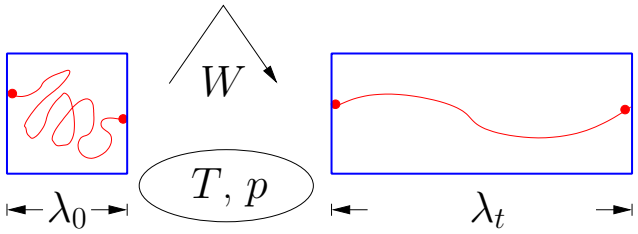
H. Wang and G. Oster (1998). Nature 396:279-282.

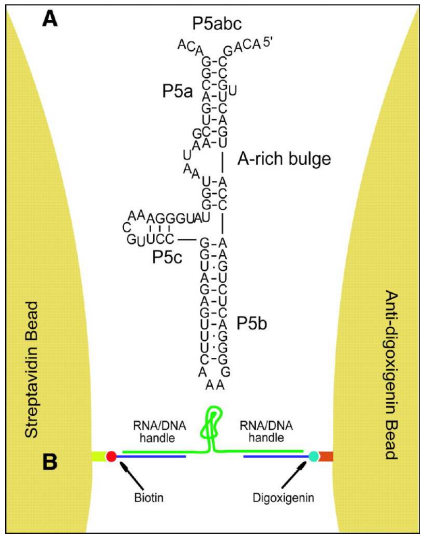
driving: mechanical (bio)chemical

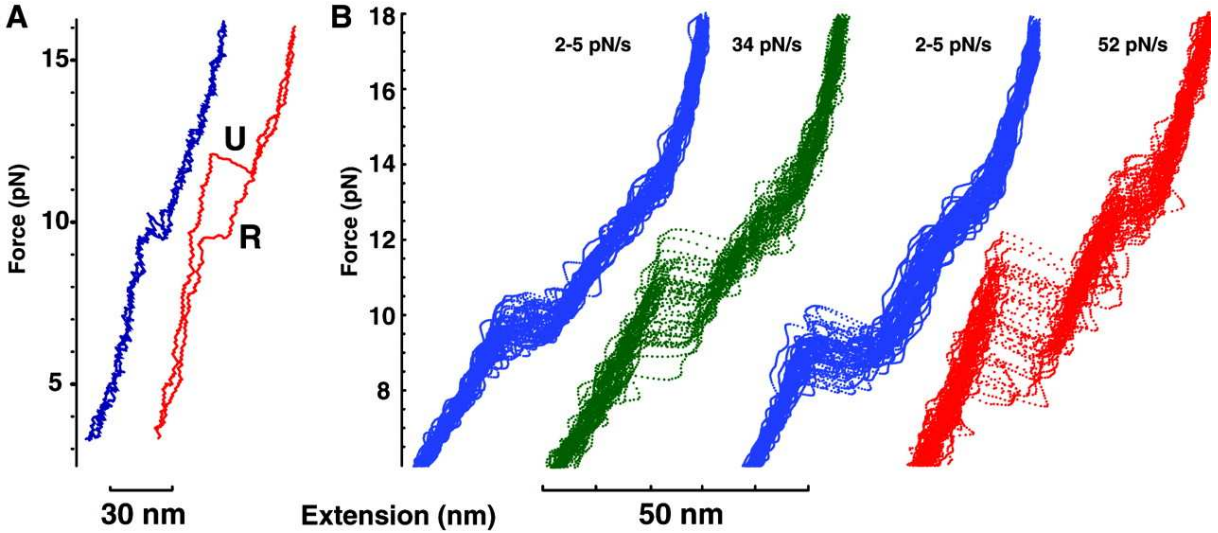
- First law: how to define work, internal energy and exchanged heat?
- fluctuations imply distributions: $p(W; \lambda(\tau))$ ...
- entropy: distribution as well?

- Nano-experiment: Stretching of RNA

[Liphardt et al, Science **296** 1832, 2002.]







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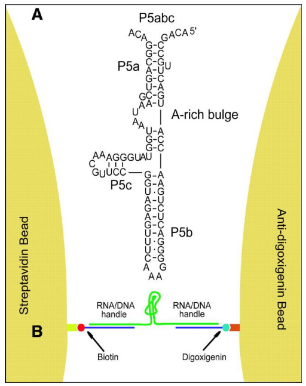
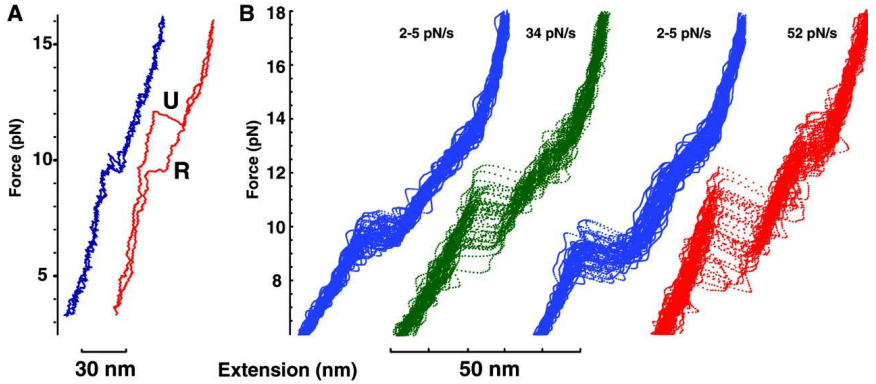
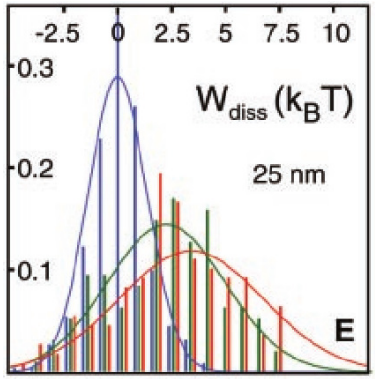




– distribution of dissipated work

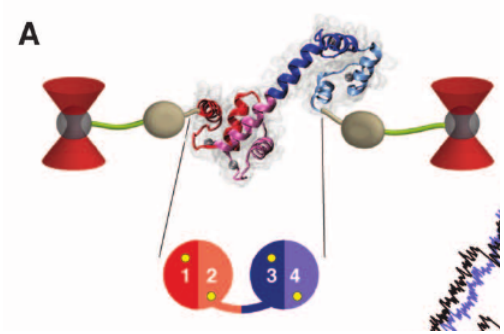
$W_{\text{diss}} = W - \Delta F$

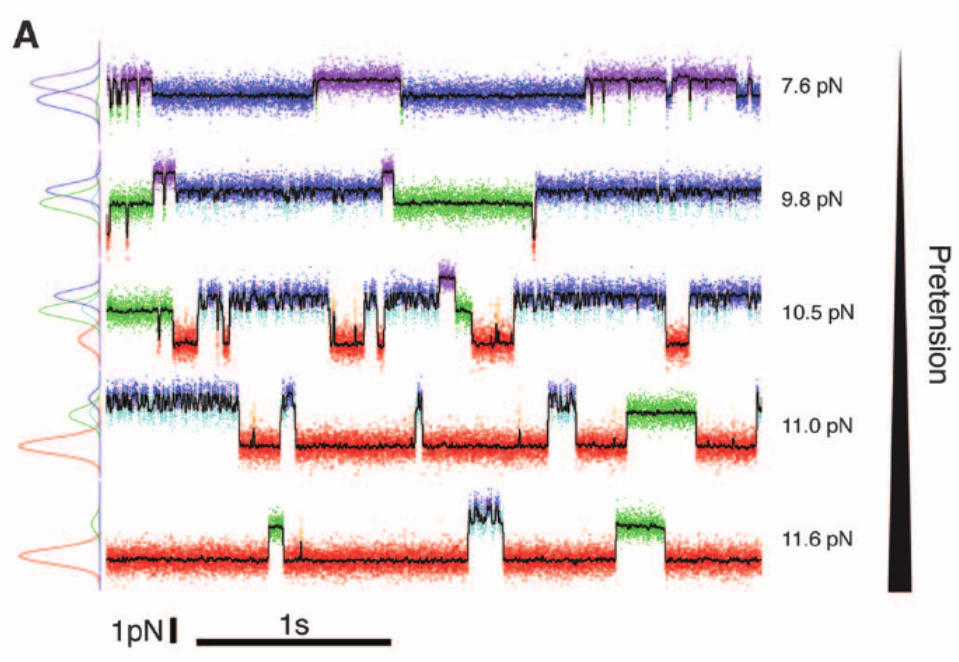


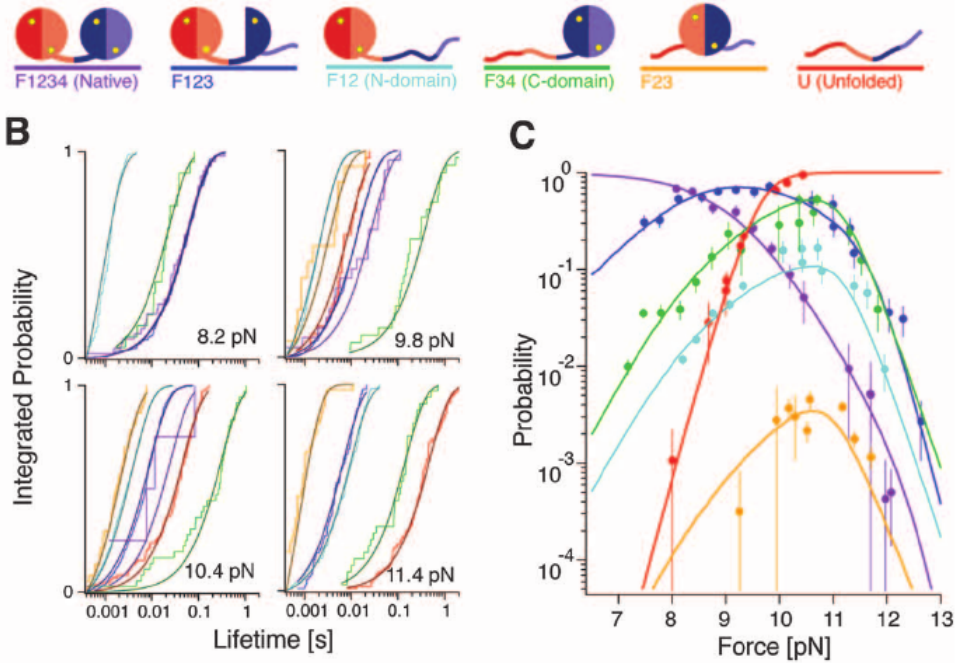
– Jarzynski relation (1997): $\boxed{\langle \exp[-W/k_B T] \rangle_{neq} = \exp[-\Delta F/k_B T]}$

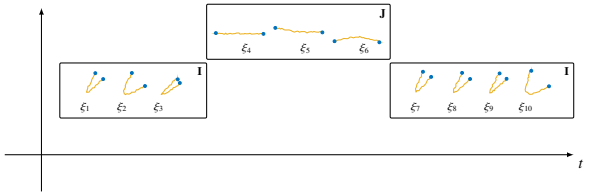
- Biomolecules in equilibrium: Meso-states of calmodulin

[J. Stigler et al, Science **334** 512 (2011)]









- Closed system in thermal equilibrium
  - micro-states $\{\xi\}$ with energy $H(\xi)$ in contact with a heat bath at β
  - free energy, internal energy and entropy

$$F = -(1/\beta)\ln\sum_{\xi}\exp[-\beta H(\xi)], \quad E = \partial_\beta(\beta F), \quad S = \beta(E-F)$$

  - meso-states $\{I\}$ to which many micro-states $\xi \in I$ contribute
    - probability

$$P_I^e = \sum_{\xi\in I}\exp[-\beta(H(\xi)-F)] \equiv \exp[-\beta(F_I - F)]$$

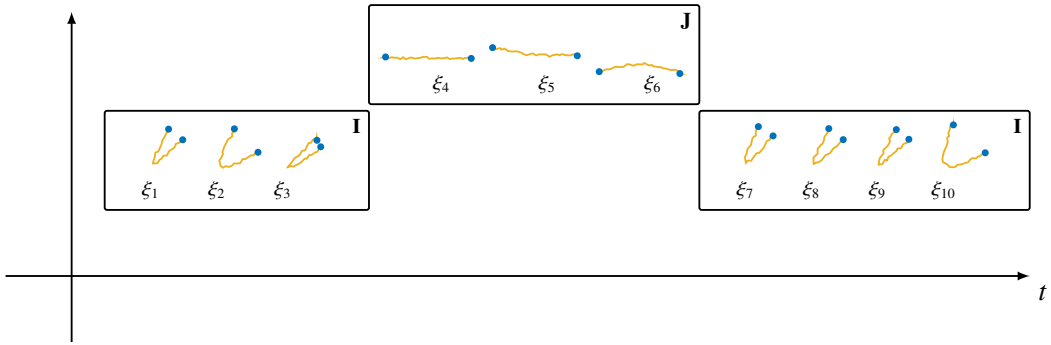
    - free energy, internal energy, entropy

$$F_I \equiv -(1/\beta)\ln\sum_{\xi\in I}\exp[-\beta H(\xi)], \quad E_I = \partial_\beta(\beta F_I), \quad S_I \equiv \beta(E_I - F_I)$$

    - recoverable from equilibrium trajectories

$$\tau_I/\tau_J = P_I^e/P_J^e = \exp[\beta(F_J - F_I)]$$

- Thermodynamically consistent markovian dynamics on meso-states

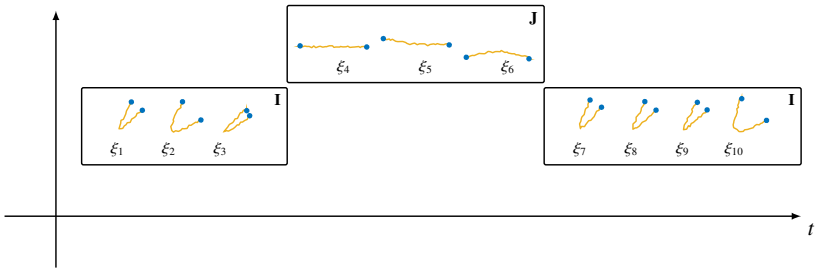


  - trajectory $I(t)$
  - crucial time-scale separation:
    * transitions between meso-states are slow
    * transitions between the micro-states belonging to one meso-state are fast
  - master equation

$$\partial_t P_I(t) = \sum_J [P_J(t) K_{JI} - P_I(t) K_{IJ}].$$

  - local detailed balance condition on the rates $\{K_{IJ}\}$

$\Rightarrow$ $\boxed{K_{IJ}/K_{JI} = P^e_J/P^e_I = \exp(-\beta \Delta_{IJ} F) = \exp(-\beta \Delta_{IJ} E + \Delta_{IJ} S)}$



- Thermodynamics along a trajectory $I(t)$ and in the ensemble
  - internal energy $E(t) = E_{I(t)}$ becomes stochastic
  - first law (Sekimoto 1998)

$$\Delta_{IJ}E \equiv E_J - E_I = -Q_{IJ}$$

  - entropy change of bath βQ_{IJ}
  - entropy of "system"

$$S^{\text{sys}}(t) \equiv S_{I(t)} - \ln[P_{I(t)}(t)]$$

    * intrinsic entropy $S_{I(t)}$
    * stochastic entropy $-\ln[P_{I(t)}(t)]$ [U.S., PRL 2005]
  - total entropy change in a transition from I to J at time t

$$\Delta_{IJ}S^{\text{tot}}(t) = \beta Q_{IJ} + \Delta_{IJ}S^{\text{sys}}(t) = \ln[P_I(t)K_{IJ}/P_J(t)K_{JI}]$$

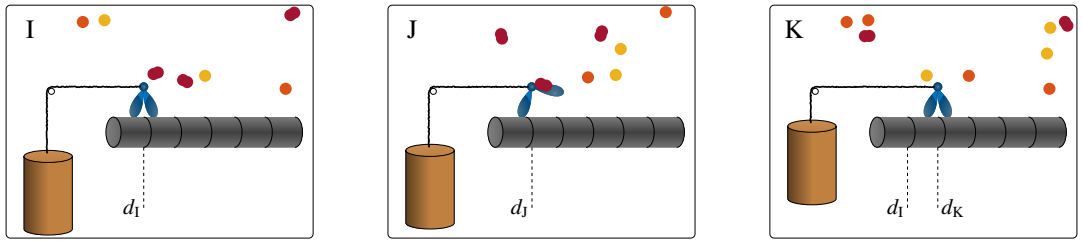
  - integral fluctuation theorem for total entropy production

$$\langle \exp[-\Delta S^{\text{tot}}] \rangle = 1 \quad \Rightarrow \langle \Delta S^{\text{tot}} \rangle \geq 0$$

    any lengths t, any initial distribution $\{P_I^0\}$
  - second law on ensemble level (Schnakenberg 1976)

$$\langle \dot{S}^{\text{tot}}(t) \rangle \equiv \sum_{IJ} P_I(t) K_{IJ} \Delta_{IJ} S^{\text{tot}}(t) \geq 0$$

- From a closed to an open system in a non-eq steady state (NESS)



$$ATP \rightarrow ADP + P_i$$

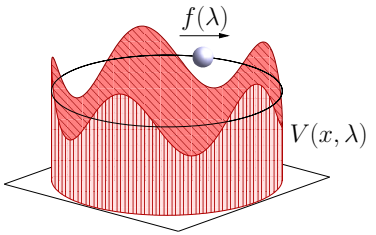
  - system = core system (enzyme/mol motor) + surrounding solution
  - change in free energy difference

$$\Delta_{IJ}F = F_{i_J} - F_{i_I} - \sum_\alpha \mu^\alpha \Delta_{ij} N^\alpha + f d_{IJ}$$

  - local detailed balance condition

$$k_{ij}/k_{ji} = \exp[-\beta(\Delta_{ij}F - \sum_\alpha \mu^\alpha \Delta_{ij} N^\alpha + f d_{ij})]$$

  - for fixed chemical potentials and force f: NESS



- Stochastic th'dynamics of NESS: Driven colloidal particle as paradigm
  - Langevin dynamics $\dot{x} = \mu[-V'(x) + f] + \zeta$ with $\langle \zeta_1 \zeta_2 \rangle = 2\mu k_B T \delta(t_2 - t_1)$
  - first law [(Sekimoto, 1997)]: $\boxed{dw = du + dq}$
    - applied work: $dw = f\ dx$
    - internal energy : $du = dV$
    - dissipated heat: $dq = dw - du = [-\partial_x V(x) + f]dx = T ds_{\text{res}}$
  - total entropy as quantitive measure of broken time reversal symmetry $x(t) \to \tilde{x}(t) \equiv x(\mathcal{T} - t)$

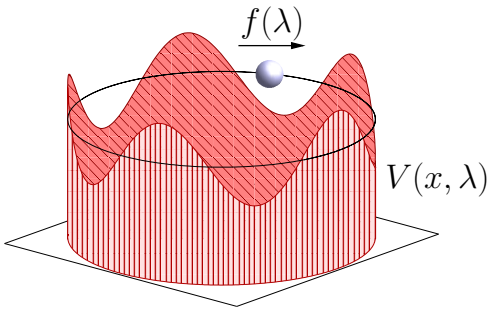
$$\boxed{\Delta s^{\text{tot}}[x(t)] \equiv \ln[p[x(t)]/p[\tilde{x}(t)]] = \Delta[-\ln p(x)] + q/T}$$

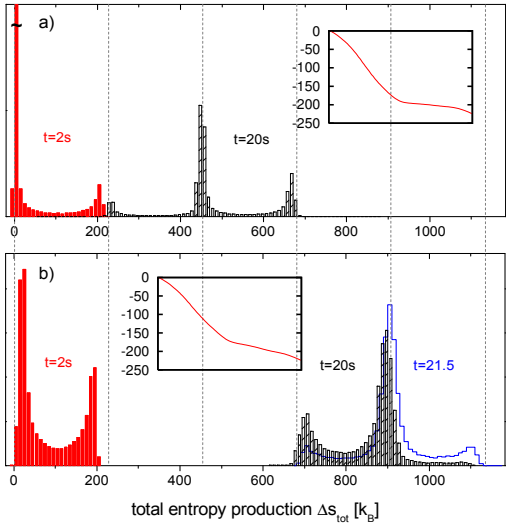
  - "affinity" $\mathcal{A} \equiv 2\pi R f$

- Fluctuation theorem $\boxed{p(-\Delta s^{\rm tot})/p(\Delta s^{\rm tot}) = \exp(-\Delta s^{\rm tot})}$ in any NESS

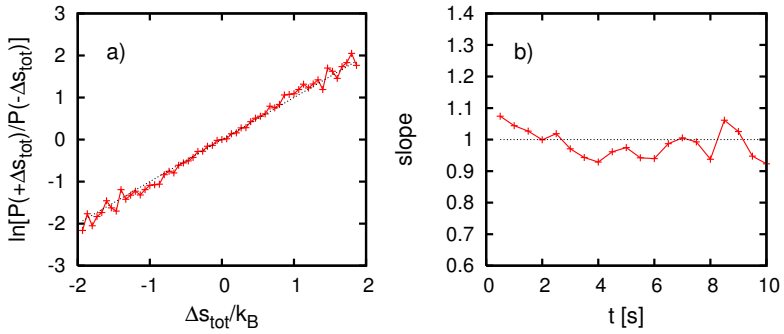
  Evans et al (1993), Gallavotti & Cohen (1995), Kurchan (1998), Lebowitz & Spohn (1999), U.S. (2005)

  – experimental data [Speck, Blickle, Bechinger, U.S., EPL **79** 30002 (2007)]

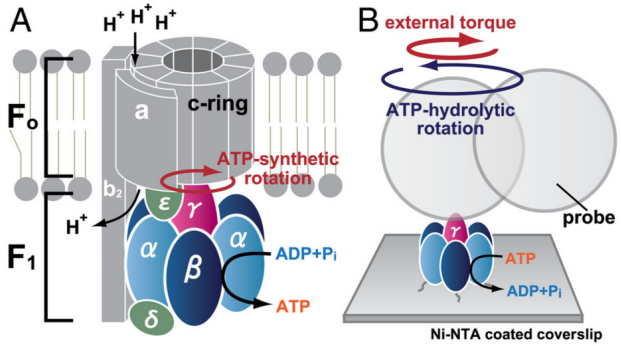


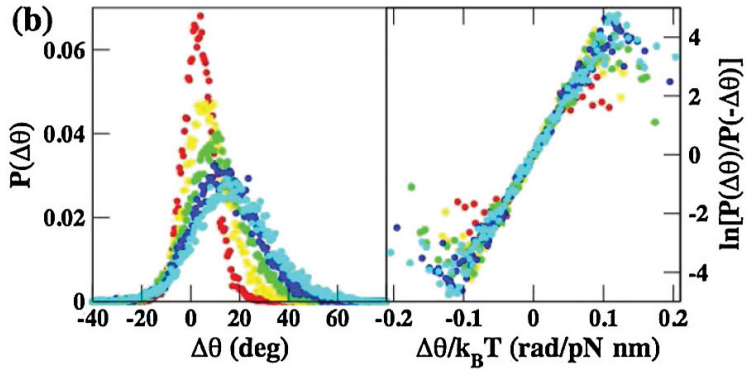


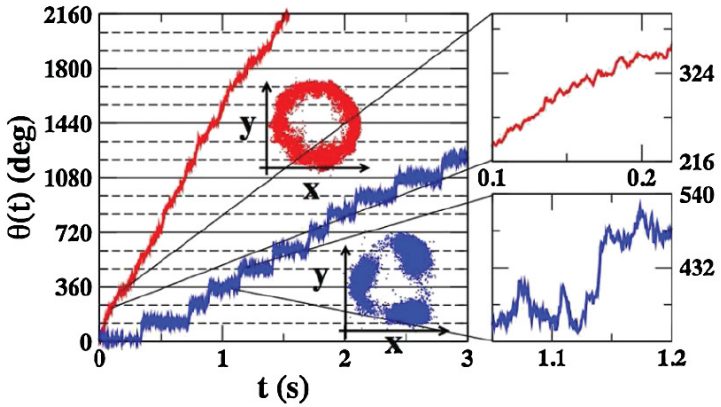
  – FT-representation:

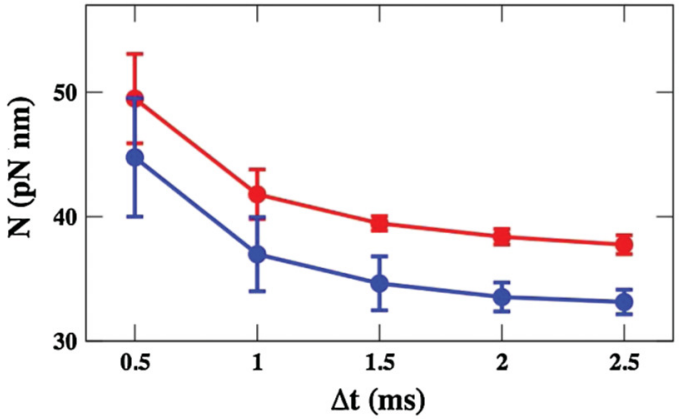


- F1-ATPase and the fluctuation theorem [K. Hayashi et al, PRL 104, 218103 (2010)]









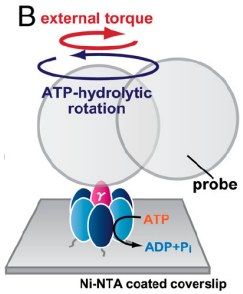
$$-\Gamma\dot{\theta} = N + \zeta$$

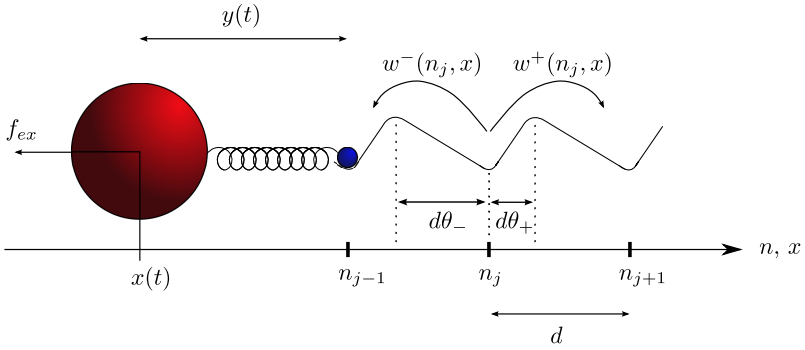
$$\Rightarrow \ln[p(\Delta\theta)/p(-\Delta\theta)] = N\Delta\theta/k_BT$$

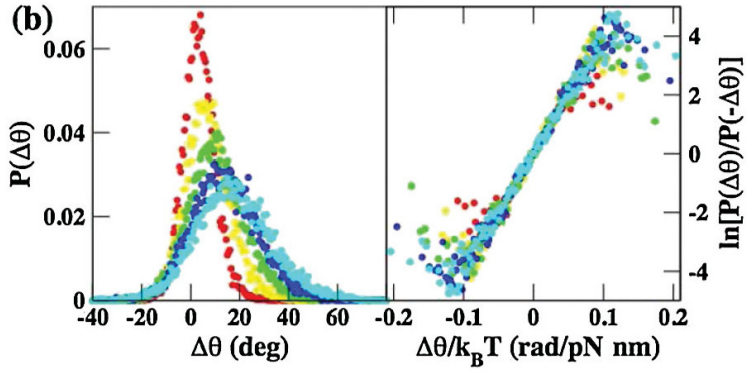
independent of friction coefficient Γ

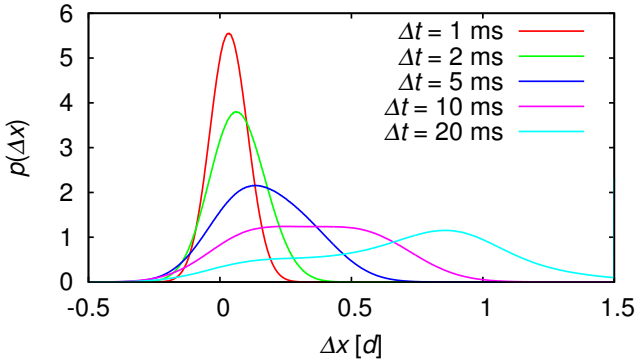
time-dependence?

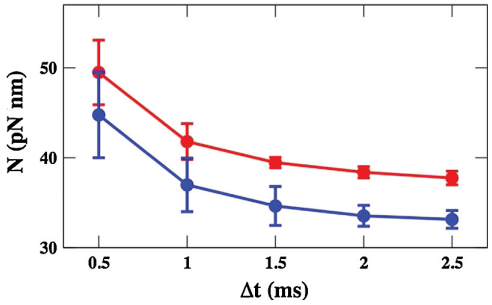
- Hybrid model [E. Zimmermann and U.S., New J. Phys. 14, 103023, 2012]

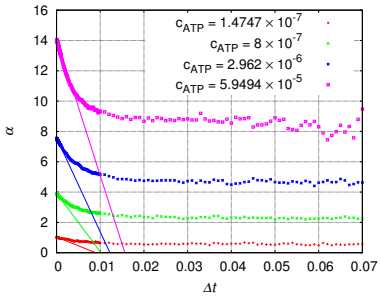




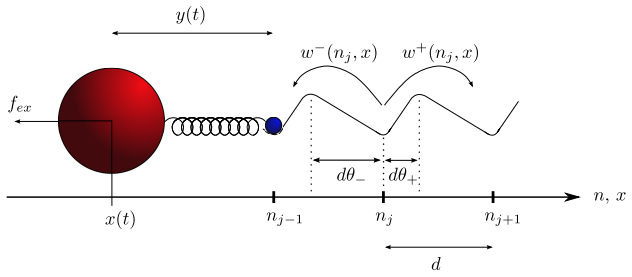








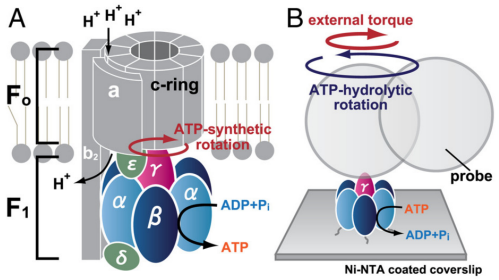
- Efficiency of F_1-ATPase as a thermodynamic machine



  - First law

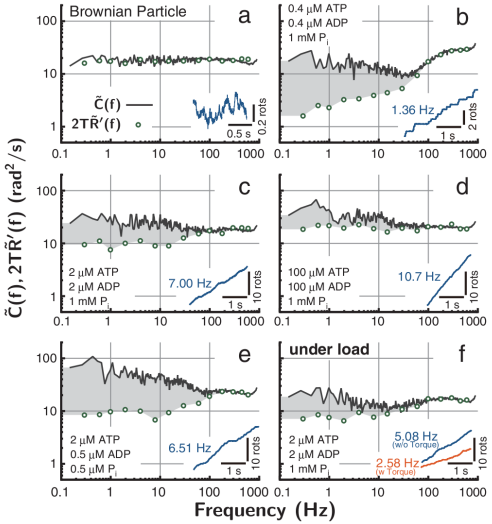
(i) probe	$-f^{\mathrm{ex}}\Delta x$	$=$	$\Delta q_p + \Delta V_{\vert p}$	Sekimoto '97
(ii) motor	0	$=$	$\Delta q_m + \Delta V_{\vert m} + \Delta E_{sol}$	U.S., EPJE **34** 26, 2011
mean	$-f^{\mathrm{ex}}v$	$=$	$\dot{Q}_p + \dot{Q}_m + \Delta \dot{E}_{sol}$	$\Delta E_{sol} = -\Delta\mu + T\Delta S_{sol}$
$\rightarrow$	$\dot{\Delta}\mu - f^{\mathrm{ex}}v$	$=$	$\dot{Q}_p + \underbrace{\dot{Q}_m + T\dot{S}_{sol}}_{\text{not distinguishable}}$	

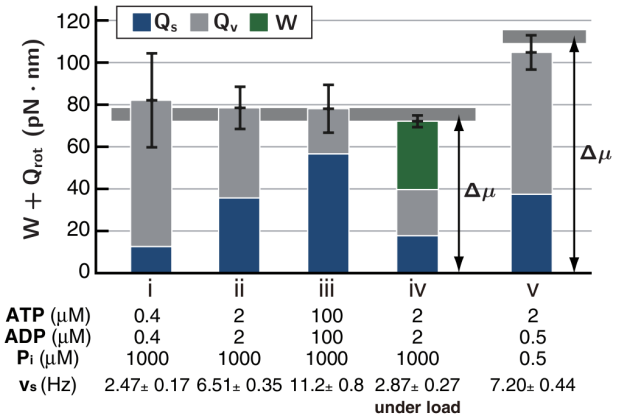
- Inferring the efficiency of a molecular motor



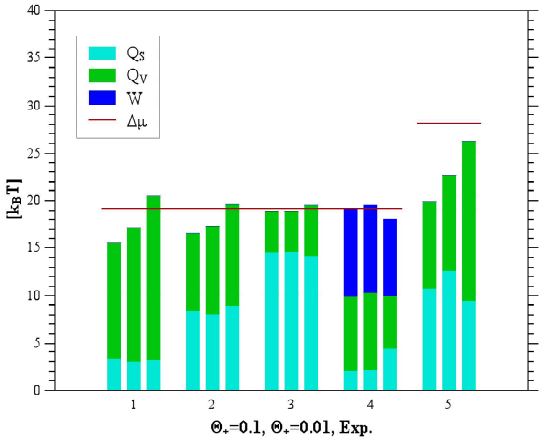
Harada-Sasa relation (PRL 2006)

$$\mu \dot{Q}_P = v^2 + \int d\omega [C_{\dot{x}}(\omega) - 2k_B T \ \mathrm{Re} R_{\dot{x}}(\omega)]$$





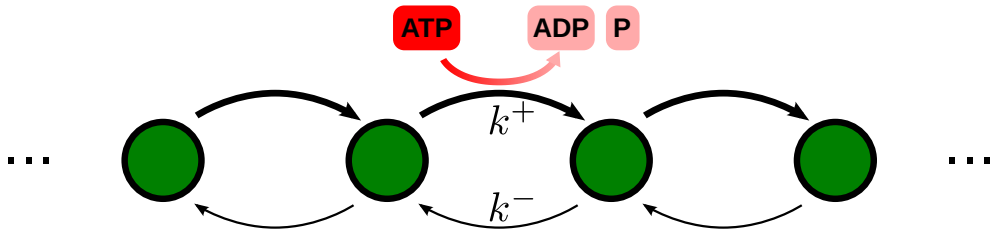
S. Toyabe et al, PRL 104, 198103 (2010)



E. Zimmermann and US, NJP 2012

- Thermodynamic uncertainty relation: Cost of precision

[AC Barato and US, Phys. Rev. Lett. 114, 158101, 2015; full proof by Gingrich et al, PRL 2016]



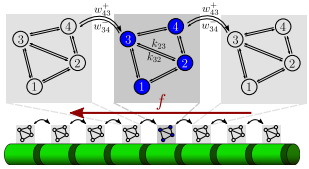
– output $n(t)$ with $\langle n \rangle = Jt = (k^+ - k^-)t$

– variance $\langle (n(t) - \langle n \rangle)^2 \rangle = 2Dt = (k^+ + k^-)t$

– uncertainty $\epsilon^2 \equiv \text{var}/\text{output}^2 = 2D/J^2 t$

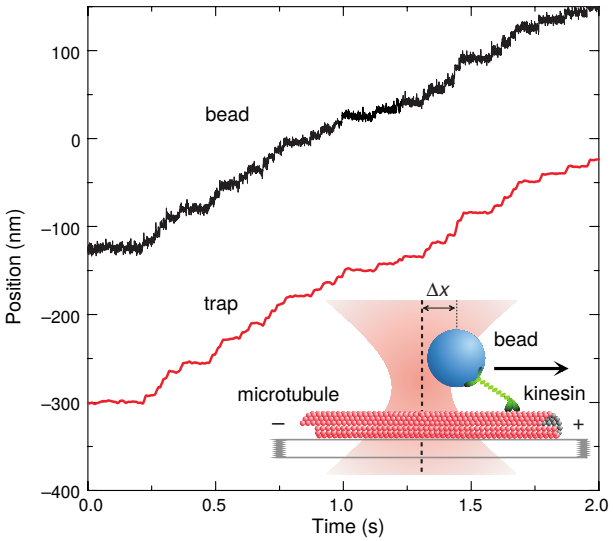
– th'dyn cost $\mathcal{C} = \sigma t = (k^+ - k^-) \ln(k^+/k^-)t$ with $\sigma \equiv$ rate of entropy production

– $\boxed{\mathcal{C}\epsilon^2 = 2\sigma D/J^2 \geq 2k_B T}$ independent of run time t



– inevitable, universal cost of precision (within any model based on a stationary Markov process)

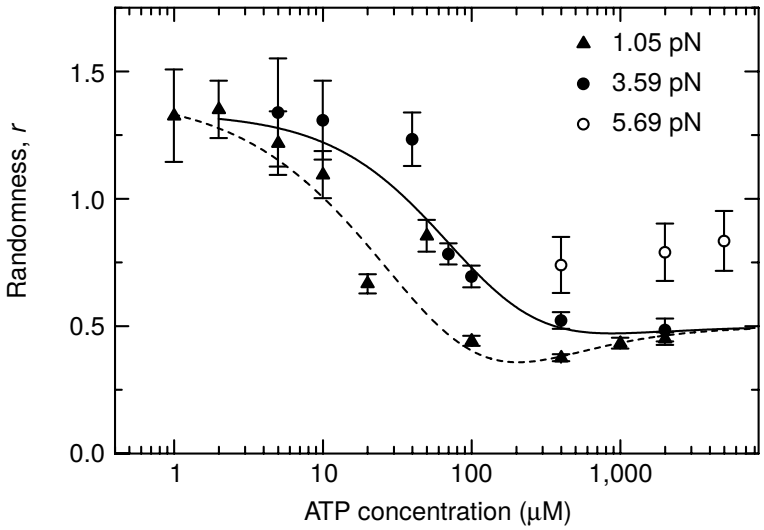
- Thermodynamic inference: Efficiency of a molecular motor

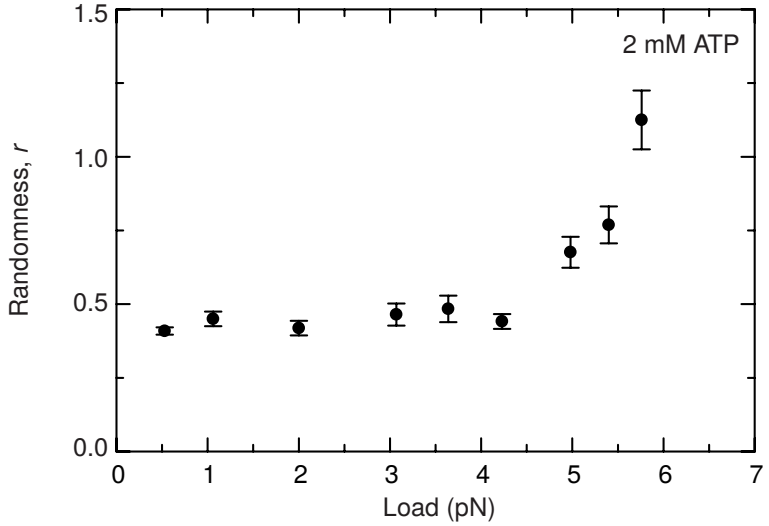


[Visscher et al, Nature, 1999]

– experimental data on

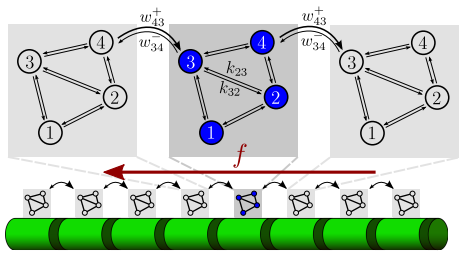
  * velocity v
  * diffusion constant D
  * randomness parameter $r \equiv 2D/v\ell$





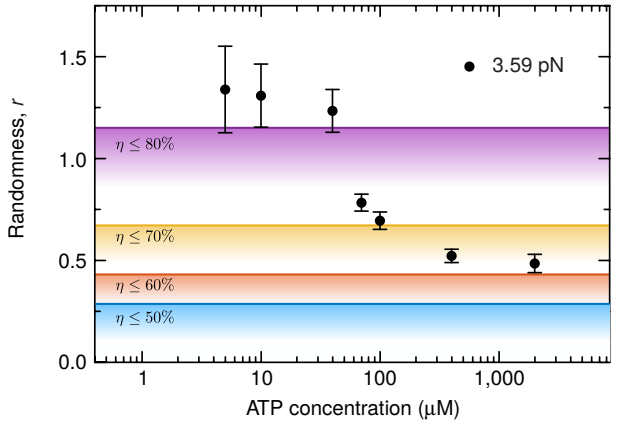
- Thermodynamic inference: Universal bound on the efficiency of molecular machines

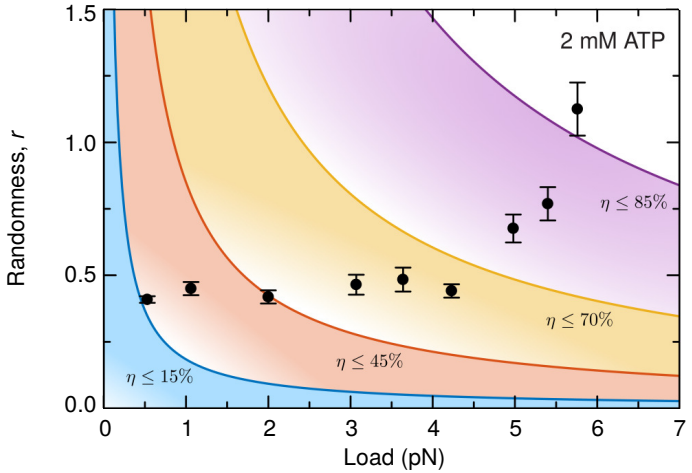
  [P. Pietzonka, AC Barato, U.S., J Stat Mech, 124004, 2016; U.S., Physica A 504, 176, 2018]



  - entropy production rate $\sigma = P^{\text{in}} - P^{\text{out}} = \text{"chem energy"} - fv \geq v^2/D$
  - efficiency

$$\eta \equiv \frac{P^{\text{out}}}{P^{\text{in}}} = \frac{fv}{\text{unknown}} = \frac{fv}{fv+\sigma} \leq \frac{1}{1+vk_BT/(Df)}$$

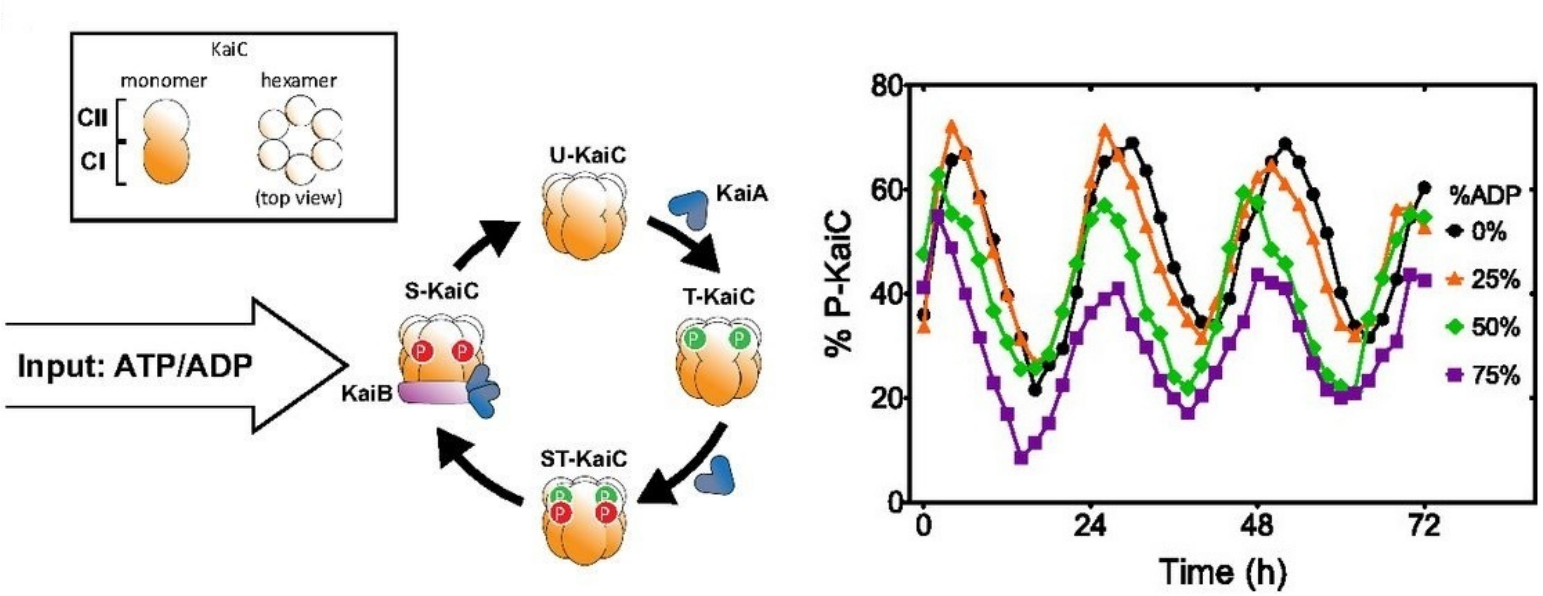




  - completely independent of the specific chemo-mechanical cycles and of $\Delta\mu$

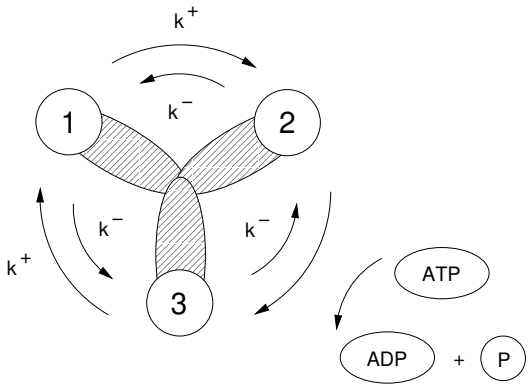
- Temporal precision in an aqueous finite temperature environment

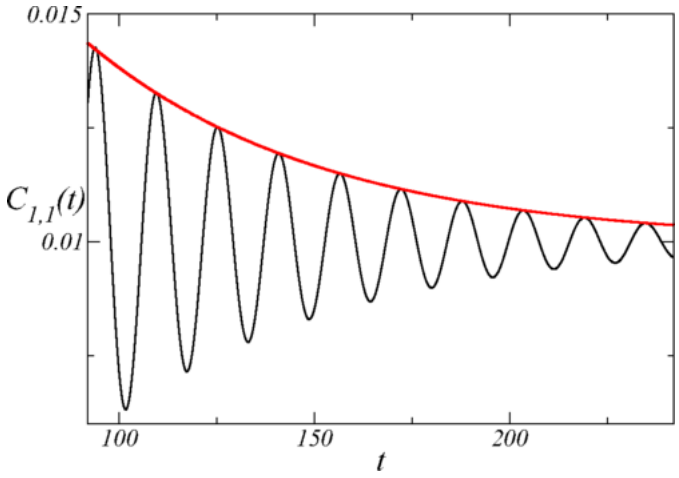
- Biochemical oscillators
  - Kai-system circadian clock reconstructed from cyanobacterium



C. Phong *et al.* PNAS **110**, 1124 (2013).

- Toy model [AC Barato and U.S, Phys Rev E 95, 062409 (2017)]
  - Unicycle with N equivalent states and driving affinity $\mathcal{A} = N \ln(k^+/k^-)$





$N = 100, \mathcal{A} = 200 \Rightarrow \mathcal{N} \simeq 4$

  - Correlation function $C(1,t|1,0) = p_1^s + \sum_{j=2}^{N} c_j \exp[-\lambda_j t]$

  - coherence is lost after

$$\mathcal{N} \equiv \frac{t_{\rm rel}}{t_1} = \frac{\Im\lambda_2}{2\pi\Re\lambda_2} = \frac{\tanh(\mathcal{A}/2N)}{2\pi\tan(\pi/N)} \leq \frac{1}{4\pi^2}\min(\mathcal{A}, 2N) \qquad \text{cycles}$$

  - bounded by the ...
    - number of states: $\mathcal{N} \leq N/2\pi^2$
    - free energy spent per cycle: $\mathcal{N} \leq \mathcal{A}/4\pi^2 \quad \Rightarrow \quad$ cost/cycle $\geq 4\pi^2\mathcal{N}$ $\quad (\simeq 400 k_B T$ for $\mathcal{N} = 10)$

- Continuum version: "Langevin clock"

  - angle driven by torque $\mathcal{T}$

$$\dot{\phi} = \mu\mathcal{T} + \zeta$$

  - affinity

$$\mathcal{A} = 2\pi\mathcal{T}$$

  - cycle time

$$t_1 = 2\pi/\mu\mathcal{T}$$

  - coherence lost if

$$\Delta\phi \simeq \pi/2$$

  - decoherence time

$$t_{\rm dec} = \pi^2/8\mu$$

  - number of coherent oscillations

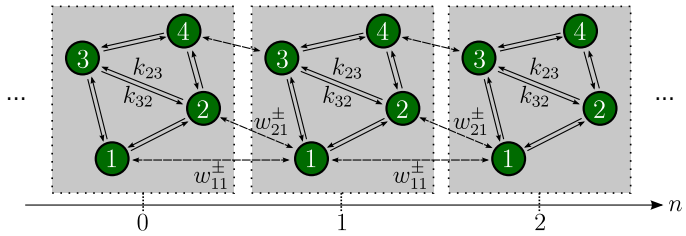
$$\mathcal{N} = t_{\rm dec}/t_1 = \mathcal{A}/32$$

  - cf discrete relation

$$\mathcal{N} \leq \mathcal{A}/4\pi^2$$

- Conjecture for an arbitrary multicyclic network (based on limiting cases and lots of numerics)

  [AC Barato and U.S, Phys Rev E 95, 062409 (2017)]

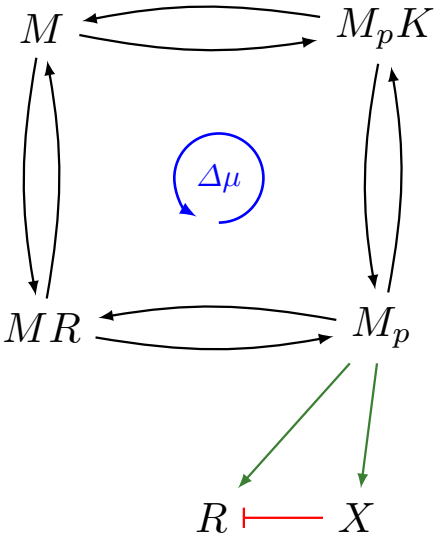


  – number of coherent oscillations is bounded by "best" cycle in the network

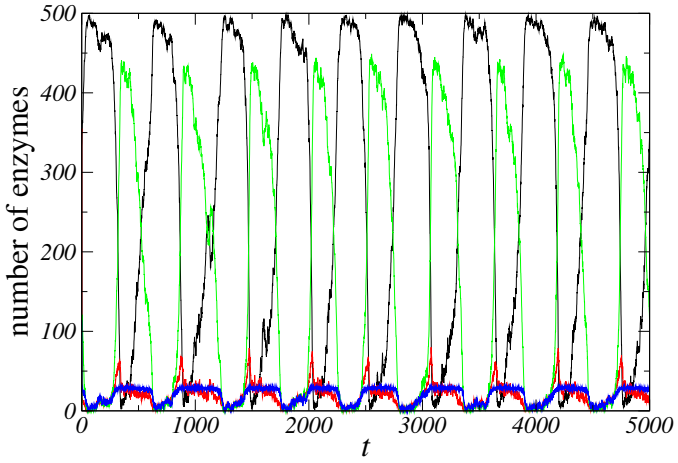
$$\mathcal{N} \leq \max_{\text{cycles}} \frac{\tanh(\mathcal{A}/2N)}{2\pi \tan(\pi/N)} \leq \frac{\max \mathcal{A}}{4\pi^2}$$

- Activator-inhibitor model

[AC Barato and U.S, Phys Rev E 95, 062409 (2017)] inspired by Y. Cao, ..., Y. Tu, Nat. Phys **11**, 772 (2015)]



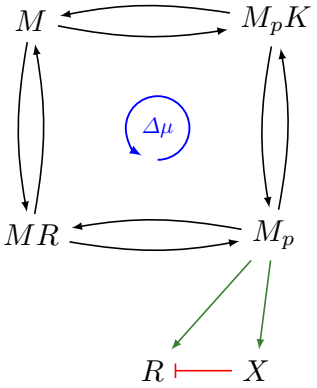
$$M_p + S \rightleftharpoons M_p + R$$
$$M_p + S \rightleftharpoons M_p + X$$
$$X + R \rightleftharpoons X + S$$
$$X \rightleftharpoons S$$

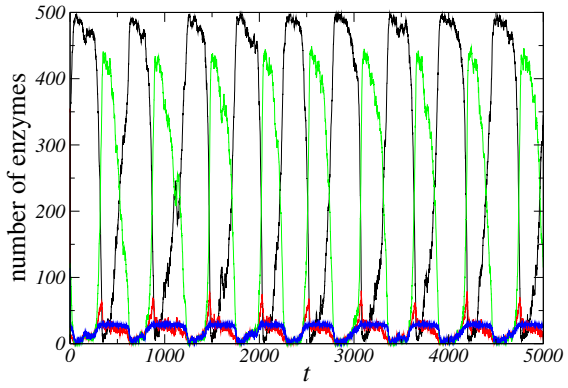


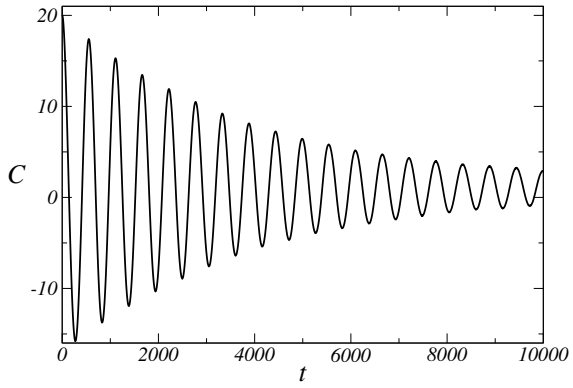
$M+MR+M_p+M_pK = N_M = const \quad K+M_pK = N_K = const \quad \Delta\mu = 12, N_M = 500, N_K = 30$

- Coherence of oscillations

$$C(t) \equiv \langle (N_X(t) - \langle N_X \rangle)(N_X(0) - \langle N_X \rangle) \rangle$$





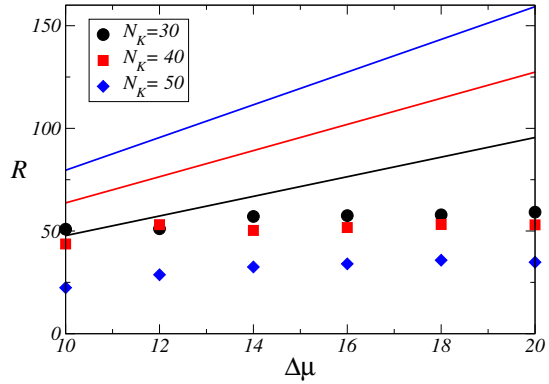


– $\mathcal{A}$ and N of best cycle in this enormous space of states?

chemical master equation

$$\partial_t P(\mathbf{N}, t) = -\sum_\rho \left[\nu_{+\rho}(\mathbf{N}) P(\mathbf{N}, t) - \nu_{-\rho}(X + \nabla_\rho)\, p(\mathbf{N} + \nabla_\rho, t) \right]$$

with $\mathbf{N} \equiv (M, MR, M_p, M_pK, K, X, R)$



$$\mathcal{N}_{\text{est}} = N_K \Delta\mu / 4\pi^2$$

- Generalizations to periodically driven systems with period $\mathcal{T} = 2\pi/\Omega$

  – thermodynamic uncertainity relation

  $\sigma(\Omega)D(\Omega)/j(\Omega)^2 \geq (1 - j'(\Omega)/j(\Omega))^2 \quad \Rightarrow \quad$ dissipationless precision

  [T. Koyuk and U.S., Phys. Rev. Lett. 122, 230601, 2019]

  – no N-dependent fundamental limit on number of coherent oscillations

  [L. Oberreiter, U.S, AC Barato, Phys. Rev. E 100, 012135, 2019]

- Summary
  - stochastic thermodynamics along individual trajectories
    - first law, fluctuation theorems as refinements of the second law
    - efficiency of molecular machines
  - universal bounds through the thermodynamic uncertainty relation for NESSs
  - thermodynamic inference can reveal hidden properties of molecular motors and biochemical networks
  - inevitable cost of temporal precision: coherent oscillations

- Acknowledgments
  - molecular motor P Pietzonka ($\rightarrow$ U of Cambridge), E Zimmermann
  - thermodynamic uncertainty relation and bounds AC Barato ($\rightarrow$ U of Houston), P Pietzonka