ICTS program "Non-equilibrium statistical physics", Bangalore, November 2015

Current fluctuations in biomolecular systems

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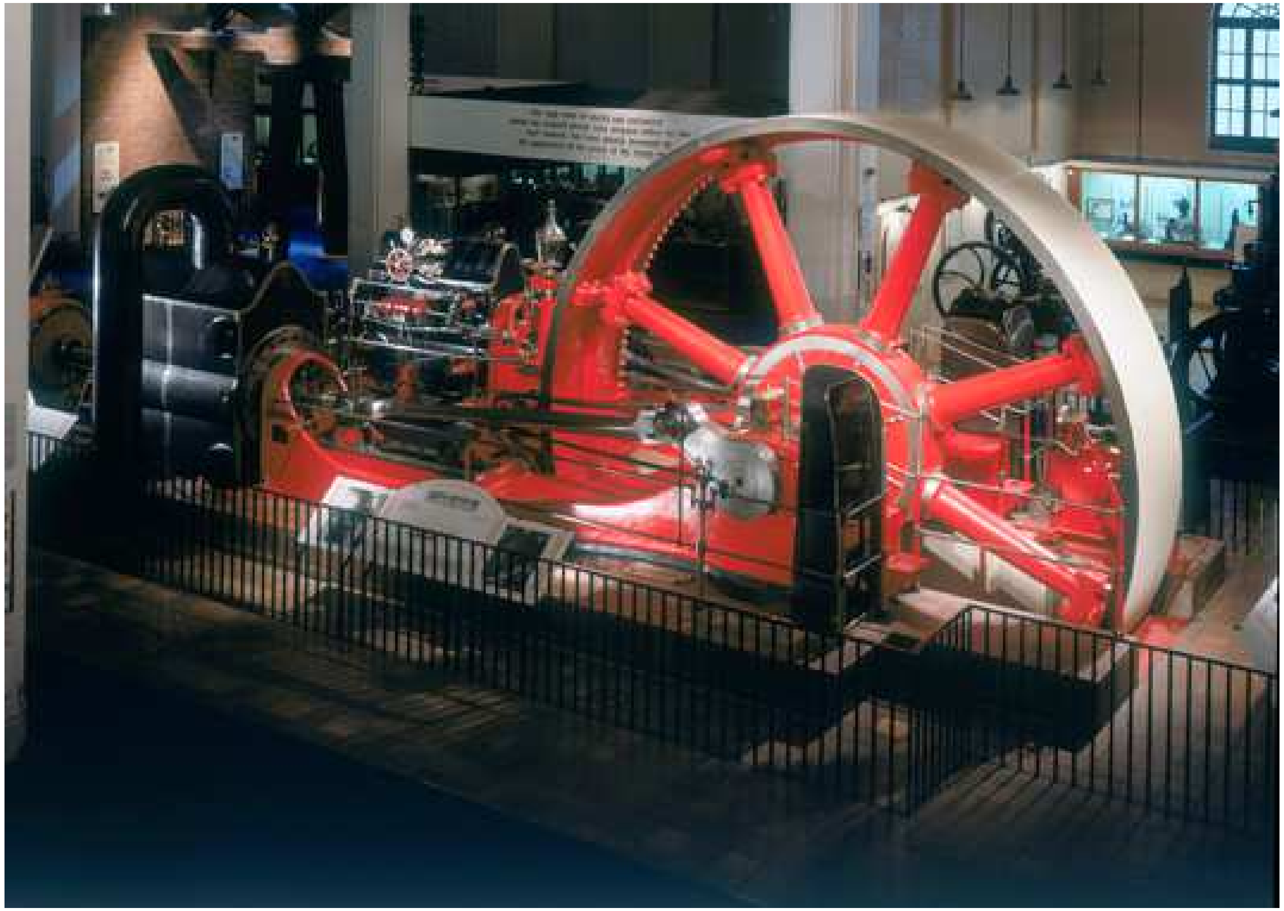
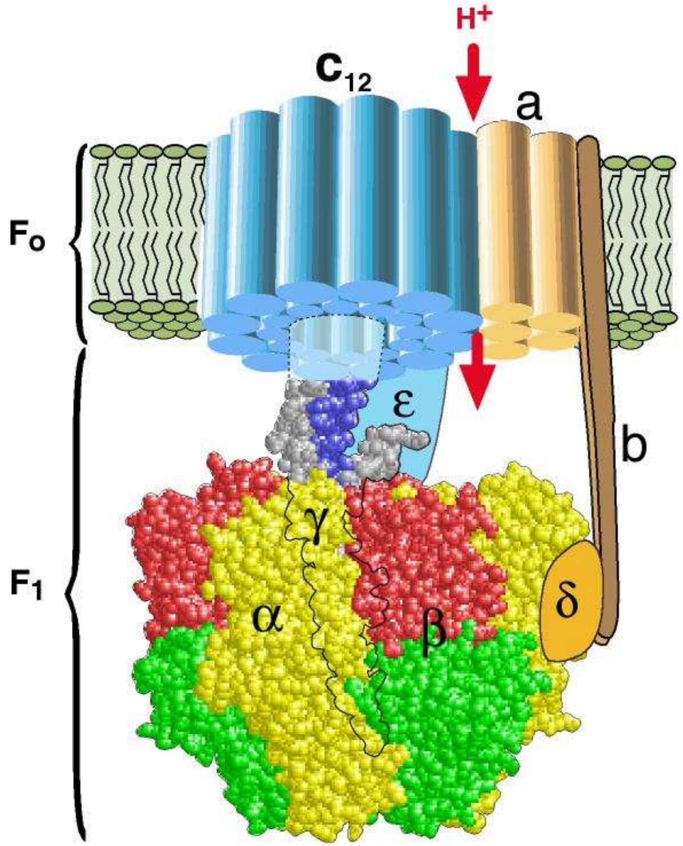
- Intro: Stochastic thermodynamics and molecular motors
- Fine-structured fluctuation theorem   E Zimmermann + P Pietzonka
- Thermodynamic uncertainty relation   AC Barato

• Classical vs stochastic thermodynamics

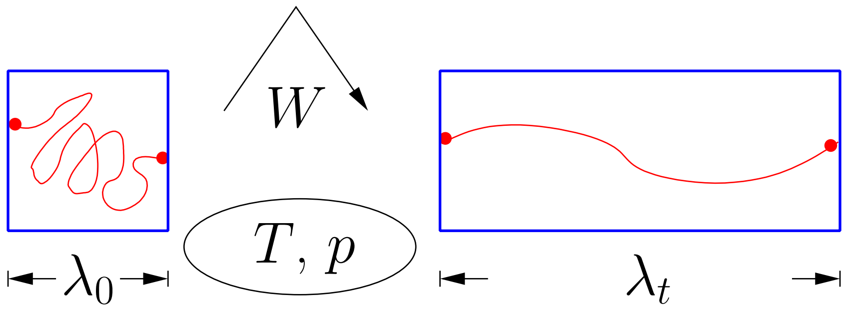


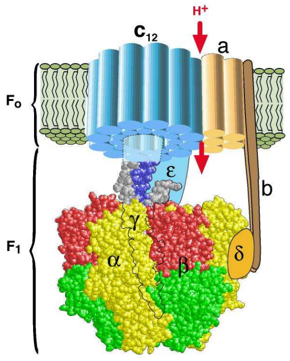


H. Wang and G. Oster (1998). Nature 396:279-282.

Steam engine (Science museum London) F_1ATP-ase

- **Stochastic thermodynamics** applies to such systems where
  - non-equilibrium is caused by mechanical or chemical forces
  - ambient solution provides a thermal bath of well-defined T and μ_i
  - fluctuations are relevant due to small numbers of involved molecules





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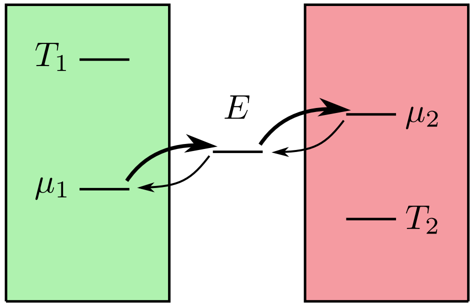
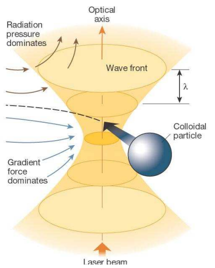


- Main idea: Energy conservation (1^{st} law) and entropy production (2^{nd} law) along an individual stochastic trajectory

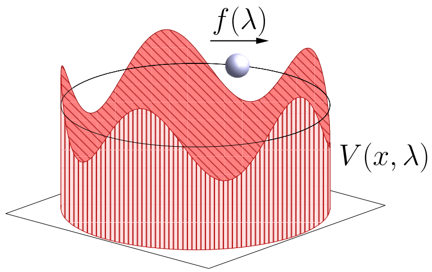
- Review: U.S., Rep. Prog. Phys. **75** 126001, 2012.

- Stochastic th'dynamics for a driven colloidal particle

  – Langevin dynamics



D.G. Grier A revolution in optical manipulation, Nature **424**, 810 (2003)



$$\dot{x} = \mu[-V'(x,\lambda) + f(\lambda)] + \zeta$$

with $\langle \zeta_1 \zeta_2 \rangle = 2\mu k_B T \delta_{12}$

  – external driving $\lambda(\tau)$

- First law [(Sekimoto, 1997)]: $dw = du + dq$

  – applied work: $dw = \partial_\lambda V(x,\lambda) d\lambda + f\ dx$

  – internal energy: $du = dV$

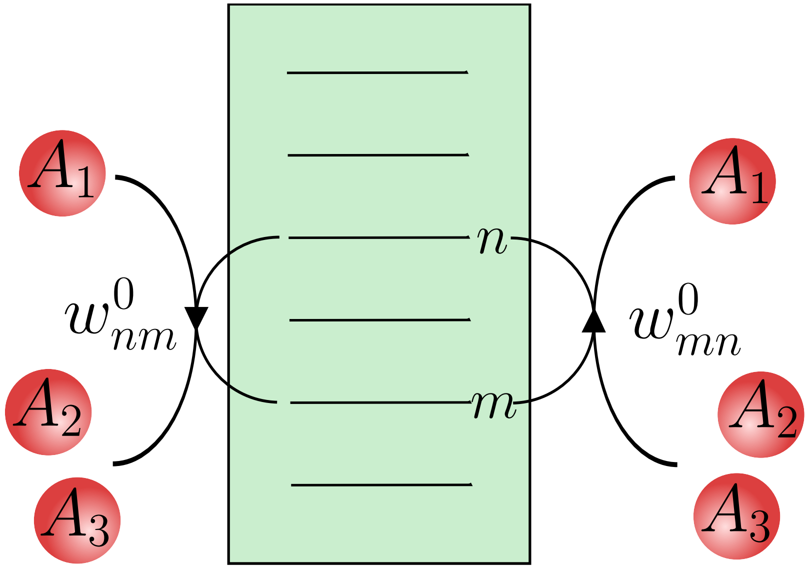
  – dissipated heat: $dq = dw - du = [-\partial_x V(x,\lambda) + f] dx = T ds_{\mathrm{m}}$

- stochastic entropy and second law [U.S., PRL 95, 040602, 2005]

$$ds \equiv -d\ [\ln p(x,t)] \quad \Rightarrow \langle \exp[-\Delta(s + s_{\mathrm{m}})] \rangle = 1 \quad \Rightarrow \langle \Delta s_{\mathrm{tot}} \rangle \geq 0$$

- Stochastic th'dynamics of a driven enzym with internal states

  [T.Schmiedl, T.Speck and U.S., JSP **128** 77, 2007; U.S., EPJ E **34** 26, 2011]



  – $A_1 + n \underset{w_{mn}}{\overset{w_{nm}}{\rightleftharpoons}} m + A_2 + A_3$

  – $F_n = E_n - TS_n$

  – mass action law kinetics:

  – $\frac{w_{nm}}{w_{mn}} = \frac{w^0_{nm}}{w^0_{mn}}[A_1]/[A_2][A_3]$

  – th'dynamically consistent rates $\boxed{\ln w_{nm}/w_{mn} = \Delta\mu - (F_m - F_n)}$

  – first law

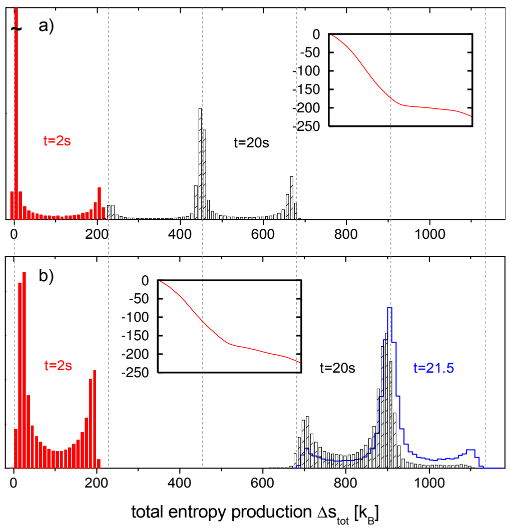
$$
\begin{aligned}
0 &= \Delta E + q \\
&= (E_m - E_n) + \Delta E^{\text{sol}} + q^{nm} \\
\Rightarrow \Delta\mu &= \mu_1 - \mu_2 - \mu_3 = q^{nm} + (E_m - E_n) + \Delta S^{\text{sol}}
\end{aligned}
$$

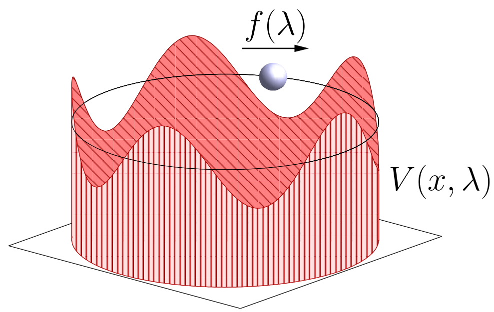
- NESS: Fluctuation theorem $\boxed{p(-\Delta s_{\text{tot}})/p(\Delta s_{\text{tot}}) = \exp(-\Delta s_{\text{tot}})}$

long-time limit: Evans et al (1993), Gallavotti & Cohen (1995), Kurchan (1998), Lebowitz & Spohn (1999) ... finite times: U.S., PRL'05

  – experimental data

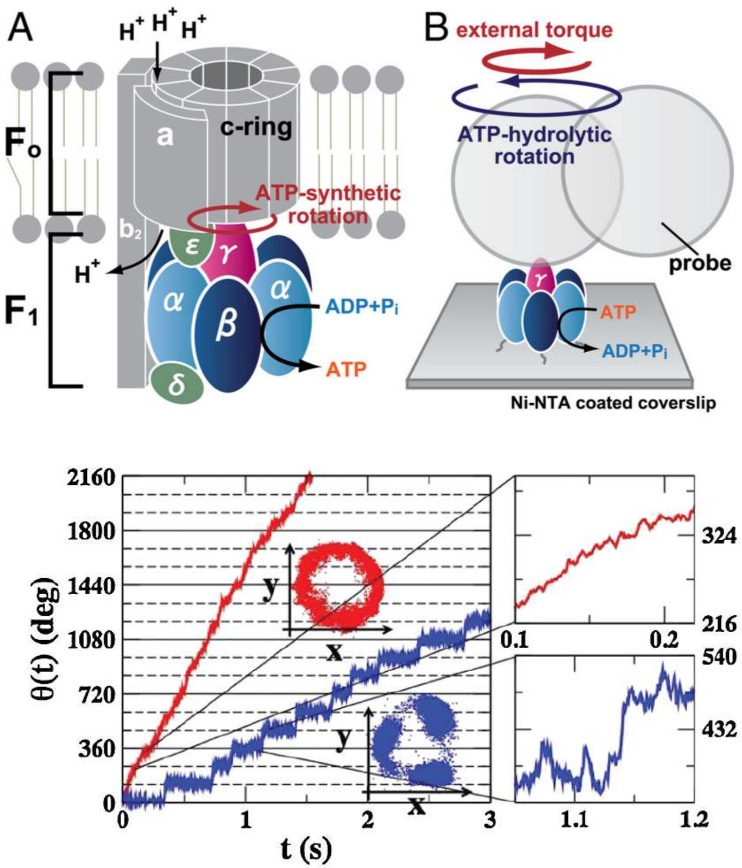
    [Speck, Blickle, Bechinger, U.S., EPL **79** 30002 (2007)]





- An isothermal nano-rotor: F1-ATP-ase

[K. Hayashi, ... H. Noji, PRL 104, 218103 (2010)]



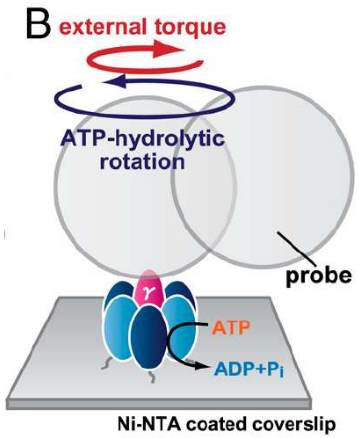
– kinetics vs thermodynamics

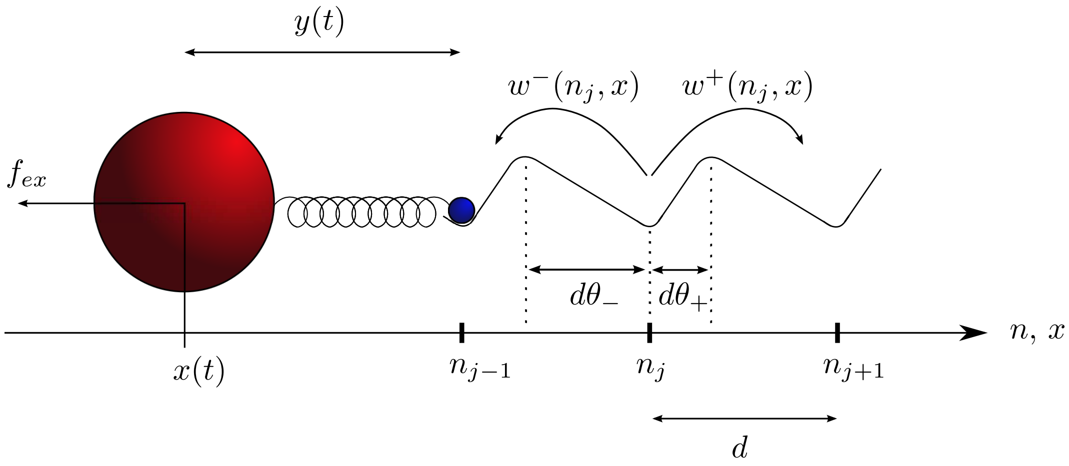
– first law?

– efficiency(ies)?

- Hybrid model

[E. Zimmermann and U.S., NJP 14, 103023, 2012; PRE 91, 22709, 2015]





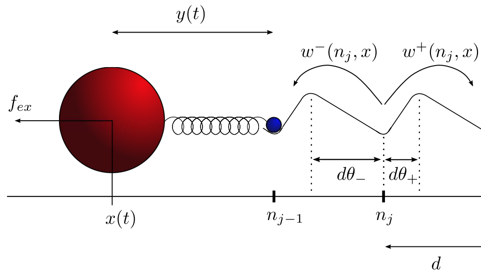
- probe particle

  - $*$ $\dot{x} = \mu(-\partial_y V(y) + f^{\text{ex}}) + \zeta$ with $y(\tau) \equiv n(\tau) - x(\tau)$

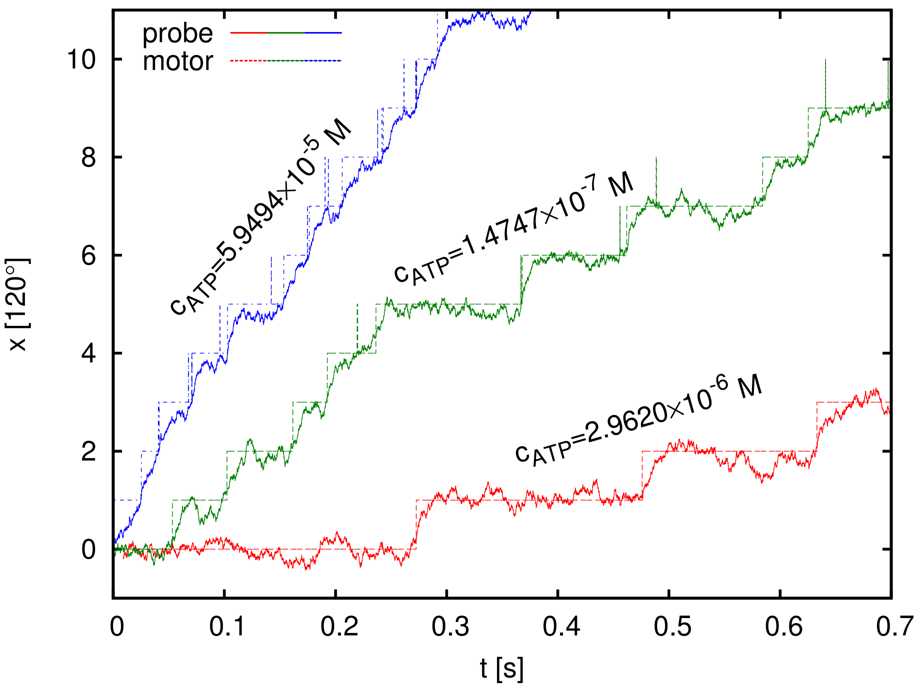
- motor

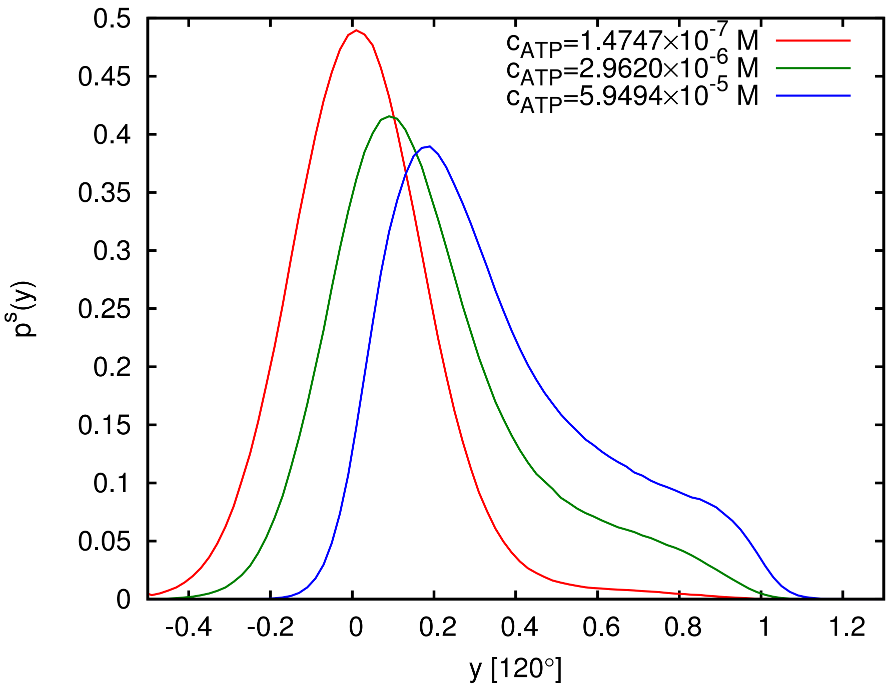
  - $*$ $w^+/w^- = \exp[\Delta\mu - V(n+d,x) - V(n,x)]$

  - $*$ local detailed balance condition



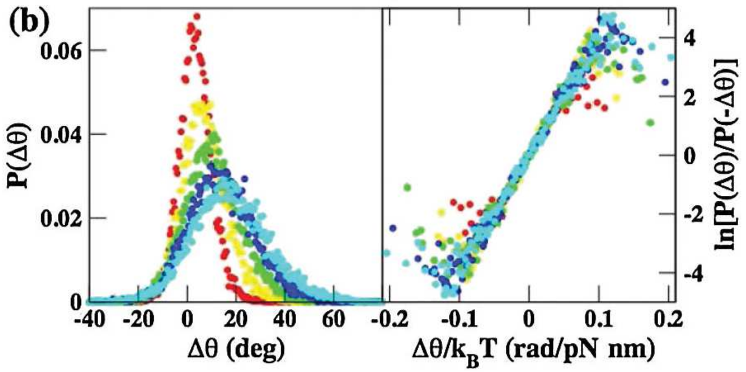
- Simulated trajectories and stationary distribution $p^s(y)$

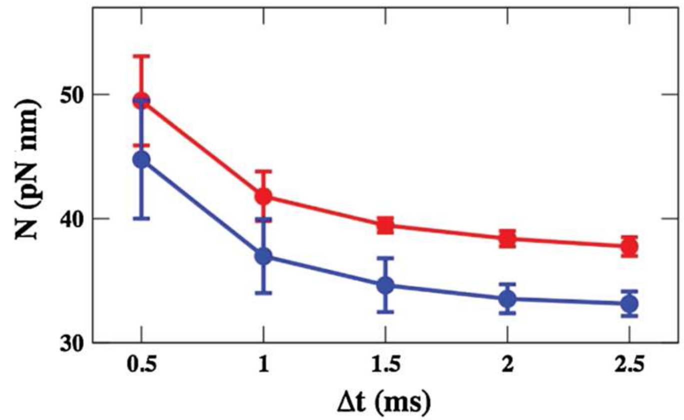




- F1-ATPase and the fluctuation theorem

  [K. Hayashi, ... H. Noji, PRL 104, 218103 (2010)]





  – $\Gamma\dot{\theta} = N + \zeta \quad \langle \zeta_1 \zeta_2 \rangle = 2\Gamma k_B T \delta(\tau_1 - \tau_2)$

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

    independent of friction coefficient

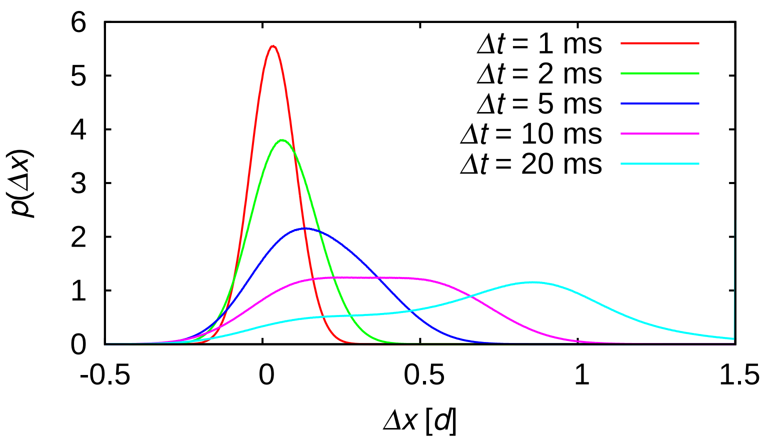
  – cf f'theorem

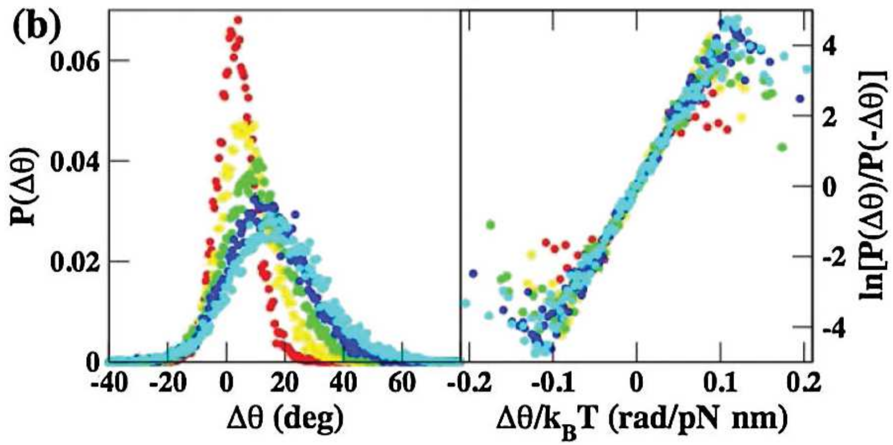
    $\ln[p(\Delta s_{\text{tot}})/p(-\Delta s_{\text{tot}})] = \Delta s_{\text{tot}}/k_B$

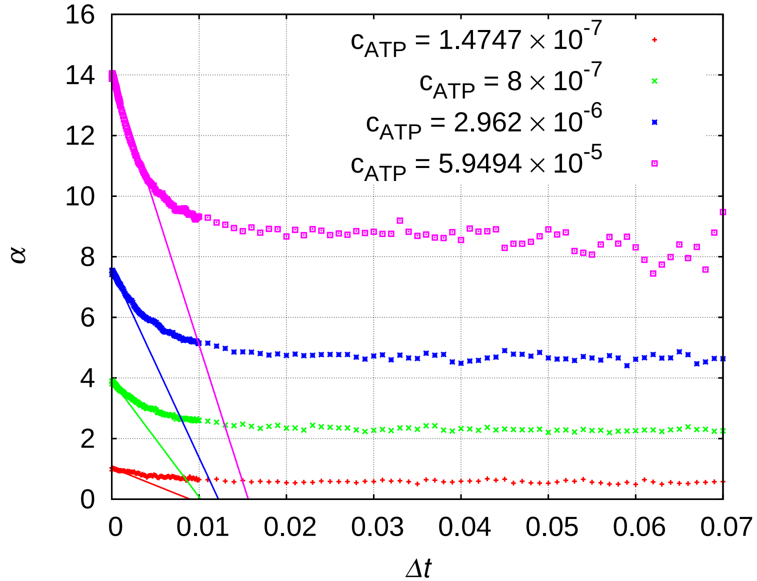
time-dependence?

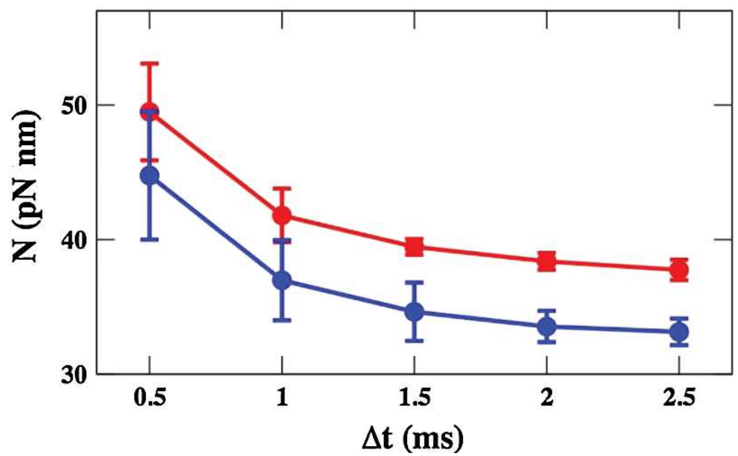
torque from $\Delta t \to \infty$?

- FT-slope from simulations vs experiment









$\Delta t \to 0$ limit yields average force/torque

- F'theorem and slow hidden degrees of freedom

  [J. Mehl, B. Lander, C. Bechinger, V. Blickle and U.S., PRL 108, 220601, 2012]

  – total entropy production in the NESS

  $$\Delta s_{\text{tot}} \equiv \int_0^t d\tau [\dot{x}_1 \nu_1(x_1, x_2) + \dot{x}_2 \nu_2(x_1, x_2)]$$

  with $\nu_1(x_1, x_2) \equiv \langle \dot{x}_1 | x_1, x_2 \rangle$

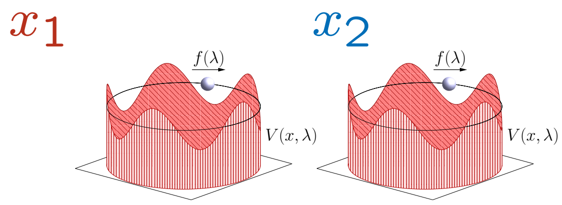
  obeys FT $\quad p(\Delta s_{\text{tot}})/p(-\Delta s_{\text{tot}}) = \exp \Delta s_{\text{tot}}$

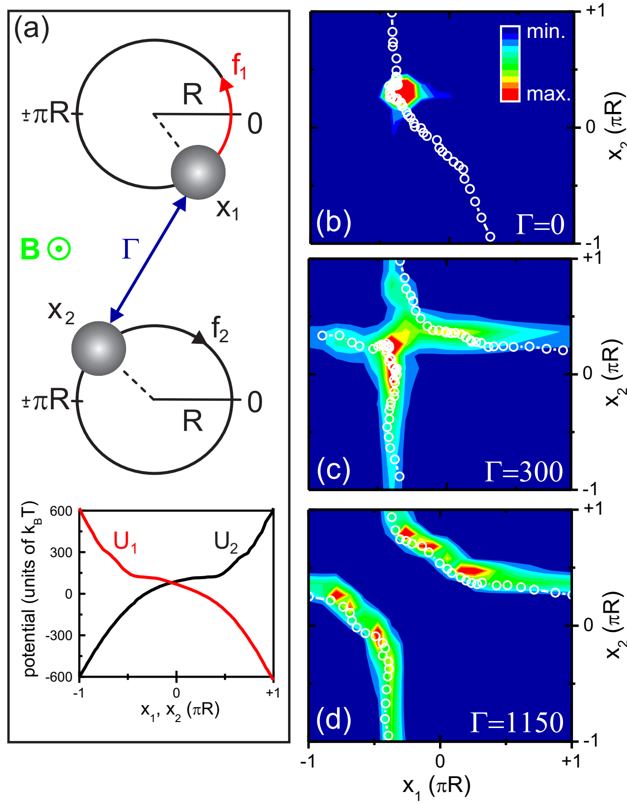
  – suppose x_2 is hidden:

  $$\tilde{\nu}_1(x_1) \equiv \int \nu(x_1, x_2) p(x_2 | x_1) dx_2$$

  – apparent entropy production

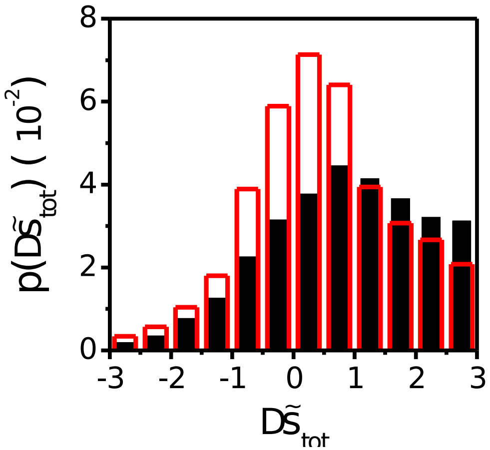
  $\Delta \tilde{s}_{\text{tot}} \equiv \int_0^t d\tau \dot{x}_1 \tilde{\nu}_1(x_1) \qquad$ obeys FT ??

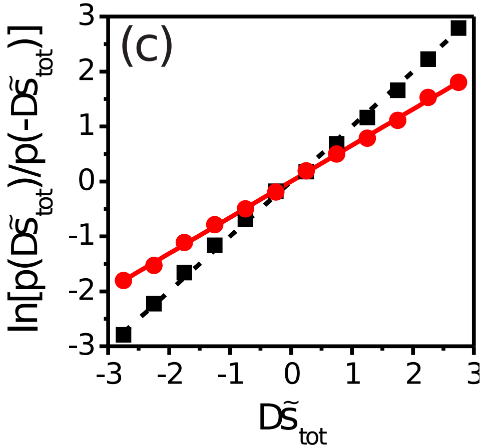


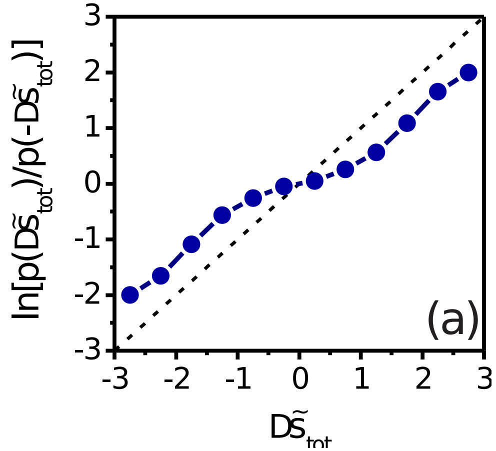


- Experimental data

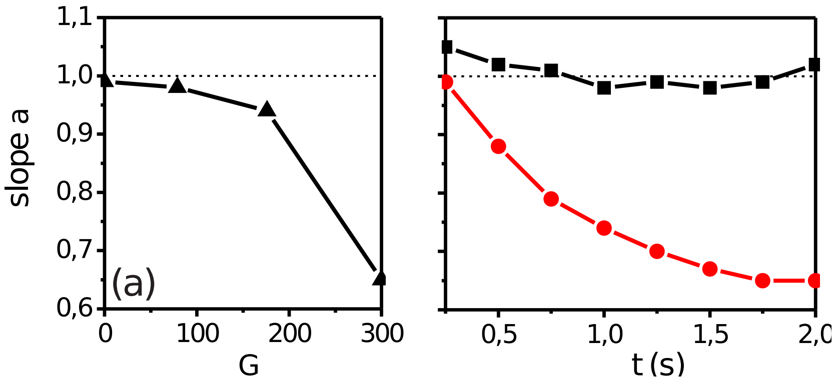
  – with and without coupling [rarely:]





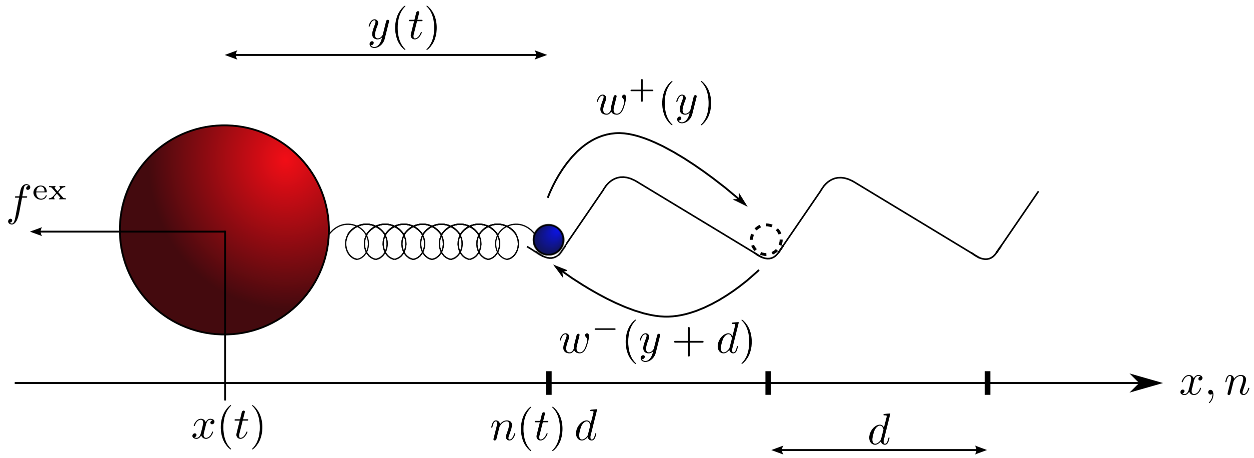


  – FT-slope



- Fine-structured large deviations

  [P. Pietzonka, E. Zimmermann and U.S., EPL **107** 20002, 2014]



  - dynamics $\partial_t p(n,y,t) = (L_1 + L_2)p(n,y,t)$

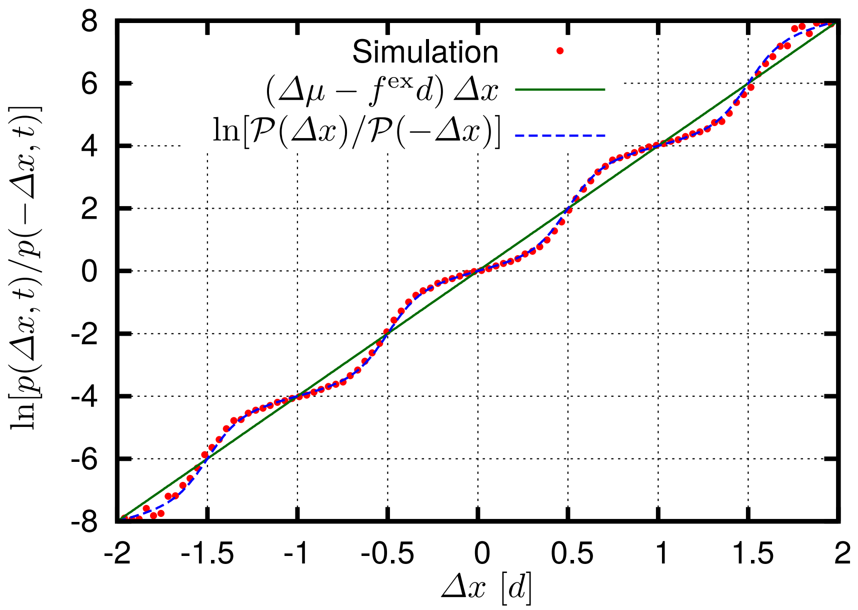
  - generating function $g(\lambda,y,t) \equiv \sum_{n=-\infty}^{\infty} \mathrm{e}^{\lambda n} p(n,y,t) \approx e^{\alpha_0(\lambda)t} Q(\lambda,y,y_0)$

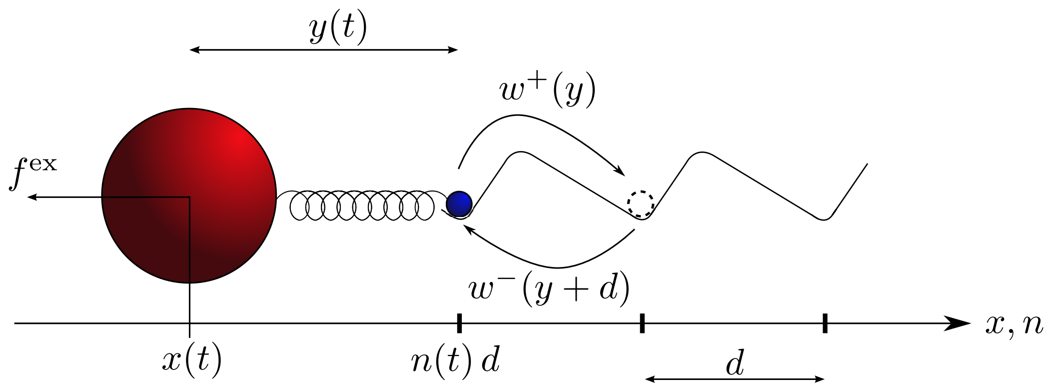
  - large deviation form with amplitude

$$p(n,y,t|y_0) \approx \mathrm{e}^{-th(n/t)} Q(\lambda(n/t),y,y_0)$$

  - rate function $h(u) \equiv u\lambda(u) - \alpha_0(\lambda(u))$

• Fine-structured fluctuation theorem





- for $t \to \infty$: discrete symmetry: $\mathcal{P}(\Delta x + m) = e^{-\lambda_0 m}\mathcal{P}(\Delta x)$

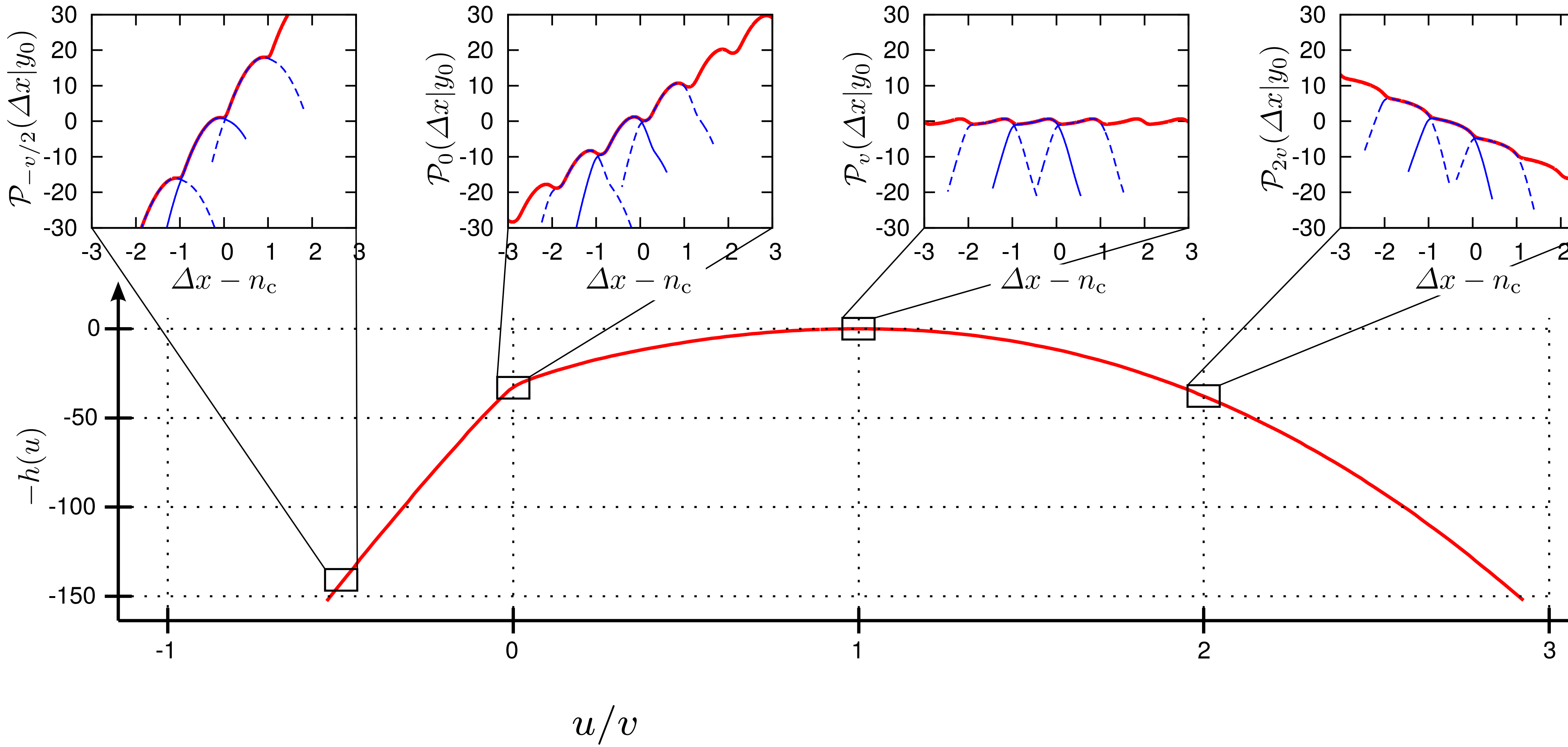
- $\ln \frac{\mathcal{P}(\Delta x)}{\mathcal{P}(-\Delta x)} = -2\lambda_0 \Delta x + \psi(\Delta x)$ with $\lambda_0 = -(\Delta\mu - f^{ex} d)/2.$

  and periodic antisymmetric $\psi(\Delta x)$

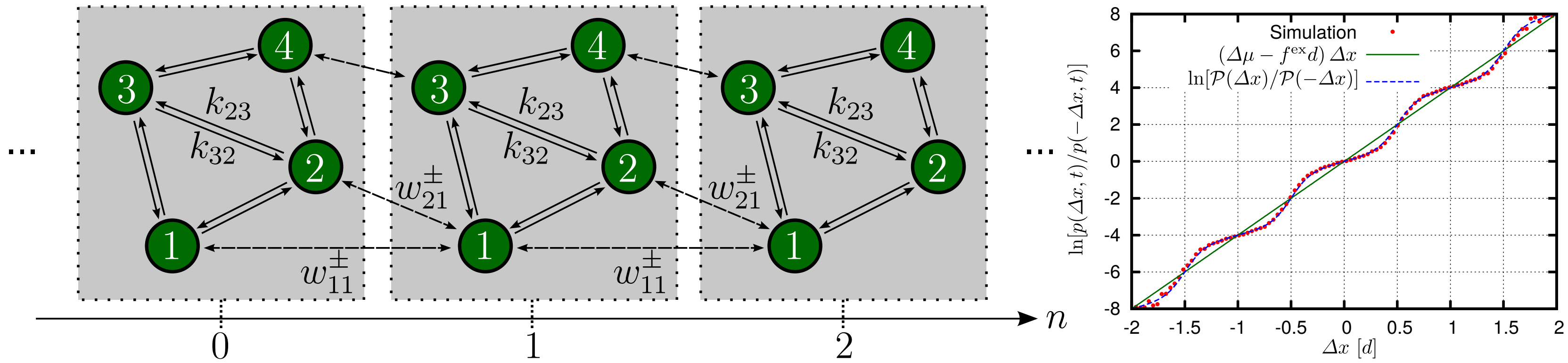
- slope at 0 model specific, certainly not given by entropy production

- "finite-difference slope" determines ent' production

- Fine structure at any "base point" $n_c = ut$



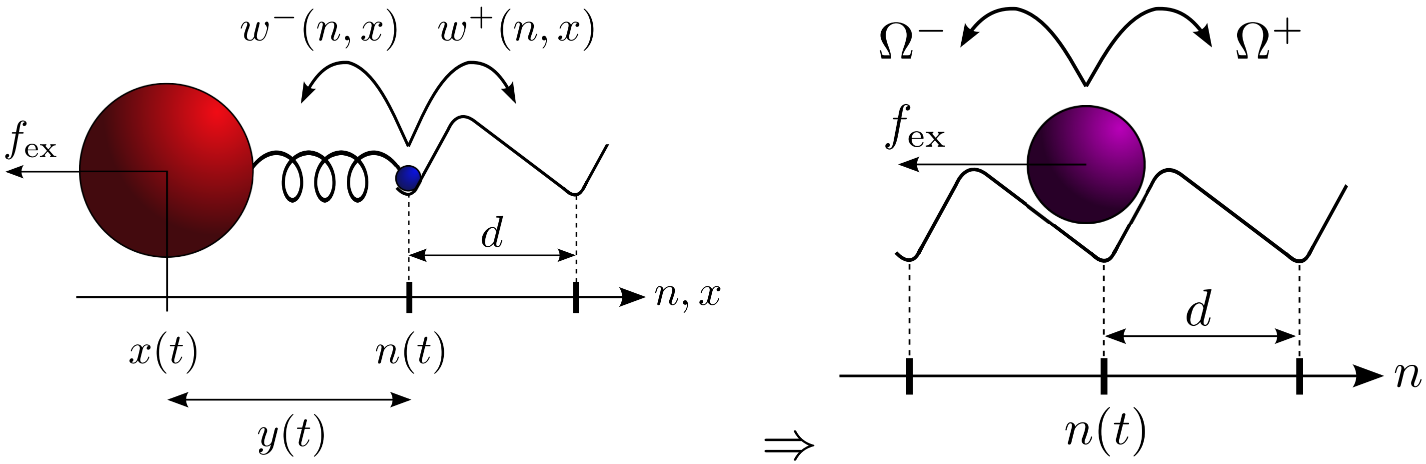
- Generalizations
  - fine structure holds for any model with spatial periodicity and hidden degrees of freedom



- Dynamically and thermod'y consistent coarse-graining of molecular motor models

  [E. Zimmermann and U.S., Phys Rev E 91, 022709, 2015]

  – one-state motor



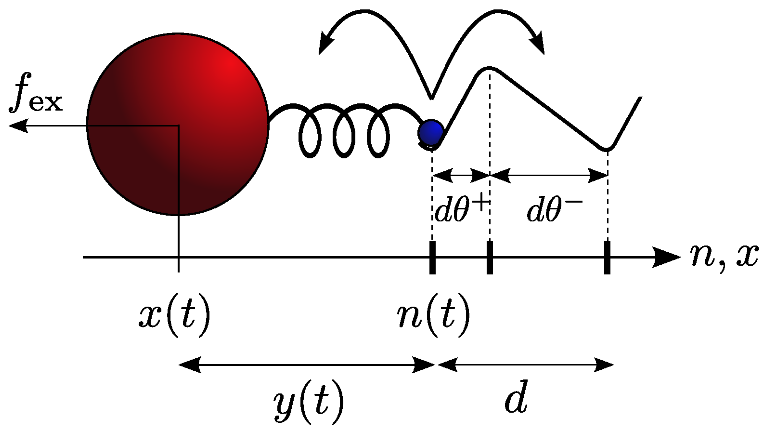
  – conditions: $v = d(\Omega^+ - \Omega^-)$ $\qquad \frac{\Omega^+}{\Omega^-} = \exp[\Delta\mu - f_{\text{ex}} d]$

  – coarse-grained rates

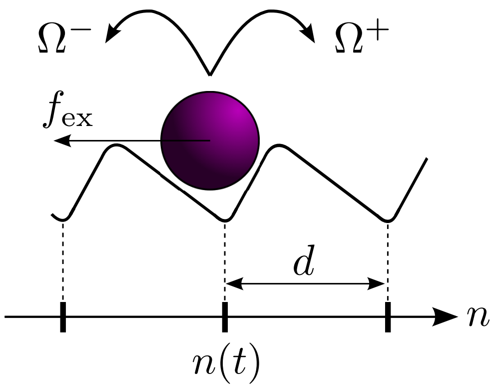
$$\Omega^+ = \frac{v \exp[\Delta\mu - f_{\text{ex}} d]/d}{\exp[\Delta\mu - f_{\text{ex}} d] - 1} \qquad \Omega^- = \frac{v/d}{\exp[\Delta\mu - f_{\text{ex}} d] - 1}$$

- Coarse-graining versus traditional model

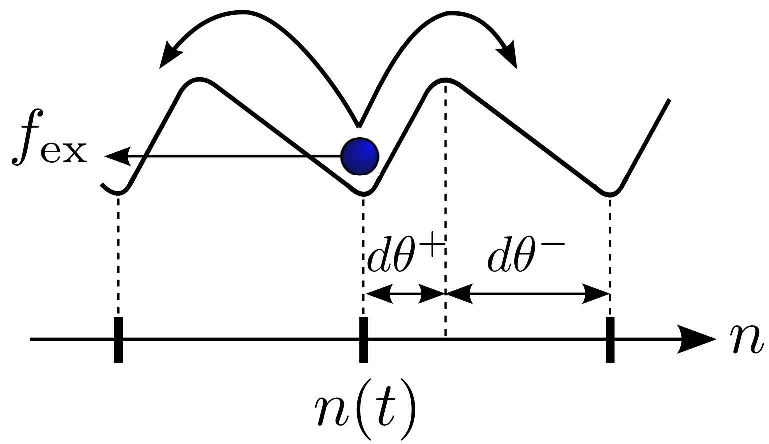
$w^-(y) = k^- e^{\Delta V^-(y,\theta^-)}$ $w^+(y) = k^+ e^{-\Delta V^+(y,\theta^+)}$



$\Downarrow$



$\hat{w}^-(f_{\rm ex}) = k^- e^{f_{\rm ex} d\theta^-}$ $\hat{w}^+(f_{\rm ex}) = k^+ e^{-f_{\rm ex} d\theta^+}$

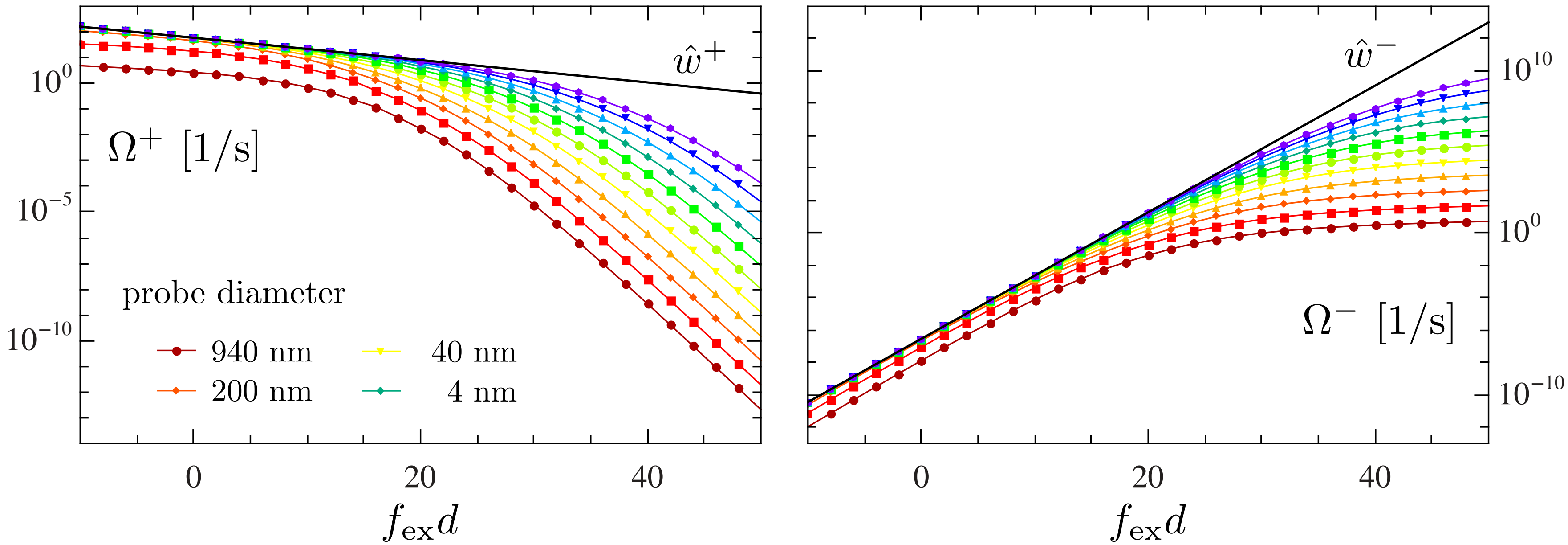


– probe particle omitted

– external force assumed to act directly on the motor

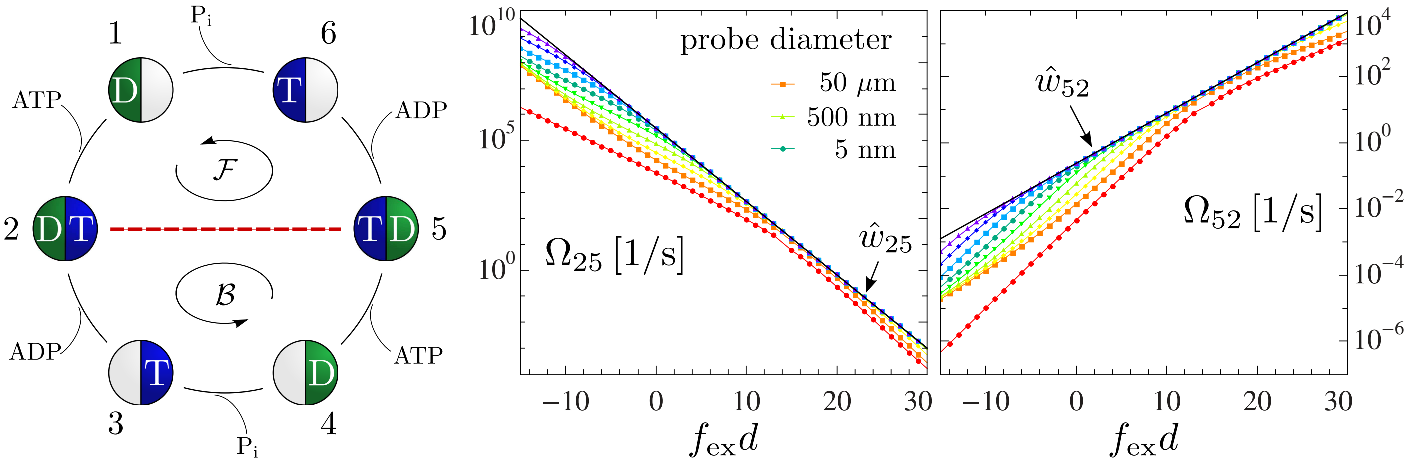
– exponential dependence of the rates on the external force

- Example: F_1-ATPase

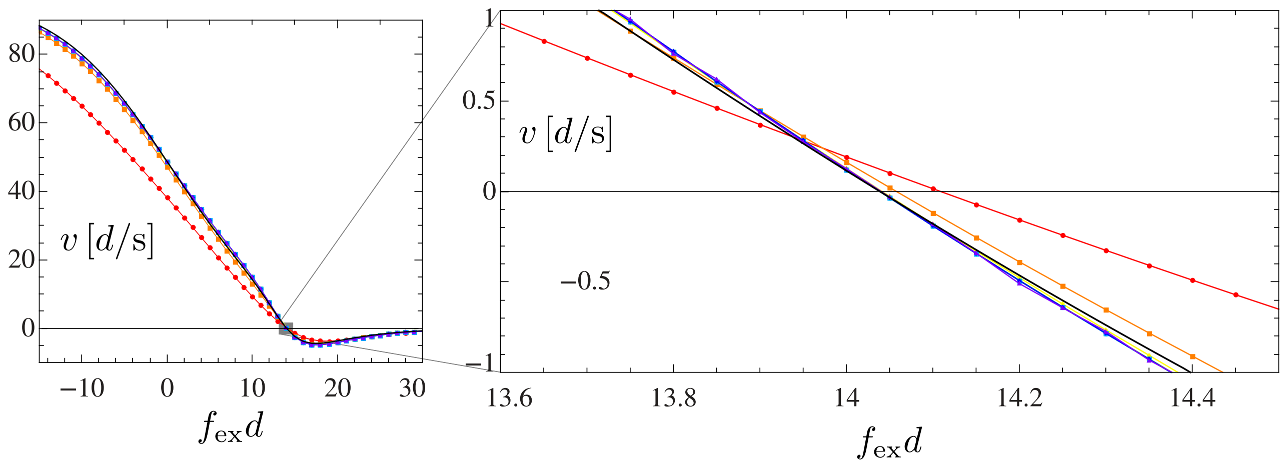


  - $\Omega^\pm$ approach $\hat{w}^\pm$ with decreasing probe size
  - non-exponential dependence of $\Omega^\pm$ on external force

- Coarse-graining multi-state models (Example: Kinesin)

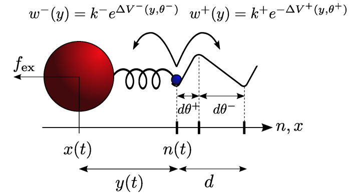


[S. Liepelt et al, PRL 98 (2007)]



– stall force depends on probe size

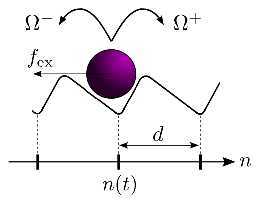
- Invariance of entropy production under coarse-graining

  – detailed model with explicit dynamics of the probe particle:

$$\dot{S}_{\text{tot}} = \underbrace{\sum_i \int \frac{\gamma j_i^{x2}}{p_i(y)} \mathrm{d}y}_{\text{probe}} + \underbrace{\sum_{i,j} \int p_i(y) w_{ij}(y) \ln \frac{p_i(y) w_{ij}(y)}{p_j(y+d_{ij}) w_{ji}(y+d_{ij})} \mathrm{d}y}_{\text{motor}}$$

$$= \sum_{i<j} \Delta\mu_{ij} j_{ij} - f_{\text{ex}} v$$

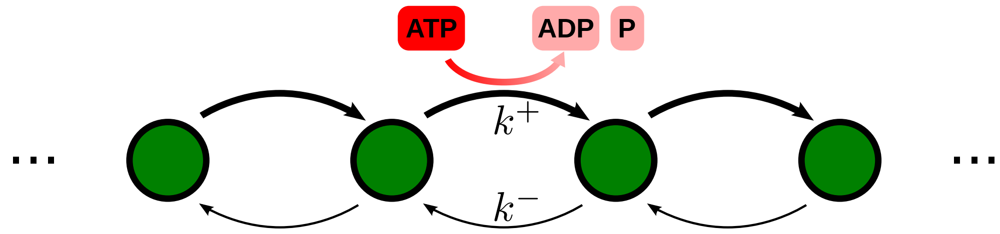
  

  – coarse-grained model:

$$\dot{S}_{\text{tot}} = \sum_{i,j} P_i \Omega_{ij} \ln \frac{P_i \Omega_{ij}}{P_j \Omega_{ji}} = \sum_{i<j} \Delta\mu_{ij} j_{ij} - f_{\text{ex}} v$$

  – entropy production is conserved

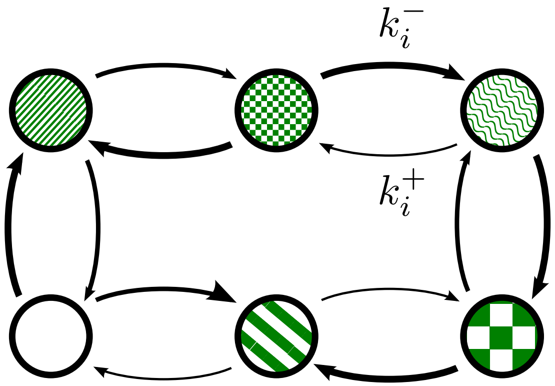
- A th'dynamic perspective on an asymmetric random walk



  - output X with $\langle X \rangle = Jt = (k^+ - k^-)t$
  - variance $\langle (X - \langle X \rangle)^2 \rangle = 2Dt = (k^+ + k^-)t$
  - uncertainty $\epsilon^2 \equiv \text{var}/\text{output}^2 = 2D/J^2 t$
  - th'dyn cost $\mathcal{C} = T\sigma t = J\mathcal{A}t$
  - with affinity $\mathcal{A} = k_B T \ln(k^+/k^-) = \mu_{\text{ATP}} - \mu_{\text{ADP}} - \mu_{\text{P}}$
  - $\boxed{\mathcal{C}\epsilon^2 = \mathcal{A} \coth[\mathcal{A}/2k_B T] \geq 2k_B T}$

- Thermodynamic uncertainty relation: General unicyclic process

[AC Barato and US, Phys. Rev. Lett. 114, 158101, 2015]



$\mathcal{A} \equiv k_B T \ln[\Pi_i(k_i^+/k_i^-)]$, N states

$$\boxed{\mathcal{C}\epsilon^2 \geq (\mathcal{A}/N)\coth[\mathcal{A}/2Nk_BT] \geq 2k_BT}$$

– 1st bound saturates for uniform rates $k_i^\pm = k_i^\pm$

– 2nd bound saturates close to equilibrium (i.e. in LR)

i.e. lowest cost, longest time

- Modified generator

$$[\mathcal{L}^\alpha(z)]_{ij} = \begin{cases} k_{ij}\,\mathrm{exp}(zd_{ij}^\alpha) & \text{if } i \neq j \\ -\sum_j k_{ij} & \text{if } i = j \end{cases} .$$

  - Maximum eigenvalue $\lambda(z) \to J_\alpha = \lambda', D_\alpha = \lambda''$
  - Calculating $\lambda(z)$ is in general hard
  - Expression for diffusion coefficient through characteristic polynomial

$$P(z,y) \equiv \det\left(yI - \mathcal{L}^\alpha(z)\right) = \sum_{n=0}^{N} C_n(z) y^n$$

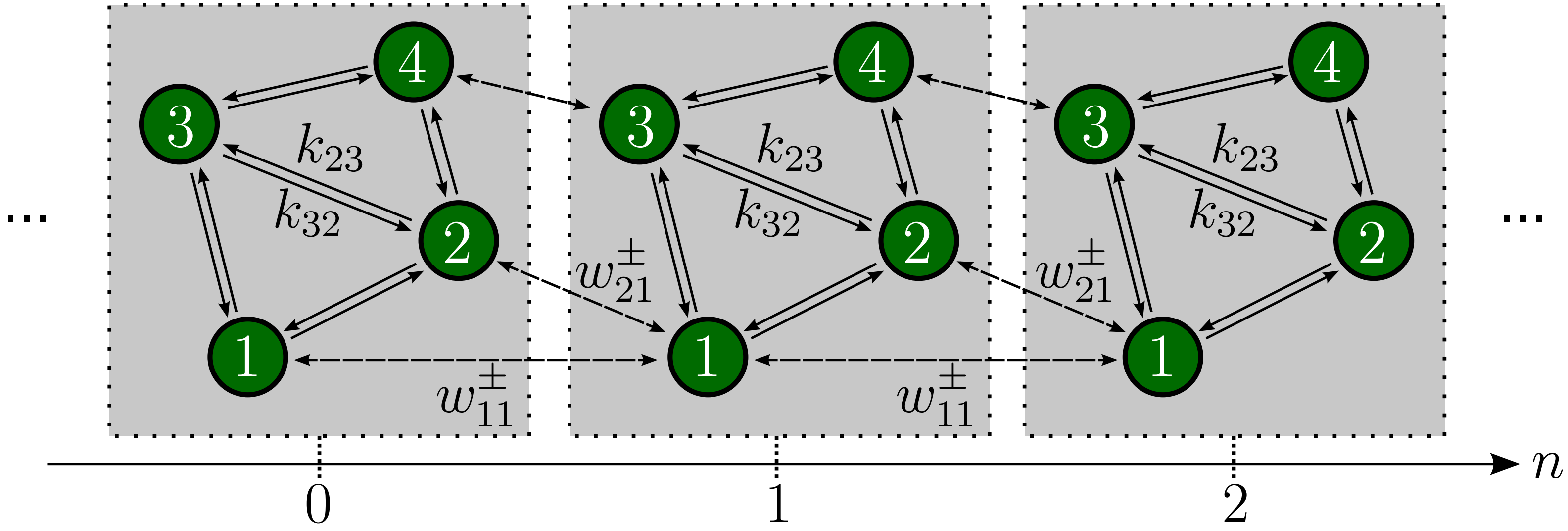
$$\lambda \text{ is a root} \Longrightarrow \sum_{n=0}^{N} C_n(z)\lambda^n(z) = 0$$

$$\text{From } \lambda(0) = 0 \Longrightarrow \begin{cases} J_\alpha = \lambda' = -C_0'/C_1 \\ D_\alpha = \lambda'' = -[C_0'' + 2C_1'\lambda' + 2C_2(\lambda')^2]/(C_1) \end{cases}$$

  - from Z. Koza, JPA 32, 7637, 1999.

- Thermodynamic uncertainty rel'n cont'd: General multicyclic process

[AC Barato and US, Phys. Rev. Lett. 114, 158101, 2015]



– $\boxed{\mathcal{C} \geq 2k_BT/\epsilon^2}$ for any th'dyn consistent process at finite T

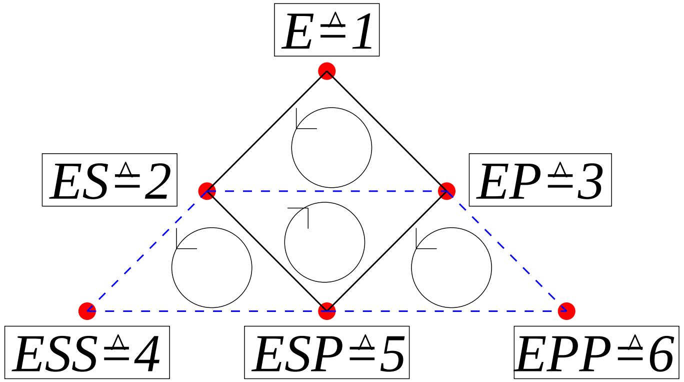
– a precision of 1% costs at least 20.000 k_BT

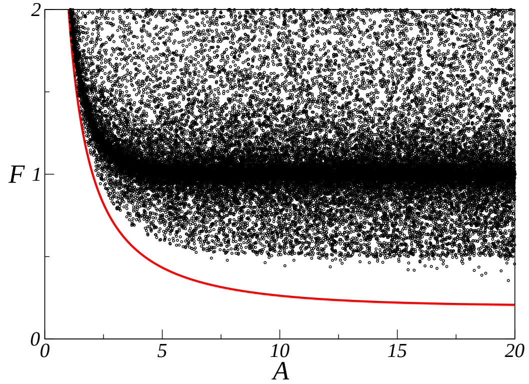
– adding cycles to a unicycle increases fluctuations, i.e., uncertainty

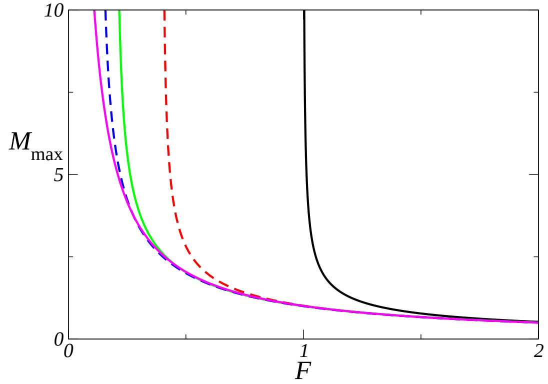
  * math proven in linear response
  * extensive numerics beyond LR

- Implications for single enyzme (statistical) kinetics

  [AC Barato and U.S., J. Phys. Chem. B, 2015, 119, 6555, 2015]







$M_{\text{max}} = 5$ $\qquad$ $\mathcal{A} = \infty \quad 5 \quad 2$

  – Fano factor

$$\mathcal{F} \equiv \frac{\langle (X - \langle X \rangle)^2 \rangle}{\langle X \rangle} \geq \frac{1}{M_{\text{max}}} \coth[\mathcal{A}/2M_{\text{max}}] \geq \frac{2}{\mathcal{A}}$$

  bounded by the cycle with the largest effective length $M = (N/n)$

  – diagnostic tool for network topology

- ST as quantitative framework for biochemical/biophysical processes
  - efficiency of molecular motor F_1-ATPase E Zimmermann + P Pietzonka
  - fine-structured FT
  - coarse-graining in ST

- Thermodynamic uncertainty relation provides constraints on AC Barato
  - ... cost of any process with given ϵ at finite T
  - ... Fano factor in enzyme kinetics
  - ... the topology of the network

  - open: mathematical proof for multicyclic case