Stochastic thermodynamics*

for biomolecular and cellular processes

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• 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

F₁ATP-ase

- Macroscopic vs mesoscopic vs molecular machines

[Bustamante et al, Physics Today, July 2005]
### Perspective

- **1820 ≃ 1850**
  - Classical thermodynamics
  - $dW = dU + dQ$
  - $dS \geq 0$

- **≃ 1900**
  - Equilibrium statistical physics
  - $p_i = \exp\left[-\frac{(E_i - F)}{k_B T}\right]$

- **1930 ≃ 1960**
  - Non-equilibrium linear response
  - Onsager
  - Green-Kubo, FDT

- **≥ 1993**
  - Non-equilibrium beyond linear response
  - Stochastic thermodynamics
  - Fluctuation theorem
  - Jarzynski relation

- **2015**
  - Thermodynamics uncertainty relation
• Thermodynamics of macroscopic systems

- First law energy balance:
  \[ W = \Delta E + Q = \Delta E + T\Delta S_{\text{res}} \]

- Second law:
  \[ \Delta S_{\text{tot}} \equiv \Delta S + \Delta S_{\text{res}} > 0 \]
  \[ W > \Delta E - T\Delta S \equiv \Delta F \]
  \[ W_{\text{diss}} \equiv W - \Delta F > 0 \]
• Stochastic thermodynamics for small systems

- First law: how to define work, internal energy and exchanged heat?

- Fluctuations imply distributions: $p(W; \lambda(\tau))$ ...

- Entropy: distribution as well?

Driving: mechanical (bio)chemical
Nano-experiment: Stretching of RNA

[Lehrhart et al, Science 296 1832, 2002.]
- distribution of dissipated work
  \[ W_{\text{diss}} = W - \Delta F \]

- Jarzynski relation (1997):
  \[ \langle \exp[-W/k_B T] \rangle_{\text{neq}} = \exp[-\Delta F/k_B T] \]
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 \( \beta \)
  
  – 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
      
      \[ P_e^I = \sum_{\xi \in I} \exp[-\beta (H(\xi) - F)] \equiv \exp[-\beta (F_I - F)] \]

    * 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
      
      \[ \tau_I/\tau_J = P_e^I/P_e^J = \exp[\beta (F_J - F_I)] \]
- 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 \( \{K_{IJ}\} \)

\[
\Rightarrow K_{IJ}/K_{JI} = P_I^e/P_J^e = \exp(-\beta \Delta_{IJ}F) = \exp(-\beta \Delta_{IJ}E + \Delta_{IJ}S)
\]
- 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 $\beta Q_{IJ}$
  - 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
    \[
    \langle \exp[-\Delta S_{\text{tot}}] \rangle = 1 \Rightarrow \langle \Delta S_{\text{tot}} \rangle \geq 0
    \]
    any lengths $t$, any initial distribution $\{P^0_I\}$
  - second law on ensemble level (Schnakenberg 1976)
    \[
    \langle S_{\text{tot}}(t) \rangle \equiv \sum_{IJ} P_I(t)K_{IJ}\Delta_{IJ} S_{\text{tot}}(t) \geq 0
    \]
- From a closed to an open system in a non-eq steady state (NESS)

\[ \Delta_{IJ}F = F_{ij} - F_{ii} - \sum_{\alpha} \mu^\alpha \Delta_{ij}N^\alpha + fd_{IJ} \]

- local detailed balance condition

\[ \frac{k_{ij}}{k_{ji}} = \exp[-\beta(\Delta_{ij}F - \sum_{\alpha} \mu^\alpha \Delta_{ij}N^\alpha + fd_{ij})] \]

- for fixed chemical potentials and force $f$: NESS

\[ ATP \rightarrow ADP + Pi \]

- system = core system (enzyme/mol motor) + surrounding solution
- change in free energy difference
- 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)]:
  \[
dw = du + dq
  \]

  * applied work: \( dw = f \, dx \)
  * internal energy: \( du = dV \)
  * dissipated heat: \( dq = dw - du = [-\partial_x V(x) + f]dx = T ds_{res} \)

- total entropy as quantitative measure of broken time reversal symmetry \( x(t) \rightarrow \tilde{x}(t) \equiv x(T - t) \)
  \[
  \Delta s^{tot}[x(t)] \equiv \ln[p[x(t)]/p[\tilde{x}(t)]] = \Delta[-\ln p(x)] + q/T
  \]

- "affinity" \( A \equiv 2\pi R f \)
- **Fluctuation theorem**: 

\[ \frac{p(-\Delta s^{tot})}{p(\Delta s^{tot})} = \exp(-\Delta s^{tot}) \] in any NESS


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

- FT-representation:
F1-ATPase and the fluctuation theorem  

\[ \Gamma \dot{\theta} = N + \zeta \]

\[ \Rightarrow \ln \left[ \frac{p(\Delta \theta)}{p(-\Delta \theta)} \right] = N\Delta \theta / k_B T \]

independent of friction coefficient \( \Gamma \)

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Efficiency of $F_1$-ATPase as a thermodynamic machine

- First law

(i) probe \[ -f^{\text{ex}} \Delta x = \Delta q_p + \Delta V|_p \]

(ii) motor \[ 0 = \Delta q_m + \Delta V|_m + \Delta E_{\text{sol}} \]

mean \[ -f^{\text{ex}}v = \dot{Q}_p + \dot{Q}_m + \dot{E}_{\text{sol}} \]

\[ \Delta E_{\text{sol}} = -\Delta \mu + T \Delta S_{\text{sol}} \]

\[ \Delta \mu - f^{\text{ex}}v = \dot{Q}_p + \dot{Q}_m + T \dot{S}_{\text{sol}} \]

not distinguishable
Inferring the efficiency of a molecular motor

Harada-Sasa relation (PRL 2006)

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

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

E. Zimmermann and US, NJP 2012
Thermodynamic uncertainty relation: Cost of precision


- 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 \( \epsilon^2 \equiv \text{var/output}^2 = 2D/J^2t \)

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

- \( C\epsilon^2 = 2\sigma D/J^2 \geq 2k_B T \) 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

-v bead bead trap microtubule kinesin + –

Time (s) 0.0 0.5 1.0 1.5 2.0

Position (nm) 100 –100 –200 –300 –400

∆x


-experimental data on

* velocity $v$

* diffusion constant $D$

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

1.5 1.0 0.5 0.0

Randomness, $r$

Load (pN)

Randomness, $r$

2 mM ATP

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Thermodynamic inference: Universal bound on the efficiency of molecular machines


- entropy production rate \( \sigma = P_{in} - P_{out} = "chem energy" - f v \leq v^2 / D \)
- efficiency

\[
\eta \equiv \frac{P_{out}}{P_{in}} = \frac{f v}{unknown} = \frac{fv}{fv + \sigma} \leq \frac{1}{1 + vk_BT/(Df)}
\]

- 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

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

- Unicycle with \( N \) equivalent states and driving affinity \( \mathcal{A} = N \ln(k^+/k^-) \)

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

- Coherence is lost after

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

- Bounded by the ...
  * Number of states: \( \mathcal{N} \leq N/2\pi^2 \)
  * Free energy spent per cycle: \( \mathcal{N} \leq \mathcal{A}/4\pi^2 \Rightarrow \text{cost/cycle} \geq 4\pi^2 \mathcal{N} \simeq 400k_BT \text{ for } \mathcal{N} = 10 \)
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
  \[ t_1 = \frac{2\pi}{\mu} \]
- coherence lost if
  \[ \Delta \phi \simeq \pi/2 \]
- decoherence time
  \[ t_{\text{dec}} = \frac{\pi^2}{8\mu} \]
- number of coherent oscillations
  \[ \mathcal{N} = \frac{t_{\text{dec}}}{t_1} = \frac{\mathcal{A}}{32} \]
- cf discrete relation
  \[ \mathcal{N} \leq \frac{\mathcal{A}}{4\pi^2} \]
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

\[ N \leq \max_{\text{cycles}} \frac{\tanh(A/2N)}{\frac{2\pi}{N}} \leq \frac{\max \, A}{4\pi^2} \]
• 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)]

\[ M + M R + M_p + M_p K = N_M = \text{const} \]
\[ K + M_p K = N_K = \text{const} \]
\[ \Delta \mu = 12, N_M = 500, N_K = 30 \]
- Coherence of oscillations

\[ C(t) \equiv \langle (N_X(t) - \langle N_X \rangle)(N_X(0) - \langle N_X \rangle) \rangle \]

\[ M \longrightarrow M_{pK} \]

\[ MR \longrightarrow M_p \]

\[ R \longrightarrow X \]

\[ \Delta \mu \]

number of enzymes

\[ 0 \quad 1000 \quad 2000 \quad 3000 \quad 4000 \quad 5000 \]

\[ t \]

\[ 0 \quad 1000 \quad 2000 \quad 3000 \quad 4000 \]

\[ N \equiv (M, MR, M_p, M_pK, K, X, R) \]

- \( A \) and \( N \) of best cycle in this enormous space of states?

chemical master equation

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

with \( N \equiv (M, MR, M_p, M_pK, K, X, R) \)

\[ N_{est} = N_K \Delta \mu / 4\pi^2 \]
• Generalizations to periodically driven systems with period $T = 2\pi/\Omega$
  
  - thermodynamic uncertainty relation

$$\frac{\sigma(\Omega)D(\Omega)}{j(\Omega)^2} \geq (1 - \frac{j'(\Omega)}{j(\Omega)})^2 \Rightarrow \text{dissipationless precision}$$


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

• 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

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