Stochastic Thermodynamics and Thermodynamics of Information

Lecture V: Stochastic thermodynamics in biological systems

Luca Peliti

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Statistical Physics, SISSA and SMRI (Italy)

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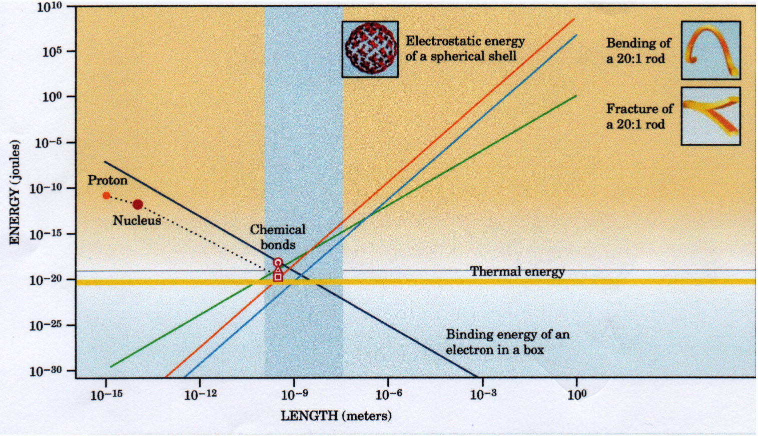
Energy scale vs. length scale

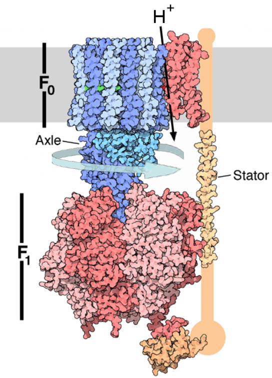


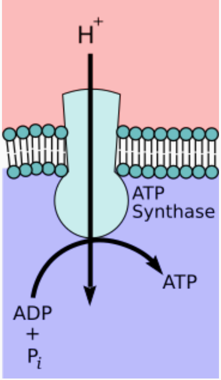
□: hydrogen bond; △: phosphate bond; ○: covalent bond

Phillips and Quake, 2006

A rotary motor: ATP synthase

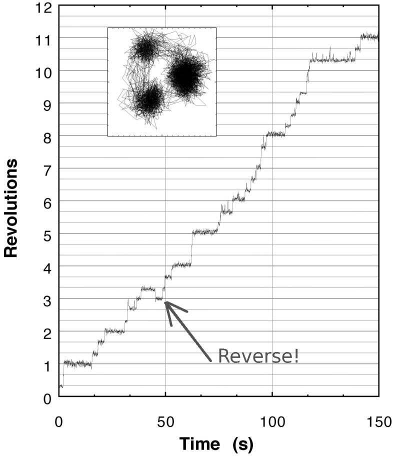
Yasuda et al., 2002





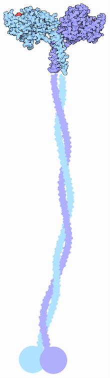
A rotary motor: ATP synthase

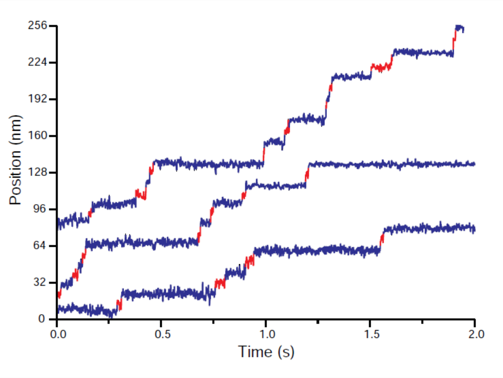
YASUDA ET AL., 2002



ATP Synthase motion is *reversible*: ATP degradation ⟶ proton gradient

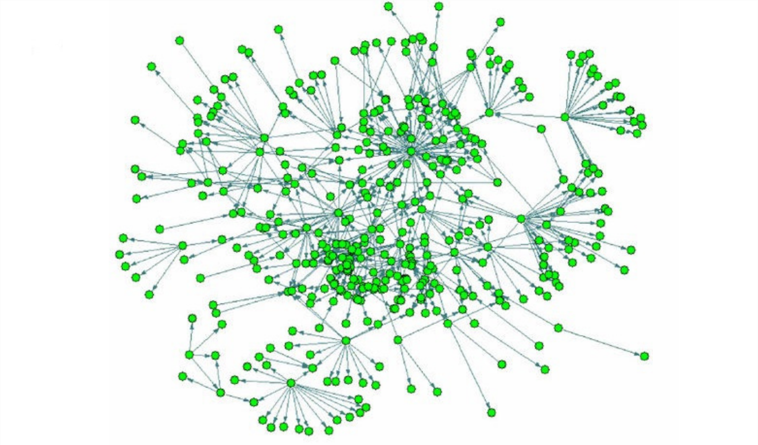
A processing motor: kinesin





Fehr, Asbury and Block, 2008

A signalling network



Ma, Buer and Zeng, 2004

Passive catalysis

Formalism developed in a simple case

- Enzyme E catalyzing the isomerization:

$$\mathsf{A} + \mathsf{E} \underset{k_1^-}{\overset{k_1^+}{\rightleftharpoons}} \mathsf{E}^* \underset{k_2^-}{\overset{k_2^+}{\rightleftharpoons}} \mathsf{B} + \mathsf{E}$$

- Define $\epsilon^* = \epsilon_{\mathsf{E}^*} - \epsilon_{\mathsf{E}}$
- Ratios of reaction rates:

$$\frac{k_1^+}{k_1^-} = \mathrm{e}^{-(\epsilon^* - \epsilon_{\mathsf{A}})/k_\mathrm{B}T} \qquad \frac{k_2^+}{k_2^-} = \mathrm{e}^{(\epsilon^* - \epsilon_{\mathsf{B}})k_\mathrm{B}T}$$

- Therefore

$$\frac{k_1^+ k_2^+}{k_1^- k_2^-} = \mathrm{e}^{-(\epsilon_{\mathsf{B}} - \epsilon_{\mathsf{A}})/k_\mathrm{B}T}$$

Passive catalysis

- Set

$$k_1^+ = \omega_1 \, \mathrm{e}^{-(\epsilon^* - \epsilon_{\mathsf{A}})/k_{\mathrm{B}}T} \qquad k_1^- = \omega_1$$
$$k_2^+ = \omega_2 \qquad k_2^- = \omega_2 \, \mathrm{e}^{-(\epsilon^* - \epsilon_{\mathrm{B}})/k_{\mathrm{B}}T}$$

- Rate equations (average):

$$\frac{\mathrm{d}\left\langle n \right\rangle}{\mathrm{d}t} = k_2^+ [\mathsf{E}^*] - k_2^- [\mathsf{E}][\mathsf{B}]$$
$$\frac{\mathrm{d}[\mathsf{E}^*]}{\mathrm{d}t} = k_1^+ [\mathsf{E}][\mathsf{A}] + k_2^- [\mathsf{E}][\mathsf{B}] - \left(k_1^- + k_2^+\right) [\mathsf{E}]$$

- Production of B-molecules vanishes at equilibrium:

$$\frac{[\mathsf{B}]}{[\mathsf{A}]} = \frac{k_1^+ k_2^+}{k_1^- k_2^-} = \mathrm{e}^{-(\epsilon_{\mathrm{B}} - \epsilon_{\mathsf{A}})/k_{\mathrm{B}}T}$$

i.e.

$$[\mathsf{A}] \, \mathrm{e}^{-\epsilon_{\mathrm{A}}/k_{\mathrm{B}}T} = [\mathsf{B}] \, \mathrm{e}^{-\epsilon_{\mathrm{B}}/k_{\mathrm{B}}T}$$

Master equation

Beyond the rate equations:

- Number of B-molecules synthesized: n
- Enzyme free (0) or bound (1)
- Chemostats fix [A] and [B]
- Master equation for p_{in}, $i \in \{0, 1\}$, $n \in \mathbb{Z}$

$$\frac{\mathrm{d}p_{0n}}{\mathrm{d}t} = k_1^- p_{1n} + k_2^+ p_{1,n-1} - \left(k_1^+ [\mathsf{A}] + k_2^- [\mathsf{B}]\right) p_{0n}$$
$$\frac{\mathrm{d}p_{1n}}{\mathrm{d}t} = k_1^+ [\mathsf{A}]\, p_{0n} + k_2^- [\mathsf{B}]\, p_{0,n+1} - \left(k_1^- + k_2^+\right) p_{1n}$$

Non-equilibrium steady state

Chemostat [A] and [B] away from the equilibrium values:

$$[\mathsf{A}]\,\mathrm{e}^{-\epsilon_{\mathrm{A}}/k_{\mathrm{B}}T} \neq [\mathsf{B}]\,\mathrm{e}^{-\epsilon_{\mathrm{B}}/k_{\mathrm{B}}T}$$

Free-energy imbalance:

$$\Delta G = \epsilon_{\mathsf{B}} - k_{\mathrm{B}}T\log[\mathsf{B}] - (\epsilon_{\mathsf{A}} - k_{\mathrm{B}}T\log[\mathsf{A}]) = k_{\mathrm{B}}T\log\frac{k_1^+ k_2^+ [\mathsf{A}]}{k_1^- k_2^- [\mathsf{B}]}$$

Steady-state probability of charged enzyme:

$$p_1 = \frac{k_1^+[\mathsf{A}] + k_2^-[\mathsf{B}]}{k_1^- - k_1^+[\mathsf{A}] + k_2^+ - k_2^-[\mathsf{B}]}$$

Net production rate (cf. rate equation):

$$\frac{\mathrm{d}\,\langle n\rangle}{\mathrm{d}t} = \frac{k_1^+ k_2^+[\mathsf{A}] - k_1^- k_2^-[\mathsf{B}]}{k_1^- - k_1^+[\mathsf{A}] + k_2^+ - k_2^-[\mathsf{B}]}$$

Large deviations

Generating function:

$$\Psi_\alpha(\mu,t) = \sum_{n=-\infty}^{+\infty} \mathrm{e}^{\mu(n+\alpha/2)} p_{\alpha,n}(t) \qquad \alpha \in \{0,1\}$$

Evolution equation:

$$\frac{\mathrm{d}}{\mathrm{d}t} \begin{pmatrix} \Psi_0 \\ \Psi_1 \end{pmatrix} = \mathcal{L}(z) \begin{pmatrix} \Psi_0 \\ \Psi_1 \end{pmatrix} \qquad z = \mathrm{e}^{\mu/2}$$

$$\mathcal{L}(z) = \begin{pmatrix} -\left(k_1^+[\mathsf{A}] + k_2^-[\mathsf{B}]\right), & z^{-1}k_1^- + zk_2^+ \\ zk_1^+[\mathsf{A}] + z^{-1}k_2^-[\mathsf{B}], & -(k_1^- + k_2^+) \end{pmatrix}$$

$\Psi \sim \mathrm{e}^{t\,\theta(\mu)}$ $\qquad$ $\theta(\mu)$: largest e.v. of $\mathcal{L}$

Large deviations

Distribution function of n: $P(n,t) = \mathrm{e}^{-t\,\omega(J)}$, $J = n/t$

$$\theta(\mu) = \max_J \left(\mu J - \omega(J)\right)$$

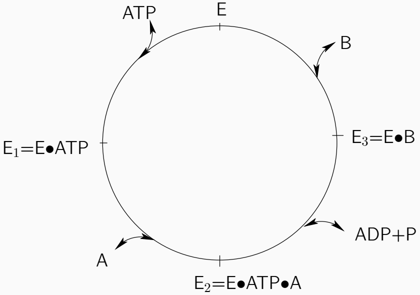
E.v.'s of $\mathcal{L}(z)$ depend only on $z^{-2}k_1^+k_2^+[\mathsf{A}] + z^2k_1^-k_2^-[\mathsf{B}]$
Gallavotti-Cohen symmetry: $z \longrightarrow \bar{z}$:

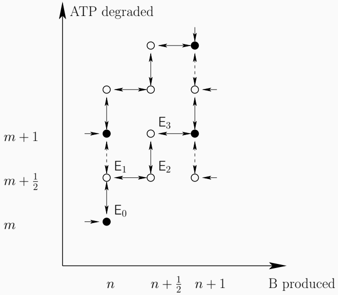
$$\bar{z}^{-2}k_1^-k_2^-[\mathsf{B}] = z^2k_1^+k_2^+[\mathsf{A}] \quad \Leftrightarrow \quad \mu \longrightarrow \bar{\mu} = \Delta G/k_\mathrm{B}T - \mu$$

$$\begin{aligned} \theta(\mu) &= \theta(\Delta G/k_\mathrm{B}T - \mu) \\ J(\mu) &= -J(\Delta G/k_\mathrm{B}T - \mu) \\ \omega(J) - \omega(-J) &= J\,\Delta G/k_\mathrm{B}T = \dot{S} \end{aligned}$$

Active catalysis

Reaction scheme: $\mathrm{ATP} + \mathrm{A} \rightleftharpoons \mathrm{ADP} + \mathrm{P} + \mathrm{B}$





Rate equations

$$\frac{\mathrm{d}[\mathsf{E}]}{\mathrm{d}t} = k_4^+[\mathsf{E_3}] + k_1^-[\mathsf{E_1}] - k_1^+[\mathsf{E}][\mathsf{ATP}] - k_4^-[\mathsf{E}][\mathsf{B}]$$

$$\frac{\mathrm{d}[\mathsf{E_1}]}{\mathrm{d}t} = k_1^+[\mathsf{E}][\mathsf{ATP}] + k_2^-[\mathsf{E_2}] - k_1^-[\mathsf{E_1}] - k_2^+[\mathsf{E_1}][\mathsf{A}]$$

$$\frac{\mathrm{d}[\mathsf{E_2}]}{\mathrm{d}t} = k_2^+[\mathsf{E_1}][\mathsf{A}] + k_3^-[\mathsf{E_3}][\mathsf{ADP}][\mathsf{P}] - (k_2^- + k_3^+)[\mathsf{E_2}]$$

$$\frac{\mathrm{d}[\mathsf{E_3}]}{\mathrm{d}t} = k_3^+[\mathsf{E_2}] + k_4^-[\mathsf{E}][\mathsf{B}] - (k_4^+ + k_3^-[\mathsf{ADP}][\mathsf{P}])[\mathsf{E_3}]$$

Detailed balance:

$$\frac{k_i^+}{k_i^-} = \mathrm{e}^{-\Delta\epsilon_i/k_\mathrm{B}T}$$

$$\frac{k_1^+k_2^+k_3^+k_4^+}{k_1^-k_2^-k_3^-k_4^-} = \mathrm{e}^{-(\Delta\epsilon_\mathsf{A}+\Delta\epsilon_\mathsf{ATP})/k_\mathrm{B}T}$$

$$\Delta\epsilon_\mathsf{A} = \epsilon_\mathsf{B} - \epsilon_\mathsf{A}$$

$$\Delta\epsilon_\mathsf{ATP} = \epsilon_\mathsf{ADP} + \epsilon_\mathsf{P} - \epsilon_\mathsf{ATP}$$

Generating function

$$\frac{\partial \Psi_0}{\partial t} = k_4^+ \mathrm{e}^{\mu_1/2}\Psi_3 + k_1^+ \mathrm{e}^{-\mu_2/2}\Psi_1 - \left(k_1^+[\mathsf{ATP}] + k_4^-\right)\Psi_0$$
$$\frac{\partial \Psi_1}{\partial t} = k_1^+[\mathsf{ATP}]\,\mathrm{e}^{\mu_2/2}\Psi_0 + k_2^- \mathrm{e}^{-\mu_1/2}\Psi_2 - \left(k_1^- + k_2^+[\mathsf{A}]\right)\Psi_1$$
$$\frac{\partial \Psi_2}{\partial t} = k_2^+[\mathsf{A}]\mathrm{e}^{\mu_1/2}\Psi_1 + k_3^-[\mathsf{ADP}][\mathsf{P}]\,\mathrm{e}^{-\mu_2/2}\Psi_3 - \left(k_2^- + k_3^+\right)\Psi_2$$
$$\frac{\partial \Psi_3}{\partial t} = k_3^+\,\mathrm{e}^{\mu_2/2}\Psi_2 + k_4^-[\mathsf{B}]\,\mathrm{e}^{-\mu_1/2}\Psi_0 - \left(k_4^- + k_3^+[\mathsf{ADP}][\mathsf{P}]\right)\Psi_3$$

$$\frac{\partial \boldsymbol{\Psi}}{\partial t} = \mathcal{L}_{\boldsymbol{\mu}}\,\boldsymbol{\Psi},$$

The Gallavotti-Cohen symmetry involves the simultaneous change of μ_1, μ_2:

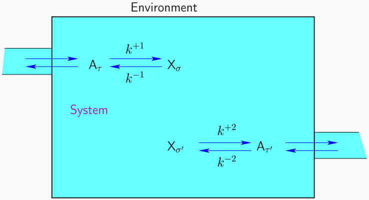
$$\mathcal{L}_{\overline{\boldsymbol{\mu}}} = \mathsf{Q}^{-1}\mathcal{L}_{\boldsymbol{\mu}}^{\dagger}\mathsf{Q}$$

$$\mathrm{e}^{\overline{\mu}_1} = \frac{k_2^- k_4^-[\mathsf{B}]}{k_2^+ k_4^+[\mathsf{A}]}\,\mathrm{e}^{-\mu_1} \qquad \mathrm{e}^{\overline{\mu}_2} = \frac{k_1^- k_3^-[\mathsf{ADP}][\mathsf{P}]}{k_1^+ k_3^+[\mathsf{ATP}]}\,\mathrm{e}^{-\mu_2}$$

Fluctuation relations

Gaspard, 2005

Chemical Reaction Network:



$$\sum_\sigma \nabla^\sigma_{+\rho} X_\sigma + \sum_\tau \nabla^\tau_{+\rho} A_\tau \underset{k^{+\rho}}{\overset{k^{-\rho}}{\leftrightharpoons}} \sum_\sigma \nabla^\sigma_{-\rho} X_\sigma + \sum_\tau \nabla^\tau_{-\rho} A_\tau$$

Stoichiometric matrix:

$$\nabla_{\pm\rho} = (\nabla^{\sigma,\tau}_{\pm\rho}) \qquad \nabla^{\sigma,\tau}_{\pm\rho} \in \mathbb{N}$$

$$\nabla_\rho = \nabla_{-\rho} - \nabla_{+\rho} \qquad \nabla^{\sigma,\tau}_{\rho} \in \mathbb{Z}$$

Chemical species: $X = (X_\sigma)$, $A = (A_\tau)$

X_σ : intermediate $\qquad$ A_τ : chemostatted

Transitions

Elementary transitions:

$$X \xrightarrow{\pm\rho} X' : \quad X' - X = \pm\nabla_\rho$$

Mass-action law:

$$R^{\pm\rho}_{X'X} = \delta_{X',X\mp\nabla_\rho}\,\Omega\,k_{\pm\rho}\prod_\tau[\mathsf{A}_\tau]^{\nu^\tau_{\pm\rho}} \\ \times\prod_\sigma\left(\frac{X^\sigma}{\Omega}\frac{X^\sigma-1}{\Omega}\cdots\frac{X^\sigma-\nabla^\sigma_{\pm\rho}+1}{\Omega}\right)$$

Master equation:

$$\frac{\mathrm{d}p_X}{\mathrm{d}t} = \sum_{\epsilon=\pm1}\sum_\rho\left[R^{\epsilon\rho}_{XX'}p_{X'} - R^{-\epsilon\rho}_{X'X}p_X\right] = (\mathcal{L}\,p)_X$$

Steady state $p^{\mathrm{ss}}(X)$ (not trivial to evaluate)

Average entropy production

Entropy of a state p_X:

$$S(P) = \underbrace{\sum_X S^{(0)}(X) p_X}_{\text{“internal”}} \underbrace{- k_{\mathrm{B}} \sum_X p_X \log p_X}_{\text{Shannon}}$$

Total average entropy production:

$$\dot{S}^{\mathrm{tot}} = \frac{\mathrm{d}S}{\mathrm{d}t} - \frac{\mathrm{d}S^{(\mathrm{r})}}{\mathrm{d}t}$$

$$J_\rho(X;t) = R^\rho_{X'X} p_X - R^{-\rho}_{XX'} p_{X'}$$

$$A_\rho(X;t) = k_{\mathrm{B}} \log \frac{R^\rho_{XX'} p_{X'}}{R^{-\rho}_{X'X} p_X}$$

$$-\frac{\mathrm{d}S^{(\mathrm{r})}}{\mathrm{d}t} = \underbrace{\sum_{X,\rho} S^{(0)}(X) J_\rho(X;t)}_{\text{advection}} \underbrace{- \frac{1}{2} \sum_{X,\rho} J_\rho(X;t) \log \frac{R^\rho_{XX'}}{R^{-\rho}_{X'X}}}_{\text{Heat flow } \mathcal{Q}/T}$$

$$\dot{S}^{\mathrm{tot}} = \frac{1}{2} \sum_{X,\rho} J_\rho(X;t) A_\rho(X;t) \geq 0$$

Fluctuation relation

- Trajectory:

$$\boldsymbol{X} = (X(t)) = (X_0, t_0) \xrightarrow{\rho_1} (X_1, t_1) \xrightarrow{\rho_2} \cdots \xrightarrow{\rho_n} (X_n, t_n) \to t_\mathrm{f}$$

- Time-reversed trajectory $\hat{\boldsymbol{X}}$
- Probability density of a path $\mathcal{P}(\boldsymbol{X})$
- Detailed fluctuation relation:

$$\frac{\mathcal{P}(\boldsymbol{X}|X_0)}{\mathcal{P}(\hat{\boldsymbol{X}}|X_\mathrm{f})} = \prod_{k=1}^{n} \frac{R_{X_k X_{k-1}}}{R_{X_{k-1} X_k}} = \mathrm{e}^{\mathcal{Q}(\boldsymbol{X})/k_\mathrm{B}T}$$

- $\mathcal{Q}/T \neq -\Delta S^{(\mathrm{r})}$ because of the advection term
- Integral fluctuation relation:

$$\frac{\mathcal{P}(\boldsymbol{X})}{\mathcal{P}(\hat{\boldsymbol{X}})} = \mathrm{e}^{(\mathcal{Q}(\boldsymbol{X}) - \Delta\mathcal{S}(\boldsymbol{X}))/k_\mathrm{B}T}$$

- $\Delta\mathcal{S}$ cancels the advection term…

Thus

$$\left\langle \mathrm{e}^{-(\mathcal{Q} - \Delta\mathcal{S})/k_\mathrm{B}T} \right\rangle = 1$$

Generating function

Define

$$\Psi_X(\mu;t) = \int \mathrm{d}\boldsymbol{X}\ \mathcal{P}^{\mathrm{ss}}(\boldsymbol{X})\,\delta_{X(t)X}\,\mathrm{e}^{-\mu\,Q(\boldsymbol{X})/k_{\mathrm{B}}T}$$

it satisfies

$$\Psi_X(\mu;t_0) = p_X^{\mathrm{ss}}$$

$$\frac{\partial \Psi_X}{\partial t} = (\mathcal{L}\,\Psi)_X - \sum_\rho \sum_{X'\,(\neq X)}{}' \left(\frac{R^\rho_{XX'}}{R^{-\rho}_{X'X}}\right)^\mu \Psi_{X'} = (\mathcal{L}_\mu\,\Psi)_X$$

Therefore

$$\Psi \underset{t\to\infty}{\sim} \mathrm{e}^{-t\,\theta(\mu)}$$

where

$$\theta(\mu) = -\log \Lambda_{\max}(\mathcal{L}_\mu)$$

Gallavotti-Cohen symmetry

We have of course

$$\mathcal{P}^{\mathrm{ss}}(\boldsymbol{X})\left(\frac{\mathcal{P}^{\mathrm{ss}}(\hat{\boldsymbol{X}})}{\mathcal{P}^{\mathrm{ss}}(\boldsymbol{X})}\right)^{\mu}=\mathcal{P}^{\mathrm{ss}}(\hat{\boldsymbol{X}})\left(\frac{\mathcal{P}^{\mathrm{ss}}(\boldsymbol{X})}{\mathcal{P}^{\mathrm{ss}}(\hat{\boldsymbol{X}})}\right)^{1-\mu}=\mathcal{P}^{\mathrm{ss}}(\boldsymbol{X})\left(\frac{\mathcal{P}^{\mathrm{ss}}(\boldsymbol{X})}{\mathcal{P}^{\mathrm{ss}}(\hat{\boldsymbol{X}})}\right)^{1-\mu}$$

which implies the Gallavotti-Cohen symmetry:

$$\theta(\mu)=\theta(1-\mu)$$

The large-deviation (Cramér) function $\omega(s)$ is defined by

$$\mathrm{Prob}(Q,t)\underset{t\to\infty}{\sim}\mathrm{e}^{-t\,\omega(s)},\qquad \frac{Q}{k_{\mathrm{B}}T}=s\,t$$

since

$$\int \mathrm{d}Q\;\mathrm{Prob}(Q,t)\,\mathrm{e}^{-\mu Q/k_{\mathrm{B}}T}=\sum_{X}\Psi_X(\mu;t)\sim\mathrm{e}^{-t\,\theta(\mu)}$$

we have (if the saddle-point integration can be inverted!)

$$\omega(s)=\max_{\mu}\left(\theta(\mu)-\mu\,s\right)$$

and $\omega(s)-\omega(-s)=-s$

Simulation of chemical reactions

Chemical reaction rates with a given number of particles:

$$\sum_\sigma \nabla^\sigma_{+\rho} X_\sigma + \sum_\tau \nabla^\tau_{+\rho} A_\tau \overset{k^{-\rho}}{\underset{k^{+\rho}}{\leftrightharpoons}} \sum_\sigma \nabla^\sigma_{-\rho} X_\sigma + \sum_\tau \nabla^\tau_{-\rho} A_\tau$$

Rates for reaction $\rho\,(= \pm\rho)$:

$$\begin{aligned} R^\rho_{X'X} = \delta_{X',X+\nabla_\rho}\,\Omega\,k_\rho \prod_\tau [\mathsf{A}_\tau]^{\nu^\tau_\rho} \\ \times \prod_\sigma \left(\frac{X^\sigma}{\Omega} \frac{X^\sigma - 1}{\Omega} \cdots \frac{X^\sigma - \nabla^\sigma_\rho + 1}{\Omega} \right) \end{aligned}$$

Simulation of chemical reactions

Simulation algorithm: Gillespie, 1976, 1977

1. Given the time t number $\{n_\sigma\}$ of all species involved, evaluate the rates R_ρ of all possible reactions
2. Define $R = \sum_\rho$ and extract the time τ to the next reaction, exponentially distributed with average R^{-1}: update t to $t+\tau$
3. Choose the next reaction ρ^{next} with probability R_ρ/R
4. Change the number of the affected species according to the stoichiometry of the reaction ρ^{next} and return to step 1

Difficulties:

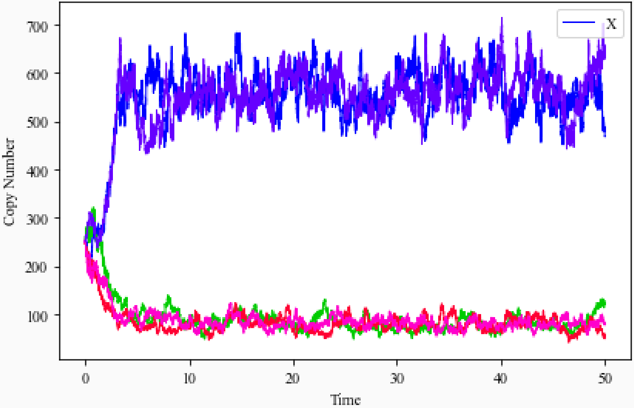
- The number of possible reactions can become large
- Thus τ can become too small—simulation sluggish!
- Several tricks have been invented to speed up the simulation, at some cost in precision

Simulation of chemical reactions

```
# Schlögl model (1972)

FIX: A B

# Reactions
R1:
    A + {2} X > {3} X
    1/2*c1*A*X*(X-1)

R2:
    {3} X > A + {2} X
    1/6*c2*X*(X-1)*(X-2)
R3:
    B > X
    c3 * B
R4:
    X > B
    c4*X

# Fixed species
A = 100000
B = 200000

# Variable species
X = 250

c1 = 3*10**-7
c2 = 10**-4
c3 = 10**-3
c4 = 3.5
```

Simulation of chemical reactions

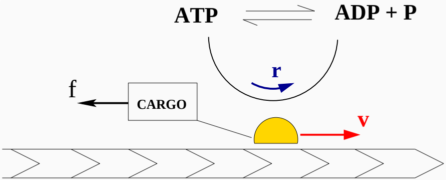
Python module: `stochpy`



Fluctuation Theorem for molecular motors

Gaspard, 2006; Lacoste, Lau and Mallick, 2008

A model of a molecular motor:



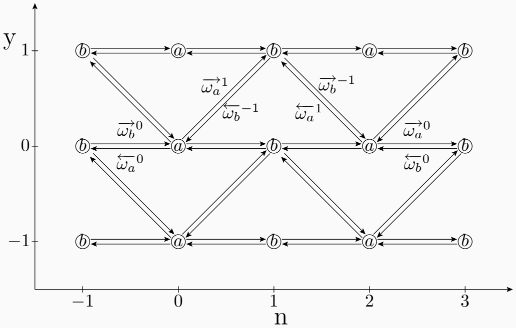
The motor is kept in a nonequilibrium state by the chemical imbalance of the ATP $\rightleftharpoons$ ADP $+$ P reaction:

$$\frac{[\mathrm{ATP}]}{[\mathrm{ADP}][\mathrm{P}]} \neq \mathrm{e}^{(\epsilon_{\mathrm{ATP}}-\epsilon_{\mathrm{ADP}}-\epsilon_{\mathrm{P}})/k_{\mathrm{B}}T}$$

The “product” is displacement

The model

Nishinari et al., 2005 *et al.*



The model

NISHINARI ET AL., 2005 *et al.*

States:

1: Bound to ATP

2: Bound to ADP or empty

Moves:

Brownian motion: $(i,2) \xrightarrow{\omega_{\mathrm{B}}} (i \pm 1, 2)$

ATP binding: $(i,2) \xrightarrow{\omega_{\mathrm{s}}} (i,1)$

Ratchet: $(i,1) \xrightarrow{\omega_{+}} (i+1,2)$

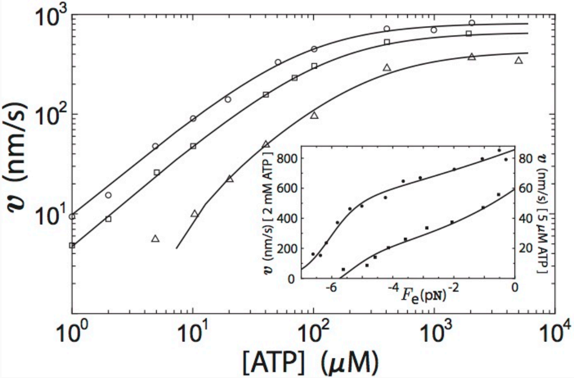
Reverse ratchet: $(i,2) \xrightarrow{\omega_{-}} (i-1,1)$

Hydrolysis: $(i,1) \xrightarrow{\omega_{\mathrm{h}}} (i,2)$

Rates $\omega = \{\omega(f, \Delta\mu)\}$ with a few measurable and 4 adjustable kinetic parameters, constrained by a thermodynamic relation

Application to kinesin

Lacoste, Lau and Mallick, 2008



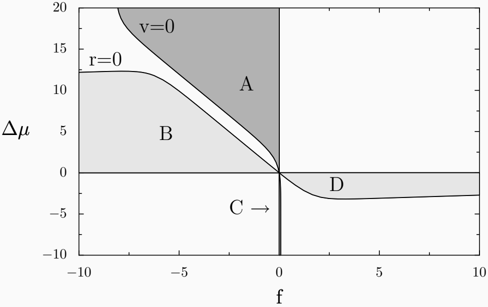
Data from Schnitzer and Block, 1995

Lines for $f = -1.05, -3.59, -5.63\text{pN}$

Inset: v vs. f for fixed [ATP] $2\mu\text{M}$ $5\mu\text{M}$

The phase diagram

LACOSTE, LAU AND MALLICK, 2008



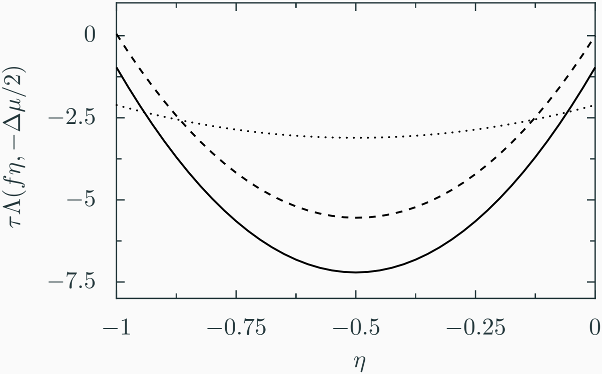
v: average velocity r: average ATP consumption rate

Modes: A: ATP consumed, work performed; B: work consumed to produce ATP

C: ADP consumed to produce work; D: Work consumed to produce ADP

The symmetry

Lacoste, Lau and Mallick, 2008



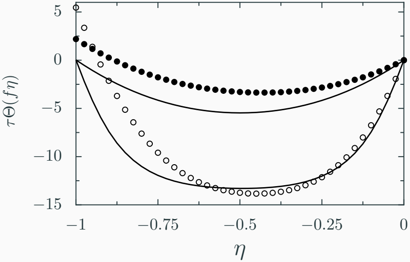
Normalized eigenvalue of $\mathcal{L}_{(fd/k_{\mathrm{B}}T)\eta,-\Delta\mu/2k_{\mathrm{B}}T}$ vs. η (parameter of the generating function) for various values of $(fd/k_{\mathrm{B}}T, \Delta\mu/k_{\mathrm{B}}T)$: $(5, 0)$ (dashed), $(5, 10)$ (solid), $(2, 10)$ (dotted)

Comments

- The Gallavotti-Cohen symmetry appears in the pdf of the fluxes v, r:

$$\ln \frac{P(v,r,\mathcal{T})}{P(-v,-r,\mathcal{T})} \sim \underbrace{[(f/k_\mathrm{B}T)v + (\Delta\mu/k_\mathrm{B}T)r]\mathcal{T}}_{\text{entropy production}}$$

- The *reduced* distribution $P_i(n,t) = \sum_y P_i(n,y,t)$ does not exhibit the symmetry:



Lack of symmetry hints at the existence of hidden dynamical variables

Information processing

Information processing in the cell:

Copy: Transcription (DNA⟶RNA), Replication (DNA⟶DNA)

Translation: DNA⟶Proteins

tRNA aminoacylation: The “interpreters” of the genetic code are tRNA, carrying the *anticodon* on one side and the corresponding amino acid on the other. Amino acids are charged by *activation enzymes*

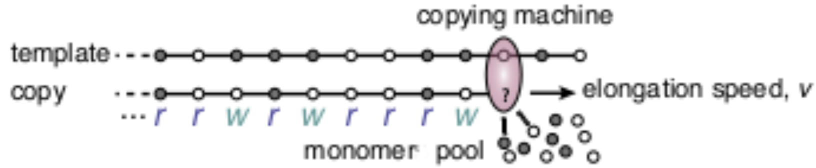
Sensing: All processes which monitor the envirnoment

“High fidelity” is a requirement

Template-assisted polymerization

Andrieux and Gaspard, 2008, 2009; Sartori and Pigolotti, 2014, 2015

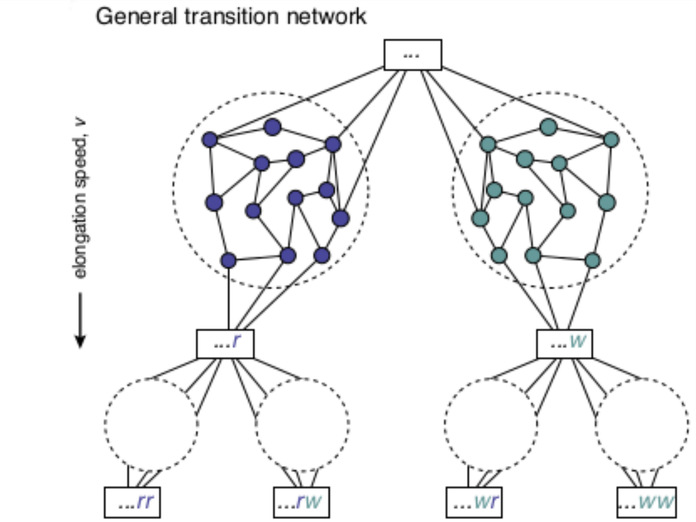
Transcription, translation, replication are instances of *template-assisted polymerization*



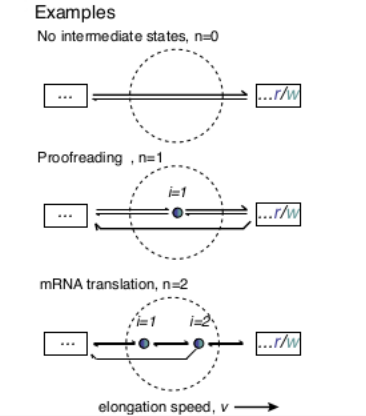
r: Right residue

w: Wrong residue

Template-assisted polymerization



Template-assisted polymerization

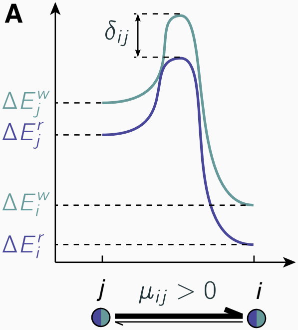


- Elongation speed v
- Error rate η
- Rate of "right" incorporations: $v^{\mathrm{r}} = (1-\eta)\,v$
- Rate of "wrong" incorporations: $v^{\mathrm{w}} = \eta\,v$
- Equation for the error η:

$$\frac{\eta}{1-\eta} = \frac{v^{\mathrm{w}}(\eta)}{v^{\mathrm{r}}(\eta)}$$

Reaction rates

Rates: μ_{ij} chemical driving, δ_{ij} kinetic barrier



B

$$k_{ij}^r = \omega_{ij} \exp[(\Delta E_j^r + \mu_{ij} + \delta_{ij})/T]$$

$$k_{ij}^w = \omega_{ij} \exp[(\Delta E_j^w + \mu_{ij})/T]$$

$$k_{ji}^r = \omega_{ij} \exp[(\Delta E_i^r + \delta_{ij})/T]$$

$$k_{ji}^w = \omega_{ij} \exp[\Delta E_i^w/T]$$

Dictionary: $k \longrightarrow R$, $T \longrightarrow k_{\mathrm{B}}T$

Definitions

Definitions:

- Entropy produced per incorporated monomer: ΔS^{tot}
- Entropy produced per *wrong* incorporated monomer: $\Delta S^{\mathrm{tot,w}}$

$$\begin{aligned}
\Delta W &= \sum_{(ij),\alpha\in\{\mathrm{r},\mathrm{w}\}} J_{ij}^{\alpha}\mu_{ij}/v \\
\Delta F^{\mathrm{eq}} &= -k_{\mathrm{B}}T\log\sum_{\alpha}\mathrm{e}^{-\Delta E^{\alpha}/k_{\mathrm{B}}T} \\
\eta^{\mathrm{eq}} &= \exp\left[\left(-\Delta E^{\mathrm{w}}+\Delta F^{\mathrm{eq}}\right)/k_{\mathrm{B}}T\right] \\
D_{\mathrm{KL}}(\eta\|\eta^{\mathrm{eq}}) &= \eta\log\frac{\eta}{\eta^{\mathrm{eq}}}+(1-\eta)\log\frac{1-\eta}{1-\eta^{\mathrm{eq}}} \\
\Delta W^{\mathrm{w}} &= \sum_{(ij)} J_{ij}^{\mathrm{w}}\mu_{ij}/v^{\mathrm{w}}
\end{aligned}$$

Main results

In the steady state:

$$\begin{aligned} T\Delta S^{\mathrm{tot}} &= \Delta W - \Delta F^{\mathrm{eq}} - k_{\mathrm{B}} T D_{\mathrm{KL}}(\eta \| \eta^{\mathrm{eq}}) \geq 0 \\ T\Delta S^{\mathrm{tot,w}} &= \Delta W^{\mathrm{w}} - \Delta F^{\mathrm{eq}} - k_{\mathrm{B}} T \log \frac{\eta}{\eta^{\mathrm{eq}}} \geq 0 \end{aligned}$$

Therefore

$$\boxed{\eta = \eta^{\mathrm{eq}} \exp\left[\left(-\Delta S^{\mathrm{tot,w}} + \left(\Delta W^{\mathrm{w}} - \Delta F^{\mathrm{eq}}\right)\right)/k_{\mathrm{B}} T\right]}$$

Possible copying regimes:

Error amplification: $\Delta W^{\mathrm{w}} - \Delta F^{\mathrm{eq}} > 0$ and $\eta > \eta^{\mathrm{eq}}$

Demon: $\Delta W^{\mathrm{w}} - \Delta F^{\mathrm{eq}} < 0$ and $\eta < \eta^{\mathrm{eq}}$ (but $\Delta W - \Delta F^{\mathrm{eq}} > 0$ due to right matches)

Error correction: $\Delta W^{\mathrm{w}} - \Delta F^{\mathrm{eq}} > 0$ and $\eta < \eta^{\mathrm{eq}}$, thus $\eta \geq \eta^{\mathrm{eq}}\, \mathrm{e}^{-\Delta S^{\mathrm{tot,w}}/k_{\mathrm{B}}}$

Single-step polymerization machines

Two regimes:

Energetic discrimination: $\Delta E = \Delta E^{\mathrm{w}} - \Delta E^{\mathrm{r}} \geq \delta$

Kinetic discrimination: $\Delta E < \delta$

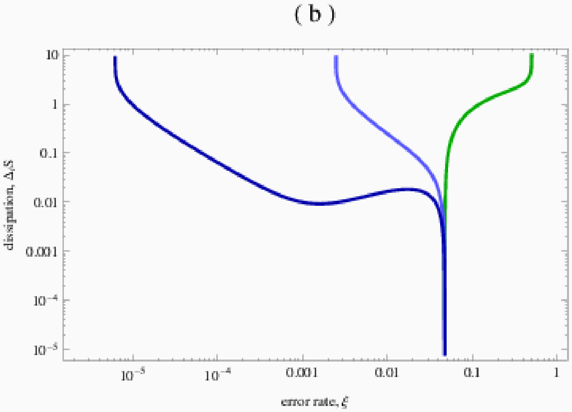
In energetic discrimination:

- $\eta \geq \eta^{\mathrm{eq}}$ (error amplification)
- η monotonically *decreases* as v decreases, minimum error at zero dissipation

In kinetic discrimination:

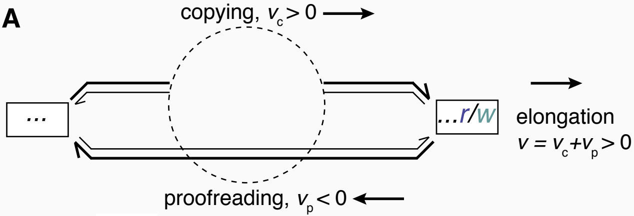
- $\eta^{\mathrm{eq}} \geq \eta \geq \eta^{\mathrm{min}} = \mathrm{e}^{-\delta/k_{\mathrm{B}}T}$
- η decreases as v and dissipation increases

Single-step polymerization machines



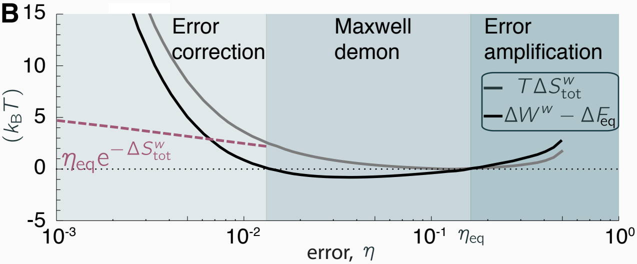
Proofreading

Ninio, Hopfield, 1974, 1975



Extra pathway with negative velocity $v_\mathrm{p} \leq 0$ preferentially removes wrong monomers

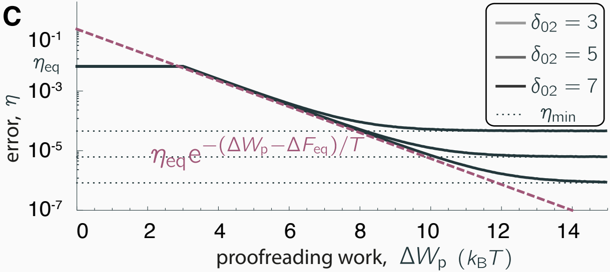
Proofreading



Since $\dot{S}_{\rm p}^{{\rm tot},w} \geq 0$ and $v_{\rm p} \leq 0$ one can show

$$\eta \geq \eta^{\rm eq} \exp\left(\frac{-\Delta W_{\rm p} + \Delta F^{\rm eq}}{k_{\rm B} T}\right)$$

Proofreading



$$\eta^{\min} \simeq \mathrm{e}^{(-\delta+\delta_{\mathrm{p}}-\Delta E^{\mathrm{w}}+\Delta E^{\mathrm{r}})/k_{\mathrm{B}}T}$$

Stochastic polymerization dynamics

- State of the growing polymer: $\mathrm{rrwr}\ldots$
- State of the machine: $i \in \{1, \ldots, n\}$
- Intermediate states (with a *tentatively* matched monomer): rrwrr_i or rrwrw_i
- Copying protocol: network of transitions $j \longrightarrow i$ with rates $R^{\mathrm{r,w}}_{ij}$
- Discrimination is due to differences in rates
- Probabilities: $P(\ldots\mathrm{r})$, $P(\ldots\mathrm{w})$, $P(\ldots\mathrm{r}_i)$, $P(\ldots\mathrm{w}_i)$ satisfying master equations:

$$\frac{\mathrm{d}}{\mathrm{d}t}P(\ldots\mathrm{r}_i) = \sum_{j=0}^{n+1} \mathcal{J}^{\mathrm{r}}_{ij}(\ldots) \qquad \frac{\mathrm{d}}{\mathrm{d}t}P(\ldots\mathrm{w}_i) = \sum_{j=0}^{n+1} \mathcal{J}^{\mathrm{w}}_{ij}(\ldots)$$

- Currents: $\mathcal{J}^{\mathrm{r}}_{ij}(\ldots) = R^{\mathrm{r}}_{ij}P(\ldots\mathrm{r}_j) - R^{\mathrm{r}}_{ji}P(\ldots\mathrm{r}_i)$
- $j = 0 \longrightarrow j = n+1$ corresponds to the incorporation of a monomer
- All transitions are reversible

Stochastic polymerization dynamics

- Rates of incorporation:

$$\frac{\mathrm{d}}{\mathrm{d}t}P(\ldots\mathrm{w}) = \sum_{j=0}^{n+1}\left[\underbrace{\mathcal{J}^{\mathrm{w}}_{n+1,j}(\ldots)}_{\text{incorporation}}\underbrace{-\mathcal{J}^{\mathrm{r}}_{j0}(\ldots\mathrm{w}) - \mathcal{J}^{\mathrm{w}}_{j0}(\ldots\mathrm{w})}_{\text{attempted incorp.}}\right]$$

  and analog for r
- Assume errors are uncorrelated:

$$P(\ldots) \propto \eta^{N_{\mathrm{w}}}\,(1-\eta)^{N-N_{\mathrm{w}}}$$

- Then

$$P(\ldots\mathrm{r}) = P(\ldots)(1-\eta) \qquad P(\ldots\mathrm{w}) = P(\ldots)\,\eta$$

- Assume states i-occupancy $p_i^{\mathrm{r},\mathrm{w}}$ to be independent of $(\ldots)$. Then

$$P(\ldots\mathrm{r}_i) = P(\ldots)\,p_i^{\mathrm{r}} \qquad P(\ldots\mathrm{w}_i) = P(\ldots)\,p_i^{\mathrm{w}}$$

- Occupation fluxes:

$$J^{\mathrm{r}}_{ij} = \mathcal{N}\left(R^{\mathrm{r}}_{ij}p_j - R^{\mathrm{r}}_{ji}p_i\right) \qquad \mathcal{J}^{\mathrm{r}}_{ij}(\ldots) = P(\ldots)J^{\mathrm{r}}_{ij}/\mathcal{N}$$

Entropy production rate

$$\frac{\mathrm{d}S^{\mathrm{tot}}}{\mathrm{d}t} = k_{\mathrm{B}} \underbrace{\frac{\sum_{\ldots} P(\ldots)}{\mathcal{N}}}_{=1} \sum_{(ij),\alpha\in\{\mathrm{r},\mathrm{w}\}} \left[J_{ij}^{\alpha} \log\left(\frac{R_{ij}^{\alpha} p_j^{\alpha}}{R_{ji}^{\alpha} p_i^{\alpha}} \right) \right]$$

$$\frac{\mathrm{d}S^{\mathrm{tot}}}{\mathrm{d}t} = k_{\mathrm{B}} \sum_{(ij),\alpha} \frac{J_{ij}^{\alpha}\mu_{ij}}{k_{\mathrm{B}}T} - \eta v \left(\log\eta + \frac{\Delta E^{\mathrm{w}}}{k_{\mathrm{B}}T} \right) + (1-\eta) v \left(\log\left(1-\eta + \frac{\Delta E^{\mathrm{r}}}{k_{\mathrm{B}}T} \right) \right)$$

Thus ΔS^{tot} per incorporated monomer is given by

$$\Delta S^{\mathrm{tot}} = \frac{1}{v}\frac{\mathrm{d}S^{\mathrm{tot}}}{\mathrm{d}t} = \frac{1}{T}\left(\Delta W - \Delta F^{\mathrm{eq}} - k_{\mathrm{B}} T D_{\mathrm{KL}}(\eta \| \eta^{\mathrm{eq}})\right) \geq 0$$

Entropy production per *wrong* incorporated polymer:

$$\Delta S^{\mathrm{tot,w}} = \frac{1}{T}\left(\Delta W^{\mathrm{w}} - \Delta F^{\mathrm{eq}} - k_{\mathrm{B}} T \log\frac{\eta}{\eta^{\mathrm{eq}}} \right) \geq 0$$

Summary

- ST helps in setting up a unified frame for discussing dissipation in several biochemical processes
- Several regimes can be exhibited: we discussed no general “tradeoff” principle

The interplay between speed, dissipation and accuracy has been addressed in the so-called “uncertainty relations” in ST

Thank you!

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