Stochastic Thermodynamics and Thermodynamics of Information

Lecture V: Stochastic thermodynamics in biological systems

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May 18, 2018

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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

ATP Synthase motion is *reversible*: ATP degradation $\rightarrow$ proton gradient

Yasuda et al., 2002
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:

\[
A + E \rightleftharpoons_{k_1^-}^{k_1^+} E^* \rightleftharpoons_{k_2^-}^{k_2^+} B + E
\]

- Define \( \epsilon^* = \epsilon_{E^*} - \epsilon_E \)

- Ratios of reaction rates:

\[
\frac{k_1^+}{k_1^-} = e^{-\left(\epsilon^* - \epsilon_A\right)/k_B T} \quad \frac{k_2^+}{k_2^-} = e^{\left(\epsilon^* - \epsilon_B\right)/k_B T}
\]

- Therefore

\[
\frac{k_1^+ k_2^+}{k_1^- k_2^-} = e^{-\left(\epsilon_B - \epsilon_A\right)/k_B T}
\]
Passive catalysis

• Set

\[
\begin{align*}
    k_1^+ &= \omega_1 \, e^{-(\epsilon^* - \epsilon_A)/k_BT} \\
    k_2^+ &= \omega_2 \\
    k_1^- &= \omega_1 \\
    k_2^- &= \omega_2 \, e^{-(\epsilon^* - \epsilon_B)/k_BT}
\end{align*}
\]

• Rate equations (average):

\[
\begin{align*}
    \frac{d\langle n \rangle}{dt} &= k_2^+ [E^*] - k_2^- [E][B] \\
    \frac{d[E^*]}{dt} &= k_1^+ [E][A] + k_2^- [E][B] - (k_1^- + k_2^+) [E]
\end{align*}
\]

• Production of B-molecules vanishes at equilibrium:

\[
\begin{align*}
    \frac{[B]}{[A]} &= \frac{k_1^+ k_2^+}{k_1^- k_2^-} = e^{-(\epsilon_B - \epsilon_A)/k_BT} \\
    \text{i.e.} \quad [A] \, e^{-\epsilon_A/k_BT} &= [B] \, e^{-\epsilon_B/k_BT}
\end{align*}
\]
Beyond the rate equations:

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

\[
\frac{dp_{0n}}{dt} = k_1^- p_{1n} + k_2^+ p_{1,n-1} - (k_1^+ [A] + k_2^- [B]) p_{0n}
\]

\[
\frac{dp_{1n}}{dt} = k_1^+ [A] p_{0n} + k_2^- [B] p_{0,n+1} - (k_1^- + k_2^+) p_{1n}
\]
Non-equilibrium steady state

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

\[ [A] e^{-\epsilon_A/k_B T} \neq [B] e^{-\epsilon_B/k_B T} \]

Free-energy imbalance:

\[ \Delta G = \epsilon_B - k_B T \log[B] - (\epsilon_A - k_B T \log[A]) = k_B T \log \frac{k_1^+ k_2^+ [A]}{k_1^- k_2^- [B]} \]

Steady-state probability of charged enzyme:

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

Net production rate (cf. rate equation):

\[ \frac{d \langle n \rangle}{dt} = \frac{k_1^+ k_2^+ [A] - k_1^- k_2^- [B]}{k_1^- - k_1^+ [A] + k_2^+ - k_2^- [B]} \]
Large deviations

Generating function:

\[ \Psi_\alpha(\mu, t) = \sum_{n=\infty}^{+\infty} e^{\mu(n+\alpha/2)} p_{\alpha,n}(t) \quad \alpha \in \{0, 1\} \]

Evolution equation:

\[
\frac{d}{dt} \begin{pmatrix} \Psi_0 \\ \Psi_1 \end{pmatrix} = \mathcal{L}(z) \begin{pmatrix} \Psi_0 \\ \Psi_1 \end{pmatrix} \quad z = e^{\mu/2}
\]

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

\[\Psi \sim e^{t\theta(\mu)} \quad \theta(\mu) : \text{largest e.v. of } \mathcal{L}\]
Large deviations

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

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

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

Gallavotti-Cohen symmetry: $z \rightarrow \bar{z}$:

$$\bar{z}^{-2}k_1^- k_2^- [B] = z^2 k_1^+ k_2^+ [A] \iff \mu \rightarrow \bar{\mu} = \Delta G/k_B T - \mu$$

$$\theta(\mu) = \theta(\Delta G/k_B T - \mu)$$

$$J(\mu) = -J(\Delta G/k_B T - \mu)$$

$$\omega(J) - \omega(-J) = J \Delta G/k_B T = \dot{S}$$
Active catalysis

Reaction scheme: \( \text{ATP} + A \Leftrightarrow \text{ADP} + P + B \)
Rate equations

\[
\frac{d[E]}{dt} = k_4^+ [E_3] + k_1^- [E_1] - k_1^+ [E][ATP] - k_4^- [E][B]
\]

\[
\frac{d[E_1]}{dt} = k_1^+ [E][ATP] + k_2^- [E_2] - k_1^- [E_1] - k_2^+ [E_1][A]
\]

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

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

Detailed balance:

\[
\frac{k_i^+}{k_i^-} = e^{-\Delta \epsilon_i / k_B T}
\]

\[
\frac{k_1^+ k_2^- k_3^+ k_4^+}{k_1^- k_2^- k_3^- k_4^-} = e^{-(\Delta \epsilon_A + \Delta \epsilon_{ATP}) / k_B T}
\]

\[
\Delta \epsilon_A = \epsilon_B - \epsilon_A
\]

\[
\Delta \epsilon_{ATP} = \epsilon_{ADP} + \epsilon_P - \epsilon_{ATP}
\]
Generating function

\[
\begin{align*}
\frac{\partial \Psi_0}{\partial t} &= k_4^+ e^{\mu_1/2} \Psi_3 + k_1^+ e^{-\mu_2/2} \Psi_1 - \left(k_1^+ [\text{ATP}] + k_4^-\right) \Psi_0 \\
\frac{\partial \Psi_1}{\partial t} &= k_1^+ [\text{ATP}] e^{\mu_2/2} \Psi_0 + k_2^- e^{-\mu_1/2} \Psi_2 - \left(k_1^- + k_2^+ [\text{A}]\right) \Psi_1 \\
\frac{\partial \Psi_2}{\partial t} &= k_2^+ [\text{A}] e^{\mu_1/2} \Psi_1 + k_3^- [\text{ADP}][\text{P}] e^{-\mu_2/2} \Psi_3 - \left(k_2^- + k_3^+\right) \Psi_2 \\
\frac{\partial \Psi_3}{\partial t} &= k_3^+ e^{\mu_2/2} \Psi_2 + k_4^- [\text{B}] e^{-\mu_1/2} \Psi_0 - \left(k_4^- + k_3^+ [\text{ADP}][\text{P}]\right) \Psi_3 \\
\frac{\partial \Psi}{\partial t} &= \mathcal{L}_\mu \Psi,
\end{align*}
\]

The Gallavotti-Cohen symmetry involves the simultaneous change of \(\mu_1, \mu_2\):

\[
\mathcal{L}_{\bar{\mu}} = Q^{-1} \mathcal{L}_\mu^\dagger Q
\]

\[
e^{\bar{\mu}_1} = \frac{k_2^- k_4^- [\text{B}]}{k_2^+ k_4^+ [\text{A}]} e^{-\mu_1} \quad \quad e^{\bar{\mu}_2} = \frac{k_1^- k_3^- [\text{ADP}][\text{P}]}{k_1^+ k_3^+ [\text{ATP}]} e^{-\mu_2}
\]
Fluctuation relations

Chemical Reaction Network:

\[
\sum_{\sigma} \nabla_{+\rho}^\sigma X_{\sigma} + \sum_{\tau} \nabla_{+\rho}^\tau A_{\tau} \stackrel{k_{-}\rho}{\rightleftharpoons} \sum_{\sigma} \nabla_{-\rho}^\sigma X_{\sigma} + \sum_{\tau} \nabla_{-\rho}^\tau A_{\tau}
\]

Stoichiometric matrix:

\[
\nabla_{\pm\rho} = (\nabla_{\pm\rho}^{\sigma,\tau}) \quad \nabla_{\pm\rho}^{\sigma,\tau} \in \mathbb{N}
\]

\[
\nabla_{\rho} = \nabla_{-\rho} - \nabla_{+\rho} \quad \nabla_{\rho}^{\sigma,\tau} \in \mathbb{Z}
\]

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

\( X_{\sigma} \): intermediate \quad \( A_{\tau} \): chemostatted
Transitions

Elementary transitions:

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

Mass-action law:

\[
\begin{align*}
R_{X',X}^{\pm \rho} &= \delta_{X',X\pm \nabla_{\rho}} \Omega k_{\pm \rho} \prod_{\tau} [A_{\tau}]^{\nu_{\pm \rho}} \\
\times \prod_{\sigma} \left( \frac{X^{\sigma}}{\Omega} \frac{X^{\sigma} - 1}{\Omega} \ldots \frac{X^{\sigma} - \nabla_{\pm \rho}^{\sigma} + 1}{\Omega} \right)
\end{align*}
\]

Master equation:

\[
\frac{dp_X}{dt} = \sum_{\epsilon = \pm 1} \sum_{\rho} \left[ R_{X,X'}^{\epsilon \rho} p_{X'} - R_{X',X}^{-\epsilon \rho} p_X \right] = (\mathcal{L} p)_X
\]

Steady state \( p^{ss}(X) \) (not trivial to evaluate)
Average entropy production

Entropy of a state $p_X$:

$$S(P) = \sum_X S^{(0)}(X)p_X - k_B \sum_X p_X \log p_X$$

"internal"  Shannon

Total average entropy production:

$$\dot{S}^{\text{tot}} = \frac{dS}{dt} - \frac{dS^{(r)}}{dt}$$

$$J_\rho(X; t) = R_{X', X}^\rho p_X - R_{X, X'}^{-\rho} p_{X'}$$

$$A_\rho(X; t) = k_B \log \frac{R_{X', X}^\rho p_{X'}}{R_{X, X'}^{-\rho} p_X}$$

$$- \frac{dS^{(r)}}{dt} = \sum_{X, \rho} S^{(0)}(X) J_\rho(X; t) - \frac{1}{2} \sum_{X, \rho} J_\rho(X; t) \log \frac{R_{X, X'}^\rho}{R_{X', X}^{-\rho}}$$

advection  Heat flow $Q/T$

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

• Trajectory:

\[ \mathbf{X} = (X(t)) = (X_0, t_0) \xrightarrow{\rho_1} (X_1, t_1) \xrightarrow{\rho_2} \cdots \xrightarrow{\rho_n} (X_n, t_n) \to t_f \]

• Time-reversed trajectory \( \hat{\mathbf{X}} \)

• Probability density of a path \( \mathcal{P}(\mathbf{X}) \)

• Detailed fluctuation relation:

\[
\frac{\mathcal{P}(\mathbf{X}|X_0)}{\mathcal{P}(\hat{\mathbf{X}}|X_f)} = \prod_{k=1}^{n} \frac{R_{X_k}X_{k-1}}{R_{X_{k-1}}X_k} = e^{Q(\mathbf{X})/k_B T}
\]

• \( Q/T \neq -\Delta S^{(r)} \) because of the advection term

• Integral fluctuation relation:

\[
\frac{\mathcal{P}(\mathbf{X})}{\mathcal{P}(\hat{\mathbf{X}})} = e^{(Q(\mathbf{X})-\Delta S(\mathbf{X}))/k_B T}
\]

• \( \Delta S \) cancels the advection term...

Thus

\[ \left\langle e^{-(Q-\Delta S)/k_B T} \right\rangle = 1 \]
Define

$$
\Psi_X(\mu; t) = \int dX \ P^{ss}(X) \delta_{X(t)X} e^{-\mu Q(X)/k_B T}
$$

it satisfies

$$
\Psi_X(\mu; t_0) = p^{ss}_X
$$

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

Therefore

$$
\Psi \sim e^{-t \theta(\mu)} \quad \text{as} \quad t \to \infty
$$

where

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

\[ \mathcal{P}^{ss}(X) \left( \frac{\mathcal{P}^{ss}(\hat{X})}{\mathcal{P}^{ss}(X)} \right)^\mu = \mathcal{P}^{ss}(\hat{X}) \left( \frac{\mathcal{P}^{ss}(X)}{\mathcal{P}^{ss}(\hat{X})} \right)^{1-\mu} = \mathcal{P}^{ss}(X) \left( \frac{\mathcal{P}^{ss}(X)}{\mathcal{P}^{ss}(\hat{X})} \right)^{1-\mu} \]

which implies the Gallavotti-Cohen symmetry:

\[ \theta(\mu) = \theta(1 - \mu) \]

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

\[ \text{Prob}(Q, t) \xrightarrow{t \to \infty} e^{-t \omega(s)}, \quad \frac{Q}{k_B T} = s t \]

since

\[ \int dQ \ \text{Prob}(Q, t) e^{-\mu Q/k_B T} = \sum_X \Psi_X(\mu; t) \sim e^{-t \theta(\mu)} \]

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

\[ \omega(s) = \max_\mu(\theta(\mu) - \mu s) \]

and \( \omega(s) - \omega(-s) = -s \)
Chemical reaction rates with a given number of particles:

\[
\sum_{\sigma} \nabla_{+\rho}^{\sigma} X_{\sigma} + \sum_{\tau} \nabla_{+\rho}^{\tau} A_{\tau} \xrightleftharpoons[k_{\rho}^{-\rho}, k_{\rho}^{+\rho}] \sum_{\sigma} \nabla_{-\rho}^{\sigma} X_{\sigma} + \sum_{\tau} \nabla_{-\rho}^{\tau} A_{\tau}
\]

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

\[
R_{X',X}^\rho = \delta_{X',X+\nabla_{\rho}} \Omega k_{\rho} \prod_{\tau} [A_{\tau}]^{\nu_{\rho}^{\tau}}
\times \prod_{\sigma} \left( \frac{X_{\sigma} X_{\sigma} - 1}{\Omega} \cdots \frac{X_{\sigma} - \nabla_{\rho}^{\sigma} + 1}{\Omega} \right)
\]
Simulation algorithm:  

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

Difficulties:

- The number of possible reactions can become large.
- Thus \( \tau \) 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 \rightarrow \{3\} X
   \frac{1}{2}c1*A*X*(X-1)

R2:
   \{3\} X \rightarrow A + \{2\} X
   \frac{1}{6}c2*X*(X-1)*(X-2)

R3:
   B \rightarrow X
   c3 * B

R4:
   X \rightarrow 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
The motor is kept in a nonequilibrium state by the chemical imbalance of the ATP $\rightleftharpoons$ ADP + P reaction:

$$\frac{[\text{ATP}]}{[\text{ADP}][\text{P}]} \neq e^{(\epsilon_{\text{ATP}} - \epsilon_{\text{ADP}} - \epsilon_{\text{P}})/k_B T}$$

The “product” is displacement
The model

NISHINARI ET AL., 2005 et al.
The model

States:

1: Bound to ATP
2: Bound to ADP or empty

Moves:

Brownian motion: \((i, 2) \xrightarrow{\omega_B} (i \pm 1, 2)\)
ATP binding: \((i, 2) \xrightarrow{\omega_s} (i, 1)\)
Ratchet: \((i, 1) \xrightarrow{\omega_+} (i + 1, 2)\)
Reverse ratchet: \((i, 2) \xrightarrow{\omega_-} (i - 1, 1)\)
Hydrolysis: \((i, 1) \xrightarrow{\omega_h} (i, 2)\)

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

Data from Schnitzer and Block, 1995
Lines for $f = -1.05, -3.59, -5.63 \text{pN}$
Inset: $v$ vs. $f$ for fixed [ATP] 2µM 5µM
The phase diagram

$\Delta \mu$ $f$

$v=0$

$r=0$

Modes: A: ATP consumed, work performed; B: work consumed to produce ATP
C: ADP consumed to produce work; D: Work consumed to produce ADP

$v$: average velocity $r$: average ATP consumption rate

LACOSTE, LAU AND MALLICK, 2008
Normalized eigenvalue of $\mathcal{L}(fd/k_B T)\eta, -\Delta \mu / 2k_B T$ vs. $\eta$ (parameter of the generating function) for various values of $(fd/k_B T, \Delta \mu / k_B T)$: $(5, 0)$ (dashed), $(5, 10)$ (solid), $(2, 10)$ (dotted)
• The Gallavotti-Cohen symmetry appears in the pdf of the fluxes \( v, r \):

\[
\ln \frac{P(v, r, T)}{P(-v, -r, T)} \sim \left[ (f/k_B T) v + (\Delta \mu/k_B T) r \right] \mathcal{T}
\]

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 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 environment

“High fidelity” is a requirement
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 $\eta$
- Rate of “right” incorporations: $v^r = (1 - \eta) v$
- Rate of “wrong” incorporations: $v^w = \eta v$
- Equation for the error $\eta$:

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

Rates: $\mu_{ij}$ chemical driving, $\delta_{ij}$ kinetic barrier

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

Dictionary: $k \rightarrow R$, $T \rightarrow k_B T$
Definitions:

- Entropy produced per incorporated monomer: $\Delta S_{\text{tot}}$
- Entropy produced per \textit{wrong} incorporated monomer: $\Delta S_{\text{tot},w}$

\[
\Delta W = \sum_{(ij), \alpha \in \{r, w\}} J_{ij}^\alpha \mu_{ij} / v
\]

\[
\Delta F_{\text{eq}} = -k_B T \log \sum_{\alpha} e^{-\Delta E_{\alpha} / k_B T}
\]

\[
\eta_{\text{eq}} = \exp \left[ (-\Delta E^w + \Delta F_{\text{eq}}) / k_B T \right]
\]

\[
D_{\text{KL}}(\eta||\eta_{\text{eq}}) = \eta \log \frac{\eta}{\eta_{\text{eq}}} + (1 - \eta) \log \frac{1 - \eta}{1 - \eta_{\text{eq}}}
\]

\[
\Delta W^w = \sum_{(ij)} J_{ij}^w \mu_{ij} / v^w
\]
Main results

In the steady state:

\[ T \Delta S^{\text{tot}} = \Delta W - \Delta F^{\text{eq}} - k_B T D_{\text{KL}}(\eta || \eta^{\text{eq}}) \geq 0 \]

\[ T \Delta S^{\text{tot},w} = \Delta W^w - \Delta F^{\text{eq}} - k_B T \log \frac{\eta}{\eta^{\text{eq}}} \geq 0 \]

Therefore

\[ \eta = \eta^{\text{eq}} \exp \left[ (\Delta S^{\text{tot},w} + (\Delta W^w - \Delta F^{\text{eq}})) / k_B T \right] \]

Possible copying regimes:

Error amplification: \( \Delta W^w - \Delta F^{\text{eq}} > 0 \) and \( \eta > \eta^{\text{eq}} \)

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

Error correction: \( \Delta W^w - \Delta F^{\text{eq}} > 0 \) and \( \eta < \eta^{\text{eq}} \), thus

\[ \eta \geq \eta^{\text{eq}} e^{-\Delta S^{\text{tot},w} / k_B} \]
Single-step polymerization machines

Two regimes:

**Energetic discrimination:** \( \Delta E = \Delta E^w - \Delta E^r \geq \delta \)

**Kinetic discrimination:** \( \Delta E < \delta \)

In energetic discrimination:

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

In kinetic discrimination:

- \( \eta^{eq} \geq \eta \geq \eta^{min} = e^{-\delta/k_BT} \)
- \( \eta \) decreases as \( v \) and dissipation increases
Single-step polymerization machines
Proofreading

NINIO, HOPFIELD, 1974, 1975

Extra pathway with negative velocity $v_p \leq 0$ preferentially removes wrong monomers
Since $\dot{S}_{p}^{\text{tot},w} \geq 0$ and $v_p \leq 0$ one can show

$$\eta \geq \eta^{\text{eq}} \exp \left( \frac{-\Delta W_p + \Delta F^{\text{eq}}}{k_B T} \right)$$
Proofreading

$$\eta_{\text{eq}} e^{-\left(\Delta W_p - \Delta F_{\text{eq}}\right)/T}$$

$$\eta_{\text{min}} \approx e^{-\delta + \delta_p + \Delta E^w + \Delta E^r}/k_B T$$
Stochastic polymerization dynamics

- State of the growing polymer: $rrwr\ldots$
- State of the machine: $i \in \{1, \ldots, n\}$
- Intermediate states (with a tentatively matched monomer): $rrwri$ or $rrwri$
- Copying protocol: network of transitions $j \rightarrow i$ with rates $R_{ij}^{r,w}$
- Discrimination is due to differences in rates
- Probabilities: $P(\ldots r)$, $P(\ldots w)$, $P(\ldots ri)$, $P(\ldots wi)$ satisfying master equations:

$$\frac{d}{dt}P(\ldots ri) = \sum_{j=0}^{n+1} J_{ij}^{r}(\ldots)$$
$$\frac{d}{dt}P(\ldots wi) = \sum_{j=0}^{n+1} J_{ij}^{w}(\ldots)$$

- Currents: $J_{ij}^{r}(\ldots) = R_{ij}^{r}P(\ldots rj) - R_{ji}^{r}P(\ldots ri)$
- $j = 0 \rightarrow j = n + 1$ corresponds to the incorporation of a monomer
- All transitions are reversible
Stochastic polymerization dynamics

- Rates of incorporation:

\[
\frac{d}{dt} P(\ldots w) = \sum_{j=0}^{n+1} \left[ \mathcal{J}_{n+1,j}^{\text{w}} (\ldots) - \mathcal{J}_{j0}^{\text{r}} (\ldots w) - \mathcal{J}_{j0}^{\text{w}} (\ldots w) \right]
\]

and analog for \( r \)

- Assume errors are uncorrelated:

\[
P(\ldots) \propto \eta^{N_w} (1 - \eta)^{N - N_w}
\]

- Then

\[
P(\ldots r) = P(\ldots)(1 - \eta) \quad P(\ldots w) = P(\ldots) \eta
\]

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

\[
P(\ldots r_i) = P(\ldots) p_i^r \quad P(\ldots w_i) = P(\ldots) p_i^w
\]

- Occupation fluxes:

\[
J_{ij}^r = \mathcal{N} \left( R_{ij}^r p_j - R_{ji}^r p_i \right) \quad \mathcal{J}_{ij}^r (\ldots) = P(\ldots) J_{ij}^r / \mathcal{N}
\]
Entropy production rate

\[
\frac{dS^{\text{tot}}}{dt} = k_B \sum \frac{P(\ldots)}{N} \sum_{(i,j), \alpha \in \{r, w\}} J_{ij}^\alpha \log \left( \frac{R_{ij}^\alpha p_j^\alpha}{R_{ji}^\alpha p_i^\alpha} \right)
\]

\[
\frac{dS^{\text{tot}}}{dt} = k_B \sum_{(i,j), \alpha} \frac{J_{ij}^\alpha \mu_{ij}}{k_B T} - \eta v \left( \log \eta + \frac{\Delta E^w}{k_B T} \right) + (1-\eta) v \left( \log \left( 1 - \eta + \frac{\Delta E^r}{k_B T} \right) \right)
\]

Thus \(\Delta S^{\text{tot}}\) per incorporated monomer is given by

\[
\Delta S^{\text{tot}} = \frac{1}{v} \frac{dS^{\text{tot}}}{dt} = \frac{1}{T} \left( \Delta W - \Delta F^{\text{eq}} - k_B T D_{\text{KL}}(\eta || \eta^{\text{eq}}) \right) \geq 0
\]

Entropy production per wrong incorporated polymer:

\[
\Delta S^{\text{tot}, w} = \frac{1}{T} \left( \Delta W^w - \Delta F^{\text{eq}} - k_B T \log \frac{\eta}{\eta^{\text{eq}}} \right) \geq 0
\]
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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