Improved Bounds on Entropy Production in Living Systems

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February 14, 2025

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1 Introduction

Overview

- **Living systems maintain or increase local order by working against the second law of thermodynamics**

- Optimization framework: thermodynamic infererence of improved lower bounds on entropy production rates

Deduction of thermodynamic quantities from partial observations.

- Non-zero bounds for entropy production by considering transition statistics beyond one-step dynamics

Present Problems

- Entropy production estimators fail when
  - Only a small set of observables is accessible
  - Nonequilibrium transport currents vanish

- Many degrees of freedom are typically hidden in experiments

- Sometimes trajectories *appear* symmetric in time

  ⇒ don’t obey detailed balance, no relative entropy!

Biological Examples

- Overview of biological data analyzed

- Bacterial flagellar motor
- Microtubule growth
- Calcium oscillation in human embryonic kidney cells

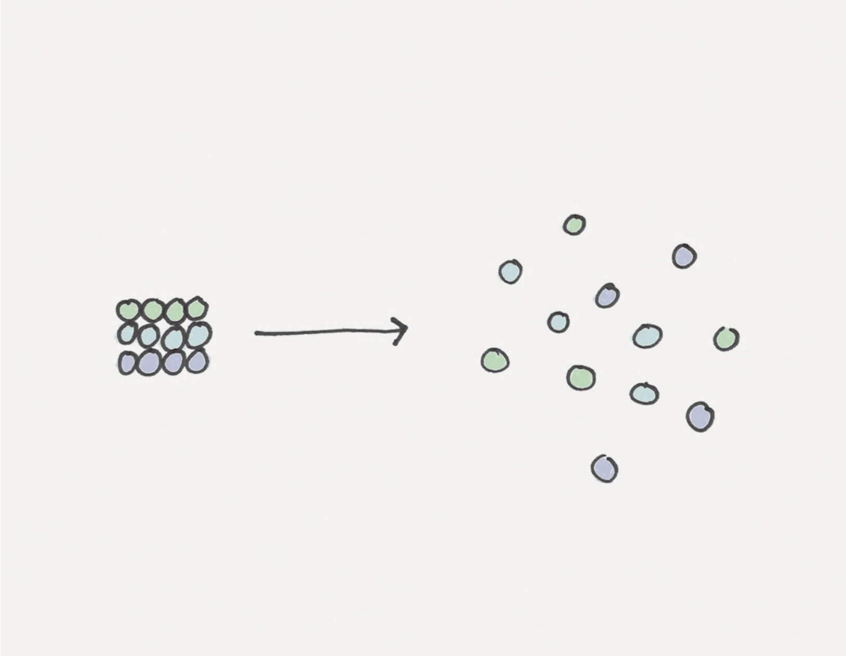
What is Entropy?

- Entropy as a measure of "disorder"
- Classically, entropy is a measure of the unavailability of a system's energy to do work

$$\Delta S = \frac{\Delta Q}{T}$$

- Entropy change can be experimentally measured

$$\underbrace{\Delta G}_{\text{Gibbs energy}} = \underbrace{\Delta U}_{\text{internal energy}} - T\Delta S$$



What is Entropy?

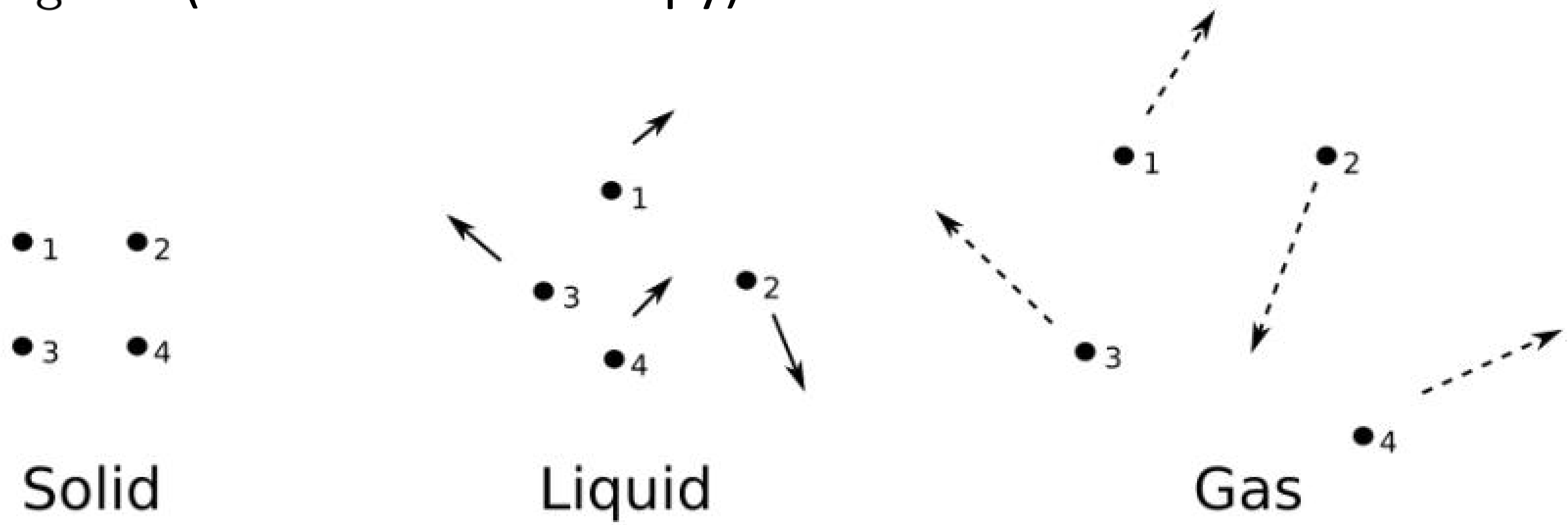
- Entropy as a probabilistic idea
- There seems to be more “disordered states” than there are “ordered states”

$S = k_\mathrm{B} \log \Omega$ (Boltzmann’s entropy)

Example (Phases of matter)

- More possible configurations in a gaseous system

⇒ gas has more entropy than solid



What is Entropy?

- As a number associated to a probability distribution over a finite sample space

$$H = -\sum_{i=1}^{N} p_i \log p_i$$

p_i is the probability of being in the state *i*

(Shannon entropy)

- Consistent with entropy in statistical physics (Cf. Boltzmann)

What is Entropy?

- As a number associated to a probability distribution over a finite sample space

$$H = -\sum_{i=1}^{N} p_i \log p_i$$

(Shannon entropy)

p_i is the probability of being in the state *i*

- The most compressed amount of code needed to encompass the content of a signal (information)
- We can reinterpret “disorder” as “information content”

What is Entropy?

- An event E happens with probablity $\mathbb{P}(E)$
- $s(E)$ is the information content of E ⇒ function of $\mathbb{P}(E)$

1. Decreasing function of $\mathbb{P}(E)$
2. If events E_1 and E_2 are independent, then $s(E_1 \cap E_2) = s(E_1) + s(E_2)$

⇒ $s(E)$ is proportional to $-k \log \mathbb{P}(E), \quad k > 0$

Entropy is the expectation value of information content

Entropy in Biology

- Second Law of Thermodynamics:

  The entropy of the universe tends to a maximum.

- Biological organisms are highly ordered ⇒ nonequilibrium

  locally, entropy can be lowered by external action

  increase in environmental entropy ⇒ the Second Law

2 Literature Review

Upper Bound to Entropy Production Rates

- This paper gives a lower bound for entropy production
- An upper bound for steadystate has been derived:

$$a = \sum_{i<j} (\pi_i q_{ji} + \pi_j q_{ij}) \qquad R = \max_{i \neq j} \frac{q_{ij}}{q_{ji}} \geq 1$$

$$\Rightarrow \quad \sigma \leq a \, (\log R) \left(\frac{R-1}{R+1} \right)$$

(Ref.) Nishiyama, T.; Hasegawa, Y. (2023). *Upper bound for entropy production in Markov processes*.

Thermodynamic Uncertainty Relations

- Thermodynamic uncertainty relations (TURs) can constrain nonequilibrium fluctuations

$$\Sigma_\tau \geq 2k_B \frac{\langle J_\tau \rangle^2}{\mathrm{Var}(J_\tau)}$$

- Classic lower bound for entropy production rate

(Ref.) Horowitz, J. M.; Gingrich, T. R. (2020). *Thermodynamic uncertainty relations constrain non-equilibrium fluctuations*.

3 Theory

Entropy Production Rate

spends a fraction π_i
of the time in state *i*

- Systems in thermal equilibrium obey detailed balance: $\pi_i q_{ij} = \pi_j q_{ji}$

⇒ This is a reversible Markov process

rate of transition
from state *i* to *j*

- The entropy production rate in steadystate is

$$\sigma = \frac{k_B}{2} \sum_{i,j} (\pi_i q_{ij} - \pi_j q_{ji}) \log\left(\frac{\pi_i q_{ij}}{\pi_j q_{ji}}\right)$$

Detailed Balance

$$\sigma = \frac{k_B}{2} \sum_{i,j} (\pi_i q_{ij} - \pi_j q_{ji}) \log \left(\frac{\pi_i q_{ij}}{\pi_j q_{ji}} \right)$$

No entropy production when system is in equilibrium

Always positive

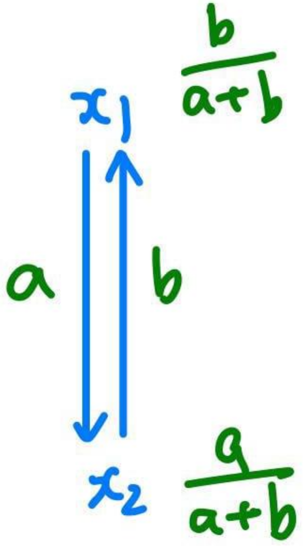
- Organisms operate far from equilibrium. Violations of detailed balance increase environment entropy

- Apply the formula? Not all microstates are accessible

⇒ Estimate σ from coarse-grained data

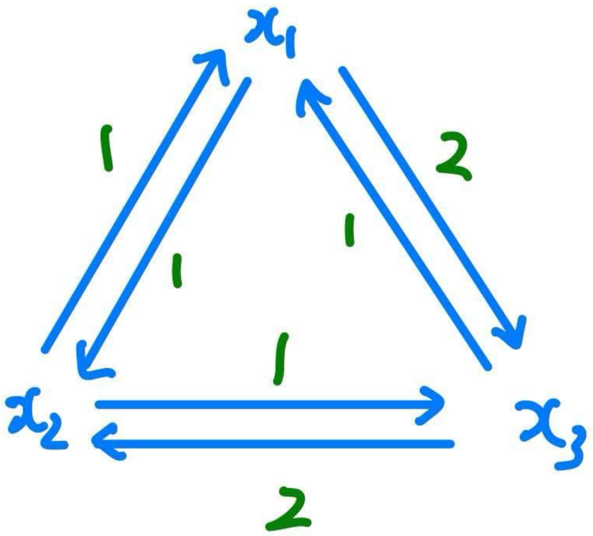
Detailed Balance

Example (Two nodes)



Equilibrium is guaranteed

Example (Three nodes)



Equilibrium is not guaranteed

Detail balance is a strong condition

Markov Processes

- Markov property (discrete): $X = (X_1, X_2, \dots, X_N, \dots)$

$$\mathbb{P}(X_{n+1} = x_{n+1} \mid X_n = x_n, \dots, X_1 = x_1) = \mathbb{P}(X_{n+1} = x_{n+1} \mid X_n = x_n) \text{ for all } n \in \mathbb{N}.$$

- A continuous time Markov process a sequence of random variables with the Markov property

$$\mathbb{P}(X_t = j | X_0 = i) = P_{ij}(t) = (e^{Qt})_{ij}$$

Markov Processes

- History independence
- We may assume our biological system to be microscopically Markovian

⇒ Why do we emphasize “microscopic”?

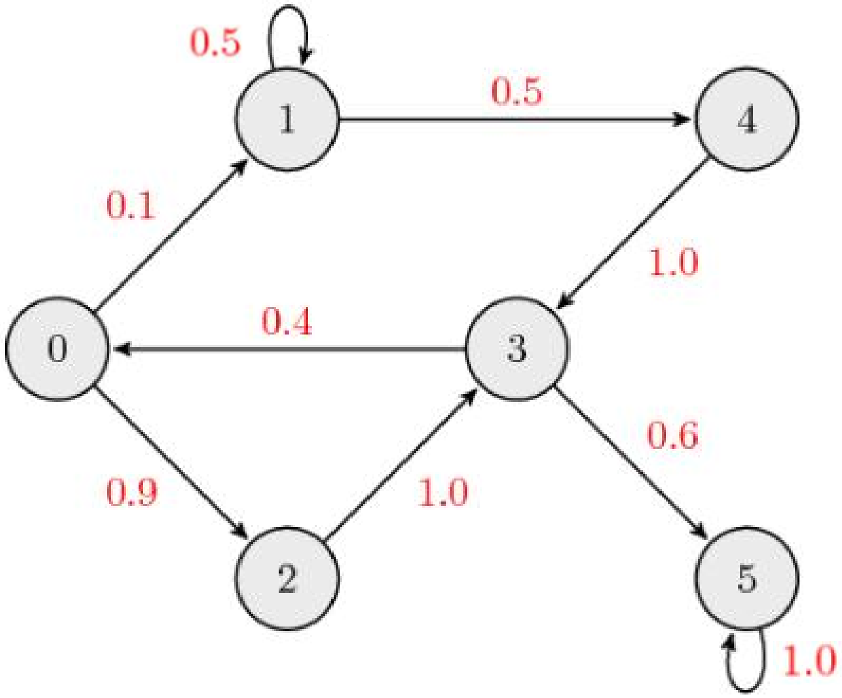
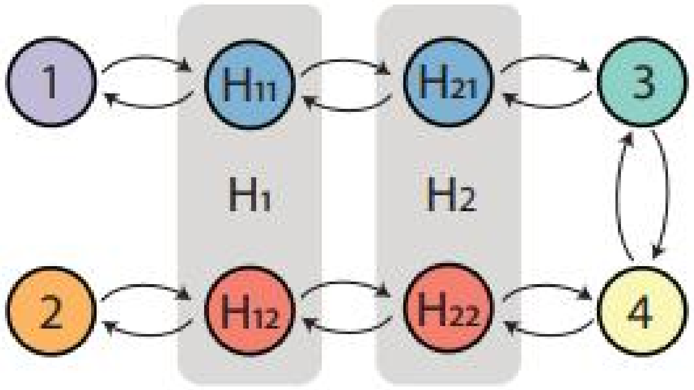


FIG. Example of a Markov chain

An Example



- System currently in macrostate H_1

  The probabilities of jumping to 1 or 2 are both non-zero

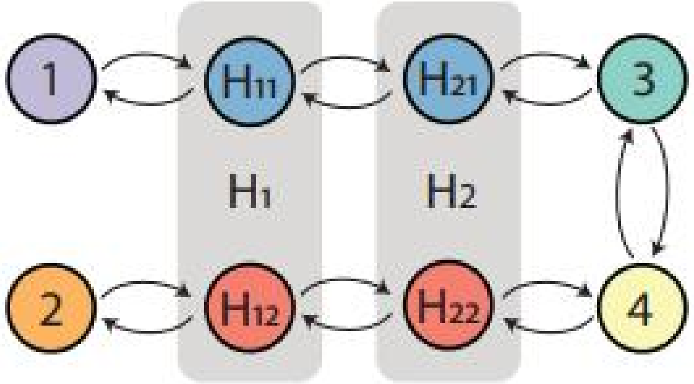
- Previous observed macrostate was 1

  The probability of transitioning to 2 is zero

- Coarse-grained observables may be non-Markovian!

  ⇒ History dependence emerges from partial observation

An Example



- Arbitrary trajectory $(3, H_2, H_1, H_2, \ldots, H_1)$

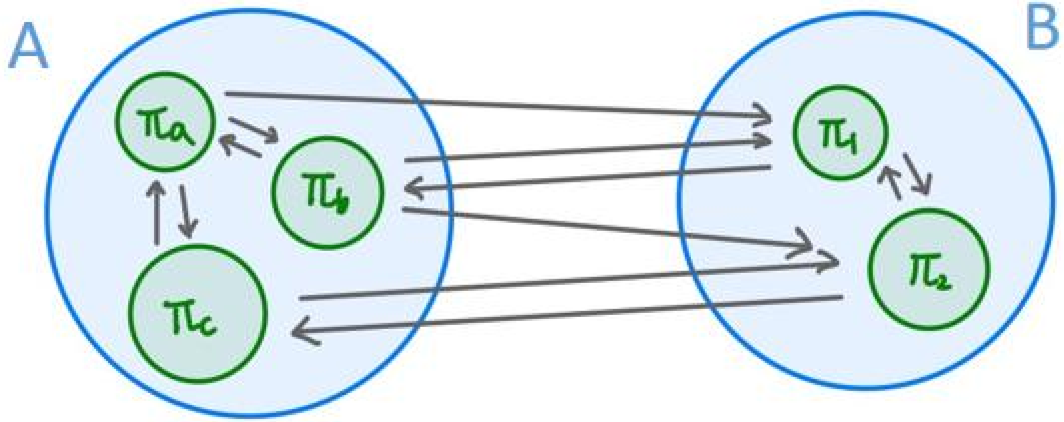
  The probability of transitioning to 2 is zero

- Truncate the trajectory to length N : $(H_2, H_1, H_2, \ldots, H_1)$

  Can the process transition to 2? It shouldn't! We lose information

Markovian Systems

- No finite set of observables guaranteed to describe the system ⇒ Construct an estimator that preserves the statistics
- Observable: $\hat{n}_{AB} = \sum_{i \in A} \sum_{j \in B} \pi_i q_{ij}$



Example calculation:

$$A = \{a, b, c\}, \quad B = \{1, 2\}.$$

$$\hat{n}_{AB} = \sum_{i=a,b,c} \sum_{j=1,2} \pi_i q_{ij}$$
$$= \pi_a q_{a1} + \pi_b q_{b1} + \pi_b q_{b2} + \pi_c q_{c2}$$

As as Optimization Problem

set of all possible macroscopic observables for our system

The best possible estimator is

$$\sigma(\mathcal{S}) \geq \min\{\sigma(\mathcal{R}) | \mathcal{O}(\mathcal{R}) = \mathcal{O}(\mathcal{S})\}.$$

$$\Downarrow$$

This is not practical

Let’s look at a subset of the observable space

$$\sigma(\mathcal{S}) \geq \min\{\sigma(\mathcal{R}) | \mathcal{O}_k(\mathcal{R}) = \mathcal{O}_k(\mathcal{S})\},$$

Unique stationary distribution, use *n* as observable

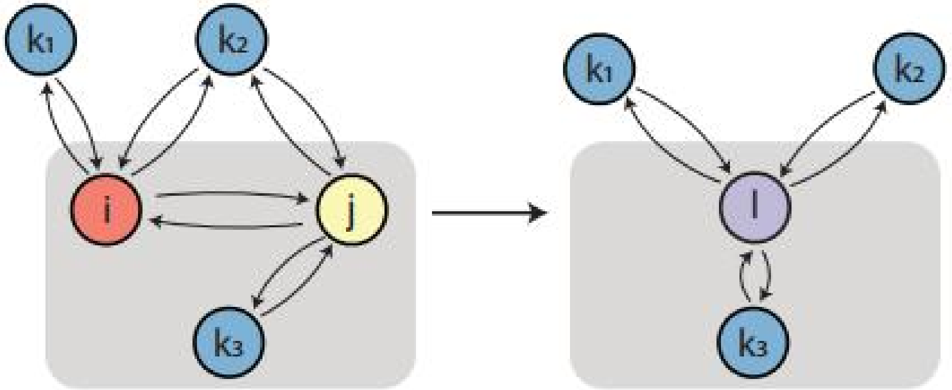
$$\sigma = \frac{k_B}{2} \sum_{i \neq j} (n_{ij} - n_{ji}) \log \left(\frac{n_{ij}}{n_{ji}} \right)$$

One-Step Estimator

- We can simplify the internal topology without affecting $\mathcal{O}_1$ observables

$$(n_{ik} - n_{ki}) \log \left(\frac{n_{ik}}{n_{ki}} \right) + (n_{jk} - n_{kj}) \log \left(\frac{n_{jk}}{n_{kj}} \right)$$

$$\mapsto \; ((n_{ik} + n_{jk}) - (n_{ki} + n_{kj})) \log \left(\frac{n_{ik} + n_{jk}}{n_{ki} + n_{kj}} \right)$$



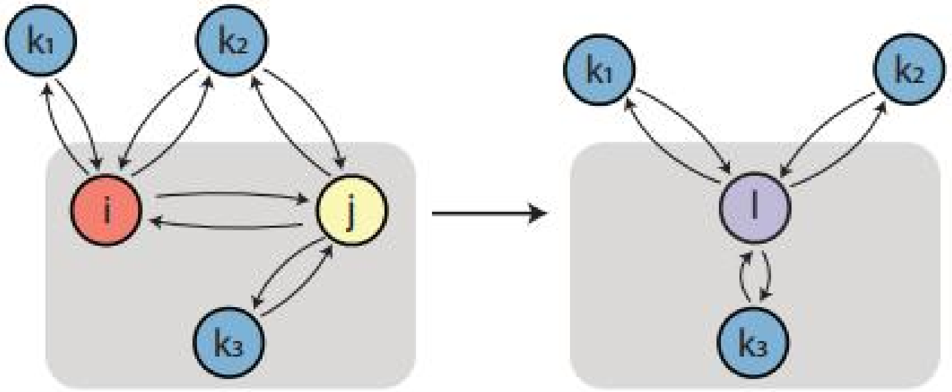
$$\mathcal{O}_1 = \{n_{IJ} | I, J \text{ macrostates}\}$$

One-Step Estimator

- Convexity + Jensen’s inequality

  ⇒ Entropy production rate decreases

- Markovian system with no hidden states and the same statistics (observables)



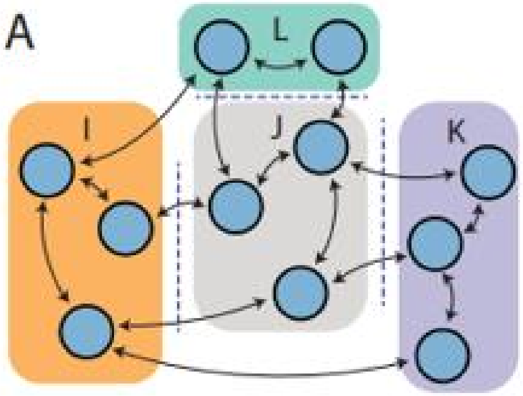
$$\mathcal{O}_1 = \{n_{IJ} | I, J \text{ macrostates}\}$$

Two-Step Estimator

$$\mathcal{O}_2 = \{n_{UV}, n_{UVW} | U, V, W \text{ macrostates}\}$$

- We can obtain a bound for each macrostate, consistent with $\mathcal{O}_2$ observables

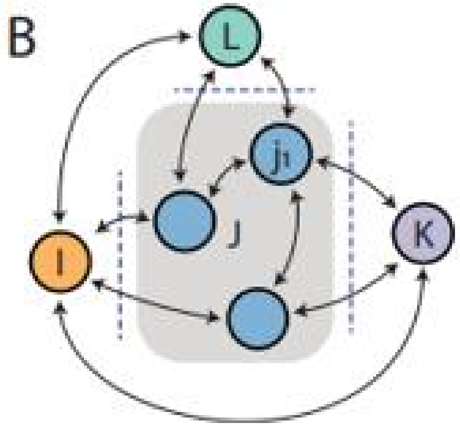
- Example: find the minimal EP rate across the edges (*J*, *I*), (*J*, *K*), and (*J*, *L*)



Example network

$\Longrightarrow$

Apply σ_1 to simplify *I*, *K*, *L*

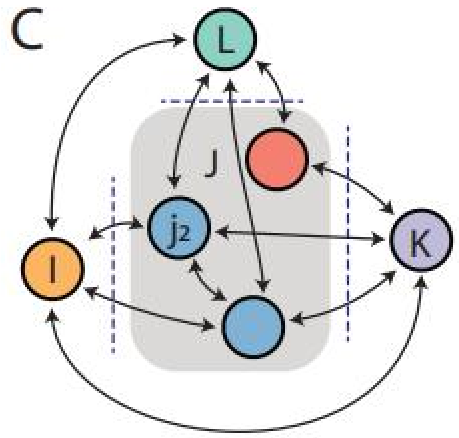


$$\sigma(j) = \sum_{i \in \mathcal{K}} (n_{ij} - n_{ji}) \log\left(\frac{n_{ij}}{n_{ji}}\right)$$

The entropy production along edges connected to *j*

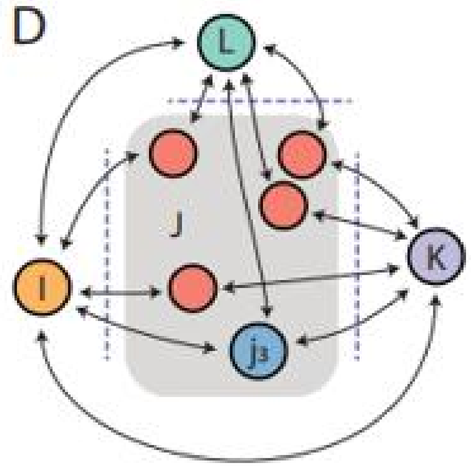
Two-Step Estimator

$\Longrightarrow$



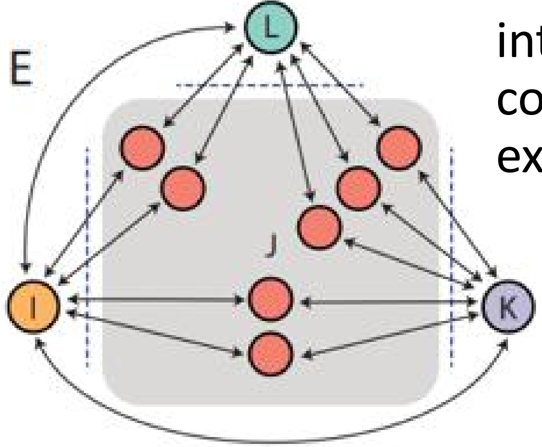
Rerouting the network
does not increase
entropy production

$\Longrightarrow$



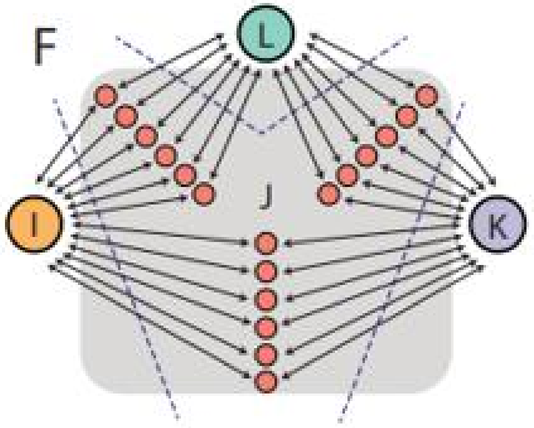
Iteration

$\Longrightarrow$



Canonical form: each internal state in *J* is connected only to two external macrostates

$\Downarrow$



It is always possible to optimize over 6 internal states connecting any two macrostates

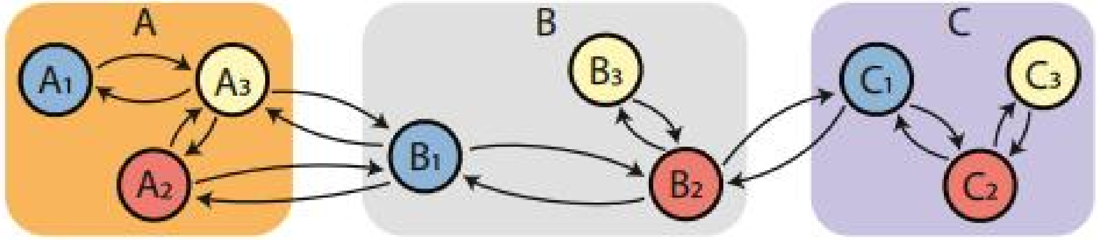
- Summing over all macrostates gives the $\mathcal{O}_2$ estimator

$$\sigma_2 = \frac{1}{2} \sum_J \sigma_2(J) \leq \sigma$$

Two-Step Estimator

$$\sigma_2 = \frac{1}{2}\sum_J \sigma_2(J) \leq \sigma$$

- For a simple system A-B-C, $\sigma_2(B)$ is the optimal bound
- Less computation required



A three state topology with no “loops”

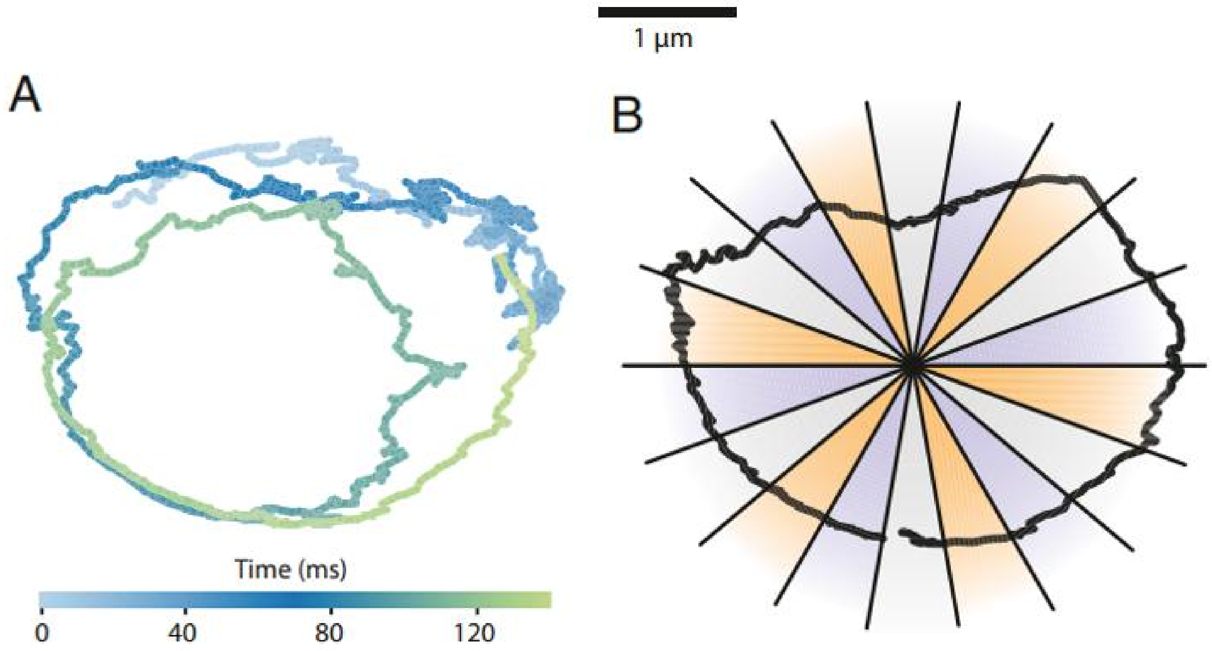
3 Results

Ex 1. Microbial Flagellar Motor

- Each flagellum is driven by a motor

- Stochastic direction switching

  ⇒ May not violate time-irreversibility



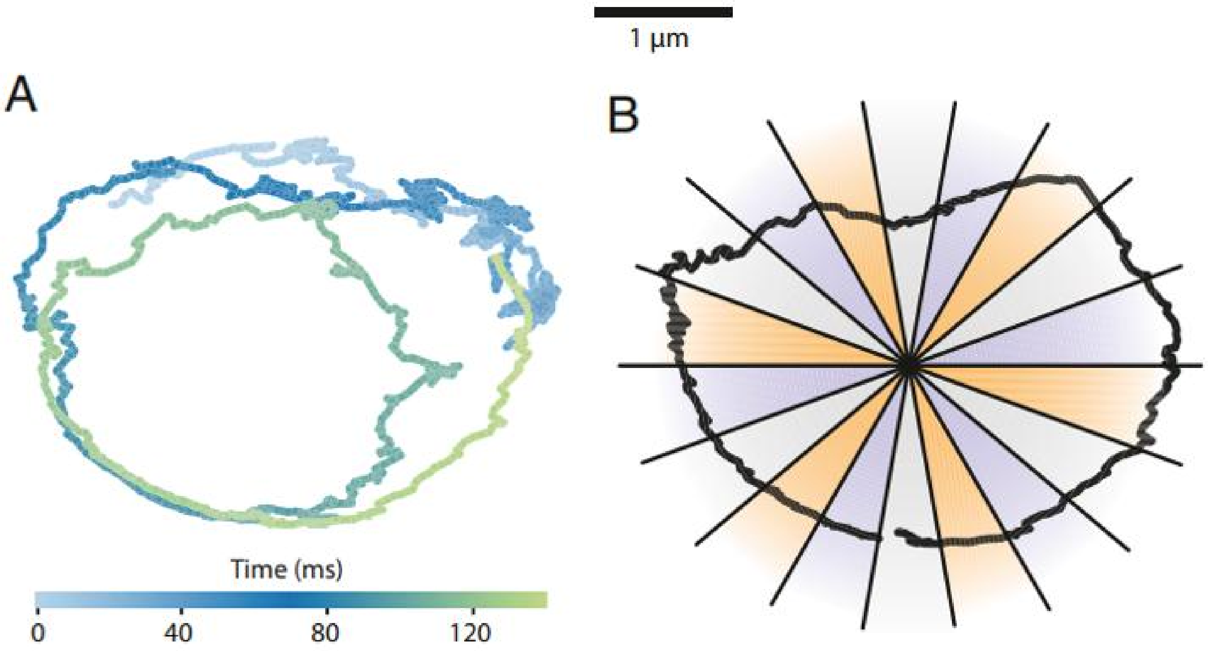
This example exhibits small net fluxes

Ex 1. Microbial Flagellar Motor

- Coarse-grain space into 3 regions, in total $3N$ segments ($N = 6$)

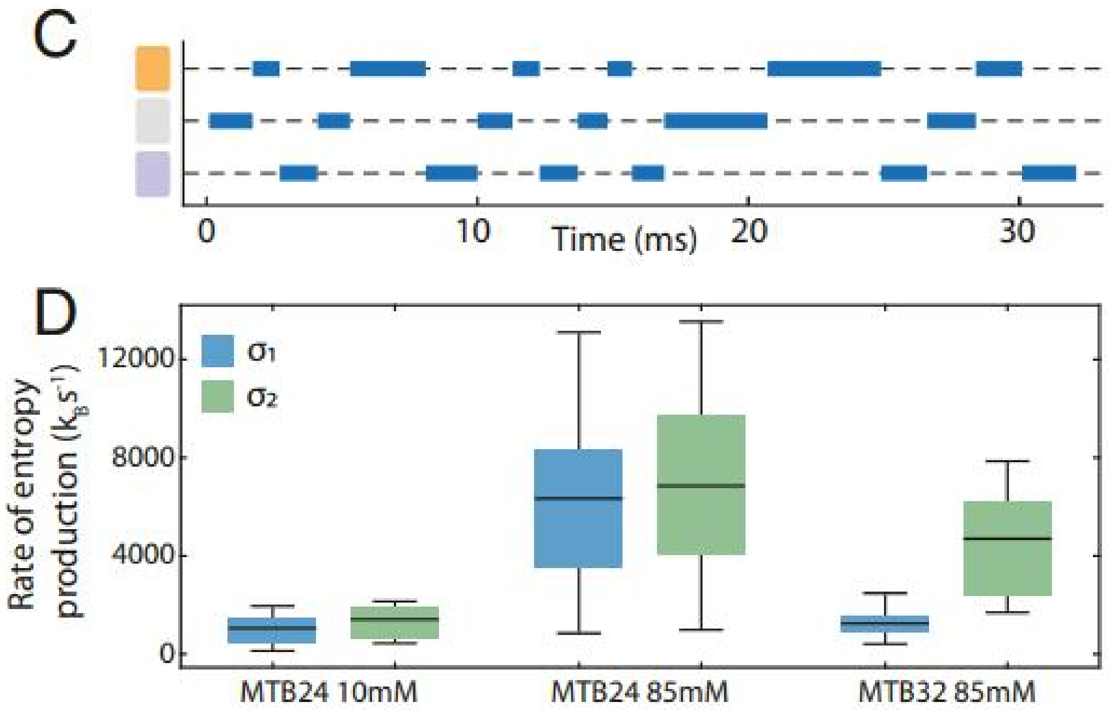
⇒ The σ_2 gives a nontrivial lower bound

- The quantity σT is interpreted as the free energy consumption rate



This example exhibits small net fluxes

Ex 1. Microbial Flagellar Motor



Compare: specimen with single turning direction and stochastically switching direction

Ex 2. Microtubule Growth

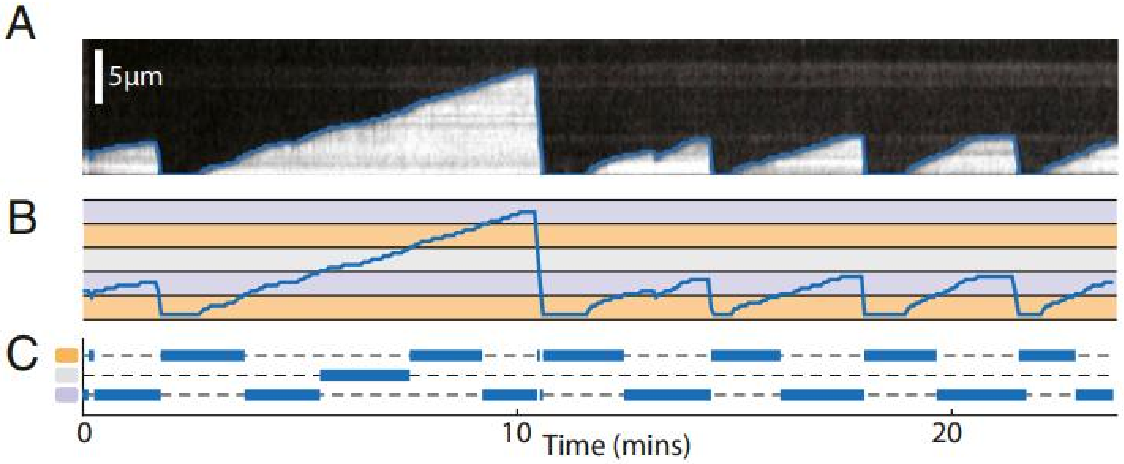
Recap: periods of steady growth before stochastically swicthing into rapid shrinking

Ex 2. Microtubule Growth

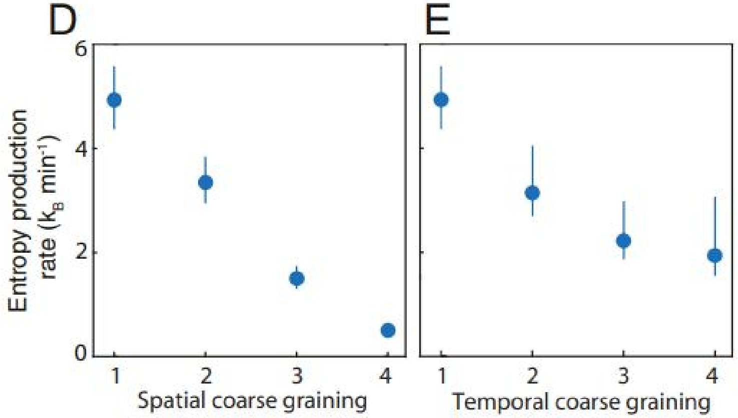
- Length oscillates around its mean value ⇒ no net flux

- Coarse-grain space modulo 3 and apply σ_2
  nontrivial bound of entropy production

- Higher-resolution experiments promise improved bounds



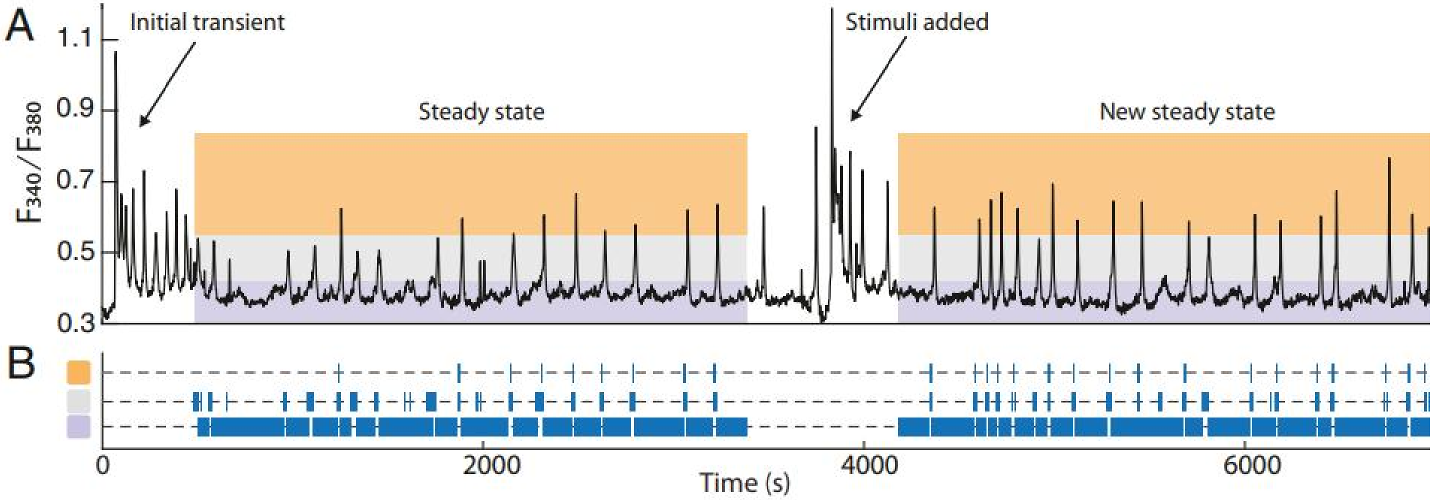
(A) Kymograph from experimental observations and (B)(C) corase-grained data



(D) Coarse-graining over space and (E) coarse-graining over time

Ex 3. Calcium Oscillation

- A cell responses to external stimuli via intracellular signaling



Manipulation of the concentration of calcium ions within the cytosol of human embryonic kidney cells

- Coarse-graining (modulo 3) followed by optimization
- The entropy production increases after stimulation with carbachol

$$4\, k_\mathrm{B} \cdot \mathrm{min}^{-1} \longrightarrow 8\, k_\mathrm{B} \cdot \mathrm{min}^{-1}$$

Relative Entropy

- Entropy production rates depend on the relative entropy between forward and backward trajectories

$$H(\mathbf{P},\mathbf{Q}) = \sum_{i\in X} P_i \log\left(\frac{P_i}{Q_i}\right)$$

$$e_p \overset{\text{def}}{=} \lim_{n\to+\infty} \frac{1}{n} H\left(\mathbf{P}|_{\mathcal{F}_0^n}, \mathbf{P}^-|_{\mathcal{F}_0^n}\right)$$

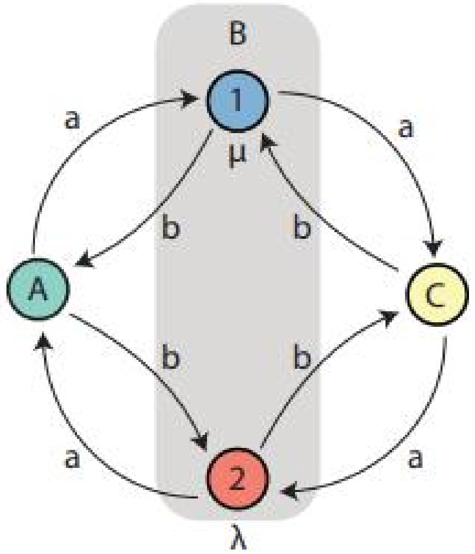
forward Markov chain

backward (time-reversed)
Markov chain

- Sometimes relative entropy appears to be zero!

An Example

Brownian clock on four microstates {1, 2, A, C}



States 1 and 2 are not distinguished by observation

$\mathbb{P}(\bar{Y}) = (1/4)a^{n-k}b^k$

- Consider the trajectory $X = (A, B, C, B, C, B)$

  The trajectories $Y = (A, 1, C, 2, C, 2)$ and $\bar{Y} = (A, 2, C, 1, C, 1)$ cannot be distinguished

  $\mathbb{P}(Y) = (1/4)a^k b^{n-k}$

- Sum over all *Y*

  Forward and backward trajectories are equally probable...

  Partial observation causes us to think the system is time-symmetric

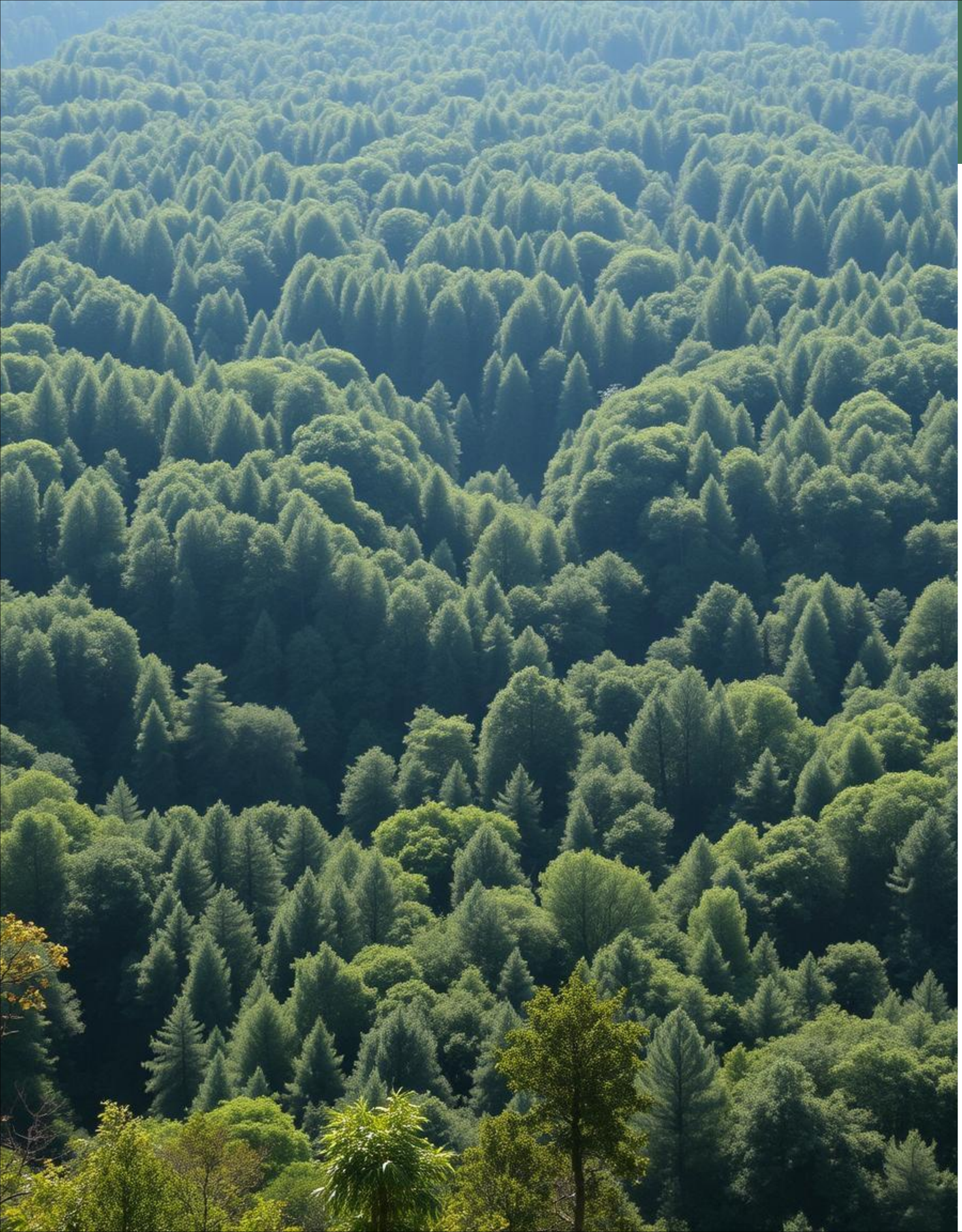
4 Concluding Remarks

Outlook

- Apply coarse graining to a small network ⇒ Larger networks
- Increased data resolution and trajectory length will lead to better bounds

  ⇒ imaging annd other experimental techniques

- Quantify tradeoffs between the faithful execution of a biological function and the actual energy expended



Conclusion

- Living systems expend entropy to maintain biological functions
- Ability to infer entropy production rates from partial experimental observations using optimization

  E.g. bacterial motors, microtubules, and calcium oscillations
- Tighter bounds on entropy production when systems appear time symmetric

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