Universal Thermodynamic Bounds on Symmetry Breaking in Living Systems

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1. Introduction

Living systems are maintained out-of-equilibrium by external driving forces. At stationarity, they exhibit emergent selection phenomena that break equilibrium symmetries and originate from the expansion of the accessible chemical space due to non-equilibrium conditions.

We derive universal thermodynamic bounds on these symmetry-breaking features in biochemical systems. Our bounds are independent of the kinetics and hold for both closed and open reaction networks. We also extend our results to master equations in the chemical space. Using our framework, we recover the **thermodynamic constraints in kinetic proofreading**. Finally, we show that **the contrast of reaction-diffusion patterns can be bounded only by the non-equilibrium driving force.** Our results provide a general framework for understanding the role of non-equilibrium conditions in shaping the steady-state properties of biochemical systems.

Equilibrium Symmetry → **Non-Equilibrium Driving Forces** → Non-Equilibrium Symmetry Breaking

2. How to describe out-of-equilibrium system: Local Detailed Balance

A chemical network of N species whose probabilities follow a rate equation:

$$\frac{d}{dt}p_i = \sum_{j(\neq i)} \overbrace{(k_{ij}p_j - k_{ji}p_i)}^{=0,\text{stationary}}$$
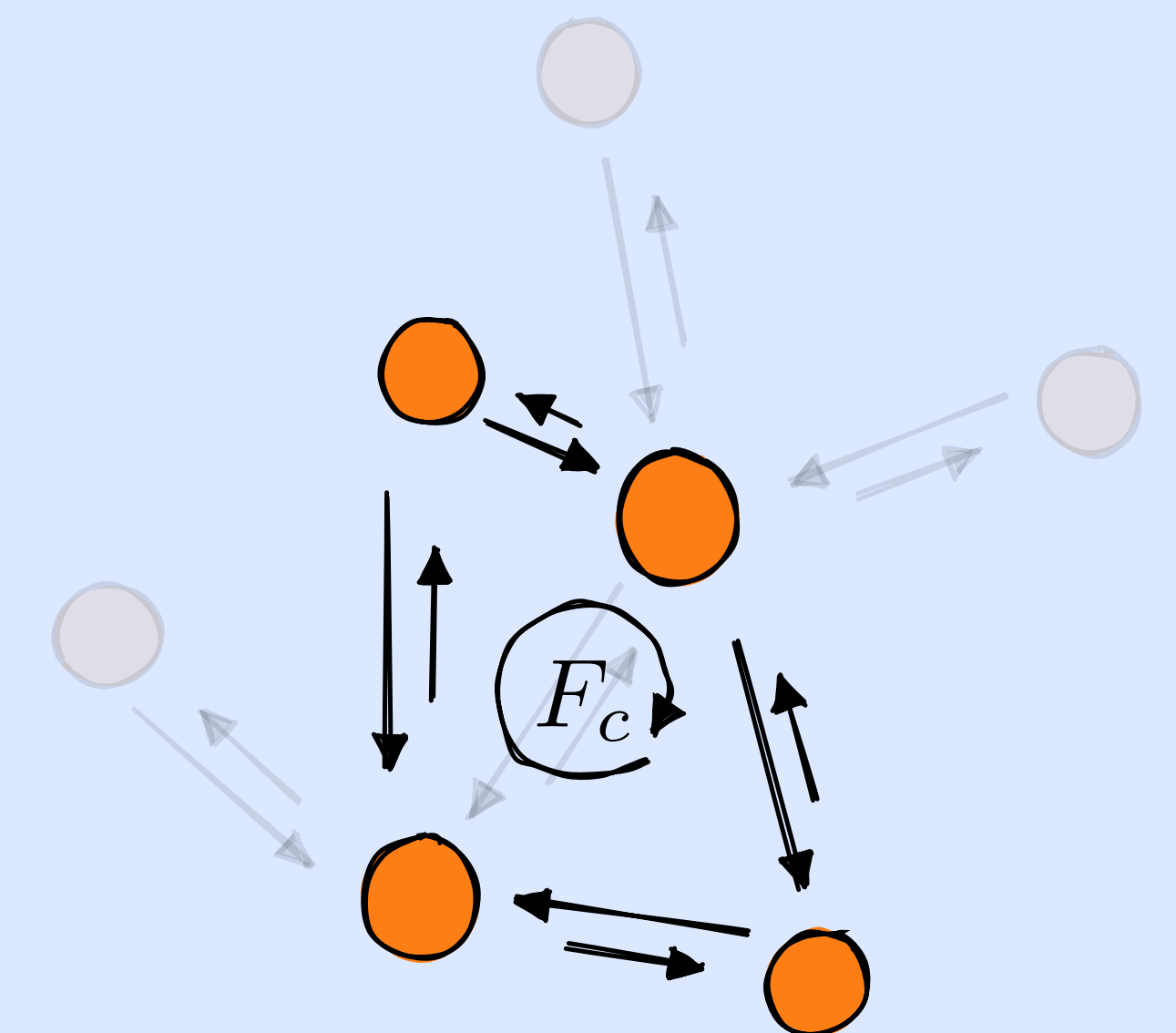
(=0, stationary) (=0, equilibrium)

The transition rates follow the local detailed balance relation

$$\frac{k_{ij}}{k_{ji}} = e^{-\beta(E_i - E_j - F_{ij})}$$
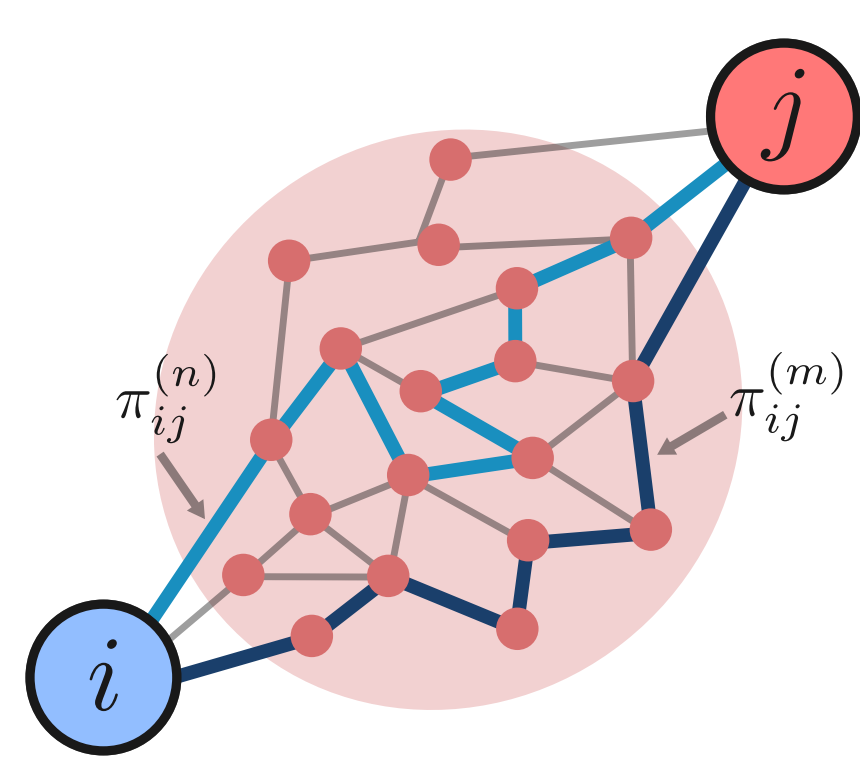
energy difference — Driving force

Out-of-equilibrium condition: non-zero cycle affinity

$$F_c \equiv \ln\left[\frac{\prod_{\circlearrowleft} k_{i\to i+1}}{\prod_{\circlearrowleft} k_{i+1\to i}}\right] \neq 0$$

3. Non-equilibrium condition from paths

In a chemical reaction system, we can identify multiple paths between two given states in the network.

$$K_{ij}^{\pi_{ij}^{(m)}} \equiv \prod_{\pi_{ij}^{(m)}} \frac{k_f}{k_b}$$
$$= e^{-\beta(\Delta E_{ij} - F_{ij}^{(m)})}$$
$$= \left.\frac{p_i}{p_j}\right|_{eq}^{\pi_{ij}^{(m)}}$$

Along each reaction path, an **equilibrium constant** can be defined according to the local detailed balance condition, which represents the corresponding equilibrium ratio of the populations on two end states in the absence of all other paths.

Path criteria for non-equilibrium:
If there exist two paths between the same start and end states with different equilibrium constants, then the system is out of equilibrium. This is equivalent to the cycle-affinity criteria, since combining two paths forms a cycle.

4. Main result: bound on steady state ratio
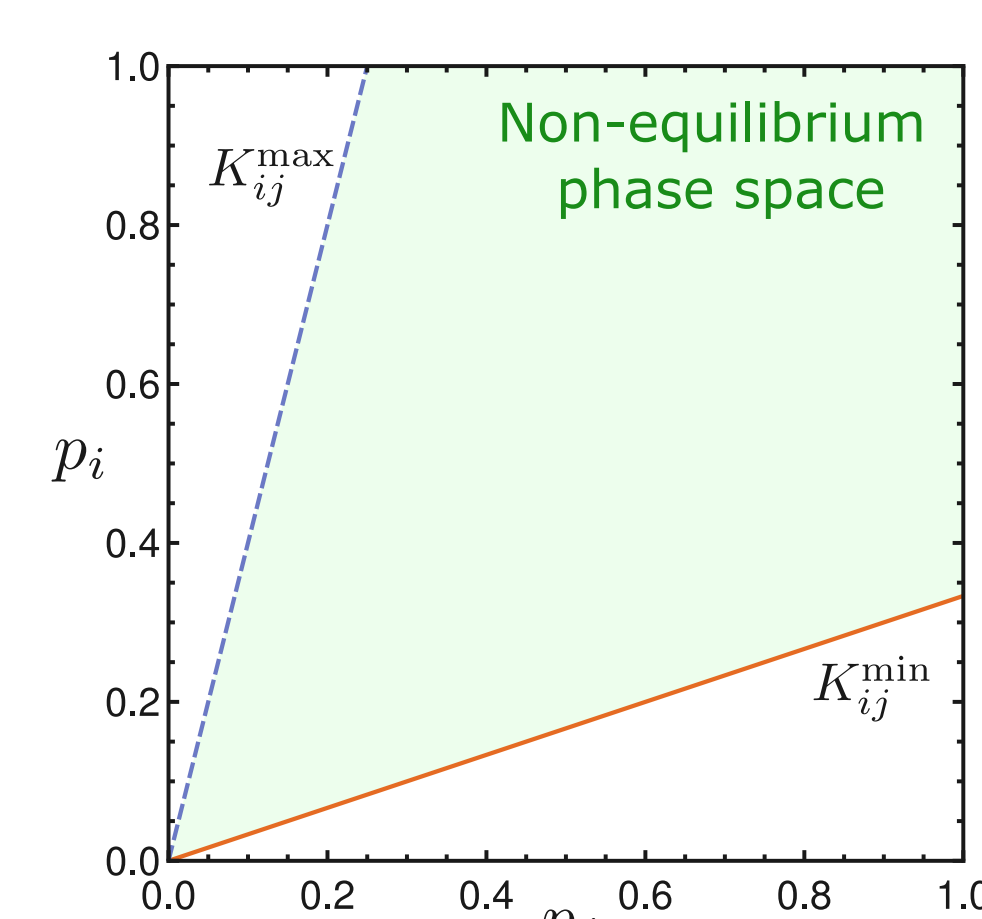
The steady-state ratio of two state occupations is bounded by the maximum and minimum equilibrium constants among all possible paths between these two states. These two bounds determine the nonequilibrium phase space. At thermodynamic equilibrium, two bounds collapse to a single line.

$$K_{ij}^{min} \leq \left.\frac{p_i}{p_j}\right|_{ss} \leq K_{ij}^{max}$$
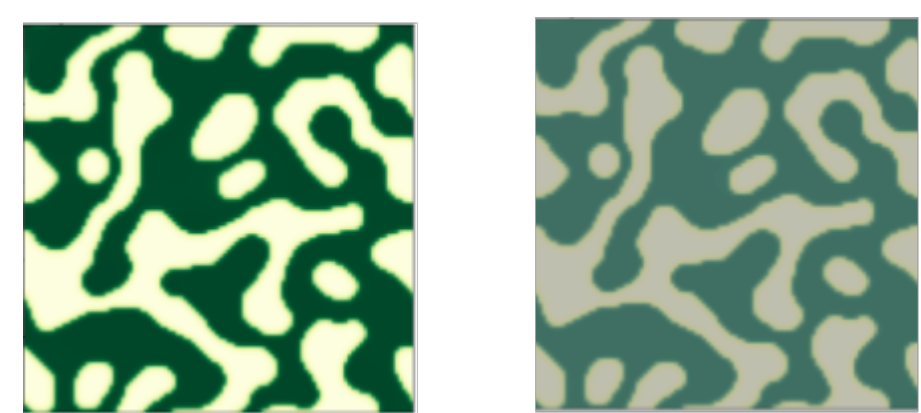
Formal proof: matrix-tree theorem
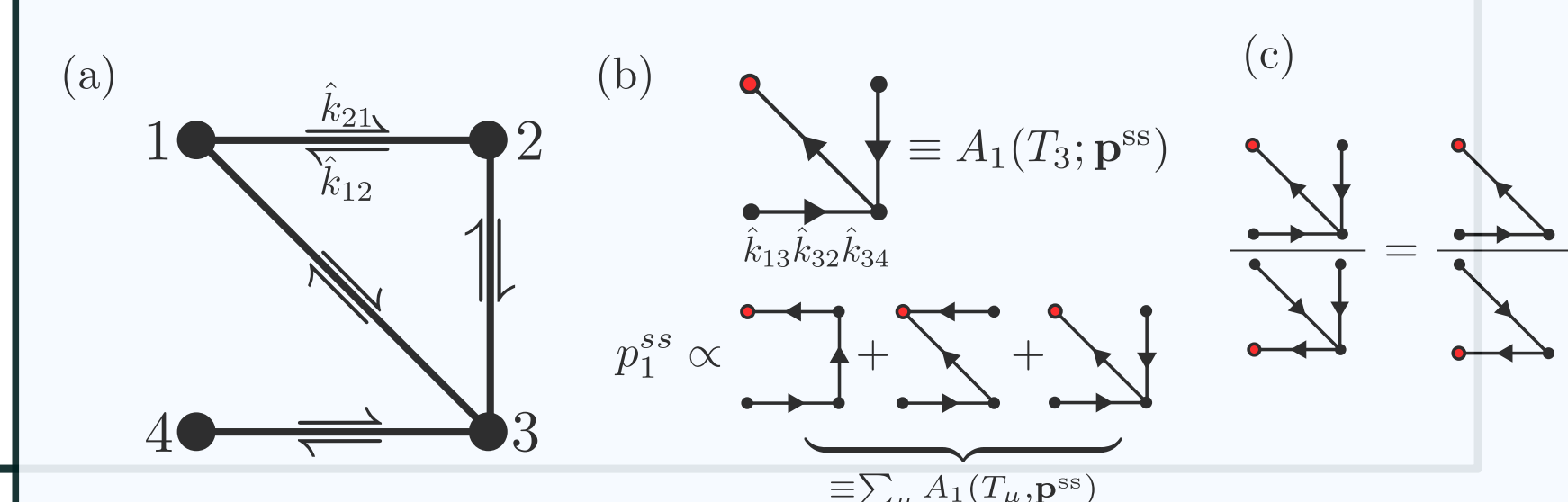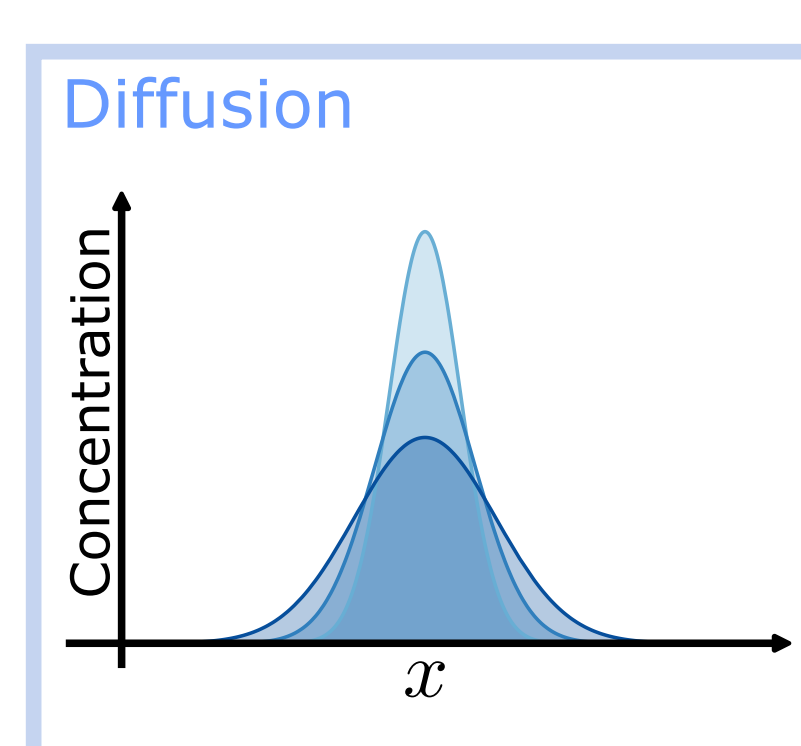
5. Bound on the contrast of reaction-diffusion patterns

(mass conserving) reaction-diffusion system

$$\partial_t u = D_u \nabla^2 u + f(u,v)$$
$$\partial_t v = D_v \nabla^2 v - f(u,v)$$

Diffusion / Reaction

High Contrast   Low Contrast

Diffusion

Reaction: ADP + Pi + 3U, ATP + 3U, w_f, w_b, k_f, k_b, $\Delta\mu$, U, V

Flux-balance subspace
$$D_u u + D_v v = const$$
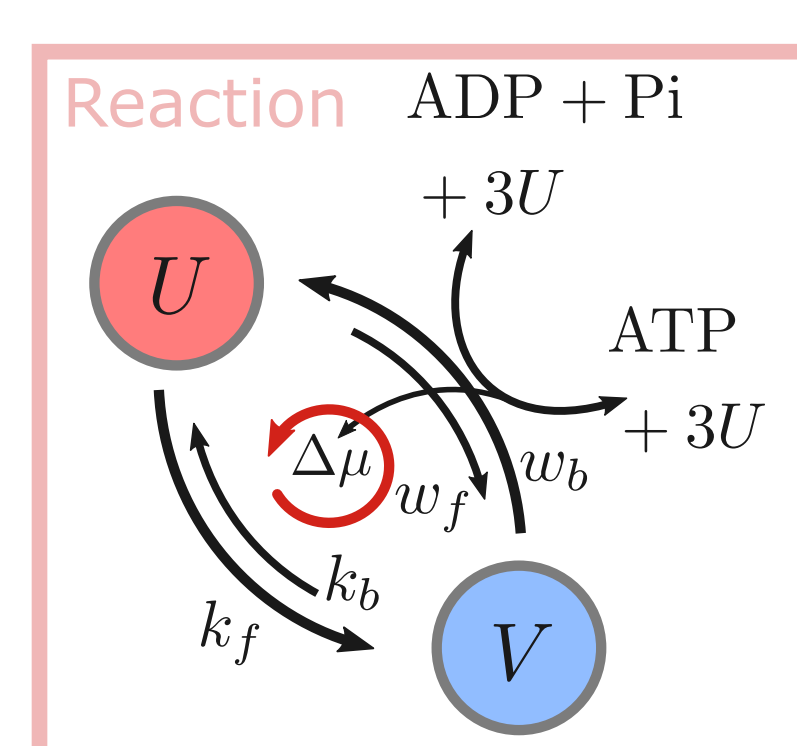
Reactive nullcline
$$f(u,v) = 0$$

The **non-equilibrium phase space of mass-conserving reaction-diffusion systems constrains the phase-space geometry.** The bound on the maximum and minimum concentration in a stationary pattern is determined by the intersections of the flux-balance subspace and the boundary of non-equilibrium phase space.
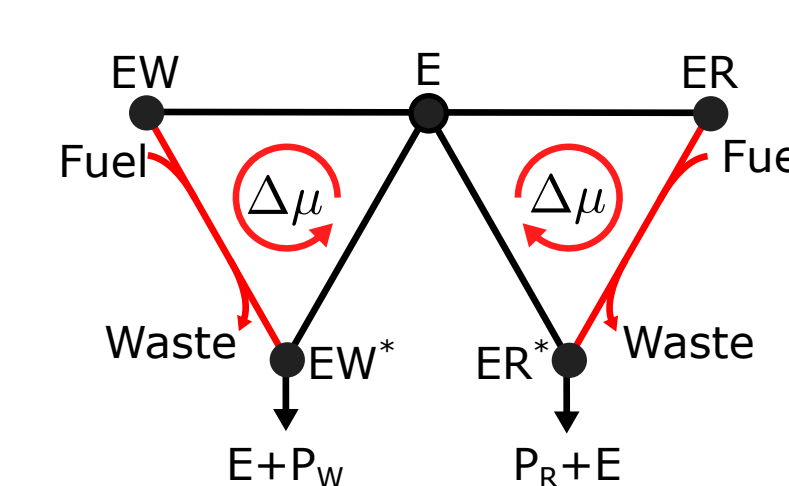
$$\frac{u_{\max}^*}{u_{\min}^*} \leq e^{\beta\Delta\mu}$$
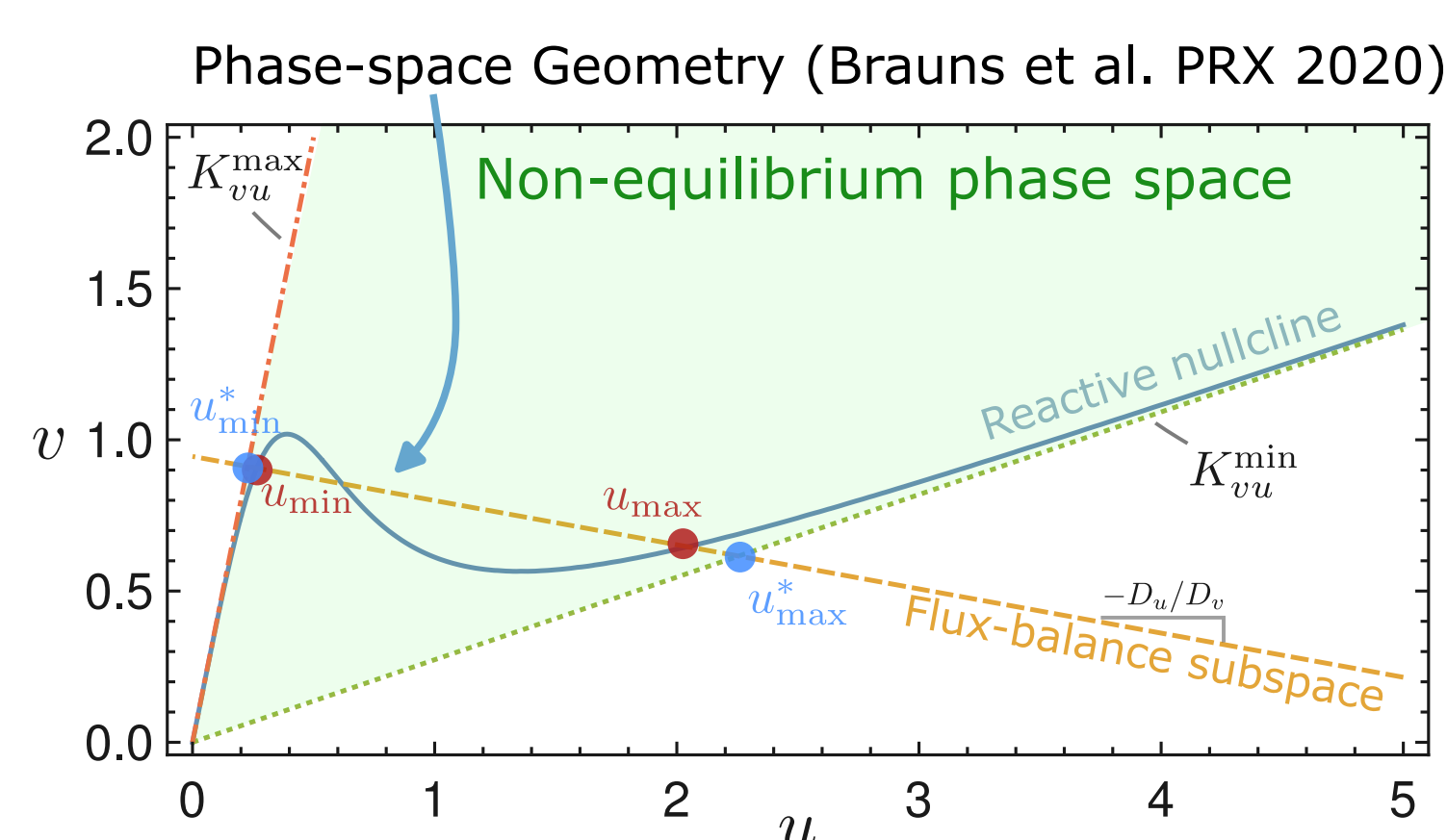
Phase-space Geometry (Brauns et al. PRX 2020)

Thermodynamic bound on contrast (visibility)

$$\mathcal{C}_u \equiv \frac{u_{\max} - u_{\min}}{u_{\max} + u_{\min}} \leq \frac{u_{\max}^* - u_{\min}^*}{u_{\max}^* + u_{\min}^*} \leq \tanh(\beta\Delta\mu/2)$$

This inequality immediately tells that pattern formation is a sheer consequence of non-equilibrium conditions, as at equilibrium the non-equilibrium phase-space shrinks into a line and the contrast goes to zero. Moreover, we only need to know the thermodynamic force driving the system out of equilibrium to bound the contrast of a pattern, independently of the details of the kinetics. Although we inspected a simple two-state system, the presented approach is valid for any mass-conserving RD systems.

Pattern visibility is upper bounded by the non-equilibrium driving force. Two corresponding 1D patterns are plotted in the subpanel.

6. Bound on error rate

Living systems encode information in the form of RNA and DNA. Genome duplication, translation and transcription are processes that use this information to select the correct substrate with high fidelity, ensuring the survival of the organism. Since the accuracy of this selection is severely limited by equilibrium constraints, back in 1974 Hopfield proposed the existence of energy-consuming intermediate steps that favor kinetic discrimination.

Equilibrium discrimination
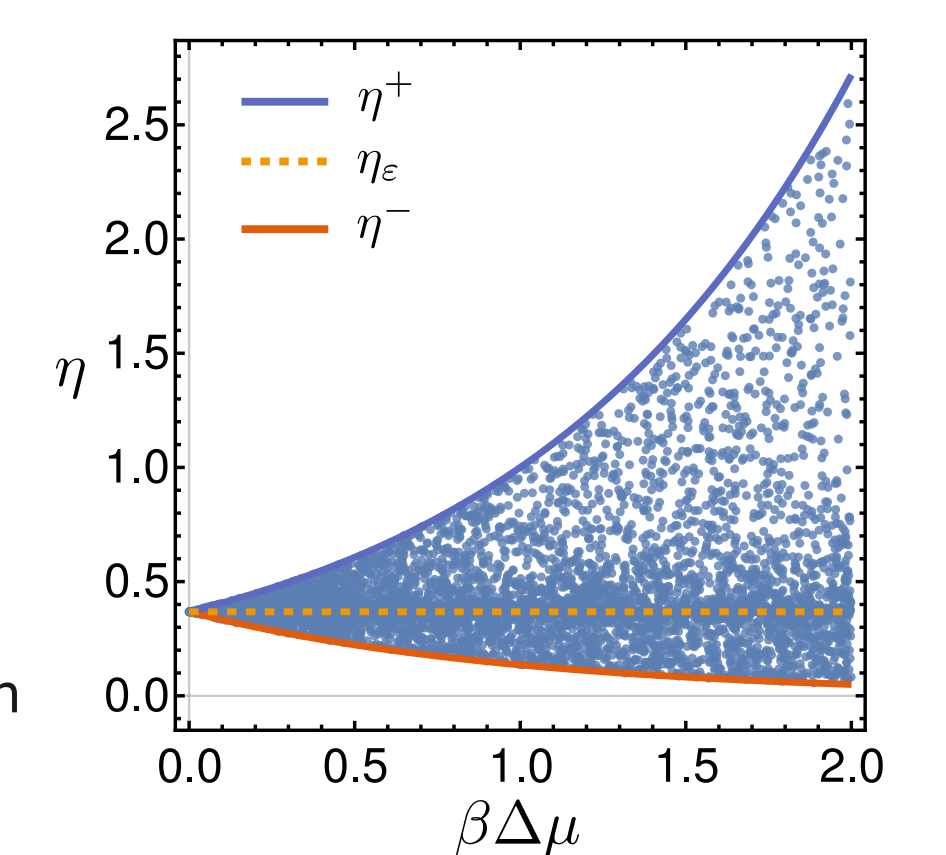
$$\eta_\varepsilon = e^{-\beta\varepsilon}$$

The equilibrium error rate depends on the energy difference between the wrong and right substrate.

Thermodynamics bound on kinetic proofreading

$$\eta^- \leq \eta \leq \eta^+$$

$$\eta^- = \eta_\varepsilon e^{-\beta\Delta\mu} \qquad \eta^+ = \eta_\varepsilon e^{\beta\Delta\mu}$$

The lower bound is saturated when all driving force is utilized to push the wrong state to the right state.

7. Conclusion

Thermodynamic bound:
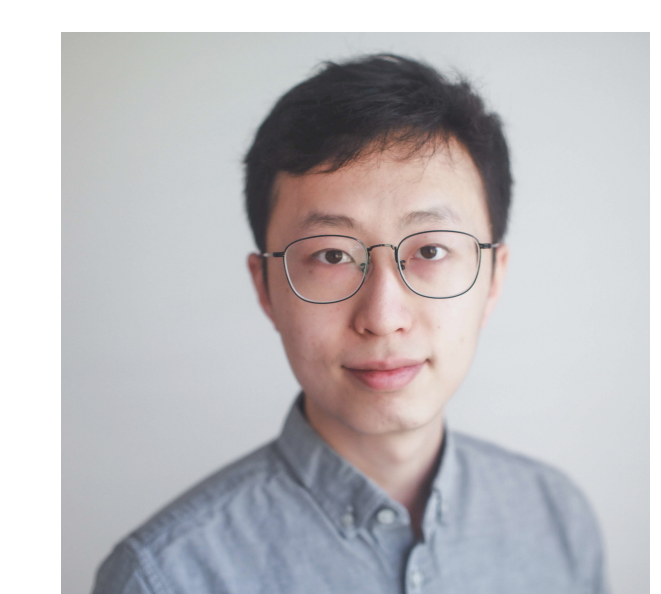Know thermodynamic driving force, know the **thermodynamically accessible phase space.**

Design principle:
To design a desired symmetry breaking system with several fixed points, **minimal energetic cost** is desired to expand a phase space to enclose all fixed points.

Ref: Liang, S., De Los Rios, P., & Busiello, D. M. (2022). **Universal thermodynamic bounds on symmetry breaking in biochemical systems**. *arXiv preprint arXiv:2212.12074.*

About me

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