Thermodynamic bound on cross-correlations for biological information processing

Building a bridge between non-equilibrium statistical physics and biology

4th July 2023

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Naruo Ohga, Sosuke Ito and Artemy Kolchinsky, *to appear in* Physical Review Letters (2023). [arXiv:2303.13116]

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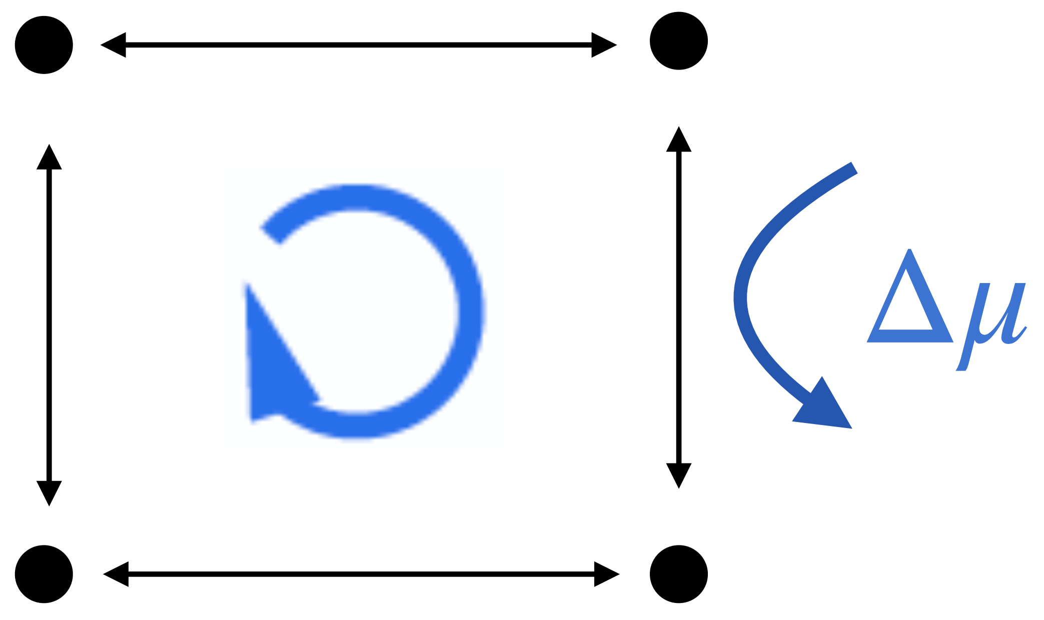
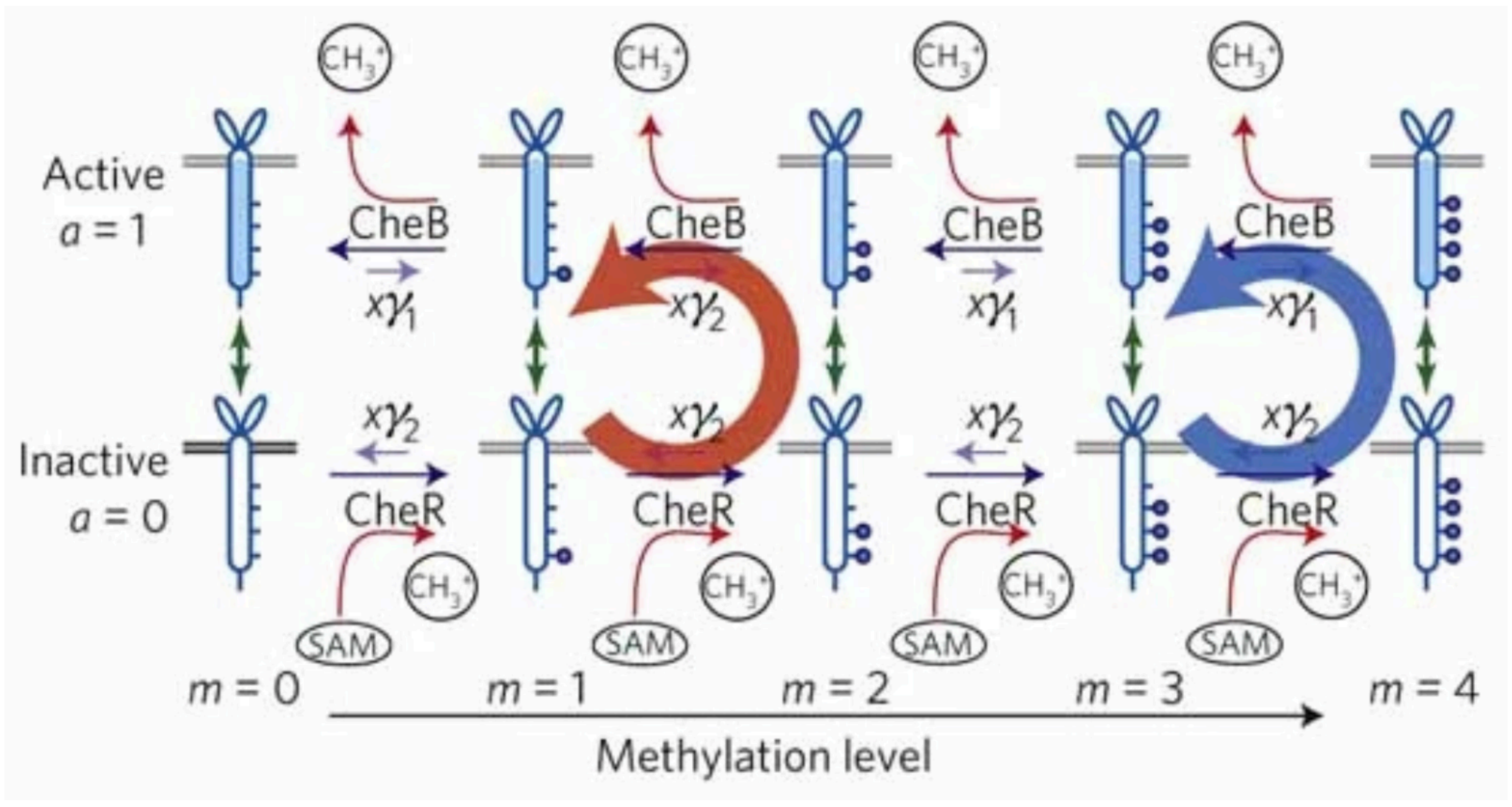
Introduction: Biological information processing

- Biological information processing is a non-equilibrium phenomenon where a thermodynamic driving force (e.g., chemical potential difference in a cycle) exists.

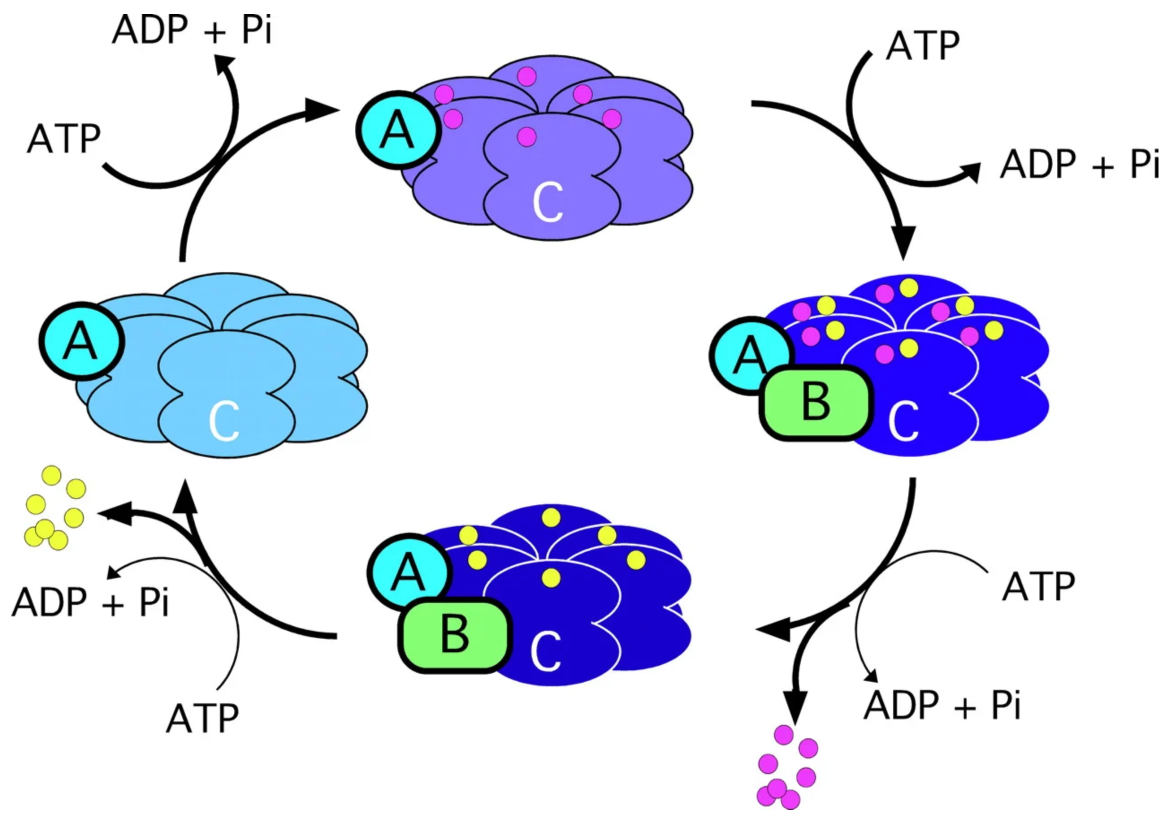


Sensory adaptation



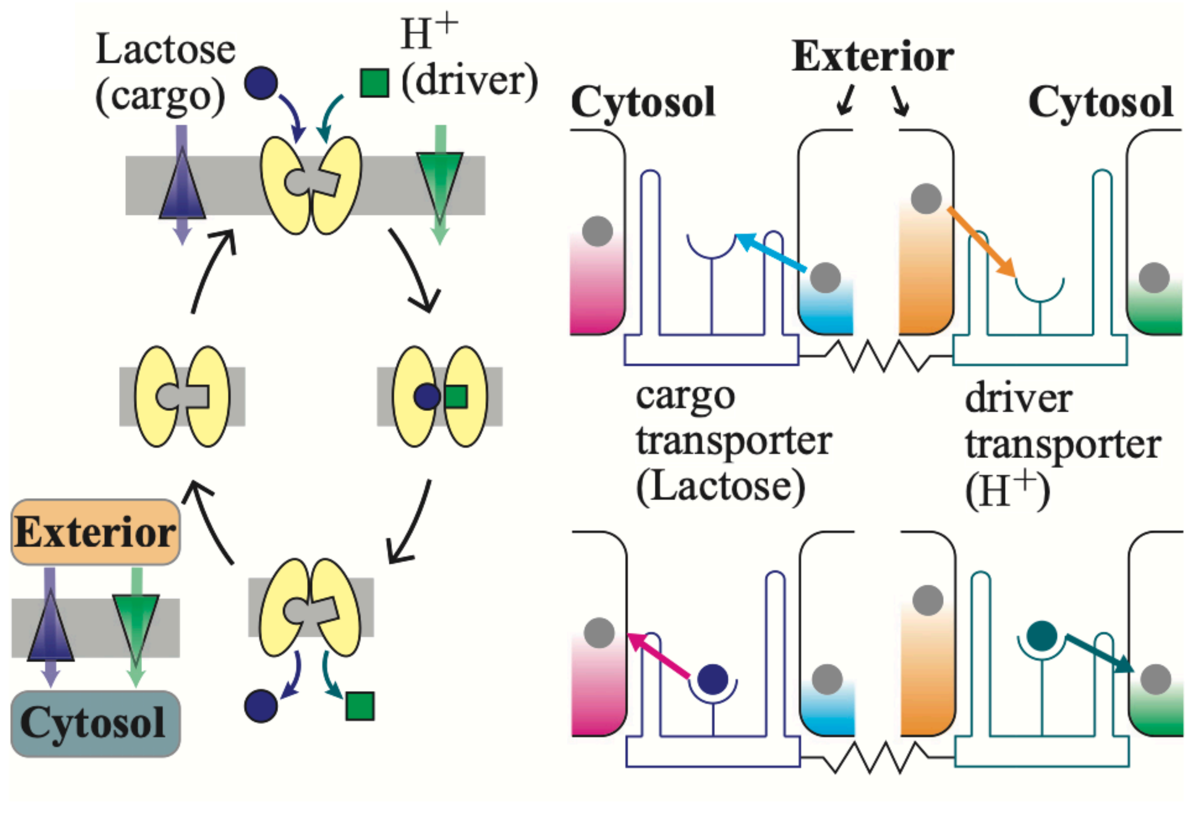
G. Lan, P. Sartori, S. Neumann, V. Sourjik & Y. Tu, *Nature physics*, *8*, 422 (2012).

Circadian clock



C. R. McClung, *Proceedings of the National Academy of Sciences*, *104*, 16727 (2007).

Membrane transport



S. Yoshida, Y. Okada, E. Muneyuki, & S. Ito, *Physical Review Research*, *4*, 023229 (2022).

Why must biological systems be non-equilibrium?

- In an equilibrium state

“Microscopic reversibility” [Microscopic basis of Onsager reciprocal relations]

$$\langle a(t)b(t+\tau)\rangle_{\mathrm{eq}} = \langle a(t+\tau)b(t)\rangle_{\mathrm{eq}} \qquad \text{for any observables } a(t), b(t)$$

[without odd degrees of freedom: $a(t)$, $b(t)$ are even functions of the velocities.]

L. Onsager, *Physical review*, *37*, 405 (1931).
H. B. G. Casimir, *Reviews of Modern Physics*, *17*, 343 (1945).

There exists no directed information flow between a and b.

Why must biological systems be non-equilibrium?

- In a non-equilibrium steady state (NESS)

$$\langle a(t)b(t+\tau)\rangle_{\text{ness}} \neq \langle a(t+\tau)b(t)\rangle_{\text{ness}} \quad \text{for some observables } a(t), b(t)$$

[without odd degrees of freedom: $a(t)$, $b(t)$ are even functions of the velocities.]

There exists a directed information flow between a and b.

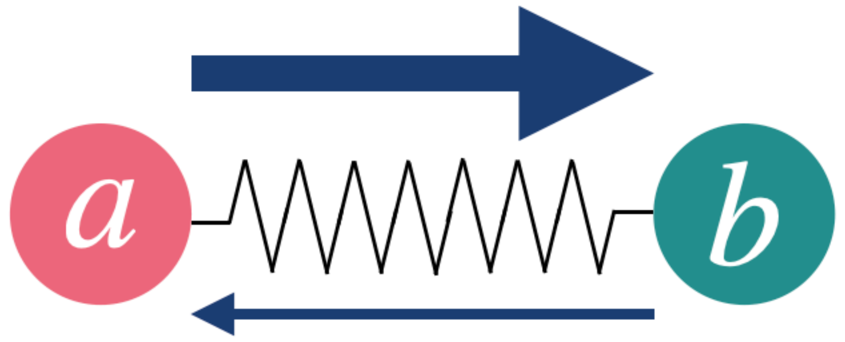
<u>The directed information flow is essential in biological information processing.</u>

<u>e.g.), Signal transduction, cell cycle, active motion ...etc.</u>

This talk

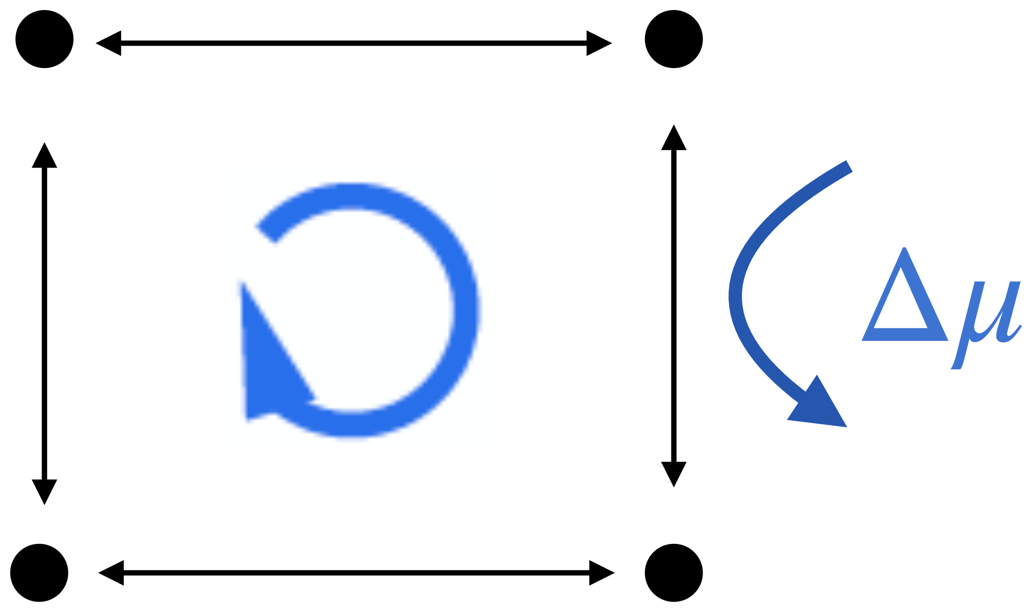
Asymmetry of cross-correlations

$$\langle a(t)b(t+\tau)\rangle_{\rm ness} \neq \langle a(t+\tau)b(t)\rangle_{\rm ness}$$

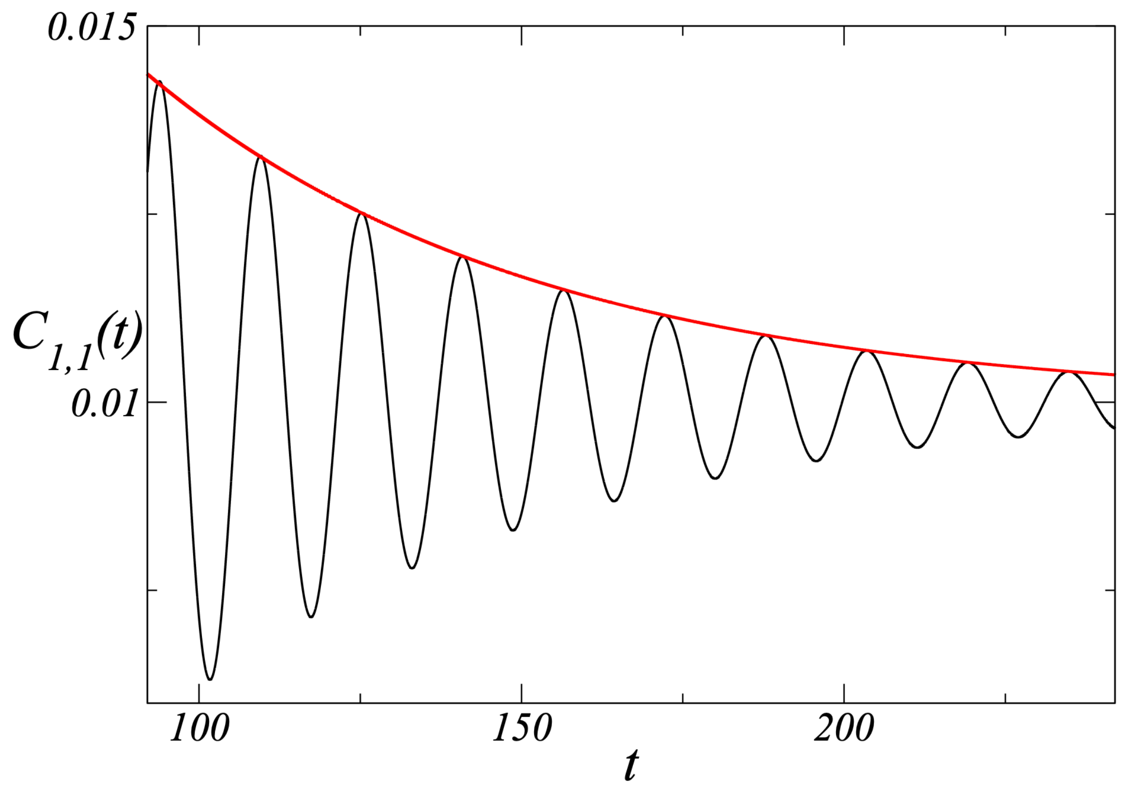


Building a universal link

Thermodynamic driving force

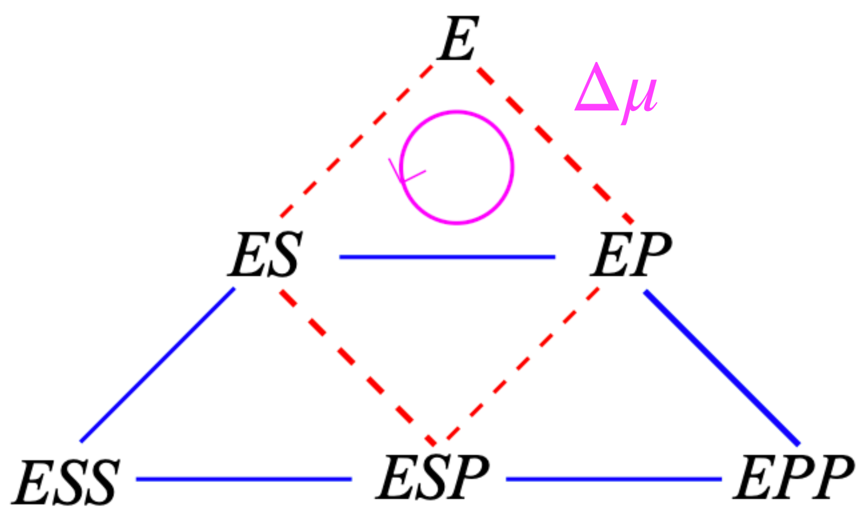


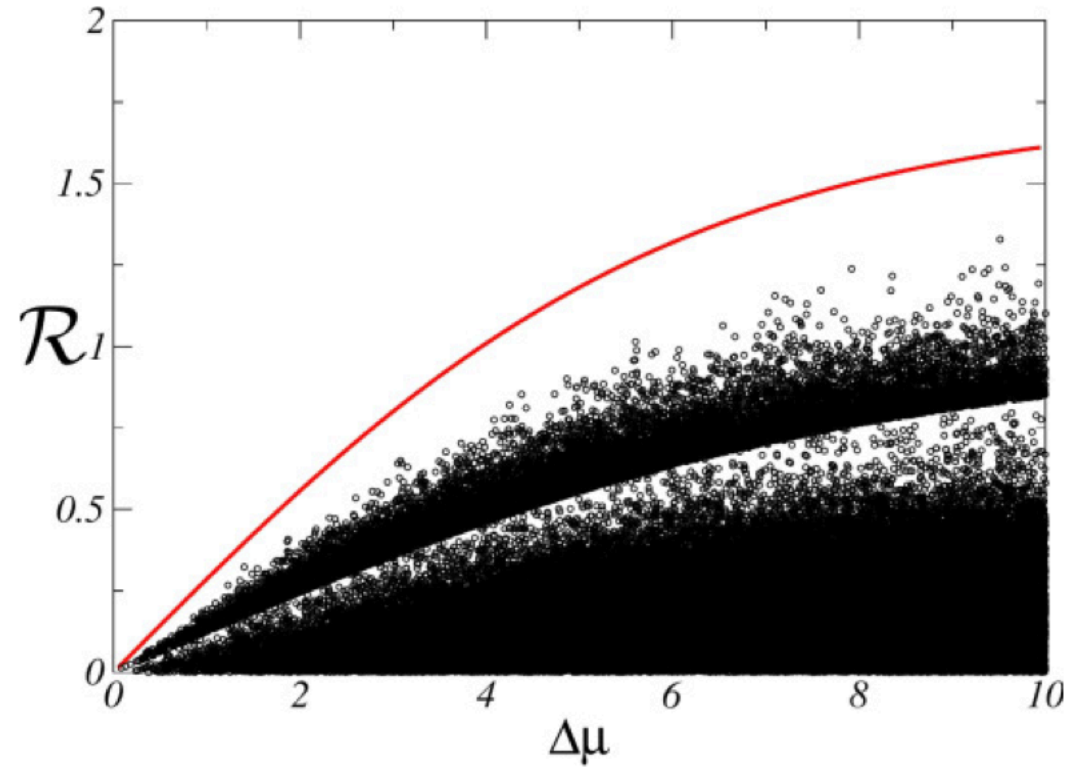
As a corollary, we rigorously proved
the numerical conjecture by Barato and Seifert (2017) for the number of coherent oscillations.



The number of coherent oscillations:

$$\frac{\mathscr{R}}{2\pi} = \frac{\text{(Decay time)}}{\text{(Period of oscillations)}}$$





A. C. Barato, & U. Seifert, *Physical Review E*, *95*, 062409 (2017).

Setup

- Master equation $\dfrac{d}{dt}\boldsymbol{p} = \mathsf{R}\boldsymbol{p}$

$\boldsymbol{p} = (p_1, \ldots, p_n)^\top$: Probability distribution $[p_i \geq 0, \sum_i p_i = 1]$

R: $(n \times n$ time-independent) rate matrix $[\mathsf{R}_{jj} = -\sum_{i \neq j} \mathsf{R}_{ij},\ \mathsf{R}_{ij} \geq 0\ (i \neq j)]$

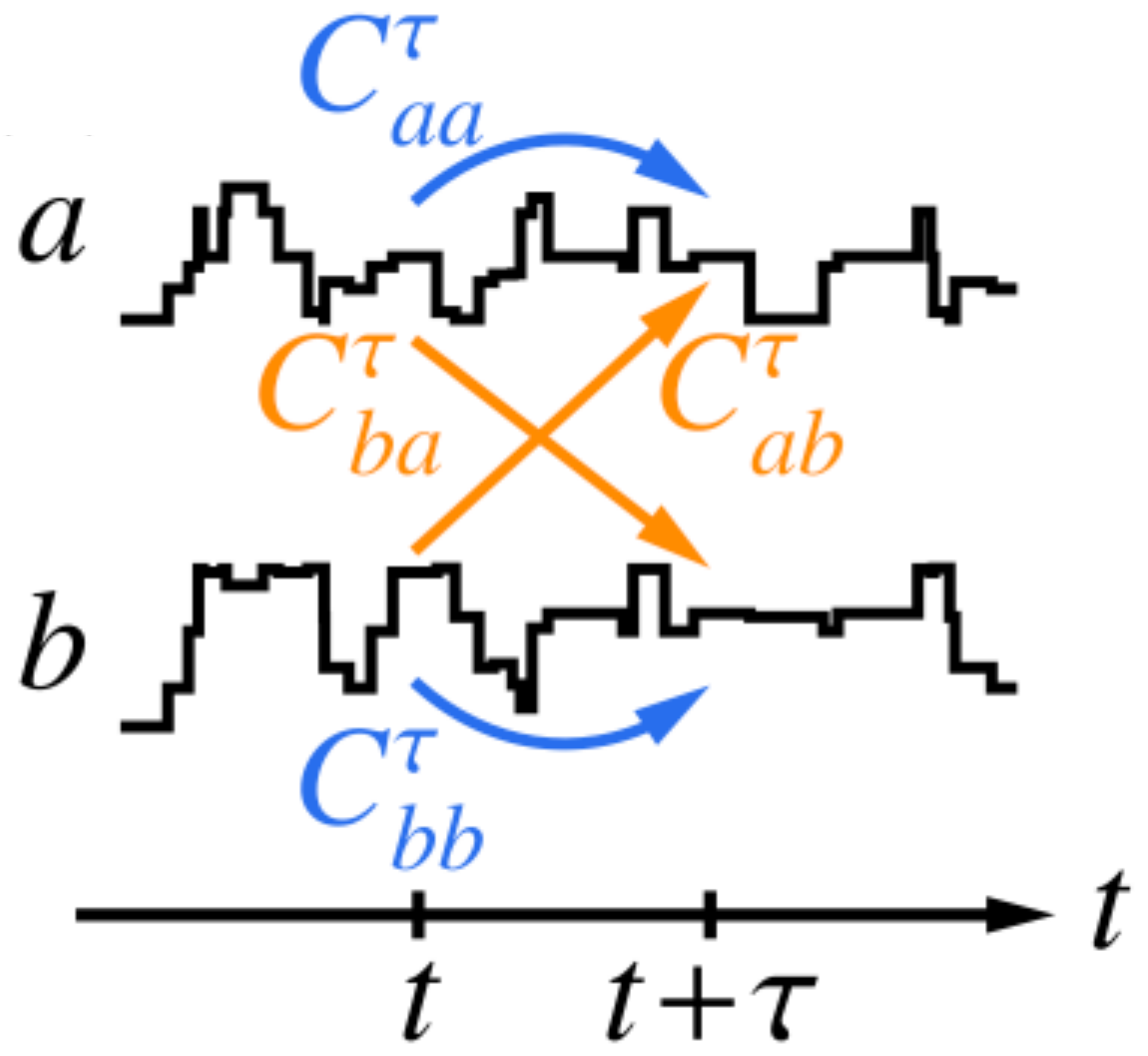
$\boldsymbol{p}^{\mathrm{st}}$: Steady-state distribution$[\mathsf{R}\boldsymbol{p}^{\mathrm{st}} = \mathbf{0}]$

- Cross-correlation C_{ba}^{τ}

$$C_{ba}^{\tau} = \langle b(t+\tau)a(t)\rangle_{\mathrm{ness}} = \sum_{i,j} b_i (e^{\tau\mathsf{R}})_{ij} p_j^{\mathrm{st}} a_j$$

$$= \sum_i b_i a_i p_i^{\mathrm{st}} + \tau \sum_{i,j} b_i a_j \mathscr{T}_{ij} + O(\tau^2)$$

$$(\mathscr{T}_{ij} = \mathsf{R}_{ij} p_j^{\mathrm{st}})$$



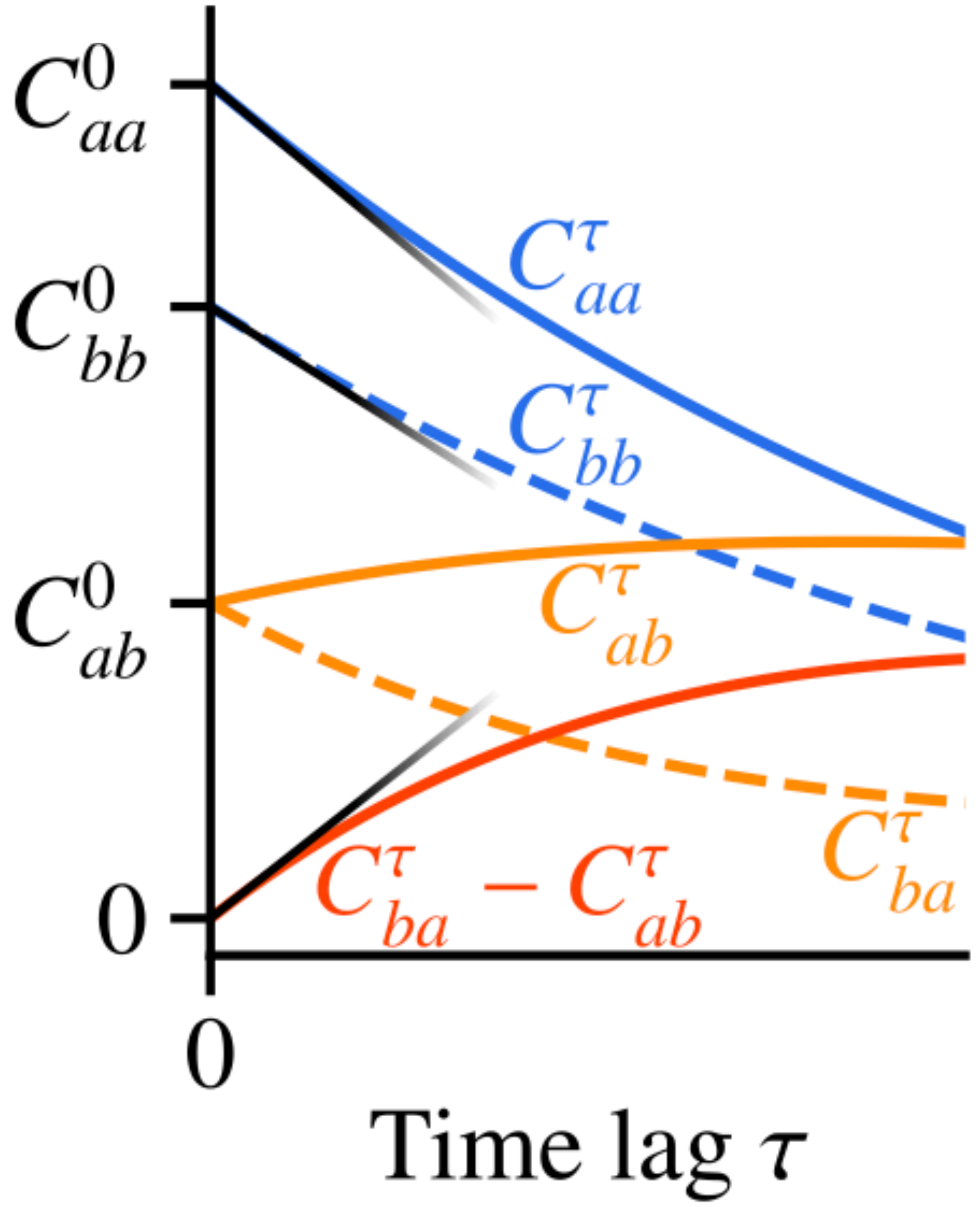
Measure of asymmetry

- Normalized measure of asymmetry χ_{ba}

Asymmetry of cross-correlations

$$\chi_{ba} = \lim_{\tau \to 0} \frac{C_{ba}^{\tau} - C_{ab}^{\tau}}{2\sqrt{(C_{aa}^{\tau} - C_{aa}^{0})(C_{bb}^{\tau} - C_{bb}^{0})}} = \left. \frac{\partial_\tau C_{ba} - \partial_\tau C_{ab}}{2\sqrt{(\partial_\tau C_{aa})(\partial_\tau C_{bb})}} \right|_{\tau=0}$$

Decay of auto-correlations



In a equilibrium state, $\chi_{ba} = 0$ for any observables a, b

In a NESS, $|\chi_{ba}| > 0$ for some observables a, b

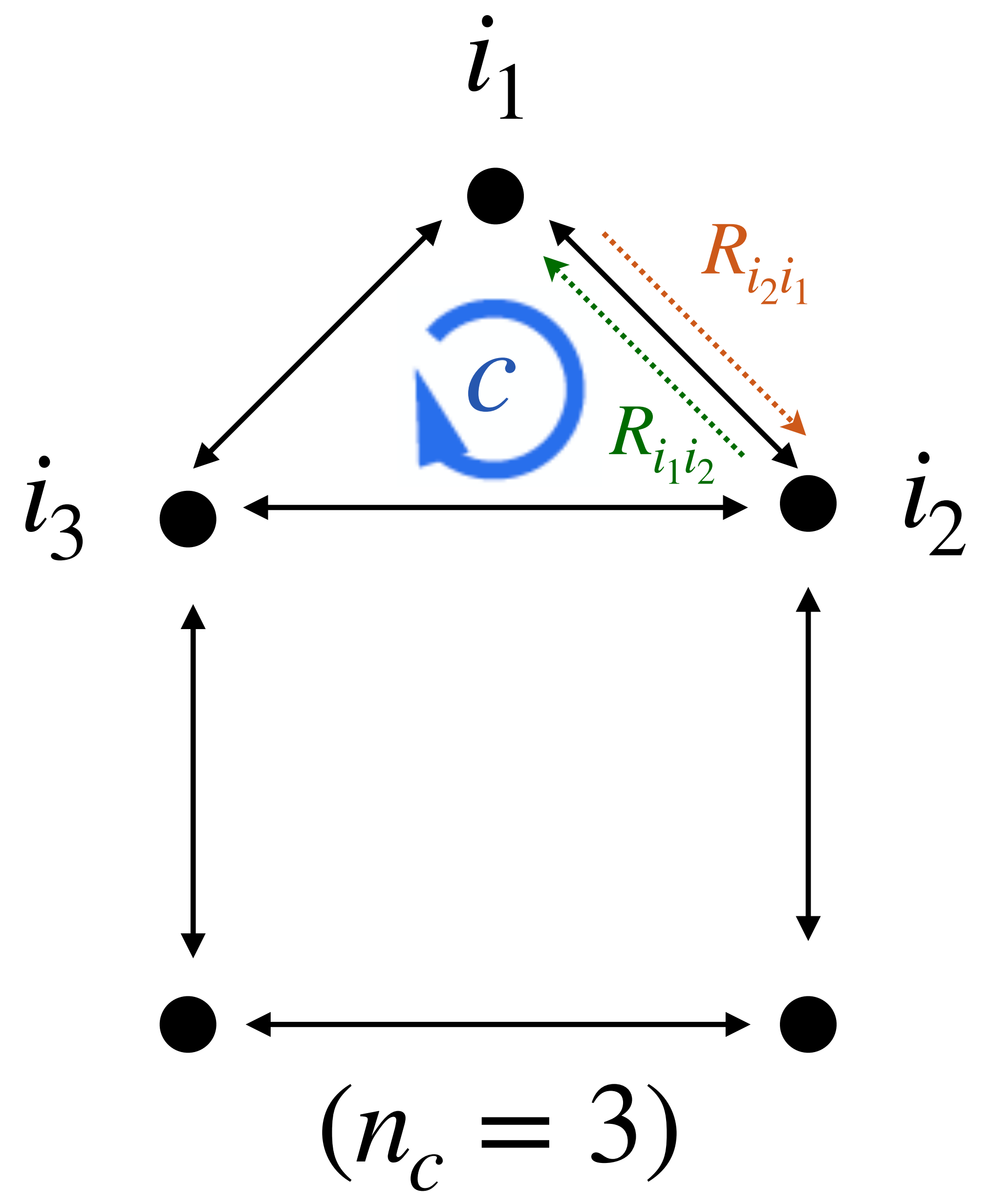
Measure of thermodynamic driving force

- Cycle affinity (thermodynamic driving force) $\mathcal{F}_c$

$$\mathcal{F}_c = \ln \frac{R_{i_2 i_1} R_{i_3 i_2} \cdots R_{i_{n_1} i_{n_c}}}{R_{i_1 i_2} R_{i_2 i_3} \cdots R_{i_{n_c} i_1}}$$

Cycle (closed path): $c = (i_1 \to i_2 \to \cdots \to i_{n_c} \to i_1)$

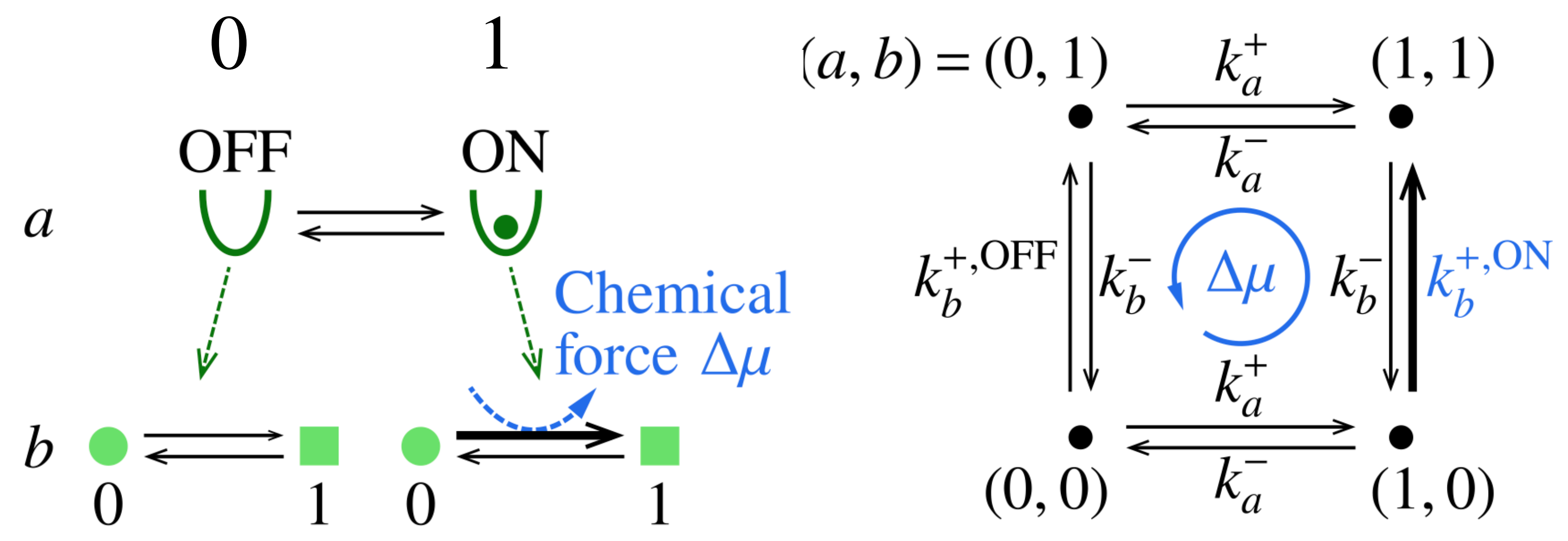
$(R_{i_k i_{k+1}} \neq 0, R_{i_{k+1} i_k} \neq 0)$



e.g.,) 4-state model

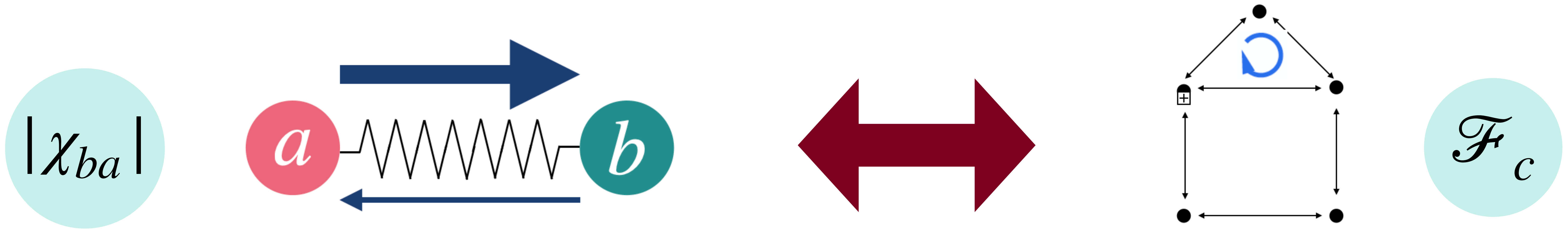
$$c = ((0,0) \to (1,0) \to (1,1) \to (0,1) \to (0,0))$$

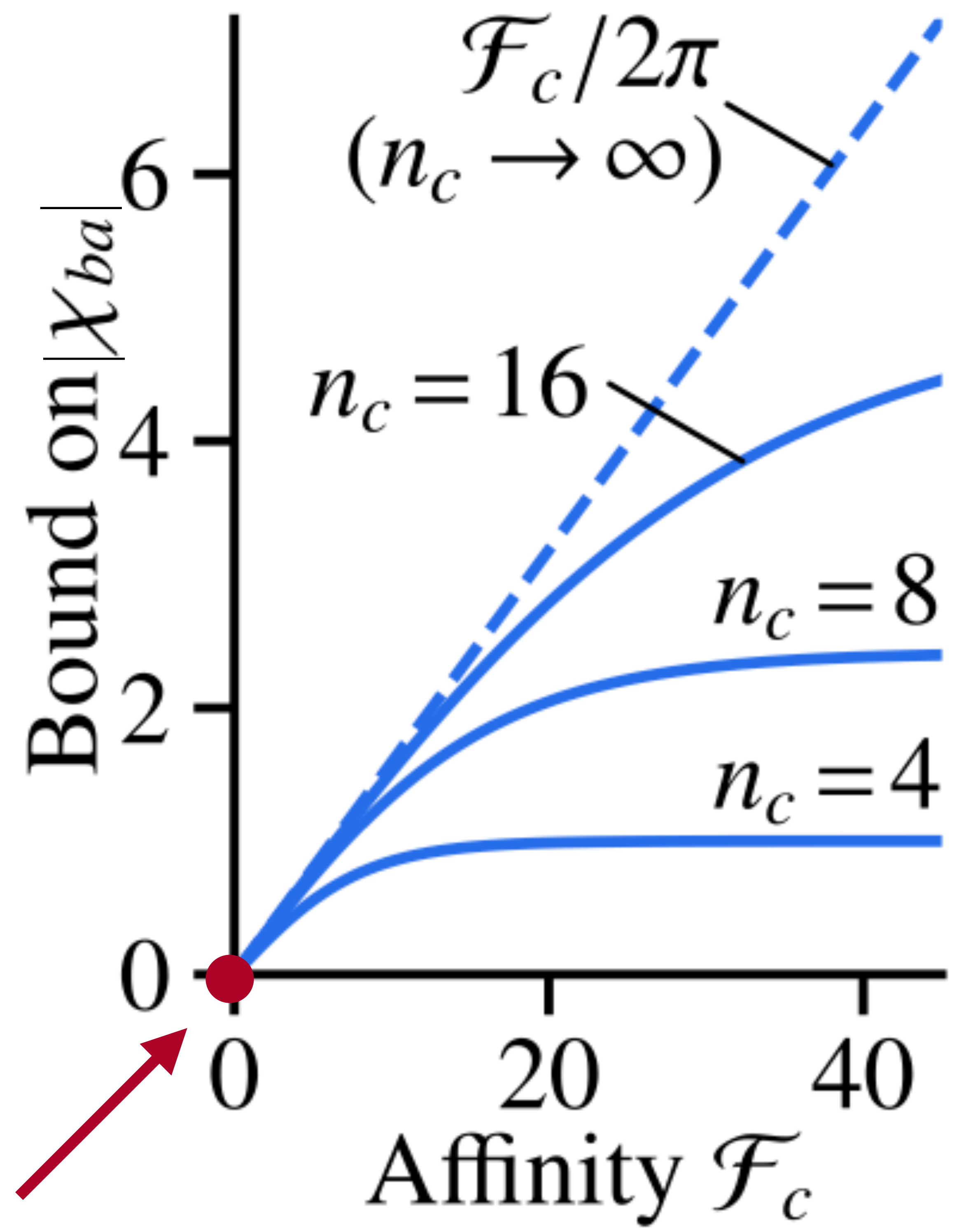
$$\mathcal{F}_c = \ln \frac{k_a^+ k_b^{+,\mathrm{ON}} k_a^- k_b^-}{k_a^- k_b^- k_a^+ k_b^{+,\mathrm{OFF}}} = \ln \frac{k_b^{+,\mathrm{ON}}}{k_b^{+,\mathrm{OFF}}} = \frac{\Delta\mu}{k_\mathrm{B} T}$$



Main result

$$|\chi_{ba}| \le \max_{c\in\mathscr{C}^*} \frac{\tanh[\mathscr{F}_c/(2n_c)]}{\tan(\pi/n_c)} \le \max_{c\in\mathscr{C}^*} \frac{\mathscr{F}_c}{2\pi}$$





"Microscopic reversibility"

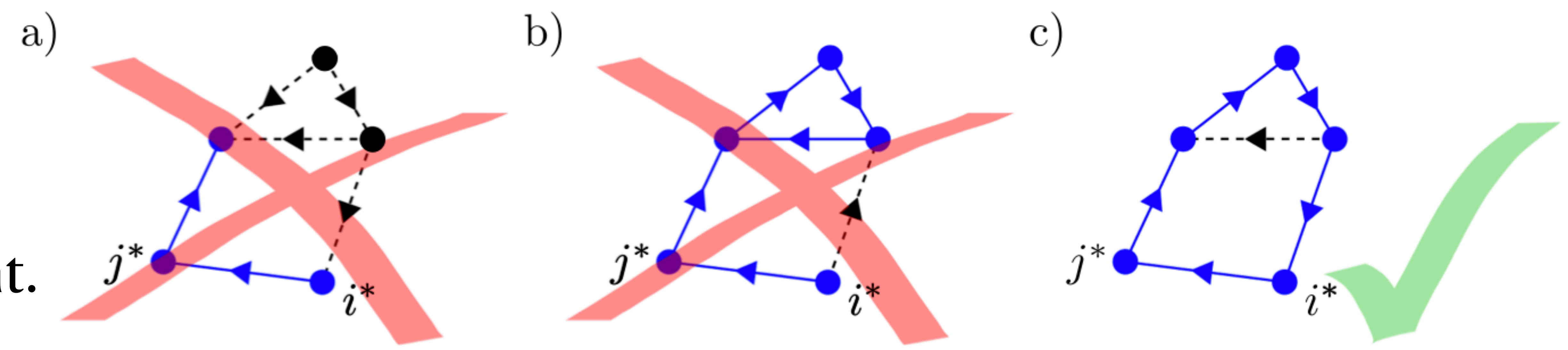
Set of cycle $\mathscr{C}^*$: $\mathscr{C}^* = \{c = (i_1 \to \cdots \to i_{n_c} \to i_i)\,|\, c \in \mathscr{C}_{\mathrm{uni}}, \sum_k (b_{i_{k+1}} a_{i_k} - b_{i_k} a_{i_{k+1}}) \neq 0\}$

Set of "uniform cycle" $\mathscr{C}_{\mathrm{uni}}$:

P. Pietzonka, A. C. Barato, & U. Seifert, *Journal of Physics A: Mathematical and Theoretical*, *49*, 34LT01 (2016).

(i) All stationary cycle currents are strictly positive.

(ii) Edges of every cycle are aligned with the stationary current.



Universal thermodynamic trade-offs

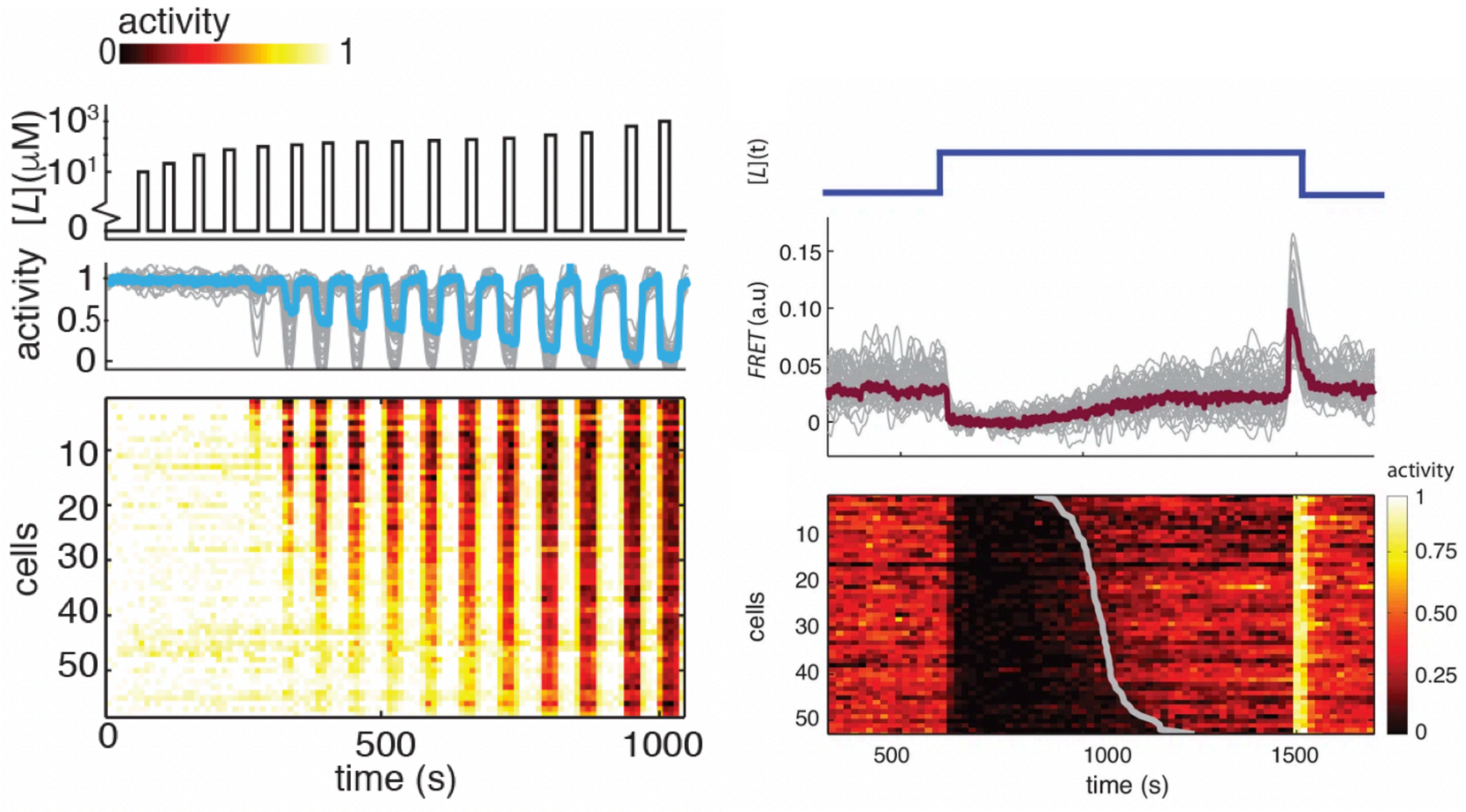
$$|\chi_{ba}| \leq \max_{c\in\mathscr{C}^*} \frac{\mathscr{F}_c}{2\pi}$$

In a equilibrium state, $\max_{c\in\mathscr{C}^*} \mathscr{F}_c = 0$. Thus, $\chi_{ba} = 0$ for any observables a, b.

In a NESS, $\max_{c\in\mathscr{C}^*} \mathscr{F}_c \neq 0$. Thus, $\chi_{ba} \neq 0$ for some observables a, b.

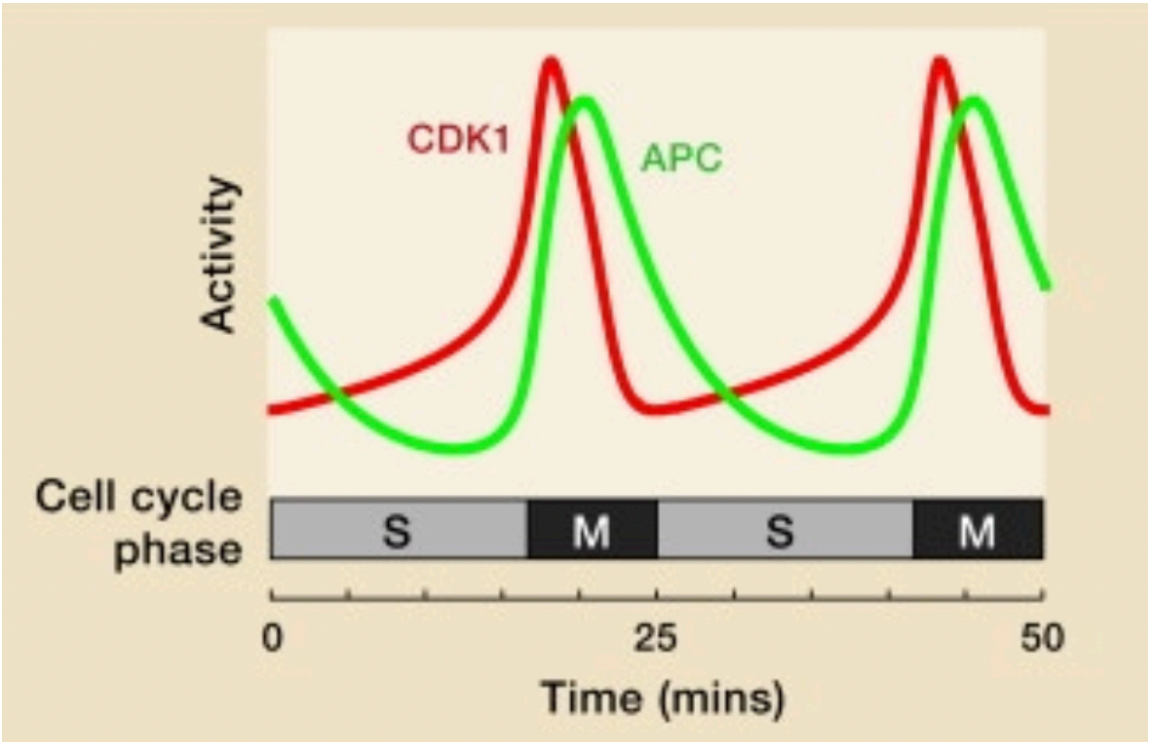
It explains how large the thermodynamic driving force must be needed to maintain the directed information flow in biological information processing.

Signal transduction



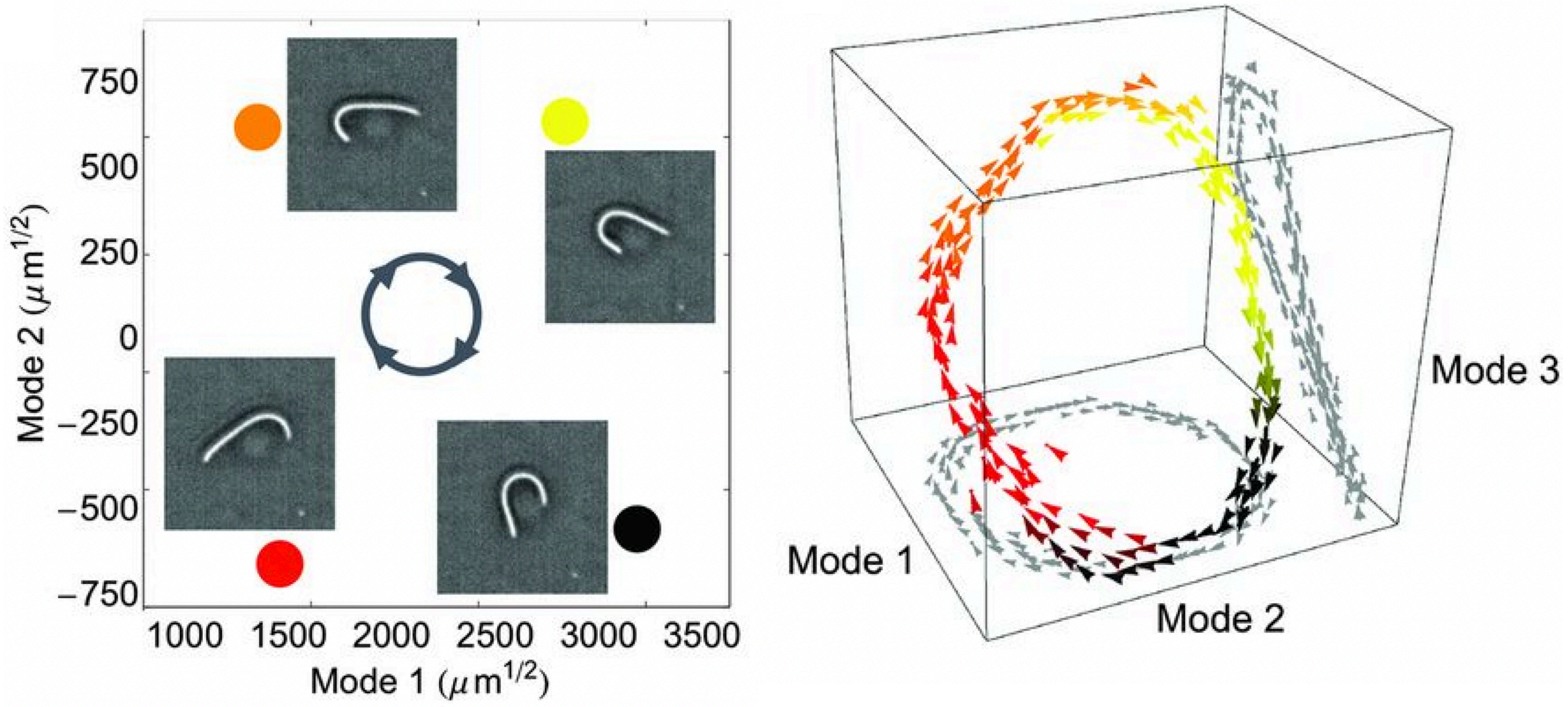
J. M. Keegstra, K. Kamino, F. Anquez, M. D. Lazova, T. Emonet, & T. Shimizu, *Elife*, *6*, e27455 (2017).

Cell cycle



J. E. Ferrell, T. Y. C. Tsai, & Q. Yang, *Cell*, *144*, 874 (2011).

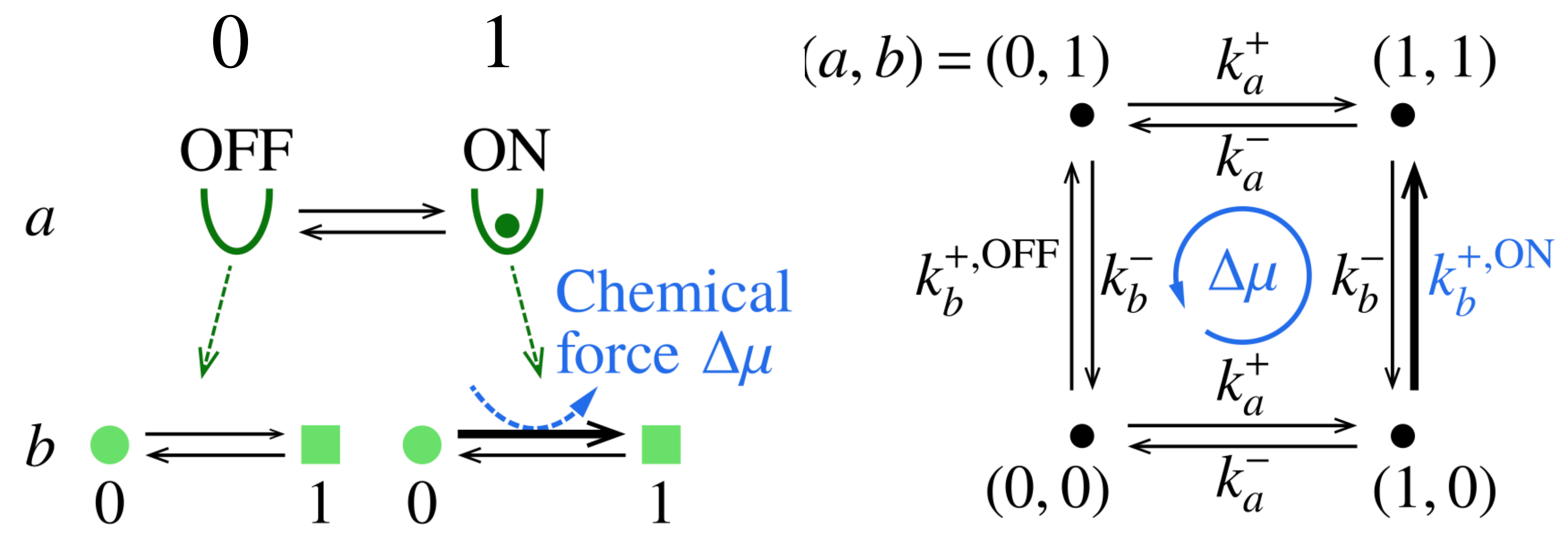
Active motion



C. Battle, C. P. Broedersz, N. Fakhri, V. F. Geyer, J. Howard, C. F. Schmidt & F. C. MacKintosh, *Science*, *352*, 604-607 (2016).

Numerics

4-state model

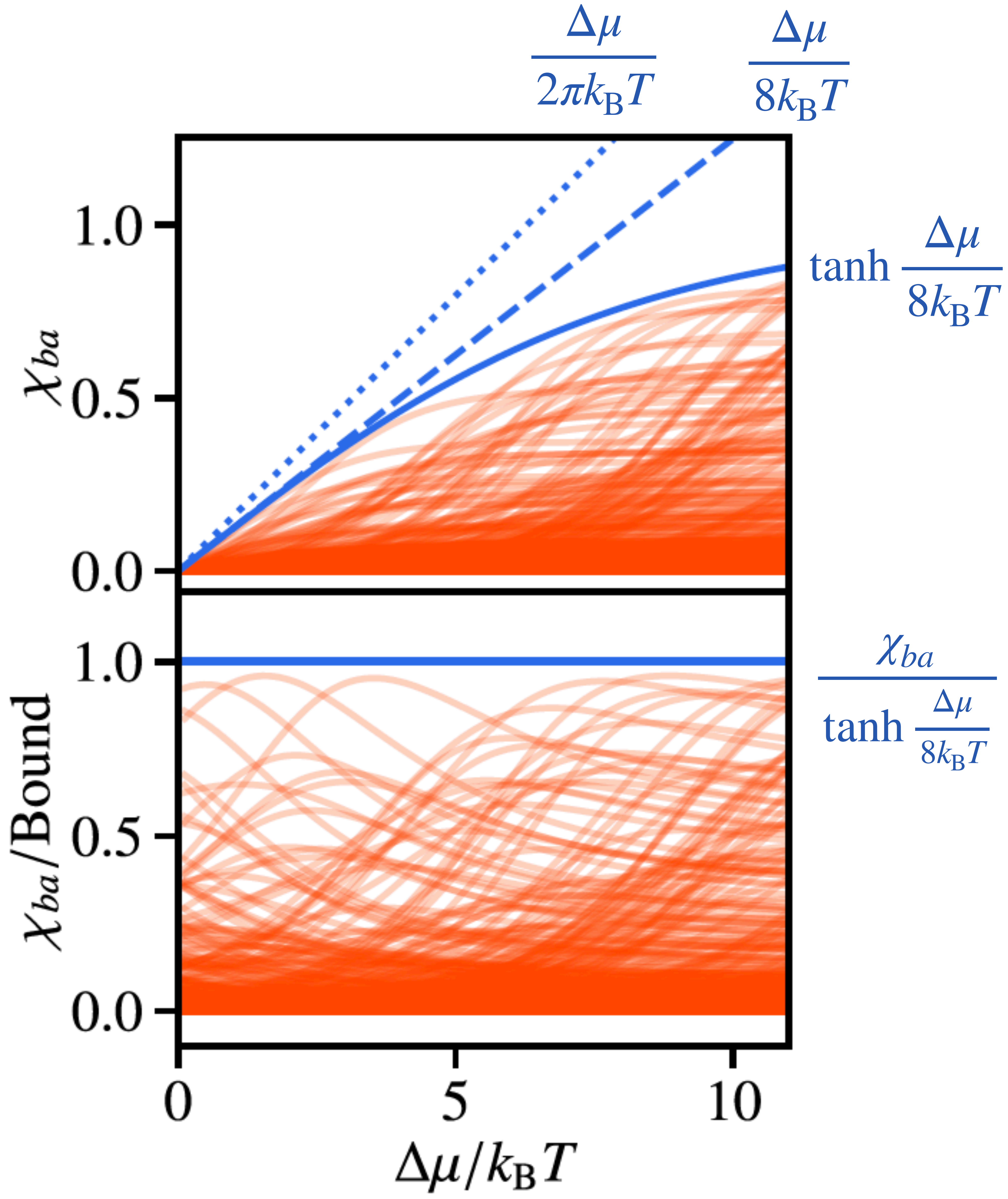


$$c = ((0,0) \to (1,0) \to (1,1) \to (0,1) \to (0,0)) \quad n_c = 4$$

$$\mathscr{F}_c = \ln \frac{k_b^{+,\mathrm{ON}}}{k_b^{+,\mathrm{OFF}}} = \frac{\Delta\mu}{k_\mathrm{B}T}(\geq 0) \quad (\chi_{ba} \geq 0) \qquad \mathscr{C}^* = \{c\}$$

$$|\chi_{ba}| \leq \max_{c\in\mathscr{C}^*} \frac{\tanh[\mathscr{F}_c/(2n_c)]}{\tan(\pi/n_c)} \leq \left(\max_{c\in\mathscr{C}^*} \frac{\mathscr{F}_c/(2n_c)}{\tan(\pi/n_c)} \leq \right) \max_{c\in\mathscr{C}^*} \frac{\mathscr{F}_c}{2\pi}$$

$$\Rightarrow \quad \chi_{ba} \leq \tanh \frac{\Delta\mu}{8k_\mathrm{B}T} \leq \left(\frac{\Delta\mu}{8k_\mathrm{B}T} \leq \right) \frac{\Delta\mu}{2\pi k_\mathrm{B}T}$$



Varying $k_b^{+,\mathrm{ON}}$ (Other kinetic rates are set to random.)

Corollary : Rigorous proof of the numerical conjecture (2017)

Numerical conjecture (Barato-Seifert, 2017):

[for the smallest non-zero real eigenvalue $\lambda^{\mathrm{R}}_{\alpha_{\max}}$]

A. C. Barato, & U. Seifert, *Physical Review E*, *95*, 062409 (2017).

$$\frac{|\lambda^{\mathrm{I}}_{\alpha_{\max}}|}{2\pi\lambda^{\mathrm{R}}_{\alpha_{\max}}} \leq \max_{c\in\mathscr{C}^*} \frac{\tanh[\mathscr{F}_c/(2n_c)]}{2\pi\tan(\pi/n_c)}$$

$\lambda_1, \lambda_2, \cdots, \lambda_n$: Eigenvalues of R

$\lambda_\alpha = -\lambda^{\mathrm{R}}_\alpha + \mathrm{i}\lambda^{\mathrm{I}}_\alpha$

The number of coherent oscillations: $\dfrac{|\lambda^{\mathrm{I}}_\alpha|}{2\pi\lambda^{\mathrm{R}}_\alpha} = \dfrac{\text{(Decay time)}}{\text{(Period of oscillations)}}$

$(\lambda^{\mathrm{R}}_\alpha)^{-1}$: Decay time $\quad 2\pi|\lambda^{\mathrm{I}}_\alpha|^{-1}$:Period of oscillations

Corollary: Rigorous proof of the conjecture

$a_i = \mathrm{Im}\dfrac{u_i^{(\alpha)}}{p_i^{\mathrm{st}}}, b_i = \mathrm{Re}\dfrac{u_i^{(\alpha)}}{p_i^{\mathrm{st}}},$

$\boldsymbol{u}^{(\alpha)}$: α-th right eigenvector of R

$\left(\sum_i |u_i^{(\alpha)}|^2/p_i^{\mathrm{st}} = 1\right)$

$$(\partial_\tau C_{ba} - \partial_\tau C_{ab})\Big|_{\tau=0} = \lambda^{\mathrm{I}}_\alpha \qquad 2\sqrt{(\partial_\tau C_{aa})(\partial_\tau C_{bb})}\Big|_{\tau=0} \leq -(\partial_\tau C_{aa} + \partial_\tau C_{bb})\Big|_{\tau=0} = \lambda^{\mathrm{R}}_\alpha$$

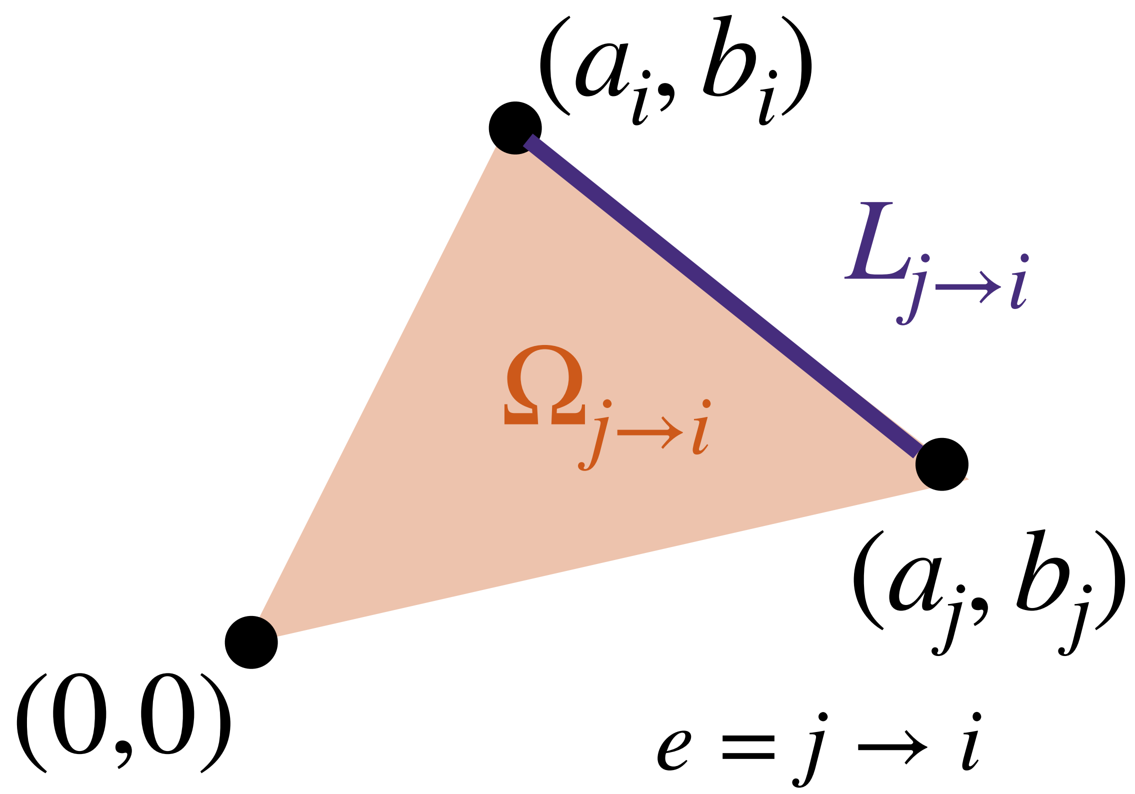
$$|\chi_{ba}| = \frac{|\partial_\tau C_{ba} - \partial_\tau C_{ab}|}{2\sqrt{(\partial_\tau C_{aa})(\partial_\tau C_{bb})}}\Bigg|_{\tau=0} \leq \max_{c\in\mathscr{C}^*} \frac{\tanh[\mathscr{F}_c/(2n_c)]}{\tan(\pi/n_c)}$$

$$\Rightarrow \quad \frac{|\lambda^{\mathrm{I}}_\alpha|}{2\pi\lambda^{\mathrm{R}}_\alpha} \leq \max_{c\in\mathscr{C}^*} \frac{\tanh[\mathscr{F}_c/(2n_c)]}{2\pi\tan(\pi/n_c)}$$

for any α. ($\lambda^{\mathrm{R}}_\alpha > 0$)

A sketch of the proof (1/3) - Geometric interpretation

① Geometric interpretation of χ_{ba}



Scaling $c \in \mathbb{R}$: $a \leftarrow ca$ $(\chi_{ba} = \chi_{b(ca)})$
s.t.
$$\sum_{i,j} \mathcal{T}_{ij} c a_i c a_j = \sum_{i,j} \mathcal{T}_{ij} b_i b_j$$

$$\Rightarrow \quad \chi_{ba} = \frac{2\sum_{i,j}\mathcal{T}_{ij}(b_i a_j - b_j a_i)}{\sum_{i,j}\mathcal{T}_{ij}((a_i - a_j)^2 + (b_i - b_j)^2)} = \frac{4\sum_e \mathcal{J}_e \Omega_e}{\sum_e \mathcal{A}_e (L_e)^2}$$

Dynamic activity: $\mathcal{A}_{j\to i} = \mathcal{T}_{ij} + \mathcal{T}_{ji} = \mathsf{R}_{ij} p_j^{\mathrm{st}} + \mathsf{R}_{ji} p_i^{\mathrm{st}}$

Currents: $\mathcal{J}_{j\to i} = \mathcal{T}_{ij} - \mathcal{T}_{ji} = \mathsf{R}_{ij} p_j^{\mathrm{st}} - \mathsf{R}_{ji} p_i^{\mathrm{st}}$

Signed area: $\Omega_{j\to i} = \dfrac{1}{2}(b_i a_j - a_i b_j)$

Length: $L_{j\to i} = \sqrt{(a_i - a_j)^2 + (b_i - b_j)^2}$

Cycle decomposition: $\mathcal{J}_e = \sum_{c \in \mathcal{C}_{\mathrm{uni}}} S_{ec} \mathcal{J}_c$ $\qquad S_{ec} = +1, \ -1, \ 0$
$(e \in c), (-e \in c), (\text{otherwise})$

$$|\chi_{ba}| \le \frac{4\sum_{c\in\mathcal{C}_{\mathrm{uni}}} \mathcal{J}_c \left|\sum_{e\in c}\Omega_e\right|}{\sum_e \mathcal{A}_e (L_e)^2} \le \frac{4\sum_{c\in\mathcal{C}^*} \mathcal{J}_c \left|\sum_{e\in c}\Omega_e\right|}{\sum_{c\in\mathcal{C}^*} \mathcal{J}_c \left(\sum_{e\in c} \frac{\mathcal{A}_e}{\mathcal{J}_e}(L_e)^2\right)} \le \max_{c\in\mathcal{C}^*} \frac{4\left|\sum_{e\in c}\Omega_e\right|}{\left(\sum_{e\in c} \frac{\mathcal{A}_e}{\mathcal{J}_e}(L_e)^2\right)}$$

↑ Triangle inequality

↑ Definition of $\mathcal{C}^*$
$(|\sum_{e\in c}\Omega_e| \neq 0, c \in \mathcal{C}^*)$

↑ Inequality $(\sum_c x_c)/(\sum_c y_c) \le \max_c (x_c/y_c)$

A sketch of the proof (2/3) - Short-time-TURs-like inequality

② Short-time-thermodynamic-uncertainty-relations-(TURs)-like inequality

Short-time TURs: S.Otsubo, S. Ito, A. Dechant, & T. Sagawa, *Physical Review E*, *101*, 062106 (2020).

① : $$|\chi_{ba}| \le \max_{c\in\mathscr{C}^*} \frac{4\left|\sum_{e\in c}\Omega_e\right|}{\left(\sum_{e\in c}\frac{\mathscr{A}_e}{\mathscr{J}_e}(L_e)^2\right)}$$

$$\frac{\left(\sum_{e\in c}L_e\right)^2}{\left(\sum_{e\in c}\frac{\mathscr{A}_e}{\mathscr{J}_e}(L_e)^2\right)} \le \sum_{e\in c}\frac{\mathscr{J}_e}{\mathscr{A}_e}$$

←Cauchy-Schwartz inequality

①+② $\Longrightarrow$ $$|\chi_{ba}| \le \max_{c\in\mathscr{C}^*} \frac{4\left|\sum_{e\in c}\Omega_e\right|}{\left(\sum_{e\in c}L_e\right)^2}\sum_{e\in c}\frac{\mathscr{J}_e}{\mathscr{A}_e}$$

③ Relation between $\mathscr{J}_e/\mathscr{A}_e$ and $\mathscr{F}_c$

$$\mathscr{F}_c = \sum_{e\in c}\ln\frac{\mathscr{T}_e}{\mathscr{T}_{-e}} = \sum_{e\in c}\ln\frac{\mathscr{A}_e+\mathscr{J}_e}{\mathscr{A}_e-\mathscr{J}_e} = 2n_c\sum_{e\in c}\frac{1}{n_c}\tanh^{-1}\left(\frac{\mathscr{J}_e}{\mathscr{A}_e}\right) \ge 2n_c\tanh^{-1}\left(\sum_{e\in c}\frac{\mathscr{J}_e}{n_c\mathscr{A}_e}\right)$$

↑ Jensen's inequality
($\mathscr{J}_e \ge 0$, convexity of $\tanh^{-1}$)

①+②+③ $\Longrightarrow$ $$|\chi_{ba}| \le \max_{c\in\mathscr{C}^*} \frac{4n_c\left|\sum_{e\in c}\Omega_e\right|}{\left(\sum_{e\in c}L_e\right)^2}\tanh\left(\frac{\mathscr{F}_c}{2n_c}\right)$$

A sketch of the proof (3/3) - Isoperimetric inequality

④ Isoperimetric inequality (n_c-polygons):

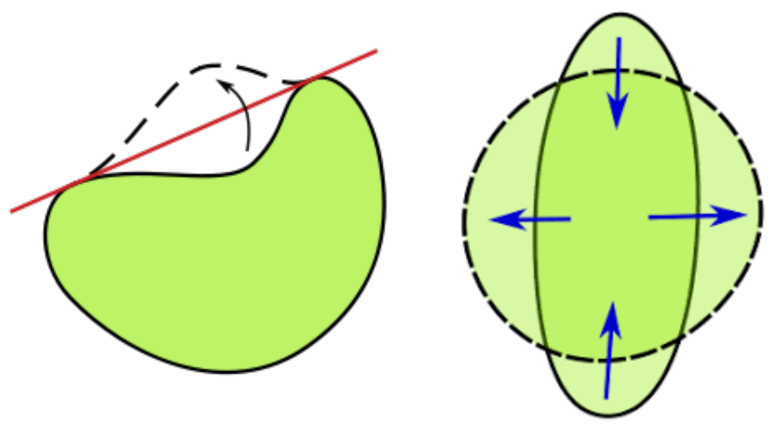
①+②+③ $\Longrightarrow$ $$|\chi_{ba}| \leq \max_{c \in \mathscr{C}^*} \frac{4n_c |\sum_{e\in c} \Omega_e|}{\left(\sum_{e \in c} L_e\right)^2} \tanh\left(\frac{\mathscr{F}_c}{2n_c}\right)$$

$$4n_c \tan(\pi/n_c)\Omega \leq L^2$$

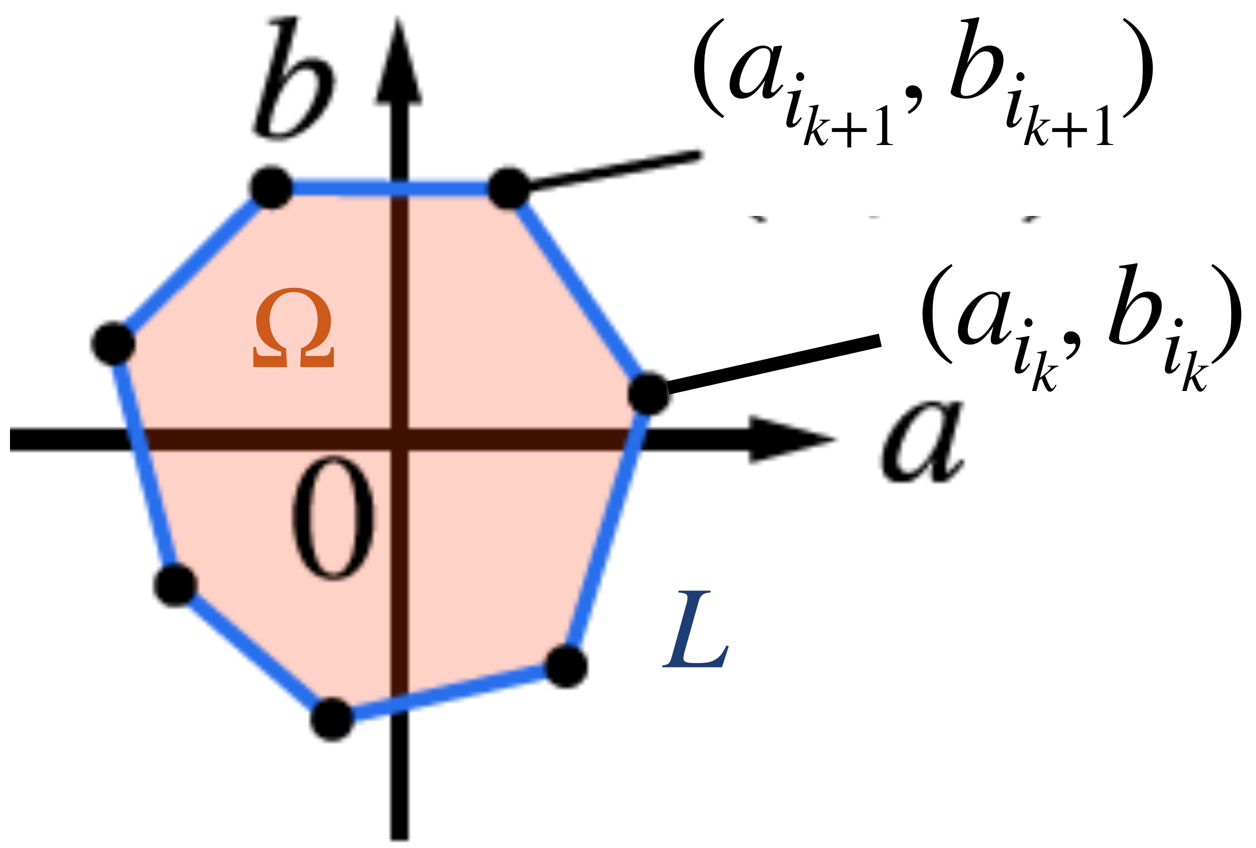
Perimeter: $L = \sum_{e \in c} L_e$, Area: $\Omega = |\sum_{e\in c} \Omega_e|$

↑ For a given perimeter L,
an area of n_c-polygons Ω is maximized
when the n_c-polygons is regular.

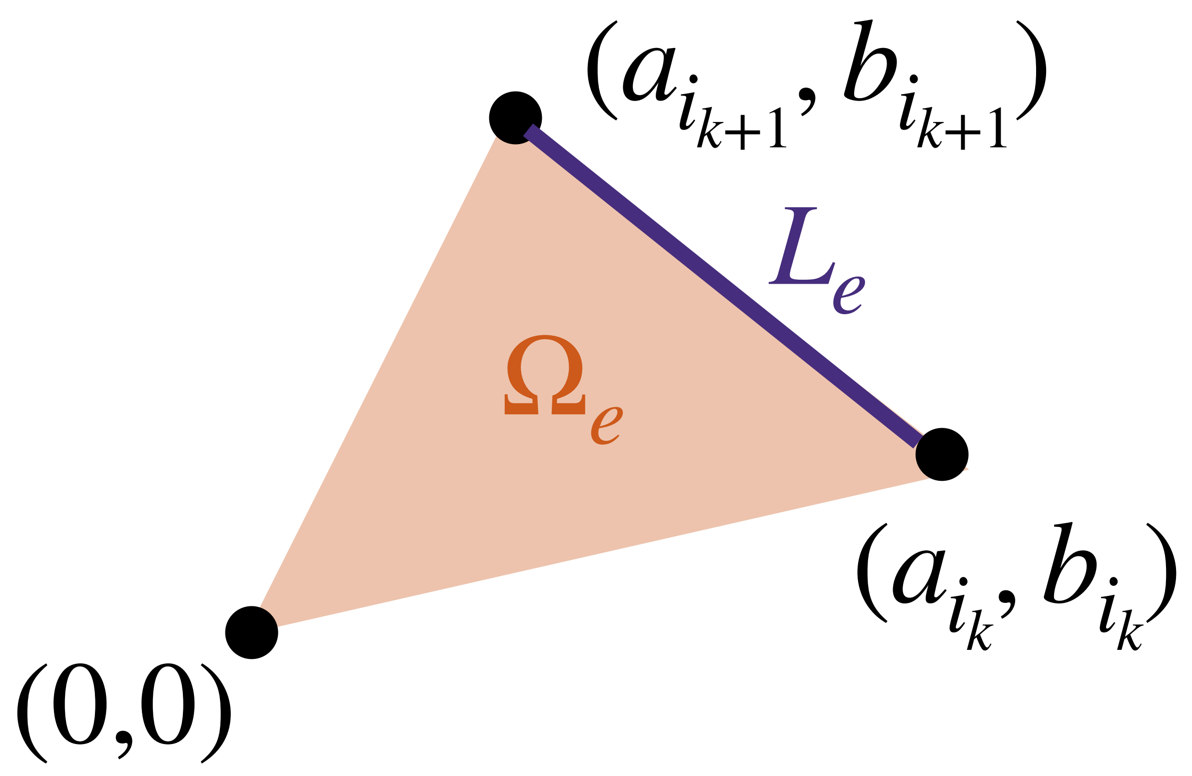
cf.) Isoperimetric inequality [$n_c \to \infty$]
(circle): $4\pi\Omega \leq L^2$



Figures from Wikipedia



$c = (i_1 \to \cdots \to i_{n_c} \to i_1)$



$e = (i_k \to i_{k+1}) \in c$

①+②+③+④ $\Longrightarrow$ Main result $$|\chi_{ba}| \leq \max_{c \in \mathscr{C}^*} \frac{\tanh[\mathscr{F}_c/(2n_c)]}{\tan(\pi/n_c)}$$

Summary

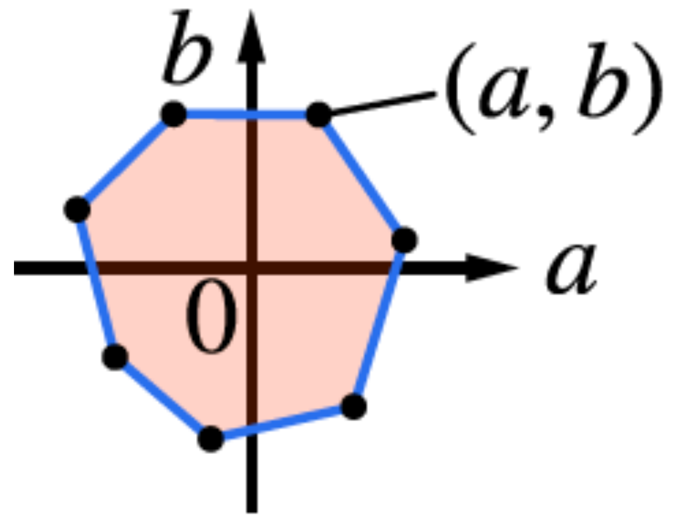
- We derive a trade-off relation between the asymmetry of cross-correlations χ_{ba} and a thermodynamic driving force $\mathcal{F}_c$.

$$|\chi_{ba}| \le \max_{c\in\mathscr{C}^*} \frac{\tanh[\mathcal{F}_c/(2n_c)]}{\tan(\pi/n_c)} \le \max_{c\in\mathscr{C}^*} \frac{\mathcal{F}_c}{2\pi}$$

- Our result provides rigorous proof of the numerical conjecture by Barato-Seifert (2017) for the number of coherent oscillations.

$$\frac{|\lambda_\alpha^{\mathrm{I}}|}{2\pi\lambda_\alpha^{\mathrm{R}}} \le \max_{c\in\mathscr{C}^*} \frac{\tanh[\mathcal{F}_c/(2n_c)]}{2\pi\tan(\pi/n_c)}$$

- The proof is based on TURs-like inequality and the isoperimetric inequality (n_c-polygons).



- Our result may be useful for understanding how large the thermodynamic driving force must be needed to maintain the directed information flow in biological information processing.

Naruo Ohga, Sosuke Ito and Artemy Kolchinsky, *to appear in* Physical Review Letters (2023). [arXiv:2303.13116]