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Thermodynamic Bound on the Asymmetry of Cross-Correlations

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The principle of microscopic reversibility says that, in equilibrium, two-time cross-correlations are symmetric under the exchange of observables. Thus, the asymmetry of cross-correlations is a fundamental, measurable, and often-used statistical signature of deviation from equilibrium. Here we find a simple and universal inequality that bounds the magnitude of asymmetry by the cycle affinity, i.e., the strength of thermodynamic driving. Our result applies to a large class of systems and all state observables, and it suggests a fundamental thermodynamic cost for various nonequilibrium functions quantified by the asymmetry. It also provides a powerful tool to infer affinity from measured cross-correlations, in a different and complementary way to the thermodynamic uncertainty relations. As an application, we prove a thermodynamic bound on the coherence of noisy oscillations, which was previously conjectured by Barato and Seifert [Phys. Rev. E **95**, 062409 (2017)]. We also derive a thermodynamic bound on directed information flow in a biochemical signal transduction model.

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One of the most common ways to characterize a physical system is by studying its spatiotemporal correlations. Imagine measuring a pair of observables $a(t)$ and $b(t)$ in a stochastic system in steady state, e.g., 2 degrees of freedom, counts of two chemical species, fluorescence intensity of two colors, voltages of two points, etc. [Fig. 1(a)]. The two-time correlation between a and b at time lag τ is

$$C^{\tau}_{ba} := \langle b(t+\tau)a(t)\rangle, \tag{1}$$

where $\langle\cdot\rangle$ indicates average across time or trials (it does not depend on t due to the steady-state assumption). When $a = b$, C^{τ}_{aa} is the autocorrelation function of a. When $a \neq b$, C^{τ}_{ba} captures the cross-correlation from a to b.

A classic result in statistical physics states that cross-correlations reflect thermodynamic properties of the steady state [1]. In systems without odd degrees of freedom, cross-correlations in equilibrium obey the symmetry $C^{\tau}_{ba} = C^{\tau}_{ab}$ for all a, b, and τ. This is called the principle of microscopic reversibility, and it serves as the basis of the celebrated Onsager reciprocity [1,2]. Thus, violation of this symmetry is a fundamental and often-used statistical signature of nonequilibrium steady states [3–15].

To maintain a nonequilibrium steady state, a system must be subjected to thermodynamic driving, such as a temperature gradient, a chemical potential gradient, or an external force. In discrete-state stochastic systems as considered here, the strength of different kinds of driving can be quantified in a unified way by the "cycle affinity" [16,17]. Given a cycle (cyclic sequence of states) c, the cycle affinity $\mathcal{F}_c$ is the sum of the thermodynamic forces acting on the system around the cycle. Equivalently, each time the system completes the cycle, the thermodynamic entropy of the environment increases by $\mathcal{F}_c$ [18]. Cycle affinity vanishes in equilibrium, and it is a fundamental thermodynamic signature of nonequilibrium steady states.

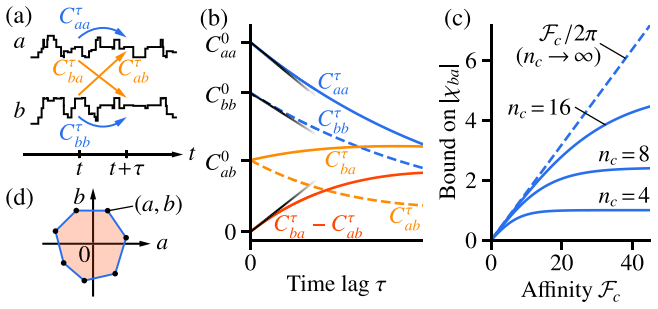

FIG. 1. (a) A pair of observables $a(t)$ and $b(t)$ is measured in a stochastic system in steady state, from which the two-time correlations are calculated. (b) We define a normalized measure of asymmetry of cross-correlation χ_{ba} in Eq. (2) based on the short-time behavior of the correlation functions (black). (c) Our main result is a thermodynamic relation between χ_{ba} and cycle affinity, Eq. (3). (d) The result is derived in part by considering χ_{ba} as the ratio between the area and perimeter of the polygon formed by the values (a, b) over a cycle and then using the isoperimetric inequality.

Until now, however, these thermodynamic and statistical signatures of deviation from equilibrium have not been universally and quantitatively related.

In this Letter, we prove a universal and simple relationship between asymmetry of cross-correlations and cycle affinity in steady state. To introduce our result, we first define a normalized measure of asymmetry between a and b,

$$\chi_{ba} \coloneqq \lim_{\tau\to 0} \frac{C^\tau_{ba} - C^\tau_{ab}}{2\sqrt{(\Delta_\tau C_{aa})(\Delta_\tau C_{bb})}}. \tag{2}$$

This measure is dimensionless and invariant under shifting and scaling of observables and time. The normalization terms $\Delta_\tau C_{aa} \coloneqq C^0_{aa} - C^\tau_{aa}$ and $\Delta_\tau C_{bb} \coloneqq C^0_{bb} - C^\tau_{bb}$ quantify the decay of autocorrelations of a and b [Fig. 1(b)]. They may also be interpreted as measures of diffusion (mean-squared displacements), since $\Delta_\tau C_{aa} = \frac{1}{2}\langle[a(t+\tau) - a(t)]^2\rangle$.

Our main result is an inequality between cycle affinity and normalized asymmetry between any pair of observables,

$$|\chi_{ba}| \le \max_c \frac{\tanh(\mathcal{F}_c/2n_c)}{\tan(\pi/n_c)} \le \max_c \frac{\mathcal{F}_c}{2\pi}, \tag{3}$$

where $\max_c$ is the maximum over all simple cycles and n_c is the number of states in cycle c [see Fig. 1(c)]. The second bound, which refers to cycle affinity per radian, is approached in the limit $n_c \to \infty$ at a fixed cycle affinity. Some tighter versions of Eq. (3) are provided below.

Our result is physically meaningful and experimentally accessible. It provides a fundamental bound on the asymmetry of cross-correlations achievable at a given level of affinity. This suggests the existence of thermodynamic trade-offs for various physical functions that can be quantified by such asymmetry, including directed interactions and information flow [19–24], nonequilibrium oscillations and circulation [13,25–30], nonreciprocal motion [31–33], and anomalous response (such as odd viscosity) [34–37].

The normalized asymmetry χ_{ba} is also experimentally accessible, since it depends only on the short-time two-time correlation functions. In fact, χ_{ba} can be expressed in terms of the slopes of auto- and cross-correlation functions, $\chi_{ba} = (\partial_\tau C^\tau_{ba} - \partial_\tau C^\tau_{ab})/[2\sqrt{(\partial_\tau C^\tau_{aa})(\partial_\tau C^\tau_{bb})}]$, where the derivative $\partial_\tau \equiv \partial/\partial\tau$ is evaluated at $\tau = 0$ [Fig. 1(b)]. Such correlations can be measured using, for example, fluorescence cross-correlation spectroscopy [38–40], microscopy [11,41], and other experimental techniques [42,43]. In fact, even a single time series can be used if one of the observables is taken to be a nonlinear transformation of the other, such as $b(t) = a(t)^2$. Equation (3) therefore provides a powerful tool for inferring thermodynamic properties from experimental data, in complement to existing techniques like thermodynamic uncertainty relations (TURs) [44–47]. We contrast our bound with TURs below.

The derivation of our result, found at the end of this Letter, combines existing techniques from stochastic thermodynamics with some new ideas. Our most important new idea is to interpret Eq. (2) as the ratio between the area and circumference of the polygon swept out by (appropriately scaled) observables a and b over a cycle [Fig. 1(d)]. We then employ the isoperimetric inequality [48], which says that the area of n-sided polygon with a given circumference is maximized by the regular n-sided polygon [49].

Below, we illustrate our result with a theoretical and a practical application. As a theoretical application, we relate χ_{ba} to the eigenvalues of the rate matrix. This leads to a proof of a thermodynamic bound on the coherence of noisy oscillations, which was previously conjectured by Barato and Seifert [52]. As a practical application, we show that chemical driving force bounds directed information flow in biochemical signal transduction.

System and formulation.—Here we describe our physical setup and define the quantities that appear in our result. We consider a stochastic system modeled as a Markov jump system with a finite number of mesoscopic states $i \in \{1, 2, \ldots, n\}$, where the transition rate from state j to i is R_{ij} for $i \neq j$. We define the rate matrix $\boldsymbol{R} \equiv (R_{ij})$ by filling the diagonal elements with $R_{ii} = -\sum_{k:k\neq i} R_{ki}$. The dynamics of the probability distribution $\boldsymbol{p} = (p_1, \ldots, p_n)^\mathsf{T}$ obeys $d\boldsymbol{p}/dt = \boldsymbol{R}\boldsymbol{p}$. We use $\boldsymbol{q}$ to indicate a steady-state distribution satisfying $\boldsymbol{R}\boldsymbol{q} = \boldsymbol{0}$. For convenience, we use $\mathcal{T}_{ij} = R_{ij}q_j$ to indicate the one-way steady-state flux from j to i (with diagonals $\mathcal{T}_{ii} = R_{ii}q_i \le 0$).

We define observables a and b to be any functions of the states, denoted by a_i and b_i. In steady state, their cross-correlation at time lag τ can be written as

$$C^\tau_{ba} = \sum_{i,j} (e^{\tau R})_{ij} q_j b_i a_j \approx \sum_i q_i b_i a_i + \tau \sum_{i,j} \mathcal{T}_{ij} b_i a_j, \tag{4}$$

where $\approx$ means equality to first order in τ, which follows by expanding the exponential. The normalization terms in Eq. (2) can be written as

$$\Delta_\tau C_{aa} \approx -\tau \sum_{i,j} \mathcal{T}_{ij} a_i a_j = \frac{\tau}{2} \sum_{i,j} \mathcal{T}_{ij} (a_i - a_j)^2, \tag{5}$$

which follows from $\sum_i \mathcal{T}_{ij} = \sum_j \mathcal{T}_{ij} = 0$. Plugging into (2) gives

$$\chi_{ba} = \frac{\sum_{i,j} \mathcal{T}_{ij}(b_i a_j - b_j a_i)}{2\sqrt{-\sum_{i,j} \mathcal{T}_{ij} a_i a_j}\sqrt{-\sum_{i,j} \mathcal{T}_{ij} b_i b_j}}. \tag{6}$$

A simple cycle $c = (i_1 \to i_2 \to \cdots \to i_{n_c} \to i_1)$ is a closed path of $n_c \ge 3$ distinct states with $R_{i_{k+1} i_k} > 0$ for $k \in \{1, \ldots, n_c\}$ (we use the convention $n_c + 1 \equiv 1$).

According to stochastic thermodynamics [16,17], the cycle affinity $\mathcal{F}_c$ is related to the transition rates by

$$\mathcal{F}_c = \ln\left(\frac{R_{i_2 i_1} R_{i_3 i_2} \cdots R_{i_1 i_{n_c}}}{R_{i_1 i_2} R_{i_2 i_3} \cdots R_{i_{n_c} i_1}}\right). \tag{7}$$

With these definitions, the main result (3) holds. This bound can be saturated, even in systems arbitrarily far from equilibrium. In particular, for a unicyclic system consisting of a single cycle $c = (1 \to 2 \to \cdots \to n \to 1)$, the first (tighter) bound holds with equality if and only if the one-way fluxes are translation invariant, i.e., $\mathcal{T}_{12} = \mathcal{T}_{23} = \cdots = \mathcal{T}_{n1}$ and $\mathcal{T}_{21} = \mathcal{T}_{32} = \cdots = \mathcal{T}_{1n}$, and there exists a scaling constant γ such that the points $(\gamma a_1, b_1), \ldots, (\gamma a_n, b_n)$ form a regular n-sided polygon on the a–b plane in this order.

Tighter bounds.—Under the same setup, we can prove a tighter version of our result,

$$|\chi_{ba}| \le \max_{c\in\mathcal{C}^*} \frac{n_c \tanh(\mathcal{F}_c/2n_c)}{n_c' \tan(\pi/n_c')} \le \max_{c\in\mathcal{C}^*} \frac{\mathcal{F}_c/2n_c'}{\tan(\pi/n_c')} \le \max_{c\in\mathcal{C}^*} \frac{\mathcal{F}_c}{2\pi}. \tag{8}$$

Here, n_c' is the number of times the joint value (a, b) changes over course of cycle c, which satisfies $n_c' \le n_c$. $\mathcal{C}^* \coloneqq \mathcal{C}_{\text{asy}} \cap \mathcal{C}_{\text{uni}}$ is a restricted set of cycles. $\mathcal{C}_{\text{asy}}$ is the set of simple cycles $c = (i_1 \to \cdots \to i_{n_c} \to i_1)$ that satisfy $\sum_{k=1}^{n_c} (b_{i_{k+1}} a_{i_k} - b_{i_k} a_{i_{k+1}}) \neq 0$, namely, simple cycles with nonzero net asymmetry. This restriction means that cycles with zero net asymmetry cannot contribute to $C_{ba}^\tau - C_{ab}^\tau$, no matter how large $\mathcal{F}_c$ is. $\mathcal{C}_{\text{uni}}$ is a restricted set of cycles generated by the so-called uniform cycle decomposition [53]. This restriction not only makes the inequality tighter, it also provides a fast algorithm for solving the maximization over cycles. The simpler version (3) is recovered from the first bound in Eq. (8) by using $n_c' \tan(\pi/n_c') \ge n_c \tan(\pi/n_c)$ and $\max_{c\in\mathcal{C}^*}(\cdot) \le \max_c(\cdot)$. The second bound in (8), which follows from $\tanh(\mathcal{F}_c/2n_c) \le \mathcal{F}_c/2n_c$, is convenient when n_c' is known but the number of underlying states n_c is unknown.

We can also obtain a tighter result by considering a restricted setup: If the two observables are bipartite, i.e., a and b do not change simultaneously in any transition, then

$$|\chi_{ba}| \le \max_{c\in\mathcal{C}^*} \frac{n_c \tanh(\mathcal{F}_c/2n_c)}{4} \le \max_{c\in\mathcal{C}^*} \frac{\mathcal{F}_c}{8} \le \max_{c\in\mathcal{C}^*} \frac{\mathcal{F}_c}{2\pi}. \tag{9}$$

These bounds may be even tighter than Eq. (8).

Application 1: Coherence of noisy oscillation.—We present a theoretical application of our result by proving a thermodynamic bound on the coherence of noisy oscillation. Noisy oscillations are ubiquitous in biological systems [54,55], but the oscillation should be coherent in time for reliable biological functionality [56,57]. Coherence is supported at the cost of dissipation, thus the relation between thermodynamic cost and the coherence of noisy oscillations is actively studied [52,58–66].

The coherence of oscillation is quantified by the number of oscillations that occur before the steady-state autocorrelations die down. To introduce this, let $\lambda_1, \ldots, \lambda_n$ be the eigenvalues of the rate matrix R with real and imaginary parts $\lambda_\alpha = -\lambda_\alpha^{\text{R}} + \mathrm{i}\lambda_\alpha^{\text{I}}$. Suppose for simplicity that the rate matrix is diagonalizable, in which case the matrix exponential can be expressed as $e^{\tau R} = \sum_\alpha \exp(-\lambda_\alpha^{\text{R}}\tau) \exp(\mathrm{i}\lambda_\alpha^{\text{I}}\tau) \boldsymbol{u}^{(\alpha)} \boldsymbol{v}^{(\alpha)\mathsf{T}}$, where $\boldsymbol{v}^{(\alpha)}$ and $\boldsymbol{u}^{(\alpha)}$ indicate the left and right eigenvectors of R normalized so that $\boldsymbol{v}^{(\alpha)\mathsf{T}} \boldsymbol{u}^{(\alpha)} = 1$. Plugging this expression into Eq. (4) shows that any two-time correlation can be written as a sum over the eigenmodes of R, where the contribution from mode α decays with timescale $(\lambda_\alpha^{\text{R}})^{-1}$ and oscillates with period $2\pi|\lambda_\alpha^{\text{I}}|^{-1}$. The number of coherent oscillations for mode α is the ratio between the decay time and the period of the oscillations, $(\lambda_\alpha^{\text{R}})^{-1}/2\pi|\lambda_\alpha^{\text{I}}|^{-1} = |\lambda_\alpha^{\text{I}}|/2\pi\lambda_\alpha^{\text{R}}$ [52,67].

Barato and Seifert [52] conjectured, based on numerical evidence, that the slowest decay mode (with the smallest nonzero $\lambda_\alpha^{\text{R}}$) obeys a thermodynamic bound,

$$\frac{|\lambda_\alpha^{\text{I}}|}{2\pi\lambda_\alpha^{\text{R}}} \le \max_c \frac{\tanh(\mathcal{F}_c/2n_c)}{2\pi \tan(\pi/n_c)}. \tag{10}$$

This bound implies that coherent oscillations require strong thermodynamic driving. Despite its fundamental and profound nature, this inequality has not been rigorously proven.

Here we use our result (3) to prove that (10) holds for all modes α. We normalize the right eigenvector $\boldsymbol{u}^{(\alpha)}$ so that $\sum_i |u_i^{(\alpha)}|^2/q_i = 1$ and define two observables $a_i = \operatorname{Im} u_i^{(\alpha)}/q_i$ and $b_i = \operatorname{Re} u_i^{(\alpha)}/q_i$. Using Eqs. (4) and (5), the imaginary and real parts of λ_α can be written as

$$\lambda_\alpha^{\text{I}} = \lim_{\tau\to 0} \frac{C_{ba}^\tau - C_{ab}^\tau}{\tau}, \qquad \lambda_\alpha^{\text{R}} = \lim_{\tau\to 0} \frac{\Delta_\tau C_{aa} + \Delta_\tau C_{bb}}{\tau}, \tag{11}$$

as derived in the Supplemental Material [68]. Combining Eqs. (11) and (3), together with the inequality $(x + y)/2 \ge \sqrt{xy}$, proves the conjecture (10). The bound (10) is saturated in unicyclic systems with uniform transition rates for the slowest decay mode.

To our knowledge, the expression (11) is new to the literature. More generally, our analytical approach to the eigenvalues of rate matrices complements classical results on this topic [74–79], and it may contribute to ongoing research on the relationship between thermodynamics and complex eigenvalues [60–66]. For instance, Oberreiter *et al.* [65] recently conjectured another thermodynamic bound on $|\lambda_\alpha^{\text{I}}|/2\pi\lambda_\alpha^{\text{R}}$ in terms of entropy production rate. Although our approach alone cannot directly prove this newer

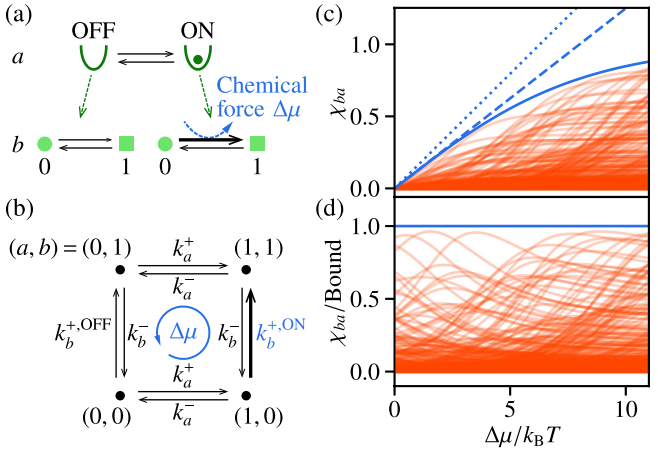

FIG. 2. (a) Simple model of biological signal transduction [80]. (b) Formulation as a Markov jump system with a nonequilibrium cycle. (c) Validation of our bounds. Orange indicates χ_{ba} for varying chemical force $\Delta\mu$, which determines the rate of the transition $k_b^{+,\mathrm{ON}}$ (other kinetic rates set to random but fixed values). χ_{ba} is nonnegative for $\Delta\mu \geq 0$ in this model. Blue indicates the three upper bounds from Eq. (12). (d) The ratio between χ_{ba} and the tightest bound $\tanh(\Delta\mu/8k_BT)$ in Eq. (12).

conjecture, it may be useful when combined with other ideas.

The result (10) also has practical implications, as it may be used to infer cyclic affinity from empirical observations, assuming some two-time correlation function exhibits a clear damped oscillation corresponding to a particular mode. In this case, one would not directly measure the "observables" a and b, but rather estimate $\lambda_\alpha^{\mathrm{I}}$ and $\lambda_\alpha^{\mathrm{R}}$ by fitting the two-time correlation function with a damped oscillation.

Application 2: Signal transduction in a biochemical system.—One of the goals of stochastic thermodynamics is to understand the costs of information processing in biochemical systems [80–90]. To illustrate a practical application of our result, we derive a thermodynamic bound on directed information flow in a standard model of biochemical signal transduction [Fig. 2(a)] [80].

The model consists of an upstream receptor and a downstream protein. The upstream receptor stochastically switches between "OFF" and "ON" states due to ligand binding, corresponding to the observable $a = 0, 1$. The downstream stochastically switches between "0" (inactive) and "1" (active) states, corresponding the observable $b = 0, 1$. When the upstream is ON, the activation of the downstream $(0 \to 1)$ is driven by a chemical force $\Delta\mu > 0$. For example, if the driving is provided by the hydrolysis of a molecule of adenosine triphosphate (ATP), $\Delta\mu = \mu_{\mathrm{ATP}} - \mu_{\mathrm{ADP}} - \mu_{\mathrm{Pi}}$, with μ_X being the environmental chemical potential of X. The bipartite dynamics are modeled as a four-state Markov jump system depicted in Fig. 2(b). The unique cycle in this system has cycle affinity $\mathcal{F} = \Delta\mu/k_BT$, where k_B is the Boltzmann constant and T is the environmental temperature.

In this model, the cross-correlation C_{ba}^τ is the joint probability of the receptor being ON at time t and the protein being active at time $t + \tau$, and vice versa for C_{ab}^τ. Therefore, the asymmetry $C_{ba}^\tau - C_{ab}^\tau$ provides a simple and natural measure of directed information flow from a to b [19–21]. As for the normalization factor, Eq. (5) implies that $\Delta_\tau C_{aa}$ is one half of the expected number of switching events of a during a short period τ, and similarly for $\Delta_\tau C_{bb}$. Therefore, χ_{ba} is normalized by the frequency of the switches of a and b.

Our general result (8) specializes to

$$|\chi_{ba}| \leq \tanh\frac{\Delta\mu}{8k_BT} \leq \frac{\Delta\mu}{8k_BT} \leq \frac{\Delta\mu}{2\pi k_BT}. \tag{12}$$

See Figs. 2(c) and 2(d). Thus, the chemical force $\Delta\mu$ bounds directed information flow, irrespective of the details of the transition rates. Even if the transition rates are perturbed, the bound is not affected as long as $\Delta\mu$ is unchanged.

Although Eq. (12) was motivated by a specific model of signal transduction [80], the result is much more general. The bound $|\chi_{ba}| \leq \Delta\mu/2\pi k_BT$ applies to any signal transduction system that includes a binary upstream and downstream, including multicyclic systems and systems with nonobserved transition and states, as long as the maximum cycle affinity is $\Delta\mu/k_BT$. The tighter bound $|\chi_{ba}| \leq \Delta\mu/8k_BT$ holds when, in addition, the upstream and downstream observables are bipartite (do not change at the same time), as follows from Eq. (9).

Derivation.—We sketch the derivation of Eq. (3), restricting our attention to unicyclic systems for simplicity. Further details, including derivation of our tighter bound (8) and consideration of multicyclic systems, are in the Supplemental Material [68].

For each transition $j \to i$, we define the net probability current $\mathcal{J}_{ij} = \mathcal{T}_{ij} - \mathcal{T}_{ji}$ and the dynamical activity $\mathcal{A}_{ij} = \mathcal{T}_{ij} + \mathcal{T}_{ji}$. We also define $\Omega_{ij} \coloneqq \frac{1}{2}(b_ia_j - b_ja_i)$ and $L_{ij} \coloneqq \sqrt{(a_i - a_j)^2 + (b_i - b_j)^2}$.

We recast χ_{ba} in a convenient form. For a unicyclic system with $c = (1 \to 2 \to \cdots \to n \to 1)$, the steady-state currents are uniform, $\mathcal{J}_{21} = \mathcal{J}_{32} = \cdots = \mathcal{J}_{1n} =: \mathcal{J}$. We assume without loss of generality that $\mathcal{J} \geq 0$ (otherwise, we may consider the cycle in reverse). Next, since $|\chi_{ba}|$ is invariant under multiplication of a and b by any pair of real numbers, we may assume without loss of generality that a and b are scaled to satisfy $\sum_{i,j}\mathcal{T}_{ij}a_ia_j = \sum_{i,j}\mathcal{T}_{ij}b_ib_j$. Combining this assumption with Eq. (5), we may rewrite the denominator of Eq. (6) as $-\sum_{i,j}\mathcal{T}_{ij}(a_ia_j + b_ib_j) = \frac{1}{2}\sum_{i>j}\mathcal{A}_{ij}L_{ij}^2$. This gives

$$\chi_{ba} = \frac{4\mathcal{J}\sum_i\Omega_{i+1,i}}{\sum_i\mathcal{A}_{i+1,i}L_{i+1,i}^2}. \tag{13}$$

We use two techniques to bound the right side of Eq. (13). First, we generalize the short-time TUR [91] to

$$\frac{(\mathcal{J}\sum_i L_{i+1,i})^2}{\sum_i \mathcal{A}_{i+1,i} L_{i+1,i}^2} \leq \mathcal{J} n \tanh\frac{\mathcal{F}}{2n}, \tag{14}$$

where $\mathcal{F}$ is the cycle affinity of the unique cycle. To prove Eq. (14), we first use the Cauchy–Schwarz inequality to show that the left-hand side is less than $\mathcal{J}^2 \sum_i \mathcal{A}_{i+1,i}^{-1}$. Next, we rewrite the affinity as $\mathcal{F} = 2n \sum_i n^{-1} \mathrm{artanh}(\mathcal{J}/\mathcal{A}_{i+1,i})$ and apply Jensen's inequality to artanh to show that $\mathcal{J}\sum_i(\mathcal{J}/\mathcal{A}_{i+1,i})$ is less than the right-hand side.

The second technique uses a geometrical interpretation of Ω_{ij} and L_{ij}. $\Omega_{i+1,i}$ is the signed area swept by the observables during the transition $(a_i, b_i) \to (a_{i+1}, b_{i+1})$, while $L_{i+1,i}$ is the length of this transition [Fig. 1(d)]. Over the course of the cycle, the total signed area is $\sum_i \Omega_{i+1,i}$ and the length of the curve is $\sum_i L_{i+1,i}$. We relate the area and length using the isoperimetric inequality,

$$\left(4n \tan\frac{\pi}{n}\right)\left|\sum_i \Omega_{i+1,i}\right| \leq \left(\sum_i L_{i+1,i}\right)^2. \tag{15}$$

As shown in the Supplemental Material [68], this inequality holds even if the curve has self-intersections. Combining Eqs. (13)–(15) leads to our main result.

Discussion.—In this Letter, we uncovered a universal thermodynamic bound on the asymmetry of cross-correlation between observables. This result holds for any pair of observables in a finite-state stochastic system in steady state. It is experimentally accessible, relying only on short-time two-point correlation functions.

Our result is similar in spirit to TURs, which also relate the statistical and thermodynamic properties of nonequilibrium steady states [44–47]. However, the two approaches differ both in statistical and thermodynamic aspects. First, our bound is defined using two-time correlations of state observables (e.g., counts of chemical species, voltages, etc.), while TURs are usually defined using the mean and variance of antisymmetric current observables (e.g., chemical reaction fluxes, electric currents, etc.). Although the asymmetry $C_{ba}^{\tau} - C_{ab}^{\tau}$ can be interpreted as the mean of a specific antisymmetric current observable, the variance of this observable lacks an intuitive physical or statistical interpretation. Second, our bound uses the cycle affinity as the measure of thermodynamic cost, while TURs use the entropy production rate. The affinity is determined by macroscopic parameters (such as environmental chemical potentials) and does not depend on the steady-state distribution. Therefore, it can be interpreted and manipulated at the macroscopic level, and it is robust against microscopic perturbations. In contrast, the entropy production rate captures the resulting dissipation rate and is sensitive to microscopic details. Thus, these two measures provide different and complementary characterizations of the thermodynamic cost. To our knowledge, there is no way to use TURs to bound cycle affinities in general (multicyclic) systems [92].

It is interesting to consider our bound (3) for finite time lags without taking the short-time limit $\lim_{\tau\to 0}$ in Eq. (2). Given numerical evidence presented in the Supplemental Material [68], we conjecture that our bound holds for all τ. Proving this conjecture is an interesting direction for future work. In addition, future work may generalize our approach to cases when cross-correlations between three or more observables are available at once. Finally, it would be interesting to extend our analysis to continuous-state systems and quantum systems.

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