Improved estimation for energy dissipation in biochemical oscillations

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Biochemical oscillations, regulating the timing of life processes, need to consume energy to achieve good performance on crucial functions, such as high accuracy of phase period and high sensitivity to external signals. However, it is a great challenge to precisely estimate the energy dissipation in such systems. Here, based on the stochastic normal form theory (SNFT), we calculate the Pearson correlation coefficient between the oscillatory amplitude and phase, and a trade-off relation between transport efficiency and phase sensitivity can then be derived, which serves as a tighter form than the estimator resulting from the conventional thermodynamic uncertainty relation (TUR). Our findings demonstrate that a more precise energy dissipation estimation can be obtained by enhancing the sensitivity of the biochemical oscillations. Moreover, the internal noise and amplitude powers effects have also been discovered.

I. INTRODUCTION

To achieve good performance of certain functions, living systems are inherently nonequilibrium and dissipative. Recently, the relationship between biochemical functions and nonequilibrium thermodynamics has been an active area in statistical physics community[1][2]. For instance, Lan et al. have revealed a powerful trade-off relation between energy dissipation rate, adaption speed and the maximum adaption accuracy underlying many sensory systems[3][4]. Lang et al. have investigated the fundamental thermodynamic constraints on statistical inference and learning of biochemical signaling network[5]. Particularly, for biochemical oscillations which are essential in regulating the timing of life processes, such as the cell cycle, circadian clocks, and glycolysis, both accuracy of the period and sensitivity to external cues can be ensured by dissipative processes simultaneously[6][7][8]. Therefore, it is important to measure the free energy dissipation in biochemical oscillation systems that maintains the cyclic dynamics. However, in actual experiments, how to infer the energy dissipation is of great challenge[9][10][11].

Recent progress in this topic is the thermodynamic uncertainty relation (TUR)[12][13] quantifying the trade-off between energy dissipation $\Delta W$, the average $\langle R \rangle$ and variance $\text{Var}(R) = \langle (R - \langle R \rangle)^2 \rangle$ of a time-integrated observable $R$ in nonequilibrium steady states (here $\beta = 1/k_B T$, $T$ is the temperature of the environment and $k_B$ is the Boltzmann constant):

$$\eta(R) = \frac{2 \langle R \rangle^2}{\beta \text{Var}(R) \Delta W} \leq 1,$$  \hspace{1cm} (1)

where $\eta(R)$ is the transport efficiency to properly quantify the performance of living systems working with high accuracy, but low energy dissipation[14]. Directly, TUR yields that the magnitude of current fluctuation provides a lower bound of energy dissipation as $\Delta W \geq \Delta W_{\text{TUR}} \equiv 2k_B T \langle R \rangle^2 / \beta \text{Var}(R)$ with $\eta(R) = \Delta W_{\text{TUR}} / \Delta W$. If $\eta(R)$ is close to 1, the TUR acts as a powerful tool for energy dissipation inference[15][16]. For instance, recently Li et al. have showed that the fluctuations in nonequilibrium currents can be utilized to infer the dissipation rate for the bead-spring model[17]. Otsubo et al. have developed a framework for dissipation estimation by using the TUR along with machine learning technique[18] to list just a few.

However, since the TUR is an inequality, only a rough bound can be provided in many cases. For instance, it has been revealed by Hwang and Hyeon that the TUR is generally not tight for several types of molecular motors[19]. Jack et al. have found that the TUR only yields a weak bound for molecular-scale energy conversion[20]. Also, in our recent work[21], we have established the TUR for general biochemical oscillations by calculating the transport efficiency $\eta(\theta) = 2 \theta^2 / \beta \text{Var}(\theta) \Delta W < 1$, where the observable oscillatory phase $\theta(\tau) = \int_0^\tau \dot{\theta}(t)dt$ is the current observable. Both the analytical and numerical results have shown that the TUR is far from tight for models of chemical oscillators, providing typically lower estimation for energy dissipation than the actual value. Therefore, how to obtain a more qualified estimation than the conventional TUR for biochemical oscillation systems is still an interesting question.

In the presented paper, we try to address this question by revealing a trade-off relation between transport efficiency and phase sensitivity[22][23][24][25][26]. The basic idea is to improve the conventional TUR by considering the Pearson correlations between the chosen current and another state-dependent observable, based on a strategy proposed by Dechant and Sasa very recently[27]. For practical purpose in biochemical oscillation systems, we choose the time integral of the oscillatory amplitude $r$ as the state-dependent observable, which reads $Q_2(\tau) = \int_0^\tau r^2(t)dt$. By using the stochastic normal form theory (SNFT) we

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established before explicit theoretical expressions of the Pearson correlations between \( Q_2 \) and \( \theta \) can be derived, which allows us to obtain the efficiency-sensitivity trade-off relation as \( \eta(\theta) \leq 1 - 2\alpha \kappa^2 \) with \( \kappa \) the phase sensitivity characterizing the ability for biochemical circuits to respond to external signals and \( \alpha > 0 \) the control parameter denoting the distance to the bifurcation point. Remarkably, this trade-off relation provides a tighter dissipation estimator for biochemical oscillations than the conventional TUR, and the precision of this estimator can be further improved by enhancing the sensitivity. Finally, we demonstrate our statements by detailed numerical simulations in a circadian clock model.

II. IMPROVED ESTIMATION OF THE ENERGY DISSIPATION

A. Stochastic Normal Form Theory (SNFT)

We consider a general biochemical system of size \( V \) including \( N \) well-stirred species and \( M \) reactions as \( (R_1, \ldots, R_M) \). Generally, the reaction \( R_\rho \) can be written as:

\[
X \rightarrow X + v_\rho
\]

where \( X = (X_1, X_2, \ldots, X_N) \) with \( X_j \) the number of species \( j \), and \( v_\rho = (v_\rho^1, v_\rho^2, \ldots, v_\rho^N) \) with \( v_\rho^j \) the stoichiometric change of species \( j \) in \( R_\rho \). In a mesoscopic system wherein intrinsic noise cannot be neglected, with the assumption of existence of a “macro-infinitesimal” time scale \( \varepsilon \), the system’s dynamics can be described by the chemical Langevin equations (CLEs) as

\[
\dot{x}_j = \sum_{\rho=1}^{M} v_\rho^j w_\rho(x) + \frac{1}{\sqrt{V}} \sum_{\rho=1}^{M} v_\rho^j \sqrt{w_\rho(x)} \xi_\rho(t), \quad j = 1, \ldots, N.
\]

where \( x = (x_1, \ldots, x_N)^T = X/V \) denotes the concentration vector, \( w_\rho(x) \) is the reaction rate of \( \rho \) as a function of the concentrations \( x \), and \( \xi(t) = (\xi_1, \ldots, \xi_M)^T \) is a vector of independent Gaussian white noises with zero mean and correlations \( \langle \xi_\rho(t) \xi_{\rho'}(s) \rangle = \delta_{\rho \rho'} \delta(t-s) \).

In the thermodynamic limit with \( V \rightarrow \infty \), the noise term disappears and the dynamics is described by the deterministic equation

\[
\dot{x}_j = F_j(x) = \sum_{\rho=1}^{M} v_\rho^j w_\rho(x)
\]

Generally, to the occurrence of biochemical oscillation, we assume that the system undergoes a supercritical Hopf bifurcation (HB) with the change of a certain control parameter \( \mu \). Eq. (3) has a unique stable point \( x_* \) with \( F(x_*) \equiv 0 \), which loses stability at the HB point \( \mu = \mu_c \), in the way that the Jacobian matrix \( J \) with components \( J_{ij} = \langle \partial f_i/\partial x_j \rangle \big|_{x=x_*} \) has a pair of conjugate eigenvalues \( \lambda_{\pm} = \alpha(\mu) \pm i\omega \) with \( \alpha(\mu_c) = 0 \) (henceforth we uses \( \alpha = \alpha(\mu) \) to represent the control parameter). In the so-called supercritical region \( \alpha > 0 \) (\( \mu > \mu_c \)), the deterministic system shows a stable oscillation with frequency given by \( \omega \) and amplitude growing from zero. In the subcritical region with \( \alpha < 0 \) (\( \mu < \mu_c \)), no deterministic oscillation can be observed. In the case where the system size is not large such that the internal noise term in Eq. (2) can not be ignored, such as for intracellular biochemical oscillation systems considered here, an interesting phenomenon known as noise induced oscillations (NIOs) has been observed even in the subcritical region where \( \alpha < 0 \), demonstrating the constructive role of internal noise in mesoscopic chemical oscillation systems. In addition, an optimal system size exists where the NIO shows best performance, known as internal noise coherence resonance (INCR).

In our previous works, we have developed a stochastic normal form theory (SNFT) to successfully elucidate the mechanism underlying NIO and INCR. When the system locates near the HB, the motion of the oscillatory mode is much slower than the other \( N-2 \) stable modes due to time-scale separation. Hence, the system’s dynamics will be dominated by the oscillatory motion on a 2D center manifold. According to SNFT, the stochastic dynamics governing the evolution of the oscillation amplitude \( r \) and the amplitude growing from zero. In the deterministic limit (\( \varepsilon \rightarrow \infty \)) and phase angle \( \theta \) can be described by (see Appendix A for details)

\[
\dot{r} = \alpha r + C_r r^3 + \frac{\varepsilon^2}{2Vr} + \frac{\varepsilon}{\sqrt{V}} \eta_r(t),
\]

\[
\dot{\theta} = \omega + C_\theta r^2 + \frac{\varepsilon}{r \sqrt{V}} \eta_\theta(t)
\]

wherein \( C_r < 0 \) and \( C_\theta > 0 \) are system-dependent constants determined by the nonlinear terms of \( F(x) \) at the stable point, \( \eta_r \) and \( \eta_\theta \) are independent Gaussian white noises with zero mean and unit variance, \( \varepsilon \) denotes an effective noise intensity determined by the details of \( F(x) \). According to Eqs. (4) and (5), the steady-state (SS) distribution of \( r \) reads

\[
p_{ss}(r) = N_r \exp \left[ \frac{-V}{4\varepsilon^2} (2\alpha r^2 + C_r r^4) + \ln r \right]
\]

and \( \theta \) is uniformly distributed with \([0, 2\pi]\). Therefore, the system exhibits a stochastic oscillation with most-probable amplitude given by

\[
r_m = \left( -\sqrt{\alpha^2 - 2C_r \varepsilon^2 / V} + \alpha \right) / 2C_r
\]

satisfying \( \partial p_{ss}(r)/\partial r |_{r=r_m} = 0 \).

Clearly, in the deterministic limit (\( V \rightarrow \infty \)), \( r_m = \sqrt{-\alpha/C_r} \) corresponding to a stable limit cycle and frequency \( \omega_s = \omega + C_i r_m^2 = \omega + \alpha |C_r/C_r| \), which only exists for \( \alpha > 0 \) in the supercritical region. If the system size is finite, however, the internal term \( 2C_r \varepsilon^2 / V \) in
the square-root will take effect and \( r_m \) is not zero even for \( \alpha < 0 \) (subcritical region), corresponding to the occurrence of NIO. In the case \( |\alpha| \gg 2C_r \varepsilon^2/V \), one has for NIO \( r_m \simeq \varepsilon/\sqrt{-2aV} \) which scales as \( V^{-1/2} \), and the frequency is approximately \( \omega_s \simeq \omega + C_1 \varepsilon^2/(2|\alpha|V) \). Therefore,

\[
\omega_s = \begin{cases} 
\omega + \alpha |C_1/C_r| & (\alpha > 0) \\
\omega + C_1 \varepsilon^2/(2|\alpha|V) & (\alpha < 0)
\end{cases}
\] (8)

B. Transport Efficiency and Phase Sensitivity

The purpose of the present work is to figure out a way to improve the estimation of energy dissipation (or entropy production) related to the stochastic oscillations. As mentioned in the introduction, one usually uses the thermodynamic uncertain relation (TUR) as an inference of the real energy dissipation via \( \Delta W \geq \Delta W_{\text{TUR}} = 2k_B T \langle R^2 \rangle / \langle \text{Var}(R) \rangle \) where \( R \) is some well-defined current variable, and \( \text{Var}(R) = \langle R^2 \rangle - \langle R \rangle^2 \) denotes the variance of \( R \). Correspondingly, the transport efficiency for \( R \) reads \( \eta(R) = \Delta W_{\text{TUR}}/\Delta W = 2k_B T \langle R^2 \rangle / \langle \text{Var}(R) \rangle \leq 1 \). For the oscillatory dynamics considered here, it is convenient to choose \( R \) as the change of phase angle within a given time interval \((0, \tau)\), i.e., \( R(\tau) \rightarrow \theta(\tau) = \int_0^\tau \dot{\theta}(t) \, dt \). By simply rewriting and setting \( k_B T = 1 \) from now on, the transport efficiency can be expressed as \( \eta(\theta) = 2k_B T \langle \theta^2 \rangle / \langle \text{Var}(\theta) \Delta W \rangle = v_{\beta}^2/D_0 \omega_s \) where \( v_{\beta} = \lim_{\tau \to \infty} \langle \theta \rangle/t \) is the phase speed, \( D_0 = \lim_{\tau \to \infty} \langle (\theta^2 - \langle \theta \rangle^2)/2t \rangle \) is the phase diffusion constant, and \( \omega_s = \lim_{\tau \to \infty} \Delta W/\tau \) is the dissipation rate.

By using the SNFT, the mean and variance of the phase \( \theta(\tau) = \int_0^\tau \dot{\theta}(t) \, dt \) can be calculated as \( \langle \theta(t) \rangle \simeq \omega_s t \) and \( \langle (\theta(t) - \langle \theta(t) \rangle)^2 \rangle \simeq \varepsilon^2 t/V r_m^2 \). Hence the velocity \( v_{\beta} \) is simply \( \omega_s \) and the phase diffusion constant is given by \( D_0 \simeq \varepsilon^2/2V r_m^2 \). It is also possible to obtain the theoretical expression for \( W \) using the SNFT, which is after some manipulation given by \( W \simeq (L_{12} - L_{21}) V \omega_s^2 r_m^2 \), where \( L_{12} \) and \( L_{21} \) are model-dependent parameters determined by the linear transformation of \( F(x) \) at the fixed point \( x_s \) (see Appendix A for more details), and being independent of the control parameter \( \alpha \) and system size. Consequently, the efficiency reads

\[
\eta_s \simeq \frac{\omega_s}{\varepsilon^2 (L_{12} - L_{21})} = \frac{\omega + \alpha |C_1/C_r|}{\varepsilon^2 (L_{12} - L_{21})}
\] (9)

and the TUR asserts that \( \eta_s \leq 1 \). Although the expression of \( \eta_s \), Eq. (9), gives no hint that the TUR holds, we indeed demonstrate numerically in our previous work that for the well-known Brusselator model, \( \eta_s \sim 0.4 \) which is far below the upper bound 1.0 in the vicinity of the Hopf bifurcation.

For oscillation systems, another important quantity is the phase sensitivity quantifying the ability of the biochemical circuits to respond to external signals. Instead of dealing with the entire system, we employ the phase reduction method to reduce the whole state space to a single phase variable \( \phi \) characterizing the timing of oscillation, and the phase sensitivity \( \kappa \) can be obtained by comparing the phase shift after perturbations. The phase \( \phi \) in Eq. (6) is defined on the limit cycle of the unperturbed oscillations, and the definition can be expanded into the entire \( x \)-space by introducing the isochron (the two states are assigned the same phase if trajectories originated from two states converge onto the limit cycle at the same time). Following this definition, the deterministic phase evolution equation can be expressed as \( \dot{\Phi} = \Omega + \delta k |\nabla \phi \cdot \beta(t)| \). For a weak external signal \( \beta(t) \), the deterministic term reads \( \dot{\Phi}_\alpha(x) = F(x) + k \beta(t) \) with \( k \) the control parameter, and the phase shift incurred by a parametric perturbation \( k \rightarrow k + \delta k \) can be obtained as \( \dot{\Phi} = \Omega + k |\nabla \phi \cdot \dot{\beta}(t)| \). Then, the global phase sensitivity parameter \( \kappa \) can be defined as the normalized value of signal-independent factor \( \nabla \phi \cdot \beta(t) \) along the limit cycle with \( r = r_m \). For oscillations near the Hopf bifurcation with \( \sqrt{-2C_r \varepsilon^2/V} < |\alpha| \ll |C_r/C_i| \), the phase sensitivity \( \kappa \) can be approximately calculated as \( \kappa \approx \partial \omega_s/\partial \alpha \), i.e. (see Eq. (8))

\[
\kappa = \frac{\langle C_1 \rangle \varepsilon^2}{|C_r|} \quad \alpha < 0
\]

\[
\kappa = \frac{\alpha}{|C_r|} \quad \alpha > 0
\] (10)

C. Pearson Correlation Coefficient

Here, we investigate the formulation of a scheme for the characterization of correlations between the oscillatory amplitude and phase based on a statistical measure known as the Pearson correlation coefficient, which has been commonly used in the context of quantum entanglement and filtering theory. The Pearson correlation coefficient for any two random variables \( R \) and \( Q \) is defined as \( \chi(R, Q) = \text{Cov}(R, Q)/\sqrt{\text{Var}(R) \text{Var}(Q)} \) with \( \text{Cov}(R, Q) = \langle R \rangle \langle Q \rangle - \langle R \rangle \langle Q \rangle \) the covariance. The values of Pearson correlation coefficient lie between \(-1 \) and \(1 \).

Then, we start to calculate the Pearson correlation coefficient \( \chi_n^2 = \chi^2(r^n, \theta) \) between the two observables \( R(\tau) = \theta(\tau) = \int_0^\tau \dot{\theta}(t) \, dt \) and \( Q_{r,n} = \int_0^\tau r^n(t) \, dt \), where the exponent \( n \) quantifies the order of correlation between the oscillatory amplitude and phase. By using the SNFE, we find that the change rate of the covariance, \( \lim_{\tau \to \infty} \frac{1}{\tau} \text{Cov}(r^n, \theta; \tau) = \left[ \langle r^n \dot{\theta} \rangle_{ss} - \langle \theta \rangle_{ss} \langle r^n \rangle_{ss} \right] \), between oscillatory phase and amplitude is related to the higher-order moment of the amplitude as
\[
\lim_{\tau \to \infty} \frac{1}{\tau} \text{Cov}(r^n, \theta; \tau) = \frac{1}{2\pi} \int_0^{2\pi} d\theta \int_0^\infty dr^n \hat{P}_{ss}(r) \\
- (\omega + C_i \langle r^2 \rangle_{ss}) \langle r^n \rangle_{ss} \\
\approx C_i \left( \langle r^{n+2} \rangle_{ss} - \langle r^n \rangle_{ss} \langle r^2 \rangle_{ss} \right).
\]

Particularly, we choose \( n = 2 \) to calculate the covariance between oscillatory phase and amplitude. According to Eq.(6), the change rate of covariance is (see Appendix B for detailed derivation)

\[
\lim_{t \to \infty} \frac{1}{t} \text{Cov}(r^2, \theta; \tau) = \begin{cases} 
- \frac{2C_i C_r r^4 \epsilon^2}{\alpha^2 V^2} & \alpha > 0 \\
0 & \alpha < 0.
\end{cases}
\]

Here, we need to emphasize that our theoretical expression for normal oscillations (\( \alpha > 0 \)) holds in the region near the Hopf bifurcation where \( \sqrt{-2C_r^2 C_i^2 V} < \alpha \ll |C_r/C_i| \). It can be found that the phase and amplitude are highly decoupled with the covariance \( \text{Cov}(r^2, \theta; \tau) \approx 0 \) in the subcritical region (\( \alpha < 0 \)). The highly decoupling feature is also the reason why the sensitivity for noise-induced oscillations (\( \kappa \sim V^\delta, \delta = -1 \)) is typically smaller than the normal oscillations (\( \kappa \sim V^\delta, \delta = 0 \)), i.e., the oscillatory amplitude’s adaptation to phase shift incurred by perturbation is much slower in the subcritical region.

Then, we start to calculate the Pearson correlation coefficient \( \chi_2^2 = \chi^2(r^2, \theta) \), which reads as

\[
\chi_2^2 = \frac{\{\text{Cov}(r^2, \theta)^2\}}{\text{Var}(r^2) \text{Var}(\theta)} \\
\approx \frac{C^2}{\text{Var}(r^4_{ss} - \langle r^2 \rangle_{ss}^2)}.
\]

From Eqs. (12) and (13), the Pearson correlation coefficient \( \chi_2^2 \) for normal oscillations (\( \alpha > 0 \)) can be obtained as

\[
\chi_2^2 = \begin{cases} 
2\alpha \left( \frac{\alpha}{C_r} \right)^2 & \alpha > 0 \\
0 & \alpha < 0
\end{cases}.
\]

which is independent of the system size \( V \). The Pearson correlation coefficient \( \chi_2^2 = \chi^2(r^n, \theta) \) for \( n \neq 2 \) can be calculated numerically.

**D. Improved TUR**

Recently, it was proposed by Dechant and Sasa that increasing the number of observables will achieve tighter bounds than the conventional TUR. To be precise, they defined a generalized transport efficiency as

\[
\eta(R, Q) = \eta(R) + \chi^2(R, Q), \quad \text{where } Q = \int_0^\infty dq(x, t) \text{ is the time-integral of a state-dependent (non-current) observable } q(x, t), \text{ and } \chi(R, Q) \text{ is the Pearson correlation coefficient between } Q \text{ and the current observable } R. \text{ Interestingly, they found that the generalized transport efficiency, } \eta(R, Q), \text{ is also smaller than 1 just like the conventional one, } \eta(R). \text{ Therefore, the generalized transport efficiency } \eta(R, Q) \geq \eta(R) \text{ provides an improved estimator for energy dissipation than the conventional one,}
\]

\[
\Delta W_{\text{TUR}} = \frac{2k_BT \langle \dot{R} \rangle^2}{\text{Var}(R)} \\
\leq \Delta W_1 = \frac{2k_BT \langle \dot{R} \rangle^2}{\text{Var}(R)[1 - \chi^2(R, Q)]} \\
\leq \Delta W.
\]

It can be found that how much the estimation can be improved is directly related to the value of Pearson correlation coefficient between the chosen observables, and the two observables we chose above, the oscillatory amplitude and oscillatory phase, meet the conditions of use.

Based on Eq.(14) and (15), the explicit expression for the generalized transport efficiency can be obtained as

\[
\eta(\theta) + 2\alpha \kappa^2 = \frac{v_B^2}{D_\theta W} + 2\alpha \kappa^2 \leq 1,
\]

which is the main result of our paper, showing that both phase accuracy \( D_\theta^{-1} \) and phase sensitivity \( \kappa \) can be improved simultaneously only by increasing the energy dissipation rate \( W \) without sacrificing the phase speed \( v_B \).

More importantly, such trade-off relation provides an improved estimator for the dissipation rate,

\[
\Delta W_{1,2} = \frac{2k_BT \langle \dot{R} \rangle^2}{\text{Var}(\dot{R})(1 - \chi_2^2)},
\]

than the conventional TUR, and the improvement of it is

\[
\Delta W_{1,2} / \Delta W_{\text{TUR}} = \frac{\dot{W}_{1,2}}{W_{\text{TUR}}} = \frac{1}{1 - 2\alpha \kappa^2} > 1
\]

with the TUR estimator \( W_{\text{TUR}} = \lim_{\tau \to \infty} \Delta W_{\text{TUR}} / \tau \) and the improved estimator \( \dot{W}_{1,2} = \lim_{\tau \to \infty} \Delta W_{1,2} / \tau \).

Several conclusions can be obtained as follows. Firstly, according to the trade-off relation Eq.(16), it can be found that the precision of dissipation inference will be further improved by enhancing the phase sensitivity of biochemical oscillations. In actual experimental design, a feasible strategy to achieve a higher phase sensitivity of the networks is to enhance the phase-amplitude coupling strength \( C_i \) by maximizing the net flux of the phase-advancing pathway relative to that of the phase-retreating pathway. Thus, we believe that our analyses
provide realizable guidelines for improving the precision of dissipation estimation for biochemical oscillations.

Secondly, we find that the generalized transport efficiency \( \eta(x^2, \theta) = \eta(\theta) + 2a(C_i/C_r)^2 \) is independent of the system size \( V \). Since the magnitude of the internal noise is proportional to \( V^{-1/2} \), it can be revealed that our improved scheme is not negatively affected by the internal noise in the system.

Thirdly, since the phase and amplitude are highly decoupled in subcritical region \( (\alpha < 0) \), such scheme cannot be applied to improve the estimation of the energy dissipation for noise-induced oscillations.

In the following, we further highlight our motivation. As stated above, it has been proposed that the TUR provides a powerful tool to estimate energy dissipation. Recently, this bound has been optimized to provide a more accurate estimation\(^{38,39,41,72}\) and even realize equality\(^{39,41,63,72}\), which is of great significance. Particularly, Manikandan et al. have found that the TUR estimates entropy production exactly in the very short time limit, if the observed current is optimally chosen, which provides a powerful strategy for the dissipation inference\(^{39}\). Some optimization procedure needs to be utilized to obtain the optimal current, where the similar manipulations have been used to get the hyperaccurate current\(^{38,63,72}\). Other techniques such as the gradient ascent in machine learning have also been applied to construct the short-time limit TUR estimator by Otsubu et al\(^{39,41}\) and Vu et al\(^{39}\). However, the related procedure may be difficult to follow than measuring the dissipation itself\(^{39}\). To be specific, in Ref\(^{39}\), Manikandan et al. tested their inference scheme by numerically calculating the optimal current rely on linear combinations of the basis. In Ref\(^{41}\), Otsubu et al. demonstrated that their learning protocol performs well by numerical experiments in nonlinear Langevin dynamics. In addition to the TUR-based approach, Frishman and Ronceray proposed a principled method, stochastic force inference, to evaluate the corresponding entropy production based on approximating force fields and diffusion coefficient\(^{72}\). To sum up, all the dissipation estimations mentioned above require some specific preprocessing, thus increasing the statistical effort. As a comparison, only the oscillatory phase and amplitude need to be tracked by using the scheme proposed by us, which is readily accessible, showing its benefit for experimentally application. Also, the results of our manuscript have demonstrated that the estimation of energy dissipation is considerably improved by considering the correlations between observables, no matter how far from equilibrium the system is. In addition, since biochemical functional benefits from operating at the edge of instability, studying the oscillatory behavior near Hopf bifurcation points can bring general inspiration\(^{72}\). Therefore, we believe that our formulations provide an efficient estimator in terms of experimentally accessible quantities.

![Graph](image_url)

**FIG. 1.** (a) Pearson correlations \( \chi^2 \) as a function of the control parameter \( \alpha \) for the circadian clock model. The value of \( \chi^2 \) changes sharply near the critical point \( \alpha = 0 \), due to the bifurcation phenomenon. Line: theory. Dots: simulation. (b) The Pearson correlations \( \chi^2 \) as a function of the phase sensitivity \( \kappa = |C_i/C_r| \) (green and pink dots). The slopes \( \nu \) for \( \chi^2 \propto \kappa^\nu \) have been calculated from fitting the numerical data. (c) The slope \( \nu \) and goodness \( R^2 \) for the linear fit between \( \ln(\chi^2) \) and \( \ln \kappa \) as a function of the control parameter \( \alpha \). The gray circle and blue dotted line represent the range in which the scaling behavior \( \chi^2 \propto \kappa^\nu \) holds. The establishment of the scaling behavior reveals how far from the Hopf bifurcation the trade-off relation between dissipation and phase sensitivity satisfies. The system size \( V = 1.6 \times 10^5 \).

**III. SIMULATIONS**

In this section, we illustrate the formal analytical results of the above section within numerical simulations of the circadian clock model\(^{52}\), describing how living systems keep an internal sense of time. The circadian clock model considered here incorporates the transcription of the gene (G) involved in the biochemical clock and transport of the mRNA (R) into the cytosol where it is translated into clock proteins (P_C) and degraded. The protein can be degraded or transported into the nucleus (P_N) where it exerts a negative regulation on the expression of its gene. For the parameters we examine (see Appendix C for details), the Hopf bifurcation point locates at \( v_s \simeq 0.25725 \) with \( v_s \) the transcription rate of mRNA. In addition, parameter values used in the stochastic normal form theory can be calculated from simulations as \( C_r \simeq -0.3474, C_i \simeq 0.5722 \) and \( \varepsilon^2 \simeq 0.3556 \). By adjusting the transition rates, the values of \( C_i \) and \( C_r \) will change, and can also be obtained.

By using the Euler methods, we numerically calculate Eqs.\(^{[4]}\) and \([5]\) with a time step of 0.002. Generally, after a long time \( t_{ss} = 10^5 \) to ensure the system reaches the steady state, \( 2 \times 10^5 \) trajectories with the length
On the other hand, the exact dissipation rate $\dot{W}$ as a function of the control parameter $\alpha$ for the circadian clock model. The value range $\alpha = 0.02$ (Numerical) $\alpha = 0.02$ (Theoretical) $\alpha = 0.04$ (Numerical) $\alpha = 0.04$ (Theoretical) $\alpha > 0$. It can be observed that the improved estimator $W_{I,1.2}$ outperforms the TUR estimator $W_{TUR}$. The parameters of circadian clock model can be found in Appendix C. (b) The improvement of the tighter bound $W_{I,1.2}/W_{TUR}$ as a function of the phase sensitivity $\kappa = |C_i/C_r|$. The numerical results (dots) verify our analytical expressions (lines). The system size $V = 1.6 \times 10^5$. $t_0 = 1$ are used to get the Pearson correlation coefficient, $\chi^2_{r,n} = \chi^2(r^n, \theta) = [\text{Cov}(r^n, \theta)]^2/\text{Var}(r^n)\text{Var}(\theta)$ for $Q_{r,n} = \int_0^T r^n(t) dt$ with $n > 0$ the power, which yields the corresponding improved estimator as

$$\Delta W_{I,n} = \frac{2k_B T (\theta)^2}{\text{Var}(\theta)(1 - \chi^2_{r,n})}.$$

Then, the TUR estimator $\dot{W}_{TUR} = \lim_{\tau \to \infty} \Delta W_{TUR}/\tau$ and the improved estimator $\dot{W}_{I,n} = \lim_{\tau \to \infty} \Delta W_{I,n}/\tau$ can be obtained numerically. The corresponding improvement reads as

$$\frac{\dot{W}_{I,n}}{\dot{W}_{TUR}} = \frac{1}{1 - \chi^2(r^n, \theta)} > 1.$$

On the other hand, the exact dissipation rate $\dot{W}$ is obtained from the simulation data of Eq. (2) (see Appendix A for details). In Fig. 1(a), the dependence of the Pearson correlations $\chi^2_{r,n}$ ($n = 1, 2, 3$) on the control parameter $\alpha$ are depicted for the circadian clock model. The value range of the control parameter $\alpha$ ensures the establishment of the SNF. For noise-induced oscillations in the subcritical region ($\alpha < 0$), the Pearson correlation coefficients are almost zero, and they increase significantly after the control parameter crossing the critical point $\alpha = 0$ to reach the supercritical region for normal oscillations ($\alpha > 0$). Those results verify our prediction that the correlation between oscillatory phase and amplitude is highly decoupled and not sufficient to improve the estimation of energy dissipation for noise-induced oscillations. In addition, we notice that numerical results (dots) of the Pearson correlations are in good agreement with our theoretical predictions, Eq. (14) (line). Further, in Fig. 1(b), we plot the Pearson correlations $\chi^2_{r,n}$ as a function of the phase sensitivity $\kappa = |C_i/C_r|$. The scaling behaviors are consistent with our analytical result $\chi^2_{r,n} \propto \kappa^2$, further confirming our theory. It can be found that the slope $\nu$ for $\chi^2_{r,n} \propto \kappa^2$ is closer to the analytical prediction $\nu = 2$ for smaller $\alpha$, showing that our theory is more accurate for near Hopf bifurcation region. To further explore the extent to which our formulation holds generally away from a Hopf Bifurcation, we plot the slope $\nu$ and goodness $R^2$ for the linear fit between $\ln(\chi^2_{r,n})$ and $\ln \kappa$ as a function of the control parameter $\alpha$ in Fig. 1(c). The gray circle and blue dotted line represent the range in which the scaling behavior $\chi^2_{r,n} \propto \kappa^2$ holds ($R^2 \geq 0.97$). The establishment of the scaling behavior reveals how far from the Hopf bifurcation the trade-off relation between dissipation and phase sensitivity satisfies. For the circadian clock model, our formulation holds for $\alpha \leq 0.055$.

In Fig. 2(a), we show both the TUR estimator $\dot{W}_{TUR}$ and the improved estimator $\dot{W}_I$ for the circadian clock model to demonstrate how much the estimation of energy dissipation can be improved. The conventional TUR, while a commonly used dissipation estimator, only provides a trivial bound with the 0.6 efficiency, and the improved estimator $\dot{W}_I$ is much closer to the exact value $\dot{W}$. On the other hand, it can be found that $\dot{W} \geq \dot{W}_I$, which verifies the efficiency-sensitivity trade-off relation we proposed [Eq. (16)]. In Fig. 2(b), we show the relationship between the improvement of the tighter bound $\dot{W}_I/\dot{W}_{TUR}$ and phase sensitivity $\kappa = |C_i/C_r|$. The theoretical predictions $\dot{W}_I/\dot{W}_{TUR} = 1 - 2\alpha \text{Cov}(r^n, \theta)$ are in good agreement with the numerical results, which demonstrates that the estimation of the dissipation can be improved by enhancing the phase sensitivity of biochemical oscillations.

In Fig. 3(a), we have shown that the improvements of the dissipation estimation $\dot{W}_{I,n}/\dot{W}_{TUR}$ change little with the system size $V$ in normal oscillations ($\alpha > 0$). Moreover, we numerically test whether the power of amplitude observables $n$ affect the improvement $\dot{W}_{I,n}/\dot{W}_{TUR}$ in details. In Fig. 3(b), it can be observed that values of $\dot{W}_{I,n}/\dot{W}_{TUR}$ change little for different choices of the power of the amplitude observable $Q_{r,n}(\tau) = \int_0^T r^n(t) dt$. To further demonstrate the broad application of the proposed improved estimation, we have also applied them to another well-known biochemical oscillation system, the Brusselator model. Other details of the model and pa-
FIG. 3. (a) The improvements of the dissipation estimation $W_{1}/W_{TUR}$ ($n = 1, 2, 3$) as a function of the system size $V$ for the circadian clock model in normal oscillation region ($\alpha > 0$). The control parameter $\alpha = 0.05$. (b) The improvements of the dissipation estimation $W_{1}/W_{TUR}$ as a function of the power of the amplitude, $n$, for the circadian clock model. The values are independent of the power. The error bars represent the standard deviation obtained from independent trials. The system size $V = 1.6 \times 10^{5}$.

FIG. 4. (a) Pearson correlations $\chi^2$ as a function of the control parameter $\alpha$ for the Brusselator model. The value of $\chi^2$ changes sharply near the critical point $\alpha = 0$, due to the bifurcation phenomenon. Line: theory. Dots: simulation. (b) Estimations of the dissipation rate as a function of the exact dissipation rate for the Brusselator model. As expected, the conventional TUR estimator only yields a loose bound, and our improved estimator $W_{1}$ is much more accurate.

In this paper, we proposed an improved estimation for the energy dissipation of biochemical oscillations by using the Pearson correlations between oscillatory phase and amplitude, which are easily accessible in experimental observations. Both the analytical and numerical results demonstrate that such scheme can be further improved by enhancing the phase sensitivity of systems. In addition, it has been revealed by us that the validity of our scheme is independent of the system size and the power of oscillatory amplitude.

In our previous work, we have found that the dissipation rate $\dot{W} \sim V^{\gamma}$, with $\gamma = 1$ for supercritical region ($\alpha > 0$), $\gamma = 1/2$ for the critical point ($\alpha = 0$) and $\gamma = 0$ for subcritical region ($\alpha < 0$), showing that biochemical oscillations have a much lower energy dissipation for noise-induced oscillation. Intuitively, one might think that less dissipation will lead to a easier estimation, however, the estimator $\Delta W_{1}$ introduced by us is not applicable for improving the estimation of dissipation due to the highly decoupling of the phase and amplitude, which is deserved for further study.

Biomolecules, especially proteins, can act as tiny and highly functional machines, such as kinesin and ribosome. To probe the operation of these bimolecular machines, it is not enough just to know their structure, one needs to understand how the structure generates specific conformational dynamics. Meanwhile, how much energy the biological machine dissipates to perform certain functions is also a major issue. Particularly, molecular dynamics (MD) simulation is a primary technique for studying bimolecular machines, producing information about the conformational dynamics with spatial and temporal resolutions. For the molecular systems, the key ingredients of the slow kinetics can be obtained by using SNFT based on stochastic averaging or variational approach with MD simulations. (Perhaps some short time dynamics with energy input). Then, the findings of this manuscript that correlations between observables can yield improved estimation could be applied in these systems based on the accurate capture of the dominant motion. However, it is still important to note that fast processes may also have finite correction to the thermodynamic quantities. As stochastic normal form equations can be extended to other oscillatory systems related to other types of bifurcations, such as relaxation oscillations, we believe that our scheme may have a wider range of applications.

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AUTHOR DECLARATIONS

The authors have no conflicts to disclose.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Appendix A: The derivation of normal form and calculation of transport efficiency

In this section, we introduce the derivation of stochastic normal form equation and the calculation of conventional transport efficiency for self-consistency.

1. Stochastic normal form theory

Firstly, we assume that the deterministic form of the chemical Langevin equation, Eq. (2), has a unique stable point \( x_s \) with \( \mathbf{F}(x_s) \equiv 0 \), which loses stability at the supercritical HB \( \mu = \mu_c \), where \( \mu \) is the control parameter. Based on the Hopf theorem, the Jacobian matrix \( \mathbf{J} \), whose components \( J_{ij} = (\partial f_i/\partial x_j)|_{x=x_s} \), has a pair of conjugate eigenvalues \( \lambda_\pm = \alpha(\mu) \pm i\omega \) with \( \alpha(\mu_c) = 0 \). The other \( N-2 \) eigenvalues of \( \mathbf{J} \), \( -\lambda_{j>2} \), all have negative real parts with absolute values considerably larger than 0. Performing the variable transformation \( \mathbf{u} = \mathbf{T}^{-1}(x-x_s) \), the linear part of Eq. (2) can be transformed to Jordan form as \( \mathbf{u} = \mathbf{A} \mathbf{u} + \mathbf{O}(\mathbf{u}^2) + \frac{1}{\sqrt{\nu}} \mathbf{\eta}(t) \), where \( \mathbf{A} = \begin{pmatrix} \alpha & -\omega \\ \omega & \alpha \end{pmatrix} \oplus \text{diag}(-\lambda_1, \ldots, -\lambda_N) \) and \( \mathbf{\eta} = \mathbf{T}^{-1} \mathbf{\zeta}(x_s,t) \) with \( \mathbf{\zeta}(x,t) = \sum_p v_p \sqrt{w_p} \mathbf{x}(t) \). The variances of \( \mathbf{\eta} \) are \( \langle \eta_i(t) \eta_j(s) \rangle = 2D_{ij} \delta(t-s) \) with \( \mathbf{D} = \mathbf{T}^{-1} \mathbf{G} \mathbf{T}^{-1} \). The transformation is done as follows. Firstly, we calculate the eigenvector \( \mathbf{u}_+ \) whose eigenvalue \( \lambda_+ = \alpha + i\omega \), and normalize it to ensure the first non-vanishing component is 1. Secondly, we construct a matrix \( \mathbf{T} = (Re \mathbf{u}_+, -Im \mathbf{u}_+, r_3, \ldots, r_n) \) with \( (r_3, \ldots, r_n) \) are any set of real vectors which span the union of the eigenspaces for \( \lambda_3, \ldots, \lambda_n \). Finally, it is allowed to perform the change of variables \( x = x_s + T \mathbf{u} \).

When the system locates near the HB \( (|\alpha| \ll 1) \), the evolution of the oscillatory mode related to \( (u_1, u_2) \) is much slower than the other \( N-2 \) stable modes due to the time-scale separation. Hence, the system’s dynamics will be dominated by the slow motion on a 2D center manifold spanned by the eigenvectors of \( \lambda_+ \). The oscillatory mode are ruled by a normal form equation involving the time evolution of a complex variable \( Z = u_1 + iu_2 \), or a pair of coupled equations for the oscillation amplitude \( r \) and phase \( \theta \) via \( Z = re^{i\theta} \). We follow the standard procedure to get the normal form,

\[
\frac{dZ}{dt} = (\alpha + i\omega) Z + (C_r + iC_i) |Z|^2 Z + \frac{1}{\sqrt{V}} \sum_p (v'_{1p} + iv'_{2p}) \sqrt{w_p} \xi_p,
\]

(A1)

where \( \mathbf{v'}_{j\rho} = (T^{-1} \mathbf{v})_{j\rho} \), i.e.,

\[
\frac{dr}{dt} = (\alpha r + C_r r^3) + \frac{1}{\sqrt{V}} \sum \chi_{rp} \circ \xi_p, \quad \text{(A2)}
\]

\[
\frac{d\theta}{dt} = (\omega + C_i r^2) + \frac{1}{\sqrt{V}} \sum \chi_{\theta p} \circ \xi_p, \quad \text{(A3)}
\]

with

\[
\chi_{rp} = (v'_{1p} \cos \theta + v'_{2p} \sin \theta) \sqrt{w_p}, \quad \text{(A4)}
\]

\[
\chi_{\theta p} = \frac{1}{r} (-v'_{1p} \sin \theta + v'_{2p} \cos \theta) \sqrt{w_p}. \quad \text{(A5)}
\]

By using the “stochastic averaging” method, the following equation can be obtained

\[
\frac{dr}{dt} = \alpha r + C_r r^3 + \frac{K(r)}{V} + \frac{\xi_r}{\sqrt{V}}, \quad \text{(A6)}
\]

and

\[
\frac{d\theta}{dt} = \omega + C_i r^2 + \frac{K(\theta)}{V} + \frac{\xi_{\theta}}{r \sqrt{V}}. \quad \text{(A7)}
\]

Here,

\[
K(r) = \frac{1}{2\pi} \sum_{\rho} \int_0^{2\pi} d\theta \chi_{rp} \partial_r \chi_{\theta p} + \chi_{\theta p} \partial_r \chi_{rp}, \quad \text{(A8)}
\]

\[
K(\theta) = \frac{1}{2\pi} \sum_{\rho} \int_0^{2\pi} d\theta \chi_{rp} \partial_\theta \chi_{\theta p} + \chi_{\theta p} \partial_\theta \chi_{rp}, \quad \text{(A9)}
\]

which is related to the coupling effects between amplitude and phase. \( \varepsilon_r^2 = \frac{1}{2\pi} \sum_{\rho} \int_0^{2\pi} d\theta \chi_{rp}^2 \) and \( \varepsilon_\theta^2 = \frac{1}{2\pi} \sum_{\rho} \int_0^{2\pi} d\theta \chi_{\theta p}^2 \) are the averaged noise intensities. The main purpose of this method is to approximate the system’s dynamics as the Markovian stochastic process when the system reaches the steady state. Further, by expanding the reaction rates, \( w_p = \sum_{i+j=\rho} w^{ij}_p \left(r \cos \theta\right)^i \left(r \sin \theta\right)^j \). \( K(\theta) \) is zero. Thus, the averaged noise intensities read as

\[
\varepsilon_r^2 = \varepsilon_\theta^2 = \frac{1}{2} \sum_{\rho} \left[(v'_{1p})^2 + (v'_{2p})^2\right] w_p^{00}. \quad \text{(A10)}
\]
near the Hopf bifurcation point, i.e., the stochastic normal form equation can be obtained as

$$
\dot{r} = \alpha r + C_r r^3 + \frac{\varepsilon^2}{2V_r} + \frac{\varepsilon}{\sqrt{V}} \eta_r(t),
$$

(A11)

$$
\dot{\theta} = \omega + C_{\theta} \theta^2 + \frac{\varepsilon}{r \sqrt{V}} \eta_\theta(t),
$$

(A12)

where the \(i + j \geq 2\) terms are neglected.

2. Steady state dissipation rate and conventional transport efficiency

In order to obtain the transport efficiency, we start to calculate the steady state dissipation rate \(W\). Based on the framework of stochastic thermodynamics \cite{57,58}, the entropy balance equation reads as \(s_\text{tot}(\tau) = \dot{s}_m(\tau) + \dot{s}(\tau)\), where \(s_\text{tot}(\tau)\) is the total entropy production, \(s(\tau)\) is the Shannon entropy and \(s_m(\tau)\) is the entropy flux. As \(s(\tau) = -\ln p(\mathbf{x}, \tau)\), the change rate of the Shannon entropy is

$$
\dot{s}(\tau) = -\partial_r p(\mathbf{x}, \tau) + \frac{2V}{p(\mathbf{x}, \tau)} \sum_{i,j} \Gamma_{ij} j_i |_{\mathbf{x}(\tau)} \dot{x}_i - V \sum_i H_i \dot{x}_i,
$$

(A13)

where

$$
H_j = 2 \sum_k f_{jk} f^*_k \left( \Gamma = G^{-1} \right) \text{ with } f_k = f_k - 1/(2V) \sum_j (\partial G_{kj}) / (\partial x_j).
$$

Then, the entropy production rate and entropy flux rate can be identified as

$$
\dot{s}_\text{tot}(\tau) = -\partial_r p(\mathbf{x}, \tau) + \frac{2V}{p(\mathbf{x}, \tau)} \sum_{i,j} \Gamma_{ij} j_i |_{\mathbf{x}(\tau)} \dot{x}_i
$$

and

$$
\dot{s}_m(\tau) = V \sum_i H_i \dot{x}_i.
$$

As \(s(\tau) = \lim_{t \to \infty} (\Delta s) / t\) vanishes in the steady state, the averaged entropy production rate can be obtained as

$$
\dot{S}_\text{tot} = \lim_{t \to \infty} \langle \dot{s}_m \rangle / t = V \sum \langle H_i \dot{x}_i \rangle
$$

(A14)

with \(\langle \cdot \rangle_{ss}\) denotes the average over time and steady state \cite{56}.

By using the variable transform, the theoretical expression of the entropy production rate can be calculated in terms of \(\mathbf{u}\), which reads

$$
\dot{S}_\text{tot} = 2V \langle \left( \bar{f}^T \Gamma^T \mathbf{x} \right) \rangle_{ss}.
$$

By approximating \(\bar{f}(\mathbf{x}) \approx J^T \mathbf{u}\), the entropy production reads

$$
\dot{S}_\text{tot} = 2V \langle \left( \mathbf{u}^T L \mathbf{u} \right) \rangle_{ss} = 2V \sum_{i,j} L_{ij} h_{ij}
$$

(A15)

with \(h_{ij} = \langle \langle u_i \dot{u}_j \rangle \rangle_{ss}\). \(L = T^T J^T \Gamma^T T\) are model-dependent parameters taken at the stable point \(\mathbf{x}_s\). Note that in the steady state, \(\frac{d}{dt} \langle \langle u_i \dot{u}_j \rangle \rangle_{ss} = 0\), thus we have \(h_{ij} = -h_{ji}\). Then, we have that

$$
h_{12} = -h_{21} = \frac{1}{2\pi} \int_0^{2\pi} \int_0^\infty r^2 p_{ss}(r) \theta d \theta \approx \frac{1}{2} \omega_s \langle \mathbf{r}^2 \rangle,
$$

(A16)

where the time average is substituted by averaging over \(\theta\) due to dominant oscillatory mode. \(\omega_s = \omega + C_r r_m^2\) is the effective phase angular velocity. Meanwhile, for \(j > 2\), we have \(h_{13} = \langle \langle r \cos \theta \dot{u}_j \rangle \rangle_{ss} \approx 0\) and \(h_{2j} = \langle \langle r \sin \theta \dot{u}_j \rangle \rangle_{ss} \approx 0\). For \(i, j > 2\), one can obtain that

$$
h_{ij} = \langle \langle u_i \dot{u}_j \rangle \rangle_{ss} = (\lambda_i - \lambda_j) D_{ij} / (\lambda_i + \lambda_j) V.
$$

Therefore, the averaged entropy production rate is

$$
\dot{S}_\text{tot} = V (L_{12} - L_{21}) \omega_s \langle \mathbf{r}^2 \rangle + 2 \sum_{i,j > 2} L_{ij} \frac{\lambda_i - \lambda_j}{\lambda_i + \lambda_j}.
$$

(A17)

Here, \(r_m\) is the most probable value of the amplitude in the steady state with \(\partial_r P_{ss}(r)|_{r=r_m} = 0\). By going through our derivation, the contributions from the remaining other \(N - 2\) stable modes can also be identified as \(S_{fast} = 2 \sum_{i,j > 2} L_{ij} \lambda_i / (\lambda_i + \lambda_j)\), which is absent in the expressions obtained by the conventional steady state formula \cite{55}. Further, the steady state dissipation rate (here we set \(k_B T = 1\))

$$
\dot{W} = k_B T \dot{S}_\text{tot} \approx V (L_{12} - L_{21}) \omega_s r_m^2
$$

(A18)

Now, we start to calculate the transport efficiency \(\eta_\theta\). The mean and variance of the phase \(\theta(\tau) = \int_0^\tau \dot{\theta} dt\) can be calculated as \(\langle \theta(t) \rangle = \omega_s t\) and \(\langle (\theta(t) - \langle \theta(t) \rangle)^2 \rangle = \varepsilon^2 t / V r_m^2\), and the phase diffusion constant is given by

$$
D_\theta = \lim_{t \to \infty} \langle (\theta(t) - \langle \theta(t) \rangle)^2 \rangle / 2t \approx \varepsilon^2 / 2V r_m^2.
$$

The transport efficiency reads as

$$
\eta_\theta = \frac{\varepsilon^2}{D_\theta W} \approx \frac{2\omega_s}{\varepsilon^2 (L_{12} - L_{21})}.
$$

(A19)

In the main text, we use the Eq. (A14) allows us to numerically calculate the exact dissipation rate \(W\) in Fig. 2. Since \(\dot{x}_i\) and \(H_i\) can be obtained from the dynamics generating from Eq. (2), \(\dot{s}_m\) can be calculated numerically. By averaging over trajectories in steady states, \(\dot{S}_\text{tot}\) and \(\dot{W}\) can then be obtained.

Appendix B: Pearson correlation coefficient

In this section, we calculate the Pearson correlation coefficient \(\chi^2(R, Q)\) between the phase \(R(\tau) = \theta(\tau) = \int_0^\tau \dot{\theta} (t) dt\) and the amplitude \(Q(\tau) = \int_0^\tau r^2 (t) dt\). The change rate of the covariance, \(\frac{d}{dt} \text{Cov}(r^2, \theta)\), of these two variables can be calculated as

$$
\frac{d}{dt} \text{Cov}(r^2, \theta) = \frac{1}{2} \left( \text{Cov}(r^2, \theta) \right).
$$
\[ \lim_{\tau \to \infty} \frac{1}{\tau} \text{Cov}(r^n, \theta; \tau) = \frac{1}{2\pi} \int_0^{2\pi} d\theta \int_0^{\infty} dr r^n \hat{\theta} P_{ss}(r) \]
\[ - (\omega + C_i \langle r^2 \rangle_{ss} ) \langle r^n \rangle_{ss} \approx C_i \langle r^{n+2} \rangle_{ss} - \langle r^n \rangle_{ss} \langle r^2 \rangle_{ss}. \]
(B1)

Note that the integrals (averages) we are going to calculate all take the form
\[ I_n = \int_0^{\infty} r^{2n} \exp[\Phi V \varepsilon^2 (\frac{1}{2} r^2 + C_i r^4)] dr \]
\[ = \int_0^{\infty} x^n \exp[\Phi V \varepsilon^2 (\frac{1}{2} x + \frac{C_i}{C_r} x^3)] dx. \]
By setting \( y = \rho(x/A - 1) = \sqrt{\frac{V C_i}{\Phi C_r} (x + \frac{C_i}{C_r})} \) with \( \rho = \frac{\alpha}{2} \sqrt{-C_r \varepsilon^2 / V} \) and \( A = -\alpha/C_r \approx r_s^2 \) (for \( \alpha > 0 \)), we have
\[ I_n = \exp \left( \rho^2 \right) \left( \frac{r_s^2}{\rho} \right)^{n+1} \int_{-\rho}^{\infty} (y + \rho)^n e^{-y^2} dy. \]  
(B2)

For \( \alpha > 0 \), integrals \( \int_0^{\infty} p_n(y) e^{-y^2} dy \) are polynomials of degree \( n \) can be obtained by simple Gaussian integrals \( \int_{-\infty}^{\infty} p_n(y) e^{-y^2} dy \), for \( \alpha = 0 \) integrals read \( \int_0^{\infty} p_n(y) e^{-y^2} dy \) and for \( \alpha < 0 \) integrals are approximately zero. For \( \alpha > 0 \), the covariance reads
\[ C(r^2, \theta) \approx C_i \left[ \frac{r_s^4}{\rho^2} \left( 1 + \frac{1}{2\rho^2} \right) - \left( \frac{r_s^2}{\rho^2} \right)^2 \right] = -\frac{2C_i C_r^2 r_s^4 \varepsilon^2}{\alpha^2 V}. \]
(B3)

We need to emphasize that such equation holds in the region where \( \sqrt{-2C_r \varepsilon^2 / V} < \alpha \ll |C_r/C_r| \) due the above approximation. Thus, for normal oscillation region (\( \alpha > 0 \)), the Pearson correlation coefficient \( \chi^2 (r^2, \theta) \) can be calculated as
\[ \chi^2 (r^2, \theta) = 2\alpha(C_i/C_r)^2 < 1, \]
(B4)
which means that such scheme works well for oscillators with high value of \( |C_i/C_r| \) (independent of the system size).

Generally, for \( Q_{r,t} = \int_0^t r^n(t) dt \) with \( n \) the power of oscillatory amplitude, the change rate of the covariance between oscillatory phase and amplitude is related to the higher-order moment of amplitude as
\[ \lim_{\tau \to \infty} \frac{1}{\tau} \text{Cov}(r^n, \theta; \tau) \]
\[ = \frac{1}{2\pi} \int_0^{2\pi} d\theta \int_0^{\infty} dr r^n \hat{\theta} P_{ss}(r) \]
\[ - (\omega + C_i \langle r^2 \rangle_{ss} ) \langle r^n \rangle_{ss} \approx C_i \langle r^{n+2} \rangle_{ss} - \langle r^n \rangle_{ss} \langle r^2 \rangle_{ss}. \]
(B5)

and the Pearson correlation coefficient \( \chi_n^2 = \chi^2 (r^n, \theta) \) can be calculated as

\[ \chi_n^2 = \frac{(\text{Cov}(r^n, \theta))^2}{\text{Var}(r^n) \text{Var}(\theta)} \]
\[ \approx \frac{C_i^2 (\langle r^{n+2} \rangle_{ss} - \langle r^n \rangle_{ss} \langle r^2 \rangle_{ss})^2}{D_{\theta}(\langle r^{2n} \rangle_{ss} - \langle r^n \rangle_{ss}^2)}. \]
(B6)

Appendix C: Details of the models

1. The circadian clock model

Here, we describe the details of the circadian clock model studied in the main text. The vector \( \mathbf{x} = (x_1, x_2, x_3) \) stands for the concentrations of \( (R, P_C, P_N) \). The transcription rate of mRNA is chosen as the control parameter, represented by \( v_s \). As stated in the main text, the Hopf bifurcation point locates at \( v_s \approx 0.25725 \). The the deterministic reaction equations for the current model reads with \( \mathbf{w} \) the transition rates
\[ \frac{dx_1}{dt} = w_1 - w_2, \]
\[ \frac{dx_2}{dt} = w_3 - w_4 - w_5 + w_6, \]
\[ \frac{dx_3}{dt} = w_5 - w_6. \]

The descriptions of the reaction channels and values of parameters are listed in Table I. Typical trajectories for the concentrations of \( (R, P_C, P_N) \) in this model have been shown in Fig. 5. In Fig. 6 (a), we plot the the transport efficiencies as a function of the control parameter \( \alpha \) for the circadian clock model. It can be observed that the estimator proposed by us yields a significant improvement over the conventional TUR.
TABLE I: Descriptions of the circadian clock model

| Reaction                  | Transition rate | Biochemical function |
|---------------------------|-----------------|----------------------|
| 1. G → R + G              | \( \frac{v_1}{k_1+r^2} \) | Transcription        |
| 2. R → R + P_C            | \( \frac{v_2}{r^2+k^2} \) | R degradation        |
| 3. R + P_C \rightarrow P  | \( \frac{k_3}{k_1} \) | Translation          |
| 4. P_C \rightarrow P_N    | \( \frac{k_4}{k_2} \) | Degradation of P_C   |
| 5. P_N \rightarrow P_C    | \( \frac{k_5}{k_3} \) | Transport of P_C into the nucleus |
| 6. P_N \rightarrow P_C    | \( \frac{k_6}{k_4} \) | Transport of P_N out of the nucleus |

\( k_1 = 2.0 \text{ nM}, n = 4, v_m = 0.3 \text{ nM h}^{-1}, k_m = 0.2 \text{ nM}, k_e = 2.0 \text{ h}^{-1}, v_d = 1.5 \text{ nM h}^{-1}, k_d = 0.1 \text{ nM}, k_1 = k_2 = 0.2 \text{ h}^{-1} \)

2. The Brusselator model

Here, we introduce the Brusselator model, involving two distinct biochemical species \( X, Y \), whose time evolution is governed by the following deterministic kinetic equations:

\[
\frac{dX}{dt} = A - (B + 1)X + X^2Y,
\]

\[
\frac{dY}{dt} = BX - X^2Y.
\]

In the deterministic limit, the system has a stable point \( X_s = A, Y_s = B/A \), which loses stability when the control parameter \( B \) exceeds the Hopf bifurcation point \( B_c = 1 + A^2 \). The normal biochemical oscillation happens for \( B > B_c \). By choosing \( A = 0.3 \), we calculate the parameters in stochastic normal form theory as \( C_1 \approx -2.9028, C_1 \approx 5.2506, \varepsilon^2 = 4, \omega = 1, \) and \( \alpha = (B - 1 - A^2)/2 \). In Fig. 6(b), the the transport efficiencies as a function of the control parameter \( \alpha \) for the Brusselator model have been depicted. As expected, the improved estimator proposed by us is much more accurate than the TUR bound.

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