Design principles for biochemical oscillations with limited energy resources

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As biochemical systems may frequently suffer from limited energy resources so that internal molecular fluctuation has to be utilized to induce random rhythm, it is still a great theoretical challenge to understand the elementary principles for biochemical systems with limited energy resources to maintain phase accuracy and phase sensitivity. Here, we address the issue by deriving the energy-accuracy and the sensitivity-accuracy trade-off relations for a general biochemical model, analytically and numerically. We find that, biochemical systems consume much lower energy cost by noise-induced oscillations to keep almost equal efficiency to maintain precise processes than that by normal oscillations, elucidating clearly the survival mechanism when energy resources are limited. Moreover, an optimal system size is predicted where both the highest sensitivity and accuracy can be reached at the same time, providing a new strategy for the design of biological networks with limited energy sources.

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For a living system to survive and grow, it needs to meet certain regulatory function and sensory adaptation with energy constantly injected and dissipated. In particular, for biochemical oscillations which are crucial in controlling the timing of life processes, such as cell cycle, circadian clocks, glycolysis, both accurate determination of the period and sensitive response to external signals are expected to be ensured\cite{16}. Recently, several experimental findings have implied that there may be some underlying trade-off relations preventing them from being reached simultaneously\cite{9,10}. Understanding such relations is then of great importance to uncover design principles for biochemical oscillations to maintain enhanced phase accuracy of internal period and phase sensitivity to external signals. So far, it has been revealed that, for a biochemical oscillation system with sufficient energy supplies, additional energy exceeding a critical value can be used to enhance the system’s phase accuracy and phase sensitivity\cite{11,14}. However, biochemical oscillation systems in real world may frequently suffer from limited energy resources\cite{15,17}, so that the critical energy to maintain the oscillatory behavior may even lack and internal molecular fluctuation has to be utilized to induce random rhythm. It is then still a great theoretical challenge to understand the elementary principles for biochemical systems with limited energy resources to maintain phase accuracy and phase sensitivity.

Here, we address the issue by studying the trade-off relations for a general biochemical model theoretically, starting from which both normal oscillation for sufficient energy sources and noise-induced oscillations for limited energy supplies can be described well in a unified theoretical framework. By applying the concepts of stochastic thermodynamics as well as phase reduction method, the energy-accuracy and the sensitivity-accuracy trade-off relations are finally derived, which provide general design principles for biochemical oscillations. Application of these principles shows that the biochemical systems can keep almost equal efficiency to maintain precise processes at much lower energy cost by noise-induced oscillations for limited energy resources than that by normal oscillations for sufficient energy supplies. Moreover, an optimal system size is found where both the high sensitivity and high accuracy can be reached at the same time, predicting a new design strategy for biological networks with limited energy sources.

For a general biochemical system of size $V$ including $N$ well-stirred species and $M$ reactions ($R_1, \ldots, R_M$), its dynamics can be described by the well-known chemical Langevin equation (CLE)\cite{18}

$$\dot{x}_j = \sum_{\rho=1}^{M} v^\rho_j w^\rho(x) + \frac{1}{\sqrt{\nu}} \sum_{\rho=1}^{M} v^\rho_j \sqrt{w^\rho(x)} \xi^\rho(t), \quad j = 1, \ldots, N.$$  \hspace{1cm} (1)

where $x = (x_1, \ldots, x_N)^T$ is the concentration vector, $v^\rho_j$ is the stoichiometric coefficient of $x_j$ in reaction $R_\rho$, $w^\rho(x)$ is the transition probability, and $\xi(t)$ is independent Gaussian white noises with zero mean and time correlation $\langle \xi^\rho(t) \xi^\rho(s) \rangle = \delta_{\rho \rho'} \delta(t - s)$. The corresponding chemical Fokker-Planck equation (CFPE)\cite{19} is then $\partial_t p(x, \tau) = -\sum_{i,j} \partial_{x_i} [f_j(x)p(x, \tau)] + (1/2) \sum_{i,j} V \partial_{x_i} \partial_{x_j} [G_{ij}(x)p(x, \tau)]$ where $p(x, \tau)$ is the time-varying probability density function, $G_{ij}(x) = \sum_{\rho=1}^{M} v^\rho_i v^\rho_j w^\rho(x)$, and the drift $f_j(x) = \sum_{\rho=1}^{M} v^\rho_j w^\rho(x)$ is the macroscopic rate under thermodynamic limit $V \gg 1$. If there is a Hopf bifurcation for the systems as some control parameters change, biochemical oscillation will occur. Above the bifurcation, a normal oscillation will be observed, while near but below the bifurcation stochastic oscillation can emerge due to the internal noise. A general theoretical description of the oscillation dynamics including both the normal one and noise-induced oscillation (NIO)\cite{20,21} can be achieved by the stochastic normal form theory we established before\cite{22,23}, i.e.,
the time evolution of oscillation amplitude \( r \) and phase \( \theta \) is

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

\[
\dot{\theta} = \omega + C_{\theta} r^2 + \frac{\varepsilon}{r V} \eta_{\theta}(t), \tag{3}
\]

where \( C_{r} \) and \( C_{\theta} \) are negative constants, \( \varepsilon^2 \) is the averaged noise intensity, \( \eta_r(t) \) and \( \eta_{\theta}(t) \) are the averaged independent Gaussian white noises with unit variances (see details in the supplemental information, SI). Specially, \( \alpha \) can be related to the energy resources \([16]\) which determines the oscillatory behaviors of the systems. For large enough \( V \), normal oscillations with the amplitude \( r_m^2 = -\frac{\varepsilon^2}{\varepsilon^2 + \frac{2}{\omega s^2} V^{-1} + o(V^{-2})} \) can be observed when \( \alpha > 0 \). When \( \alpha < 0 \), the energy resources are not enough to support normal oscillations. However, there is still a nonzero amplitude solution \( r_m^2 = \frac{\varepsilon^2}{2} V^{-1} + o(V^{-2}) \), indicating that the internal noise could be utilized to induce stochastic rhythms to maintain the system’s function\([17, 25]\) in such a situation.

Energy-accuracy trade-off relation describes the constraint that how accurate a biochemical oscillator can be with given energy sources. As the time translation symmetry of the biochemical system is inherently broken, the phase of the oscillation exhibits a diffusive behavior. The coefficient of phase diffusion \( D_\theta \) can be used to measure the accuracy of the oscillators. By Eq. (2) and (3), one can derive that the steady-state probability distribution reads \( p_s(r) = C_0 r \exp \left[ (\alpha r^2 + \frac{1}{2} C_{r} r^4) / (\varepsilon^2 / V) \right] \) with \( C_0 \) a normalization constant. Notice that, \( p_s(r) \) shows a maximum at \( r = r_m \), indicating that there is an attractor of limit cycle and the system will fluctuate around it due to internal noise. Then, one can calculate the mean and variance of \( \theta \), i.e., \( \langle \theta(t) \rangle = (\omega + C_{r} r_m^2) t \equiv \omega_s t \) and \( \langle \theta(t)^2 \rangle - \langle \theta(t) \rangle^2 \approx \varepsilon^2 / (V r_m^2) \), where \( \omega_s = \omega + C_{r} r_m^2 \) is the effective phase angular velocity of the attractor. Thus, the diffusion constant of the phase fluctuation is given by

\[
D_\theta = \frac{\varepsilon^2}{V r_m^2}. \tag{4}
\]

Besides, the explicit expression for energy dissipation in one cycle is \( \Delta W = S_{tot} T_{cyc} \) with \( S_{tot} \) the total entropy production rate and \( T_{cyc} = 2 \pi / \omega_s \) the period of the oscillation. At last, by applying the concepts of stochastic thermodynamics\([26]\), the total entropy production rate is found to be \( S_{tot} = (k_b + k_a V r_m^2) / (2 \pi) \), where \( k_a, k_b \) are system dependent parameters (see Supplemental information for details). Now, we arrive at the first main result of this paper, namely, the energy-accuracy trade-off relation (see SI for details)

\[
D_\theta = \begin{cases} 
\frac{k_a \varepsilon^2}{\omega} \left( \Delta W + \frac{k_b C_{r}}{C_{r} + \omega V} \right)^{-1} + D_\theta^{\alpha < 0} \quad \alpha < 0 \\
\frac{k_a \varepsilon^2}{\omega} \left( \Delta W - \frac{k_b C_{r}}{\omega V} \right)^{-1} + D_\theta^{\alpha > 0} \quad \alpha > 0
\end{cases} \tag{5}
\]

Here, Eq. (5) provides a general design principle to quantitatively describe the balance between energy cost and phase accuracy for not only normal oscillations (\( \alpha > 0 \)) but also NIOs (\( \alpha < 0 \)).

Several conclusions can be obtained. Firstly, Eq. (5) can recover to the reported one for normal oscillations\([11]\)

\[
D_\theta = W_0 / (\Delta W - W_r) \quad \text{with} \quad W_0 = k_a \varepsilon^2 / \omega, \quad W_r = -k_b C_{r} / (C_{r} + \omega V)
\]

and an additional \( D_\theta^{\alpha < 0} \) (for \( \alpha > 0 \), \( D_\theta^{\alpha < 0} = -C_{r} / (\omega V) \); for \( \alpha < 0 \), \( D_\theta^{\alpha < 0} = -2 \alpha C_{r} / (\omega V) \)). Secondly, Eq. (5) shows that phase diffusion can be suppressed by increasing thermodynamic cost \( \Delta W \), while there is always a minimal phase diffusion constant \( D_\theta \) that cannot be completely eliminated even for infinite cost.

Thirdly, as \( D_\theta = \varepsilon^2 / (V r_m^2) \), the scaling law for the energy cost \( \Delta W \) of the system size \( V \) can be derived from Eq. (5) as

\[
\Delta W \sim V^{\nu}, \quad \nu = \begin{cases} 
0 & \alpha < 0 \\
\frac{1}{2} & \alpha = 0 \\
1 & \alpha > 0
\end{cases} \tag{6}
\]

i.e., for normal oscillations, \( \Delta W \) increases linearly as \( V \) increases, while for NIOs \( \Delta W \) is independent on the system size \( V \). Finally, a transport efficiency \( \eta_T \) quantitatively determining the efficiency of consuming energy to maintain precise processes for biochemical networks can be derived from the energy-accuracy trade-off relation Eq. (5) via the thermodynamic uncertainty relation (see SI for details)\([28, 30]\)

\[
\eta_T = \frac{(\dot{\theta})^2}{D_\theta S_{tot}}. \tag{7}
\]

More importantly, according to Eq. (6) and (7), it will be found that the biochemical systems need significantly less energy cost to maintain accuracy for NIOs than for normal ones, which will be elucidated more clearly in numerical simulations.

As biochemical oscillations with high sensitivity are vulnerable to external perturbation and fluctuation, accuracy and sensitivity can be treated as two trade-off properties\([13, 14, 31, 32]\). To achieve the sensitivity-accuracy relation, we now try to figure out the sensitivity \( \chi \) as follows. The deterministic evolution equation of Eq. (1) can be expressed as \( \dot{\phi} = \nabla \phi \cdot f(x) \). In the presence of an external signal \( \beta(t) \), the deterministic term obeys \( \dot{f}_k(x) = f(x) + k \beta(t) \), where \( k \) is a parameter to be perturbed. Then, the phase response curve function (PRC) \( Z_k(\phi) = \nabla \phi \cdot \beta(t) \) characterizing the ability of the biochemical circuits to respond to external signals is obtained by comparing the phase shift after delivering a perturbation at a given duration of time\([33, 34]\). By similar definition of phase as in Ref. \([35, 36]\) and the stochastic normal form theory, the sensitivity is then defined as the normalized value of key signal-independent factor \( \nabla \phi \) in PRC\([13]\) at \( r = r_m \) (see SI for details)

\[
\chi_m = \chi(r_m) = -\frac{C_r r_m^2}{\sqrt{\alpha^2 - 2 C_r \varepsilon^2 / V}}. \tag{8}
\]

Based on Eq. (8), we can derive the second main result of this paper

\[
2 \log \chi_m^* = C_0 + \log D_\theta \tag{9}
\]
with $C_0 = \log \left(2\pi C_i^2 r_i^4/\left[\varepsilon^2 k_r(\alpha^2 - 2C_i\varepsilon^2/V)\right]\right)$ and $\chi_m = \chi_m/\sqrt{S_{tot}}$. Eq. (9) shows that an increase in phase accuracy $D_\theta^{-1}$ cannot be accompanied by an increase in the normalized phase sensitivity $\chi_m$, which can be treated as the sensitivity-accuracy trade-off relation under fixed energy condition (see SI for detailed analysis of Eq. (9)). Such trade-off relationship always holds when system parameters change, providing another design principle for biochemical systems to measure the balance between the sensory to external signals and the regulatory of the internal oscillation. More interestingly, we can also obtain a scaling law for phase sensitivity $\chi_m$ of the system size $V$ as

$$\chi_m \sim V^\kappa, \begin{cases} \kappa = -1 & \alpha < 0 \\ \kappa = -\frac{1}{2} & \alpha = 0 \\ \kappa = 0 & \alpha > 0 \end{cases} (10)$$

In addition, a dynamic efficiency can be defined to quantitatively describe the ability of biochemical systems to maintain the sensory adaptation for external signals and the regulatory of the internal function at the same time

$$\eta_S = \frac{\chi_m^2}{D_\theta} = \frac{C_i^2 V r_m^6}{\varepsilon^2 (\alpha^2 - 2C_i\varepsilon^2/V)}. (11)$$

The obtained dynamic efficiency can further be related to the information inequality $v_{k,\phi}/D_\theta \leq \hat{D}_{PE}$ where $v_{k,\phi}$ is the change rate of the current difference $\langle \phi \rangle_k - \langle \phi \rangle$ (here $\langle \phi \rangle$ is the mean of phase for the original dynamics, $\langle \phi \rangle_k$ is the mean for the dynamics perturbed by the signal), and $\hat{D}_{PE}$ is the Pearson divergence between the original dynamics and the perturbed dynamics which show similar evolutionary behavior to the total entropy production. The quantity $v_{k,\phi}$ is proportional to the system sensitivity, $\hat{D}_{PE}$ determines the upper bound of the dynamic efficiency. Moreover, as the total entropy production rate hardly changes with system size in NIOs, we find that dynamic efficiency can be approached to upper bound by adjusting the size parameter $V$ of biochemical oscillation systems. Therefore, one can design a biochemical system to enhance the sensitivity and reduce the fluctuation simultaneously by changing its internal properties to maximize $\eta_S$. Interestingly, an optimal system size $V_{opt}$ can be achieved by setting $\partial (\eta_S)/\partial V = 0$, where biochemical systems with limited energy sources can reach their best performance of both high sensitivity and high accuracy.

Now, we apply the above analytical results to a well-known biochemical oscillation system, the Brusselator model involving two distinct biochemical species $X_1, X_2$, four reaction channels,

$$A \rightarrow X_1, \quad B + X_1 \rightarrow X_2,
X_1 \rightarrow C, \quad 2X_1 + X_2 \rightarrow 3X_1.$$ 

Here $w = (A, BX_1, X_1, X_2^2 X_2)$ represent the corresponding transition rates. In the thermodynamic limit where the internal noise terms can be ignored, a supercritical Hopf bifurcation occurs for $\alpha = (B - B_c)/2$ with $B_c = A^2 + 1$. We numerically simulate Eq. (4) by Euler methods with a time step $10^{-4}$. After long enough transition time, $10^5$ trajectories are used to calculate the energy cost $\Delta W$.

Both the trade-off relations Eq. (5) and (9) are shown in Fig. 1. It can be observed that, the phase diffusion constant $D_\theta$ is inversely proportional to the energy cost $\Delta W$, confirming that the accuracy-energy trade-off relation holds for both NIOs and normal oscillations (Fig. 1a)). Similarly, the normalized sensitivity $\chi_m$ also increases as $D_\theta$ increases, which verifies the sensitivity-accuracy trade-off relation for both normal oscillations and NIOs (Fig. 1b)).

![FIG. 1: Trade-off relations for biochemical oscillations with sufficient ($\alpha > 0$) or limited ($\alpha < 0$) energy sources. (a) The simulated energy-accuracy trade-off relation for $\alpha > 0$ and $\alpha < 0$ shows that the phase fluctuation constant $D_\theta$ decreases as the free energy cost $\Delta W$ increases, which agrees well with analytical curves fitted according to Eq. (9). Besides, there is always a minimal phase diffusion constant $D_\theta^*$ (the black dash line for $\alpha > 0$ and the purple dash line for $\alpha < 0$ in (a)) cannot be completely eliminated even for infinite cost. (b) The simulated sensitivity-accuracy trade-off relation for $\alpha > 0$ and $\alpha < 0$ shows that phase sensitivity $\chi_m$ also increases as the phase diffusion constant $D_\theta$ increases.](image-url)
Dependence of the energy cost $\Delta W$ and the transport efficiency $\eta_T$ on the system size $V$ is shown in Fig.2(a) and (b), respectively. Simulated $\Delta W$ increases proportionally as $V$ increases for normal oscillations and is nearly unchanged for NIOs, which is in good consistence with the scaling law (10) (Fig.2(a)). Additionally, as $\eta_T$ is almost equal for different types of oscillations (Fig.2(b)) and $\Delta W$ for NIOs is always smaller than that for normal oscillations for fixed $V$, it thus leads to a quite interesting conclusion that, for NIOs, the system can keep almost the same efficiency to maintain precise processes at much lower energy cost, elucidating clearly the advantage of noise-induced oscillations in limited energy supplies.

As shown in Fig.2(a), the phase sensitivity $\chi_m$ changes little with increasing system size $V$ for normal oscillations and is inversely proportional to $V$ for NIOs, agree with the scaling law Eq.(10) very well. Remarkably, the dynamic efficiency $\eta_S$ for NIOs in Fig.3(b) shows a maximum for an optimal system size $V_{opt}$, where $\chi_m$ still changes little. This finding predicts a new strategy for the design of biological networks in limited energy resources to achieve both high accuracy and sensitivity, simultaneously, which is absent for systems with sufficient energy supplies (see SI for details).

In conclusion, energy-accuracy and sensitivity-accuracy trade-off relations have been revealed for a general biochemical system by applying the framework of stochastic thermodynamics as well as phase reduction method. According to these relations, it was found that biochemical systems may maintain their necessary regulatory function via noise-induced oscillation to save the energy cost when energy resources limited. More interestingly, an optimal system size for systems to achieve both high accuracy and sensitivity has also been derived by the trade-off relations, predicting a new strategy for the design of biological networks with limited energy sources. As our findings are of important relevance to many rhythmic processes in biochemical systems, and can be extended to other realistic systems straightforwardly, it is our hope that the reported principles will certainly enhance our ability in designing new biochemical systems for practical applications.
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