Pumped Biochemical Reactions, Nonequilibrium Circulation, and Stochastic Resonance

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Based on a master equation formalism for mesoscopic, unimolecular biochemical reactions, we show the periodic oscillation arising from severe nonequilibrium pumping is intimately related to the periodic motion in recently studied stochastic resonance (SR). The white noise in SR is naturally identified with the temperature in the biochemical reactions; the drift in the SR is associated with the circular flux in nonequilibrium steady state (NESS). As in SR, an optimal temperature for biochemical oscillation is shown to exist. A unifying framework for Hill's theory of NESS and the SR without periodic forcing is presented. The new formalism provides an analytically solvable model for SR.

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Chemical reactions under nonequilibrium steady state (NESS) are fundamental to living organisms [1–4]. Biochemical reactions are often on the level of a few molecules. Hence a stochastic description is required. The continuous-time discrete-state master equation with Q matrix is well established as a cogent model for reactions on the mesoscopic level [5]. A Q matrix has all nondiagonal elements $q_{ij} \geq 0$ and summation of each row being 0. It can be classified either as reversible or irreversible [6,7], corresponding to the physical system being detail balanced or under pumping [2,4]. The respective long time behaviors are equilibrium and NESS [8]. A reversible Q matrix has only nonpositive real eigenvalues [9]. Hence, the time-correlation functions of equilibrium fluctuations are multiexponential and monotonic. When a reaction is pumped, the eigenvalues of the irreversible Q can be complex (but never purely imaginary [10]), known as power spectrum "peaking" [9]. It has also been shown that a sufficient and necessary condition for NESS is the existence of *circulation* (probabilistic flux) in a system [1,4], and the stationarity is maintained via circular balance rather than detail balance [7]. Circulation leads to positive entropy production [11].

Periodic motion in a stochastic (noisy) system is studied as stochastic resonance without periodic forcing (SRWOF) [12]. Different from the conventional stochastic resonance in which a periodic force is present [13,14], SRWOF focuses on the intrinsic periodic motion in a system under a constant drift. It has been noted that the constant drift term is essential in stochastic resonance (SR) behavior. While all studies on SRWOF up to date are based on continuous-time continuous-state stochastic models with Fokker-Planck equations (FPE), it is easy to show that the constant drift term is equivalent to the circulation in the Q-matrix models [15]. In fact, the FPE on a circle shares much of the essential features of a master equation for a cyclic reaction.

This Letter seeks a unifying nonequilibrium framework for SRWOF and its relation to the circulation of NESS [1,7]. We use cyclic reactions and their master equations to demonstrate our results. Such reactions are found in biophysics, e.g., the ATP-hydrolysis driven biosynthesis [2] and motor protein movement [4]. The strength of white noise in SR is identified with the temperature in the chemical reaction. According to Kramers' theory [16], each element in a Q matrix $q_{ij} = q_{ij}^0 T e^{-U_{ij}/T}$, where T is the temperature. T in the prefactor comes from the diffusion coefficient and the exponential term is due to activation energy barrier U_{ij}. We show that a necessary, but not sufficient, condition for SRWOF is the system being in NESS with circulation; furthermore, the periodic motion in SRWOF corresponds to the oscillation in nonequilibrium reactions far from equilibrium. The insight from SRWOF, on the other hand, is that an optimal temperature exists for observing a biochemical oscillation. Having established the correspondence above, the problem of SR is shown to be analytically solvable.

The simplest model capable of capturing the essence of NESS is a 3-state kinetic cycle $1 \underset{q_{21}}{\overset{q_{12}}{\rightleftharpoons}} 2 \underset{q_{32}}{\overset{q_{23}}{\rightleftharpoons}} 3 \underset{q_{13}}{\overset{q_{31}}{\rightleftharpoons}} 1$. If $r = \frac{q_{12}q_{23}q_{31}}{q_{21}q_{32}q_{13}} = 1$, the Q matrix is reversible, and in general the two nonzero, real eigenvalues are not equal. Therefore, when the r is slightly greater (or less) than 1, Q still has two real eigenvalues: NESS does not necessarily lead to oscillation. When the pumping is severe, i.e., $r \gg 1$ (or $\ll 1$), complex eigenvalues are possible. One particular example is the 3-state one-way cycle

$$\begin{pmatrix} -1 & 1 & 0 \\ 0 & -1 & 1 \\ 1 & 0 & -1 \end{pmatrix} \tag{1}$$

with nonzero eigenvalues $-(3 \pm i\sqrt{3})/2$ and a NESS $(\frac{1}{3}, \frac{1}{3}, \frac{1}{3})$. Figure 1 shows the autocorrelation function $C(\tau)$ and corresponding power spectrum $S(\omega)$ of the NESS of this system, obtained from both stochastic simulation and analytical calculation. It is seen that even though there is a cosine term in the correlation function, both $C(\tau)$ and $S(\omega)$ are monotonic. The oscillation is not

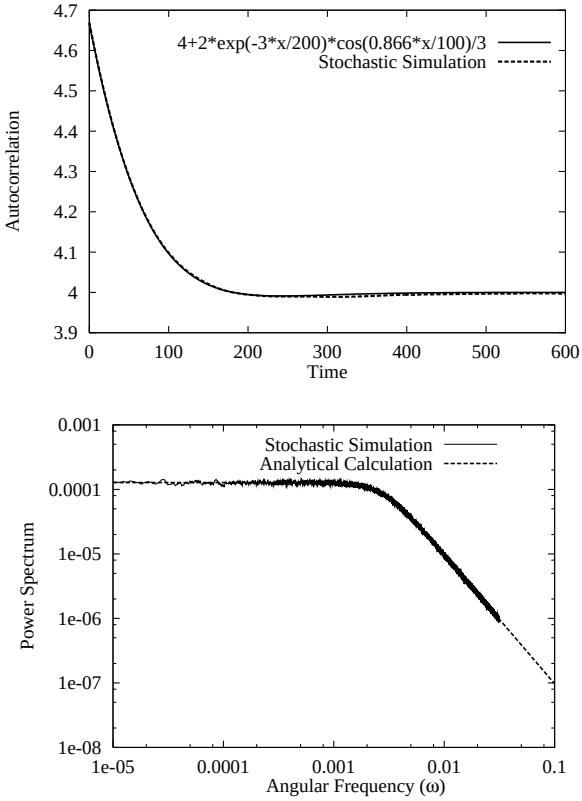

FIG. 1. NESS autocorrelation function $C(\tau)$ and power spectrum $S(\omega)$ of a 3-state cycle model: $C(\tau) = 4 + \frac{2}{3}e^{-\mu\tau} \times \cos(\nu_0\tau)$, $S(\omega) = (\mu/2)\{[\mu^2 + (\omega + \nu_0)^2]^{-1} + [\mu^2 + (\omega - \nu_0)^2]^{-1}\}$ where $\mu = 0.01 \times \frac{3}{2}$, $\nu_0 = 0.01 \times \frac{\sqrt{3}}{2}$. Note the cosine term in $C(\tau)$ and nonzero ν_0 in $S(\omega)$.

significant enough to be observed. Figure 2 shows that the critical condition for observing an off-zero peak in a power spectrum is when the ratio between imaginary to real parts (IR ratio) $\mu/\nu > 1/\sqrt{3}$, where $\mu + i\nu = \lambda$ is a complex eigenvalue. For the 3-state kinetics, this ratio is exactly $1/\sqrt{3}$. Hence, no peak is observed.

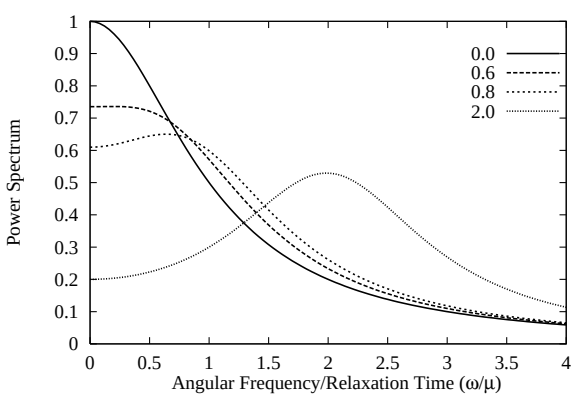

FIG. 2. For an oscillatory correlation function $C(t) = e^{-\mu|t|}\cos(\nu t)$, its power spectrum $S(\omega) = (\mu/2)\{[\mu^2 + (\omega + \nu)^2]^{-1} + [\mu^2 + (\omega - \nu)^2]^{-1}\}$. It is shown how the ν/μ ratio (indicated by the keys) are affecting the shape of the power spectrum. A peak appears when the ratio is $>1/\sqrt{3}$. The shape of the solid curve is known as Lorentzian.

Observing a significant peak requires the IR ratio $\gg 1$. However, since all the λ's of a Q matrix are confined in a closed disk of radius α centered at $-\alpha$ [10], an imaginary part can not be large while the real part is small. There is a stringent constraint. We give an example which escapes this dilemma. For an n-state one-way cycle, it is easy to show that the n eigenvalues, $e^{i\pi\ell/n} - 1$ ($\ell = 1, 2, \ldots, n - 1$), are distributed on the unit circle centered at -1. The largest possible IR ratio is $\tan[(n - 1)\pi/2n]$. Therefore the IR ratio can be large for systems with a large n. Figure 3 shows the relationship between the IR ratio and the NESS circulation (J) for an arbitrary 3×3 Q matrix. A positive, though not precise, correlation is observed.

Periodicity and its probabilistic interpretation.—What is the mechanistic origin of the periodicity in stochastic motion? How is a chemical reaction system with exponential kinetics giving rise to oscillation with frequency ν? Insight into this question is provided below by completely solving the 3-state one-way cycle model [Eq. (1)]. This approach can be generalized to more complex n-state cyclic models. We use $P(k, t\,|\,\ell)$ to denote the conditional probability of the system being in state k at time t given it was in state ℓ at time 0. $P(k, t\,|\,\ell)$ can be solved from the master equation with initial condition $P(m) = \delta_{m\ell}$. The autocorrelation function then is $C(\tau) = \sum_{\ell,m} \ell m P(m, \tau\,|\,\ell) P^{ss}(\ell)$, where P^{ss} is the steady-state distribution. We have the respective forward, backward, and dwell conditional probabilities,

$$P(2, t\,|\,1) = \frac{1}{3}[1 - (\cos\nu_0 t - \sqrt{3}\,\sin\nu_0 t)e^{-3t/2}], \quad (2)$$

$$P(1, t\,|\,2) = \frac{1}{3}[1 - (\cos\nu_0 t + \sqrt{3}\,\sin\nu_0 t)e^{-3t/2}], \quad (3)$$

$$P(1, t\,|\,1) = \frac{1}{3}[1 + 2e^{-3t/2}\cos\nu_0 t], \quad (4)$$

where $\nu_0 = \sqrt{3}/2$. Because of rotational symmetry,

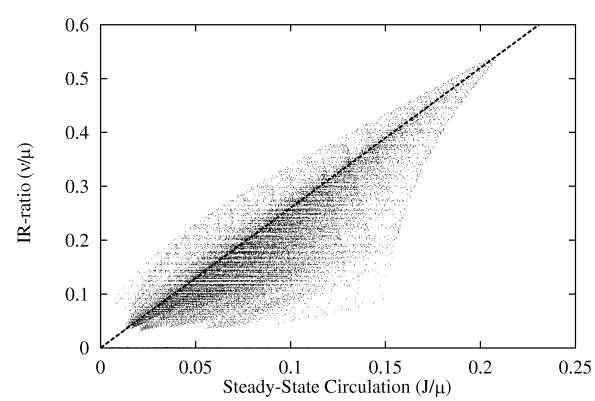

FIG. 3. The relation between the IR ratio and NESS circulation J for a 3×3 Q matrix. The six nondiagonal q_{ij} are uniformly sampled with step 0.1 between $[0, 1]$. Each dot in the figure is $(J/\mu, \nu/\mu)$ for one matrix with eigenvalue $\mu \pm i\nu$. Circulation $J = q_{12}P_1^{ss} - q_{21}P_2^{ss} = q_{23}P_2^{ss} - q_{32}P_3^{ss}$, where P^{ss} is the steady state of the matrix. The largest IR ratio and the largest circulation correspond to the matrix in (1) with $\mu = \frac{3}{2}$, $\nu = \frac{\sqrt{3}}{2}$, and $J = \frac{1}{3}$. The dashed line represents $\nu{:}\mu{:}J = \sqrt{3}{:}3{:}\frac{2}{3}$.

$P(3,t\,|\,2) = P(2,t\,|\,1)$, etc. All the conditional probabilities have oscillatory terms, which contribute to the oscillation in $C(\tau)$. These oscillatory terms have a clear probabilistic origin from which Eqs. (2)–(4) can be derived alternatively as follows without solving the master equation. We note that the stochastic motion along the one-way cycle is in complete accord with a Poisson point process with rate 1 starting at 0. A mapping can be established between the Poisson process along a line and the cyclic motion among the three states. For the Poisson process, the probability of reaching k at time t is $t^k e^{-t}/k!$. Therefore, the total probability of remaining in 0, *and* reaching $3n$ ($n = 1, 2, \ldots$) should be equivalent to the forward conditional probability along the cycle; this is indeed the case [17]: $\sum_{n=0}^{\infty} \frac{t^{3n}}{(3n)!} e^{-t} = P(1,t\,|\,1)$. Similarly, $\sum_{n=1}^{\infty} \frac{t^{3n+1}}{(3n+1)!} e^{-t} = P(2,t\,|\,1)$; $\sum_{n=1}^{\infty} \frac{t^{3n+2}}{(3n+2)!} e^{-t} = P(1,t\,|\,2)$. Therefore, in stochastic systems, the oscillatory behavior is related to the residence-time distribution function [12,14]. With an increasing number of cycles, the variance in the distribution increases; thus the amplitude of the distribution decays with time. Even though each individual step in a chemical reaction is exponentially distributed, the sum of two steps will be $t^2 e^{-t}/2!$ with a peak at 2 (mean and variance both being 3). With n steps, the gamma distribution $t^{n-1}e^{-t}/(n-1)!$ peaks at $t = (n-1)$, with mean and variance being n. The relative width of the distribution $\sim n^{-1/2}$. The above discussion is based on the simple Q matrix (1) which corresponds to a Poisson process. For a general Q the theory of Markov renewal processes [18] has to be employed.

Stochastic resonance in biochemical reaction.—We now turn to SR of the model. Since the periodicity in a 3-state model is not sufficient for the manifestation of SR, we consider the following most typical 5-state cyclic reaction:

$$1 \underset{q_{21}}{\overset{q_{12}}{\rightleftharpoons}} 2 \underset{q_{32}}{\overset{q_{23}}{\rightleftharpoons}} 3 \underset{q_{43}}{\overset{q_{34}}{\rightleftharpoons}} 4 \underset{q_{54}}{\overset{q_{45}}{\rightleftharpoons}} 5 \underset{q_{15}}{\overset{q_{51}}{\rightleftharpoons}} 1\,, \tag{5}$$

where $q_{ij} = q_{ij}^0 T e^{-U_{ij}/T}$ and T is the temperature (in arbitrary units). In our calculation, $U_{12} = U_{23} = 0.1$, $U_{34} = U_{45} = U_{51} = 0.05$, $U_{21} = U_{32} = U_{43} = U_{54} = U_{15} = 5.0$. All $q_{ij}^0 = 1$. Therefore

$$r = \frac{q_{12}q_{23}q_{34}q_{45}q_{51}}{q_{21}q_{32}q_{43}q_{54}q_{15}} = \frac{e^{-(U_{12}+U_{23}+U_{34}+U_{45}+U_{51})/T}}{e^{-(U_{21}+U_{32}+U_{43}+U_{54}+U_{15})/T}} = e^{24.65/T}. \tag{6}$$

The exponent 24.65 in (6) is equivalent to the constant drift in SRWOF [12] where white noise is added to a nonlinear dynamical system with a limit cycle. The limit cycle is eliminated when a constant drift term is below a critical value [19]. This corresponds to the emerging of an activation barrier. With the presence of the noise, the noise activated barrier crossing appears. The nonzero drift along the circle corresponds to $r \neq 1$ (see below).

Figure 4 shows the power spectra for three T's. With increasing T the peak (corner) frequency shifts right, corresponding to an increase in time scale. For both large and small T, the oscillation disappears. There is an optimal temperature at which the reaction oscillates. This corresponds to SRWOF [12]. The top panel should be compared with model 1 of Hu *et al.* with drift <1 [12]. The eigenvalues of the systems are particularly telling. In Table I the IR ratio ν/μ is the largest for $T = 0.5$. With increasing and decreasing T, complex eigenvalues turn to real. Therefore, the IR ratio is a good indicator for the quality of peaking. In the case of 3-state, this ratio behaves in a similar fashion but the maximum IR ratio ($= 0.577$) is still not sufficiently large to yield an off-zero spectral peak.

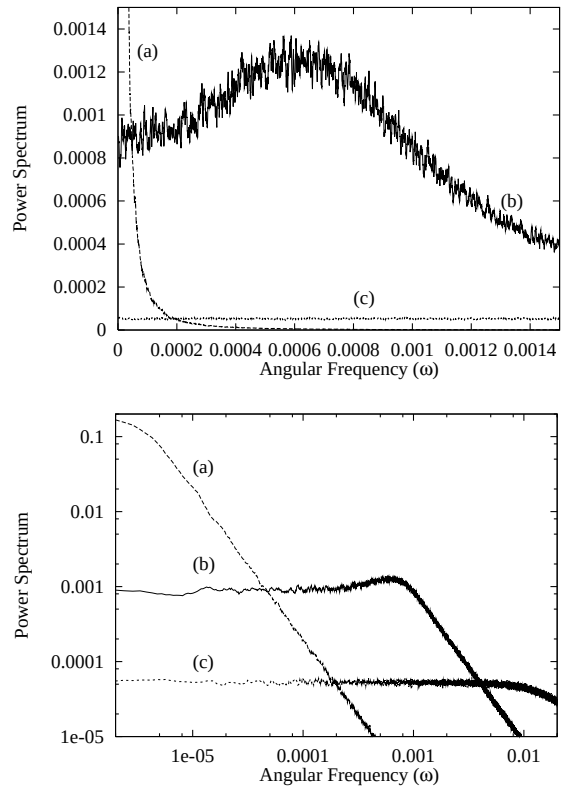

FIG. 4. Stochastic resonance in a pumped cyclic biochemical reaction with five states (lower panel in logarithmic scales). An optimal temperature (in arbitrary unit $T = 0.5$) exists at which the power spectrum of nonequilibrium steady state exhibits pronounced off-zero peak, indicating oscillatory motion. With increasing and decreasing T, the oscillation disappears. (a) $T = 0.025$; (b) $T = 0.5$; (c) $T = 10$.

Q matrix as approximation for stochastic resonance.—The master equations with $Q = (q_{ij})_{n\times n}$ are actually a good approximation for the FPE approach in SR when n is large. Both by direct physical argument and by the finite-difference scheme of a FPE lead to $2D/(\Delta x)^2 = q_+ + q_-$ and $F/\Delta x = q_+ - q_-$, where $q_\pm$ are forward and backward rate constants in a Q matrix. Thus

$$\begin{aligned} q_{j,j+1} &= n^2 D + \frac{n}{2} F\left(\frac{j}{n}\right), \\ q_{j+1,j} &= n^2 D - \frac{n}{2} F\left(\frac{j+1}{n}\right) \end{aligned} \tag{7}$$

TABLE I. Nonzero eigenvalues and circular flux for various T.

T	$\lambda_{1,2}$	$\lambda_{3,4}$	IR ratio	Circulation
$\to 0$	$0, q_{34} \to 0$	$q_{34} \to 0$	0.0	$\frac{q_{12}}{2} \to 0$
0.025	$-0.0039 \pm 0.0069i$	$-0.0016 \pm 0.000\,28i$	0.176, 0.171	0.000 19
0.5	$-0.79 \pm 0.26i$	$-0.30 \pm 0.41i$	0.32, **1.37**	0.087
10	$-28.9 \pm 2.27i$	$-11.1 \pm 3.68i$	0.079, 0.33	0.77
$\to \infty$	$-\frac{5+\sqrt{5}}{2}$	$-\frac{5-\sqrt{5}}{2}$	0.0	$\frac{24.65}{25}$

for a continuous FPE $\partial_t P(x,t) = D\partial_{xx}P(x,t) - \partial_x[F(x)P(x,t)]$, where $x \in [0,1]$ representing a point on a circle. The correspondence immediately leads to

$$r \triangleq \frac{\prod q_{j,j+1}}{\prod q_{j+1,j}} = 1 + \frac{1}{D}\int_0^1 F(x)\,dx + o\left(\frac{1}{n}\right). \quad (8)$$

Therefore, $r = 1$ corresponds to the above integral (i.e., the drift) being zero.

In summary, we have obtained not only the main characteristics of SRWOF in a cyclic chemical reaction, established a concrete bridge between the SR and NESS, but also provided an analytical means to determine the peak frequency ν_0, which has not been possible in a conventional approach to SR by a purely numerical simulation.

A cyclic model like (5) has been extensively studied in connection with motor proteins [4]. While most previous investigations have focused on the movement of a motor protein along its linear track, the internal conformational dynamics of the protein is cyclic. Hence a spectroscopic study of conformational fluctuations could be a testing case for the present theory. Such experiments have not been carried out, but their outcome will greatly enhance our understanding of NESS. The oscillatory behavior in our model also provides the "power-stroke-" like motor movement with a possible theoretical basis. In fact, it is tempting to classify NESS near and far from equilibrium according to the existence of complex eigenvalues. In our view, there is no doubt the oscillation in a severely pumped reaction is the start point of temporal organization in states far from thermodynamic equilibria.

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[10] Consider Q with $q_{ii} = -\sum_{j\neq i} q_{ji} < 0$. Introducing an $\alpha > \max\{-q_{ii}\}$, then $R = Q + \alpha I$ is a positive matrix. By the Perron-Frobenius theorem [8], R has a positive eigenvalue r equal to the spectral radius of R and the corresponding eigenvector $\mathbf{u}$ is non-negative. $\mathbf{u}$ is also the eigenvector of Q: $Q\mathbf{u} = (R - \alpha I)\mathbf{u} = (r - \alpha)\mathbf{u}$. Any Q has a zero eigenvalue with associated left eigenvector $\mathbf{l} = (1, 1, \ldots, 1)$. Hence $0 = \langle \mathbf{l}Q, \mathbf{u}\rangle = (r - \alpha)\langle \mathbf{l}, \mathbf{u}\rangle$. Since $\mathbf{u}$ is non-negative, $r = \alpha$. Hence, all the eigenvalues of Q are in the closed disk of radius α centered at $-\alpha$. In other words, all the eigenvalues have nonpositive real parts and no eigenvalue is purely imaginary.

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