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Internal noise enhanced oscillation in a delayed circadian pacemaker

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ABSTRACT

The effect of internal noise in a delayed circadian oscillator is studied by using both chemical Langevin equations and stochastic normal form theory. It is found that internal noise can induce circadian oscillation even if the delay time τ is below the deterministic Hopf bifurcation τ_h. We use signal-to-noise ratio (SNR) to quantitatively characterize the performance of such noise induced oscillations and a threshold value of SNR is introduced to define the so-called effective oscillation. Interestingly, the τ-range for effective stochastic oscillation, denoted as $\Delta\tau_{EO}$, shows a bell-shaped dependence on the intensity of internal noise which is inversely proportional to the system size. We have also investigated how the rates of synthesis and degradation of the clock protein influence the SNR and thus $\Delta\tau_{EO}$. The decay rate K_d could significantly affect $\Delta\tau_{EO}$, while varying the gene expression rate K_e has no obvious effect if K_e is not too small. Stochastic normal form analysis and numerical simulations are in good consistency with each other. This work provides us comprehensive understandings of how internal noise and time delay work cooperatively to influence the dynamics of circadian oscillations.

1. Introduction

Gene regulation processes usually involve large timescale separations. Fast reactions such as the binding or release of a transcription factor to an operator site or the dimerization of some proteins occur on timescales of seconds, while the transcription or translation of a gene may take minutes or even hours. Generally, transcriptional and translational processes are not only slow but also involve numbers of elementary reactions. These multi-step processes could be treated as delayed reactions, in which the initiating events are separated from the appearance of products by certain interval of time delay. Recent studies indicate that such types of delay could be pivotal in inducing oscillations in gene regulation [1,2]. Specifically, it is proved experimentally that time delay is an important mechanism in circadian systems such as Neurospora and Drosophila [3–5]. Several theoretical models have been proposed to address the importance of delay in circadian rhythm oscillations [6–10]. For example, a general delay model based on the kinetics of synthesis and degradation of a clock protein and its messenger RNA has been proposed, which displays a rich and realistic repertoire of circadian rhythm behavior [6]. Lema et al. introduced a model with a delayed negative feedback exerted by a protein on the expression of its gene, which fulfills most of the necessary characteristics of a realistic representation of natural circadian clocks [8]. Smolen et al. constructed two detailed models for Neurospora and Drosophila with both negative and positive feedback loops [7]. They also came up with a reduced model involving the basic biochemical elements of the circadian rhythm generator. Such reduced model contains only two differential equations, each with a time delay [9]. All these models mentioned above take advantage of time delay to represent the slow processes whose details are too complex or uncertain to model, and it is found that delay is the dominant source of large deterministic variability, which is usually recognized as the Hopf bifurcation [11].

Biochemical reactions, in which the number of reactant molecules is usually small, are inherently stochastic and the internal noise is non-ignorable. The effect of internal noise in biological systems has gained much research interest in recent years [12–14]. On one hand, internal noise may be a source of disorder, and considerable attentions have been paid to the underlying mechanism regarding how the system shows robustness and resistance against such fluctuations [13,15,16]. On the other hand, recent studies showed that internal noise could also play constructive roles in gene regulatory processes under certain circumstances [17–27]. For example, noise in gene expression may increase population diversity and thus enhance survival in the face of environmental uncertainty [17,18]. Internal noise can selectively sustain the intrinsic frequency and optimize the noise-induced signals in mesoscopic hormone signaling system [20]. Specifically, for systems located outside but close to the deterministic oscillatory region, noise can induce stochastic oscillations, whose performance, characterized by a well-defined signal-to-noise ratio (SNR), may show maxima with the variation of the internal noise level, generally known as internal noise

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coherence resonance. Since the internal noise strength is inversely proportional to the system size, this phenomenon also indicates a kind of optimal system size effect [28,29]. Such interesting phenomenon has been observed in many mesoscopic biochemical systems, including circadian oscillators [25,26]. In most previous works, the effects of internal noise are mainly investigated by simulation methods. Very recently, our group have developed the stochastic normal from theory (SNFT) [22,30–32], an analytical method which not only reproduces the optimal size effect quantitatively well, but also provides deep understanding about how the system shows robustness to, or even takes advantage of the internal noise. Nevertheless, the constructive roles of internal noise in circadian clock systems with *delay*, e.g., noise induced oscillation (NIO), internal noise coherence resonance and related behaviors, have not been well investigated [16].

In this paper, we have studied the effects of internal noise near the Hopf bifurcation induced by time delay τ in a circadian oscillator model both numerically and theoretically. We find that internal noise can sustain circadian oscillation in a wider τ-range than that predicted by the deterministic model. Those NIO with good performances, i.e., their SNR are larger than a certain threshold, are defined as effective oscillations (EO). The τ-range for the occurrence of EO, denoted as $\Delta\tau_{EO}$, are calculated at different system sizes. Interestingly, $\Delta\tau_{EO}$ typically exhibits a maxima at an optimal system size V. The dependence of $\Delta\tau_{EO}$ on the expression rate K_e and degradation rate K_d are also studied. The results show that $\Delta\tau_{EO}$ depends strongly on K_d but not that much on K_e. To get a deeper understanding of such nontrivial features, we have also performed theoretical analysis based on the SNFT. The theory clearly shows that the SNR is determined by an effective noise intensity which is related to K_e, K_d and the delay time τ. The results obtained by SNFT show rather good agreements with the simulation results.

The rest of the paper is organized as follows. We present our model and methods in Section 2. Results for numerical simulation and theoretical analysis are given in Section 3, followed by conclusions in Section 4.

2. Model and methods

2.1. Deterministic description

In the present paper, we are mainly interested in the interplay between internal noise and delay in circadian clock systems. Recent study on *Neurospora crassa* has shown that negative feedback and time delay are the two essential aspects for circadian oscillation [10,33]. For simplicity, we consider the model proposed by Lema [8], which has taken these two basic factors into account. The model simply involves two steps: the birth step of the clock protein via the gene expression, which is regulated by a delayed negative feedback by the protein itself, and the death step due to the degradation of the protein. The deterministic model for such a circadian oscillator is given by the following equation,

$$\frac{dx(t)}{dt} = K_e G(t-\tau) - K_d x(t), \tag{1}$$

where $x(t)$, K_e and K_d denote the concentration, synthesis rate constant, and degradation rate constant of the clock protein, respectively. The first term on the right side describes the synthesis of clock gene with delayed feedback, where

$$G(t-\tau) = \frac{1}{1 + [x(t-\tau)/K_i]^n} \tag{2}$$

represents the level of gene activation, with K_i the inhibition rate constant and n the Hill coefficient. In our study, we fix the parameters $K_i = 0.5$ and $n = 4$ unless otherwise specified.

Choosing τ as the control parameter, the system (1) may show a supercritical Hopf bifurcation (HB). One should note, however, Eq. (1) is not autonomous due to the delay, and the determination of the HB value, τ_h, is somewhat different from that of autonomous ordinary differential equations. To do so, one may perform linear stability analysis around the fixed point x_s of Eq. (1), satisfying $dx/dt|_{x=x_s} = 0$. For tiny perturbations $\delta x = x - x_s$ and $\delta x_\tau = x_\tau - x_s$, where $x_\tau = x(t-\tau)$, we have

$$\delta\dot{x} = -a\delta x - b\delta x_\tau + g(\delta x, \delta x_\tau), \tag{3}$$

where $a = k_d$, $b = 64k_e x_s^3/(1+16x_s^4)^2$ are linear coefficients, $g(\delta x, \delta x_\tau)$ stands for the nonlinear terms of δx and δx_τ. Assuming Eq. (3) has a solution with the form $\delta x(t) \sim ce^{\lambda t}$, one gets the following equation for eigenvalue λ

$$\lambda = -a - be^{-\lambda\tau}. \tag{4}$$

Typically, Eq. (4) has infinitely many solutions λ_q ($q \in Z$) [34]. Given b larger than a, the system described by Eq. (3) may exhibit a pair of pure imaginary eigenvalues $\pm\omega i$ corresponding to the principal solution with $q = 0$, leading to a Hopf bifurcation. The HB value for delay time can be readily obtained as $\tau_h = cos^{-1}(-a/b)/\sqrt{b^2-a^2}$.

2.2. The chemical Langevin equation (CLE)

The circadian clock system is regulated by a gene network on the molecular level, such that internal noise must be considered. In order to take internal noise into account, we can describe the chemical reaction system as a birth/death stochastic process governed by a chemical master equation. Usually, the master equation can not be solved directly, but it provides the basis for kinetic Monte Carlo simulations. In 1977, Gillespie proposed the well-known stochastic simulation algorithm (SSA) which can exactly account for the stochastic nature of the reaction events [35]. For large systems, however, the SSA approach could be rather expensive and is not particularly efficient. For reaction systems of typically mesoscopic size or involving intermediate number of reactant molecules, several approximation methods can be used instead of SSA. Typically, for a system with the existence of a so-called 'macro-infinitesimal time scale', one may use some kind of leaping method, which focus on how many times each reaction process will happen in the following leaping time interval. If these reaction times are not too small, one may also further approximate the dynamics by a stochastic differential equation, namely, the CLE [36]. In previous works, it has been shown that CLEs do work quite well for mesoscopic chemical oscillation systems [25], at least qualitatively, for the issues we want to address in the present study. In addition, the CLE clearly includes a deterministic part and a noise part, which makes it convenient to compare with the deterministic modeling, thus unravel the very role that played by the internal noise.

For the minimal system considered here, we may consider two reaction channels involving the change of the number X of the clock protein, namely, $X \to X+1$ for the birth and $X \to X-1$ for the death. Correspondingly, the propensity functions (or rates) can be approximately given by $W_1 = w_1 V = \frac{K_e V}{1 + [x(t-\tau)/K_i]^n}$ and $W_2 = w_2 V = K_d V x(t)$, respectively. In its general form, the CLE then reads [37],

$$\frac{dx(t)}{dt} = (w_1 - w_2) + \frac{1}{\sqrt{V}}(\sqrt{w_1}\eta_1(t) - \sqrt{w_2}\eta_2(t)) \tag{5}$$

where η_1 and η_2 are two independent Gaussian noises with zero mean and unit variance. In this study, the numerical results are obtained by simulation of Eq. (5).

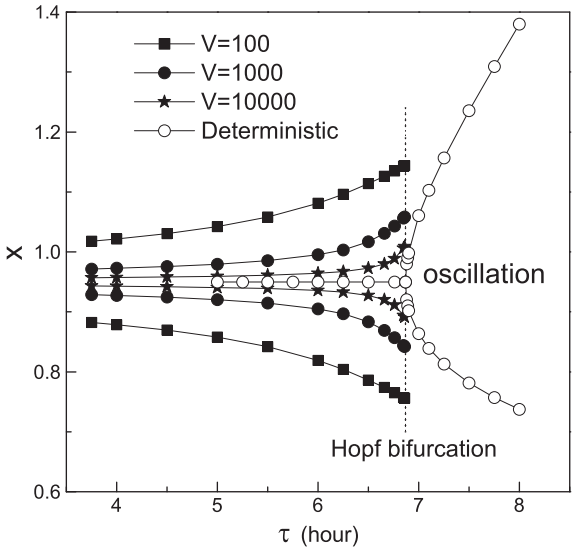

Fig. 1. Range of noise induced oscillations for different system sizes. The deterministic bifurcation diagram is also shown for comparison. Parameters are $K_e = 1.0$ and $K_d = 0.075$.

Taking noise into account, Eq. (3) now changes to

$$\delta\dot{x} = -a\delta x - b\delta x_\tau + \xi(t) + g(\delta x, \delta x_\tau) \tag{6}$$

where $\xi(t)$ is Gaussian noise with $\langle\xi(t)\rangle = 0$ and $\langle\xi(t)\,\xi(t')\rangle = 2D\delta(t-t')$. The noise intensity is given by $2D = \frac{1}{V}[w_1(x_s) + w_2(x_s)]$, where $w_1(x_s) = \frac{K_e}{1 + (x_s/K_i)^n}$ and $w_2(x_s) = K_d x_s$ are the values of propensity functions at the fix point x_s.

2.3. Analytical method: SNFT

In this section, we briefly outline the theoretical methods we used in the present work, the SNFT. In our previous works [22,30], the basic ideas of SNFT have been described in much detail. Here we readdress some relevant contents here for two-fold reasons. First, we note here that to apply the SNFT to a delayed stochastic system is not that straightforward and a number of technical difficulties should be overcome. Secondly, some analytical results need to be shown here for self-consistency of the present work.

As is shown in Ref. [38], the solution of the linear inhomogeneous Eq. (6) could be expanded by time-dependent coefficients $C_q(t)$ corresponding to the eigenvalues λ_q given by Eq. (4) as $\delta x(t) = \sum_q C_q(t)$. These expansion coefficients obey the following equation

$$\dot{C}_q(t) = \lambda_q C_q(t) + \frac{g(x, x_\tau)}{N_q} + \frac{\xi(t)}{N_q}, \tag{7}$$

where the coefficient $N_q = 1 + a\tau + \lambda_q\tau$ is associated with the q^{th} eigenvalue λ_q. These equations are free of the delay term in Eq. (6) and are analytically solvable. From the combination of the time evolution for different $C_q(t)$, one could calculate the time evolution of $x(t)$. These coefficients are sort in the order of the real part of eigenvalues and the two conjugate eigenvalues corresponding to the principal solution with $q = 0$ have the largest $\mathrm{Re}(\lambda)$ [39], whose absolute value is the smallest. Therefore, the relevant coefficients C_0 and $\overline{C}_0$ evolve much slower than the other coefficients and they essentially define the center manifold. According to the bifurcation theory [40], the system's dynamics can thus be described by a normal form equation on this two-dimensional center manifold in the vicinity of HB. By suitable near-identity nonlinear variable transformation and keeping the so-called resonant terms to the lowest order, one can get the stochastic normal form equation for the complex amplitude $Z = re^{i\theta}$, where r and θ are the oscillation amplitude and phase angle respectively,

$$\dot{Z} = \lambda Z + (C_r + iC_i)Z^2\overline{Z} + \frac{\xi(t)}{N_0}. \tag{8}$$

One notes here a τ-dependent factor N_0 enters the noise term, which is the very consequence of the delay feedback. The coefficients C_r and C_i are derived from the nonlinear terms $g(x, x_\tau)$ and can also be calculated numerically.

From Eq. (8), following similar steps including stochastic averaging [41,42] as those described in Refs. [22] and [30], we get the

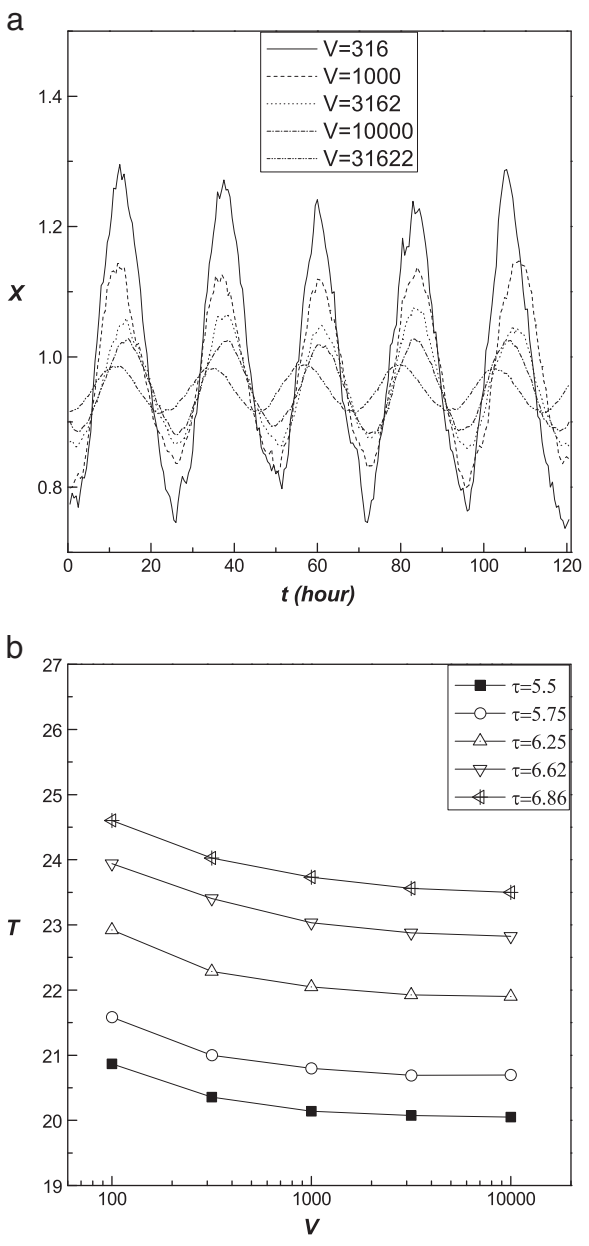

Fig. 2. (a) Typical time series for internal noise induced circadian oscillation with delay time $\tau = 6.78$. (b) The dependence of average oscillation period on V for different τ. $K_e = 1.0$, $K_d = 0.075$.

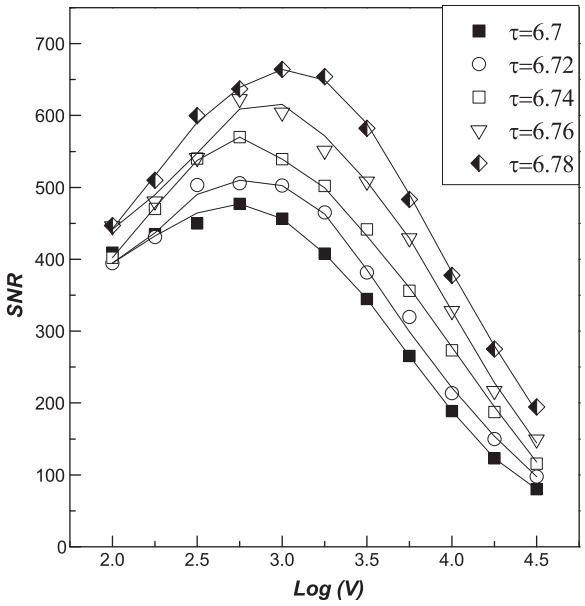

Fig. 3. SNR plotted as a function of V for different τ. $K_e = 1.0$, $K_d = 0.075$. Lines are drawn to guide the eyes.

stochastic normal form equations for the phase angle θ and the oscillation amplitude r of the noise induced oscillation that are solvable as follows,

$$\dot{r} = \alpha r + C_r r^3 + \frac{\sigma^2}{2r} + \sigma\xi_r(t) \tag{9a}$$

$$\dot{\theta} = \omega_0 + C_i r^2 + \frac{\sigma}{r}\xi_\theta(t) \tag{9b}$$

where $\alpha<0$ and $\omega_0>0$ are the real and imaginary parts of λ_0, respectively. ξ_r and ξ_θ are two independent Gaussian white noises and σ is the effective noise intensity. Since phase angle θ evolves much faster than the oscillation amplitude r, it is clear from Eq. (9b) that under the influence of Gaussian noise, the phase angle $\theta(t)$ shows Gaussian response around $\omega_0 + C_r\langle r^2\rangle_s$ in long time limit, with $_s$ the average in the steady state. On the other hand, Eq. (9a) is a non-linear equation of oscillation amplitude r and the stationary distribution of r exhibits non-Gaussian distribution, which is given by

$$P_s(r) = C_0 r \exp\left(\frac{2\alpha r^2 + C_r r^4}{2\sigma^2}\right). \tag{10}$$

Herein, C_0 is the normalization constant. When the system is distant from Hopf bifurcation or the noise intensity is small, such non-Gaussian behavior can be treated in Gaussian approximation. However, in the vicinity of Hopf bifurcation with relatively large fluctuation, the distinction from the Gaussian distribution has to be taken into account. It is easy to prove that Eq. (10) has a maximum which corresponds to the most probable value of the oscillation amplitude r_m as described below.

$$r_m = \left(\frac{\alpha + \sqrt{\alpha^2 - 2C_r\sigma^2}}{-2C_r}\right)^{1/2} \tag{11}$$

The analytical form of the auto-correlation time has the following form,

$$\tau_c = 2r_m^2/\sigma^2. \tag{12}$$

Herein, the effective noise intensity σ is given by

$$\sigma^2 = \frac{4D}{|N_0|^2} = \frac{2[w_1(x_s) + w_2(x_s)]}{V[(1 + a\tau + \alpha\tau)^2 + (\omega_0\tau)^2]}. \tag{13}$$

The SNR, which is defined as the peak height of the power spectrum divided by its half-height width, can be readily calculated as

$$\mathrm{SNR} = (r_m\tau_c)^2 = \frac{4r_m^6}{\sigma^4}. \tag{14}$$

From the above equations, one can see that the parameter σ plays the most important role to determine the properties of NIO, r_m, τ_c and SNR. According to Eq. (13), it is clear that σ depends not only on system size V, but also on the delay time τ. Besides, the parameters D and λ_0 both depend on K_e and K_d. Therefore, such analytical formulae provide lots of information about how the NIO performance is influenced by the system parameters.

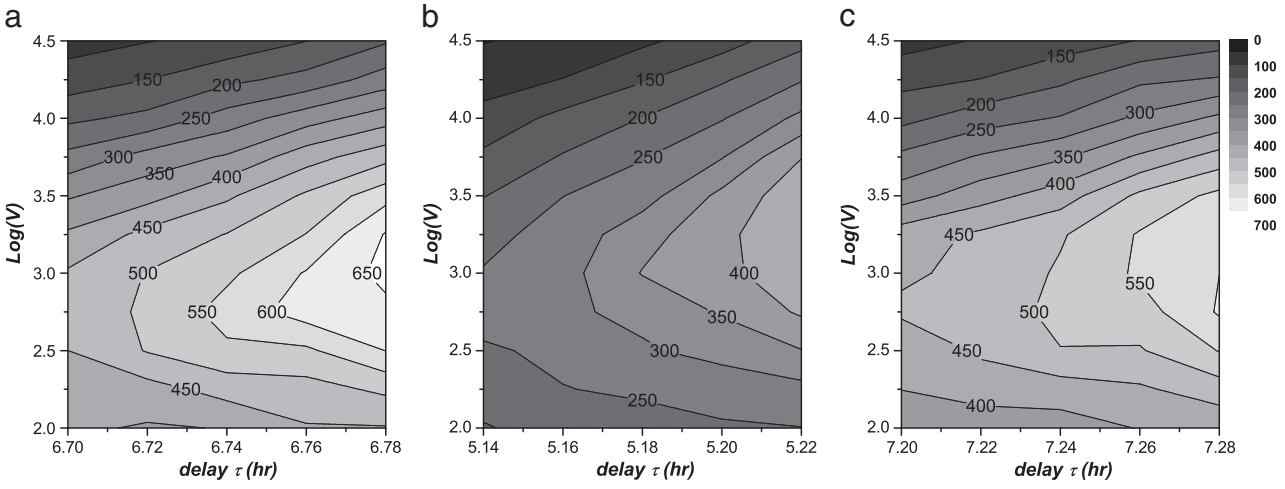

Fig. 4. The contour of SNR for different V and τ are obtained by numerical simulations with (a) $K_e = 1.0$, $K_d = 0.075$ (b) $K_e = 1.0$, $K_d = 0.1$ (c) $K_e = 0.5$, $K_d = 0.075$, respectively.

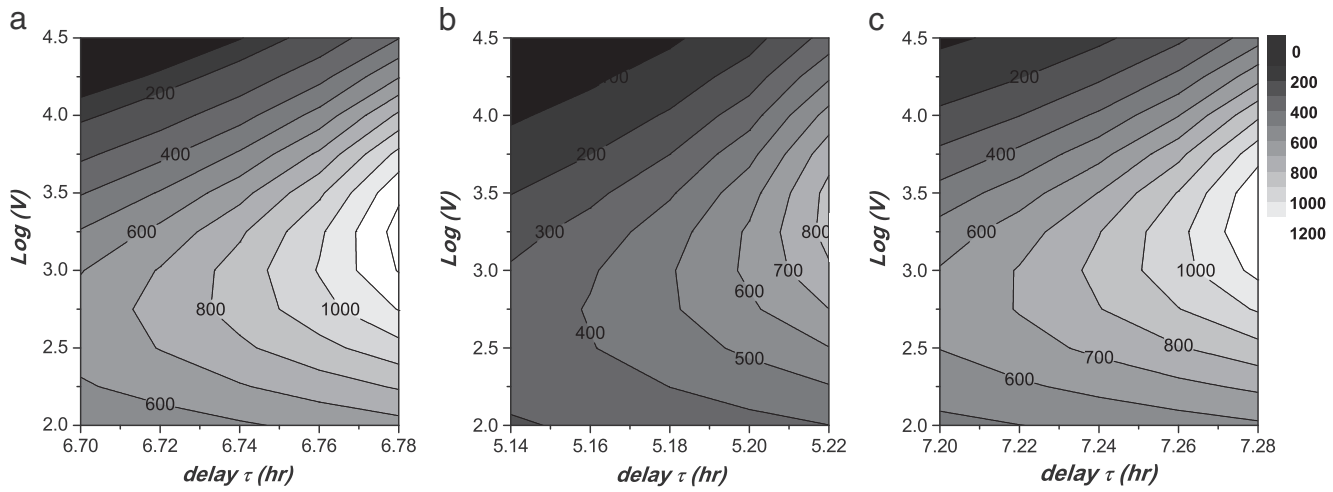

Fig. 5. The contour of SNR for different V and τ are obtained by theoretical analysis with the same parameters as those in Fig. 4.

3. Results and discussions

In the present study, we mainly focus on the effect of noise in the parameter region $\tau \lesssim \tau_h$. In this region, the deterministic description does not show oscillations. We perform numerical simulation of the CLE, Eq. (5), to generate trajectories $x(t)$. 16,384 data points with more than 200 periods are used to calculate the power spectrum, from which we can estimate the SNR. The final SNR values reported in the present study are all averaged over at least 200 independent trajectories. The time step used is 0.001 h, and the first 20,000 h is discarded before we record the data.

In Fig. 1, the amplitude of the NIO observed is shown for different system sizes, in comparison with the deterministic bifurcation diagram. The reaction rate constants for synthesis and degradation are $K_e = 1.0$ and $K_d = 0.075$, respectively, which give rise to a Hopf bifurcation at $\tau_h = 6.87$. Obviously, NIO can be triggered in a much wider region than that predicted by the deterministic model. Taking internal noise into account, the condition for circadian oscillation is much more relaxed. Since delay times in real biochemical reactions are often Gaussian distributed, the occurrence of NIO thus indicates a type of robustness of circadian oscillation to time delay. This is also consistent with recent works that for real circadian systems, the delay time required for oscillation is usually smaller than the theoretical prediction [7,43].

In Fig. 2a, typical time series of NIO for different system sizes are present with the same K_e and K_d in Fig. 1. The delay time is $\tau = 6.78$, which is near the Hopf bifurcation but in the subcritical region. We note that the period of NIO keeps nearly the same when V changes, as further demonstrated in Fig. 2b for other values of τ. That is, the period of noise induced circadian oscillation is quite robust to the internal noise. However, the period is quite sensitive to the parameter τ. Apparently, when τ is very small, $\tau < 5.0$ in this case, the period of the oscillation will be too small to be a typical circadian rhythm.

As shown in Fig. 1, the NIO-amplitude increases monotonically as the system size goes small, i.e., the internal noise goes large. However, this does not correspond to the increment in the regularity of NIO. Rather, one should use the SNR to characterize the performance of the NIO, which is a kind of trade-off between the regularity and strength of the NIO, as indicated by Eq. (14). Intuitively, with the decrease of system size, the NIO-amplitude r_m increases, while the auto-correlation time τ_c decreases. At an intermediate system size, the SNR may undergo a maximum.

In Fig. 3, numerical results for SNR are plotted as a function of the system size V for different τ. As expected, a clear-cut maximum shows up in each of the curves. Such phenomenon is usually recognized as internal noise coherent resonance (INCR).

To get a global view of the cooperative effect of τ and V, the contour plot of SNR as functions of both delay time τ and system size V is shown in Fig. 4a with $K_e = 1.0$, and $K_d = 0.075$. SNR becomes larger when τ is closer to the Hopf bifurcation τ_h. With decreasing τ, the system size corresponding to the best SNR becomes smaller. It has been found experimentally that circadian oscillations can be affected by stimulus such as light through modulation of synthesis and degradation of key molecular species [44–46]. Thus here we also study how the variation of K_e and K_d would affect the SNR. Fig. 4b is plotted with a larger decay parameter $K_d = 0.01$ and Fig. 4c has a smaller expression rate $K_e = 0.5$. One notes that the main features shown in Fig. 4a to c are similar. Using Eq. (14), we theoretically obtain the contour of SNR in Fig. 5 with the same parameters as those shown in Fig. 4. It can be seen that the analytical results agree with the simulation qualitatively well.

We emphasize that oscillations that are too irregular contribute little to biological systems. Therefore, although internal noise can induce stochastic oscillations even for $\tau < \tau_h$, which indicates the constructive role of internal noise, not all the NIO are useful. If SNR is too small, the NIO actually contributes little to signal transfer. Therefore, it is convenient for us to define the so-called effective oscillation (EO) if SNR is larger than a given threshold value. In the present study, we choose the threshold value to be SNR = 250.0, which is almost the largest value of SNR that the system could reach at a small system size $V = 100$ with $K_d = 0.01$. We note that changing this somewhat arbitrary threshold value does not change the qualitative results shown below. For a given system size, SNR decreases monotonically when τ decreases from τ_h. Assuming that SNR reaches the threshold value at τ_s, then we can define $\Delta\tau_{EO} = \tau_h - \tau_s$ as the range for the occurrence of EO. The wider $\Delta\tau_{EO}$ is, the more robustness the circadian system has.

In Fig. 6a, we plot $\Delta\tau_{EO}$ as a function of system size for different decaying rates K_d with $K_e = 1.0$. One can see that $\Delta\tau_{EO}$ shows non-monotonic dependence on V when K_d is large. If K_d is small enough, $\Delta\tau_{EO}$ decreases monotonically with increasing V. With the increment of K_d, the τ-range for effective oscillation shrinks remarkably. If K_d is of moderate value, $K_d = 0.075$ for instance, $\Delta\tau_{EO}$ shows no obvious change between $V = 100$ and $V \approx 3000$, indicating robustness against large internal fluctuation. For large K_d, on the other hand, small system size could decrease $\Delta\tau_{EO}$ significantly, as the curve $K_d = 0.1$ shows. It is worth mentioning that for $K_d = 0.1$, the maximum of $\Delta\tau_{EO}$ is around 10^3, which seems to match the real biological system size

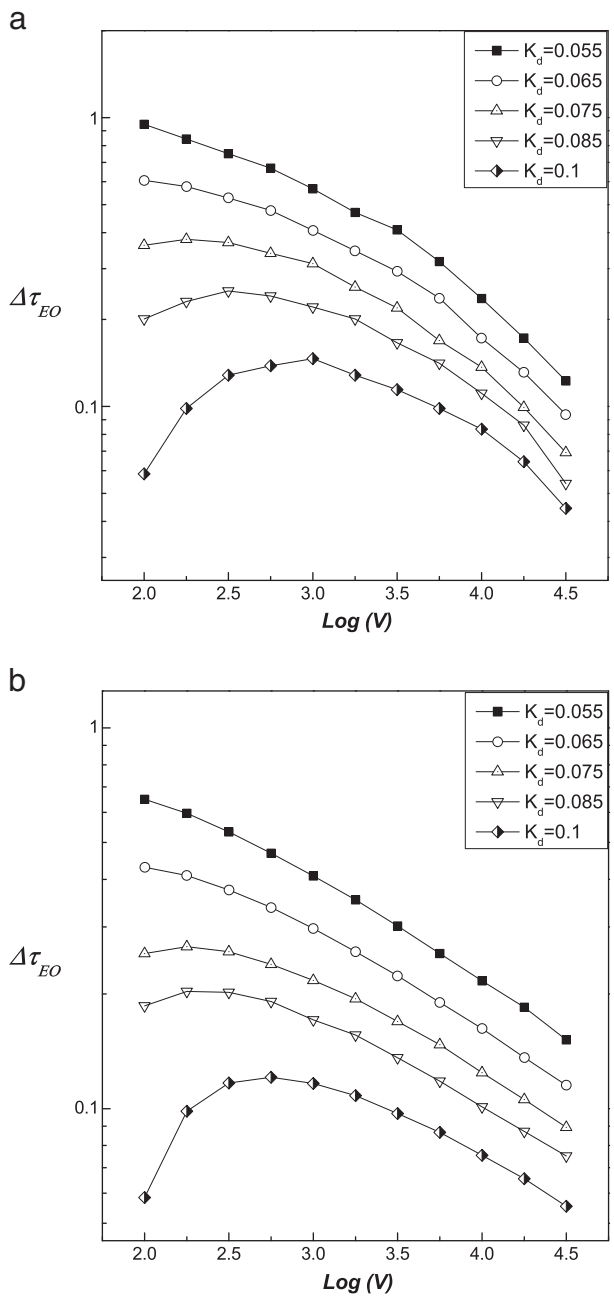

Fig. 6. The τ-range for the effective oscillation region $\Delta\tau_{EO}$ as a function of system size for different K_d. (a) Simulation results. (b) Theoretical results.

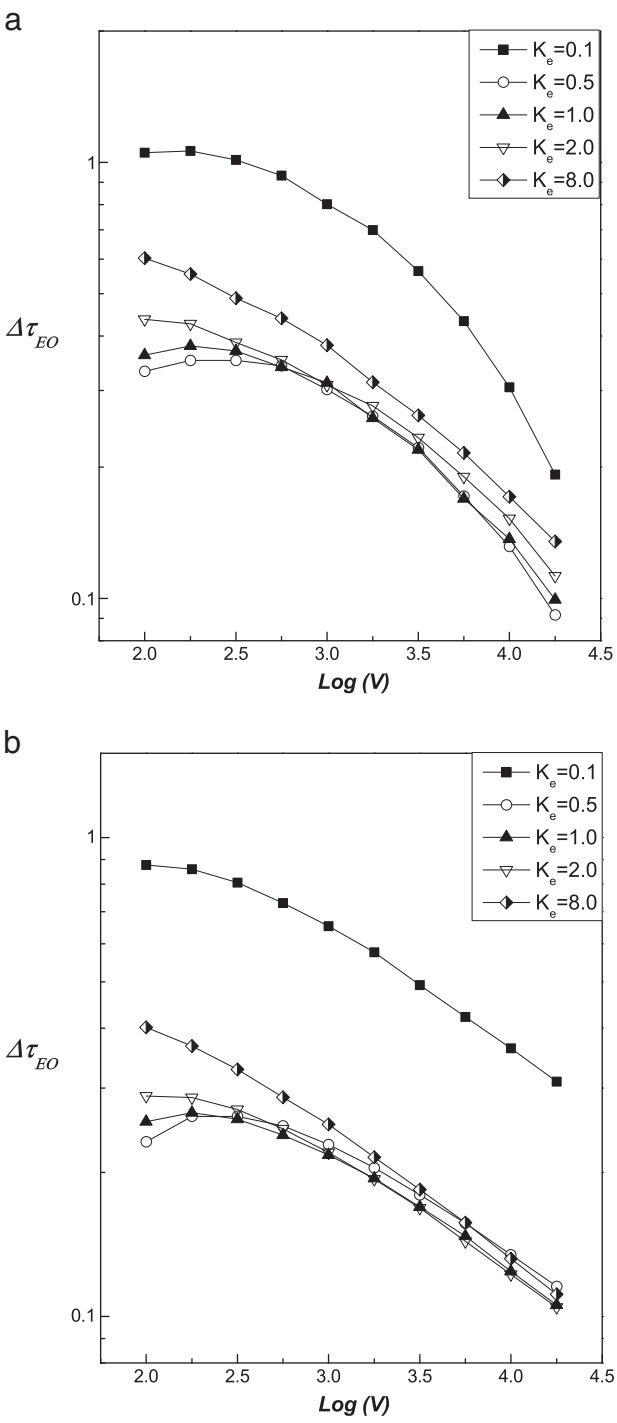

Fig. 7. The τ-range for the effective oscillation region $\Delta\tau_{EO}$ as a function of system size for different K_e. (a) Numerical results. (b) Theoretical results.

[47,48]. According to Fig. 6a, it seems that smaller decay rate tends to enlarge $\Delta\tau_{EO}$. However, if K_d is too small, τ_h will be too large and the average period of stochastic oscillation will be quite long. For instance, with $K_d = 0.055$ and $K_e = 1.0$, the bifurcation shifts to about $\tau_h = 9.18$ where the oscillation period is around 31 h. For this reason, the degradation rate should not be too small if one needs to obtain a typical circadian oscillation. For different K_e, on the other hand, the phenomenon is quite different. As is shown in Fig. 7a, the maxima of $\Delta\tau_{EO}$ is between $V = 316$ and $V = 562$ at moderate K_e. When K_e is large enough, $\Delta\tau_{EO}$ is a monotonically decreasing function of V. For $V > 10^3$, $\Delta\tau_{EO}$ shows no significant dependence on K_e, showing some kind of robustness. However, when the system size is small, higher expression rate could help enhance the performance of NIO in a larger delay time region, as the curve of $K_e = 8.0$ shows. When K_e is small enough, $K_e = 0.1$ for instance, $\Delta\tau_{EO}$ can be greatly enlarged. However, very small K_e may also lead to large τ_h and long period for stochastic oscillation. Therefore, moderate K_e is necessary to sustain a typical circadian oscillation. In Figs. 6b and 7b, $\Delta\tau_{EO}$ obtained from the theoretical formulae are presented, where the parameters are the same as those in Figs. 6a and 7a. We use the same rule for selecting the threshold value of EO as in Figs. 6a and 7a. Again, the main features observed in Figs. 6a and 7a are well reproduced.

4. Conclusions

In this paper, the effect of internal noise is studied in the vicinity of delay induced Hopf bifurcation. It is found that internal noise could induce circadian oscillation when the delay alone is not large enough to sustain deterministic oscillations. We calculate the SNR of the stochastic oscillations by numerical simulations of the CLE and using analytical formulae derived from the SNFT. It is shown that SNR shows maximum with the variation of system size, demonstrating a kind of optimal size effect. A threshold for SNR is introduced to distinguish the effective stochastic oscillations and the τ-range for their occurrence may also show non-monotonic dependence on the system size. The influence of gene expression and degradation rates on such phenomena is also investigated. This work provides us a comprehensive understanding on how internal noise and delay would affect circadian oscillations.

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