Light-noise-induced suprathreshold circadian oscillations and coherent resonance in *Drosophila*

Ming Yi*

Department of Physics, Central China Normal University, Wuhan 430079, China

Ya Jia†

CCAST (World Laboratory), P. O. Box 8730, Beijing 100080, China and Department of Physics, Central China Normal University, Wuhan 430079, China

Based on a reduced circadian oscillator model in *Drosophila* [Smolen *et al.*, Biophys. J. **83**, 2349 (2002)], the effects of light noise and time delay on a circadian oscillator near a Hopf bifurcation are studied by using numerical computation. When the light-controlled parameter is suprathreshold, it was found that the circadian oscillations can be induced by light fluctuation. There is an optimal light noise intensity at which a remarkable coherent circadian oscillation is observed, which implies a significant resonance phenomenon in the sense of preferred biological circadian oscillations. Time delay can control the coherence of noise-induced circadian oscillations and the strength of coherent resonance achieves a maximum under a moderate time delay.

Nearly all living organisms have developed the capability of generating autonomously sustained oscillations with a period close to 24 h [1,2]. These oscillations, known as circadian rhythms, are endogenous and can regulate many behavioral, physiological, and cellular processes. In *Drosophila*, like many other organisms, several genes are involved in sustaining the circadian rhythms. Among them, three genes (per, tim, and dclock) are rhythmically expressed. These genes define a transcription-translation-based negative autoregulatory feedback loop that comprises the core elements generating circadian rhythmicity [3].

Many mathematical models for circadian rhythms have been proposed based on these experimental observations [4]. These models are of a deterministic nature and take the form of a system of coupled ordinary differential equations. However, noisiness is an unavoidable by-product in real biological systems. Fluctuations in temperature, light, and humidity can affect chemical reaction rates and may perturb oscillatory behavior. Specifically, as an important control element for circadian rhythms, light controls circadian clock and the expression of genes in *Drosophila* by enhancing the degradation of phosphorylated TIM [5]. The fluctuation in light will be introduced into the clock system through *Drosophila* photoreceptors which can transduce light signals to the central oscillator [6]. We show that these light fluctuations give rise to a form of resonance behavior in this oscillatory system.

Stochastic resonance (SR) arises when noise amplifies a weak signal past a nonlinearity. Noisy nonlinear systems, however, can display SR-like behavior even without an external signal [7–9]. This phenomenon has been called autonomous SR [7] or coherence resonance (CR) [8]. Originally CR has been found in a simple dynamical system in the vicinity of a saddle-node bifurcation [7] and is due to nonuniformity of the noise-induced limit cycle [10]. In [8], CR was studied in excitable systems for the FitzHugh-Nagumo model near a supercritical Hopf bifurcation. A kind of CR that occurs in noisy dynamical systems close to the onset of bifurcation was explained in terms of two competing mechanisms based on noisy precursors [9]. Recently, Hou and co-workers have investigated CR in chemical reaction systems near Hopf bifurcation and reported a different mechanism of CR [11]. Their work implies that the structure of the bifurcation diagram plays an important role in the observed noisy dynamic behavior near the bifurcation point.

In this Brief Report, by employing a two-variable model proposed by Smolen *et al.* [12] for circadian oscillations in *Drosophila*, we have investigated the effects of light noise and time delay on a circadian oscillator near a Hopf bifurcation. It was found that the circadian oscillations can be induced by the light fluctuation. We have explained the observed CR phenomenon in terms of the underlying physical mechanisms and analyzed the dependence of CR strength on time delay.

The two-variable model is a minimal representation of the transcriptional regulation essential for circadian rhythmicity in *Drosophila* (as shown in Fig. 1). This model contains both a negative feedback loop, in which the protein PER binds the protein dCLOCK and thereby deactivates transcription of the per gene, and a positive feedback loop, in which activation of per transcription by dCLOCK results in binding of dCLOCK by PER and derepression of dclock. The reduced model consists of two differential equations, each with a time delay. The differential equations for PER concentration P and dCLOCK concentration L have two terms, one for synthesis and the other for degradation:

$$\dot{P}(t) = v_{sp}R_{sp} - k_{dp}P(t), \tag{1}$$

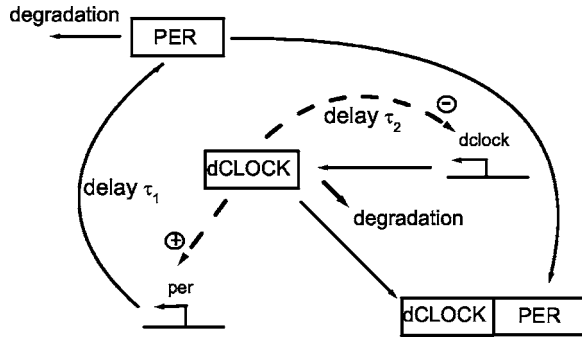$$\dot{L}(t) = v_{sc}R_{sc} - k_{dc}L(t), \tag{2}$$

with

FIG. 1. Schematic of model. A time delay τ_1 is included between changes in dCLOCK concentration and in PER synthesis, and a delay τ_2 is included between changes in dCLOCK concentration and in dCLOCK synthesis.

$$R_{sp} = \frac{L_{free}(t - \tau_1)}{K_1 + L_{free}(t - \tau_1)}, \qquad (3)$$

$$R_{sc} = \frac{K_2}{K_2 + L_{free}(t - \tau_2)}, \qquad (4)$$

with $L_{free}=(L-P)$ or zero, whichever is greater. The parameter values are $\tau_1=10$ h, $\tau_2=10$ h, $v_{sp}=0.5$ nM h^{-1}, $v_{sc}=0.25$ nM h^{-1}, $k_{dc}=0.5$ h^{-1}, $K_1=0.3$ nM, $K_2=0.1$ nM. Light controls the *Drosophila* clock by triggering PER degradation; the first-order degradation rate constant for PER, k_{dp} in Eq. (1), increases with light, accordingly. Therefore, k_{dp} is a light-controlled parameter. The bifurcation diagram for PER concentration with the increment of light-controlled parameter k_{dp} is plotted in Fig. 2(a). The concentration of PER oscillates when $0 < k_{dp} < 2.8$ h^{-1}. In the oscillation region the period of PER oscillations decreases with increasing light-controlled parameter k_{dp} at first [see Fig. 2(b)], reaches a minimum, and then increases slightly. Finally, the period keeps a constance value; the corresponding parameter region is from about 2.5 to 2.8 h^{-1} [see the inset graph in Fig. 2(b)]. It can be seen in Fig. 2(b) that to ensure the circadian oscillations with a period close to 24 h, k_{dp} should be greater than 0.35 h^{-1}.
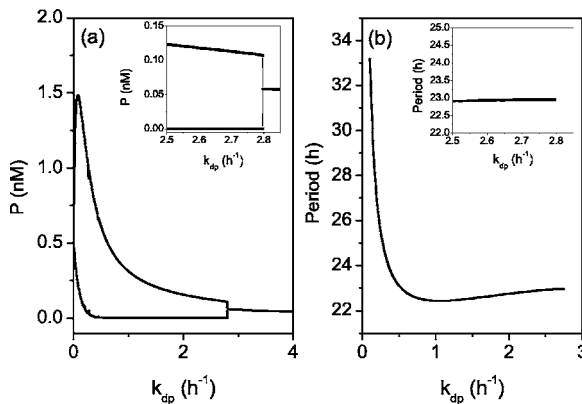

FIG. 2. (a) Bifurcation diagram for the deterministic model. Inset: The amplitude near the Hopf bifurcation point k_{dp}^*. (b) Dependence of the period on k_{dp}. Inset: The period near k_{dp}^*.
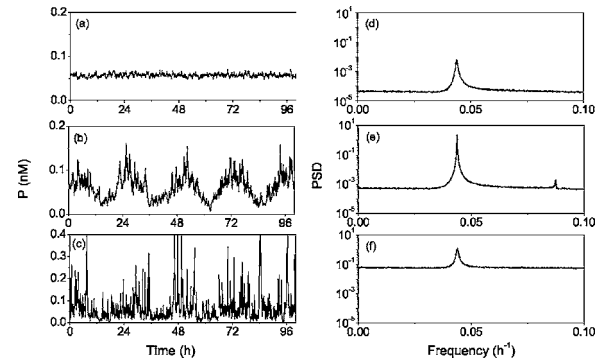

FIG. 3. Time series [(a)–(c)] and the power spectral density [(d)–(f)] of PER concentration for different light noise intensity: from top to bottom $D=0.002$, 0.02, and 0.2.

In order to study the effects of light fluctuation on circadian rhythms in *Drosophila*, we assume that the light-controlled parameter k_{dp} in Eq. (1) is a stochastic process and takes the form of

$$k_{dp} = k_{dp}^0[1 + \xi(t)], \qquad (5)$$

where $k_{dp}^0=2.85$ h^{-1} is a suprathreshold value at which there is no circadian oscillations in the absence of noise. $\xi(t)$ is Gaussian white noise with zero mean, and its autocorrelation function is $\langle \xi(t)\xi(t')\rangle=2D\delta(t-t')$, where D is the light noise intensity. In the absence of light noise, the system is a stable steady state at $k_{dp}^0=2.85$ h^{-1}. In the presence of light noise, however, the noise lets the system visit the oscillatory region now and then, and results in stochastic oscillation. Equations (1)–(5) were integrated by a simple forward Euler algorithm with a fixed time step of 0.01 h. The temporal course of PER concentration is shown by Figs. 3(a)–3(c) for different noise intensity, respectively. For the small and large noise intensities, it can be seen that the rhythmicity of suprathreshold circadian oscillations is inconspicuous. For the moderate noise intensity, however, circadian oscillations (period close to 24 h) are clearly observed. This result shows that light fluctuation plays a constructive role in the *Drosophila* circadian oscillations.

The effects of light fluctuation on the circadian oscillations can be investigated by utilizing the power spectral density (PSD) of proteins concentration. Figures 3(d)–3(f) plot the PSD of PER concentration for different noise intensity D, respectively. Clear peaks appear in the PSD, which implies that the time series contains periodic information. The main frequency (0.0436 h^{-1}) in the PSD of the stochastic oscillations induced by light fluctuations is close to that of the real biological circadian oscillation (i.e., $1/23.2 \approx 0.0431$ h^{-1}). For an intermediate noise intensity D, the peak is the most pronounced among the three. Moreover, the inset graph in Fig. 4 displays the variation of height H of the peak with the increasing of D. The height of the peak increases at first, reaches a maximum, and then decreases with noise intensity, which qualitatively reflects the remarkable periodicity of circadian oscillations induced by light fluctuation can be achieved under a proper noise intensity.
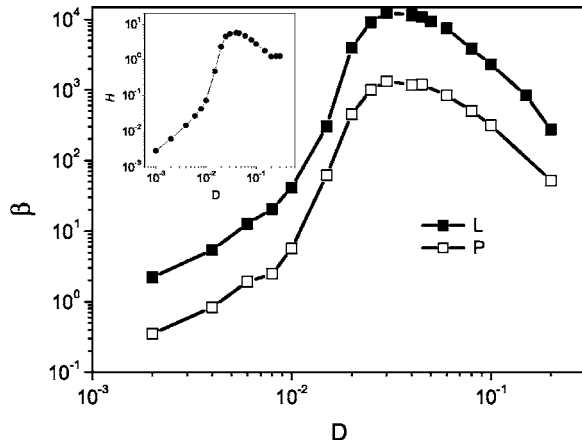
FIG. 4. The measure of coherent (β) for PER and dCLOCK against the light noise intensity D. Inset: Spectral peak height H for PER vs D.

FIG. 5. The PSD of PER for different time delays τ_2 when D =0.02, k_{dp}^0=2.85 h^{-1}. Inset: The dependence of the main frequency f_p in the PSD on τ_2.

To characterize this circadian oscillation, we have calculated an appropriate measure parameter β [7]:

$$\beta = H(\Delta f/f_p)^{-1}, \tag{6}$$

where f_p is the frequency of the peak in the PSD, Δf is the width of the peak at its half maximal height, and thus $\Delta f/f_p$ reasonably corresponds to the relative width of the peak. In fact, β represents the degree of CR and is actually the signal-to-noise ratio [7]. Figure 4 shows the signal-to-noise ratio β for both PER and dCLOCK vs light noise intensity D, respectively. For each protein there is an optimal noise intensity $D_{opt} \approx 0.03$ at which β is maximum. It means that there is an optimal noise intensity at which the remarkable circadian coherent oscillations induced by light fluctuation occur in the circadian oscillation of *Drosophila*. This effect of the light noise is a significant resonance phenomenon, in the sense that the maximum implies a preferred biological circadian oscillation, which is the well known CR since there is no external periodic signal in this system.

The mechanism of CR in this system is different from that previously reported in [8,10]. One only needs to account for the increment of the CR strength in the small D range. Near the Hopf bifurcation point k_{dp}^*, there exists a particular parameter region from about 2.5 to 2.8 h^{-1} (see Fig. 2), which is very crucial for the observed CR phenomenon. First, in the parameter region, the period is nearly a constant value (22.96 h) in the deterministic model. With the increment of D from zero, the system will pass across the distance $k_{dp}^0 - k_{dp}^*$ and visit the region randomly but achieve the same period. So noise-induced oscillations will produce an expanded peak at the frequency ($1/22.96 \approx 0.0436$ h^{-1}) in the PSD. The more frequently the system visits the region, the more pronounced the spectral peak becomes. Then the strength of noise-induced coherent oscillations could be enhanced. Second, similar to that in some chemical reaction systems, the bifurcation character can also be responsible for the observed CR [11]. The farther the light-controlled parameter is from k_{dp}^*, the stronger is the deterministic oscillation in the particular region. With the increment of D from zero,
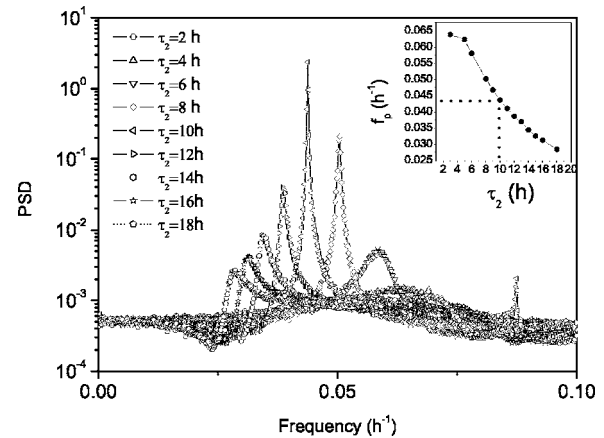
the chance for the system to enter the stronger oscillation region would increase. Of course, if D is too large, the coherent oscillations will be annihilated by the noise. Through the above mechanisms, CR will be constructed in the region. One expects that a proper theoretical model would help in understanding this behavior.

Then we will investigate the influence of time delay on the coherence of noise-induced circadian oscillations. Because τ_1 has been experimentally determined [12], we only need to investigate the effect of τ_2 on the circadian oscillator. In Fig. 5 we fixed k_{dp}^0=2.85 h^{-1} at which the system is a stable steady state for every time delay, and then plotted the PSD of noise-induced oscillations for different τ_2. When τ_2 comes close to 10 h, the main frequency f_p in the PSD is close to 0.0436 h^{-1}, just the frequency of circadian rhythm (see the inset graph in Fig. 5). In order to ensure the biological validity, τ_2 should be restricted to a range from about 8 to 12 h. Figure 6 shows the signal-to-noise ratio β for PER vs D. It was found that the coherence of noise-induced oscillations increases or decreases depending on τ_2 and reaches a maximum at $\tau_2 \approx 9$ h. One reason is that the bifurcation point varies as τ_2 so that the distance from k_{dp}^0 to k_{dp}^* changes.
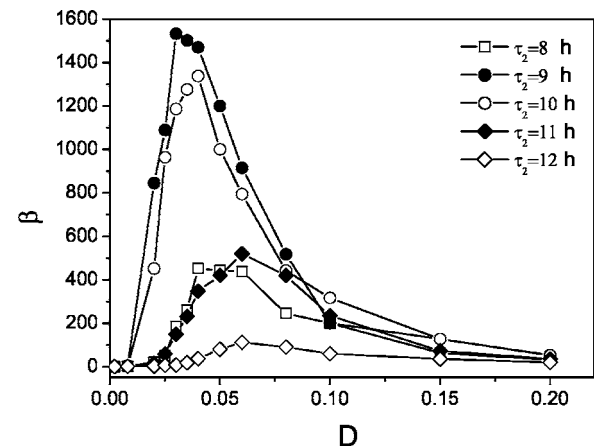

FIG. 6. The measure of coherence (β) against the light noise intensity D for different choices of time delay τ_2.

Some other studies also have shown that time delay can be considered as a mechanism of delay-induced coherence resonance [13] and a means of control of noise-induced motion [14].

In conclusion, the effects of light fluctuations and time delay on the *Drosophila* circadian oscillator near a Hopf bifurcation were investigated. It was found that circadian oscillations can be induced by light fluctuation. There is an optimal light noise intensity at which a remarkable coherent circadian oscillation was observed, which implies a significant resonance phenomenon in the sense of preferred biological circadian oscillations. The coherence of noise-induced circadian oscillations can be controlled by time delay and achieves a maximum under a moderate time delay. Circadian oscillations can be robust to light noise due to CR, we expect that the observed CR is a generic phenomenon even for other detailed models of circadian oscillator.

It should be pointed out the stochastic kinetic equations [i.e., Eqs. (1) and (2)] considered here are only valid when the molecule numbers of proteins are large. Indeed, most models of circadian clocks use intracellular genetic networks based on positive and negative regulatory elements, where the number of reactant molecules is often low [15], then the discrete nature of the proteins might become important, and a Markov chain might serve as a better model. An important point is that molecular noise will not destroy circadian rhythm [16], it may even play a constructive role [17]. Therefore, it would be an interesting work to study the dependence of CR on molecular number and environmental noise.

[1] M. C. Moore-Ede, F. M. Sulzman, and C. A. Fuller, *The Clocks that Time U s: Physiology of the Circadian Timing System* (Harvard University Press, Cambridge, MA, 1982).

[2] L. N. Edmunds, *Cellular and Molecular Bases of Biological Clocks* (Springer, New York, 1988).

[3] J. C. Dunlap, Cell **96**, 271 (1999); M. W. Young, Trends Biochem. Sci. **25**, 601 (2000); M. W. Young and S. A. Kay, Nat. Rev. Genet. **2**, 702 (2001).

[4] A. Goldbeter, *Biochemical Oscillations and Cellular Rhythms* (Cambridge University Press, Cambridge, U.K., 1996); J. C. Leloup and A. Goldbeter, J. Biol. Rhythms **13**, 70 (1998); J. C. Leloup, D. Gonze, and A. Goldbeter, *ibid.* **14**, 433 (1999); P. Smolen, D. A. Baxter, and J. H. Byrne, J. Neurosci. **21**, 6644 (2001).

[5] M. P. Myers, K. Wager-Smith, A. Rothenfluh, and M. W. Young, Science **271**, 1736 (1996).

[6] P. Emery, W. V. So, M. Kaneko, J. C. Hall, and M. Rosbash, Cell **95**, 669 (1998).

[7] G. Hu, T. Ditzinger, C. Z. Ning, and H. Haken, Phys. Rev. Lett. **71**, 807 (1993).

[8] A. Pikovsky and J. Kurths, Phys. Rev. Lett. **78**, 775 (1997).

[9] A. Neiman, P. I. Saparin, and L. Stone, Phys. Rev. E **56**, 270 (1997).

[10] W. J. Rappel and S. H. Strogatz, Phys. Rev. E **50**, 3249 (1994).

[11] Z. H. Hou, and H. W. Xin, Phys. Rev. E **60**, 6329 (1999); Z. H. Hou, L. F. Yang, and H. W. Xin, J. Chem. Phys. **111**, 1592 (1999); Z. W. Wang, Z. H. Hou, and H. W. Xin, Chem. Phys. Lett. **362**, 51 (2002).

[12] P. Smolen, D. A. Baxter, and J. H. Byrne, Biophys. J. **83**, 2349 (2002).

[13] T. Ohira and Y. Sato, Phys. Rev. Lett. **82**, 2811 (1999); L. S. Tsimring and A. Pikovsky, *ibid.* **87**, 250602 (2001).

[14] N. B. Janson, A. G. Balanov, and E. Schöll, Phys. Rev. Lett. **93**, 010601 (2004).

[15] N. Barkai and S. Leibler, Nature (London) **403**, 267 (1999).

[16] D. Gonze, J. Halloy, and A. Goldbeter, Proc. Natl. Acad. Sci. U.S.A. **99**, 673 (2002).

[17] R. Steuer, C. S. Zhou, and J. Kurths, BioSystems **72**, 241 (2003).