Biophysical Chemistry 145 (2009) 57–63

Contents lists available at ScienceDirect

Biophysical Chemistry

journal homepage: http://www.elsevier.com/locate/biophyschem

# Internal noise-driven circadian oscillator in *Drosophila*

Qianshu Li *, Hengyu Li

*The Institute for Chemical Physics, Beijing Institute of Technology, Beijing, 100081, China*

ARTICLE INFO

*Article history:*
Received 6 July 2009
Received in revised form 27 August 2009
Accepted 29 August 2009
Available online 6 September 2009

*Keywords:*
Circadian rhythms
Noise-sustained oscillator
Intrinsic coherence resonance

ABSTRACT

An internal noise-driven oscillator was studied in a two-variable *Drosophila* model, where both positive feedback and negative feedback are crucial to the circadian oscillations. It is shown that internal noise could sustain reliable oscillations for the parameter which produces a stable steady state in the deterministic system. The noise-sustained oscillations are interpreted by using phase plane analysis. The period of such oscillations fluctuates slightly around the period of deterministic oscillations and the coherence of oscillations becomes the best at an optimal internal noise intensity, indicating the occurrence of intrinsic coherence resonance. In addition, in the oscillatory region, the coherence of noisy circadian oscillations is suppressed by the internal noise, but the period is hardly affected, demonstrating the robustness of the *Drosophila* model for circadian rhythms to the intrinsic noise.



## 1. Introduction

Nearly all living organisms have developed the capability of generating circadian rhythms to anticipate daily changes in the environment [1,2]. The molecular mechanism for these rhythms relies on negative feedback exerted by a protein on the expression of its gene [3–8]. This negative feedback provides basis for many theoretical models of circadian rhythms [9–12], which successfully predict that in a certain range of parameter values, the genetic regulatory network undergoes sustained oscillations corresponding to circadian rhythmic behavior. Recent experimental studies in *Neurospora* [13], *Drosophila* [14,15] and *Mammalian* [16] indicate that positive feedback presents in circadian clock system and interacts with negative feedback. Furthermore, in *Drosophila*, some theoretical studies also suggest that positive feedback is needed in circadian rhythm and a few detailed models composing of both positive and negative feedback loops have been developed [17–21]. In these models, several possible functions that positive feedback plays in circadian clocks were proposed. For example, Tyson et al. [18] found that positive feedback decreased the sensitivity of the oscillatory period to some crucial parameters in *Drosophila*, and the oscillations would vanish if the positive feedback was removed. Hasting [21] suggested that an additional positive feedback loop to a single negative-feedback model would increase the precision and the stability of oscillation to stochastic fluctuations. And a recent theoretical study indicates that positive feedback can make the system achieve a widely tunable frequency and near-constant amplitude and be more robust and easier to evolve [22].

Because the number of molecules involved in the regulatory mechanism at the cellular level may be small, internal noise, resulting from random fluctuations of biochemical reaction events in finite-size biochemical systems [23], is remarkable and must be considered in the regulatory processes. In the past decade, based on the assumption that the internal noise is destructive, most studies mainly focused on the robustness or resistance of circadian clock systems to the noise [24,25]. Actually, it is well-known that in biological systems [26–30] noise could play some constructive roles, such as stochastic resonance [31] and coherence resonance [32]. Especially, Perc et al. further demonstrated that internal noise could induce spatial coherence resonance [33,34]. Very recently, the constructive effects of internal noise were also found in circadian clock systems [35–37]. For example, internal noise induces stochastic oscillations in a region subthreshold to the deterministic oscillatory dynamics [35] and such oscillations could show best regularity at an optimal noise level [36,37], demonstrating the internal noise coherence resonance. However, these studies are carried out in the model consisting of only negative feedback and time delay. Since time delay could provide a noise-independent mechanism for circadian oscillation [38], it remains unclear that whether internal noise could induce circadian oscillations independently in a circadian model. Furthermore, to the best of our knowledge, few studies on noise effects have been made in those models composed of positive and negative feedbacks. We would address this issue here.

In this paper, the effects of internal noise in a simple *Drosophila* model proposed by Tyson [18] have been investigated and it is found that internal noise can produce circadian oscillations in the deterministic model with a steady state. Furthermore, the noise-sustained circadian oscillation shows best performance at an optimal noise level, demonstrating the occurrence of intrinsic coherence resonance (ICR). In

* Corresponding author. Fax: +86 10 6891 2665.
*E-mail address:* qsli@bit.edu.cn (Q. Li).

0301-4622/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.bpc.2009.08.009

addition, in the oscillatory region, the coherence of noisy circadian oscillations is suppressed by the internal noise, but the period is hardly affected, demonstrating the robustness of the *Drosophila* model for circadian rhythms to the intrinsic noise.

## 2. Model description

The model used in the present study is a simple two-component model of circadian rhythms based on dimerization and proteolysis of PER and TIM proteins [18]. This model contains both a negative feedback loop and a positive feedback loop. PER and TIM proteins are synthesized in the cytoplasm, and then they may combine to produce relatively stable heterodimers or be destroyed by proteolysis. Heterodimeric complexes are transported into the nucleus, and inhibit transcription of *per* and *tim* mRNA, which forms the negative feedback loop. PER monomers are more rapidly phosphorylated by DBT and then degraded, whereas PER dimers are poorer substrates for DBT. In this condition, PER/TIM dimers protect PER protein from degradation and accelerate its accumulation, constructing the positive feedback loop. The detail mechanism can be found in Ref. [18]. The system can be described as follows:

$$\frac{dm}{dt} = \frac{v_m}{1 + (p_2/P_{\text{crit}})^n} - k_m m, \tag{1}$$

$$\frac{dp_1}{dt} = v_p m - \frac{k_{p1}' p_1}{J_p + p_1 + r p_2} - k_{p3} p_1 - 2k_a p_1^2 + 2k_d p_2, \tag{2}$$

$$\frac{dp_2}{dt} = k_a p_1^2 - k_d p_2 - \frac{k_{p2} p_2}{J_p + p_1 + r p_2} - k_{p3} p_2, \tag{3}$$

where the variables $m$, $p_1$ and $p_2$ denote the concentrations of *per* mRNA , PER protein monomer and PER protein dimer respectively. As described in Ref. [18], if PER monomers and dimers are in rapid equilibrium, and the equilibrium coefficient $K_{\text{eq}} = k_a/k_d$, $p_2 = K_{\text{eq}} p_1^2$, let total protein $p_t = p_1 + 2p_2$, $q = p_1/p_t$. And both the Hill coefficient $n$ and the ratio of enzyme–substrate dissociation constants $r$ are chosen to be 2. Then, the model can be reduced to two different equations:

$$\frac{dm}{dt} = \frac{v_m}{1 + (p_t(1-q)/2P_{\text{crit}}))^2} - k_m m, \tag{4}$$

$$\frac{dp_t}{dt} = v_p m - \frac{k_{p1} p_t q + k_{p2} p_t}{J_p + p_t} - k_{p3} p_t, \tag{5}$$

with

$$q = \frac{2}{1 + \sqrt{1 + 8K_{\text{eq}} p_t}}, \tag{6}$$

where, $k_{p1} = k_{p1}' - k_{p2} \approx k_{p1}'$. And the detail simplification process can be found in Ref. [18]. Note that this reduced model is mainly used in the present paper. Because the phosphorylation of PER is a prelude to its degradation and evidently affects the period of the clock [39], the maximum monomer phosphorylation rate $k_{p1}$, which is temperature dependent, is chosen as the control parameter. And a set of parameters is used in the present paper as follows: $v_m = 1\ \text{nM h}^{-1}$, $k_m = 0.1\ \text{h}^{-1}$, $v_p = 0.5\ \text{h}^{-1}$, $k_{p2} = 0.03\ \text{nM h}^{-1}$, $k_{p3} = 0.1\ \text{h}^{-1}$, $K_{\text{eq}} = 50\ \text{nM}^{-1}$, $J_p = 0.05$ nM, $P_{\text{crit}} = 0.1$ nM. The detailed descriptions of the parameters and their values can be also found in Ref. [18].

To account for internal noise, the deterministic description is no longer valid. Generally, one can describe such a reaction system as a birth–death stochastic process governed by a chemical master equation which describes the time evolution of the probability of having a given number of molecules of reaction species [40]. There is no procedure to solve this master equation analytically, but it provides a starting point for numerical simulations. One of the widely used simulation algorithms is the exact stochastic simulation (ESS) method introduced by Gillespie in 1977 [41], which stochastically determines what is the next reaction step and when it will happen according to the transition probability of each reaction event. In accordance with the ESS method, the number of *per* mRNA is introduced as $M$ and the total number of PER protein as $P$, such that the concentrations of the reactants are obtained as $m = M/V$, $p_t = P/V$, where $V$ is the system size and has a dimension of volume. Then, the biochemical reactions in the *Drosophila* model can be decomposed into five elementary reaction steps. See Table 1 for the corresponding transition rates. Note that the transition rates are proportional to $V$.

The ESS method has been widely used to study effects of internal noise in many systems, but it is too time consuming when the system size is large. Furthermore, the ESS methods cannot afford us a clear perspective on the origin and magnitude of internal noise in a system. To overcome this problem, an alternative method, the chemical Langevin method, to study internal noise was proposed by Gillespie [42]. It was proved that the system can be well approximated by a chemical Langevin equation (CLE) if a macroinfinitesimal time scale exists in the system. Such a CLE clearly shows how internal noise depends on the parameter values and the system size, as well as the state variables evolving with time. The CLE for the current model reads:

$$\frac{dm}{dt} = (a_1 - a_2) + \frac{1}{\sqrt{V}}[\sqrt{a_1}\zeta_1(t) - \sqrt{a_2}\zeta_2(t)], \tag{7}$$

$$\frac{dp_t}{dt} = (a_3 - a_4 - a_5) + \frac{1}{\sqrt{V}}[\sqrt{a_3}\zeta_3(t) - \sqrt{a_4}\zeta_4(t) - \sqrt{a_5}\zeta_5(t)], \tag{8}$$

where $a_i$ $(i = 1,\ldots,5)$ are the transition rates per volume, as shown in Table 1, and $\zeta_i$ $(i = 1,\ldots,5)$ are independent Gaussian white noises with $<\zeta_i(t)> = 0$ and $<\zeta_i(t)\,\zeta_j(s)> = \delta_{ij}\delta(t-s)$. In the absence of second terms in the brackets at the right side of Eqs. (7) and (8), these equations are equivalent with the deterministic Eqs. (4) and (5), respectively. According to the description in Ref. [42], internal noise is actually denoted by the second terms in the bracket at the right side of Eqs. (7) and (8), from which it is clearly seen that the magnitude of internal noise scales as $1/\sqrt{V}$ and depends on the control parameters and the concentrations of PER and *per*.

In the present article, the CLE method is used for numerical simulation, while the ESS method is only used to show consistency with the CLE method if necessary. To investigate the influences of internal noise in the *Drosophila* model, the magnitude of internal noise should be scanned over a relatively wide range. Furthermore, the corresponding deterministic kinetics should be kept unchanged so as to obtain the pure effect of internal noise. The deterministic kinetics does not depend on the system size $V$. So the magnitude of the internal noise could be varied via changing $V$.

## 3. Results and discussion

To investigate the effect of internal noise, it is necessary to study the corresponding deterministic kinetics for comparison. Eqs. (4) and

**Table 1**
Reaction steps and corresponding transition rates involved the *Drosophila* model.

| Transition processes | Description | Transition rate |
|---|---|---|
| $M \to M+1$ | The synthesis of mRNA *per* | $W_1 = a_1 V = \frac{v_m}{1 + (p_t(1-q)/2P_{\text{crit}}))^2} V$ |
| $M \to M-1$ | The degradation of mRNA | $W_2 = a_2 V = k_m M$ |
| $P \to P+1$ | The translation of protein from mRNA | $W_3 = a_3 V = v_p M$ |
| $P \to P-1$ | The phosphorylation of protein PER (monomer and dimer) | $W_4 = a_4 V = \frac{k_{p1} p_t q + k_{p2} p_t}{J_p + p_t} V$ |
| $P \to P-1$ | The proteolysis of protein PER | $W_5 = a_5 V = k_{p3} P$ |

(5) are integrated numerically by Eular method with a time step of 0.001 h. The simulation results show that, when increasing the control parameter $k_{p1}$, the system undergoes two *Hopf bifurcation* (HB) points at $k_{p1} \approx 3.389$ and $k_{p1} \approx 25.55$. The maximum and minimum values of the variable $p_t$ are plotted in Fig. 1(a), and the corresponding periods are shown in Fig. 1(b), which are obtained from the inverse of the frequency of the highest peak in the corresponding power spectrum (see Fig. 4, discussed below). Two HB points divide the parameter space into three regions: the high steady state to the left hand side (HSS region), the oscillation state in the middle (OSC region), and the low steady state to the right hand side (LSS region).

It has been reported that external noise or internal noise often has constructive effects in the steady state region near the bifurcation point [43–45]. Therefore, influences of internal noise are investigated firstly in the *Drosophila* oscillator within the SS regions near the HB point. Eqs. (7) and (8) are calculated using the Euler–Maruyama method [46] with the time step of 0.001 h. In Fig. 1(a), the maximum and minimum values of $p_t$ in the stochastic model with the system size $V = 1000$ is plotted. Good qualitative agreement between the ESS and CLE methods is shown in this figure. And it is clearly seen that, in the stochastic case, the HB points defined by the deterministic dynamics disappear, and 'stochastic' oscillations appear in the SS regions near the HB points. Periods of such oscillations are also close to the periods of deterministic oscillations, as shown in Fig. 1(b). These results indicate that the phenomenon of noise-sustained oscillation is in agreement with the recent report that, for the dynamics of an irreversible biochemical reaction system in the mesoscopic world, circular motion is a necessary characteristic of nonequilibrium steady state even when the corresponding macroscopic system shows no sign of oscillation [47]. Since these oscillations are supported by internal noise, one may call them noise-sustained circadian oscillations (NSCO).

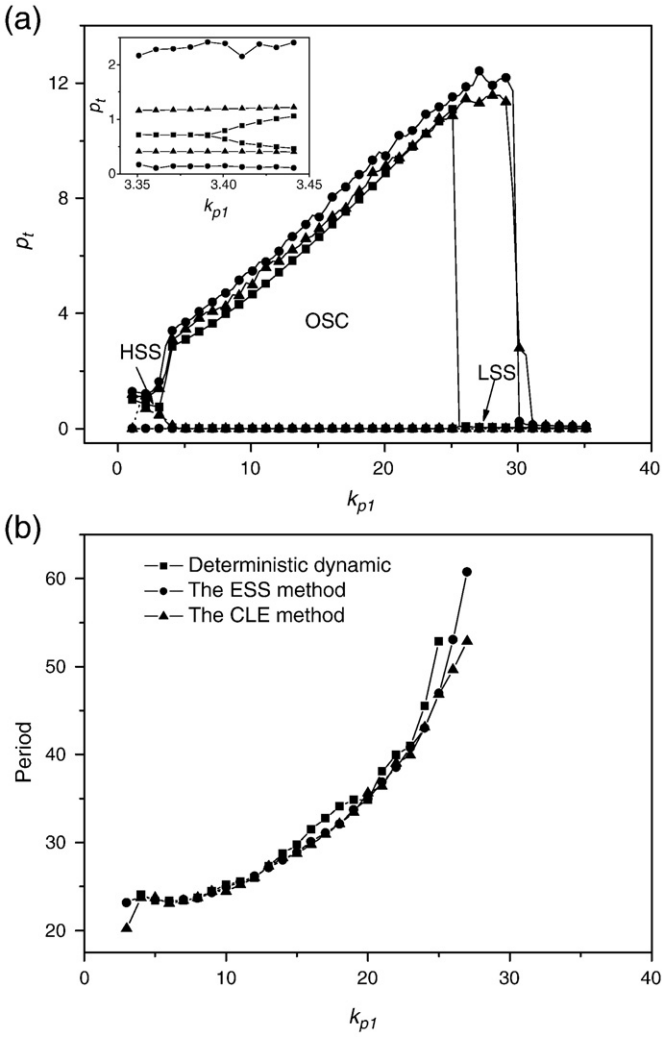


**Fig. 1.** (a) The bifurcation diagram of the stochastic reduced model with respect to the control parameter $k_{p1}$, obtained with ESS method (circles) and CLE method (triangles), and the diagram of the deterministic model (squares). The inset is the enlarged figure near the left HB point. (b) The corresponding periods of the stochastic and deterministic oscillations as function of the $k_{p1}$. Here the stochastic simulation is carried out for $V = 1000$ and two HB points in the deterministic limit are $k_{p1} \approx 3.389$ and $k_{p1} \approx 25.55$.

Recently, it is reported that commonly used reduced models that ignore fast operator reactions can not describe full stochastic behavior because the stochastic dynamics near the fixed point might be changed remarkably by adiabatic elimination of the fast processes [48]. Therefore, the stochastic dynamic of the unreduced model described with Eqs. (1)–(3) is also investigated here. Eqs. (1)–(3) are integrated numerically with $k_a = 50$, $k_d = 1$ and other parameters same to those in Fig. 1(a). And the stochastic dynamic of this model are simulated in CLE method with $V = 1000$. The deterministic and the stochastic bifurcation diagrams (not shown) are similar to those obtained in the reduced model. And NSCO is also obtained, which means that the reduced model could be adopted to explain noise effects on the mechanism for circadian rhythms in *Drosophila*.

Because there are only two variables in this model, the phase plane analysis could be taken to explain the aforementioned behavior. The M-nullcline and P-nullcline obtained by $dm/dt = 0$ and $dp_t/dt = 0$ are given as [18]:

$$\text{M} - \text{nullcline}: \quad m = \frac{v_m}{k_m[1 + (\frac{p_t(1-q)}{2P_{\text{crit}}})^2]}, \tag{9}$$

$$\text{P} - \text{nullcline}: \quad m = \frac{k_{p1}p_t q + k_{p2}p_t}{v_p(J_p + p_t)} + \frac{k_{p3}p_t}{v_p}. \tag{10}$$

Fig. 2 shows the phase plane portraits for $k_{p1} = 26$. It is shown that the M-nullcline and P-nullcline intersect at a stable fixed point, i.e. the deterministic system stays at a steady state. However, the system near the HB point has excitability [49], which means that, for a sufficiently large perturbation, the system will go through a large excursion in phase-space before it comes back to the stable fixed point again (see line a in Fig. 2 for the orbit for return to the stable fixed point). Therefore, when noise comes into play, the system is driven far away from the steady state with finite probability and thus is able to exhibit stochastic oscillations that correspond to a stochastic limit cycle in phase space (see line b in Fig 2 for the stochastic limit cycle with $V = 800$), resulting in the NSCO.

Barkai and Leibler [23] have suggested that the ability to maintain constant circadian periodicity despite global change in the state of the cell is probably necessary for the circadian clock to be embedded successfully within the cell, because the variations in nutrition, growth conditions or temperature may induce global change in transcription and translation rates and affect the period of transcription or translation-based oscillators. Herein, Fig. 1(a) shows that the deterministic model sustains circadian oscillations in a precise region of the parameter space, whereas the stochastic model could sustain the oscillations in a wider region due to NSCO. Moreover, as shown in Fig. 1(b), the periods of stochastic oscillations fluctuate slightly around periods of circadian oscillations in the OSC region of the deterministic model. This implies that, in *Drosophila*, the circadian oscillations become more robust to the variation of the control parameter in virtue of the internal noise. Because the control parameter is affected by temperature, these results might provide another point of view to explain the temperature compensation [50,51].

In the following, the influence of noise intensity is considered on the oscillations. The control parameter $k_{p1}$ is chosen to 26, near the

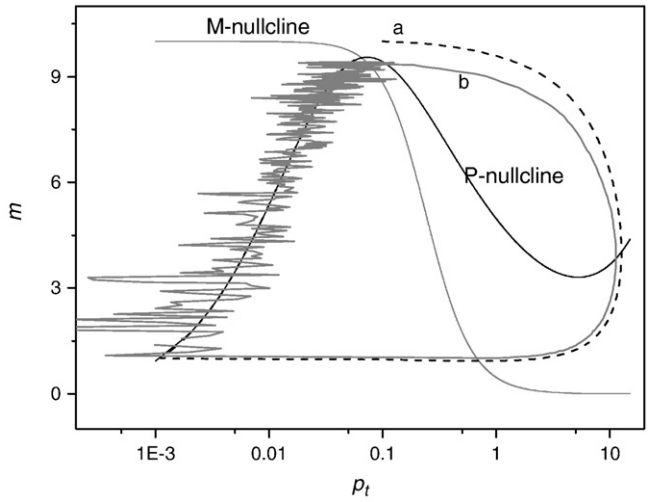


**Fig. 2.** Phase plane portrait for the deterministic and stochastic dynamics with $k_{p1}=26$. Line a: the orbit along which the deterministic system with initial state $p_t=10$, $m=0.1$ returns to the stable fixed point; line b: the stochastic trajectory for corresponding stochastic system with $V=800$.

right HB point, which gives rise to a steady state in the deterministic system. Figs. 3 and 4 display the time series of PER concentration and the corresponding power spectrum for the system size $V=20$, 800, and 100,000, respectively. Both the time series and power spectrum are obtained through the CLE method. Note that the time series used to calculate the power spectrum contain 16,384 data points with an average time interval 0.2 h. A Welch window function [52] is used during the estimation of the power spectrum. The smoothed curves in Fig. 4 are obtained by nearest averaging over 15 points from the original ones. It is seen that, in Fig. 3(c), the system size ($V=100{,}000$) is large, the internal noise is so small that the NSCO shows a weak periodicity. In Fig. 3(a), the system size ($V=20$) is small, the amplitudes of NSCO are irregular, demonstrating that the coherence is broken by the strong noise. However, as shown in Fig. 3(b), for intermediate system size ($V=800$), the NSCO performs much better than in the other two figures. In Fig. 4, when the system size decreases from 100,000 to 20, both the signal level and the noise background increase at the peak. However, the peak for the intermediate system size is the most pronounced. Figs. 3 and 4 both indicate that the performance of the NSCO might be best at an appropriate system size, demonstrating a resonance behavior.

To measure the coherence of NSCO quantitatively, an effective signal-to-noise ratio (SNR) is defined as $\beta=R/(\Delta\omega/\omega_p)$ [36,37], where $\omega_p$ is the frequency at the peak; $R=P(\omega_p)/P(\omega_2)$, and $P(\bullet)$ the power spectrum density(PSD) for a given frequency and $P(\omega_2)$ is the smallest PSD value between $P(0)$ and $P(\omega_p)$; $\Delta\omega$ is the width between $\omega_p$ and the frequency $\omega_1$ satisfying $\omega_1\geq\omega_p$ and $P(\omega_1)=P(\omega_p)/e$. It should be noted that the values of $\beta$ are calculated by averaging the results of 30 independent runs throughout this article. The dependence of effective SNR $\beta$ on the system size $V$ for $k_{p1}=26$ is plotted in Fig. 5(a). The simulation result by CLE method demonstrates that an obvious peak appears at a certain system size in the figure, displaying system size resonance. Interestingly, the optimal system size $V$ is near 1000, which is of the same order of real living cells in vivo [53,54]. Because the magnitude of internal noise is changed by varying the system size, the presence of the maximum of $\beta$ in Fig. 5(a) also indicates that the NSCO plays the best performance at an optimal internal noise intensity, charactering ICR. Using the methods discussed above, we also studied the influence of internal noise when the control parameter is tuned near the left HB point but at the LSS region. The NSCO is also obtained in this region, and ICR occurs. Fig. 5(b) shows the dependence of effective SNR $\beta$ on the system size $V$ for $k_{p1}=3.35$.

Some previous studies about circadian rhythms have concluded that internal noise often plays a destructive role in the oscillatory region of a circadian system because of the phenomenon of noise-induced phase diffusion of the oscillations [55,56], but recently it is reported that, even in the oscillatory region, regularity of the oscillations of a deterministic gene regulatory system could be enhanced by intrinsic noise [26]. Hence, it is necessary to investigate

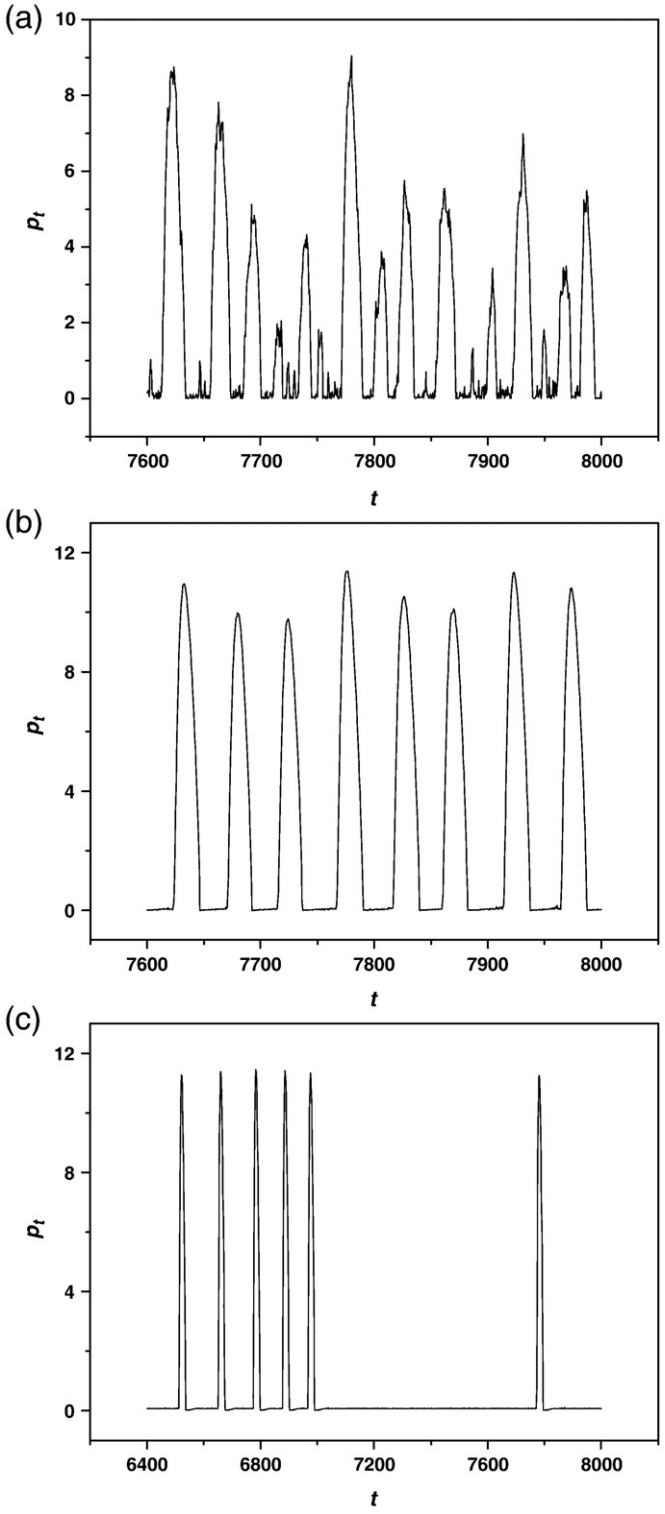


**Fig. 3.** The time series of the PER concentration $p_t$ for $k_{p1}=26$ and system size $V=20$ (a), 800 (b) and 100,000 (c), respectively. All curves are obtained by the CLE method.

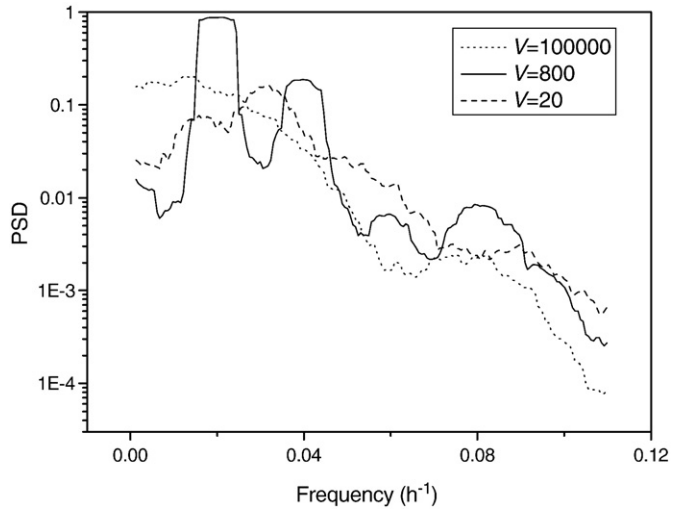


**Fig. 4.** The power spectrum of the oscillations in the PER concentration at $k_{p1}=26$ with $V=20$ (dash), 800 (solid) and 100,000 (dot) respectively. All curves are obtained by the CLE method.

the effect of internal noise on the deterministic oscillation in the OSC region. As shown in Fig. 1(a), compared to the deterministic oscillations, the amplitudes of the noisy oscillations in the OSC region are obviously enhanced by internal noise. However, the coherence of oscillations decreases monotonically with the increase of internal noise level, because of noise-induced phase diffusion. As shown in Fig. 6(a), when the noise intensity is small, noise induces the phase portrait fluctuate around the deterministic limit cycle. But if noise is too strong, as shown in Fig. 6(b), the phase portrait almost fills the phase plane, demonstrating the system is overwhelmed by noise. The dependence of effective SNR $\beta$ on the system size for $k_{p1}=15$ is plotted in Fig. 7. And it is shown that the effective SNR decreases monotonically with the increase of internal noise level. That is, internal noise decreases the coherence of circadian oscillations and plays a destructive role in the OSC region. However, despite the decrease of the coherence, the periods of the noisy oscillations fluctuate just slightly around the ones of the deterministic oscillations, as shown in Fig. 1(b), which demonstrates that the deterministic oscillations are robust to internal noise. This implies that the simple model could provide a reliable picture of the working of circadian clocks in *Drosophila* and can be used to study the molecular mechanism of circadian rhythms.

## 4. Summary

In the present article, the constructive effects of internal noise in a two-variable *Drosophila* model for circadian rhythm are investigated, using the exact stochastic simulation and the chemical Langevin

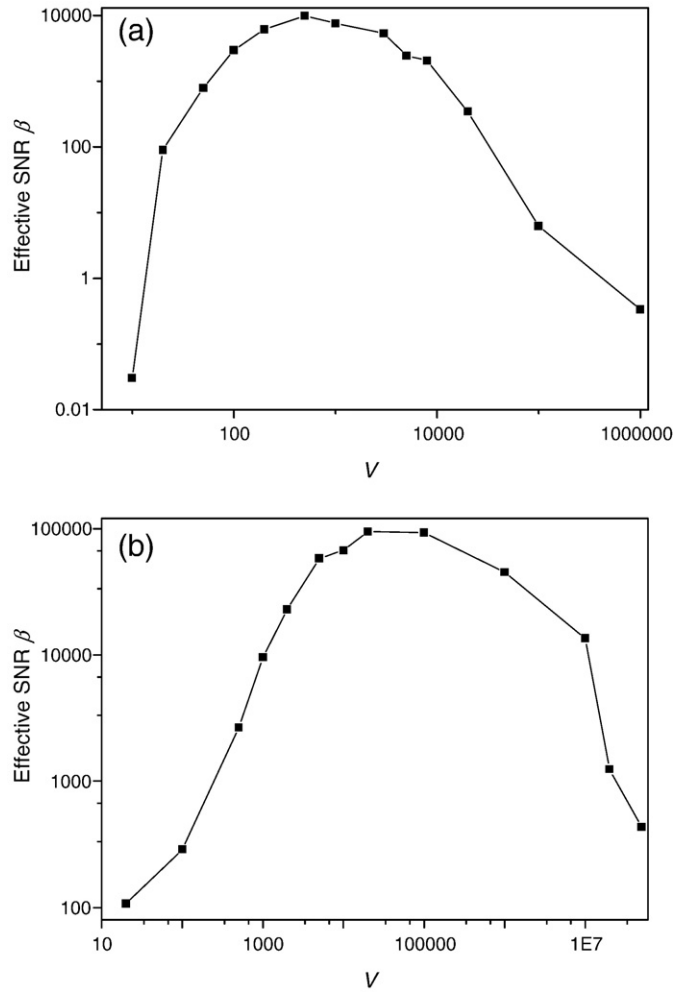


**Fig. 5.** Dependence of the effective SNR $\beta$ on the system size $V$ for the system with (a) $k_{p1}=26$, (b) $k_{p1}=3.35$, obtained by the CLE method.

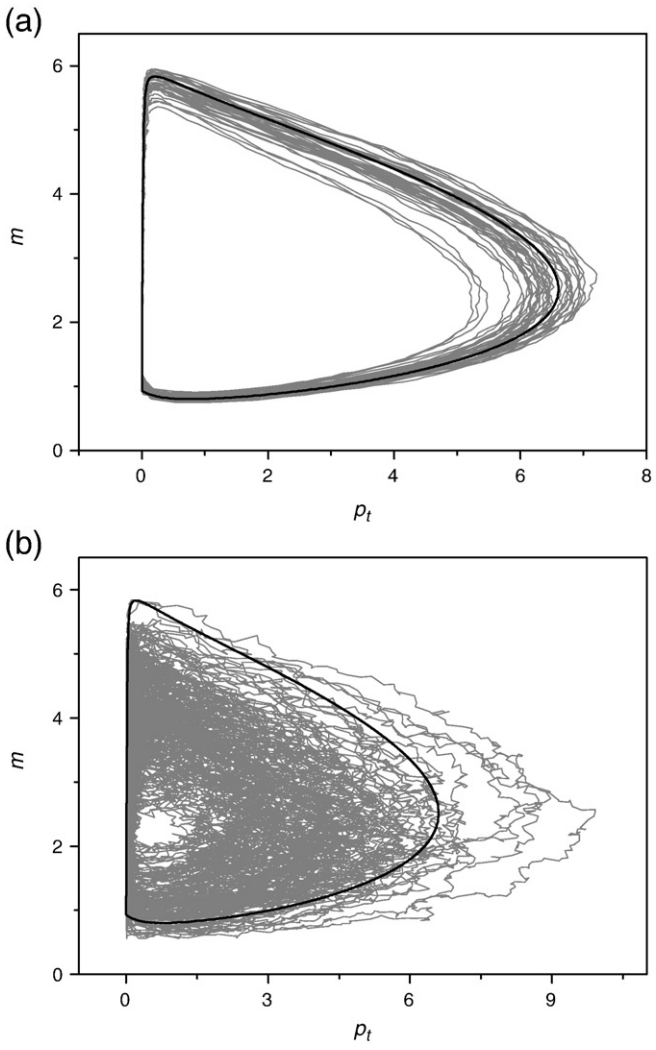


**Fig. 6.** Phase portrait of the noisy oscillation (gray) with $k_{p1}=15$ and (a) $V=800$, (b) $V=20$. For comparison, the deterministic limit cycle is also plotted with black line.

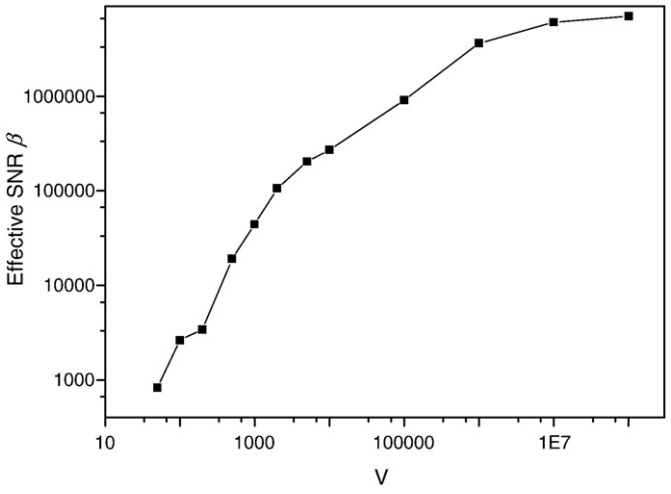


**Fig. 7.** Effective SNR $\beta$ as a function of the system size with the control parameter $k_{p1} = 15$, obtained by the CLE method.

equation method. It is found that internal noise could induce oscillation in a region of the parameter space where the deterministic system produces steady state. And the noise-sustained oscillations could be explained by using phase plane analysis. The coherence of noise-sustained oscillation undergoes a maximum with variation of internal noise intensity, which demonstrates the occurrence of intrinsic coherence resonance. And since the intensity of the internal noise is determined by the system size, this phenomenon also indicates a kind of system size resonance. In the oscillatory region of the deterministic model, the coherence of circadian oscillations decreases monotonously with the increase of internal noise strength because of noise-induced phase diffusion of the oscillation, whereas the period hardly changes for various noise intensities, indicating that the deterministic oscillation is robust to internal noise. Based on the aforementioned findings, it was argued that some of the cellular regulatory systems might utilize internal noise to perform their functions under the conditions in which these functions would not be possible solely by deterministic means [57,58].

## Acknowledgements

This work was supported by the 111 project (B07012) in China. We are grateful to acknowledge Dr. Xiufeng Lang for helpful discussions.

## References

[1] M.C. Moore-Ede, F.M. Sulzman, C.A. Fuller, The Clocks that Time Us: 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, Molecular Bases for Circadian Clocks, Cell 96 (1999) 271–290.
[4] M.W. Young, Life's 24-hour clock: molecular control of circadian rhythms in animal cells, Trends Biochem. Sci. 25 (2000) 601–606.
[5] J.A. Williams, A. Sehgal, Molecular components of the circadian system in *Drosophila*, Annu. Rev. Physiol. 63 (2001) 729–755.
[6] M.W. Young, S.A. Kay, Time zones: a comparative genetics of circadian clocks, Nat. Rev. Genet. 2 (2001) 702–715.
[7] S.M. Reppert, D.R. Weaver, Molecular analysis of mammalian circadian rhythms, Annu. Rev. Physiol. 63 (2001) 647–676.
[8] P.E. Hardin, J.C. Hall, M. Rosbash, Feedback of the *Drosophila* period gene product on circadian cycling of its messenger RNA levels, Nature 343 (1990) 536–540.
[9] A. Goldbeter, A model for circadian oscillations in the *Drosophila* period protein (PER), Proc. R. Soc. Lond. B 261 (1995) 319–324.
[10] P. Ruoff, L. Rensing, R. Kommedal, S. Mohsenzadeh, Modeling temperature compensation in chemical and biological oscillators, Chronobiol. Int. 14 (1997) 499–510.
[11] J.C. Leloup, A. Goldbeter, A model for circadian rhythms in Drosophila incorporating the formation of a complex between PER and TIM proteins, J. Biol. Rhythms 13 (1998) 70–87.
[12] T. Scheper, D. Klinkenberg, C. Pennartz, J. van Pelt, A mathematical model for the intracellular circadian rhythm generator, J. Neurosci. 19 (1999) 40–47.
[13] K. Lee, J.J. Loros, J.C. Dunlap, Interconnected feedback loops in the *Neurospora* circadian system, Science 289 (2000) 107–110.
[14] N. Glossop, L.C. Lyons, P.E. Hardin, Interlocked feedback loops within the *Drosophila* circadian oscillator, Science 286 (1999) 766–768.
[15] K. Bae, C. Lee, D. Sidote, K. Chuang, I. Edery, Circadian regulation of a *Drosophila* homolog of the mammalian clock gene: PER and TIM function as positive regulators, Mol. Cell. Biol. 18 (1998) 6142–6151.
[16] L.P. Shearman, et al., Interacting molecular loops in the mammalian circadian clock, Science 288 (2000) 1013–1019.
[17] R.S. Kuczenski, K.C. Hong, J. Garcia-Ojalvo, K.H. Lee, PERIOD–TIMELESS interval timer may require an additional feedback loop, Plos Comput. Biol. 3 (2007) 1468–1476.
[18] J.J. Tyson, C.I. Hong, C.D. Thron, B. Novak, A simple model of circadian rhythms based on dimerization and proteolysis of PER and TIM, Biophys. J. 77 (1999) 2411–2417.
[19] P. Smolen, D.A. Baxter, J.H. Byrne, Modeling circadian oscillations with interlocking positive and negative feedback loops, J. Neurosci. 21 (2001) 6644–6656.
[20] P. Smolen, D.A. Baxter, J.H. Byrne, A reduced model clarifies the role of feedback loops and time delays in the Drosophila circadian oscillator, Biophys. J. 83 (2002) 2349–2359.
[21] M.H. Hastings, Circadian clockwork: two loops are better than one, Nat. Rev. Neurosci. 1 (2000) 143–146.
[22] T.Y. Tsai, et al., Robust, tunable biological oscillations from interlinked positive and negative feedback loops, Science 321 (2008) 126–129.
[23] N. Barkai, S. Leibler, Circadian clocks limited by noise, Nature 403 (2000) 267–268.
[24] D. Gonze, J. Halloy, A. Goldbeter, Robust of circadian rhythms with respect to molecular noise, Proc. Natl Acad. Sci. U. S. A. 99 (2002) 673–678.
[25] T.B. Kepler, T.C. Elston, Stochasticity in transcriptional regulation: origins, consequences, and mathematical representations, Biophys. J. 81 (2001) 3116–3136.
[26] R. Steuer, C. Zhou, J. Kurths, Constructive effects of fluctuations in genetic and biochemical regulatory systems, Biosystems 72 (2003) 241–251.
[27] J.W. Shuai, P. Jung, Optimal intracellular calcium signaling, Phys. Rev. Lett. 88 (2002) 068102.
[28] M. Perc, M. Gosak, M. Marhl, Periodic calcium waves in coupled cells induced by internal noise, Chem. Phys. Lett. 437 (2007) 143–147.
[29] M. Perc, M. Gosak, M. Marhl, From stochasticity to determinism in the collective dynamics of diffusively coupled cells, Chem. Phys. Lett. 421 (2006) 106–110.
[30] M. Gosaka, M. Marhl, M. Perc, Chaos out of internal noise in the collective dynamics of diffusively coupled cells, Eur. Phys. J. B 62 (2008) 171–177.
[31] L. Gammaitoni, P. Hänggi, P. Jung, F. Marchesoni, Stochastic resonance, Rev. Mod. Phys. 70 (1998) 223–287.
[32] A.S. Pikovsky, J. Kurths, Coherence resonance in a noisedriven excitable system, Phys. Rev. Lett. 78 (1997) 775–778.
[33] M. Perc, Spatial coherence resonance in excitable media, Phys. Rev. E 72 (2005) 016207.
[34] M. Gosaka, M. Marhl, M. Perc, Spatial coherence resonance in excitable biochemical media induced by internal noise, Biophys. Chemist. 128 (2007) 210–214.
[35] J.M.G. Vilar, H.Y. Kueh, N. Barkai, S. Leibler, Mechanisms of noise-resistance in genetic oscillators, Proc. Natl Acad. Sci. U. S. A. 99 (2002) 5988–5992.
[36] Z. Hou, H. Xin, Internal noise stochastic resonance in a circadian clock system, J. Chem. Phys. 119 (2003) 11508–11512.
[37] Q. Li, X. Lang, Internal noise-sustained circadian rhythms in a *Drosophila* model, Biophys. J. 94 (2008) 1983–1994.
[38] D. Bratsun, D. Volfson, L.S. Tsimring, J. Hasty, Delay-induced stochastic oscillations in gene regulation, Proc. Natl Acad. Sci. U. S. A. 102 (2005) 14593–14598.
[39] I. Endery, L. Zwiebel, M. Dembinska, M. Rosbash, Temporal phosphorylation of the Drosophila period protein, Proc. Natl Acad. Sci. U. S. A. 91 (1994) 2260–2264.
[40] N.G. Van Kampen, Stochastic Processes in Physics and Chemistry, North-Holland, Amsterdam, 1981.
[41] D.T. Gillespie, Exact stochastic simulation of coupled chemical reactions, J. Phys. Chem. 81 (1977) 2340–2361.
[42] D.T. Gillespie, The chemical Langevin equation, J. Chem. Phys. 113 (2000) 297–306.
[43] G. Hu, T. Ditzinger, C.Z. Ning, H. Haken, Stochastic resonance without external periodic force, Phys. Rev. Lett. 71 (1993) 807–810.
[44] G. Schimid, I. Goychuk, P. Hänggi, Stochastic resonance as a collective property of ion channel assemblies, Europhys. Lett. 56 (2001) 22–28.
[45] J.W. Shuai, P. Jung, Entropically enhanced excitability in small systems, Phys. Rev. Lett. 95 (2005) 114501.
[46] D.J. Higham, An algorithmic introduction to numberical simulation of stochastic differential equations, SIAM Rev. 43 (2001) 525–546.
[47] H. Qian, S. Saffarian, E.L. Elson, Concentration fluctuations in a mesoscopic oscillating chemical reaction system, Proc. Natl Acad. Sci. U. S. A. 99 (2002) 10376–10381.
[48] R.C. Hilborn, J.D. Erwin, Stochastic coherence in an oscillatory gene circuit model, J. Theor. Biol. 253 (2008) 349–354.
[49] B. Lindner, J. García-Ojalvo, A. Neiman, L. Schimansky-Geier, Effects of noise in excitable systems, Phys. Rep. 392 (2004) 321–424.
[50] C. Pittendrigh, On temperature independence in the clock system controlling emergence time in Drosophila, Proc. Natl Acad. Sci. U. S. A. 40 (1954) 1018–1029.
[51] R.J. Konopka, C. Pittendrigh, D. Orr, Reciprocal behaviour associated with altered homeostasis and photosensitivity of Drosophila clock mutants, J. Neurogenet. 6 (1989) 1–10.

[52] W.H. Press, S.A. Teukolsky, W.T. Vetterling, B.P. Flannery, Numerical Recipes in C, Cambridge University Press, Cambridge, 1992.
[53] M.E. Gracheva, J.D. Gunton, Intercellular communication via intracellular calcium oscillations, J. Theor. Biol. 221 (2003) 513–518.
[54] M.E. Gracheva, R. Toral, J.D. Gunton, Stochastic effects in intercellular calcium spiking in Hepatocytes, J. Theor. Biol. 212 (2001) 111–125.
[55] D. Gonze, J. Halloy, P. Gaspard, Biochemical clocks and molecular noise: theoretical study of robustness factors, J. Chem. Phys. 116 (2002) 10997–11010.
[56] P. Gaspard, The correlation time of mesoscopic chemical clocks, J. Chem. Phys. 117 (2002) 8905–8916.
[57] C.V. Rao, D.W. Wolf, A.P. Arkin, Control, exploitation and tolerance of intracellular noise, Nature 420 (2002) 231–237.
[58] J. Zhang, Z. Hou, H. Xin, System-size biresonance for intracellular calcium signaling, Chem. Phys. Chem. 5 (2004) 1041–1045.