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Common noise induced synchronous circadian oscillations in uncoupled non-identical systems

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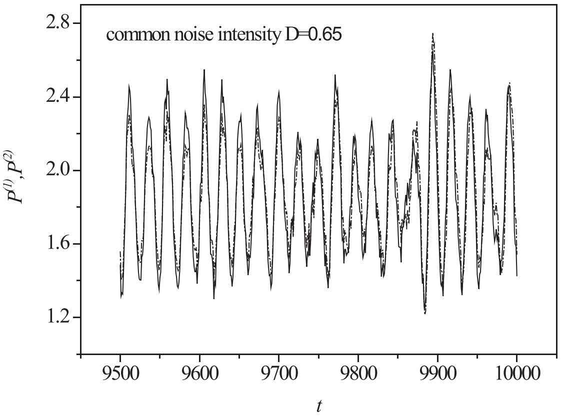
HIGHLIGHTS

- ► The influences of common noise in an elementary circadian clock model were studied.
- ► Common noise plays constructive roles on the collective behavior in the model.
- ► Noise could induce synchronous oscillations in two uncoupled non-identical systems.
- ► The common noise induced synchronous oscillations are robust to internal noise.

GRAPHICAL ABSTRACT



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ABSTRACT

The effect of common noise on the collective behavior of circadian oscillation systems was studied in an elementary circadian clock model. It is shown that common noise could induce synchronous oscillations in two uncoupled non-identical systems in the deterministic stable steady state region. The synchronicity of common noise induced oscillations is suppressed by the internal noise, but is not remarkably decreased within a wide range of internal noise intensity. This demonstrates that the common noise induced synchronous oscillations are rather robust to internal fluctuations.

1. Introduction

Many living organisms have evolved to generate an endogenous clock with a period of nearly 24 h to anticipate daily changes in the environment [1,2]. In multicellular organisms, the circadian clocks are

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generated by multiple autonomous single-cell oscillators, which are intrinsically diverse, and these individual oscillators produce synchronous oscillations [3–7]. For instance, the master clock of suprachiasmatic nucleus, composed of thousands of single-cell circadian clocks with periods ranging from 20 to 28 h, can lead to coordinated circadian outputs [7]. In recent years, several models have been developed to explain this phenomenon [8–11], most of which gain synchronization through intercellular coupling. For example, Ueda et al. [8] proposed an intercellular coupling mechanism that the circadian clock regulated synchronization factor secreted from one cell is received by the neighboring cells so that reaction rates in the circadian system are adjusted. Mcmillen et al. [10] recently achieved intercellular coupling through small molecule diffusion between cells and the environment. However, the mechanisms for the intercellular synchronization of circadian clock are far from being well understood.

In biological systems, all cells are subjected to intracellular molecular fluctuations and extracellular environment perturbations [12,13]. Many investigations have shown that noise can play a constructional role through stochastic resonance [14] or coherence resonance [15]. Recent studies in biological, chemical and physical systems have shown that noise can positively affect the collective behavior of cells [16–19]. For instances, an ensemble of independent neurons could be synchronized by the same fluctuating input current [16]. In electrochemical systems, two coupled chaotic oscillators could be synchronized by common external noise or common fluctuation in the coupling strength [18]. Very recently, in genetic oscillators, Zhou et al. also found that additional extracellular noises common to all cells can induce synchronized oscillations [20]. Moreover, there are also analytical and numerical investigations on the common noise induced synchronization in limit cycle oscillators [21,22] and chaotic systems [23,24]. To understand the mechanism of circadian clock synchronization, it is very necessary to investigate the effects of common noise on their collective behaviors. Besides, since the internal noise is inevitable and may disturb cooperative behaviors [25], it is necessary to investigate the effects of internal noise as well.

In this paper, the effects of common noise on two non-identical uncoupled circadian sub-systems are investigated. It is found that common noise can induce synchronous circadian oscillations in the deterministic steady state region. Internal noise is revealed to play a destructive role in adjusting the collective behavior. However, the synchronicity between stochastic oscillations is not affected during a wide range of internal noise, demonstrating the robustness of the synchronous oscillations to the internal noise.

2. Model and method

An elementary two-variable model [26] is employed in the present study. It is composed of a negative feedback loop, in which the effective protein inhibits the production of its mRNA, and a time delay, during which the effective protein is produced from its mRNA. The systems can be described as follows:

$$\frac{dM^{(j)}}{dt}=\frac{r_M}{1+\left(P^{(j)}/k\right)^n}-q_M M^{(j)}, \tag{1}$$

$$\frac{dP^{(j)}}{dt}=r_P M^{(j)}(t-\tau)^m-q_P^{(j)}P^{(j)}+D\xi(t), \tag{2}$$

where the variables $M^{(j)}$ and $P^{(j)}$ (the index j denotes the jth sub-system) represent the concentrations of mRNA and effective protein, respectively. r_M is the scaled mRNA production rate constant, r_P is the protein production rate constant, and q_M and $q_P{}^{(j)}$ represent the mRNA and protein degradation rate constants, respectively. n is the Hill coefficient, the exponent m denotes the nonlinearity in the protein production cascade, the delay τ represents the total duration of protein production from mRNA, and k is a scaling constant. The protein degradation rate q_P is chosen as the control parameter and characterizes the difference between individual systems since it is the only parameter that can change in a relatively wide range without apparently influencing the oscillator period [26]. Other parameters are set as: $r_M=1\ \mathrm{h}^{-1}$, $r_P=1\ \mathrm{h}^{-1}$, $n=2$, $m=3$, $\tau=4$ h, $k=1$. And q_M is chosen as 0.21 h^{-1} because only in this case, the system exhibit oscillation's period is around 24 h. For detailed information about the model or the parameter choice, see ref [26]. $\xi(t)$ is Gaussian white noises with $<\xi(t)>=0$ and $<\xi(t)\xi(s)>=\delta(t-s)$, and D characterizes the noise strength. $D\xi(t)$ represents the common external noise resulting from the common extracellular environment perturbations. Here, for simplicity, only two individual systems are considered, that is, $j=1,2$.

To investigate the effects of internal noise, the chemical Langevin method proposed by Gillespie [27] is used. The chemical Langevin equation for the current model reads:

$$\frac{dM^{(j)}}{dt}=\left(a_1^{(j)}-a_2^{(j)}\right)+\frac{1}{\sqrt{V}}\left[\sqrt{a_1^{(j)}}\zeta_1^{(j)}(t)-\sqrt{a_2^{(j)}}\zeta_2^{(j)}(t)\right], \tag{3}$$

$$\frac{dP^{(j)}}{dt}=\left(a_3^{(j)}-a_4^{(j)}\right)+\frac{1}{\sqrt{V}}\left[\sqrt{a_3^{(j)}}\zeta_3^{(j)}(t)-\sqrt{a_4^{(j)}}\zeta_4^{(j)}(t)\right]+D\xi(t), \tag{4}$$

where $a_i{}^{(j)}$ $(i=1,\ldots,4;\ j=1,2)$ are the transition rates per volume, representing the synthesis and degradation of mRNA, and protein respectively. And the expressions of $a_i{}^{(j)}$ $(i=1,\ldots,4;\ j=1,2)$ correspond to the first and second terms at the right side of Eqs. (1) and (2), respectively. $\zeta_i{}^{(j)}$ $(i=1,\ldots,4;\ j=1,2)$ are independent Gaussian white noises with $<\zeta_i{}^{(j)}(t)>=0$ and $<\zeta_i{}^{(k)}(t)\,\zeta_j{}^{(l)}(s)>=\delta_{ij}\delta_{kl}\delta(t-s)$. In simulation, they are generated independently with the external noise. According to Ref. [27], internal noise is actually denoted by the second terms in the bracket at the right side of Eqs. (3) and (4), from which it is clear that the magnitude of internal noise scales is $1/\sqrt{V}$ and depends on M, P and the control parameters. In order to keep corresponding deterministic kinetics unchanged and obtain the pure effect of internal noise, the magnitude of the internal noise is varied via changing V. For the deterministic model (Eqs. (1) and (2) with $D=0$), simulation with Runge–Kutta and Euler algorithm show no qualitative difference in both the bifurcation and dynamic behaviors, which prove that Euler method is reliable for the current system. Therefore, Euler method with time step of 0.01 h is employed to integrate the deterministic system. The noise influenced stochastic system is integrated by the standard procedure for stochastic differential equations [28]. The chemical Langevin equations (Eqs. (3) and (4)) are integrated by the Euler–Maruyama method [29] with the time step of 0.01 h and common noise intensity $D=0.8$.

3. Results and discussion

To investigate the effect of common noise, it is necessary to study the corresponding deterministic kinetics for comparison. Simulation results of the deterministic model show that when increasing the control parameter q_P, the system undergoes *Hopf bifurcation* (HB) at $q_P\approx0.127$ (Fig. 1). The HB point divides the parameter space into two regions: the steady state (SS) region to the left and the oscillatory (OSC) region to the right.

It has been reported that noise often play constructive roles in the steady state region near the bifurcation point [30–32]. Han et al. [33,34] have revealed the synchronization of noise induced oscillations in coupled coherence resonance oscillators. Therefore, we focus on the SS regions near the HB point. Fig. 1 also plotted the maximum and minimum values of P in the stochastic model with $D=0.2$. It is clear that in the stochastic case, the HB points defined by the deterministic dynamics disappear, and 'stochastic' oscillations appear in the SS regions near the

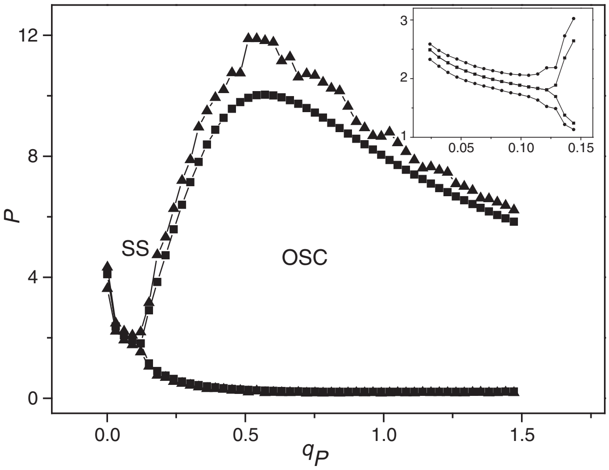

Fig. 1. The bifurcation diagram of the deterministic model (squares) and the stochastic model (triangles) with respect to the control parameter q_P. The inset is the enlarged figure near the HB point. Here the stochastic simulation is carried out for $D=0.2$ and the HB point in the deterministic limit is $q_P \approx 0.127$.

HB points. Since these oscillations are supported by noise, they may be called as noise-sustained circadian oscillations.

To investigate the effects of common noise on the collective behaviors, ${q^{(1)}}_P$ and ${q^{(2)}}_P$ are tuned to 0.12 and 0.125 respectively, which means that the two sub-systems, with slightly difference, lies in the deterministic SS region near HB point. The time series of $P^{(1)}$ and $P^{(2)}$ for $D=0.1$, 0.4 and 0.65 in Fig. 2(a), (b) and (c) show that, under weak noise with sufficient intensity (e.g. $D=0.1$), noise induced circadian oscillations occur, but the two sub-systems are obviously asynchronous. When D is increased (e.g. $D=0.4$), the two sub-systems become more synchronous. When D is large enough (e.g. $D=0.65$), phase synchronization is achieved.

To quantitatively characterize this result, the phase variable of each system is introduced. Assume that the phase increase during one oscillation interval is 2π, then reassign the oscillation sequence to a circular according to their oscillation phase so that the standardized phase could be calculated to characterize the synchronization [6,35,36]. Therefore, for arbitrary instant of time:

$$\phi^{(j)}(t) = 2\pi \frac{t-\tau_k^{(j)}}{\tau_{k+1}^{(j)}-\tau_k^{(j)}} + 2\pi k, \tau_k^{(j)}<t\leq\tau_{k+1}^{(j)}, \qquad (5)$$

where $\tau_k^{(j)}$ is the time of the kth peak of the jth system. In addition, we compute the distribution of cyclic phase difference, $P(\Delta\varphi)$, on $[-\pi,\pi]$ [37,38]. A dominant peak of this cyclic phase difference implies a preferred phase difference between the sub-systems, that is, phase synchronization could be characterized in a statistical sense [39]. The distributions of cyclic phase difference corresponding to the time series in Fig. 2(a), (b) and (c) are plotted in Fig. 3(a), (b) and (c) respectively. It is shown that, in Fig. 3(a), there is no obvious peak in the distribution map. And in Fig. 3(b), a weak peak could be observed, which means that the two systems become more synchronous. A dominant peak appears at zero in Fig. 3(c), demonstrating the occurrence of phase synchronization. With the noise induced and strengthened synchronization, the oscillation period are kept almost constant around 24 h, while the amplitude is gradually approaching the regular level. This implies that the noise induce synchronization works on the basis of keeping the rhythm constant while being put on obvious amplitude control behavior.

How can the systems produce synchronous oscillations even when the deterministic dynamics predict stable states? As shown in Fig. 1, numerical simulations demonstrate that for the deterministic system, fixed points and limit cycles are the only possible attractors in the

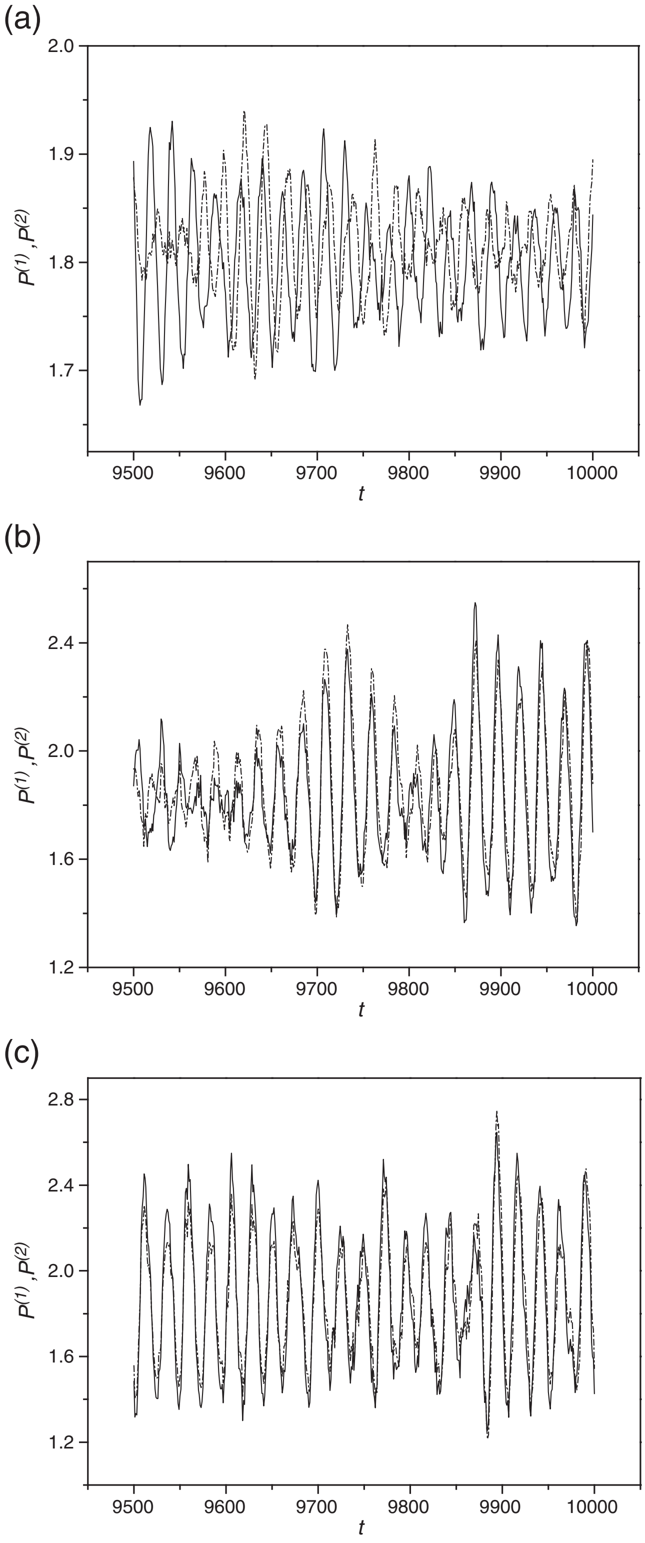

Fig. 2. The time series of $P^{(1)}$ with ${q^{(1)}}_P=0.12$ and $P^{(2)}$ with ${q^{(2)}}_P=0.125$ for $D=0.1$ (a), 0.4 (b) and 0.65 (c), respectively.

phase space of mRNA and protein. System near the HB point has excitability [3,40], which means when the system evolves toward a fixed point in the deterministic limit, a sufficiently large fluctuation will drive the system far away from the point, and the system will go along a stochastic limit cycle in phase space until it comes back to the stable fixed point again. Therefore, when noise joins in, the system is driven far away from the steady state with finite probability and thus

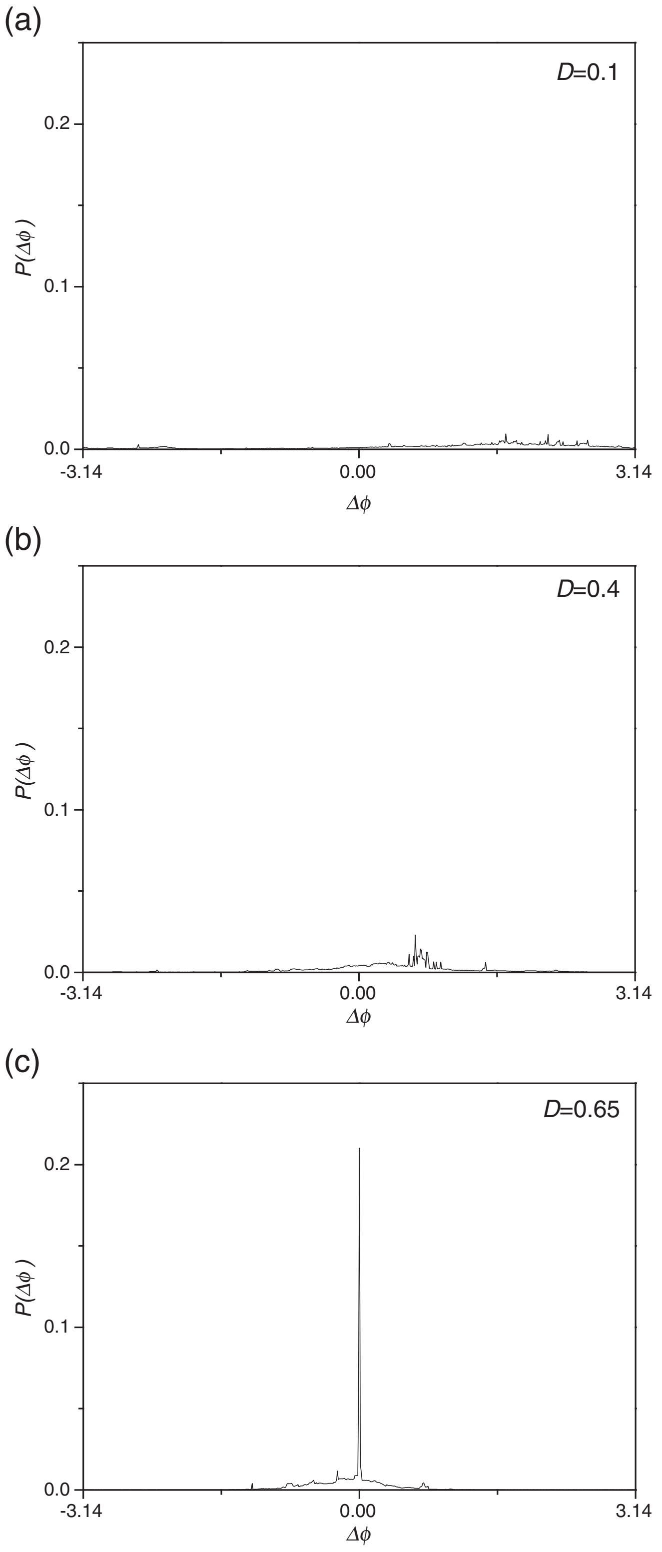

Fig. 3. The distributions of cyclic phase difference corresponding to Fig. 2(a), (b) and (c).

exhibits stochastic oscillations that correspond to a stochastic limit cycle in phase space. And the time precision of the stochastic oscillations depends on both the noise intensity and the deterministic dynamic of the system [15]. When the common noise is weak, the occurrences of oscillations are decided by the deterministic dynamic, and the two systems cannot be synchronous because of the difference in parameters value. However, the common noise, if strong enough, will overwhelm the slightly parameter mismatch and make oscillations occur simultaneously in two systems, obtaining the phase synchronization.

To quantitatively describe the phase synchronization, a synchronization factor, similar to the factor in Ref. [41], is introduced as:

$$\rho = <\rho(t)> = <\left|\frac{1}{2}\sum_{j=1}^{2} e^{i\phi^{(j)}(t)}\right|>, \qquad (6)$$

where $<\cdot>$ demonstrates the average during time, $i=\sqrt{-1}$. In this way, $\rho \approx 0$ corresponds to the anti-phase synchronization regime, and $\rho \approx 1$ to the in-phase synchronization regime, whereas $\rho \approx 0.5$ indicates the unsynchronization regime. Fig. 4 displays the dependency of the synchronization factor versus the noise intensity. Note that each ρ is obtained by averaging the results of 20 independent runs. It is clear that with the increase of noise intensity, the synchronization factor ρ first increases monotonously, when $D \approx 0.6$, ρ is close to 1, demonstrating the occurrence of phase synchronization. And after that, ρ hardly changes with the increase of noise intensity. These results are consistent with the aforementioned conjecture.

Then, we investigate the influence of intracellular noise to the phase synchronization. For simplicity, both of the sizes of these two sub-systems are supposed to be V. Fig. 5 plots the distributions of cyclic phase difference corresponding to the time series of $P^{(1)}$ and $P^{(2)}$ for $V=1000$, 10,000 and 100,000. And Fig. 6 displays the dependency of the synchronization factor ρ versus the system size V. From Figs. 5 and 6, it is clear that the synchronization decreases monotonously with the decrease of system size V (i.e. the increase of internal noise intensity). This demonstrates that the internal noise tends to destroy the synchronization of the sub-systems. However, the synchronization factor doesn't remarkably decrease during a wide range of V since a clear peak can still be observed with $V=1000$ in Fig. 5(a), demonstrating that the common noise induced synchronous oscillations are robust to internal noise. Further simulation proves that if working on three or even more number of oscillators systems, similar results without qualitative difference could be obtained.

4. Summary

In the present article, the constructive effects of common noise on the collective behaviors of circadian systems are investigated. It is found that in the deterministic steady state region near bifurcation point, common noise could induce oscillations in two non-identical sub-systems. With the increase of noise intensity, the two sub-systems become more and more synchronous. When noise is strong enough,

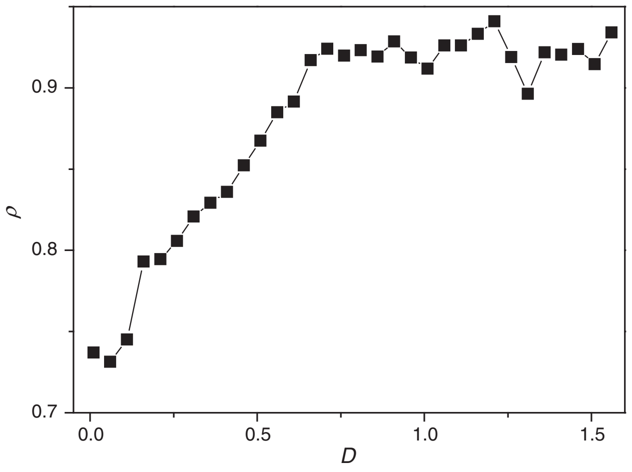

Fig. 4. The plot of synchronization factor ρ versus the noise intensity D, obtained with $q^{(1)}{}_P=0.12$ and $q^{(2)}{}_P=0.125$.

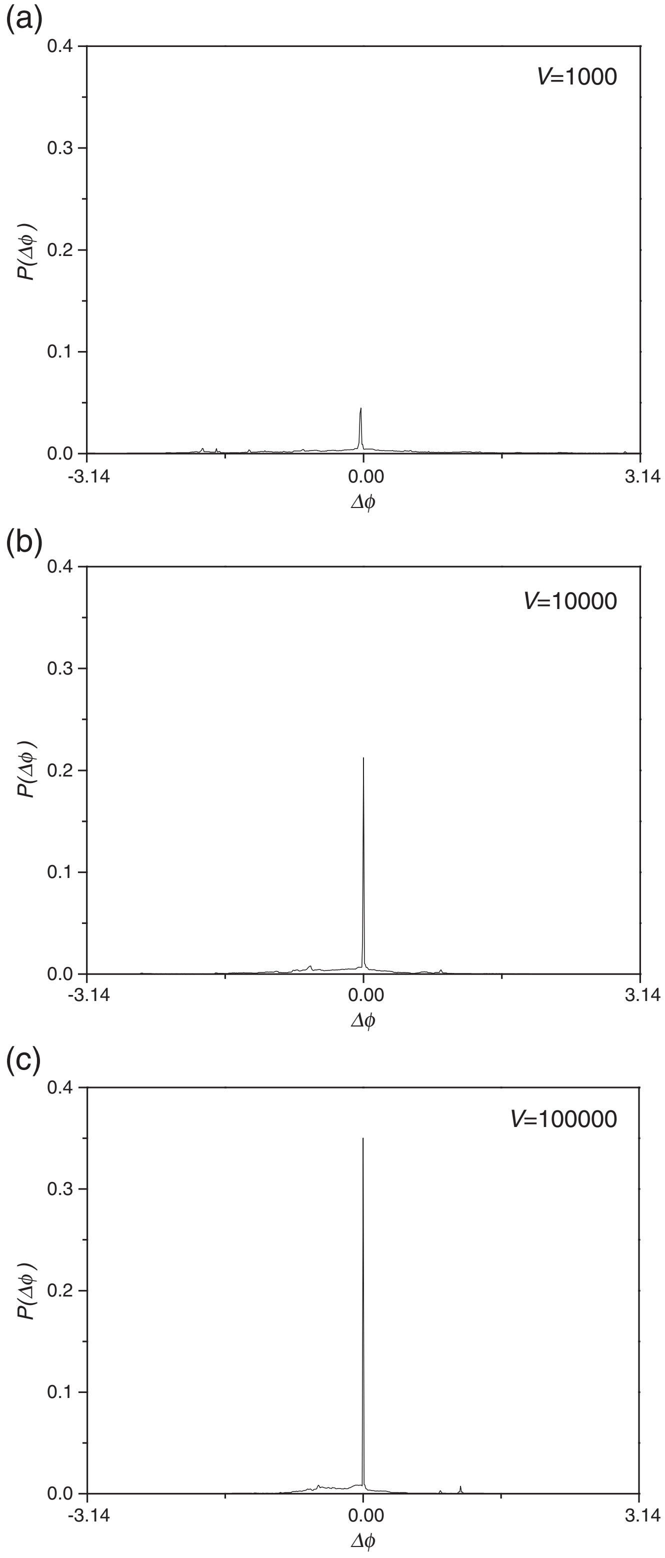

Fig. 5. The distributions of cyclic phase difference for $D=0.8$ and system size $V=1000$ (a), 10,000 (b) and 100,000 (c), calculated with $q^{(1)}{}_P=0.12$ and $q^{(2)}{}_P=0.125$.

phase synchronization could be observed. The synchronization factor decreases monotonously with the increase of internal noise, which demonstrates that internal noise tends to destroy the collective behavior. However, the synchronization factor doesn't remarkably decrease during a wide intensity scope of internal noise, demonstrating that the common noise induced synchronous oscillations are robust to internal noise.

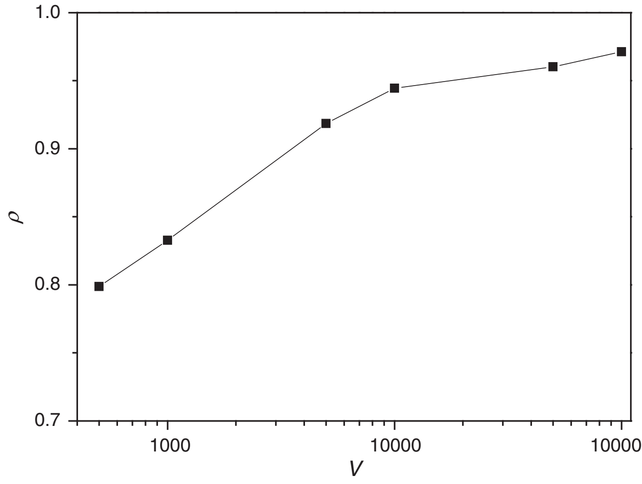

Fig. 6. The plot of synchronization factor ρ versus the system size V, obtained with $D=0.8$ and $q^{(1)}{}_P=0.12$ and $q^{(2)}{}_P=0.125$.

Previous works for circadian clock oscillation synchronization always neglect the constructive influence of noise. But in recent years, many researches show that noise could play constructive roles in biological systems, e.g. noise-enhanced propagation [42], noise-sustained oscillation and noise induced resonance [43,44]. All these results indicate that organisms will take advantage of internal or external noise to sustain biological functions. The finding in the present work indicates that common noise will play a constructive role in the collective behaviors of circadian clocks. And the synchronization works on the basis of keeping the 24 h period constant and put on obvious behavior with the control of the amplitude. Further works prove that these results could be extended to system with more sub-systems. It is expected that this results might provide new insights into the synchronization mechanism of circadian clock.

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