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
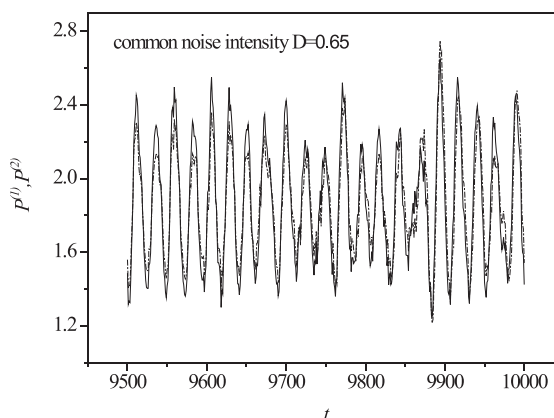
ABSTRACT

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.

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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: $r_M = 1 \text{ h}^{-1}$, $r_P = 1 \text{ h}^{-1}$, $n = 2$, $m = 3$, $\tau = 4$ 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 $a_i^{(j)}$ ($i = 1,...,4$; $j = 1,2$) are the transition rates per volume, representing the synthesis and degradation of mRNA, and protein respectively. And the expressions of $a_i^{(j)}$ ($i = 1,...,4$; $j = 1,2$) correspond to the first and second terms at the right side of Eqs. (1) and (2), respectively. $\zeta_i^{(j)}$ ($i = 1,...,4$; $j = 1,2$) 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 $q_P \approx 0.127$ (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