Biophysical Chemistry 158 (2011) 54–60

Contents lists available at ScienceDirect

Biophysical Chemistry

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

Internal noise enhanced oscillation in a delayed circadian pacemaker

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ARTICLE INFO

Article history:
Received 18 March 2011
Received in revised form 28 April 2011
Accepted 1 May 2011
Available online 6 May 2011

Keywords:
Delay
Internal noise
Circadian oscillation

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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doi:10.1016/j.bpc.2011.05.003

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).