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Coherence resonance in a noise-driven gene network regulated by small RNA

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Abstract Small RNA has recently drawn more and more attention. In this paper, we concentrate on the influence of noises on gene network regulated by small RNA using chemical Langevin equation. It shows that the noise can cause oscillation when the oscillate does not occur in the corresponding deterministic system. The coherence of the noise induced oscillation reaches a maximum for an optimal intensity of noise, and the coherence resonance appears accordingly. The findings imply probably omnipresent importance of noise in the functioning process of living organism.
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Keywords small RNA, additive noise, coherence resonance

Since the microRNAs was discovered by Lee et al.,[1] biologists paid more attention to the importance of the microRNAs. In recent years, with the discovery of a number of non-coding small RNA, more and more biological experiments indicated that non-coding small RNA has the function of regulating gene expression.[2–9] As we know that mathematical model is very useful to investigate biological system. There are some mathematical model involving small RNA[10,11] to reveal the biological mechanism by analytical and numerical methods. In the biological network, the feedback can induce time delays, and the time delays exist in the real network. Xie et al.[12] constructed a gene network regulated by small RNA and found that in the gene expression dynamics, small RNA may be a stabilizing or destabilizing factor relying upon the severity of its influence on mRNA degradation. Shen et al.[13] presented theoretical analyses of globally asymptotic stability, and sufficient conditions are also provided in the literature for the simple gene regulatory network's oscillation. However, environmental fluctuations in organisms will influence the dynamics of gene expression.[14] In the meanwhile, it is necessary to consider the effect of noise in the gene regulatory networks. Although we often assume that noise is destructive, some recent works demonstrated that noise can play a positive role in the gene expression,[15] i.e., oscillations may be induced by internal noise while deterministic system stays in the stable region.

In this letter, we investigate the effect of additive noises on a simple gene regulatory network with time delay mediated by small RNA. We find that additive noise may induce oscillations of the system when no oscillation exists in the deterministic model. It is found that for certain noise intensity, there exists an upper limit of the featured correlation time[16] of the noise inducing

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oscillations, i.e., stochastic oscillations can exhibit best performance at an optimal additive noise amplitude, showing that the occurrence of additive noise can induce coherence resonance.

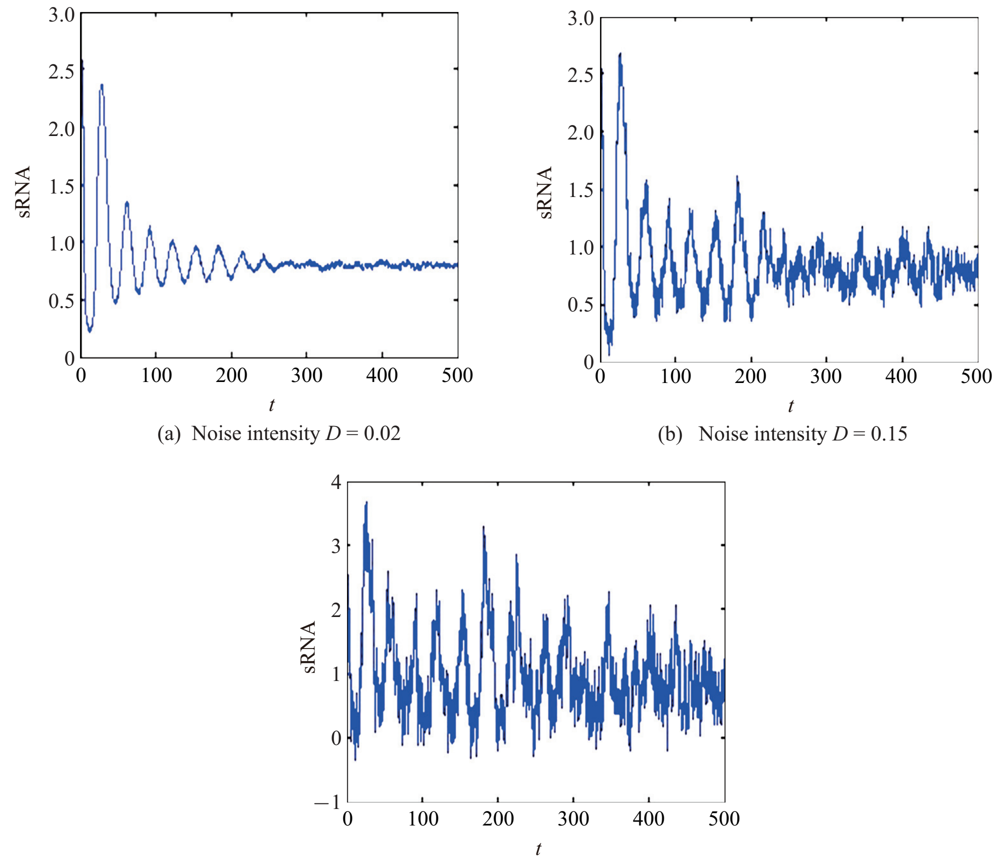
Recently, more and more work show that stochastic resonance or coherence resonance occurs in the nonlinear systems under noisy driving[16–19] and these phenomena of noise-driven stochastic oscillations have been paid more attention. In this section, we mainly consider the noises and investigate how the noises influence the expression of small RNA, and adopt a simple gene regulatory network model with time delay mediated by small RNA.[13] In Ref. 13, the authors investigated how the time delay influences the dynamics of network and found that there was Hopf bifurcation when the time delay runs up to the threshold value, however, noises are ubiquitous in nature. To describe the dynamics of gene network, we should consider the impact of noise on the network studied in Ref. 13. Here we would show how the noises affect the coherent motion when the internal noise is present. If we consider the effect of noise, the dynamics of the system can be depicted through the following stochastic differential equation.

$$\begin{aligned} \dot{m}(t) &= -cm(t) - ds(t)m(t) + g(p(t-\tau_1)), \\ \dot{s}(t) &= e - ds(t)m(t) - fs(t) + D\xi(t), \\ \dot{p}(t) &= -bp(t) + am(t-\tau_2), \end{aligned} \tag{1}$$

in which $m(t)$, $s(t)$, $p(t)$ denote the concentrations of mRNA, sRNA, protein, $g(p(t-\tau_1)) = l/[1+(p(t-\tau_1)/p_0)^n]$ denotes mRNA molecule's production rate and is presumed to decrease monotonically with l being the transcription basal rate in the absence of transcription factors, the noise $\xi(t)$ is assumed as Gaussian noise having zero mean and satisfying $\langle\xi(t)\xi(t')\rangle = \delta(t-t')$, and D represents the noise intensity, i.e., time delay represents mRNA production's detained suppression by transcription factor p produced time τ_1 ago. p_0 represents the threshold of repression, n being the Hill coefficient represents the measure of the cooperativity's degree between transcription factors in the suppressive interaction, a is the translation rate of target mRNA, b, c denote the degradation rates of protein, mRNA respectively, d is the rate of the small RNA base pairing with the target mRNA, e denotes the basal rate of production that small RNA occurs, and f represents the degradation rate of small RNA. $s(t)m(t)$ represents the effect of base pairing between s and m. Obviously, by a simple manipulation, such a single gene formalism can be expanded to a model having multiple genes (e.g., regarding (m, s, p) as vectors and (a, b, c, d, e, f) as the parameter).

In the previous work, we know that there is periodic oscillation when Hopf bifurcation appear and the time delay exceeds the threshold value τ_0. In the present work, we mainly investigate the influence of additive noise on this network when τ is close to τ_0 (smaller than τ_0), i.e., the corresponding deterministic system is stable. Firstly, we integrate system (1) numerically using Eluer–Maruyam method of stochastic differential equation (SDE). Clearly, there is no oscillation in the steady state region when the noise is not taken into account. When the noise intensity was added into the network, the steady state becomes overwhelmed and begin to oscillate, for some intermediate noise, the sustain oscillation occurs. However, when the noise intensity becomes very large, the sustain oscillation is destroyed. Evidently, the stochastic oscillation on account of noise level would be most pronounced.

The results of numerical simulation in Fig. 1 show that these oscillations of sRNA caused by different noise amplitudes are varied. The oscillations appear to be relatively flat in the presence of small noise intensity and the corresponding oscillations are very drastic when large noise amplitudes are present, while coherent oscillations are observed for moderate noise. This phenomenon is called coherence resonance which resembles stochastic resonance.[20]



(a) Noise intensity $D = 0.02$

(b) Noise intensity $D = 0.15$

(c) Noise intensity $D = 0.5$

Fig. 1. The stochastic oscillation of small RNA when $a = 1$, $b = 0.1$, $c = 0.2$, $d = 1$, $e = 1$, $f = 0.25$, $l = 2$, $p_0 = 10$, $n = 2$.

We have simulated oscillations of the system under noise and found that coherent motion of the deterministic system occur at a moderate noise intensity. To quantitatively measure the relative performance of stochastic oscillations, an effective signal-to-noise ratio (SNR) which is represented by the characteristic correlation time (CCT) is defined as[16]

$$t_{\mathrm{CCT}} = \int_0^{\infty} C^2(\tau)\,\mathrm{d}\tau, \tag{2}$$

where $C(\tau)$ is defined as auto covariance function

$$C(\tau) = \frac{\langle \bar{s}(t)\bar{s}(t+\tau)\rangle}{\langle \bar{s}^2(t)\rangle}, \quad \bar{s}(t) = s(t) - \langle s(t)\rangle. \tag{3}$$

Figure 2 displays that the variation tendency of CCT depends on noise intensity. It is clear that CCT has a maximum at the noise amplitude $D = 0.16$. The maximum indicates that the coherence resonance appears, and the system performs the best coordinated oscillation. It shows that the noise can play constructive role at a moderate intensity. For the above network, the interaction between noise and nonlinearity induces the stochastic resonance and makes the expression of small RNA very coherent, also the sustain oscillation induced by coherence resonance enables us to understand the mechanism which generates cyclic gene expression, and the predictions can be applied to the network involving Hes7 and provide examinable hypothesis for biologists to further investigate experimentally the increasing functional roles of small RNA in regulating cellular development and processes.

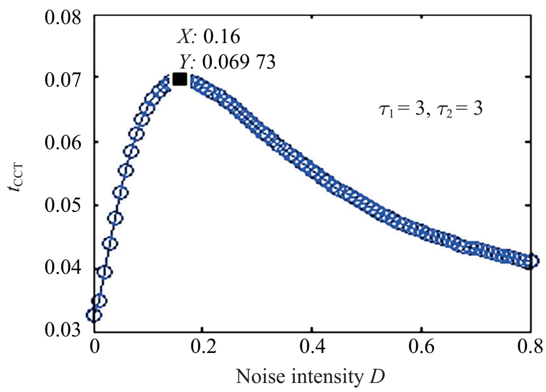


Fig. 2. Dependence of effective coherence resonance (CR) on the noise intensity D.

In this letter, we only consider the dynamical behaviors of the sRNA and analyze the effect of additive noise on the gene regulatory network mediated by small RNA. We show that noise can induce oscillations of sRNA. The interesting fact is that a characteristic correlation time of noise induced oscillations undergoes a maximum as the noise intensity increases, i.e., the coherence resonance phenomenon appears for a moderate noise amplitude.

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