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Time delay effects of stochastic resonance induced by multiplicative periodic signal in the gene transcriptional regulatory model

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HIGHLIGHTS

- We have studied the combined effects of cross-correlation noise, multiplicative periodic signal and time delay in gene transcriptional regulatory system.
- Noises, multiplicative periodic signal and time delay can induce stochastic resonance.
- The time delay always enhanced the stochastic resonance phenomenon in the three cases discussed in my paper.

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ABSTRACT

Based on the universal transcriptional regulatory model proposed by Smolen et al.in 1998, we have studied the combined effects of cross-correlation noise, multiplicative periodic signal and time delay through modifying the ordinary differential equation with time evolution in gene transcriptional regulatory system. The expression of signal-to-noise ratio (*SNR*) is derived by applying the two-state theory in adiabatic limit and approximate analytical method for small time delay. The effects of multiplicative noise intensity, additive noise intensity, cross-correlation noise intensity and time delay on *SNR* are discussed by numerical calculation and graphical analysis. The results indicate that when the *SNR* is a function of multiplicative noise intensity, the peak value of the *SNR* rises as time delay increases; when *SNR* is a function of additive noise intensity, the value of *SNR* ascends as time delay increases; when *SNR* is a function of cross-correlation noise intensity, the peak value of *SNR* goes up with time delay increased. So when *SNR* is the function of multiplicative noise intensity, additive noise intensity and cross-correlation noise intensity respectively, time delay enhances the stochastic resonance.

1. Introduction

The concept of stochastic resonance (SR) was originally put forward by Benzi et al. and Nicolis et al. aiming to explain the periodic recurrence of the Earths ice ages in 80s [1–4]. Later, the strong periodic output phenomenon caused by the collaboration of weak periodic driving and random force interference was called stochastic resonance (SR). It can be regarded as a special kind of phenomenon that weak signal is enhanced or optimized under the influence of noises [5]. Recently, because the noises and time delay are the two important factors of many complex systems, their effects on the random system have been extensively studied [6–12]. The researchers found the combination of noises and time delay

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fundamentally changes the statistical characteristics of a random system [13–28]. In the researches [21–26], they found that the combination of noises and time delay causes the regime shifts in some ecological systems. Thus it can be seen in random systems with time delay being widely studied [17–35]. In many biological and physical systems, time delays reflect the transmission times related to the transport of matter, energy and information through the system. So it is more natural to consider time delay in these situations. An approximate analytical method for stochastic systems with time delay has been established in the processing of small time delay [36–38]. The numerical simulation method can be used in the processing of large time delay. The presence of time delay changes the dynamics properties of the system, and brings a series of meaningful and significant results [21–26,30–35]. For example, time delay induced coherence resonance [32–35], multistability [33], desynchronization [34] and excitability [35].

In the exploration of gene transcriptional regulation, Smolen et al. presented the general kinetic model of gene transcriptional regulatory system [39,40]. Regulation of gene expression by noises intrinsic and extrinsic of the cell plays important roles in many biological processes. So the Earth's external environmental factors such as electromagnetic fields, solar terms, seasonal variations and tides, or periodic artificial interference such as the changing of the ambient temperature, humidity, air pressure, nutrition supply, etc. All of these regular factors will have an impact on gene transcriptional regulatory process, which means that the transcriptional regulation of gene should be periodic, and it comes from the outside. Bistable state, noises and signal exist at the same time in this case, so the collective effects of noise, external signal and time delay on stochastic resonance can be studied. The combined effects of correlated noises and time delay on the gene transcriptional regulatory model still have not been completely investigated.

Based on the model presented by Smolen et al., Liu and Jia researched the effects of noises on the mean-first-pass time [41], their results indicate that noises and correlated noises can induce gene switch processes. In the letter [42], the researches studied the SR phenomenon in a time-delayed gene transcriptional regulatory system under noises of a weak additive periodic signal. They found that the delay time τ enhances the SR of the system. In the previous work of us, we studied SR induced by the multiplicative periodic signal in the gene transcriptional regulatory system with correlated noises [43]. We found critical phenomenon occurred when *SNR* as function of the cross-correlation noise intensity λ , but we did not discuss time delay. Wang et al. studied SR in the gene transcriptional regulatory system subjected to noises and a weak periodic signal [29], and then they researched that time delay induced transition of gene switch and SR in a gene transcriptional regulatory model. But in their researches, the time delay effects of cross-correlation noise and an additive periodic signal on SR were considered [30]. The additive periodic signal here is an internal function of the system. It is noteworthy that in most cases the signal should be multiplicative fashion in some systems, such as in a membrane–protein system investigated by Fuliski and Gra [44]. They found the addition of a multiplicative noise improves the outgoing signal when the incoming one is coupled to the transmitting process in a multiplicative way. Collins et al. introduced a multiplicative aperiodic signal into a symmetric bistable potential with the presence of additive noise, and found aperiodic stochastic resonance [45]. Nicolis and Nicolis studied the stochastic resonance in the presence of slowly varying control parameters and a multiplicative periodic signal in a bistable system [46]. They offered a new method for the control of the transition rates [47]. In my research, the periodic signal comes from the external of the model of gene transcriptional regulatory in most cases. For example, the regular external changes in environment and periodic manual interference, come from the external environment of the model. So the multiplicative periodic signal is more realistic and reasonable than the additive periodic signal in this model. The time delay effects of SR induced by multiplicative periodic signal in gene transcriptional regulatory model is significant. But this issue has not been studied at present, here is my research work as below. In this paper, the above model is extended to a new model with multiplicative periodic signal, cross-correlation noise and small time delay. We studied the effects of time delay and noises intensity on SR by applying the two-state theory in adiabatic limit [48] and approximate analytical method for small time delay.

This paper is arranged as follows: in Section 2, an introduction of the gene transcriptional regulatory model. Then the expression of signal-to-noise ratio is derived by applying the two-state theory in adiabatic limit and approximate analytical method for small time delay. The effects of multiplicative noise intensity, additive noise intensity, cross-correlation noise intensity and time delay on SNR will be discussed by numerical calculation and graphical analysis in Section 3. Section 4 will be a discussion of the results of my findings.

2. The gene transcriptional regulatory model

There are a lot of theoretical models to simulate the regulation of gene transcription. In 1998, Smolen et al. presented the general kinetic model of gene transcriptional regulatory system [39,40]. The model includes the dimerization of the transcriptional factors activator (TF-A), phosphorylation of the dimers, then positive feedback of phosphorylated dimers activate the transcription, synthesis, degradation, and nonlinear interaction of TF-A. According to the biochemical reactions described in the model, these researchers obtained the ordinary differential equation of protein concentration with time evolution:

$$\frac{dx}{dt} = \frac{k_f x^2}{x^2 + K_d} - k_d x + R_{bas}, \tag{1}$$

where x is TF-A monomer concentration, k_f is the maximal rate of phosphorylated dimer TF-A activator, K_d is the dissociation concentration of the TF-A dimer from TF-REs, k_d denote the degradation reaction rate of TF-A, R_{bas} denote the synthesis reaction rate of TF-A. concentration x and concentration related parameters K_d are dimensionless constants.