Stochastic resonance in the gene transcriptional regulatory system subjected to noises*

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We have investigated in the adiabatic limit the phenomenon of stochastic resonance in the gene transcriptional regulatory system subjected to an additive noise, a multiplicative noise, and a weakly periodic signal. Using the general two-state approach for the asymmetry system, the analytic expression of signal-to-noise ratio is obtained. The effects of the additive noise intensity α, the multiplicative noise intensity D and the amplitude of input periodic signal A on the signal-to-noise ratio are analysed by numerical calculation. It is found that the existence of a maximum in the $R_{\rm SNR}$–α and $R_{\rm SNR}$–D plots is the identifying characteristic of the stochastic resonance phenomenon in the weakened noise intensity region. The stochastic resonance phenomena are restrained with increasing α and D, and enhanced with increasing A.

Keywords: gene transcriptional regulatory system, stochastic resonance, noises

PACC: 0540, 0250

1. Introduction

Stochastic resonance (SR), which was originally discovered by Benzi *et al.*[1] and Nicolis *et al.*[2] in the context of modeling the switch of the Earth's climate between ice ages and periods of relative warmth, is an important aspect in many scientific fields and has been investigated extensively due to its potential applications from both the theoretical and experimental points of view.[3−14] SR is a common case and generic enough to be observable in a large variety of nonlinear dynamical systems, including the occurrence of SR in physical systems, biological system, ecological system, laser system, etc. Generally, SR is characterised by the optimisation of the output signal-to-noise ratio (SNR) in nonlinear dynamical systems when a weak external signal is added. There are three indispensable factors in the above stochastic systems: two or more stable states, input signal (maybe contains a weak periodic signal) and noise.[15]

In the biophysics field, the study of the SR phenomenon has turned into a frontier subject. The SR phenomenon and its applications were found extensively, as in noise enhancement of information transfer in crayfish mechanoreceptors by SR.[16] It enhances the normal feeding behaviour of paddlefish,[17] it can be used as a measuring tool to quantify the ability of the human brain to interpret noise-contaminated visual patterns[18] and it also appears in an anti-tumor system modulated by a seasonal external field.[19] Oscillation and noise determine signal transduction in shark multimodal sensory cells.[20]

The studies of the gene transcriptional regulatory reveal the complex life phenomena from the view of the interaction between the gene and its products(regulatory factor), and are the main content of functional genomics. However, the external and internal noises exist widely in these physiological activities, e.g. the cells DNA reproduction, gene transcription and protein translation, etc.[21−26] The dynamic behaviour of the gene transcription can be accurately described by the stochastic models. Therefore, it is necessary to investigate the stochastic gene transcriptional system. Only rarely were some works done on this aspect, however, some interesting and meaningful phenomena have been found.[27−35] For example, the correlated noise can induce re-entrance phenomena (two switches).[30] The coloured cross-correlated time can speed up the transition between the low concentration state and the high concentration state.[31] The time delay can also induce the two switches, etc. The SR phenomenon in the gene transcriptional regulatory system has been investigated in Ref. [33]. However, the asymmetry has not been taken into account

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in these works. As is known, the gene transcriptional regulatory system with a positive feedback[27] is an asymmetric system, and the asymmetry may bring different transition probabilities. In this paper, the effects of potential asymmetry on SR in the gene transcriptional regulatory driven by white Gaussian noises are investigated. We derive the expression of SNR by applying the general two-stability theory[11,35] and discuss the effects of the noise intensity on the SR, when the potential asymmetry is taken into account for the SR.

2. Gene transcriptional regulatory system

To examine the capability of genetic regulatory systems for complex dynamic activity, Smolen *et al.*[27] developed simple kinetic models that incorporate known features of these systems. These features include autoregulation and stimulus-dependent phosphorylation of transcription factors (TFs), dimerization of TFs, crosstalk, and feedback. The simplest kinetic model of genetic regulation can be described by Fig. 1.[27]

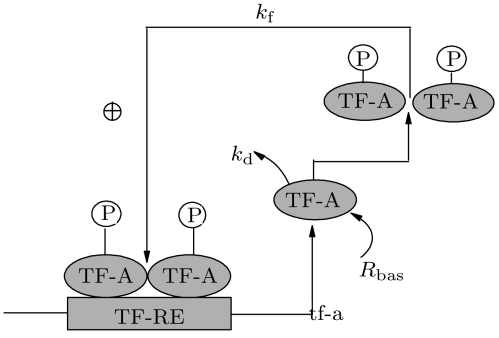


Fig. 1. Model of genetic regulation with a positive autoregulatory feedback loop. The transcription factor activator (TF-A) activates transcription with a maximal rate k_f when phosphorylated (P) and binds as a dimer to specific responsive-element DNA sequences (TF-REs). TF-A is decomposed at a rate k_d and synthesised at a rate R_{bas}.

These simplifications can give a model with a single ordinary differential equation for the concentration of TF-A

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \frac{k_f x^2}{x^2 + K_d} - k_d x + R_{bas}, \tag{1}$$

where K_d is the dissociation concentration of the TF-A dimer from TF-REs. Under the following condition of parameters

$$\left[-\left(\frac{k_f + R_{bas}}{3k_d}\right)^3 + \frac{K_d(k_f + R_{bas})}{6k_d} - \frac{K_d R_{bas}}{2k_d}\right]^2 + \left[\frac{K_d}{3} - \left(\frac{k_f + R_{bas}}{3k_d}\right)^2\right]^3 < 0, \tag{2}$$

the potential

$$V(x) = k_f\sqrt{K_d}\arctan\left(\frac{x}{\sqrt{K_d}}\right) + \frac{k_d}{2}x^2 - (R_{bas} + k_f)x, \tag{3}$$

corresponding to Eq. (1) that has two stable states

$$x_+ = 2\sqrt{-p/3}\cos(\theta) + (R_{bas} + k_f)/(3k_d), \tag{4}$$

$$x_- = 2\sqrt{-p/3}\cos(\theta + 2\pi/3) + (R_{bas} + k_f)/(3k_d), \tag{5}$$

and one unstable state

$$x_u = 2\sqrt{-p/3}\cos(\theta + 4\pi/3) + (R_{bas} + k_f)/(3k_d), \tag{6}$$

where $p = K_d - [(R_{bas} + k_f)/k_d]^2/3$, $q = K_d(k_f - 2R_{bas})/(3k_d) - 2[(R_{bas} + k_f)/(3k_d)]^3$, and $\theta = \arccos(-q/(2\sqrt{-p^3/27})/3$.

When the parameter values are taken to be $k_f = 6$, $K_d = 10$, $k_d = 1$, and $R_{bas} = 0.4$, the steady states are $x_- \approx 0.62685$ and $x_+ \approx 4.28343$, and the unstable steady state is $x_u \approx 1.48971$ as shown in Fig. 2.

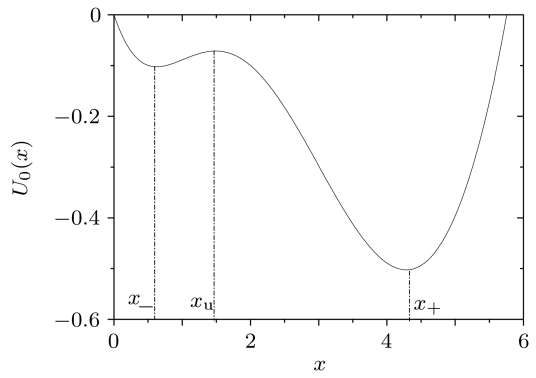


Fig. 2. The bistable potential of Eq. (3). The parameter values are $k_f = 6$, $K_d = 10$, $k_d = 1$, and $R_{bas} = 0.4$. The steady states are $x_- \approx 0.62685$ and $x_+ \approx 4.28343$, and the unstable steady state is $x_u \approx 1.48971$.

3. Signal-to-noise ratio

Recently, some experiments showed that R_{bas} and k_d are affected by the biochemical reactions, mutations, and the concentrations of other proteins, and are also fluctuant.[30] It is like the effect of noises in the

superconducting junction.[36,37] Therefore, it is reasonable to consider the fluctuation effect on the gene transcriptional regulatory system. We consider that the change of the internal temperature can cause the biochemical reaction and mutation effect on the synthesis rate $R_{\rm bas}$. On the other hand, the external environment perturbation (climate, electromagnetic field, etc.) may cause the change of the decomposition rate $k_{\rm d}$. Now we describe it via a stochastic parameter, $R_{\rm bas} \to R_{\rm bas} + \eta(t)$ and $k_{\rm d} \to k_{\rm d} + \xi(t)$. Meanwhile, in the gene transcriptional regulatory process, the external environmental factors, such as, the electromagnetic field on the earth, the solar terms, seasonal variation, are the common features. This means that the transcription of gene should have a periodic form, for example, a cosinoidal form $A\cos(\Omega t)$. If taking into account all the factors, we can rewrite Eq. (1) to obtain the stochastic differential equation (Langevin equation) as follows:

$$\begin{aligned}\frac{{\rm d}x}{{\rm d}t} &= \frac{k_{\rm f}x^2}{x^2+K_{\rm d}} - (k_{\rm d}+\xi(t))x + R_{\rm bas} \\ &\quad +\eta(t) + A\cos(\Omega t), \end{aligned} \tag{7}$$

where $\xi(t)$ and $\eta(t)$ are the Gaussian white noise with the following statistical properties

$$\langle \xi(t) \rangle = \langle \eta(t) \rangle = 0, \tag{8}$$

$$\langle \xi(t)\xi(t') \rangle = 2D\delta(t-t'), \tag{9}$$

$$\langle \eta(t)\eta(t') \rangle = 2\alpha\delta(t-t'), \tag{10}$$

where D and α denote the multiplicative and additive noise intensities, respectively. A is the amplitude of input periodic signal, and Ω is the frequency.

The Stratonovich interpretation of Eq. (7) yields the approximate Fokker–Planck equation of this systems[38,39]

$$\begin{aligned}&\frac{\partial P(x,t)}{\partial t} \\ &= -\frac{\partial}{\partial x}\left[\left(\frac{k_{\rm f}x^2}{x^2+K_{\rm d}} - k_{\rm d}x + R_{\rm bas} + Dx + A\cos(\Omega t)\right)\right. \\ &\quad \left.\times P(x,t)\right] + \frac{\partial^2}{\partial x^2}[(Dx^2+\alpha)P(x,t)]. \end{aligned} \tag{11}$$

Under the constraint $x > 0$ (the TF-A monomer concentration $x(t)$ is always higher than zero in the bistable region satisfying Eq. (2)), the quasi-steady-state distribution function $P_{\rm qst}(x,t)$ can be derived from Eq. (11) in the adiabatic limit,

$$P_{\rm qst}(x,t) = \frac{N}{B(x)^{1/2}} \exp\left[-\frac{\phi_n(x,t)}{D}\right], \tag{12}$$

where N is a normalisation constant, and $\Phi(x)$ is the generalised potential function in the following form

$$\begin{aligned}&\phi_n(x,t) \\ &= \frac{k_{\rm f}D\sqrt{K_{\rm d}}}{\alpha - DK_{\rm d}} \arctan\left[\frac{x}{\sqrt{K_{\rm d}}}\right] - \left(\frac{k_{\rm f}\alpha}{\alpha - DK_{\rm d}}\right. \\ &\quad \left.+R_{\rm bas}\right)\sqrt{\frac{D}{\alpha}} \arctan\sqrt{\frac{D}{\alpha}}x + \frac{k_{\rm d}}{2}\ln(Dx^2+\alpha) \\ &\quad -A\sqrt{\frac{D}{\alpha}} \arctan\left[\sqrt{\frac{D}{\alpha}}x\right]\cos(\Omega t). \end{aligned} \tag{13}$$

Since the frequency Ω is very small, there is enough time for the system to reach the local equilibrium during the period of $1/\Omega$. On the other hand, assuming that the amplitude of the input periodic signal is enough small ($A \ll 1$), it cannot make the particles transit from a well to another. Using the definition of mean first-passage time and steepest descent method,[15] one can obtain the expression of transition rates $W_\pm$ in terms of x_+, x_-,

$$\begin{aligned} W_+ &= \frac{\sqrt{|V''(x_+)V''(x_{\rm u})|}}{2\pi} \\ &\quad \times \exp\left[\frac{\phi_n(x_+,t) - \phi_n(x_{\rm u},t)}{D}\right], \\ W_- &= \frac{\sqrt{|V''(x_-)V''(x_{\rm u})|}}{2\pi} \\ &\quad \times \exp\left[\frac{\phi_n(x_-,t) - \phi_n(x_{\rm u},t)}{D}\right], \end{aligned} \tag{14}$$

in which $V(x)$, x_+, x_-, $x_{\rm u}$ and $\phi_n(x,t)$ have been defined by Eqs. (3)–(6) and (13), respectively.

In the general asymmetric nonlinear dynamical system, the SR phenomenon has been found, and the related theory has been developed.[11,35] Here, we only simply give this method for calculating signal-to-noise ratio (SNR).

Considering a system described by a discrete random dynamical variable x that may take two possible values: c_+ and c_-, with probabilities $n_\pm(t)$, respectively. Such probabilities satisfy the condition $n_+(t) + n_-(t) = 1$. The master equation governing the evolution of $n_\pm(t)$ is written as follows:

$$\begin{aligned} \dot{n}_+ &= -\dot{n}_- \\ &= W_-(t)n_- - W_+(t)n_+ \\ &= W_-(t) - [W_-(t) + W_+(t)]n_+, \end{aligned} \tag{15}$$

where $W_\pm(t)$ are the transition rates out of the $x = x_+$, x_- states.

The system is subjected to a time-dependent signal $A\cos(\Omega t)$, up to first order on its amplitude (as-

sumed to be small); the transition rates can be expanded by using the two-state model theory

$$\begin{aligned} W_+ &= \mu_1 - \beta_1 A\cos(\Omega t), \\ W_- &= \mu_2 + \beta_2 A\cos(\Omega t), \end{aligned} \tag{16}$$

where the constants $\mu_{1,2}$ and $\beta_{1,2}$ depend on the detailed structure of the system under study.

For the asymmetric case, $\mu_1 \neq \mu_2$ and $\beta_1 \neq \beta_2$. Using Eq. (16) one can integrate Eq. (15) for the initial condition $x(t_0) = x_0$, and obtain the conditional probability $n_1(t|x_0, t_0)$. Next, one can calculate the correlation function $\langle x(t+\tau)x(t)|x_0, t_0\rangle$ as

$$\begin{aligned} &\langle x(t+\tau)x(t)|x_0, t_0\rangle \\ &= c_+^2 n_+(t+\tau|c_+, t)n_+(t|x_0, t_0) \\ &\quad + c_+c_- n_+(t+\tau|c_-, t)n_-(t|x_0, t_0) \\ &\quad + c_+c_- n_-(t+\tau|c_+, t)n_+(t|x_0, t_0) \\ &\quad + c_-^2 n_-(t+\tau|c_-, t)n_-(t|x_0, t_0). \end{aligned} \tag{17}$$

For the t-averaged correlation function $C(\tau) = \langle \lim_{t_0\to-\infty}\langle x(t+\tau)x(t)|x_0, t_0\rangle\rangle_t$, one can obtain

$$C(\tau) = R_0 + R_1\exp(-\mu|\tau|) + R_2\cos(\omega_s\tau). \tag{18}$$

Here $\mu = \mu_1 + \mu_2$ and the constants R_i are given by

$$\begin{aligned} R_0 &= \left(\frac{c_-\mu_1 + c_+\mu_2}{\mu_1 + \mu_2}\right)^2, \\ R_1 &= \frac{(c_- - c_+)^2\mu_1\mu_2}{\mu^2} + O(A^2), \\ R_2 &= \frac{A^2(c_+ - c_-)^2(^2\beta_2\mu_1 + \beta_1\mu_2)}{2\mu^2(\mu^2 + \omega^2)}. \end{aligned} \tag{19}$$

After that, we compute the one-sided t-averaged power spectrum distribution (psd) $S(\omega)$, defined, for $\omega > 0$, as

$$\begin{aligned} S(\omega) &= \langle\tilde{S}(\omega)\rangle_t + \langle\tilde{S}(-\omega)\rangle_t \\ &= 4R_1\frac{\mu}{\mu^2 + \omega^2} + 2\pi R_2\delta(\omega - \omega_s), \end{aligned} \tag{20}$$

where $\tilde{S}(\omega)$ is the t-averaged psd as the Fourier transform of $(C(\tau) - R_0)$. R_0 is just the square of the mean value of x in the absence of signal.

For the general asymmetric case we defined $R_{\rm SNR}$, the SNR, as the ratio of the strength of the output signal and the broadband noise output evaluated at the signal frequency. Finally, the expression of SNR is given by[35]

$$R_{\rm SNR} = \frac{A^2\pi(\mu_1\beta_2 + \mu_2\beta_1)^2}{4\mu_1\mu_2(\mu_1 + \mu_2)}, \tag{21}$$

where

$$\begin{aligned} \mu_1 &= W_+|_{A\cos(\Omega t)=0}, \\ \mu_2 &= W_-|_{A\cos(\Omega t)=0}, \\ \beta_1 &= \left.\frac{{\rm d}W_+}{{\rm d}(A\cos(\omega t))}\right|_{A\cos(\Omega t)=0}, \\ \beta_2 &= \left.\frac{{\rm d}W_-}{{\rm d}(A\cos(\omega t))}\right|_{A\cos(\Omega t)=0}, \end{aligned} \tag{22}$$

4. Discussions

According to Eq. (21) for SNR, the effects of the additive noise intensity α, the multiplicative noise intensity D, and the periodic driving amplitude A on the SNR are analysed by numerical calculation. These results are plotted in Figs. 3 and 4.

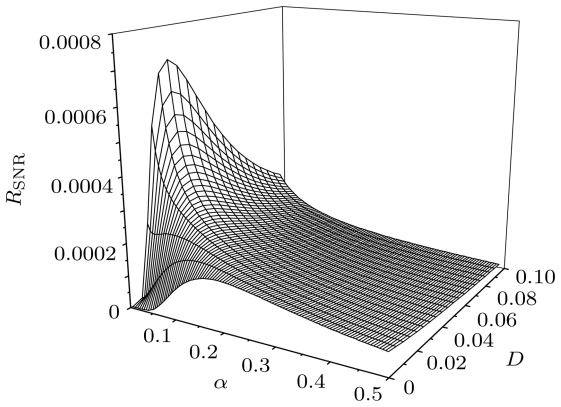


Fig. 3. $R_{\rm SNR}$ as a function of the additive noise intensity α and the multiplicative noise intensity D for $A = 0.0005$, the other parameter values are the same as those in Fig. 2.

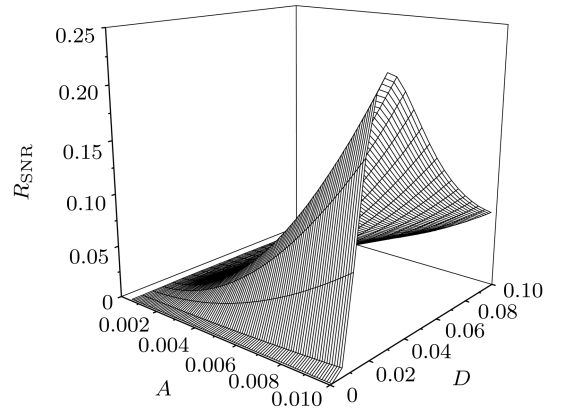


Fig. 4. $R_{\rm SNR}$ as a function of the amplitude of input periodic signal A and the multiplicative noise intensity D for $\alpha = 0.008$, the other parameter values are the same as those in Fig. 2.

The three-dimensional plot of the SNR of the gene transcriptional regulatory system as a function of the additive Gaussian noise intensity α, and the multiplicative noise intensity D is shown in Fig. 3. It is

found that there is a single peak in $R_{\rm SNR}$–α plot and $R_{\rm SNR}$–D plot, which is the identifying characteristic of the SR phenomenon.[15] However, with increasing D and α, the peak of the SNR gradually disappears, and becomes a monotonically decreasing curve. It indicates that there exists a critical value, and the SR phenomena only appear in this particular region, namely, the clearer the SR phenomena, the weaker the noise intensity.

The three-dimensional plot of the SNR of the gene transcriptional regulatory system as a function of the amplitude of input periodic signal A and the multiplicative noise intensity D is shown in Fig. 4. It is clear that the maximum of the SNR increases as A increases. This result can be also drawn from Eq. (21) directly.

5. Conclusions

The phenomenon of SR in the gene transcriptional regulatory system subjected to an additive noise, a multiplicative noise and a weakly periodic signal (a seasonal external field) has been investigated in the adiabatic limit. Using the general two-state approach[35] for the asymmetric system, the analytic expression of SNR is obtained. The effects of the additive noise intensity α and the multiplicative noise intensity D on SNR are analysed by numerical calculation. It is found that the existence of a maximum in the $R_{\rm SNR}$–α and $R_{\rm SNR}$–D plots is the identifying characteristic of the SR phenomenon, when the noise intensity is weak. The SR phenomena are restrained with increasing α and D. But the amplitude of input signal A can enhance the SR phenomena.

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