Stochastic resonance induced by a multiplicative periodic signal in the gene transcriptional regulatory system with correlated noises*

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This paper investigates the stochastic resonance (SR) induced by a multiplicative periodic signal in the gene transcriptional regulatory system with correlated noises. The expression of the signal-to-noise ratio (SNR) is derived. The results indicate that the existence of a maximum in SNR vs. the additive noise intensity α, the multiplicative noise intensity D and the cross-correlated noise intensity λ is the identifying characteristic of the SR phenomenon and there is a critical phenomenon in the SNR as a function of λ, i.e., for the case of smaller values of noise intensity (α or D), the SNR decreases as λ increases; however, for the case of larger values of noise intensity (α or D), the SNR increases as λ increases.

Keywords: gene transcriptional regulatory system, stochastic resonance, critical phenomenon
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1. Introduction

The concept of stochastic resonance (SR) was originally introduced by Benzi *et al.*[1,2] to explain the periodic recurrences of the Earth's ice ages. Benzi *et al.* advanced a bistable nonlinear climate model that is associated with the nonlinearity of the Earth to make clear the variation of climate. Then the SR phenomenon was observed in a Schmitt trigger circuit[3] and in a He–Ne bidirectional ring laser.[4] The representative character of SR is the existence of a maximum of the signal-to-noise ratio (SNR) as a function of the noise intensity. The SR phenomenon generally exists in nature and attracts considerable attention. Scientists have found the SR phenomenon in various fields, such as laser bistable loops, electromagnetics, optics, chemistry, biology, etc. The SR has been extensively investigated both theoretically and experimentally.[5]

In 1998, Smolen *et al.* put forward the general kinetic model of the genetic regulation system.[6] Based on this, the effects of fluctuation in the degradation and the synthesis reaction rate of the transcription factor have been studied.[7] After Smolen *et al.*'s study, Liu and Jia[8] investigated the mean first passage time (MFPT) of the gene transcriptional regulatory system with the inner and outside noises;[8] they found that inner and outside noise intensities and cross-correlated noise intensity can induce gene switch under certain conditions. Recently, Zeng *et al.*[9] studied the SR phenomenon in a time-delayed gene transcriptional regulatory system with an additive periodic signal and cross-correlated noises.[9] They found that the delay time τ enhances the SR of the system and the correlation intensity λ enhances the SR in a plot of SNR vs. D (D denotes the multiplicative noise intensity), but weakens the SR in a plot of SNR vs. α (α denotes the additive noise intensity). Since most periodic signals come from outside of the system, it is more reasonable that the external signal is described by the multiplicative signal. In Ref. [8], two noises may have a common origin and not be independent. In Gitterman and Berdichevsky's paper,[10,11], they advanced two possibilities. One is that two noises may have the same origin, another one is that inside and outside noises from different origins may have correlativity, namely, the stronger external noise affects inner noise via external noise. In this paper, we will study the gene transcriptional regulatory system with a multiplicative signal and correlated noises. This paper is

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arranged as follows: in Section 2, the expression of the SNR with a multiplicative periodic signal is derived and investigated in detail. Finally, a conclusion is given in Section 3.

2. The SNR of the gene transcriptional regulatory system with multiplicative signal and correlated noises

The gene transcriptional regulatory system is described by the following differential equation:[6,12]

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \frac{k_\mathrm{f}x^2}{x^2+K_\mathrm{d}} - k_\mathrm{d}x + R_\mathrm{bas}, \tag{1}$$

where x is the transcription factor (TF) monomer concentration, k_f is the maximal rate of phosphorylated dimer TF activator, K_d is the dissociation concentration of the TF activator dimer, k_d and R_bas denote the degradation reaction rate and the synthesis reaction rate of TF, respectively. The deterministic potential corresponding to Eq. (1) is

$$U(x) = k_\mathrm{f}\sqrt{K_\mathrm{d}}\arctan\left(\frac{x}{\sqrt{K_\mathrm{d}}}\right) + \frac{1}{2}k_\mathrm{d}x^2 - (R_\mathrm{bas}+k_\mathrm{f})x. \tag{2}$$

There are two steady stable states given as follows: $x_1 = 2\sqrt{-a/3}\cos(\theta) + (R_\mathrm{bas}+k_\mathrm{f})/(3k_\mathrm{d})$, $x_2 = 2\sqrt{-a/3}\cos(\theta+2\pi/3) + (R_\mathrm{bas}+k_\mathrm{f})/(3k_\mathrm{d})$, and one metastable state $x_3 = 2\sqrt{-a/3}\cos(\theta+4\pi/3)+(R_\mathrm{bas}+k_\mathrm{f})/(3k_\mathrm{d})$, here $a = K_\mathrm{d} - [(R_\mathrm{bas}+k_\mathrm{f})/k_\mathrm{d}]^2/3$, $b = K_\mathrm{d}(k_\mathrm{f}-2R_\mathrm{bas})/(3k_\mathrm{d}) - 2[(R_\mathrm{bas}+k_\mathrm{f})/(3k_\mathrm{d})]^3$ and $\theta = \arccos[-b/(2\sqrt{-a^3/27})]/3$. A bistable potential of $U(x)$ is poltted in Fig. 1.

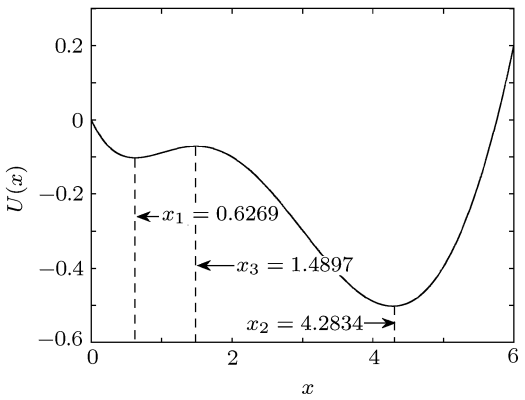


Fig. 1. The deterministic potential of Eq. (2) with $k_\mathrm{f}=6$, $K_\mathrm{d}=10$, $k_\mathrm{d}=1$ and $R_\mathrm{bas}=0.4$.

Obviously, equation (1) is deterministic, and the intrinsic fluctuations of the system are not considered there. Now, we consider the disturbance of the system such as activator, temperature, radiotherapy, etc.; the parameters k_d and R_bas should be modified as $k_\mathrm{d}+\xi(t)+x(t)A\cos(\omega)$ and $R_\mathrm{bas}+\eta(t)$, respectively.[8,13] Thus, equation (1) becomes a Langevin equation

$$\frac{\mathrm{d}x}{\mathrm{d}t} = \frac{k_\mathrm{f}x^2}{x^2+K_\mathrm{d}} - k_\mathrm{d}x + R_\mathrm{bas} - x(t)\xi(t) + \eta(t) - x(t)A\cos(\omega t), \tag{3}$$

where $\xi(t)$ and $\eta(t)$ are Gaussian white noise with zero mean and[8]

$$\langle\xi(t)\xi(t')\rangle = 2D\delta(t-t'), \tag{4}$$

$$\langle\eta(t)\eta(t')\rangle = 2\alpha\delta(t-t'), \tag{5}$$

$$\langle\xi(t)\eta(t')\rangle = \langle\eta(t)\xi(t')\rangle = 2\lambda\sqrt{D\alpha}\delta(t-t'), \quad |\lambda|<1, \tag{6}$$

where D and α denote the multiplicative and additive noise intensities, respectively, λ measures the strength of correlations between $\xi(t)$ and $\eta(t)$, A is the amplitude of the periodic signal and ω is the frequency.

The Fokker–Planck equation corresponding to Eq. (3) reads

$$\frac{\partial P(x,t)}{\partial t} = \frac{\partial}{\partial x}A(x)P(x,t) + \frac{\partial^2}{\partial x^2}B(x)P(x,t), \tag{7}$$

where

$$A(x) = \frac{k_\mathrm{f}x^2}{x^2+K_\mathrm{d}} - k_\mathrm{d}x + R_\mathrm{bas} - \lambda\sqrt{D\alpha} + Dx(t) - x(t)A\cos(\omega t), \tag{8}$$

and

$$B(x) = Dx^2 - 2\lambda\sqrt{D\alpha}x + \alpha. \tag{9}$$

Assume that the frequency ω and the amplitude A of the periodic signal are very small, thus, there is enough time for the system to reach local equilibrium positions during the period of $1/\omega$ (i.e., $\omega \ll 1$) and the variation of the potential of the system modulated by the periodic signal is small (i.e., $A \ll 1$). Then the quasi-steady state probability distribution function corresponding to Eq. (7) can be obtained in the adiabatic limit[7]

$$P_\mathrm{st}(x,t) = \frac{N}{B(x)^{1/2}}\exp\left[-\frac{\Phi(x,t)}{D}\right], \tag{10}$$

where N is a normalization constant and the modified potential is given by

$$\begin{aligned}\Phi(x,t) =\ & H\lambda\sqrt{D\alpha}K_{\rm d}\times\ln|K_{\rm d}+x^2| - H(Dk_{\rm d}-\alpha)\sqrt{K_{\rm d}}\times\arctan\left(\frac{x}{\sqrt{K_{\rm d}}}\right)\\ & -\left(H\lambda\sqrt{D\alpha}K_{\rm d}-\frac{k_{\rm d}}{2}\right)\times\ln|Dx^2-2\lambda\sqrt{D\alpha}x+\alpha|\\ & -\left\{H\times\left[\frac{2\lambda^2\sqrt{D\alpha}K_{\rm d}}{\sqrt{1-\lambda^2}}+\frac{(\alpha-DK_{\rm d})\alpha}{\sqrt{D\alpha(1-\lambda^2)}}\right]-\frac{\lambda k_{\rm d}}{\sqrt{1-\lambda^2}}+\frac{DR_{\rm bas}}{\sqrt{D\alpha(1-\lambda^2)}}\right\}\times\arctan\left(\frac{\sqrt{D/\alpha}x-\lambda}{\sqrt{1-\lambda^2}}\right)\\ & +\left[\frac{1}{2}\ln|Dx^2-2\lambda\sqrt{D\alpha}x+\alpha|+\frac{\lambda}{\sqrt{1-\lambda^2}}\times\arctan\left(\frac{\sqrt{D/\alpha}x-\lambda}{\sqrt{1-\lambda^2}}\right)\right]\times A\cos(\omega t),\end{aligned}\tag{11}$$

where

$$H=\frac{k_{\rm f}D}{2K_{\rm d}D\alpha(2\lambda^2-1)+\alpha^2+D^2K_{\rm d}^2}.\tag{12}$$

Almost all TFs are in the stable state x_2 in this model at the beginning, so we just discuss the case in which the transition is from x_2 to x_1 through x_3. Then D and α should be smaller than the height of the energy barrier, that is

$$D,\alpha<|\Phi(x_3)-\Phi(x_2)|.\tag{13}$$

The MFPT can be given by the Kramers time[14,15]

$$T(x_3\to x_2)=\frac{2\pi}{\sqrt{|U''(x_3)U''(x_2)}}\exp\left[\frac{\Phi(x_3)-\Phi(x_2)}{D}\right],\tag{14}$$

and the transition rate is[16]

$$\begin{aligned}W =\ & \frac{1}{T}=\frac{\sqrt{|U''(x_3)U''(x_2)}}{2\pi}\exp\left[\frac{\Phi(x_2)-\Phi(x_3)}{D}\right]\\ =\ & \frac{1}{2\pi}\left|\left[-\frac{2k_{\rm f}x_2}{\left(1+\frac{x_2^2}{K_{\rm d}}\right)^2K_{\rm d}}+k_{\rm d}\right]\times\left[-\frac{2k_{\rm f}x_3}{\left(1+\frac{x_3^2}{K_{\rm d}}\right)^2K_{\rm d}}+k_{\rm d}\right]\right|\\ & \times\exp\left\{\left\{H\lambda\sqrt{D\alpha}K_{\rm d}\times(\ln|K_{\rm d}+x_2^2|-\ln|K_{\rm d}+x_3^2|)\right.\right.\\ & -H(Dk_{\rm d}-\alpha)\sqrt{K_{\rm d}}\times\left[\arctan\left(\frac{x_2}{\sqrt{K_{\rm d}}}\right)-\arctan\left(\frac{x_3}{\sqrt{K_{\rm d}}}\right)\right]\\ & -\left(H\lambda\sqrt{D\alpha}K_{\rm d}-\frac{k_{\rm d}}{2}\right)\times(\ln|Dx_2^2-2\lambda\sqrt{D\alpha}x_2+\alpha|-\ln|Dx_3^2-2\lambda\sqrt{D\alpha}x_3+\alpha|)\\ & -\left\{H\times\left[\frac{2\lambda^2\sqrt{D\alpha}K_{\rm d}}{\sqrt{1-\lambda^2}}+\frac{(\alpha-DK_{\rm d})\alpha}{\sqrt{D\alpha(1-\lambda^2)}}\right]-\frac{\lambda k_{\rm d}}{\sqrt{1-\lambda^2}}+\frac{DR_{\rm bas}}{\sqrt{D\alpha(1-\lambda^2)}}\right\}\\ & \times\left[\arctan\left(\frac{\sqrt{D/\alpha}x_2-\lambda}{\sqrt{1-\lambda^2}}\right)-\arctan\left(\frac{\sqrt{D/\alpha}x_3-\lambda}{\sqrt{1-\lambda^2}}\right)\right]\\ & +\left\{\frac{1}{2}\ln|Dx_2^2-2\lambda\sqrt{D\alpha}x_2+\alpha|-\frac{1}{2}\ln|Dx_3^2-2\lambda\sqrt{D\alpha}x_3+\alpha|\right.\\ & \left.\left.+\frac{\lambda}{\sqrt{1-\lambda^2}}\times\left[\arctan\left(\frac{\sqrt{D/\alpha}x_2-\lambda}{\sqrt{1-\lambda^2}}\right)-\arctan\left(\frac{\sqrt{D/\alpha}x_3-\lambda}{\sqrt{1-\lambda^2}}\right)\right]\right\}\times A\cos(\omega t)\right\}\times\frac{1}{D}\right\}.\end{aligned}\tag{15}$$

Based on the theory of SR proposed by McNamara and Wiesenfeld,[7] we can obtain the formula of the SNR of the system

$$\mathrm{SNR}=\frac{\pi W_1^2A^2}{4W_0}\left[1-\frac{W_1^2A^2}{2(W_0^2+\omega^2)}\right]^{-1},\tag{16}$$

where

$$
\begin{aligned}
W_0 &= 2W|_{A\cos(\omega t)=0} = \frac{\sqrt{|U''(x_3)U''(x_2)|}}{\pi}\exp\left[\frac{\Phi(x_2)-\Phi(x_3)}{D}\right] \\
&= \frac{1}{\pi}\left|\left[-\frac{2k_{\rm f}x_2}{\left(1+\dfrac{x_2^2}{K_{\rm d}}\right)^2 K_{\rm d}}+k_{\rm d}\right]\times\left[-\frac{2k_{\rm f}x_3}{\left(1+\dfrac{x_3^2}{K_{\rm d}}\right)^2 K_{\rm d}}+k_{\rm d}\right]\right| \\
&\quad\times\exp\left\{\left\{H\lambda\sqrt{D\alpha}K_{\rm d}\times(\ln|K_{\rm d}+x_2^2|-\ln|K_{\rm d}+x_3^2|)\right.\right. \\
&\quad -H(Dk_{\rm d}-\alpha)\sqrt{K_{\rm d}}\times\left[\arctan\left(\frac{x_2}{\sqrt{K_{\rm d}}}\right)-\arctan\left(\frac{x_3}{\sqrt{K_{\rm d}}}\right)\right] \\
&\quad -\left(H\lambda\sqrt{D\alpha}K_{\rm d}-\frac{k_{\rm d}}{2}\right)\times(\ln|Dx_2^2-2\lambda\sqrt{D\alpha}x_2+\alpha|-\ln|Dx_3^2-2\lambda\sqrt{D\alpha}x_3+\alpha|) \\
&\quad -\left\{H\times\left[\frac{2\lambda^2\sqrt{D\alpha}K_{\rm d}}{\sqrt{1-\lambda^2}}+\frac{(\alpha-DK_{\rm d})\alpha}{\sqrt{D\alpha(1-\lambda^2)}}\right]-\frac{\lambda k_{\rm d}}{\sqrt{1-\lambda^2}}+\frac{DR_{\rm bas}}{\sqrt{D\alpha(1-\lambda^2)}}\right\} \\
&\quad\left.\left.\times\left[\arctan\left(\frac{\sqrt{D/\alpha}x_2-\lambda}{\sqrt{1-\lambda^2}}\right)-\arctan\left(\frac{\sqrt{D/\alpha}x_3-\lambda}{\sqrt{1-\lambda^2}}\right)\right]\right\}\times\frac{1}{D}\right\}, \qquad (17)
\end{aligned}
$$

$$
\begin{aligned}
W_1 &= 2\frac{{\rm d}W}{{\rm d}A\cos(\omega t)}\bigg|_{A\cos(\omega t)=0} \\
&= \left\{\frac{1}{2D}(\ln|Dx_2^2-2\lambda\sqrt{D\alpha}x_2+\alpha|-\ln|Dx_3^2-2\lambda\sqrt{D\alpha}x_3+\alpha|)\right. \\
&\quad\left.+\frac{\lambda}{D\sqrt{1-\lambda^2}}\times\left[\arctan\left(\frac{\sqrt{D/\alpha}x_2-\lambda}{\sqrt{1-\lambda^2}}\right)-\arctan\left(\frac{\sqrt{D/\alpha}x_3-\lambda}{\sqrt{1-\lambda^2}}\right)\right]\right\}W_0. \qquad (18)
\end{aligned}
$$

According to Eqs. (16), (17) and (18), the SR phenomenon of the system can be analysed by numerical computation. The results of the numerical computation of the SNR as a function of α and λ, and as a function of D and λ are plotted on Figs. 2 and 4, respectively.

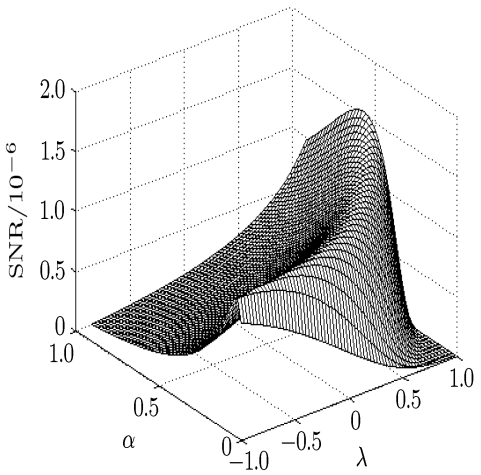


Fig. 2. The SNR as a function of α and λ with $A = 0.0001$, $\omega = 0.0001$ and $D = 0.01$.

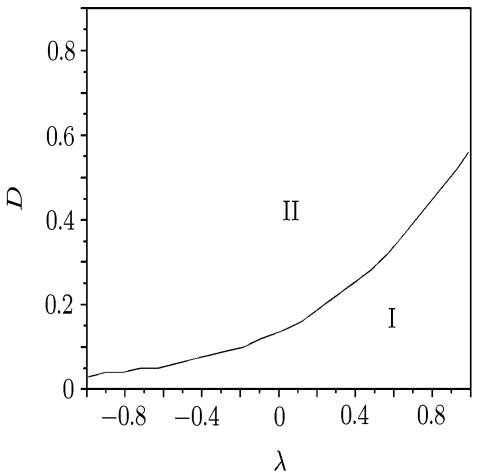


Fig. 3. The critical curve in the α–λ plane corresponding to Fig. 2.

Figure 2 shows that the existence of a maximum in SNR vs. α and λ is the identifying characteristic of the SR phenomenon. The SNR decreases as λ increases for the case of smaller values of α; however, the SNR increases as λ increases for the case of larger values of α. There is a critical phenomenon in SNR vs. λ, that is, below or above the critical value of α, λ has an opposite effect on the SNR of the system. The critical curve in the α–λ plane corresponding to Fig. 2 is plotted on Fig. 3. The SNR decreases as λ increases in region I of Fig. 3 and the SNR increases as λ increases in region II of Fig. 3.

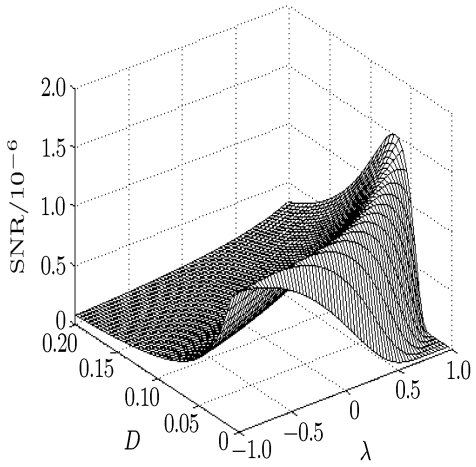


Fig. 4. The SNR as a function of D and λ with $A = 0.0001$, $\omega = 0.0001$ and $\alpha = 0.06$.

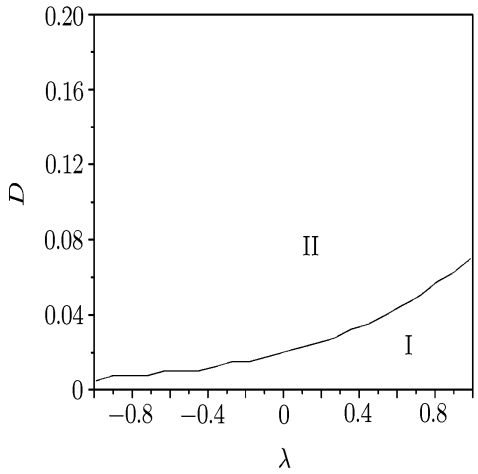


Fig. 5. The critical curve in the D–λ plane corresponding to Fig. 4.

Figure 4 shows that the existence of a maximum in SNR vs. D and λ is the identifying characteristic of the SR phenomenon. The SNR decreases as λ increases for the case of smaller values of D; however, the SNR increases as λ increases for the case of larger values of D. There is also a critical phenomenon in SNR vs. D, that is, below or above the critical value of D, λ has an opposite effect on the SNR of the system. The critical curve in the D–λ plane corresponding to Fig. 4 is plotted on Fig. 5. The SNR decreases as λ increases in region I of Fig. 5 and the SNR increases as λ increases in region II of Fig. 5.

3. Conclusions

Using the SNR theory proposed by McNamara and Wiesenfeld,[4,7] we have investigated the SR phenomenon in the gene transcriptional regulatory system with the multiplicative signal and correlated noises. Our results indicate that there are critical phenomena in the SNR as a function of the intensity of cross-correlated noise λ, i.e., for the case of smaller values of noise intensity (α or D), the SNR decreases as λ increases; however, for the case of larger values of noise intensity (α or D), the SNR increases as λ increases. The behaviour of SNR in the gene transcriptional regulatory system with the multiplicative signal and correlated noises is very different from that in the system with the additive signal and correlated noises.

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