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Pure multiplicative stochastic resonance of a theoretical anti-tumor model with seasonal modulability

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Pure multiplicative noise-induced stochastic resonance, which appears in an anti-tumor system modulated by a seasonal external field, is studied by using theoretical analyses of the generalized potential and numerical simulations. For optimally selected values of the multiplicative noise intensity stochastic resonance is observed, which is manifested by the quasisymmetry of two potential minima. Theoretical results and numerical simulations are in good quantitative agreement.

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Chemotherapy remains a traditional form of therapy for most advanced cancers. Immunotherapy, however, is a less conventional treatment modality. Usually, chemotherapy and immunotherapy have been regarded as unrelated forms of therapy, so relatively few researchers have investigated the relationship between these two therapies. Chemotherapy kills tumor cells in a special periodic way while immunotherapy restrains the growth of tumor cells in a more likely linear way. Recent studies suggested that these various responses of tumor cells to the treatments, once taken together, imply that there is an interesting and significant case for combining chemotherapy and immunotherapy in tumor treatments [1–4].

More than ever, cancer research is now an interdisciplinary effort that requires a basic knowledge of commonly used terms, facts, issues, and concepts. In the past decade, many studies have focused on the growth law of tumor cells via dynamics, especially noise dynamics [5–13]. Phase transition in the tumor growth induced by noises is one of the most novel fundamental issues in recent years. Another phenomenon, known as stochastic resonance (SR), shows that adding noise to a system can sometimes improve its ability to transfer information. The basic three ingredients of stochastic resonance are a threshold, a noise source, and a weak input. It is clear that stochastic resonance is a common case and generic enough to be observable in a large variety of nonlinear dynamical systems [14,15], including the occurrence of SR in a tumor dynamical system.

The mean field approximation is a conventional theory for SR, and is originally proposed for symmetrical bistable systems with an additive noise source [16]. The improvements of the theory of SR have included monostable systems [17,18], asymmetrical systems [19], and double-noise (*multiplicative and additive noises*) systems [20,21]. However, in all these studies, the systems have an additive noise source and an independent external field. For a pure multiplicative noise system, especially for a more complex dynamical system, the equations are too complex to be solved simply by using the mean field approximation. Thus numerical methods are comparatively convenient options to deal with these complex dynamical systems [22,23].

In this Rapid Communication, chemotherapy and immunotherapy are joined by an anti-tumor model with three elements: (1) a fluctuation of growth rate, (2) an immune form, and (3) a weak seasonal modulability induced by chemotherapy. On the basis of the analyses of the stochastic differential equation and relevant Fokker-Planck equation, we investigate a new type of SR phenomenon of an anti-tumor model through both theoretical analyses and numerical computations. We designate this effect as pure multiplicative stochastic resonance (PMSR) to emphasize the role the pure multiplicative noise may play in inducing a synchronization, which can be described by the symmetry of the potential wells. Additionally, a presupposition is also given that SR has a close relationship with the responses of a tumor to the treatments.

Lefever and Garay [24] studied the growth of the tumor under immune surveillance against cancer using the enzyme dynamics model. The model is,

$$\text{Normal Cells} \xrightarrow{\gamma} X,$$

$$X \xrightarrow{\lambda} 2X,$$

$$X + E_0 \xrightarrow{k_1} E \xrightarrow{k_2} E_0 + P,$$

$$P \xrightarrow{k_3}, \tag{1}$$

in which X, P, E_0, and E are cancer cells, dead cancer cells, immune cells and the compounds of cancer cells and immune cells, respectively. The symbols, γ, λ, k_1, k_2, and k_3, are velocity coefficients. This model reveals that normal cells can transform into cancer cells, and then the cancer cells reproduce, decline, and die out ultimately. We can simplify this model to an equivalent single-variable deterministic dynamics differential equation [7],

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$$\frac{dx_n}{d\tau} = r_n x_n\left(1 - \frac{x_n}{K_n}\right) - \varphi(x_n), \tag{2}$$

where x_n is the population of tumor cells, r_n is their linear per capita birth rate, and K_n is the carrying capacity of the environment, respectively. $\varphi(x_n)$, defined as $\varphi(x_n)=\beta x_n^2/(\epsilon^2+x_n^2)$ [7,25], quantifies the abilities of immune cells to identify and attack tumor cells. Here β is the immune coefficient and ϵ gives a measure of the threshold at which the immune system is "switched on." For convenience, we set $x=x_n/\epsilon$, $r=r_n\epsilon$, $K=K_n/\epsilon$, $t=\tau/\epsilon$ to obtain a nondimensional form of Eq. (2),

$$\frac{dx}{dt} = rx\left(1 - \frac{x}{K}\right) - \frac{\beta x^2}{1+x^2}. \tag{3}$$

Like most species, seasonal growth is a common feature of tumor cells, especially when they are under a periodic chemotherapeutic treatment [2]. This means that the growth rate of tumor cells should have a periodic form, for example, a cosinoidal form. If considering the environmental fluctuations, we can rewrite the growth rate r in Eq. (3) as $r_0+A_0\cos(\omega t)+\xi(t)$, where A_0 and ω represent the drug concentration and the frequency of a chemotherapy, respectively. $\xi(t)$ is the Gaussian white noises defined as $\langle\xi(t)\rangle=0$ and $\langle\xi(t)\xi(t')\rangle=2M\delta(t-t')$, in which M is the noise intensity. The equivalent stochastic differential equation of Eq. (3) can be generated as,

$$\frac{dx}{dt} = r_0 x\left(1 - \frac{x}{K}\right) - \frac{\beta x^2}{1+x^2} + x\left(1 - \frac{x}{K}\right)A_0\cos(\omega t) + x\left(1 - \frac{x}{K}\right)\xi(t). \tag{4}$$

In the absence of an external field, i.e., $A_0=0$, if setting $f(x)=r_0x(1-x/K)-\beta x^2/(1+x^2)$ and $g(x)=x(1-x/K)$, one can obtain the Fokker-Planck equation of Eq. (4) [14,20],

$$\frac{\partial P(x,t)}{\partial t} = -\frac{\partial[A(x)P(x,t)]}{\partial x} + \frac{\partial^2[B(x)P(x,t)]}{\partial x^2} \tag{5}$$

in which

$$A(x) = f(x) + Mg(x)g'(x),$$

$$B(x) = Mg^2(x). \tag{6}$$

The stationary probability distribution of the system obtained from Eqs. (5) and (6) is

$$P_{\rm st}(x) = N\exp\left[-\frac{U_{\rm eff}(x)}{M}\right], \tag{7}$$

where N is a normalization constant, and the generalized potential

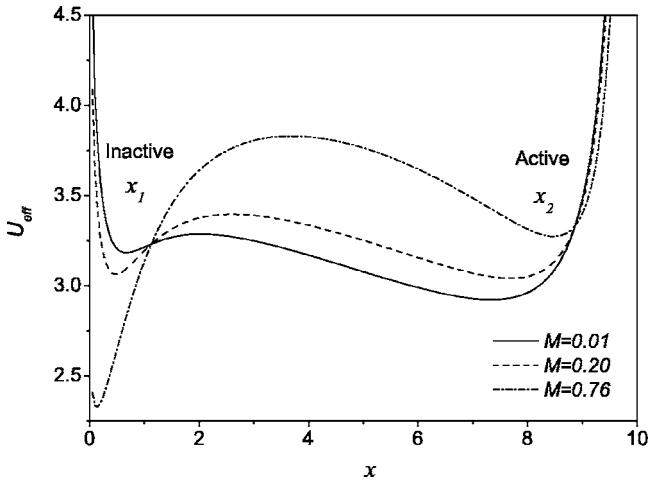

FIG. 1. Generalized potential for different intensities of multiplicative noise $M=0.01$ (solid), 0.20 (dashed), and 0.76 (dashed-dotted). The remaining parameters are $r_0=1.0$, $\beta=2.0$, and $K=10.0$.

$$U_{\rm eff}(x) = \frac{2\beta K^3}{(1+K^2)^2}\left(\ln\left|\frac{\sqrt{1+x^2}}{K-x}\right| + K\arctan x\right) + (r_0+M)\ln\left|\frac{K-x}{x}\right| + \frac{\beta K^2}{1+K^2}\left(\frac{1}{K-x} - \arctan x\right) + M\ln\left|\frac{x^2}{K}\right|. \tag{8}$$

The generalized potential, $U_{\rm eff}(x)$, versus the populations of tumor cells, x, is plotted in Fig. 1 for different noise intensities, M. Obviously, the potential has two stable states, and its minima are obtained from $A(x)-B'(x)=0$, i.e., $r_0(1-x/K)-\beta x/(1+x^2)-M(1-x/K)(1-2x/K)=0$. The positions of the potential minima, x_1 and x_2, shown in Fig. 1, are regarded as the inactive state and the active state of tumor cells, respectively. The generalized potential is an asymmetrical bistable potential well and its values at x_1 and x_2 change with the noise intensity, M. We observe a minimum at a nonzero noise level in Fig. 2 after defining the difference between the potential at x_1 and that at x_2 as $\Delta U=|U_{\rm eff}(x_1)-U_{\rm eff}(x_2)|$ and plotting the relationship between the potential difference, ΔU, and the noise strength, M. According to Fig. 2, the multiplicative noise intensity controls the symmetry of the potential wells. The potential wells are quasisymmetrical and ΔU tends to zero at suitable noise intensity, although they are asymmetrical at high and low values of a noise intensity. This change makes the occurrence of SR possible in the systems with asymmetry potential wells. Due to this characteristic generalized potential, the system modulated by an external field undergoes a special response to multiplicative noise.

If a seasonal signal, $A_0\cos(\omega t)$, is inputted, as shown in Eq. (4), a time series is taken to monitor the responses of an anti-tumor system to the seasonal signal through a numerical method for stochastic differential equations [23]. At low values of A_0 and ω (i.e., $A_0\ll 1, \omega\ll 1$), the symmetry of two potential wells decides the synchronization of the probability

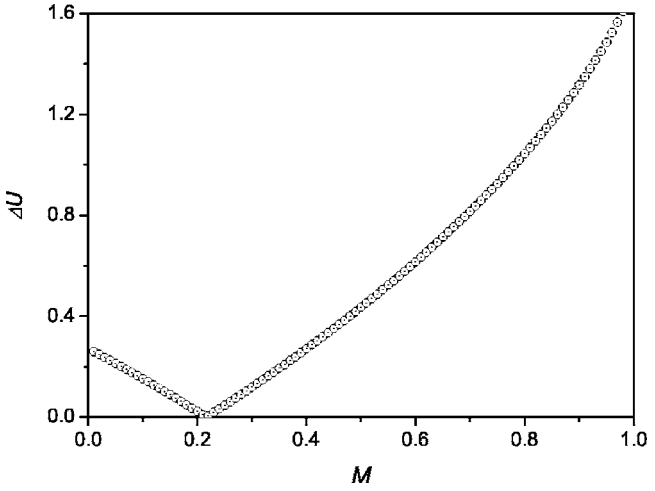

FIG. 2. Dependence of the differences of two potential wells on the multiplicative noise intensities. The parameters are the same as for Fig. 1.

skips between two states. In the presence of additive noise, the relationship between the signal-to-noise ratio (SNR_1) and the height of the potential barrier (ΔU_k) is given by $SNR_1 = 4\pi A r_k / D$ and $r_k = N_k \exp(-2\Delta U_k / D)$, in which N_k, A, and D are an independent constant, the external field amplitude, and the additive noise intensity, respectively [16]. This relationship indicates that the height of the potential barrier affects the existence of SR. In the absence of the additive noise, however, the above formulas of the traditional theory

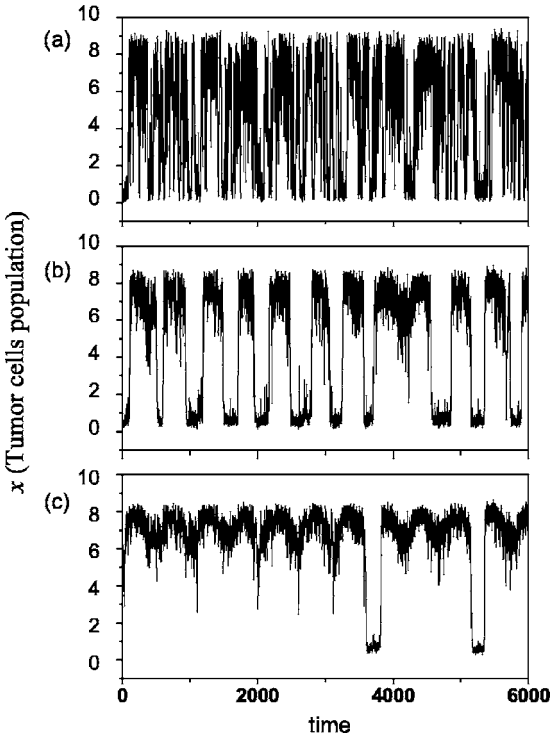

FIG. 3. Time evolution of the populations of tumor cells for different noise levels (a) $M=0.80$, (b) $M=0.20$, and (c) $M=0.02$. The values of the remaining parameters are the same as for Fig. 1 and $A_0=0.14$, $\omega=0.012$.

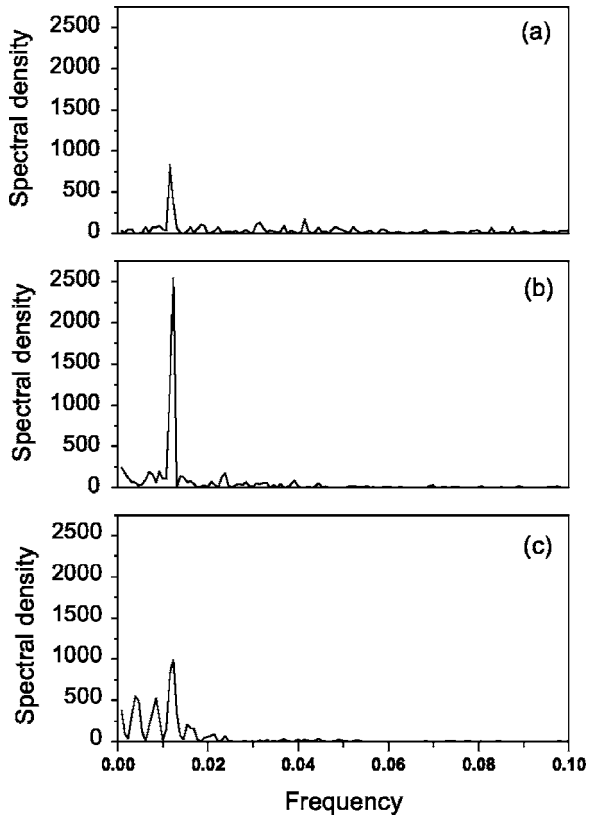

FIG. 4. Corresponding power spectral intensity of Fig. 3 for different parameters (a) $M=0.80$, (b) $M=0.20$, and (c) $M=0.02$. The remaining parameters are the same as for Fig. 3.

of SR are not suitable for this pure multiplicative noise problem. Here the symmetry of the potential has the main effects on the synchronized hopping between the two states, i.e., the existence of SR is determined by the differences of the potential wells instead of the height of the potential barrier. Accordingly, for the sake of simplicity, we have proposed an approximate substitute (R_1) for the SNR, which has the same

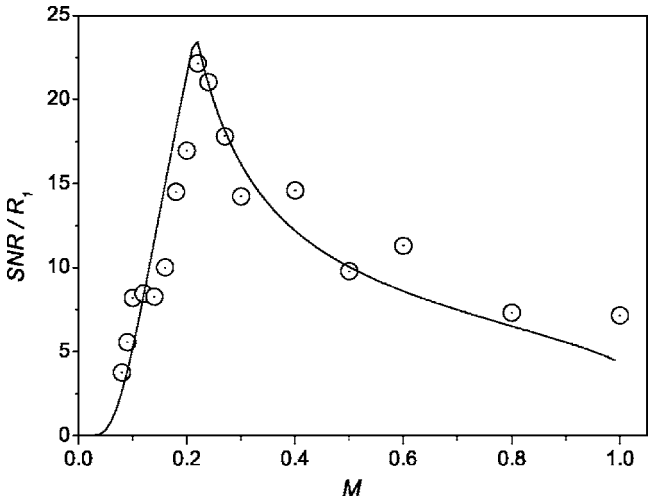

FIG. 5. Effects of multiplicative noise on SNR and R_1. The solid line corresponds to the analytical estimations in Eq. (9) for $N_0=24$. The circles are obtained from numerical calculations.

form as that of SNR_1 mentioned above and is simply written as

$$R_1 = N_0 \exp\left(\frac{-\Delta U}{M}\right), \tag{9}$$

where N_0 is a nondimensional proportional coefficient.

Figure 3 shows selected time series at different multiplicative noise intensities, and their associated power spectral intensities are shown in Fig. 4. For the right value of a noise intensity, the populations of tumor cells skip back and forth between active states and inactive states, indicating the synchronous response of tumor cells to the treatments at an optimal fluctuation in their growth rate. The SNR is defined as the ratio of the peak height of the power spectral intensity to the height of the noisy background at the same frequency. Figure 5 displays the changes of SNR and R_1 with the noise intensity. By increasing the multiplicative noise intensity, M, the trend of the SNR closely matches that of R_1. Stochastic resonance induced by the multiplicative noise is clear and marked with a sharp increase in SNR and R_1 at $M \sim 0.22$. This stochastic resonance is apparently a pure multiplicative type.

In conclusion, we have investigated the stochastic resonance induced by pure multiplicative noise in an antitumor system. The seasonal factor, reflecting the influence of chemotherapy on tumor cells, is introduced into the conventional tumor growth model under immune systems surveillance. On the basis of the analyses of the asymmetrical generalized potential, we have defined a parameter to substitute SNR, which consists with the numerical results very well. Our works offer a method to analyze some complex stochastic differential equations, although they are insufficient to give an exact description of a real tumor growth. Moreover, the synchronous response of tumor cells to chemotherapy is one of the novel findings. We expect that these analyses and numerical findings will stimulate theoretical and experimental works to verify pure SR in real anti-tumor systems with seasonal treatments.

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