Cent. Eur. J. Phys. • 12(6) • 2014 • 383-391
DOI: 10.2478/s11534-014-0460-0

VERSITA

Central European Journal of **Physics**

Delay-induced state transition and resonance in periodically driven tumor model with immune surveillance

Research Article

Tao Yang[1], Qinglin Han[1], Chunhua Zeng[1,2*], Hua Wang[2], Yunchang Fu[1], Chun Zhang[1]

1 *Faculty of Science, Kunming University of Science and Technology, Kunming 650093, Yunnan, China*

2 *State Key Laboratory of Complex Nonferrous Metal Resources Clean Utilization, Kunming University of Science and Technology, Kunming 650093, China*

Received 15 October 2013; accepted 23 February 2014

Abstract: The phenomenon of stochastic resonance (SR) in a tumor growth model under the presence of immune surveillance is investigated. Time delay and cross-correlation between multiplicative and additive noises are considered in the system. The signal-to-noise ratio (SNR) is calculated when periodic signal is introduced multiplicatively. Our results show that: (i) the time delay can accelerate the transition from the state of stable tumor to that of extinction, however the correlation between two noises can accelerate the transition from the state of extinction to that of stable tumor; (ii) the time delay and correlation between two noises can lead to a transition between SR and double SR in the curve of SNR as a function of additive noise intensity, however for the curve of SNR as a function of multiplicative noise intensity, the time delay can cause the SR phenomenon to disappear, and the cross-correlation between two noises can lead to a transition from SR to stochastic reverse-resonance. Finally, we compare the SR phenomenon for the multiplicative periodic signal with that for additive periodic signal in the tumor growth model with immune surveillance.

PACS (2008): 05.40.-a; 02.50.-r

Keywords: noise • time delay • tumor growth model • stochastic resonance

1. Introduction

Since stochastic resonance (SR) was discovered by Benzi *et al.* to explain periodic recurrences of the earth's ice age, this phenomenon has been extensively investigated theoretically and experimentally [1–4]. The effect of SR is that the output signal of a system may be amplified in the presence of noise and a weak periodic signal. It has been observed in many complex systems [5–7], including biological systems [8, 9], laser systems [10], and bistable systems [11–14].

Over the past decade, the mechanics of tumor cell growth

*E-mail: zchh2009@126.com

has attracted much attention [15–20]. There are several mathematical functions for describing tumor growth, such as the logistic model [21], Eden model [22] and Gompertzian growth model [23]. The logistic model has been used as a basic model of tumor cell growth. A more refined logistic model without immune response was presented in [24–26]. A similar model, including the presence of correlated noises for the case of correlation time, has also been considered [27]. The statistical properties of the same model subject to colored noises were studied in [28, 29].

All of the above works on tumor cell growth models neglect the impact of immune surveillance. In fact, a sufficient amount of experimental and epidemiological evidence has been accumulated to demonstrate that the immune system can suppress tumors [30, 31]. In the presence of immune surveillance as the immunotherapy in tumor treatments, the simplest model which describes the noise-resonant effects in cancer growth, influenced by external fluctuations and periodic treatment, is given by a Langevin equation with additive white noise [32]. In [33], Zeng *et al.* had studied the effect of the correlated noise on the extinction rate in a tumor growth system under immune response, and the SR in the same system was then investigated with an additive periodic signal [34].

Historically, research on SR has focused mostly on tumor growth under immune treatments, in the deterministic or stochastic case. However, these investigations on tumor growth under immune treatments may neglect the effects induced by time delays. In a more common context of bistable dynamical systems with memory, the system behavior relies on its past through some memory kernel. Such a kernel is equivalent to a time delay [35, 36]. In practice, in many physical as well as biological systems, time delays always exist and play a significant role in the dynamics of the system [37–40]. Well-known examples include biophysiological controls [41], neuronal networks [42] , and optical cavities [43, 44]. At the same time, it appears that the combination of time delay and noise is ubiquitous in nature and often changes fundamentally the dynamics of the system [45–49]. From the discussion above, a significant and intriguing question naturally arises: what will happen if time delay and noises are simultaneously considered in a tumor growth model under immune surveillance, when periodic signals are introduced both multiplicatively and additively?

In this paper, we will study the SR phenomenon in the tumor growth model under immune surveillance when the time delay and noises are accounted for. Our main goal is to provide a theoretical analysis of the SR in the system with time delay and noises. In Section 2, we construct a stochastic delayed differential equation and the corresponding delay Fokker-Planck equation. Afterward, the SR of the tumor growth model under the presence of immune surveillance with multiplicative periodic signal is discussed. Finally, we compare the SR for the multiplicative periodic signal with that for additive periodic signal in this system. The discussion and conclusion are given in Section 3.

2. The SNR

The tumor cell growth model with immune surveillance is described by the following logistic differential equation [50]:

$$\frac{dx}{dt} = x(1-\theta x) - \beta\frac{x}{x+1}, \tag{1}$$

where x is the population of the tumor cells, θ is a constant parameter and β is the immune rate.

In most practically relevant cases, the state of the system should be affected in the first place by its immediate past, with additional correction arising from the time delay [37–40]. After introducing a time delay into the tumor cell growth model, one obtains:

$$\frac{dx}{dt} = x(1-\theta x_\tau) - \beta\frac{x}{x+1}. \tag{2}$$

Here x_τ denotes the time delayed state variables with $x_\tau = x(t-\tau)$, and τ is the delay time, which is the reaction time of the population of the tumor cells to environmental constraints.

The seasonal growth of tumor cells is a common feature to most species, especially when they are under periodic chemotherapeutic treatment [51]. This means that the immune rate β should take a periodic form, such as a cosine function. Meanwhile, if we consider the external environmental fluctuations (e.g., temperature, the dosage of the medicine in chemotherapy, the intensity of the ray in radiotherapy), the immune rate β can be rewritten as $\beta + \epsilon(t) + A\cos\omega t$, where A and ω are the amplitude and frequency of the periodic signal, respectively. Likewise, a fluctuation of tumor cell population is inevitable, which behaves in the form of additive noise [15]. As a result, we get

$$\begin{aligned}\frac{dx}{dt} &= x(1-\theta x_\tau) - \beta\frac{x}{x+1} - \epsilon(t)\frac{x}{x+1} \\ &- \frac{x}{x+1}A\cos\omega t + \Gamma(t),\end{aligned} \tag{3}$$

in which $\epsilon(t)$ and $\Gamma(t)$ are multiplicative and additive Gaussian white noises, respectively. Their statical properties can be given by

$$\langle\epsilon(t)\rangle = \langle\Gamma(t)\rangle = 0,$$

$$\langle \epsilon(t)\epsilon(t')\rangle = 2D\delta(t-t'), \quad \langle \Gamma(t)\Gamma(t')\rangle = 2\alpha\delta(t-t'),$$

$$\langle \Gamma(t)\epsilon(t')\rangle = \langle \epsilon(t)\Gamma(t')\rangle = 2\lambda\sqrt{D\alpha}\delta(t-t'), \qquad (4)$$

where D and α are the intensities of multiplicative and additive noises, respectively. λ is the strength of correlation between $\epsilon(t)$ and $\Gamma(t)$ with $|\lambda| \leqslant 1$. The deterministic potential corresponding to Eq. (1) reads as

$$V(x) = -\frac{x^2}{2} + \theta\frac{x^3}{3} + \beta x - \beta\ln(x+1), \qquad (5)$$

which has two stable states $x_1 = 0$ (the extinction state), $x_2 = (1-\theta+\sqrt{(1+\theta)^2-4\beta\theta})/(2\theta)$ (the tumor stable state), and an unstable state $x_u = (1-\theta-\sqrt{(1+\theta)^2-4\beta\theta})/(2\theta)$. **This bistable asymmetric potential is plotted in Fig. 1.** The $V(x)$ can be viewed as an "energy landscape".

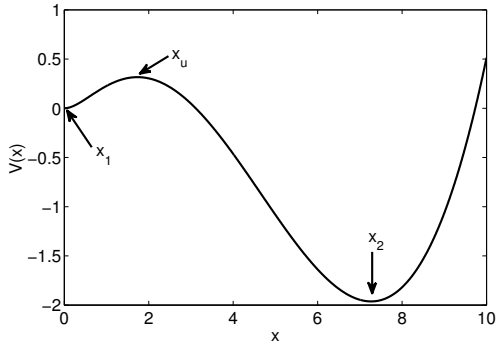

Figure 1. A plot of the deterministic potential $V(x)$ as a function of x with $\theta = 0.1$ and $\beta = 2.26$.

Next, we discuss the quasi-stationary probability density of the stochastic process. Using the approximation of the probability density approach [52–56], Eq. (3) can be rewritten as

$$\frac{dx}{dt} = f_{eff}(x) + g(x)\epsilon(t) + \Gamma(t). \qquad (6)$$

where the subscript eff stands for "effective". Then $g(x)$ and the effective coefficient $f_{eff}(x)$ of Eq. (6) can be obtained as

$$g(x) = -\frac{x}{x+1},$$

$$f_{eff}(x) = \int_{-\infty}^{+\infty}\left[x(1-\theta x_\tau) - \beta\frac{x}{x+1} - \frac{x}{x+1}A\cos\omega t\right]P(x_\tau, t-\tau|x,t)dx_\tau, \qquad (7)$$

where $P(x_\tau, t-\tau|x,t)dx_\tau$ is the conditional probability density of the stochastic process x, and can be expressed as

$$P(x_\tau, t-\tau|x,t)dx_\tau = \sqrt{\frac{1}{2\pi B(x)\tau}} \times \exp\left\{-\frac{[x_\tau - x - f(x)\tau]^2}{2B(x)\tau}\right\}, \qquad (8)$$

with

$$f(x) = x(1-\theta x) - \beta\frac{x}{x+1} - \frac{x}{x+1}A\cos\omega t,$$

$$B(x) = Dg(x)^2 + 2\lambda\sqrt{D\alpha}g(x) + \alpha. \qquad (9)$$

Substituting Eq. (9) into Eq. (7), we have

$$f_{eff}(x) = (1-\tau\theta x)\left[x(1-\theta x) - \beta\frac{x}{x+1} - \frac{x}{x+1}A\cos\omega t\right]. \qquad (10)$$

Then, it is shown [53, 56] that the approximate delay Fokker-Planck equation described by Eq. (6) takes the form

$$\frac{\partial P(x.t)}{\partial t} = -\frac{\partial}{\partial x}A(x)P(x,t) + \frac{\partial^2}{\partial x^2}B(x)P(x,t), \qquad (11)$$

where

$$A(x) = (1-\tau\theta x)\left[x(1-\theta x) - \beta\frac{x}{x+1} - \frac{x}{x+1}A\cos\omega t\right] + \frac{Dx}{(x+1)^3} - \frac{\lambda\sqrt{D\alpha}}{(x+1)^2}, \qquad (12)$$

$$B(x) = D\left(\frac{x}{x+1}\right)^2 - 2\lambda\sqrt{D\alpha}\frac{x}{x+1} + \alpha. \qquad (13)$$

In the presence of the periodic signal, the potential of the tumor system is modulated by the periodic signal $(A\cos\omega t)$. Here we assume that the signal amplitude is small enough (i.e., $A \ll 1$) that it is insufficient to force a particle to move from one well to the other in the absence of any noise, and it can be considered that $x_{1,2}$ and x_u are still the stable states and the unstable state of the model, respectively. We also assume that the variation of the periodic signal is slow enough (i.e., $\omega \ll 1$) that there is enough time for the system to reach its local equilibrium positions during period of $1/\omega$. Thus, the quasi-stationary probability distribution function (SPDF) $P_{st}(x,t)$ can be derived from Eq. (11) with Eqs. (12) and (13) in the adiabatic limit as

$$P_{st}(x,t) = \frac{N}{B^{1/2}(x)}\exp\left[-\frac{\Phi(x,t)}{D}\right], \qquad (14)$$

where N is a normalization constant **and** $\Phi(x,t)$ **is the effective potential function, which can be expressed exactly as**

$$\Phi(x,t) = -D\int^{x} \frac{(1-\tau\theta x)\left[x(1-\theta x) - \beta\frac{x}{x+1} - \frac{x}{x+1}A\cos\omega t\right]}{D(\frac{x}{x+1})^2 - 2\lambda\sqrt{D\alpha}\frac{x}{x+1} + \alpha}\,dx. \tag{15}$$

Integrating Eq. (15), we obtain

$$\begin{aligned}\Phi(x,t) = \quad & -\frac{\tau\theta^2}{4m}x^4 + \frac{\gamma_1}{3m}x^3 + \frac{\gamma_2}{2m}x^2 + \frac{\gamma_3}{m}x + \frac{\gamma_4}{2m}\ln\left|x^2 + \frac{n}{m}x + R\right| - \frac{2\gamma_5}{\sqrt{4mR-n^2}}\arctan\frac{2mx+n}{\sqrt{4mR-n^2}} \\ & + \Big[-\frac{\tau\theta}{2m}x^2 + \frac{a}{m}x + \frac{b}{2m}\ln\left|x^2 + \frac{n}{m}x + R\right| - \frac{2c}{\sqrt{4mR-n^2}}\arctan\frac{2mx+n}{\sqrt{4mR-n^2}}\Big]A\cos\omega t, \end{aligned} \tag{16}$$

where

$$\begin{aligned} R &= \alpha/D, \quad m = 1 - 2\lambda\sqrt{R} + R, \quad n = 2(R - \lambda\sqrt{R}), \\ \gamma_1 &= \theta + \tau\theta - 2\tau\theta^2 + \frac{\tau\theta^2 n}{m}, \\ \gamma_2 &= 2\theta - 1 + 2\tau\theta - \tau\theta^2 - \tau\theta\beta + \frac{\tau\theta^2 R}{m} - \frac{n}{m}\gamma_1, \\ \gamma_3 &= \theta - 2 + \beta + \tau\theta - \tau\theta\beta - \frac{R}{m}\gamma_1 - \frac{n}{m}\gamma_2, \\ \gamma_4 &= \beta - 1 - \frac{R}{m}\gamma_2 - \frac{n}{m}\gamma_3, \quad \gamma_5 = \frac{n}{2m}\gamma_4 + \frac{R}{m}\gamma_3, \\ a &= 1 - \tau\theta + \frac{\tau\theta n}{m}, \quad b = 1 + \frac{\tau\theta R}{m} - \frac{na}{m}, \\ c &= \frac{bn}{2m} + \frac{Ra}{m}. \end{aligned} \tag{17}$$

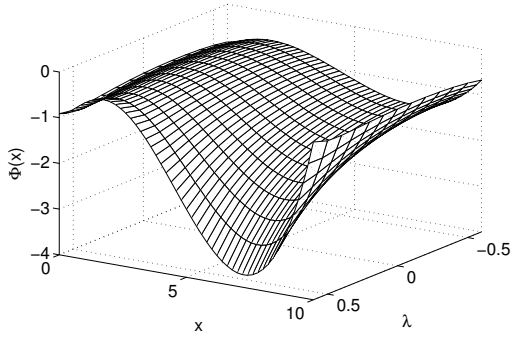

Figure 2. Three-dimensional curve of the generalized potential $\Phi(x)$ versus x and λ with $D = 0.8$, $\alpha = 0.76$, $\tau = 0.1$, $\theta = 0.1$, $\beta = 2.26$, $A = 0.0$.

The three-dimensional curves of the effective potential $\Phi(x)$ as functions of x and λ (or τ) are shown in Figs. 2 and 3, respectively. Obviously, the effective potential as defined above is the nonequilibrium potential [57], which has two stable states, and their minimum is obtained from $A(x) - B'(x) = 0$. The positions of the potential minimum,

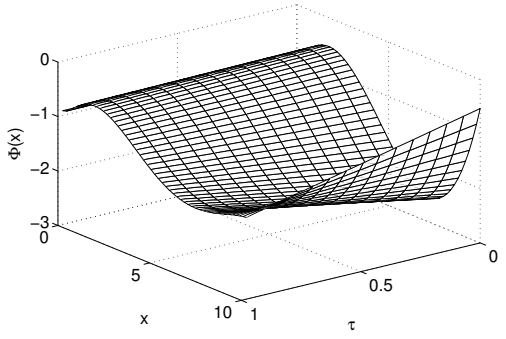

Figure 3. Three-dimensional curve of the generalized potential $\Phi(x)$ versus x and τ with $D = 0.8$, $\alpha = 0.76$, $\lambda = 0.3$, $\theta = 0.1$, $\beta = 2.26$, $A = 0.0$.

x_1 and x_2, shown in Figs. 2 and 3, are regarded as the state of extinction and the state of stable tumor, respectively. The presence of noise and time delay causes random kicks to the system state point lying in one of these minima. In general, the tumor cell growth system evolves towards the local minimum of the potential, analogous to a ball rolling towards the bottom of a cup. In physics, the minimum of $\Phi(x)$ corresponding to x_1 (or x_2) is also called the potential well, and the maximum of $\Phi(x)$ corresponding to x_u the potential barrier [58]. Thus, for convenience we call the potential well corresponding to x_1 (or x_2) the left (or right) well. Here, we define the depth of the left well as $d_l = \Phi(x_u) - \Phi(x_1)$, and, similarly, the depth of the right well is $d_r = \Phi(x_u) - \Phi(x_2)$. As shown in Fig. 2, when the value of λ increases from negative to positive value, the depth of right well increases and the depth of left well decreases. However, when λ is fixed, shown in Fig. 3, the depth of right well decreases and the depth of left well increases as the value of τ increases. Namely, the system state should be more easily attracted by the right well (x_2) with the increase of λ, while the system state should be more easily attracted by the left well (x_1)

with the increases of τ. Thus, the positive correlation between two noises can accelerate the transition from the state of extinction to that of stable tumor, while time delay τ accelerates the transition from the state of stable tumor to that of extinction. The phenomenon of noise-induced transition [59] and phase transition [60, 61] have been shown in other nonlinear systems, however here the noise-induced transition exists in the tumor growth model under immune surveillance.

In order to investigate the SR in a tumor growth model under immune surveillance, we need the SNR of the system. First, we derive transition rates between two states and then calculate the SNR of the system. Using the steepest descent method [62, 63], we can calculate the mean first passage time (MFPT) $T_{1,2}$ of the process $x(t)$ to reach the state $x_{1,2}$ with initial condition $x_{2,1}$ as given by the Kramers formula

$$T_{x_1-x_2} = T_1 = \frac{2\pi}{\sqrt{|\Phi''(x_u)\Phi''(x_1)|}} \exp\left[\frac{\Phi(x_u,t)-\Phi(x_1,t)}{D}\right], \tag{18}$$

$$T_{x_2-x_1} = T_2 = \frac{2\pi}{\sqrt{|\Phi''(x_u)\Phi''(x_2)|}} \exp\left[\frac{\Phi(x_u,t)-\Phi(x_2,t)}{D}\right]. \tag{19}$$

Note that the above result is valid only when the intensity of two types of noise, measured by D and α, are small in comparison with the energy barrier height: $D, \alpha < \Delta\Phi = |\Phi(x_u,t) - \Phi(x_{1,2},t)|$ [11]. This provides restriction on the parameters (i.e., D, α, λ, τ). We must point out that the following results are restricted to valid regions. Then, the transition rates according to $W_{1,2} = T_{1,2}^{-1}$ are:

$$\begin{aligned} W_{x_1-x_2} &= W_1 \qquad (20)\\ &= \frac{\sqrt{|\Phi''(x_u)\Phi''(x_1)|}}{2\pi} \exp\left[\frac{\Phi(x_1,t)-\Phi(x_u,t)}{D}\right], \end{aligned}$$

$$\begin{aligned} W_{x_2-x_1} &= W_2 \qquad (21)\\ &= \frac{\sqrt{|\Phi''(x_u)\Phi''(x_2)|}}{2\pi} \exp\left[\frac{\Phi(x_2,t)-\Phi(x_u,t)}{D}\right], \end{aligned}$$

where Φ'' is the second derivative of Φ with respect to x. We consider a system described by a discrete random dynamical variable x that adopts two possible values: x_1 and x_2, with probabilities $n_{1,2}$, respectively. The probabilities satisfy the condition $n_1 + n_2 = 1$. The master equation for our problem is

$$\begin{aligned} \frac{dn_1}{dt} &= -\frac{dn_2}{dt} = W_2(t)n_2(t) - W_1(t)n_1(t)\\ &= W_2(t) - [W_2(t) + W_1(t)]n_1(t), \qquad (22) \end{aligned}$$

where $W_{1,2}$ are the transition rates out of the $x_{1,2}$ states. Since we assume the signal amplitude is small enough (i.e., $A \ll 1$), the transition rates $W_{1,2}(t)$ can be expanded up to the first order of A as

$$W_1(t) = \mu_1 - \nu_1 A\cos\omega t, \quad W_2(t) = \mu_2 + \nu_2 A\cos\omega t, \tag{23}$$

where

$$\mu_1 = W_1\Big|_{S(t)=0}, \quad \nu_1 = -\frac{dW_1}{dS(t)}\Big|_{S(t)=0}, \quad S(t) = A\cos\omega t,$$

$$\mu_2 = W_2\Big|_{S(t)=0}, \quad \nu_2 = \frac{dW_2}{dS(t)}\Big|_{S(t)=0}. \tag{24}$$

Within the framework of the theory in [64, 65], the SNR is defined as the ratio of the peak height of the spectral intensity to the height of the noise background at the same frequency. Then the SNR in terms of the output signal power spectrum can be given by

$$R_M = \frac{A^2\pi(\nu_2\mu_1 + \nu_1\mu_2)^2}{4\pi\mu_1\mu_2(\mu_1+\mu_2)}. \tag{25}$$

Through Eq. (25), the effects of the noise strengths D and α, the cross-correlation strength λ and the delay time τ on the SNR are plotted in Figs. 4-7. The SNR (R_M) as a function of additive noise intensity α is plotted in Fig. 4 for different values of the cross-correlated strength λ. For $\lambda \leqslant 0.0$, as shown in Fig. 4(a). It is found that the R_M as a function of additive noise intensity α exhibits only a maximum, which corresponds to a resonant peak. The existence of the maximum in the R_M is the identifying characteristic of the SR phenomenon. As the value of $|\lambda|$ is increased, the maximum in the R_M is increased, i.e., the negative correlation between two noises with $\lambda < 0$ enhances the SR phenomenon. However for $\lambda > 0.0$, as shown in Fig. 4(b), given a small λ value (see $\lambda = 0.1$) there is only a resonant peak at a large value of α; as the value of λ increases, a second maximum in the R_M appears at a small value of α. The existence of a double-peak behavior in the R_M is the identifying characteristic of the double SR phenomenon. The double SR phenomenon has also been demonstrated in previous investigations [66], where the existence of a second peak in the SNR is associated with a regime of optimal sensitivity for intra-well dynamics, rather than for tuning the positive correlation between two noises here. At the same time, the height of double-peak decreases as λ increases, namely, the positive correlation between two noises ($\lambda > 0$) weakens the double SR phenomenon.

In Fig. 5, the R_M as a function of additive noise intensity α is plotted for different values of the delay time τ. The

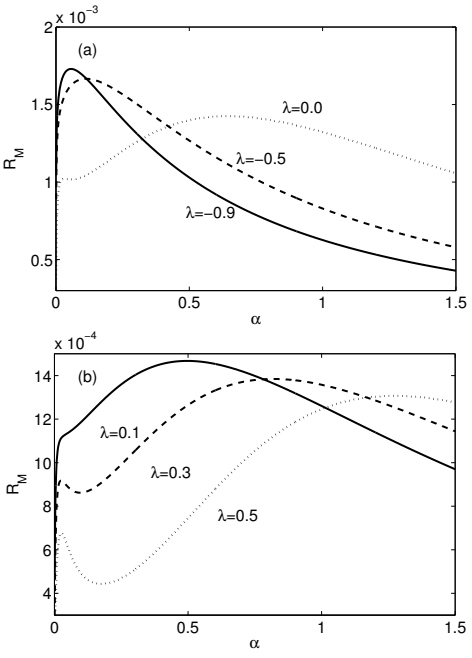

Figure 4. The SNR (R_M) versus α for different values of λ with $\tau = 0.1$, $D = 0.8$, $\theta = 0.1$, $\beta = 2.26$, $A = 0.1$.

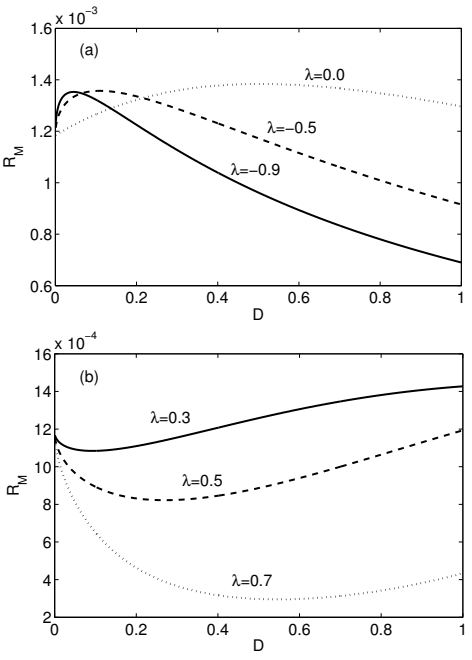

Figure 6. The SNR (R_M) versus D for different values of λ with $\tau = 0.1$,$\alpha = 0.76$, $\theta = 0.1$, $\beta = 2.26$, $A = 0.1$.

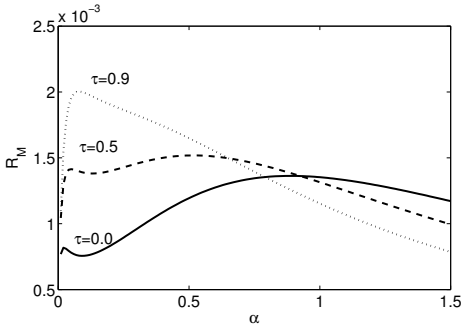

Figure 5. The SNR (R_M) versus α for different values of τ with $\lambda = 0.3$, $D = 0.8$, $\theta = 0.1$, $\beta = 2.26$, $A = 0.1$.

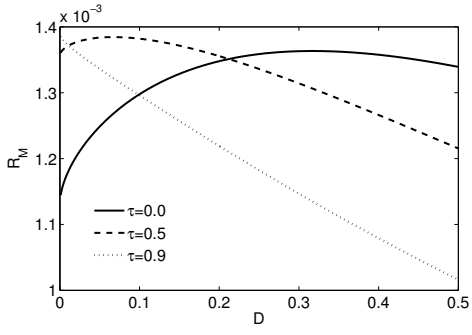

Figure 7. The SNR (R_M) versus D for different values of τ with $\lambda = -0.2$, $D = 0.8$, $\alpha = 0.76$, $\theta = 0.1$, $\beta = 2.26$, $A = 0.1$.

interesting point here is that, for $\tau = 0.0$ or small value of τ ($\tau = 0.5$), there is a double-peak in the R_M, i.e., one peak is at small α, and the other is at large α. When the value of τ is large enough ($\tau = 0.9$), the peak at large α disappears and the peak at small α increases. In other words, the time delay causes the change from double-peak to single peak, and enhances the SR phenomenon.

The R_M as a function of multiplicative noise intensity D for different values of the cross-correlated strength λ is plotted in Fig. 6. For $\lambda \leqslant 0.0$, as shown in Fig. 6(a), it is clear that the R_M exhibits a maximum. However for $\lambda > 0.0$, as shown in Fig. 6(b), it is found that the R_M exhibits a minimum. The existence of the minimum in the R_M is the identifying characteristic of the stochastic reverse-resonance phenomenon. As the value of λ is increased, the minimum in the R_M is decreased, i.e., the positive correlation between two noises ($\lambda > 0$) weakens the stochastic reverse-resonance phenomenon.

In Fig. 7, the R_M as a function of multiplicative noise intensity D is plotted for different values of the delay time τ. This figure shows that there is only a maximum for a small value of time delay τ at a large value of D. When the value of τ is increased, the maximum is increased. However, if the time delay τ is large enough (i.e., $\tau = 0.9$ in Fig. 7), the maximum will disappear. In other words, the time delay not only enhances the SR phenomenon, but also causes the SR phenomenon to disappear.

3. Discussion and conclusions

In this paper, we have investigated the SR phenomenon in a tumor cell growth model under immune surveillance, where time delay and cross-correlation between multiplicative and additive noises are considered in the system. The deterministic potential related to the deterministic force in Eq. (1) has two steady stable states, which correspond to the state of stable tumor and state of extinction, respectively. First, we are interested in how the transition from one state to the other because of the time delay and noises occurs. Our results show that the time delay can accelerate the transition from the state of stable tumor to that of extinction, but the positive correlation between two noises can accelerate the transition from the state of extinction to that of stable tumor. Then, based on the theory of SNR in [64, 65], when multiplicative periodic signal is considered, the effects of the time delay and cross-correlated intensity on the SNR are analyzed, respectively. The existence of a maximum (or minimum) in the SNR as a function of the noise intensity identifies the characteristic of the SR (or stochastic reverse-resonance) phenomenon. The time delay and cross-correlation between two noises can lead to a transition between SR and double SR in the curve of SNR as a function of additive noise intensity, while for the curve of SNR as a function of multiplicative noise intensity, the time delay can cause the SR phenomenon to disappear, and the cross-correlation between two noises can lead to a transition from SR to stochastic reverse-resonance.

Finally, we compare the SR for the multiplicative periodic signal with that for additive periodic signal in this system. When periodic signal is introduced additively, the equivalent stochastic differential equation of Eq. (3) can be generated as

$$\frac{dx}{dt} = x(1-\theta x_\tau) - \beta\frac{x}{x+1} - \epsilon(t)\frac{x}{x+1} + \Gamma(t) + B\cos\Omega t, \tag{26}$$

here B and Ω are the amplitude and frequency of the periodic signal, respectively. We calculate the SNR (R_A) by using the theory of SNR in [64, 65]. The R_A as a function of α for different values of the cross-correlated intensity λ and delay time τ are plotted in Figs. 8 and 9. In Fig. 8(a), when the cross-correlated intensity $\lambda \leq 0.0$, the SR phenomenon is not observed. When the correlation is positive, it is clear that the R_A exhibits a maximum and a minimum as shown in Fig. 8(b), and its maximum appears at a large value of α. When the cross-correlated intensity λ is large enough, a new maximum appears at a small value of α, and the maximum at large α shifts to the greater value of α. In Fig. 9, it is shown that the R_A exhibits a maximum and a minimum when time delay $\tau = 0.0$, and the maximum and minimum will disappear as τ increases.

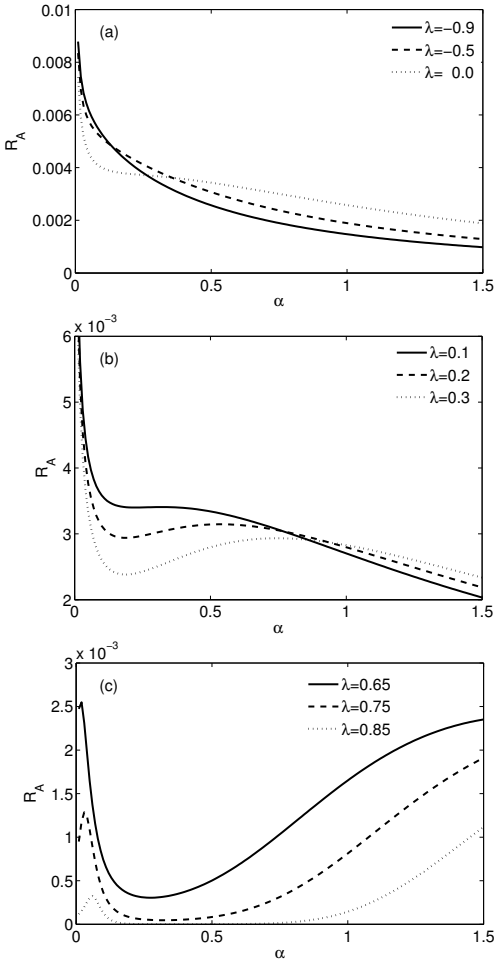

Figure 8. The SNR (R_A) versus α for different values of λ with $\tau = 0.1$, $D = 0.8$, $\theta = 0.1$, $\beta = 2.26$, $A = 0.1$.

Here, we are interested in the different effects between the multiplicative periodic signal and additive periodic signal. In Figs. 4 and 5, for the case of the SR for the multiplicative periodic signal, the time delay and cross-correlation between two noises can lead to a transition between SR and double SR in the curve of SNR as a function of additive noise intensity, while for the case of the SR for the additive periodic signal, the time delay and cross-correlation between two noises can lead to a transition between no SR and SR coupling with stochastic reverse-resonance in the curve of SNR as a function of additive noise intensity as shown in Figs. 8 and 9. After comparing the SR for the multiplicative periodic signal (Figs. 4 and 5) with that for additive periodic signal (Figs. 8 and 9), we

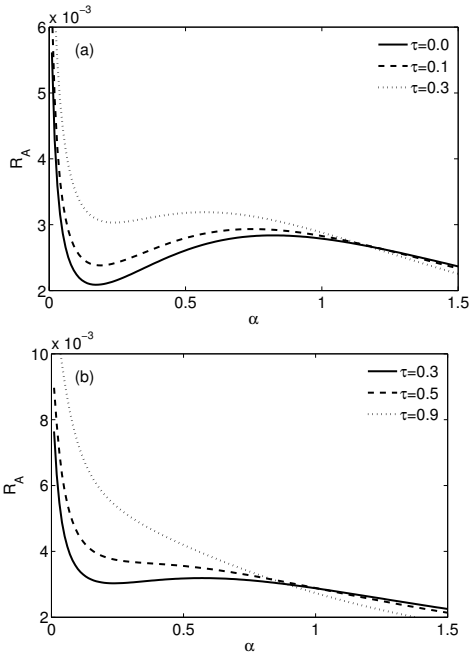

Figure 9. The SNR (R_A) versus α for different values of τ with $\lambda = 0.3$, $D = 0.8$, $\theta = 0.1$, $\beta = 2.26$, $A = 0.1$.

find that the effects of the two periodic signals are different in a time-delayed tumor growth model under immune surveillance. The different effects of the two periodic signals in the system are mainly due to the different forms of their existence. One appears in the external environmental fluctuations while another appears in the internal environmental fluctuations. However when α is fixed, the effect of cross-correlation between two noises and time delay on the R_A vs. D (figure not shown here) is same as that on the R_M vs. D, as shown in Figs. 6 and 7.

In conclusion, we have studied the effects of the time delay in a tumor cell growth model with both multiplicative periodic signal and additive periodic signal. Our work shows the synchronous response of tumor cells to treatments with time delay and noises. In addition, the synchronous response of tumor cells to chemotherapy is one of the interesting findings. We anticipate that the findings will stimulate theoretical and experimental works in a real tumor cell growth model with seasonal treatments.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (Grant No. 11305079), the Natural Science Foundation of Yunnan Province (under 2010CD031) and the Key Project of Research Fund of Education Department of Yunnan Province (under 2001Z011).

References

[1] R. Benzi, A. Sutera, A. Vulpiani J. Phys. A: Math. Gen. 14, L453 (1981)
[2] R. Benzi, G. Parisi, A. Sutera, A. Vulpiani, Tellus 34, 10 (1982)
[3] C. Nicolis, G. Nicolis, Tellus 33, 225 (1981)
[4] C. Nicolis, Tellus 34, 1 (1982)
[5] L. Gammaitoni, P. Hänggi, P. Jung, F. Marchesoni Rev. Mod. Phys. 70, 223 (1998)
[6] R. N. Mantegna, B. Spagnolo, Nuovo Cimento D 17, 873 (1995)
[7] E. Lanzara, R.N. Mantegna, B. Spagnolo, R. Zangara, Am. J. Phys. 65, 341 (1997)
[8] W. R. Zhong, Y. Z. Shao, Z. H. He, Phys. Rev. E 73, 060902 (2006)
[9] C. H. Zeng, C. W. Xie, Mod. Phys. Lett. B 13, 1651 (2009)
[10] A. Joshi, M. Xiao, Phys. Rev. A 74, 013817 (2006)
[11] Y. Jia, S. N. Yu, J. R. Li, Phys. Rev. E 62, 1869 (2000)
[12] Y. Jia, X. P. Zheng, X. M. Hu, J. H. Li, Phys. Rev. E 63, 031107 (2001)
[13] X. Q. Luo, S. Q. Zhu, Phys. Rev. E 67, 021104 (2003)
[14] D. J. Wu, S. Q. Zhu, Phys. Lett. A 363, 202 (2007)
[15] A. Fiasconaro, B. Spagnolo, A. Ochab-Marcinek, E. Gudowska-Nowak Phys. Rev. E 74, 041904 (2006)
[16] W. R. Zhong, Y. Z. Shao, Z. H. He, Phys. Rev. E 74, 011916 (2006)
[17] W. R. Zhong, Y. Z. Shao, L. Li, F. H Wang, Z. H. He, Europhys. Lett. 82, 20003 (2008)
[18] T. Bose, S. Trimper, Phys. Rev. E 79, 051903 (2009)
[19] B. Spagnolo, A. La Barbera, Physica A 315, 114 (2002)
[20] D. Valenti, A. Fiasconaro, B. Spagnolo, Physica A, 331, 477 (2004)
[21] C. H. Zeng, H. Wang, J. Stat. Phys. 141, 889 (2010)
[22] J. Yu, G. Hu, B. K. Ma, Phys. Rev. B 39, 4572 (1989)
[23] M. Molski, J. Konarski, Phys. Rev. E 68, 021916 (2003)
[24] B. Q. Ai, X. J. Wang, G. T. Liu, L. G. Liu, Phys. Rev. E 67, 022903 (2003)
[25] A. Behera, S. F. O Rourke, Phys. Rev. E 77, 013901 (2008)
[26] B. Q. Ai, X. J. Wang, L. G. Liu, Phys. Rev. E 77, 013902 (2008)
[27] D. C. Mei, C. W. Xie, L. Zhang, Eur. Phys. J. B 41, 107 (2004)
[28] C. J. Wang, Q. Wei, D. C. Mei, Mod. Phys. Lett. B 21, 789 (2007)

[29] C. J. Wang, Q. Wei, D. C. Mei, Phys. Lett. A 372, 2176 (2008)
[30] G. P. Dunn, L. J. Old, R. D. Schreiber, Annu. Rev. Immunol. 22, 329 (2004)
[31] R. Kim , M. Emi, K. Tanabe, Immunol. 121, 1 (2007)
[32] A. Fiasconaro, A. Ochab-Marcinek, B. Spagnolo, E. Gudowska-Nowak, Eur. Phys. J. B 65, 435 (2008)
[33] C. H. Zeng, X. F. Zhou, S. F. Tao, J. Phys. A: Math. Theor. 42, 495002 (2009)
[34] C. H. Zeng, Phys. Scr. 81, 025009 (2010)
[35] L. S. Tsimring, A. Pikovsky, Phys. Rev. Lett. 87, 250602 (2001)
[36] C. Masoller, Phys. Rev. Lett. 90, 020601 (2003)
[37] J. C. Cai, D. C. Mei, Mod. Phys. Lett. B 22, 2759 (2008)
[38] D. Huber, L. S. Tsimring, Phys. Rev. Lett. 91, 260601 (2003)
[39] D. Curtin et al., Phys. Rev. E 70, 031103 (2004)
[40] J. Houlihan, D. Goulding, Th. Busch, C. Masoller, G. Huyet, Phys. Rev. Lett. 92, 050601 (2004)
[41] M. C. Mackey, L. Glass, Science 197, 287 (1977)
[42] P. C. Bressoff, S. Coombes, Phys. Rev. Lett. 78, 4665 (1997)
[43] J. Garc a-Ojalvo, R. Roy, Phys. Lett. A 224, 51 (1996)
[44] C. Masoller, Phys. Rev. Lett. 86, 2782 (2001)
[45] L. S. Tsimring, A. Pikovsky, Phys. Rev. Lett. 87, 250602 (2001)
[46] X. J. Tian, X. P. Zhang, F. Liu, W. Wang, Phys. Rev. E 80, 011926 (2009)
[47] L. C. Du, D. C. Mei, Phys. Lett. A 374, 3275 (2010)
[48] C. H. Zeng, H. Wang, Chem. Phys. 402, 1 (2012)
[49] W. Guo, L. C. Du, D. C. Mei, Phys. A 391, 1270 (2012)
[50] R. Lefever, R. Garay, In: A. J. Valleron, P. D. M. Macdonald (Eds.), Local Description of Immune Tumor Rejection, Biomathematics and Cell Kinetics (Elsevier, North-Holland, Amsterdam, 1978) p. 333
[51] J. J. Kim, I. F. Tannock, Nat. Rev. Cancer 5, 516 (2005)
[52] X. Gu, S. Zhu, D. Wu, Eur. Phys. J. D 42, 461 (2007)
[53] D. J. Wu, L. Cao, S. Z. Ke, Phys. Rev. E 50, 2496 (1994)
[54] S. Guillouzic, I. L'Heureux, A. Longtin, Phys. Rev. E 59, 3970 (1999)
[55] S. Guillouzic, I. L'Heureux, A. Longtin, Phys. Rev. E 61, 4906 (2000)
[56] T. D. Frank, Phys. Rev. E 72, 011112 (2005)
[57] H. S. Wio, R. R. Deza, Eur. Phys. J. Spec. Top. 146, 111 (2007)
[58] H. Risken, The Fokker-Planck Equation: Methods of Solution and Applications (Springer, Berlin, 1992)
[59] W. Horsthemke, R. Lefever, Noise-Induced Transitions (Springer, Berlin, 1984)
[60] C. Van den Broeck, J. M. R. Parrondo, R. Toral, Phys. Rev. Lett. 73, 3395 (1994)
[61] J. Garcia-Ojalvo, J. M. Sancho, Noise in Spatially Extended Systems (Springer, Berlin, 1999)
[62] P. Hänggi, F. Marchesoni, P. Z. Grigolini, Phys. B 56, 333 (1984)
[63] R. F. Fox, Phys. Rev. A 33, 467 (1986)
[64] S. Bouzat, H. S. Wio, Phys. Rev. E 59, 5142 (1999)
[65] H. S. Wio, S. Bouzat, Braz. J. Phys. 29, 136 (1999)
[66] P. S. Burada, G. Schmid, D. Reguera, J. M. Rubi, P. Hänggi, Europhys. Lett. 87, 50003 (2009)