Cent. Eur. J. Phys. • 9(3) • 2011 • 616-620
DOI: 10.2478/s11534-010-0067-z

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Central European Journal of **Physics**

Stochastic tumor growth system with two different kinds of time delay

Rapid Communication

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Received 10 March 2010; accepted 22 July 2010

Abstract: The dynamical properties of a noise-driven tumor cell growth system are investigated when there exist two different kinds of time delays, in the deterministic and fluctuating forces, respectively. Using the approximation probability density approach, the delayed Fokker-Planck equation is obtained. The effects of two different time delays on the stationary probability distribution (SPD), the mean value and the mean passage time (MFPT) are discussed. It is found that the time delay τ_1 in the deterministic force can enhance tumor cell number, while the time delay τ_2 in the fluctuating force can induce a decrease in tumor cell numbers. On the other hand, while τ_1 can hold back the extinction of tumor cells, τ_2 can speed up their extinction.

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

Keywords: time delay • noise • tumor growth system

In recent years, time-delayed stochastic processes have been the subject of increased interest in various fields. It was recently found that noise and delay can actually be an integral part of biological information processing [1, 2]. Mainly, bistable systems with simultaneous noise and time delay have been investigated in detail. Ref. [3] founds noise induced resonance in delayed feedback systems. The dynamics of an ensemble of bistable elements with global time-delayed coupling under the influence of noise has been studied analytically and numerically [4]. The noise-induced dynamics of a prototypical bistable system with delayed feedback have been studied theoretically and numerically [5]. Wu investigated the phenomenon of stochastic resonance in a bistable system with time-delayed feedback driven by non-Gaussian noise [6]. Biological systems subjected to simultaneous noise and time delay have especially attracted interest. For example, the effects of time delay on a mutualism system has been studied and it was found that the combination of the noise and the time delay completely suppresses population explosion [7]. The effects of time delay in competitive systems in the ecological field have been also studied. The results imply that the combination of noise and time delay could provide an efficient tool for understanding real ecological systems [8]. The delay time also induces stochastic oscillations in gene regulation [9]. In many cases, the delay reflects transmission times related to the transport of matter, energy, and information through a system.

The dynamical character of a tumor cell growth system subjected to a noise disturbance, which is described by

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a logistic model, has been widely investigated. In the presence of correlated Gaussian white noise, the steady state properties of tumor cell growth have been studied [10]. Other cases including the mean first passage time, the relaxation time, etc. are investigated by our workgroups [11–15]. Color noise and negative correlation are considered by Ref. [16]. [17] shows pure multiplicative noise-induced stochastic resonance, which appears in an anti-tumor system modulated by a seasonal external field. For optimally selected values of the multiplicative noise intensity, stochastic resonance is observed, which is manifested by the quasi symmetry of two potential minima. Bose and Trimper [18] put forward a stochastic model for tumor growth with immunization, in which they assume that the death rate of the logistic model is altered by a deterministic term characterizing immunization, and introduced a multiplicative internal noise to describe the random change of the birth rate, and an external additive noise to mimic the influence of the environment. Based on this model, they analyzed the effects of the immunization rate. However, these results show that the tumor cell population is consumingly influenced by the external and internal noise, and the SR phenomenon is also found in this system. More recently, tumor cell growth systems subjected to simultaneous noise and time delay have been studied. However, in the work mentioned above, only the effect of time delay in the deterministic force has been considered [19, 20]. As we all know, the state variable can make the time delay appear in both deterministic and fluctuating terms simultaneously. There are two different kinds of time delays which may bring different effects to the tumor cell growth process, but this is not well understood yet. This is the main aim of this letter.

In this letter, the effects of two different time delays on the stationary probability distribution (SPD), the mean value and the mean passage time (MFPT) of the tumor cell growth process are discussed.

The logistic model of the tumor cell growth is written as [21, 22]

$$\frac{dx}{dt} = ax - bx^2. \tag{1}$$

This is an ideal equation, without any fluctuation, where x is the tumor mass, a the growth rate, and b the cell decay rate. The deterministic potential of the tumor cell growth system is given by $V(x) = -\frac{a}{2}x^2 + \frac{b}{3}x^3$, which has one stable state at $x_s = \frac{a}{b}$, and one unstable state at $x_u = 0$. If $a \to 0$, the stable $x_s \to x_u$.

If the environmental fluctuation due to some external factors (such as temperature, radiotherapy, geological events) is considered, the parameter a should be modified as $a + \xi(t)$, and some factors such as internal fluctuation give rise to an additive noise $\eta(t)$. On the other hand, the time delay is taken account in the tumor growth process, which denotes the reaction time of the tumor cell to environmental constraints. Considering all these factors, Eq. (1) can be rewritten as

$$\frac{dx(t)}{dt} = ax(t-\tau_1) - bx^2(t) + x(t-\tau_2)\xi(t) + \eta(t), \tag{2}$$

where τ_1 denotes the time delay in the deterministic force, while τ_2 denotes the time delay in the random force, $\xi(t)$, and $\eta(t)$ is Gaussian white noise with zero mean and correlations:

$$\begin{aligned} \langle \xi(t)\xi(t')\rangle &= 2D\delta(t-t'), \\ \langle \eta(t)\eta(t')\rangle &= 2\alpha\delta(t-t'), \\ \langle \xi(t)\eta(t')\rangle &= \langle \eta(t)\xi(t')\rangle = 2\lambda\sqrt{\alpha D}\delta(t-t'). \end{aligned} \tag{3}$$

Here α and D are the intensities of the noise terms $\eta(t)$ and $\xi(t)$, respectively, and λ denotes the coupling strength between the two noise terms.

Applying the approximation probability density approach [23, 24] and the stochastic equivalent rule [25], Eq. (2) can be rewritten as

$$\frac{dx(t)}{dt} = h_{eff}(x) + G_{eff}(x)\varepsilon(t), \tag{4}$$

where $\varepsilon(t)$ is the Gaussian white noise with $\langle \varepsilon(t)\varepsilon(t')\rangle = 2\delta(t-t')$, and $h_{eff}(x)$ and $G_{eff}(x)$ are as follows:

$$\begin{aligned} h_{eff}(x) &= (1+\tau_1)(ax - bx^2), \\ G_{eff}(x) &= \sqrt{D(1+\tau_2)^2x^2 + 2\lambda\sqrt{D\alpha}(1+\tau_2)x + \alpha}, \end{aligned} \tag{5}$$

From Eq. (4) and Eq. (5), the delayed Fokker-Planck equation corresponding to Eq. (2) and (3) can be derived as

$$\frac{\partial}{\partial t}P(x,t) = -\frac{\partial}{\partial x}A(x)P(x,t) + \frac{\partial^2}{\partial x^2}B(x)P(x,t), \tag{6}$$

where

$$\begin{aligned} A(x) &= h_{eff}(x) + G_{eff}\frac{dG_{eff}(x)}{dx}, \\ B(x) &= G_{eff}^2(x). \end{aligned} \tag{7}$$

Under the constraint $x > 0$ (the tumor cell number $x(t)$ is always greater than zero), the stationary probability distribution (SPD) corresponding to Eq. (6) is obtained with Eq. (7) [25],

$$P_{st}(x) = \frac{N}{G_{eff}}\exp[-\Phi(x)], \tag{8}$$

where N is a normalization constant, and $\Phi(x)$ is the generalized potential function with the following form:

$$\Phi(x) = q\left[\frac{bx}{m} - \left(\frac{a}{2m} + \frac{bn}{m^2}\right)\ln(mx^2 + 2nx + Q) - \frac{bQm - anm - 2n^2b}{m^2\sqrt{mQ - n^2}}\arctan\left(\frac{mx + n}{\sqrt{mQ - n^2}}\right)\right], \tag{9}$$

where

$$\begin{aligned} m &= D(1 + \tau_2)^2, \\ n &= \lambda\sqrt{D\alpha}(1 + \tau_2), q = (1 + \tau_1). \end{aligned} \tag{10}$$

By numerical calculation of Eq. (8) and Eq. (9), the effects of the two different time delays on the SPD are analyzed. The SPD as a function of the tumor cell number $x(t)$ is plotted in Figure 1. In Figure 1a, we show the SPD as a function of x and τ_1 when the other parameters are fixed. It is found that the peak of the curve of the SPD gradually becomes high, while the position of the maximum shifts from smaller to larger values of x with increase in τ_1. Since x denotes the tumor cell number, it means that the tumor cell number increases as τ_1 increases. Figure 1b shows the SPD as a function of x and τ_2 when the other parameters are fixed. It is found that the position of the peak of the SPD shifts from larger to smaller values of x with increase in τ_2. On the other hand, when $\tau_2 \in (0.5, 1.0)$, the maximum of the SPD gradually shifts to the position $x = 0$, and the curve of the SPD becomes completely monotone. This illustrates that the tumor cell number decreases as τ_2 increases. Therefore, in the tumor cell growth process, these two kinds of time delay play completely opposite roles. Namely, τ_1, which denotes the time delay in the deterministic force, can enhance the tumor cell number; meanwhile τ_2, which denotes the time delay in the random force, can restrain tumor cell growth. In order to quantitatively investigate the stationary properties of the system, the mean of tumor cell number is given by

$$\langle x\rangle_{st} = \int_0^{+\infty} xP_{st}(x)dx. \tag{11}$$

Figure 2 shows the characteristics of $\langle x\rangle_{st}$ as a function of the time delays τ_1 and τ_2, for different correlation intensities λ. It is obvious that the $\langle x\rangle_{st}$ monotonically increases with τ_1 increasing, and decreases with τ_2 increaseing, in the cases of both positive and negative correlation, which is agreement with the results seen in the Figure 1.

Next, we will quantify the effects of noise on the switch between the steady stable states using the mean first passage time (MFPT). For the tumor cell growth process, the

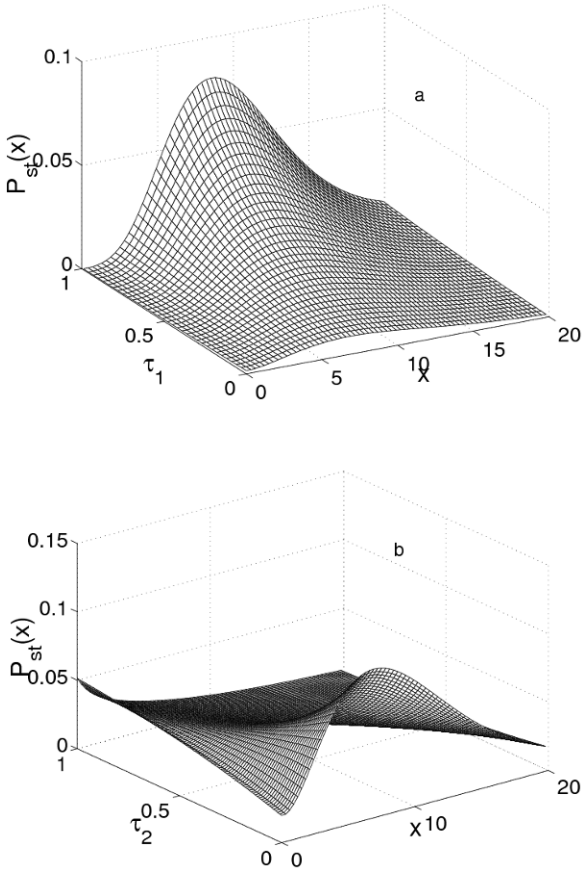

Figure 1. The stationary probability distribution function $P_{st}(x)$ is plotted as a function of x, τ_1, and τ_2, respectively. The parameters are dimensionless and are chosen as $D = 0.3, \alpha = 0.5, \lambda = 0.2$. (a) $P_st(x)$ as a function of x and τ_1 with $\tau_2 = 0$. (b) $P_{st}(x)$ as a function of x and τ_2 with $\tau_1 = 0$.

MFPT of the process $x(t)$ is defined to be the average time to reach the extinct state $x_u = 0$ with initial condition $x_s(t = 0) = \frac{a}{b}$. For small D, α and λ, applying the steepest-descent approximation, the analytic expression of MFPT is given by [26, 27],

$$T(x_s \to x_u) \approx 2\pi\left[|V''(x_s)V''(x_u)|\right]^{-\frac{1}{2}}\exp\left[\Phi(x_s) - \Phi(x_u)\right]. \tag{12}$$

Making use of the expressions of Eq. (12), Eq. (9) and $V(x) = -\frac{a}{2}x^2 + \frac{b}{3}x^3$. The effects of τ_1 and τ_2 on MFPT are shown in Figure 3. It is clear that MFPT monotonically increases with increase in τ_1, and decreases with increase in τ_2. This means that τ_1 can restrain the transition from the large tumor cell population state to the small tumor cell population state, on the contrary, τ_2 can speed up the transition from the large tumor cell population state

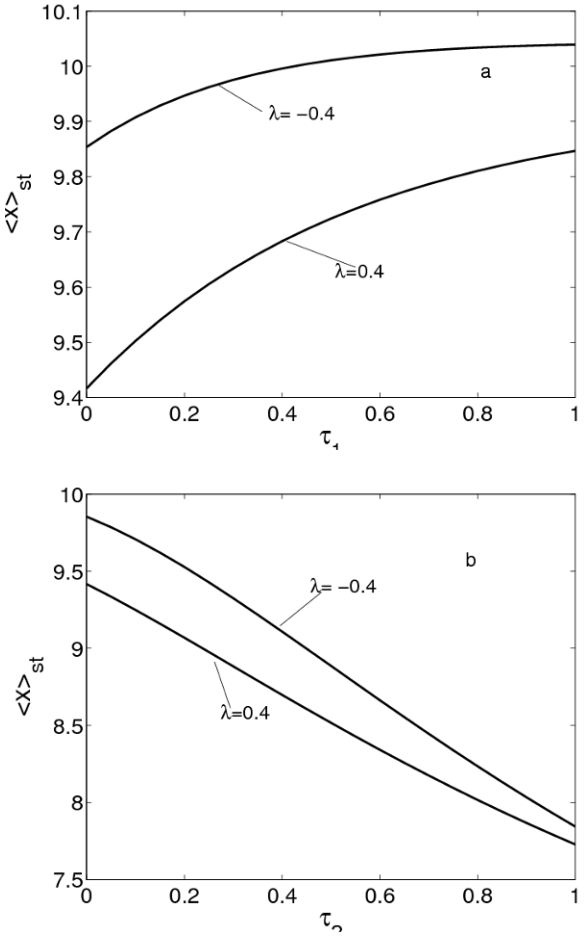

Figure 2. The mean value $\langle x\rangle_{st}$ is plotted as a function of τ_1 and τ_2, respectively. The parameters are dimensionless and are chosen as $D = 0.4, \alpha = 0.3, \lambda = 0.4, -0.4$. (a) $\langle x\rangle_{st}$ as a function of τ_1 with $\tau_2 = 0$. (b) $\langle x\rangle_{st}$ as a function of τ_2 with $\tau_1 = 0$.

to the small tumor cell population state. τ_1 and τ_2 play an opposing role in this transition.

In summary, the dynamical character of a tumor cell growth model subjected to a multiplicative noise and an additive noise with two different kinds of time delays is investigated. The effects of the two kinds of time delay τ_1 and τ_2 on the SPD, $\langle x\rangle_{st}$ and MFPT are analyzed in detail based on the approximation delay Fokker-Planck Equation. The results are as follows.

1. The two kinds of different time delays affect the SPD and the mean value $\langle x\rangle_{st}$ in different ways. The highest peak of $P_{st}(x)$ shifts from smaller to larger values of x with increase in τ_1, and shifts from larger to smaller values of x with increase in τ_2. $\langle x\rangle_{st}$ monotonically increases with increase in τ_1 and decreases with increase in τ_2. This means that the tumor population moves towards extinction with increase in τ_2, and grows with increase in τ_1.

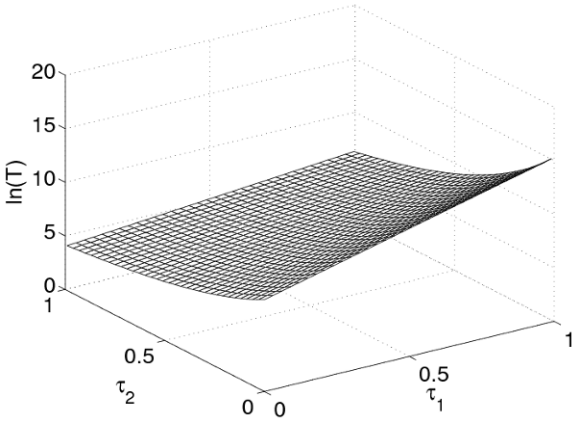

Figure 3. The mean first passage time (MFPT) T is plotted as a function of τ_1 and τ_2. The parameters are dimensionless and are chosen as $D = 0.3, \alpha = 0.5, \lambda = -0.5$.

2. The MFPT monotonically increases with increase in τ_1 and decreases with increase in τ_2. This result shows that the transition rate from large tumor cell population to small tumor cell population speeds up when τ_2 is enhanced, which is helpful as an idea to cure tumor disease. However, τ_1 restrains the transition, which is harmful.

Acknowledgments

This project supported by the Natural Science Foundation of China (Grant No. 10865006), the Science Foundation of the Education Bureau of Shaanxi Province (Grant No. 09JK331), the Natural Science Foundation of Shaanxi province of China (Grant No. 2010JQ1014) and the Science Foundation of Baoji University of Science and Arts of China (Grant No. ZK0954).

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