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Colored Noise Enhanced Stability in a Tumor Cell Growth System Under Immune Response

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Abstract In this paper, we investigate a mathematical model for describing the growth of tumor cell under immune response, which is driven by cross-correlation between multiplicative and additive colored noises as well as the nonzero cross-correlation in between. The expression of the mean first-passage time (MFPT) is obtained by virtue of the steepest-descent approximation. It is found: (i) When the noises are negatively cross-correlated ($\lambda < 0$), then the escape is faster than in the case with no correlation ($\lambda = 0$); when the noises are positively cross-correlated ($\lambda > 0$), then the escape is slower than in the case with no correlation. Moreover, in the case of positive cross-correlation, the escape time has a maximum for a certain intensity of one of the noises, i.e., the maximum for MFPT identifies the noise enhanced stability of the cancer state. (ii) The effect of the cross-correlation time τ_3 on the MFPT is completely opposite for $\lambda > 0$ and $\lambda < 0$. (iii) The self-correlation times τ_1 and τ_2 of colored noises can enhance stability of the cancer state, while the immune rate β can reduce it.

Keywords Correlation times · Mean first-passage time · Tumor cell growth system

1 Introduction

The law of tumor cell growth has been investigated extensively, that in the area of theory and the one of experiment in a large variety of physical, chemical and biological systems [1–7]. In today's world, cancer is a leading cause of death, but still little is known about the mechanisms of its growth and destruction. So scientists try to find exact measures to control tumors and cure cancers, and show that there is an interesting and significant case for immunotherapy in tumor treatments [8–10]. Accordingly, the theoretical and experimental works on the mechanisms of interaction between tumor tissue and immune system is necessary for planning efficient strategies of treatment [11–13]. In the tumor tissue, the growth

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rate and cytotoxic parameters are influenced by many environmental factors. As a result of this complexity, it is unavoidable that the parameters of the system undergo random variations, which gives them a stochastic character [14–18].

In the past decade, the logistic growth model is usually used to describe the process of tumor cell growth, it is desirable to take into account both internal and external stochastic fluctuations as well as correlation in between. Therefore, a more refined model without immune response was presented in [19], however, the stationary distribution function presented in that paper is not correct as pointed out in [20] and replied in [21]. A similar model in presence of correlated noises for the case of nonzero correlation time had been considered in [22]. The statistical properties of the same model subject to colored noises had been studied likewise in [23, 24]. In the presence of immune response 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 [25]. The effect of pure multiplicative white noise may induce stochastic resonance and non-equilibrium phase transition in an anti-tumor model [26, 27], and spatiotemporal noise can trigger infiltrative tumor growth subject to an immunosurveillance against cancer [28]. This work was investigated by Bose and Trimper [29] where they analyzed a stochastic model for tumor cell growth with immunization. A recent investigation by [14, 30] showed the co-occurrence of resonant activation and noise-enhanced stability in a model of cancer growth in the presence of immune response, which is driven by multiplicative and additive white noises that were uncorrelated. The cross-correlation enhanced stability and stochastic resonance driven by cross-correlated white noises in this model had also been studied in [31, 32]. However, more realistic models of physical systems require considering the case of colored noise, especially the stochastic system driven by colored noises [33, 34]. Actually, the correlation time of a real noise, although small it may be, is never equal to zero. For a noise with zero correlation time, its power spectral distribution which is given by the Fourier transform of its correlation function, is independent on frequency. Therefore the total power dissipated in all frequencies is infinite, but the actual power dissipated would be somewhat less than infinite. In other words, it appears as an idealization, only valid when the time scale for its correlation is much shorter than the time scale for the relaxation of the driven process. In addition, the assumption that the correlation time is zero, is usually adopted as a first step in studying the system driven by noises. Afterwards it is reasonable to relax this condition and include the finite correlation time [22, 35]. On the level of a Langevin- or Fokker-Planck-type description of a dynamical system, the presence of colored noises can affect the dynamics of the system. Colored noise processes have made their presence felt in a wide range of studies [36, 37], such as the statistical properties of a single mode laser [38], bistable kinetics [39–44], biology systems [45]. In the present work, we study the transient properties of a tumor cell growth system under immune response driven by cross-correlation between multiplicative and additive colored noises as well as the nonzero cross-correlation in between, at which the fluctuation of environmental factors affects the immune rate generating multiplicative noise, and some factors, such as drugs and radiotherapy, restrain the number of tumor cells, gives rise to a additive noise.

This paper is arranged as follows. In Sect. 2, the Novikov theorem, Fox approach and Hänggi Ansatz are applied to obtain the approximate Fokker-Planck equation, and then the expression of the MFPT is obtained by virtue of the steepest-descent approximation. The effects of the cross-correlation intensity and time, and the self-correlation times and intensities on the MFPT are discussed. The numerical simulations are performed in order to check the credibility of the approximate methods used to obtain the analytic results. Finally, results and discussions are given in Sect. 3.

2 The MFPT

In order to investigate the transient properties of the tumor cell growth system, we need the approximate Fokker-Planck equation (AFPE) of the system. First, using the Novikov theorem, Fox approach and Hänggi Ansatz, the AFPE of the system can be obtained, and then discuss the effects of the noise parameters on the MFPT of the system. The numerical simulations are performed in order to check the credibility of the approximate methods.

2.1 The AFPE

We consider the following set of stochastic differential equation:

$$\frac{dx}{dt} = f(x) + g_1(x)\xi(t) + g_2(x)\eta(t), \tag{1}$$

$$\frac{d\xi}{dt} = -\frac{1}{\tau_1}\xi + \frac{1}{\tau_1}\xi_1(t), \tag{2}$$

$$\frac{d\eta}{dt} = -\frac{1}{\tau_2}\eta + \frac{1}{\tau_2}\eta_1(t), \tag{3}$$

where $\xi_1(t)$ and $\eta_1(t)$ are Gaussian white noises and their statistical properties are given by

$$\begin{aligned}
&\langle \xi_1(t)\rangle = \langle \eta_1(t)\rangle = 0,\\
&\langle \xi_1(t)\xi_1(t')\rangle = 2D\delta(t-t'),\\
&\langle \eta_1(t)\eta_1(t')\rangle = 2\alpha\delta(t-t'),\\
&\langle \xi_1(t)\eta_1(t')\rangle = \langle \eta_1(t)\xi_1(t')\rangle = 2\lambda\sqrt{D\alpha}\delta(t-t').
\end{aligned} \tag{4}$$

It has been shown that the above three-dimensional Markovian processes (1)–(4) are stochastically equivalent to one-dimensional non-Markovian process described by (1) with Gaussian colored noises $\xi(t)$ and $\eta(t)$ [46–48]

$$\begin{aligned}
&\langle \xi(t)\rangle = \langle \eta(t)\rangle = 0,\\
&\langle \xi(t)\xi(t')\rangle = \frac{D}{\tau_1}\exp\left(-\frac{|t-t'|}{\tau_1}\right),\\
&\langle \eta(t)\eta(t')\rangle = \frac{\alpha}{\tau_2}\exp\left(-\frac{|t-t'|}{\tau_2}\right),\\
&\langle \xi(t)\eta(t')\rangle = \langle \eta(t)\xi(t')\rangle = \frac{\lambda\sqrt{D\alpha}}{\tau_3}\exp\left(-\frac{|t-t'|}{\tau_3}\right).
\end{aligned} \tag{5}$$

Here τ_1 and D are the self-correlation time and intensity of the noise $\xi(t)$, respectively. τ_2 and α are the self-correlation time and intensity of the noise $\eta(t)$, respectively. τ_3 and λ denote the time and intensity of cross-correlation between $\xi(t)$ and $\eta(t)$, respectively. Below we will use the Novikov theorem, Fox approach and Hänggi Ansatz to reduce the one-dimensional non-Markovian process to the one-dimensional Markovian process in order to obtain analytic results.

According to the stochastic Liouville equation and van Kampen's lemma $P(x,t) = \langle \delta(x(t)-x)\rangle$, the evolution equation for the probability density $P(x,t)$ is given by [38, 41, 42, 49, 50]

$$\frac{\partial P(x,t)}{\partial t} = -\frac{\partial}{\partial x} f(x) P(x,t) - \frac{\partial}{\partial x} g_1(x) \langle \xi(t)\delta(x(t)-x)\rangle - \frac{\partial}{\partial x} g_2(x) \langle \eta(t)\delta(x(t)-x)\rangle. \tag{6}$$

The average which remains in (6) may be calculated for Gaussian noises $\xi(t)$ and $\eta(t)$ by a functional formula, using the Novikov theorem [51, 52]:

$$\langle \zeta_k \Phi[\zeta_1,\zeta_2]\rangle = \int_0^t dt'\, \gamma_{kl} \frac{\delta \Phi[\zeta_1,\zeta_2]}{\delta \zeta_l} \quad (k,l=1,2),$$

where $\Phi[\zeta_1,\zeta_2]$ is a functional of ζ_1 and ζ_2, and $\gamma_{kl} = \langle \zeta_k(t)\zeta_l(t')\rangle$ are their correlation functions. Now we use the Novikov theorem to the calculation of the averages $\langle \xi(t)\delta(x(t)-x)\rangle$ in (6), we have

$$\langle \xi(t)\delta(x(t)-x)\rangle = \int_0^t dt'\, \gamma_{11}(t,t') \frac{\delta(\delta(x(t)-x))}{\delta \xi(t')} + \int_0^t dt'\, \gamma_{21}(t,t') \frac{\delta(\delta(x(t)-x))}{\delta \eta(t')}. \tag{7}$$

Applying the Fox approach [53] to (7), we obtain

$$\begin{aligned}\langle \xi(t)\delta(x(t)-x)\rangle = &-D\frac{\partial}{\partial x} g_1(x) \int_0^t dt' \frac{1}{\tau_1} \exp\left[-\frac{|t-t'|}{\tau_1}\right] \\ &\times \left\langle \delta(x(t)-x) \exp\left\{ \int_{t'}^t ds \left[f'(x(s)) - \frac{g_1'(x(s))}{g_1(x(s))} f(x(s)) \right] \right\} \right\rangle \\ &- \lambda\sqrt{D\alpha} \frac{\partial}{\partial x} g_2(x) \int_0^t dt' \frac{1}{\tau_3} \exp\left[-\frac{|t-t'|}{\tau_3}\right] \\ &\times \left\langle \delta(x(t)-x) \exp\left\{ \int_{t'}^t ds \left[f'(x(s)) - \frac{g_2'(x(s))}{g_2(x(s))} f(x(s)) \right] \right\} \right\rangle. \end{aligned} \tag{8}$$

According to the Hänggi Ansatz [54], we consider the stochastic system in the steady-state regime. Thus,

$$\begin{aligned}\langle \xi(t)\delta(x(t)-x)\rangle = &-\frac{D}{1-\tau_1[f'(x_s) - \frac{g_1'(x_s)}{g_1(x_s)} f(x_s)]} \frac{\partial}{\partial x} g_1(x) P(x,t) \\ &- \frac{\lambda\sqrt{D\alpha}}{1-\tau_3[f'(x_s) - \frac{g_2'(x_s)}{g_2(x_s)} f(x_s)]} \frac{\partial}{\partial x} g_2(x) P(x,t), \end{aligned} \tag{9}$$

in which x_s denotes the steady-state value of $\langle x(t)\rangle$.

Similarly, the average $\langle \eta(t)\delta(x(t)-x)\rangle$ in (6) is given by

$$\begin{aligned}\langle \eta(t)\delta(x(t)-x)\rangle = &-\frac{\alpha}{1-\tau_2[f'(x_s) - \frac{g_2'(x_s)}{g_2(x_s)} f(x_s)]} \frac{\partial}{\partial x} g_2(x) P(x,t) \\ &- \frac{\lambda\sqrt{D\alpha}}{1-\tau_3[f'(x_s) - \frac{g_1'(x_s)}{g_1(x_s)} f(x_s)]} \frac{\partial}{\partial x} g_1(x) P(x,t). \end{aligned} \tag{10}$$

Substituting (9) and (10) into (6), we ultimately obtain the AFPE corresponding to (1) with (5):

$$\begin{aligned}\frac{\partial P(x,t)}{\partial t} &= -\frac{\partial}{\partial x} f(x) P(x,t) + \frac{D}{1-\tau_1[f'(x_s) - \frac{g_1'(x_s)}{g_1(x_s)} f(x_s)]} \frac{\partial}{\partial x} g_1(x) \frac{\partial}{\partial x} g_1(x) P(x,t) \\ &+ \frac{\lambda\sqrt{D\alpha}}{1-\tau_3[f'(x_s) - \frac{g_2'(x_s)}{g_2(x_s)} f(x_s)]} \frac{\partial}{\partial x} g_1(x) \frac{\partial}{\partial x} g_2(x) P(x,t) \\ &+ \frac{\alpha}{1-\tau_2[f'(x_s) - \frac{g_2'(x_s)}{g_2(x_s)} f(x_s)]} \frac{\partial}{\partial x} g_2(x) \frac{\partial}{\partial x} g_2(x) P(x,t) \\ &+ \frac{\lambda\sqrt{D\alpha}}{1-\tau_3[f'(x_s) - \frac{g_1'(x_s)}{g_1(x_s)} f(x_s)]} \frac{\partial}{\partial x} g_2(x) \frac{\partial}{\partial x} g_1(x) P(x,t). \end{aligned} \tag{11}$$

This AFPE is valid for the following conditions:

$$1 - \tau_j \left[f'(x_s) - \frac{g_i'(x_s)}{g_i(x_s)} f(x_s) \right] > 0, \tag{12}$$

here $j = 1, 2, 3$ and $i = 1, 2$. Equation (12) limits the range of possible values of the correlation times τ_j.

2.2 Theoretical Analysis of the MFPT

The formulation of the model for describing the growth of cancerous tissue attacked by immune cytotoxic cells is based on a reaction scheme [55–57]

$$\begin{aligned} X &\xrightarrow{\rho} 2X, \\ X + Y &\xrightarrow{k_1} Z \xrightarrow{k_2} Y + P, \end{aligned} \tag{13}$$

in which cancer cells X are assumed to proliferate spontaneously at a rate ρ whereas their local interactions with cytotoxic cells Y are modeled by a simplified kinetics with k_1 standing for the rate of binding of immune cells to the complex Z which subsequently dissociates at a rate k_2. The dissociation results in a product P representing dead or non-replicating tumor cells. In the limit case, when the production of X-type cells inhibited by a hyperbolic activation is the slowest process under consideration, and by assuming a conserved number of immune cells $Y + Z = E = const$, the resulting kinetics can be recast in the dimensionless form of the first order differential equation by setting $x = k_1 x/k_2$, $\theta = k_1/k_2$, $\beta = k_1 E/\rho$, and $t = \rho t$ [14, 25, 55–57],

$$\frac{dx}{dt} = x(1 - \theta x) - \beta \frac{x}{x+1}, \tag{14}$$

where x is the concentration of the tumor cells, θ is the constant parameter and β is the immune rate. The growth and extension of tumor cells are affected by the environment [1, 58, 59], such as chemotherapy, radiotherapy, the degree of vascularization of tissues, the supply of oxygen, the supply of nutrients, the immunological state of the host, chemical

agents, temperature, etc. They can influence the tumor number directly as well as alter the tumor immune rate. In other words, the fluctuation of these factors affect the immune rate β generating multiplicative noise $\xi(t)$, which represents the strength of the treatment (i.e., the dosage of the medicine in chemotherapy or the intensity of the ray in radiotherapy). And some factors, such as drugs and radiotherapy, restrain the number of tumor cells, gives rise to a additive noise $\eta(t)$, it serves as the capability for expansionary transfer of the tumor cells. Then the equivalent stochastic differential equation of (14) can be generated as [31]

$$\frac{dx}{dt} = x(1-\theta x) - \beta\frac{x}{x+1} - \frac{x}{x+1}\xi(t) + \eta(t), \tag{15}$$

$\xi(t)$ and $\eta(t)$ in (15) are the same as that in (1). Comparing (15) with (1), the following relations are obtained

$$f(x) = x(1-\theta x) - \beta\frac{x}{x+1}, \tag{16}$$

$$g_1(x) = -\frac{x}{x+1}, \qquad g_2(x) = 1. \tag{17}$$

The deterministic potential related to the deterministic force $f(x)$ in (16) reads

$$V(x) = -\int f(x)\,dx = -\frac{x^2}{2} + \frac{\theta x^3}{3} + \beta x - \beta\ln(x+1), \tag{18}$$

which has two steady stable states $x_1 = 0$ (the state of extinction), $x_2 = x_s = (1-\theta+\sqrt{(1+\theta)^2-4\beta\theta})/2\theta > 0$ (the state of a stable tumor), and one unstable steady state $x_u = (1-\theta-\sqrt{(1+\theta)^2-4\beta\theta})/2\theta$. Therefore the AFPE of the system (15) is obtained by substituting (16)–(17) into (11)

$$\begin{aligned}\frac{\partial P(x,t)}{\partial t} = &-\frac{\partial}{\partial x}\left[x(1-\theta x) - \beta\frac{x}{x+1}\right]P(x,t) + \frac{D}{1-\tau_1 C_1}\frac{\partial}{\partial x}g_1(x)\frac{\partial}{\partial x}g_1(x)P(x,t)\\ &+\frac{\lambda\sqrt{D\alpha}}{1-\tau_3 C_2}\frac{\partial}{\partial x}g_1(x)\frac{\partial}{\partial x}g_2(x)P(x,t) + \frac{\alpha}{1-\tau_2 C_2}\frac{\partial}{\partial x}g_2(x)\frac{\partial}{\partial x}g_2(x)P(x,t)\\ &+\frac{\lambda\sqrt{D\alpha}}{1-\tau_3 C_1}\frac{\partial}{\partial x}g_2(x)\frac{\partial}{\partial x}g_1(x)P(x,t),\end{aligned} \tag{19}$$

in which

$$C_1 = f'(x_s) - \frac{f(x_s)}{x_s(x_s+1)}, \qquad C_2 = f'(x_s), \tag{20}$$

where $f'(x_s)$ denotes the derivation of $f(x)$ defined in (16) at the stationary point $x_s > 0$ of the potential $V(x)$, introduced in (18), and $f(x_s) = f(x)|_{x=x_s}$. To be precise the value are

$$\begin{aligned} f(x_s) &= x_s(1-\theta x_s) - \beta\frac{x_s}{x_s+1},\\ f'(x_s) &= 1 - 2\theta x_s - \beta\frac{1}{(1+x_s)^2}.\end{aligned} \tag{21}$$

Simplifying the right-hand side of (19), we have

$$\frac{\partial P(x,t)}{\partial t} = -\frac{\partial}{\partial x}A(x)P(x,t) + \frac{\partial^2}{\partial x^2}B(x)P(x,t), \tag{22}$$

where

$$A(x) = x(1-\theta x) - \beta\frac{x}{x+1} + \frac{D}{1-\tau_1 C_1}\frac{x}{(x+1)^3} - \lambda\sqrt{D\alpha}C_3\frac{1}{(x+1)^2},$$
$$B(x) = \frac{D}{1-\tau_1 C_1}\left(\frac{x}{x+1}\right)^2 - \lambda\sqrt{D\alpha}C_3\frac{x}{x+1} + \frac{\alpha}{1-\tau_2 C_2}, \tag{23}$$

with

$$C_3 = \frac{1}{1-\tau_3 C_1} + \frac{1}{1-\tau_3 C_2}. \tag{24}$$

According to (22)–(23), the stationary probability distribution $P_{st}(x)$ for $\lambda < \frac{2}{\sqrt{(1-\tau_1 C_1)(1-\tau_2 C_2)C_3}}$ reads

$$P_{st}(x) = \frac{N}{B(x)}\exp\int^x \frac{A(x')}{B(x')}dx' = \frac{N}{B^{1/2}(x)}\exp\left[-\frac{U(x)}{D}\right], \tag{25}$$

here the generalized potential $U(x)$ is

$$U(x) = -\int^x \frac{x(1-\theta x) - \beta\frac{x}{x+1}}{\frac{1}{1-\tau_1 C_1}(\frac{x}{x+1})^2 - \lambda\sqrt{\alpha/D}C_3\frac{x}{x+1} + \frac{\alpha/D}{1-\tau_2 C_2}}dx. \tag{26}$$

Integrating (26), one has

$$\begin{aligned} U(x) = {} & \frac{\theta(1-\tau_1 C_1)}{3m}x^3 + \frac{1-\tau_1 C_1}{2m}\left(2\theta - 1 - \frac{n}{m}\theta\right)x^2 - \frac{\gamma_1}{m}(1-\tau_1 C_1)x \\ & + \frac{1-\tau_1 C_1}{2m}\left(\gamma_2 - \frac{n}{m}\gamma_1\right)\ln\left|x^2 + \frac{n}{m}x + \frac{R}{m}\right| - \frac{2\gamma_3(1-\tau_1 C_1)}{\sqrt{4mR-n^2}} \\ & \times \arctan\frac{2mx+n}{\sqrt{4mR-n^2}}, \end{aligned} \tag{27}$$

and here

$$\begin{aligned} & R = \widetilde{\alpha}/\widetilde{D}, \quad \widetilde{D} = \frac{D}{1-\tau_1 C_1}, \quad \widetilde{\alpha} = \frac{\alpha}{1-\tau_2 C_2}, \quad \widetilde{\lambda} = \sqrt{(1-\tau_1 C_1)(1-\tau_2 C_2)}C_3\lambda, \\ & m = 1 - \widetilde{\lambda}\sqrt{R} + R, \qquad n = 2R - \widetilde{\lambda}\sqrt{R}, \\ & \gamma_1 = \beta - 2 + \theta - \frac{R}{m}\theta - \left(2\theta - 1 - \frac{n}{m}\theta\right)\frac{n}{m}, \\ & \gamma_2 = \beta - 1 - \left(2\theta - 1 - \frac{n}{m}\theta\right)\frac{R}{m}, \\ & \gamma_3 = \frac{\gamma_1}{m}R + \frac{n}{2m}\left(\gamma_2 - \frac{n}{m}\gamma_1\right). \end{aligned} \tag{28}$$

N in (25) is the normalization constant. Our results are in agreement with those obtained in Ref. [31] by setting $\tau_1 = \tau_2 = \tau_3 = 0$.

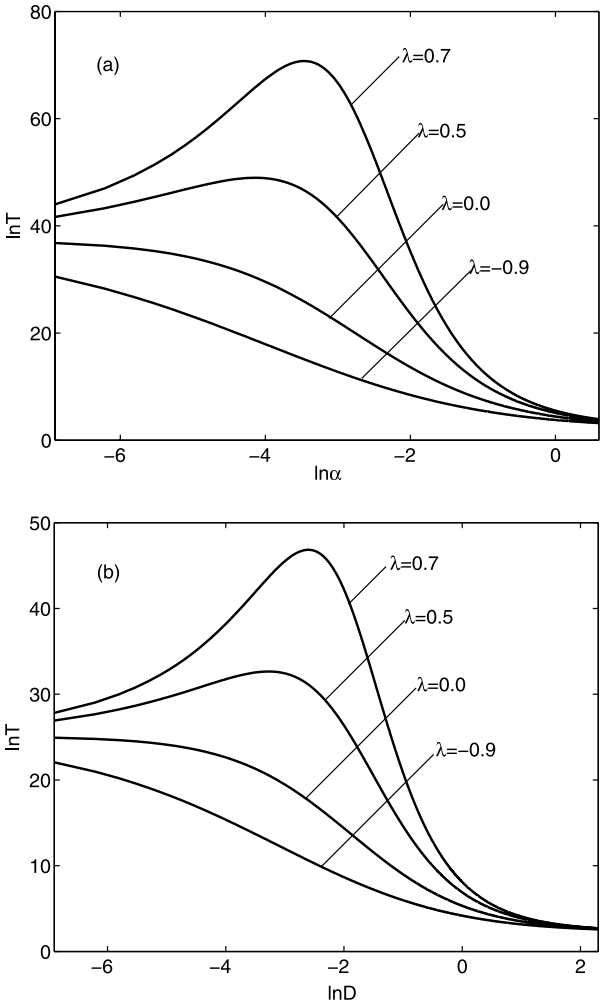

Fig. 1 The MFPT as a function of α (**a**) and as a function of D (**b**) for different values of λ. $D = 0.1$ in (**a**) and $\alpha = 0.1$ in (**b**). The parameter values are $\theta = 0.1$, $\beta = 2.26$, $\tau_1 = 0.1$, $\tau_2 = 0.1$, and $\tau_3 = 0.1$

Now we are interested in the possibility of its spontaneous extinction under the influence of random environmental perturbations. In a certain range of values of the parameters describing the immune response intensity and the maximum density of tumor, the model possesses two stable states: the state of extinction (x_1), where no tumor cells are present, and the state of a stable tumor (x_2), where its density does not increase but stays at a certain constant level. Random fluctuations present in the system can induce transitions between those two states. From this point of view, it is interesting to study the mean first-passage time (MFPT) of transition from the tumor of a given density (i.e., the state of a stable tumor) to the state of extinction. For details regarding the general treatment of MFPT calculations, is in Ref. [60]. In essence, one begins with Kolomogorov's backward equation which is equivalent

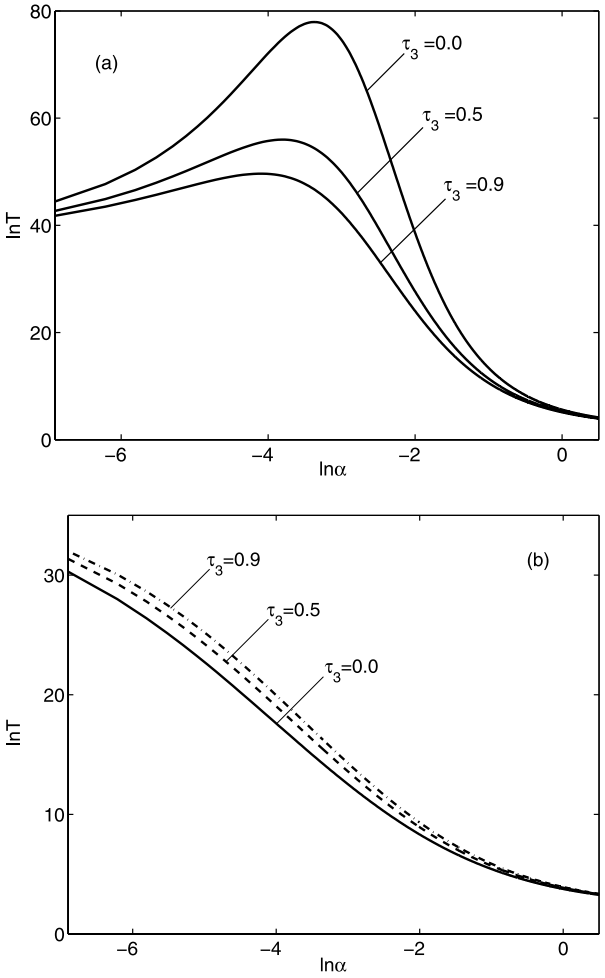

Fig. 2 The MFPT as a function of α for different values of τ_3. (**a**) $\lambda = 0.7$; (**b**) $\lambda = -0.9$. The parameter values are $\theta = 0.1$, $\beta = 2.26$, $\tau_1 = 0.1$, $\tau_2 = 0.1$, and $D = 0.1$

with (22). This ultimately leads to the MFPT equation for $T(x)$ [36, 37, 43, 44, 60],

$$A(x)\frac{\partial}{\partial x}T(x) + B(x)\frac{\partial^2}{\partial x^2}T(x) = -1, \tag{29}$$

with boundary conditions

$$\left.\frac{dT(x)}{dx}\right|_{x=x_2} = 0, \quad T(x)|_{x=x_1} = 0, \tag{30}$$

which correspond to a reflecting boundary at $x = x_2$ and an absorbing boundary at $x = x_1$. If we consider the MFPT for getting from the state of a stable tumor at $x(t = 0) = x_2$ to the

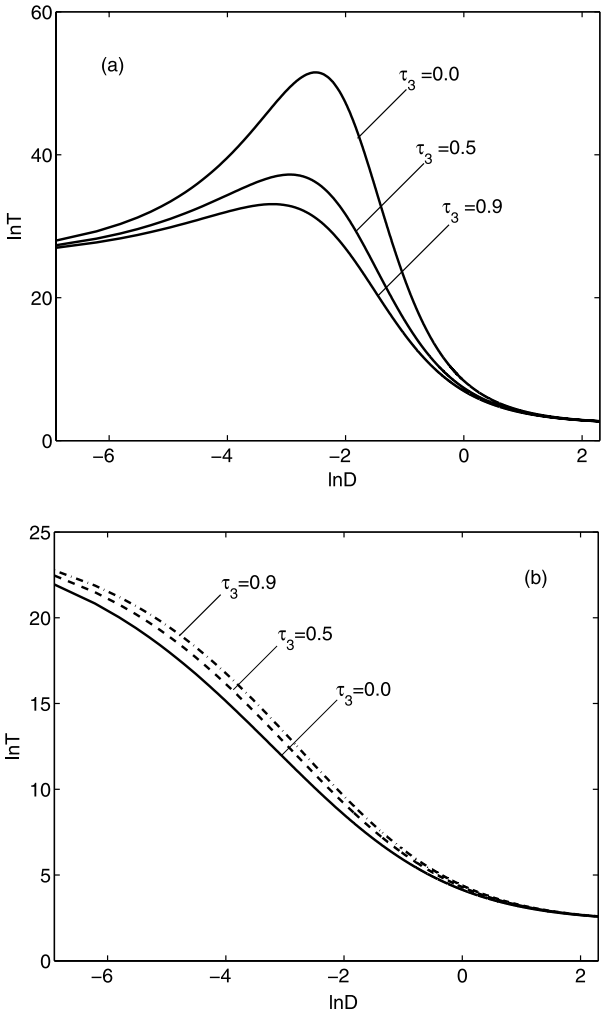

Fig. 3 The MFPT as a function of D for different values of τ_3. (**a**) $\lambda = 0.7$; (**b**) $\lambda = -0.9$. The parameter values are $\theta = 0.1$, $\beta = 2.26$, $\tau_1 = 0.1$, $\tau_2 = 0.1$, and $\alpha = 0.1$

state of extinction at x_1, then the solution to (29) with (30) can be written [40, 60, 61]

$$T_{x_2}(x_1) = \int_{x_1}^{x_2} \frac{dx}{B(x)P_{st}(x)} \int_{-\infty}^{x} dy\, P_{st}(y). \tag{31}$$

In the case in which the intensity of the two types of fluctuations, measured by α and D, is small in comparison with the energy barrier

$$D, \alpha < U(x_u) - U(x_2). \tag{32}$$

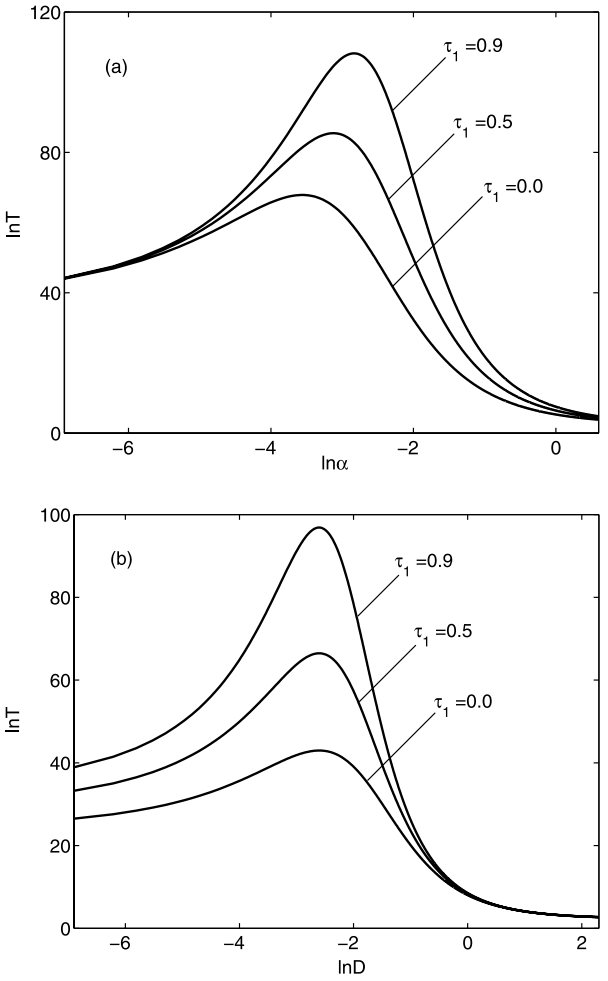

Fig. 4 The MFPT as a function of α (**a**) and as a function of D (**b**) for different values of τ_1. $D = 0.1$ in (**a**) and $\alpha = 0.1$ in (**b**). The parameter values are $\theta = 0.1$, $\beta = 2.26$, $\lambda = 0.7$, $\tau_2 = 0.1$, and $\tau_3 = 0.1$

Using the steepest-descent approximation to (31) [62–64], the MFPT of the transition to the state of extinction becomes

$$T_{x_2}(x_1) \approx T = \frac{2\pi}{\sqrt{|V''(x_u)V''(x_2)|}} \exp\left[\frac{U(x_u) - U(x_2)}{D}\right], \tag{33}$$

where the double prime denotes the second derivation with respect to x, $V(x)$ and $U(x)$ are given by (18) and (27), respectively. By numerical evaluation of the expression of the MFPT (33), the effects of the cross-correlation intensity and time, and the self-correlation times and intensities on the MFPT can be discussed. Here we must point that following analysis is only a theoretical study of transient properties of the system.

In Fig. 1 the MFPT is presented as a function of the noise intensity α and as a function of the noise intensity D for different cross-correlation intensity λ of noises. As the intensity of noise α or D increases, the MFPT decreases for the cases of $\lambda \leqslant 0$ [see $\lambda = -0.9$, and

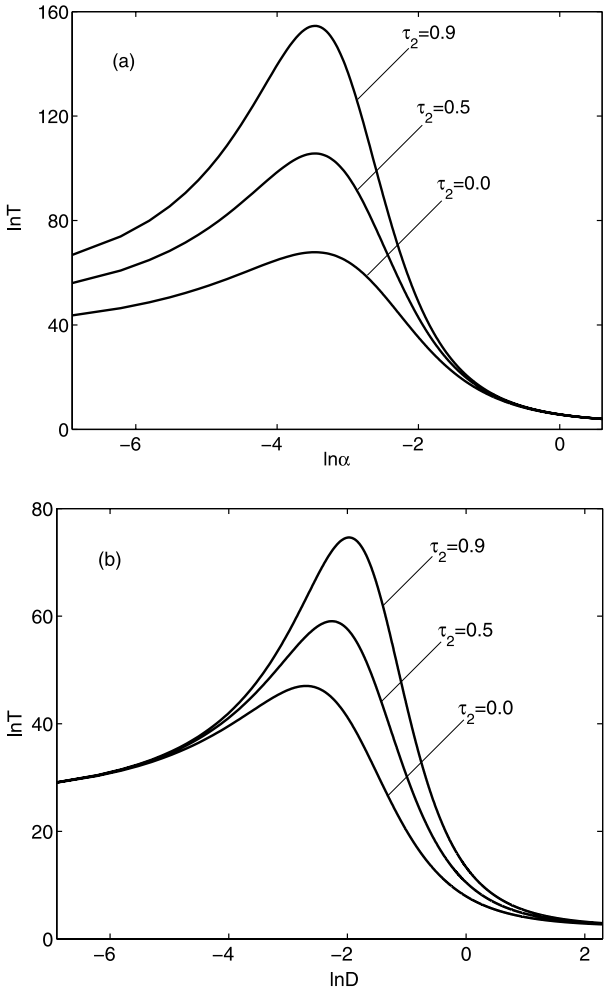

Fig. 5 The MFPT as a function of α (**a**) and as a function of D (**b**) for different values of τ_2. $D = 0.1$ in (**a**) and $\alpha = 0.1$ in (**b**). The parameter values are $\theta = 0.1$, $\beta = 2.26$, $\lambda = 0.7$, $\tau_1 = 0.1$, and $\tau_3 = 0.1$

$\lambda = 0.0$ in Figs. 1(a) and (b)]. Therefore, the increase in α or D leads to a decline of the MFPT and enhances the probability of the extinction of the cancer. However for the cases of $\lambda > 0$ [see $\lambda = 0.5$, and $\lambda = 0.7$ in Figs. 1(a) and (b)], the MFPT exhibits a maximum as α or D increases, which indicates a long-lived tumor population and the existence of an appropriate noise intensity α or D leading to a maximal MFPT. This maximum for MFPT as a function of the noise intensity identifies the noise enhanced stability of the cancer state. Simultaneously, the increase in λ leads to a increase in the MFPT [see Figs. 1(a) and (b)], i.e., the cross-correlation between two noises can enhance stability of the cancer state.

The MFPT as a function of the noise intensity α and as a function of the noise intensity D for different cross-correlation time τ_3 of noises are shown in Figs. 2 and 3, respectively. The MFPT exhibits a maximum for the case of $\lambda > 0$ [see Figs. 2(a) and 3(a)], and decreases monotonously for the case of $\lambda < 0$ [see Figs. 2(b) and 3(b)] as α or D increases. It is seen

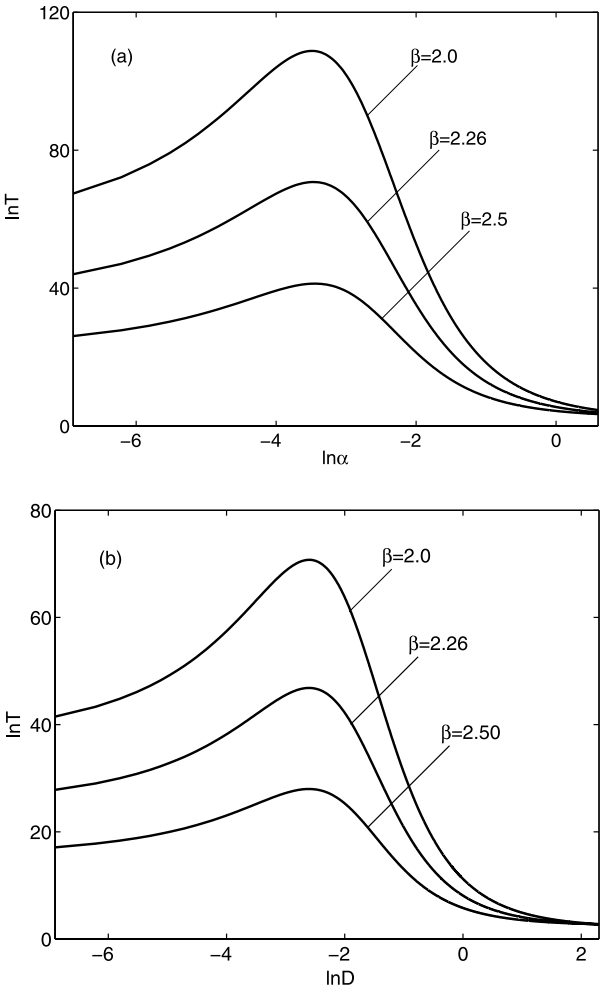

Fig. 6 The MFPT as a function of α (**a**) and as a function of D (**b**) for different values of β. $D = 0.1$ in (**a**) and $\alpha = 0.1$ in (**b**). The parameter values are $\theta = 0.1$, $\lambda = 0.7$, $\tau_1 = 0.1$, $\tau_2 = 0.1$, and $\tau_3 = 0.1$

from figures that the MFPT decreases as τ_3 increases for the case of $\lambda > 0$, but for the case of $\lambda < 0$, the MFPT increases as τ_3 increases. Thus, the effect of the cross-correlation time τ_3 on the MFPT is entirely opposite for $\lambda > 0$ and $\lambda < 0$, i.e., the increase in τ_3 causes an increase in the probability of the transition to the state of extinction for $\lambda > 0$, however for $\lambda < 0$, the increase in τ_3 is related to a slowing down of the transition to the state of extinction.

In Figs. 4, 5 and 6, we discuss the effects of the self-correlation times τ_1 and τ_2, and the immune rate β on the MFPT. The MFPT as a function of α or D exhibits a maximum, showing a long-lived tumor population. We can see from figures that the maximum in the MFPT increases as the self-correlation time τ_1 or τ_2 increases [see Figs. 4(a)–5b)], and decreases as the immune rate β increases [see Figs. 6(a) and (b)]. In other words, the self-

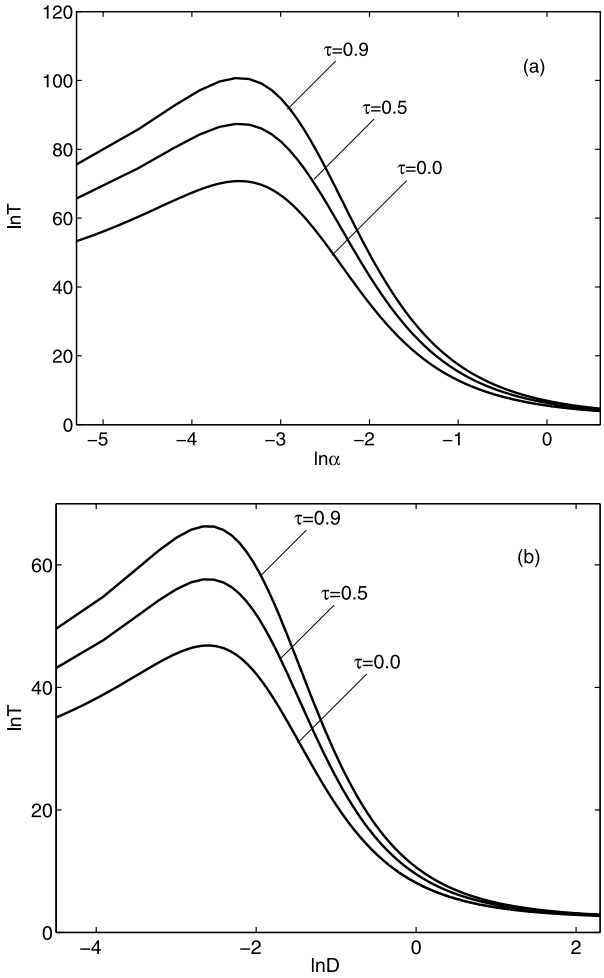

Fig. 7 The MFPT as a function of α (**a**) and as a function of D (**b**) for different values of τ. $D = 0.1$ in (**a**) and $\alpha = 0.1$ in (**b**). The parameter values are $\theta = 0.1$, $\beta = 2.26$, and $\lambda = 0.7$

correlation times τ_1 and τ_2 of colored noises enhance stability of the cancer state, while the immune rate β reduces it.

When the self-correlation times and the cross-correlation time satisfying $\tau_1 = \tau_2 = \tau_3 = \tau$, the MFPT as a function of α or D exhibits a maximum, which is shown in Figs. 7(a) and (b). It is seen that the MFPT increases as τ increases, which shows that the τ can enhance stability of the cancer state.

2.3 Numerical Simulation of the MFPT

To check the credibility of the approximate method in a tumor cell growth system under immune response, the numerical simulations of the MFPT are performed by integrating the dynamical equations of (1)–(4). The correlation between two noise terms can be separated. The Box-Mueller algorithm and a pseudo-random number generator are used to generate

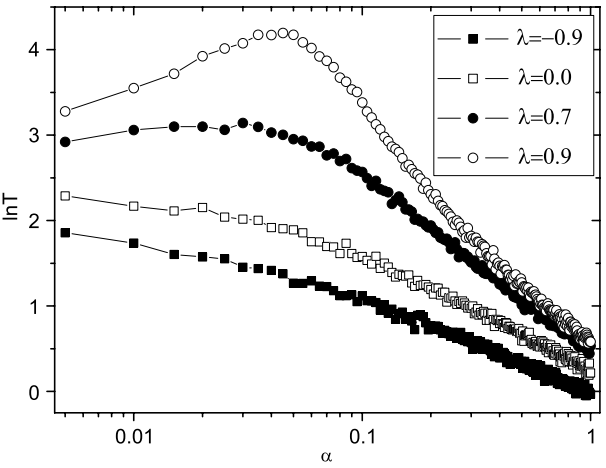

Fig. 8 The numerical simulations of the MFPT as a function of α for different values of λ. The parameter values are $\theta = 0.1$, $\beta = 2.26$, $D = 0.1$, $\tau_1 = 0.1$, $\tau_2 = 0.1$, and $\tau_3 = 0.1$

Gaussian noise. Using Euler procedure, the time-discrete numerical data are calculated with the integration step of $\Delta t = 0.01$. The data obtained are saved over 1000 different trajectories and each single trajectory evolves over 10^6 periods. Then the effects of the cross-correlation intensity and time, and the self-correlation times and intensities on the MFPT for the numerical simulations can be shown in Figs. 8, 9, 10 and 11. In these figures we present the MFPT as a function of the noise intensity α for different values of the cross-correlation intensity λ and time τ_3, and the self-correlation times τ_1 and τ_2, respectively. The behavior of MFPT versus D is similar to that of MFPT versus α. For brevity, the curves of MFPT versus D are not plotted in this paper. From Fig. 8, it is seen that the MFPT is monotonically decreased for the cases of $\lambda \leqslant 0$ [see $\lambda = -0.9$, and $\lambda = 0.0$ in Fig. 8], however for the cases of $\lambda > 0$ [see $\lambda = 0.7$, and $\lambda = 0.9$ in Fig. 8], the MFPT exhibits a maximum as α increases. For fixed α value [see Fig. 8], the MFPT is increased as λ increases. From Fig. 9, it is seen that the MFPT exhibits a maximum for the case of $\lambda > 0$ [see Fig. 9(a)], and decreases monotonously for the case of $\lambda < 0$ [see Fig. 9(b)] as α increases. For fixed α value, the MFPT decreases for the case of $\lambda > 0$ [see Fig. 9(a)] and increases for the case of $\lambda < 0$ [see Fig. 9(b)] as τ_3 increases, respectively. In Figs. 10 and 11, we can see that the MFPT as a function of α exhibits a maximum, the maximum in the MFPT increases as the self-correlation time τ_1 or τ_2 increases [see Figs. 10 and 11]. It is clear that the approximate theoretical results in the MFPT are consistent with the numerical simulations, which implies that the approximate method in a tumor cell growth system under immune response is credible.

3 Results and Discussions

In this paper, we have investigated the transient properties in a tumor cell growth system under immune response, which is driven by cross-correlation between multiplicative and additive colored noises as well as the nonzero cross-correlation in between. It is shown that the approximate theoretical results on the effects of the noise parameters (i.e., λ, τ_3, D and α, τ_1 and τ_2) on the MFPT are consistent with the numerical simulations. Research results show that the MFPT decreases for the cases of $\lambda \leqslant 0$, and exhibits a maximum for the cases of $\lambda > 0$ as α or D increases. For fixed α or D value, the MFPT increases as λ, τ_1 and τ_2

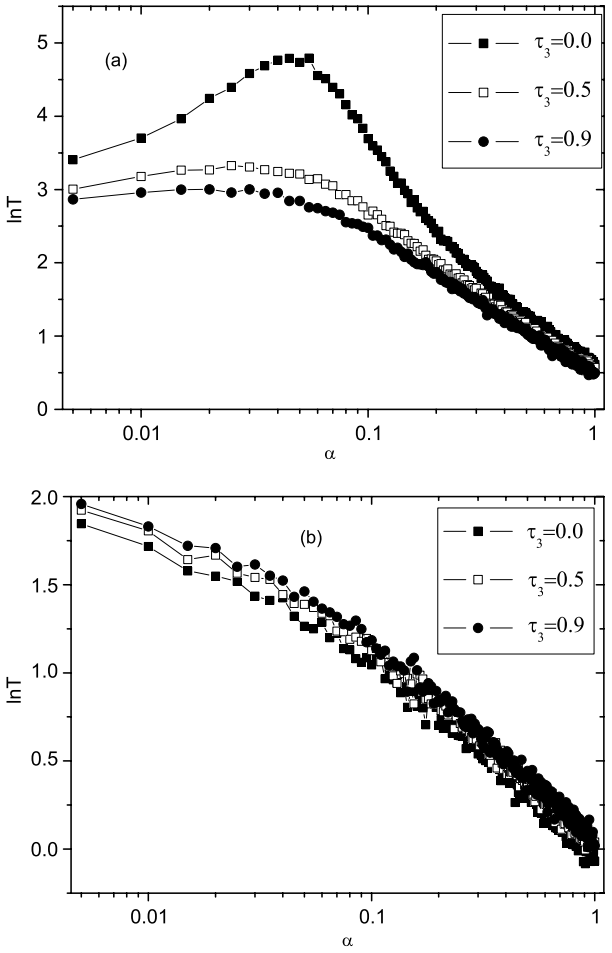

Fig. 9 The numerical simulations of the MFPT as a function of α for different values of τ_3. The parameter values are $\theta = 0.1$, $\beta = 2.26$, $D = 0.1$, $\tau_1 = 0.1$, and $\tau_2 = 0.1$. (**a**) $\lambda = 0.9$; (**b**) $\lambda = -0.9$

increase, respectively. The effect of the cross-correlation time τ_3 on the MFPT is entirely opposite for $\lambda > 0$ and $\lambda < 0$.

The mechanism of the above mentioned phenomenon can be physically understood as follows, the MFPT of transition from the state of a stable tumor to the state of its extinction mainly depends on the height of barrier for the transition in the generalized potential associated with force [35], as given by the integrand in (26)

$$\frac{x(1-\theta x)-\beta\frac{x}{x+1}}{\frac{1}{1-\tau_1 C_1}(\frac{x}{x+1})^2-\lambda\sqrt{\alpha/D}[\frac{1}{1-\tau_3 C_1}+\frac{1}{1-\tau_3 C_2}]\frac{x}{x+1}+\frac{\alpha/D}{1-\tau_2 C_2}}. \tag{34}$$

This is, the larger the generalized force is, the higher the height of barrier for the transition is. Hence the increase of the generalized force causes a slowing down of transition from the state of a stable tumor to the state of its extinction, namely, the increase of the generalized force enhances stability of the cancer state, and vice versa. From (34), whether λ is

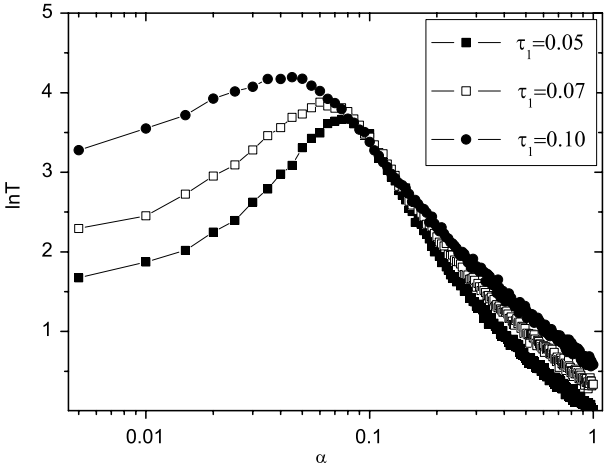

Fig. 10 The numerical simulations of the MFPT as a function of α for different values of τ_1. The parameter values are $\theta = 0.1$, $\beta = 2.26$, $D = 0.1$, $\tau_2 = 0.1$, $\lambda = 0.9$ and $\tau_3 = 0.1$

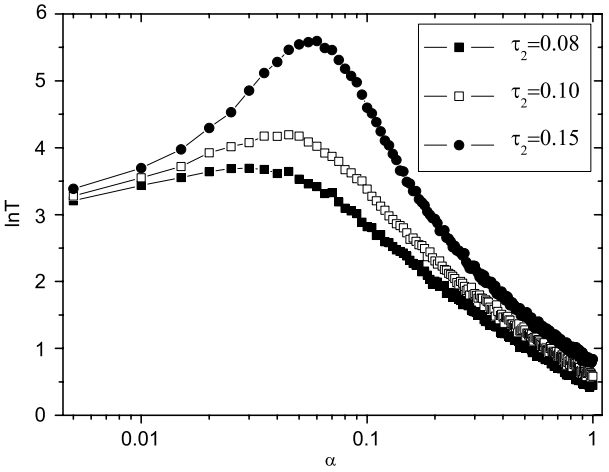

Fig. 11 The numerical simulations of the MFPT as a function of α for different values of τ_2. The parameter values are $\theta = 0.1$, $\beta = 2.26$, $D = 0.1$, $\tau_1 = 0.1$, $\lambda = 0.9$ and $\tau_3 = 0.1$

negative or positive, the generalized force can be smaller or larger than for the case when $\lambda = 0$, respectively. In other words, when the noises are negatively cross-correlated, then the transition is faster than in the case with no correlation; when the noises are positively cross-correlated, then the transition is slower than in the case with no correlation. When other parameters are fixed, with the increases of τ_1 and τ_1 the generalized force becomes larger, and smaller with β [see (34)]. Accordingly, τ_1 and τ_2 enhance stability of the cancer state, while the immune rate β reduces it. With the increase of τ_3 the generalized force becomes smaller for $\lambda > 0$ and larger for $\lambda < 0$ [see (34)]. Namely, τ_3 leads to an increase in the probability of the transition to the state of extinction for $\lambda > 0$ and a slowing down of the transition to the state of extinction for $\lambda < 0$. In consideration of the denominator of the expression (34)

$$\frac{1}{1-\tau_1 C_1}\left(\frac{x}{x+1}\right)^2 - \lambda\sqrt{\alpha/D}\left[\frac{1}{1-\tau_3 C_1} + \frac{1}{1-\tau_3 C_2}\right]\frac{x}{x+1} + \frac{\alpha/D}{1-\tau_2 C_2},$$

has a minimum at $x_c = \frac{\lambda\sqrt{\alpha/D}\Theta}{1-\lambda\sqrt{\alpha/D}\Theta} > 0$ under $1 - \lambda\sqrt{\alpha/D}\Theta > 0$ for $\lambda > 0$, where $\Theta = \frac{1-\tau_1 C_1}{1-\tau_3 C_1} + \frac{1-\tau_1 C_1}{1-\tau_3 C_2}$ [i.e., $1 - \tau_j C_i > 0$, $j = 1, 2, 3$ and $i = 1, 2$]. Thus, it is obvious that the generalized force exhibits one maximum value in the case of positive cross-correlation and consequently the MFPT has a maximum for a certain intensity of one of the noises, i.e., the maximum for MFPT as a function of the noise intensity is the noise enhanced stability of the cancer state. However, for the cases of $\lambda \leqslant 0$, $x_c = \frac{\lambda\sqrt{\alpha/D}\Theta}{1-\lambda\sqrt{\alpha/D}\Theta} \leqslant 0$ under $1 - \lambda\sqrt{\alpha/D}\Theta > 0$, since the concentration of the tumor cells x cannot be negative, the denominator of the expression (34) monotonously increases, and the generalized force decreases. Hence the increase of the noise intensities [α or D] cause a decrease of the MFPT and enhances the probability of the extinction of the cancer for $\lambda \leqslant 0$.

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