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# The stationary properties and the state transition of the tumor cell growth mode

D.C. Mei[1,2,a], C.W. Xie[1], and L. Zhang[1]

[1] Department of Physics, Yunnan University, Kunming 650091, P.R. China
[2] Yunnan Police Officer Academy, Kunming 650223, P.R. China

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**Abstract.** We study the stationary properties and the state transition of the tumor cell growth model (the logistic model) in presence of correlated noises for the case of nonzero correlation time. We derived an approximative Fokker-Planck equation and the stationary probability distribution (SPD) of the model. Based the SPD, we investigated the effects of both correlation strength ($\lambda$) and correlation time ($\tau$) of cross-correlated noises on the SPD, the mean of the tumor cell population and the normalized variance ($\lambda_2$) of the system, and calculated the state transition rate of the system between two stable states. Our results indicate that: (i) $\lambda$ and $\tau$ play opposite roles in the stationary properties and the state transition of the system, i.e. increase of $\lambda$ can produce a smaller mean value of the cell population and slow down the state transition, but increase of $\tau$ can produce a larger mean value of the cell population and enhance state transition; (ii) For large $\lambda$, there a peak structure on both $\lambda_2$-$\lambda$ plot and $\lambda_2$-$\tau$ plot. For the small $\lambda$, $\lambda_2$ increases with increasing $\lambda$, but $\lambda_2$ increases with decreasing $\tau$.

**PACS.** 87.10.+e General theory and mathematical aspects – 05.40.-a Fluctuation phenomena, random processes, noise, and Brownian motion – 02.50.Ey Stochastic processes

## 1 Introduction

Since Fulinski and Telejko pointed out that noises in some stochastic processes may have a common origin and thus can be cross-correlated [1], the cross-correlated noise processes have been studied widely in the single mode laser system [2,3], the bistable system [4–11] and the biology system [12–15]. The effects of correlations between additive and multiplicative noises, either on a stationary state or on dynamics of the system, have been extensively studied. Recently, Ai et al. studied the steady-state properties of a tumor cell growth model in the presence of cross-correlated additive and multiplicative noises for the case of zero cross-correlated time between noises [12].

The logistic growth model,

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

has been used as a basic model of the cell growth, such as tumor cell growth [16,17]. Here $x$ is the tumor mass (or denotes tumor cell population), $a$ the cell growth rate and $b$ the cell decay rate. The cell growth rate $a$ and the decay rate $b$ are always not constants, which are strongly influenced by the fluctuations of some external factors, such as temperature, drugs, radiotherapy and so on. Considering the stochastic properties of fluctuations of these external factors, physically it is reasonable and simple that the effects of these external factors are modelled by both multiplicative and additive noises. For instance, Ai et al. consider that the fluctuation of some external factors affect the growth rate $a$ generating multiplicative noise, and some factors such as drugs and radiotherapy restrain the number of tumor cells, giving rise to a negative additive noise, and obtained [12],

$$\frac{dx}{dt} = ax - bx^2 + x\epsilon(t) - \Gamma(t), \tag{2}$$

where $\epsilon(t)$ and $\Gamma(t)$ are Gaussian white noises with zero mean, and

$$\langle\epsilon(t)\epsilon(t')\rangle = 2D\delta(t-t'), \tag{3}$$

$$\langle\Gamma(t)\Gamma(t')\rangle = 2\alpha\delta(t-t'). \tag{4}$$

$$\langle\epsilon(t)\Gamma(t')\rangle = 2\lambda\sqrt{D\alpha}\,\delta(t-t'), \tag{5}$$

where $\alpha$ and $D$ are the additive and multiplicative noise intensities, respectively. $\lambda$ denotes the degree of correlation between $\epsilon(t)$ and $\Gamma(t)$ with $0 \le \lambda < 1$. Apparently, equation (5) only describes the case of the zero correlation time between additive and multiplicative noises.

Physically, the correlation time of a real noise, though small it may be, is never strictly equal to zero. For a

[a] e-mail: meidch@ynu.edu.cn

noise with zero correlation time, its power spectral distribution, which is given by the Fourier transform of its correlation function, is independent on frequency. Thus 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. On the other hand, 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 [18]. In this paper, we study the stationary properties and transient properties of the tumor cell growth model in the presence of correlated additive and multiplicative noises for the case of nonzero correlated time between additive and multiplicative noises.

## 2 The stationary properties and the transition rate of the system

In order to investigate stationary properties and calculate the state transition rate of the system, we need the stationary probability distribution (SPD) of the system. We derive the approximative Fokker-Planck equation (AFPE) of the general system, then apply it to the tumor cell growth model to get SPD.

### 2.1 The approximative Fokker-Planck equation and the stationary probability distribution of the system

The Langevin equation of the general system subject to correlated noises reads

$$\frac{dx}{dt} = f(x) + g_1(x)\epsilon(t) + g_2(x)\eta(t), \tag{6}$$

here $\epsilon(t)$ and $\eta(t)$ are zero-mean Gaussian noise, whose statistical properties are

$$\gamma_{11} = \langle \epsilon(t)\epsilon(t')\rangle = 2\alpha\delta(t-t'), \tag{7}$$

$$\gamma_{22} = \langle \eta(t)\eta(t')\rangle = 2D\delta(t-t'), \tag{8}$$

and

$$\begin{aligned}\gamma_{12} = \gamma_{21} &= \langle \epsilon(t)\eta(t')\rangle = \langle \eta(t)\epsilon(t')\rangle \\ &= \frac{\lambda\sqrt{\alpha D}}{\tau}\exp[-|t-t'|/\tau] \rightarrow 2\lambda\sqrt{\alpha D}\delta(t-t') \text{ as } \tau \rightarrow 0,\end{aligned} \tag{9}$$

where $\alpha$ and $D$ are the additive and multiplicative noise intensities, respectively. $\tau$ is correlation time of correlation between additive and multiplicative noises. The parameter $\lambda$ denotes the degree of correlation between $\epsilon(t)$ and $\eta(t)$.

A general equation satisfied by the probability distribution of the process with equations (6–9) is given by [19]

$$\begin{aligned}\frac{\partial}{\partial t}P(x,t) = -\frac{\partial}{\partial x}f(x)P(x,t) - \frac{\partial}{\partial x}g_1(x)\langle \epsilon(t)\delta(x(t)-x)\rangle \\ - \frac{\partial}{\partial x}g_2(x)\langle \eta(t)\delta(x(t)-x)\rangle,\end{aligned} \tag{10}$$

where $P(x,t) = \langle \delta(x(t)-x)\rangle$ is Van Kampen's lemma. The average $\langle \epsilon(t)\delta(x(t)-x)\rangle$ and $\langle \eta(t)\delta(x(t)-x)\rangle$ in equation (10) can be calculated by the Novikov theorem [20]

$$\langle \epsilon(t)_k \phi[\epsilon_1,\epsilon_2]\rangle = \int_0^t dt' \gamma_{k,l}\langle \frac{\delta(\phi[\epsilon_1,\epsilon_2])}{\delta\epsilon_l}\rangle, \quad (k,l=1,2), \tag{11}$$

where $\phi[\epsilon_1,\epsilon_2]$ is the functional of $\epsilon_1$ and $\epsilon_2$, here $\epsilon_1$ and $\epsilon_2$ are Gaussian noises and $\gamma_{k,l}$ are their correlation functions. The AFPE for equation (6) is obtained following [7]

$$\begin{aligned}\frac{\partial}{\partial t}P(x,t) = -\frac{\partial}{\partial x}f(x)P(x,t) + D\frac{\partial}{\partial x}g_1(x)\frac{\partial}{\partial x}g_1(x)P(x,t) \\ + \frac{\lambda\sqrt{D\alpha}}{1-\tau[f'(x_s)-(g_2'(x_s)/g_2(x_s))f(x_s)]} \\ \times \frac{\partial}{\partial x}g_1(x)\frac{\partial}{\partial x}g_2(x)P(x,t) + \alpha\frac{\partial}{\partial x}g_2(x)\frac{\partial}{\partial x}g_2(x)P(x,t) \\ + \frac{\lambda\sqrt{D\alpha}}{1-\tau[f'(x_s)-(g_1'(x_s)/g_1(x_s))f(x_s)]} \\ \times \frac{\partial}{\partial x}g_2(x)\frac{\partial}{\partial x}g_1(x)P(x,t).\end{aligned} \tag{12}$$

The AFPE is valid for the following conditions:

$$\begin{aligned}1-\tau\left[f'(x_s) - \frac{g_1'(x_s)}{g_1(x_s)}f(x_s)\right] > 0, \\ 1-\tau\left[f'(x_s) - \frac{g_2'(x_s)}{g_2(x_s)}f(x_s)\right] > 0,\end{aligned} \tag{13}$$

where $x_s$ denotes the steady-state value of the deterministic theory. Equation (13) provide the constraint on $\tau$. There are the details of derivation of equations (12–13) and about what the approximation is in reference [7].

We now consider the logistic model driven by cross-correlated noises for the case of nonzero correlation time, i.e., Langevin equation (2) with equations (7–9). This is a special case of equation (6) with

$$f(x) = ax - bx^2, \;\; g_1(x) = x, \;\; g_2(x) = 1 \text{ and } \eta(t) = -\Gamma(t). \tag{14}$$

We must point out that equation (6) in reference [12] is only a special case of equation (9) as $\tau \longrightarrow 0$. The potential

$$V(x) = -\frac{a}{2}x^2 + \frac{b}{3}x^3, \tag{15}$$

corresponding to equation (2) has two stable state $x_1 = a/b$, $x_2 = 0$. If $a \longrightarrow 0$, the stable state $x_1 \longrightarrow x_2$. We take steady-state value $x_s = a/b$. Therefore the AFPE of the system (2) is obtained by substituting (14) into (12)

$$\frac{\partial P(x,t)}{\partial t} = -\frac{\partial}{\partial x}A(x)P(x,t) + \frac{\partial^2}{\partial x^2}B(x)P(x,t), \quad (16)$$

where

$$A(x) = ax - bx^2 + Dx - \frac{\lambda\sqrt{\alpha D}}{1+a\tau}, \quad (17)$$

and

$$B(x) = Dx^2 - \frac{2\lambda\sqrt{\alpha D}}{1+a\tau}x + \alpha. \quad (18)$$

Note that this AFPE holds under the condition $1+a\tau > 0$ for all the $\tau$. Thus there is no restriction on $\tau$ so that there is not any restriction on all the parameters treated in this case. The stationary probability distribution of system can be obtained from equation (16) with equations (17) and (18)

$$P(x)_{\mathrm{st}} = NB(x)^{\beta_1 - \frac{1}{2}} \exp[-U(x)/D] \quad \textit{for} \quad 0 \le \lambda < 1, \quad (19)$$

where

$$\beta_1 = \frac{a}{2D} - \frac{\lambda b}{(1+a\tau)D}\sqrt{\frac{\alpha}{D}}, \quad (20)$$

and the generalized potential

$$U(x) = bx - \frac{\beta_2(1+a\tau)}{\sqrt{D\alpha[(1+a\tau)^2 - \lambda^2]}} \times \arctan\left\{\frac{(1+a\tau)Dx - \lambda\sqrt{D\alpha}}{\sqrt{D\alpha[(1+a\tau)^2-\lambda^2]}}\right\}, \quad (21)$$

here

$$\beta_2 = b\alpha - \left(aD + \frac{2\lambda}{1+a\tau}\sqrt{\alpha D}\right)\frac{\lambda}{1+a\tau}\sqrt{\frac{\alpha}{D}}. \quad (22)$$

$N$ in equation (19) is the normalization constant. It must be pointed out that the correlation time $\tau$ must be zero when the strength of the correlation between noises $\lambda$ is zero, however, the equation (19) is valid when $\tau = 0$. Above results fall back to equations (11–13) presented in reference [12] by taking $\tau = 0$.

## 2.2 The stationary properties of the system

By numerical calculation of equation (19), we analyze the effects of both the correlation strength $\lambda$ and the correlation time $\tau$ on the SPD. In Figures 1a and 1b, we show SPD as function of $\lambda$ and $\tau$, respectively. For fixed value of the $\tau$ and increasing $\lambda$, $P(x)_{\mathrm{st}}$ increases at small $x$, and decreases at large $x$ along with this peak disappearing. For fixed value of the $\lambda$ and decreasing $\tau$, $P(x)_{\mathrm{st}}$ increases at small $x$ and decreases at large $x$ along with this peak disappearing. Since $x$ denotes the cell population, it is obvious that the cell population decreases with the increasing of $\lambda$ and increases with the increasing of $\tau$. We must

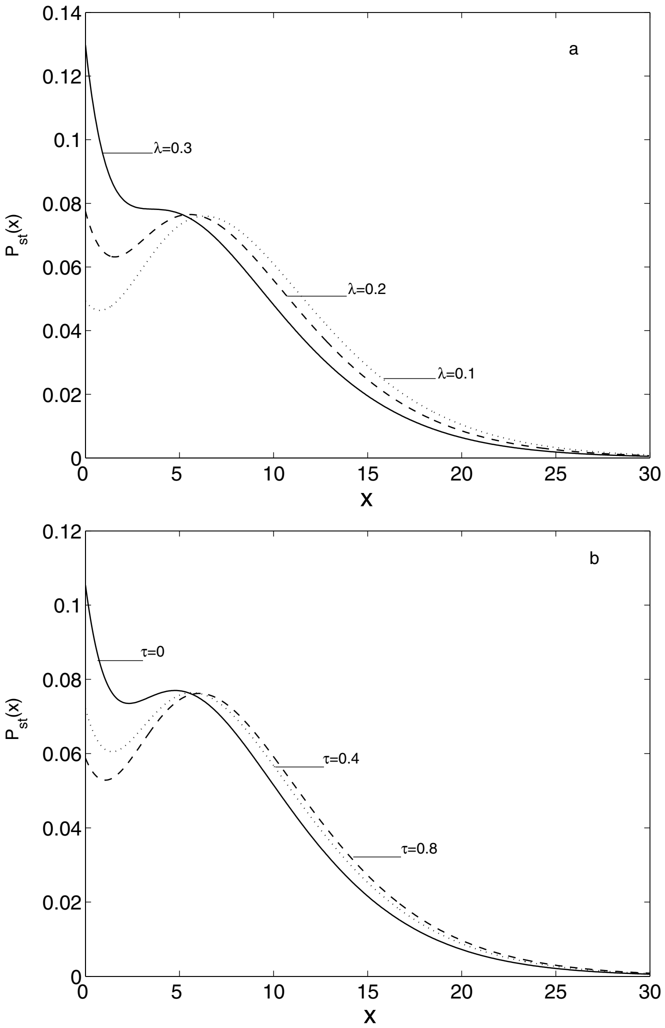


**Fig. 1.** (a) Plot of stationary probability distribution $P(x)_{\mathrm{st}}$ vs. cell number $x$ for different values of $\lambda$ with $\tau = 0.3$, $D = 0.3$, $\alpha = 3.0$, $a = 1$ and $b = 0.1$. (b) Plot of stationary probability distribution $P(x)_{\mathrm{st}}$ vs. cell number $x$ for different values of $\tau$ with $\lambda = 0.2$, $D = 0.3$, $\alpha = 3.0$, $a = 1$ and $b = 0.1$.

point that above analysis only a qualitative discussion of stationary properties of the system.

In order to quantitatively investigate the stationary properties of the system, We introduce the moments of the variable $x$, and it given by

$$\langle x^n \rangle_{\mathrm{st}} = \int_0^{+\infty} x^n P(x)_{\mathrm{st}} dx. \quad (23)$$

The mean of the state variable is

$$\langle x \rangle_{\mathrm{st}} = \int_0^{+\infty} x P(x)_{\mathrm{st}} dx, \quad (24)$$

and the normalized variance of the state variable is

$$\lambda_2 = \frac{\langle (x - \langle x \rangle_{\mathrm{st}})^2 \rangle}{\langle x \rangle_{\mathrm{st}}^2} = \frac{\langle x^2 \rangle_{\mathrm{st}}}{\langle x \rangle_{\mathrm{st}}^2} - 1. \quad (25)$$

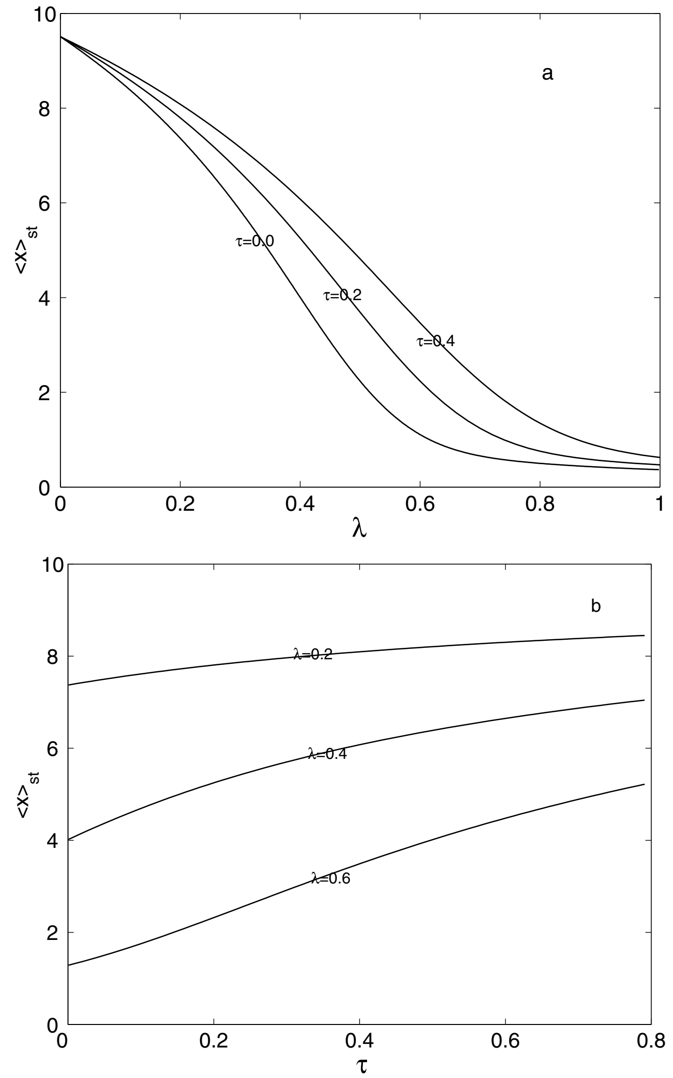


**Fig. 2.** (a) Plot of the stationary mean value $\langle x\rangle_{st}$ of cell number as a function of $\lambda$ for different values of $\tau$ with $D = 0.3$, $\alpha = 3.0$, $a = 1$ and $b = 0.1$. (b) Plot of the stationary mean value $\langle x\rangle_{st}$ of cell number as a function of $\tau$ for different values of $\lambda$ with $D = 0.3$, $\alpha = 3.0$, $a = 1$ and $b = 0.1$.

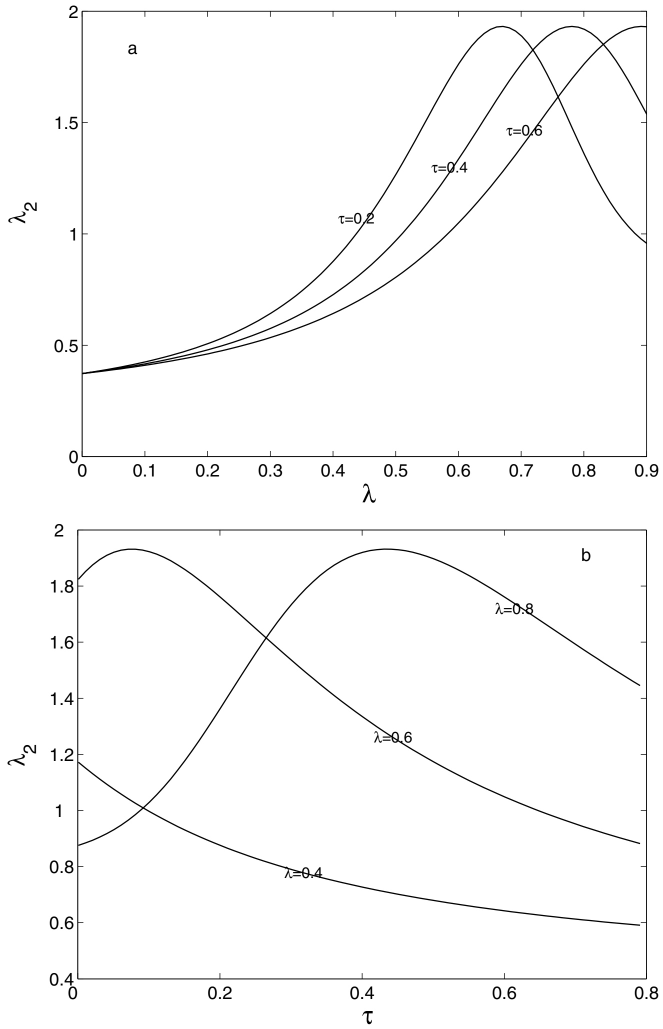


**Fig. 3.** (a) Plot of the normalized variance $\lambda_2$ of cell number as a function of $\lambda$ for different values of $\tau$ with $D = 0.3$, $\alpha = 3.0$, $a = 1$ and $b = 0.1$. (b) Plot of the normalized variance $\lambda_2$ of cell number as a function of $\tau$ for different values of $\lambda$ with $D = 0.3$, $\alpha = 3.0$, $a = 1$ and $b = 0.1$.

Making use of the expressions of equations (24) and (25), the effects of both $\lambda$ and $\tau$ on $\langle x\rangle_{st}$ and $\lambda_2$ can be analysed by the numerical calculation. The results of the numerical calculation of $\langle x\rangle_{st}$ and $\lambda_2$ as a function of $\lambda$ and $\tau$ are plotted on Figures 2 and 3.

Figures 2a and 2b show that the larger $\lambda$ is, the smaller $\langle x\rangle_{st}$ is. The larger $\tau$ is, the larger $\langle x\rangle_{st}$ is. This indicates that the effects of both $\lambda$ and $\tau$ on the cell population are different. $\lambda$ and $\tau$ play opposite roles on the cell population. Also we see that the stationary mean value of the cell population decreases with the increase of $\lambda$ and that increases with the increase of $\tau$. We must point that we have run many numerical integrations with many different parameters, and that our final result ($x$ decreases with $\lambda$ and increases with $\tau$) is always true.

As can be seen clearly from Figures 3a and 3b, the curves of normalized variance $\lambda_2$ exhibit a peak structure and the peak position shifts to larger values of $\lambda$ as increase $\tau$. For smaller $\lambda$, $\lambda_2$ increases with the increase of $\lambda$ and increases with the decrease of $\tau$. For larger $\lambda$, $\lambda_2$ decreases with increasing $\lambda$ and that decreases with decreasing $\tau$. The effects of both $\lambda$ and $\tau$ on the normalized variance $\lambda_2$ for the $\lambda$ and for the $\tau$ are also opposite.

## 2.3 The state transition rate of the system

Our prime concern here is the transient properties of the system, i.e., the system from a stable state $x_1$, the larger cell population state, transits to another stable state $x_2$, zero cell population state.

First, we consider the mean-first-passage time (MFPT) of the system from $x_1$ transiting to $x_2$. The exact expression for the MFPT of the system to reach the final point $x_2$ from the initial point $x_1$ is given by [21,22]

$$T(x_1 \to x_2) = \int_{x_1}^{x_2} \frac{dx}{B(x)P(x)_{st}} \int_{-\infty}^{x} P(y)_{\mathrm{st}} dy. \quad (26)$$

We choose $x_1 = a/b$ as the initial point, and $x_2 = 0$ as the final point. For the case of small $\alpha$ and $D$, making use of the steepest-descent approximation to equation (26), we obtain the explicit expression of MFPT [23,24]

$$\begin{aligned} T(a/b \to 0) &\simeq 2\pi [\, | V''(a/b)V''(0) | \,]^{\frac{1}{2}} \\ &\quad \times \exp\{[U(0) - U(a/b)]/D\} \\ &= 2\pi a \exp\left\{ \frac{(1+a\tau)\beta_2}{D\sqrt{D\alpha[(1+a\tau)^2 - \lambda^2]}} \right. \\ &\quad \times \left\{ \arctan\left\{ \frac{(1+a\tau)a - \lambda\sqrt{\alpha D}}{b\sqrt{D\alpha[(1+a\tau)^2-\lambda^2]}} \right\} \right. \\ &\quad \left.\left. + \arctan \frac{\lambda\sqrt{\alpha D}}{\sqrt{D\alpha[(1+a\tau)^2-\lambda^2]}} \right\} - \frac{a}{D} \right\}. \end{aligned} \quad (27)$$

Then, we get the state transition rate of $x_1$ to $x_2$ [18]

$$\kappa = \frac{1}{T(a/b \to 0)}. \quad (28)$$

According to the expression [Eq. (28)] of the transition rate of $x_1$ to $x_2$ of the system, the effects of both $\lambda$ and $\tau$ on $\kappa$ can be studied by the numerical computation. $\kappa$ as function of $\lambda$ and $\kappa$ as function of $\tau$ are plotted on Figures 4a and 4b, respectively. From Figures 4a and 4b, we can clearly see that $\kappa$ decreases as $\lambda$ increases, however $\kappa$ increases as $\tau$ increases. The effects of the $\lambda$ on $\kappa$ are slowdown the system transition and these of $\tau$ are speedup the system transition.

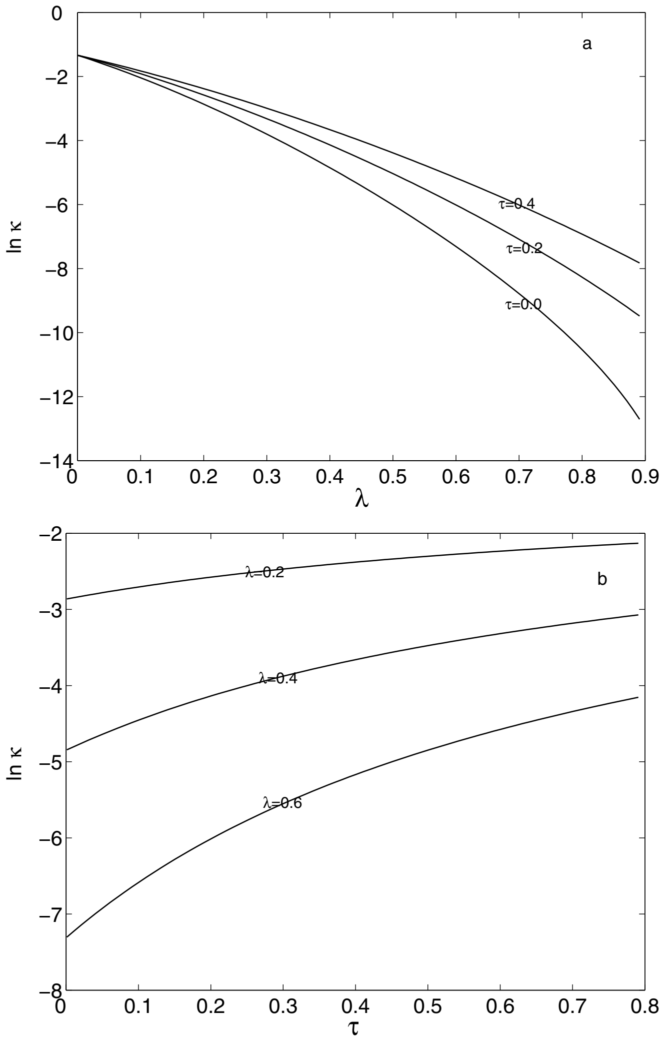


**Fig. 4.** (a) Plot of the state transition rate of system as a function of $\lambda$ for different values of $\tau$ with $D = 0.3$, $\alpha = 0.2$, $a = 1$ and $b = 0.1$. (b) Plot of the state transition rate of system as a function of $\tau$ for different values of $\lambda$ with $D = 0.3$, $\alpha = 0.2$, $a = 1$ and $b = 0.1$.

## 3 Discussion and conclusion

Based on considering the fluctuation of some external factors, such as temperature, drugs, radiotherapy, etc, random factors are introduced into the cell growth model, which can influence the cell population and alter the cell growth rate. These stochastic characteristic are described by a multiplicative noise and a additive noise. The multiplicative noise and the additive noise may be correlated due to a common origin. If more fluctuations come of common origin, the correlation strength $\lambda$ will take larger values. For the real physical process the correlated time $\tau$ between the multiplicative noise and the additive noise is not zero. If fluctuations are more lager so that the time scale for the relaxation of the driven process is more longer, a nonzero correlated time must be considered.

In this paper, we have studied the effects of both the $\lambda$ and the $\tau$ on the stationary properties and state transition rate of the tumor cell growth model driven by the cross-correlated noises for the case of nonzero correlation time. We derived an approximative Fokker-Planck equation and the stationary probability distribution of the system. Making use of the SPD, we investigated effects of both $\lambda$ and $\tau$ on the mean of the tumor cell population $\langle x \rangle_{\mathrm{st}}$, the normalized variance $\lambda_2$, and the state transition rate of the system.

The effects of the $\lambda$ can produce smaller mean value of the cell population, however, the effects of the $\tau$ produce larger mean value of the cell population. The $\lambda$ is slowdown the system transition, but,the $\tau$ is speedup the system transition.

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