The critical phenomenon and the re-entrance phenomenon in the anti-tumor model induced by the time delay

Lu-Chun Du, Dong-Cheng Mei *

Department of Physics, Yunnan University, Kunming, 650091, China

1. Introduction

It has been realized that time delays are ubiquitous in nature, and delay-induced nonequilibrium phenomena in nonlinear stochastic systems have received a great deal of attention [1–11]. The appearance of the time delay mainly due to finite transmission time related to transport of matter, energy, and information through the system. On the level of a Langevin-type description of a stochastic system, the presence of time delay changes the dynamics of the system, and brings a series of significant and interesting results, such as time delay induced traveling wave solutions [1], coherence resonance [2,3], stochastic resonance [4–6], multistability [7], desynchronization [8], excitability [9], periodically oscillate synchronously [10], and critical phenomenon [11].

Recently, a theoretical study pointed out that a particular anti-tumor model can undergo a stochastic resonance [12] and a nonequilibrium phase transition [13]. The theoretical anti-tumor model based on the logistic model, incorporates the immune response of healthy cells, a modification of the effective proliferation rate in terms of a periodic signal (due to the chemotherapeutic treatment) and a Gaussian white noise [12]. The authors of Ref. [12] restricted their model to chemotherapies that only suppress proliferation rate. However, the effects of time delay are not included in the system. For the population dynamics, there should be a reaction time of population to environmental constraints in the process of the population evolution [14,15]. On the level of a Langevin-type description of the population growth, the reaction time is simulated by a delay time. The time delay can play a crucial role on modeling biological processes [16], especially on the cellular level, which is extremely important for tumor growth [17,18]. The tumor cells need a reaction time for adapting their surrounding environment (such as external perturbations and responses from the host’s immune system). This notion was confirmed in previous work where the experimental data for Earlich Ascieties tumor in mouse was employed [17]. Thus, the anti-tumor model with time delay deserves further investigation.

The present Letter is organized as follows. In Section 2, the anti-tumor model with time delay is presented. In Section 3, the effects of time delay on the stationary properties, the stochastic resonance of the system are discussed. In Section 4, a discussion concludes the Letter.

2. The anti-tumor model with time delay driven by a multiplicative noise

Consider a anti-tumor model driven by a multiplicative noise and a periodic signal. Its Langevin equation (in the Stratonovich prescription) reads [12,16]

\[
\begin{align*}
\frac{dx(t)}{dt} & = r x(t) \left(1 - \frac{x(t)}{K}\right) - \frac{\beta x^2(t)}{1 + x^2(t)} + x(t) \left(1 - \frac{x(t)}{K}\right) \\
& \times A_0 \cos (\Omega t) + x(t) \left(1 - \frac{x(t)}{K}\right) \xi(t),
\end{align*}
\]

(1)
where \( x \) is the population of tumor cells, \( r \) is their birth rate, \( K \) is the carrying capacity of the environment, the term \((1 - \frac{x}{K})\) denotes the saturation effects in population dynamics \([14-16]\), \( \frac{\beta x^2(t)}{1 + x^2(t)} \) is the immune term, quantifies the abilities of immune cells to identify and attack tumor cells \([16]\), \( \beta \) is the immune coefficient, \( A_0 \) and \( \Omega \) represent the drug concentration and the frequency of chemotherapy respectively, and \( \xi(t) \) is the Gaussian white noise, origins from the environmental fluctuations, defined as \( \langle \xi(t) \rangle = 0 \) and \( \langle \xi(t)\xi(s) \rangle = 2D\delta(t-s) \), in which \( D \) is the noise intensity. The model in (1) can be interpreted as derived from the deterministic regime \((A_0 = 0, D = 0)\) by substituting \( r \rightarrow r(t) = r + A_0 \cos(\Omega t) + \xi(t) [12] \).

\( r(t) \) may be view as the “effective” growth rate of tumor cells under chemotherapy and environmental fluctuations. Although the deterministic growth rate \( r \) should be nonnegative, \( r(t) \) can be negative. In general, the deterministic potential

\[
V(x) = \frac{rx^3}{3K} - \frac{rx^2}{2} + \beta x - \beta \arctan x
\]

corresponding to Eq. (1) is asymmetry, it has two steady states \( x_1 \) and \( x_2 \), which represent the active state and inactive state of the tumor cells respectively, and one unstable steady state \( x_u \) (see Fig. 1), the explicit analytic expressions of \( x_1, x_2 \) and \( x_u \) are given by

\[
x_1 = a\sqrt{m} + a^2\sqrt{n} + \frac{K}{3},
\]
\[
x_2 = a^2\sqrt{m} + a\sqrt{n} + \frac{K}{3},
\]
\[
x_u = \sqrt{m} + \frac{K}{3},
\]

where \( m = \frac{2}{3} + \sqrt{(\frac{2}{3})^2 + (\frac{2}{3})^2}; \)
\( n = -\frac{2}{3} - \sqrt{(\frac{2}{3})^2 + (\frac{2}{3})^2}; \)
\( p = \frac{2}{\tau} - \frac{2}{\sqrt{3}} + 1; \)
\( q = \frac{2}{\tau} - \frac{2}{\sqrt{3}} - \frac{2}{\sqrt{3}}; \)
\( a = -\frac{1 + \sqrt{3}}{3}; \)

in our following computation, the condition \((\frac{2}{3})^2 + (\frac{2}{3})^2 < 0 \) is ensured, so the deterministic potential of Eq. (2) always has two steady states and one unstable state. In the context of population dynamics, there should be a reaction time to population to environmental constraints \([14,15]\). Now, we consider a time delay in the anti-tumor model. According to the basic principle of the population dynamics \([14-16]\), only the saturation term \((1 - \frac{x}{K}) \) of Eq. (1) which denotes environment constraints on the proliferation rate contained the time delay. Then Eq. (1) with time delay should be rewritten as

\[
\frac{dx(t)}{dt} = rx(t)\left(1 - \frac{x(t)}{K}\right) - \frac{\beta x^2(t)}{1 + x^2(t)} + x(t)\left(1 - \frac{x(t)}{K}\right)
\times A \cos(\Omega t) + x(t)\left(1 - \frac{x(t)}{K}\right)\xi(t),
\]

where \( x(t) = x(t - \tau) \), \( \tau \) is the delay time, denotes the reaction time of tumor cell population to environmental constraints.

The delay Fokker–Plank equation corresponding to Eq. (4) is given by \([19]\]

\[
\frac{\partial P(x,t)}{\partial t} = -\frac{\partial}{\partial x} \int B(x,x_\tau)P(x,t;x_\tau,t-\tau)dx_\tau
\]
\[
+ D \int \frac{\partial^2}{\partial x^2} g^2(x)P(x,t;x_\tau,t-\tau)dx_\tau,
\]

where \( P(x,t;x_\tau,t-\tau) \) is the joint probability density, \( B(x,x_\tau) = rx(1 - \frac{x}{K}) - \frac{\beta x^2}{1 + x^2} + x(1 - \frac{x}{K})A_0 \cos(\Omega t) + Dg(x)g'(x) \), and \( g(x) = x(1 - \frac{x}{K}) \) the prime denotes the differentiation with respect to the variable \( x \).

In the presence of the periodic signal \( A_0 \cos(\Omega t) \), the potential of the system is modulated by the periodic signal. However, here we assume that the signal amplitude is small enough (i.e., \( A_0 \ll 1 \)) that, in the absence of any noise, it is insufficient to force a particle to move from one well to the other, and it can be considered that \( x_1, x_2 \) and \( x_u \) are still the stable states and unstable state of the system. On the other hand, we also assume that the variation of the periodic signal is slow enough (i.e., \( \Omega \ll 1 \) or the adiabatic limit) that there is enough time to make the system reach local equilibrium in the period of \( 1/\Omega \). Therefore, under the condition of small delay time and the first order approximation \([19]\), the quasi-steady-state probability distribution function \( P_{qst}(x) \) corresponding to Eq. (5) is obtained \([20]\)

\[
P_{qst}(x) = N \exp\left[ -\frac{U(x)}{D} \right],
\]

where \( N \) is a normalization constant, and

\[
U(x) = D \ln x^2 + (D + r) \ln \left| \frac{K - x}{x} \right|
\]
\[
+ \frac{\beta K^2}{1 + K^2} \left( \frac{1}{K - x} - \arctan x \right)
\]
\[
+ \frac{2D}{(1 + K^2)^2} \left( \ln \left| \frac{\sqrt{1 + x^2}}{K - x} \right| + K \arctan x \right)
\]
\[
+ \frac{2D}{1 + K^2} \left( \ln \left| \frac{\sqrt{1 + x^2}}{K - x} - \frac{\beta K^2}{\tau} \arctan x \right| \right)
\]
\[
+ A_0 \cos(\Omega t) \left( \ln \left| \frac{K - x}{x} \right| - \frac{\tau r}{K} \ln \left| \frac{K - x}{K} \right| \right).
\]

3. The effects of time delay on the anti-tumor model with a multiplicative noise

The effects of time delay on the anti-tumor model are discussed in the absence and presence of the periodic signal, respectively.

3.1. The effects of time delay on the stationary properties of the system

In the absence of the periodic signal, i.e., setting \( A_0 = 0 \) in Eq. (6), the stationary probability distribution function \( P_{qst}(x) \) can be obtained.
expressions (8) and (9), the \(D\)ulation respectively. \(\tau\)
that for Eqs. (8) and (9). The stan-
ary mean value of the cell population, is introduced here of the system, the first order moment of the state variable \(\langle x \rangle\).

Computing the integral in Eq. (10) numerically with the analytical expressions (8) and (9), the \(\langle x \rangle_{st}\) as a function of \(D\) for different values of \(\tau\) is plotted in Fig. 3, and the symbols in Fig. 3 denote the direct simulation results of Eq. (4) for \(A_0 = 0\). Fig. 3 shows that for \(\tau = 0\), \(P_{st}(x)\) has two peaks, i.e., two stable states, which represent the inactive state and active state of the tumor cell population respectively. However, the two-peak structure of the \(P_{st}(x)\) changes with increasing \(\tau\), i.e., the inactive peak goes up and the active peak goes down simultaneously and along with \(\tau\) further increasing, the active peak disappears gradually while the inactive peak goes up, i.e., the \(P_{st}(x)\) changes into a unidomol structure and the system becomes monostable. The nonlinear mixing of additive and multiplicative zero-mean signals can induce similar results (asymmetric probability densities) in symmetrically modulated bistable devices [26,27].

In order to quantitatively investigate the stationary properties of the system, the first order moment of the state variable \(x\), i.e., the stationary mean value of the cell population, is introduced here and given by

\[
\langle x \rangle_{st} = \int_0^\infty xP_{st}(x) \, dx.
\]

The effects of \(\tau\) on \(P_{st}(x)\) can be computed numerically using Eqs. (8) and (9). The \(P_{st}(x)\) as a function of \(x\) for different values of \(\tau\) is plotted in Fig. 2, and the symbols in Fig. 2 denote the direct simulation results of Eq. (4) for \(A_0 = 0\). Fig. 2 shows that for \(\tau = 0\), \(P_{st}(x)\) has two peaks, i.e., two stable states, which represent the inactive state and active state of the tumor cell population respectively. However, the two-peak structure of the \(P_{st}(x)\) changes with increasing \(\tau\), i.e., the inactive peak goes up and the active peak goes down simultaneously and along with \(\tau\) further increasing, the active peak disappears gradually while the inactive peak goes up, i.e., the \(P_{st}(x)\) changes into a unidomol structure and the system becomes monostable.

The stationary mean value of the cell population is derived here and given by

\[
\langle x \rangle_{st} = \int_0^\infty xP_{st}(x) \, dx.
\]

The effects of \(\tau\) on \(\langle x \rangle_{st}\) can be computed numerically using Eqs. (8) and (9). The \(\langle x \rangle_{st}\) as a function of \(D\) for different values of \(\tau\) is plotted in Fig. 3, and the symbols in Fig. 3 denote the direct simulation results of Eq. (4) for \(A_0 = 0\). Fig. 3 shows that \(\langle x \rangle_{st}\) decreases with increasing \(D\) when \(\tau < 0.305\), however, \(\langle x \rangle_{st}\) almost does not change with increasing \(D\) as \(\tau = 0.305\) and \(\langle x \rangle_{st}\) increases with increasing \(D\) when \(\tau > 0.305\). There is a critical value for \(\tau_c = 0.305\) in the \(\langle x \rangle_{st}\) with change of the \(D\), i.e., the stationary mean values of the cell population display contrary behavior with change of the \(D\) when the \(\tau\) takes value above \(\tau_c\) or below \(\tau_c\).

It should be pointed out that, the behavior of \(\langle x \rangle_{st}\) in Fig. 3 is similar to the behavior of \(m\) (with the same meaning with \(\langle x \rangle_{st}\)) in Fig. 4 of Ref. [13], i.e., the stationary mean values of the cell population display contrary behavior with changes of the multiplicative noise intensity with varying parameters in the two figures. The opposite effects of multiplicative noise are induced by different values of immune coefficients \(\beta\) in Ref. [13], and by different values of \(\tau\) in our study.

### 3.2. The effects of time delay on the stochastic resonance of the system

In the presence of the periodic signal \(A_0 \cos(\Omega \tau)\), by virtue of the quasi-steady-state probability distribution function \(P_{st}(x)\) [Eq. (6)], the expression of the signal-to-noise ratio (SNR) of the time-delayed anti-tumor model in the adiabatic limit can be obtained from the two-state approach [20]

\[
R = \frac{\pi W_1^2 A_0^2}{4W_0} \left[ 1 - \frac{W_1^2 A_0^2}{2(W_0^2 + \Omega^2)} \right]^{-1},
\]

where

\[
W_0 = \sqrt{\frac{V''(x_1)}{x_1} V''(x_2)} \exp\left( \frac{[U_1(x_1) - U_1(x_2)]}{D} \right),
\]

\[
W_1 = \frac{[U_2(x_1) - U_2(x_2)]}{D} - \tau \int_{x_1}^{x_2} K - x \, dx,
\]

where \(V(x), x_1, x_2\) are given by Eqs. (2)–(3). Then, by virtue of the expression Eq. (11) of SNR, the effects of \(\tau\) on the SNR can be discussed by numerical computation. The SNR as a function of \(\tau\) is calculated and simulated. The results are plotted on Figs. 4, 5. The existence of a maximum in these curves is the identifying characteristic of the stochastic resonance phenomenon. For the case of \(\tau < 0.47\), there is a one-peak structure in SNR (see Figs. 4a and 4b) and that the position of the peak shifts to left direction of the coordinate \(D\) (Fig. 4a) (shifts to smaller value of \(D\)), however, as the value of \(\tau\) increases to 0.48, a second optimal value of stochastic resonance appears, and two peaks appear in the SNR simultaneously (Fig. 4b). Along with the value of \(\tau\) further increasing to 0.61, the one peak in SNR disappears and the two-peak structure changes to one-peak structure.
again and the height of peak is decreased as $\tau$ increases (Figs. 5a and 5b). That is, the structure of $SNR$ exhibits the transitions of one peak $\rightarrow$ two peaks $\rightarrow$ one peak as $\tau$ increases.

It is worth pointing out that the emergence of “double SR” (two peaks in $SNR$) in Fig. 5. The phenomenon of multiple peaks in the $SNR$ has also been found in Refs. [20–23] for different models. It was argued that the two peaks are mainly due to the feedback of the noise into the signal causing a dip in the $SNR$ [20]. The multiple peaks in the $SNR$ (stochastic multi-resonance) can be induced by either periodic or multiple maxima and minima in the potential [21]. The two peaks in the $SNR$ can be produced by dichotomic noise in a bistable system [22]. Besides, the “double SR” can also induced by the multiplicative noise correlation time, the correlation time and strength of the coupling between two noise terms [23]. In this Letter, the “double SR” is induced by $\tau$ when $SNR$ as a function of $D$.

The stochastic resonance reported here is an instance of the multiplicative $SR$ introduced first in Ref. [24]. The multiplicative $SR$ is of interest since multiplicative noise usually responds for the fluctuating control parameters [25]. Besides, the periodic signal is also multiplicative. The multiplicative periodic signal has been used to study $SR$ in existing literatures [11,26,27], and can bring significant results in comparison with the case for additive signal.

4. Conclusions

In this Letter, we have studied the effects of time delay $\tau$ on the anti-tumor model driven by a multiplicative noise and a periodic signal. First, we discussed the effects of $\tau$ on stationary properties of the system. The two-peak structure of the $P_{st}(x)$ changes with increasing $\tau$, i.e., it changes from a bimodal to a unimodal as $\tau$ increases. The stationary mean value of the cell population $\langle x \rangle_{st}$ decreases with increasing $D$ when $\tau < 0.305$, however, $\langle x \rangle_{st}$ almost does not change with increasing $D$ as $\tau = 0.305$ and $\langle x \rangle_{st}$ increases with increasing $D$ when $\tau > 0.305$, that is, there is a critical value of $\tau_{c} = 0.305$ when $\langle x \rangle_{st}$ as a function of the $D$. The $\langle x \rangle_{st}$ displays contrary behavior with changes of the $D$ when the $\tau$ takes value above $\tau_{c}$ or below $\tau_{c}$. The value of $\tau_{c}$ is due to the data adoption, and will be changed if the other parameters are varied.

Then, we have discussed the effects of $\tau$ on stochastic resonance of the system. By virtue of the quasi-steady-state probability distribution function $P_{qs}(x)$ in the adiabatic limit, the expression of the signal-to-noise ratio was derived. The structure of $SNR$ exhibits the transitions of one peak $\rightarrow$ two peaks $\rightarrow$ one peak as $\tau$ increases, namely, the time delay induces the re-entrance phenomenon in stochastic resonance.

From the above findings, we can obtain further understanding of the intrinsic properties of the growth of tumor population. The
time delay is inherent in the anti-tumor system, and characterizes the reaction time to the environmental constraints. Meanwhile, for a real tumor growth model, both noise and delay are inevitable, which make the growth of the tumor cells population is a very complex dynamics process. If a tumor is in the active state, its reaction time (or delay time) is approach to zero, a noise will induce its decay. On the contrary, if a tumor is in the inactive state, its reaction time (or delay time) is large, a noise can stimulate its growth. These results suggest that: it is very important to distinguish the tumor's state before a treatment is employed.

References