Effects of Lévy noise and immune delay on the extinction behavior in a tumor growth model*

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The combined effects of Lévy noise and immune delay on the extinction behavior in a tumor growth model are explored. The extinction probability of tumor with certain density is measured by exit probability. The expression of the exit probability is obtained using the Taylor expansion and the infinitesimal generator theory. Based on numerical calculations, it is found that the immune delay facilitates tumor extinction when the stability index $\alpha < 1$, but inhibits tumor extinction when the stability index $\alpha > 1$. Moreover, larger stability index and smaller noise intensity are in favor of the extinction for tumor with low density. While for tumor with high density, the stability index and the noise intensity should be reduced to promote tumor extinction.

Keywords: exit probability, Lévy noise, immune delay, tumor growth model

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1. Introduction

Cancer is one of the leading threats to human health, and its prophylaxis and treatment have drawn great attention. Traditional therapies, such as chemotherapy and radiotherapy may damage immune system when killing tumor cells due to the lack of pertinence. More effective treatments are urgently required. The appearance of cancer immunoediting hypothesis makes immunotherapy become a promising treatment, which aims to boost body immunity to control and even, in some case, eradicate tumor.[1,2] Recently, this hypothesis has been verified experimentally.[3] In 1978, Garay *et al.* proposed a mathematical model to describe the proliferation dynamics of tumor under immune surveillance based on the Michaelis–Menten mechanism.[4] Later, various counterintuitive phenomena induced by noise have been discovered in this model, which shows that noise plays a constructive role in tumor proliferation.[5–9]

In the works above, fluctuations were modeled by Gaussian noise. However, Gaussian noise is an ideal assumption for environmental fluctuations and it is not appropriate to model abrupt pulses or extreme events. Theoretically speaking, Lévy processes include Brownian motion, compound Poisson processes, α-stable processes, and so on. Thus, Lévy noise can accurately model diverse types of fluctuations.[10] In fact, Lévy noise is very common in physics and the barrier crossing problem induced by Lévy noise has attracted increasing attention.[11–14] Besides, recent experiments show that Lévy noise has been detected in real biological systems, for example, in the behavioral patterns of some open-ocean predatory fish.[15–17] Nowadays, Lévy noise has been extensively applied in tumor growth processes to model the complex environmental changes, such as temperature, radiations, chemical agents, the immunological state of the host and the supply of nutrients. Ren *et al.* illustrated the effects of Lévy noise on the mean exit time and the escape probability in a Gompertz tumor growth model.[18] The stochastic properties of a tumor growth model subjected to Lévy noise were addressed in Refs. [19] and [20]. Xu *et al.* explored stochastic bifurcation induced by Lévy noise in Ref. [21]. These studies reveal that tumor growth models driven by Lévy noise display much richer dynamical behaviors than those driven by Gaussian noise.

Biologically speaking, the reactions in the process of tumor proliferation are not instantaneous and thus time delay is unavoidable. Many efforts have been contributed to investigate the influences of the time delay on the growth and progression of tumor cells, which is used to represent incubation periods, mitosis times and transport delays.[22,23] Furthermore, it has been pointed out that the immune system needs time to identify the tumor and to react adequately in Refs. [24]–[27]. Consequently, the immune delay should be taken into account in the process of tumor proliferation. However, little work has been done on the effects of immune delay in the tumor growth model.

To fill up these gaps, we extend the model in Ref. [4] by incorporating the immune delay and Lévy noise in this paper. The joint influences of the immune delay and Lévy noise on the exit probability (EP) are studied. The outline of the paper is as follows. In Section 2, we introduce the tumor growth model including the immune delay and Lévy noise. In Sec-

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tion 3, the equation that EP satisfies is derived and the numerical algorithm is presented. In Section 4, we analyze the effects of the immune delay and Lévy noise on the EP and discuss the corresponding biological meanings. This paper ends in Section 5 with conclusions.

2. Tumor growth model in the presence of immune delay and Lévy noise

2.1. Original model

On the basis of the Michaelis-Menten mechanism, the formulation of the model describing the interactions between immune system and tumor tissue can be expressed as follows:[4,7]

$$X \xrightarrow{\lambda} 2X, \tag{1a}$$

$$X + Y \xrightarrow{k_1} Z \xrightarrow{k_2} Y + P. \tag{1b}$$

Here, λ means the rate that tumor cells X proliferate spontaneously, k_1 denotes the rate that immune cells Y bind tumor cells X to compounds Z, and k_2 stands for the rate that Z dissociates into immune cells Y and dead tumor cells P. Typical experimental values of parameters are: $\lambda = 0.2$–1.5 day^{-1}, $k_1 = 0.1$–18 day^{-1}, $k_2 = 0.2$–18 day^{-1}.[7,9] Based on the assumption that the mass of enzymes is conserved, i.e., $Y + Z = E = \text{const}$ and the scaling formulas $x = k_1 X/k_2$, $\theta = k_2/k_1$, $\beta = k_1 E/\lambda$, and $t = \lambda t$, the equivalent first-order differential equation can be obtained by using the quasi-steady-state approximation

$$\frac{\mathrm{d}x}{\mathrm{d}t} = x(1-\theta x) - \beta \frac{x}{x+1}, \tag{2}$$

with the potential function

$$U(x) = -\frac{x^2}{2} + \frac{\theta x^3}{3} + \beta x - \beta \ln(x+1). \tag{3}$$

Here, x is the normalized density of tumor cells in regard to the maximum tissue capacity at time t, β is the immune rate, and θ is a constant parameter. For a special parameter set, i.e., $\theta < 1, 0 < \beta < (1+\theta)^2/4\theta$, the potential function $U(x)$ has one maximum x_u and two minima: x_0, standing for the state of tumor extinction, and x_s, denoting the state of stable tumor (Fig. 1)

$$\begin{aligned} x_0 &= 0, \\ x_u &= \frac{1-\theta-\sqrt{(1+\theta)^2-4\beta\theta}}{2\theta}, \\ x_s &= \frac{1-\theta+\sqrt{(1+\theta)^2-4\beta\theta}}{2\theta}. \end{aligned} \tag{4}$$

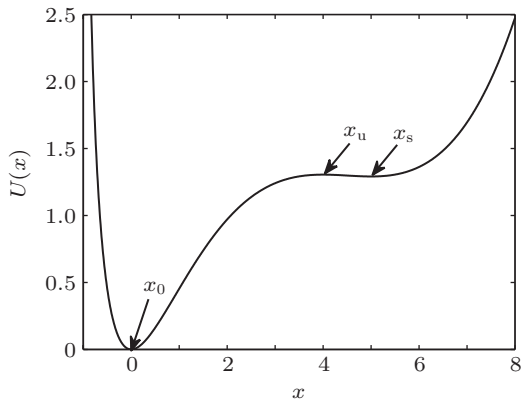


Fig. 1. The potential function $U(x)$ for $\theta = 0.1$, $\beta = 3.0$ with $x_0 = 0$, $x_u = 4$, $x_s = 5$.

2.2. Improved model

Although equation (2) can capture the essential properties of tumor growth, it fails to take two important elements into consideration: immune delay and stochastic factors. On the one hand, the impact of tumor on the immune system is not instantaneous. Instead, the immune system needs time to identify a tumor and react fully.[24–27] Thus, it is necessary to consider time delay in the process of immune response. On the other hand, the proliferation process of tumor cells is inevitably affected by environmental perturbations, such as temperature, radiations, chemical agents, the immunological state of the host and the supply of nutrients.[8,9] To model these fluctuations more accurately, Lévy noise (time derivative of Lévy process L_t) is applied to represent the source of stochastic fluxes.[15,16,18,20,21]

Consequently, equation (2) is extended by including immune delay and Lévy noise as follows:

$$\mathrm{d}X_t = f(X_t, X_\tau)\mathrm{d}t + \mathrm{d}L_t, \quad X_0 = x, \tag{5}$$

with

$$f(X_t, X_\tau) = X_t(1-\theta X_t) - \beta \frac{X_\tau}{X_\tau + 1}. \tag{6}$$

Here, $X_\tau = X(t-\tau)$, X_t is the stochastic density of tumor cells, x is the initial density, and τ is a nonnegative constant, denoting the immune delay. A scalar Lévy process L_t defined on a probability space $(\Omega, \mathcal{F}, P)$ is determined by a drift parameter μ, a variance parameter $d \geq 0$ and a non-negative Borel measure ν_α on $(\mathbb{R}, \mathcal{B}(\mathbb{R}))$, which is concentrated on $\mathbb{R} \setminus \{0\}$ and satisfies:

$$\int_{\mathbb{R}\setminus\{0\}} \min\{y^2, 1\}\, \nu_\alpha(\mathrm{d}y) < \infty. \tag{7}$$

The measure ν_α and (μ, d, ν_α) are called the Lévy jump measure and the generating triplet of L_t, respectively. In this paper, the generating triplet is selected as $(0, d, \varepsilon\nu_\alpha)$. The noise parameters d, α, ε stand for the diffusion coefficient, the stability index and the intensity of α-stable noise part (we name it noise intensity for short here), respectively. In accordance with the Lévy–Itô decomposition,[10] a Lévy process degenerates into

a symmetric α-stable process when $d = 0$. That is to say, it is a pure-jump process, whose jump measure is expressed as[18]

$$\nu_\alpha(\mathrm{d}y) = C_\alpha |y|^{-(1+\alpha)}\,\mathrm{d}y, \tag{8}$$

where

$$C_\alpha = \frac{\alpha}{2^{1-\alpha}\sqrt{\pi}}\frac{\Gamma[(1+\alpha)/2]}{\Gamma(1-\alpha/2)}. \tag{9}$$

When $d \neq 0$, it is an independent sum of a Brownian motion and an α-stable process. In other words, it is a jump-diffusion process.

3. Exit probability

In this section, we derive the equation that the EP of X_t satisfies by considering the case that the time delay in the process of immune response is a small constant.

The exit probability, labeled by $p(x)$ is defined as the likelihood that the density of tumor cells X_t, starting at x in the interval $D = (x_0, x_\mathrm{s})$, first exits from D by landing in a subset V of D^c.[18,28–30]

When the time delay is small, Taylor expansion is the most common method for solving the stochastic delay differential equation (see Refs. [31]–[33] for details). Thus, to obtain the expression of the EP of X_t, we first simplify Eq. (5) using Taylor expansion. On the basis of the method in Ref. [33], we have the following expansions in powers of τ by the Taylor expansion around X_t:

$$f(X_\mathrm{t}, X_\tau) \approx f(X_\mathrm{t}, X_\mathrm{t}) + (X_\tau - X_\mathrm{t})\frac{\partial f(X_\mathrm{t}, X_\tau)}{\partial X_\tau}\bigg|_{X_\tau = X_\mathrm{t}}. \tag{10}$$

We further expand

$$X_\tau \approx X_\mathrm{t} - \tau\frac{\mathrm{d}X_\mathrm{t}}{\mathrm{d}t}. \tag{11}$$

According to Eqs. (6), (10), and (11), we have

$$f(X_\mathrm{t}, X_\tau) \approx X_\mathrm{t}(1-\theta X_\mathrm{t}) - \beta\frac{X_\mathrm{t}}{1+X_\mathrm{t}} + \frac{\beta\tau}{(1+X_\mathrm{t})^2}\frac{\mathrm{d}X_\mathrm{t}}{\mathrm{d}t}. \tag{12}$$

Substituting Formula (12) into Eq. (5), we can rewrite Eq. (5) as:

$$\mathrm{d}X_\mathrm{t} = F(X_\mathrm{t}, \tau)\mathrm{d}t + G(X_\mathrm{t}, \tau)\mathrm{d}L_\mathrm{t}, X_0 = x, \tag{13}$$

where

$$F(X_\mathrm{t}, \tau) = \frac{X_\mathrm{t}(1-\theta X_\mathrm{t})(1+X_\mathrm{t})^2 - \beta X_\mathrm{t}(1+X_\mathrm{t})}{(1+X_\mathrm{t})^2 - \beta\tau}, \tag{14}$$

and

$$G(X_\mathrm{t}, \tau) = \frac{(1+X_\mathrm{t})^2}{(1+X_\mathrm{t})^2 - \beta\tau}. \tag{15}$$

Since L_t is a Lévy process, X_t in Eq. (13) has a càdlàg and quasi-left-continuous path.[10,34] Hence, $p(x)$ satisfies the following Balayage–Dirichlet boundary value equations:[28,35]

$$\begin{aligned} A\,p(x) &= 0, \quad x \in D, \\ p(x) &= \begin{cases} 1, & x \in V, \\ 0, & x \in D^\mathrm{c} \setminus V, \end{cases} \end{aligned} \tag{16}$$

where A is the infinitesimal generator of X_t.

According to the results obtained in Ref. [34], the generator in Eq. (16) can be expressed as:

$$\begin{aligned} Ap(x) = {} & \frac{d}{2}G^2(x,\tau)p''(x) + F(x,\tau)p'(x) \\ & + \varepsilon\int_{\mathbb{R}\setminus\{0\}} [p(x + yG(x,\tau)) - p(x) \\ & - I_{\{|y|<1\}}\, yG(x,\tau)p'(x)]\nu_\alpha(\mathrm{d}y). \end{aligned} \tag{17}$$

To solve Eq. (16), the transformation $z = yG(x,\tau)$ is applied. Then the following equation is obtained:

$$\begin{aligned} & \frac{d}{2}G^2(x,\tau)p''(x) + F(x,\tau)p'(x) \\ & + \varepsilon C_\alpha \frac{|G(x,\tau)|^{(1+\alpha)}}{G(x,\tau)} \\ & \times \int_{\mathbb{R}\setminus\{0\}} \frac{p(x+z) - p(x) - I_{\{|z|<|G(x,\tau)|\}}zp'(x)}{|z|^{1+\alpha}}\,\mathrm{d}z = 0, \end{aligned} \tag{18}$$

for $x \in (x_0, x_s)$. The boundary conditions are $p(x) = 1$ for $x \in V$ and $p(x) = 0$ for $x \in D^c \setminus V$. Then, by the numerical algorithm presented in Ref. [35], we can obtain the EP in Eq. (16).

4. Numerical results and biological explanations

In this section, we analyze the probability of tumor extinction measured by EP. In terms of the definition of EP, the EP means the probability of tumor extinction for $V = (-\infty, x_0]$. The EP stands for the probability that tumor worsens for $V = (x_s, +\infty]$. In the clinical trial, it is of great interest to study the probability of tumor extinction induced by environmental fluctuations, thus the interval V is selected as $(-\infty, 0]$. In this situation, a higher EP indicates a higher probability of tumor extinction. In the following, system parameters are fixed as $\theta = 0.1$, $\beta = 3.0$. Therefore, for the deterministic Eq. (2), the state of tumor extinction is $x_0 = 0$ and the state of stable tumor is $x_s = 5.0$. It is seen that the EP depends on the initial density of tumor cells x, the immune delay τ, the stability index α and the noise intensity ε from Eq. (18). To illustrate the roles of these parameters, we evaluate their influences on the EP when the initial density $x \in D = (0, 5)$.

First, we consider the evolution of the EP in the pure-jump case, which implies the stochastic fluctuations rise from an α-stable noise (i.e., $d = 0$) (shown in Figs. 2–4). In

Fig. 2, the EP is presented as a function of the initial density x for different values of immune delay τ under fixed stability index α. For fixed x, the EP increases as the immune delay τ increases when $\alpha < 1$ (Fig. 2(a)); while the EP increases as the immune delay τ decreases when $\alpha > 1$ (Fig. 2(c)). Furthermore, when $\alpha = 1$, the EP does not change with the immune delay τ (Fig. (b)). This means that $\alpha = 1$ is a critical value. In the biological view, the immune delay plays a positive role in inducing tumor extinction when $\alpha < 1$, whereas the immune delay inhibits tumor extinction when $\alpha > 1$.

Figure 3 displays the EP as a function of the initial density x for various values of the stability index α. Figure 3(a) shows the EP in the absence of immune delay ($\tau = 0$). We find that there exists a critical interval I_τ, where the EP has complex variations. For the initial density x on the left of I_τ, an increasing α brings about a higher EP, while for the initial density x on the right of I_τ, a decreasing α leads to a higher EP. When the immune delay is added to the system (see Fig. 3(b)), the overall evolution of the EP is the same as that without immune delay. But the increase of immune delay makes the difference of the EP arising from the stability index α become smaller. Furthermore, I_τ shifts towards smaller x comparing with the case without immune delay. With regard to biological aspects, increasing stable index is beneficial for tumor extinction for the patients at early stage. While the stability index should

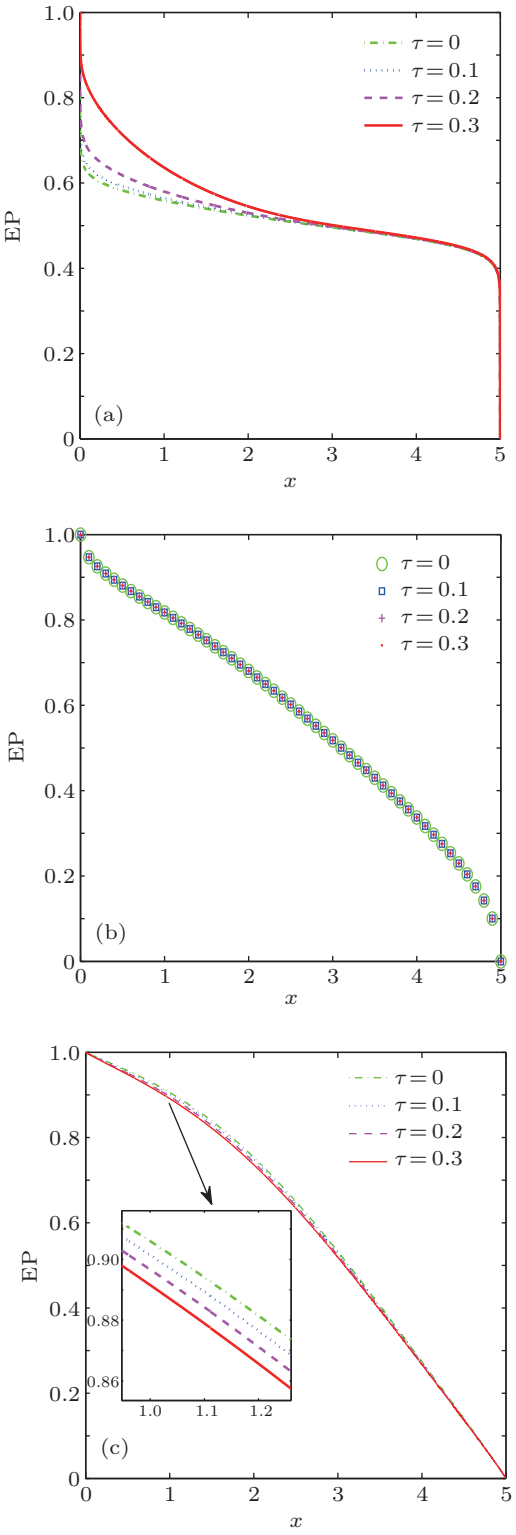


Fig. 2. (color online) Exit probability $p(x)$ for $d = 0.0$, $\varepsilon = 1.0$: (a) $\alpha = 0.1$; (b) $\alpha = 1.0$; (c) $\alpha = 1.9$.

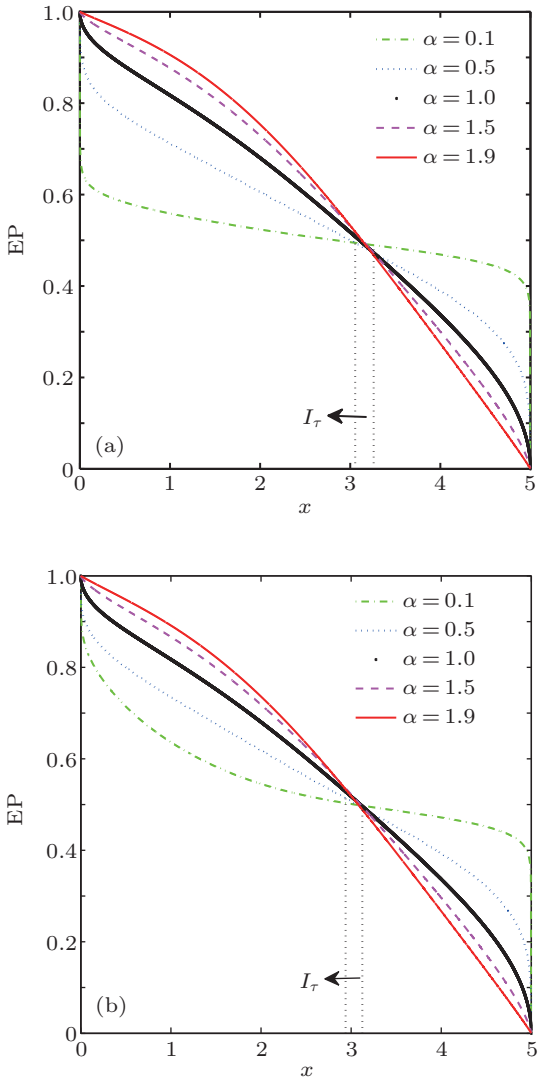


Fig. 3. (color online) Exit probability $p(x)$ for $d = 0.0, \varepsilon = 1.0$: (a) $\tau = 0.0$; (b) $\tau = 0.3$.

be reduced to promote tumor extinction for the patients at advanced stage.

To explore the influences of the noise intensity ε on the EP, figure 4 exhibits the EP versus the initial density x for different values of immune delay τ under fixed stability index α and noise intensity ε. Comparing Fig. 2 with Fig. 4, we observe that the decrease of the noise intensity ε makes the EP observably increase. Consequently, in the pure-jump case, smaller noise intensity facilitates the elimination of tumor cells at the same conditions.

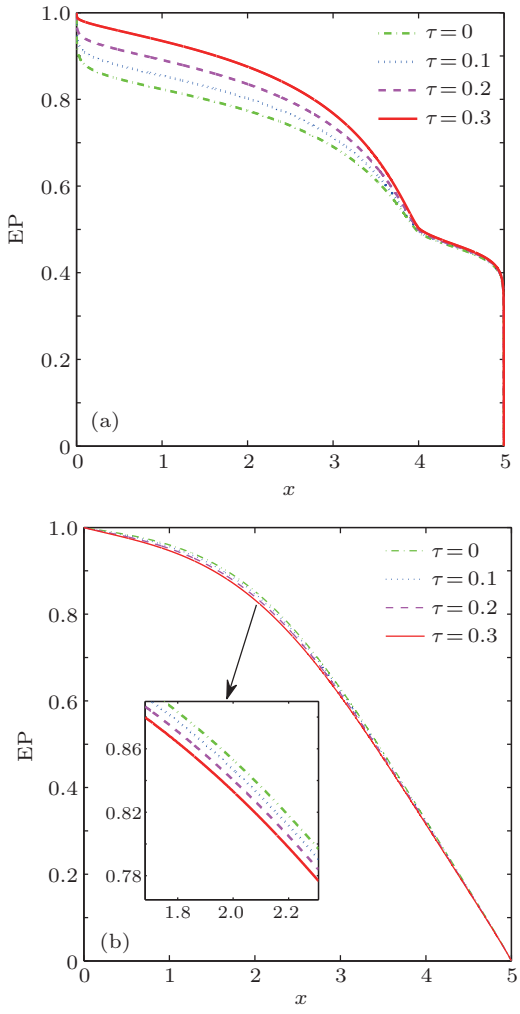


Fig. 4. (color online) Exit probability $p(x)$ for $d = 0.0$: (a) $\varepsilon = 0.1$, $\alpha = 0.1$; (b) $\varepsilon = 0.5$, $\alpha = 1.9$.

Next, we consider the evolution of the EP in the jump-diffusion case, which means an independent Gaussian noise is added to the α-stable noise (i.e., $d \neq 0$, here we choose $d = 1$). In Figs. 5 and 6, the EP is provided as a function of the initial density x for different values of the immune delay τ and the stability index α. Comparing all the figures, we discover that the addition of Gaussian noise does not change the overall evolution rules of the EP. But the inclusion of Gaussian noise reduces the difference of the EP caused by both stability index α and immune delay τ (comparing Figs. 2 and 3 with Figs. 5 and 6). In some point of view, the role of the Gaussian noise part is similar to that of the immune delay τ.

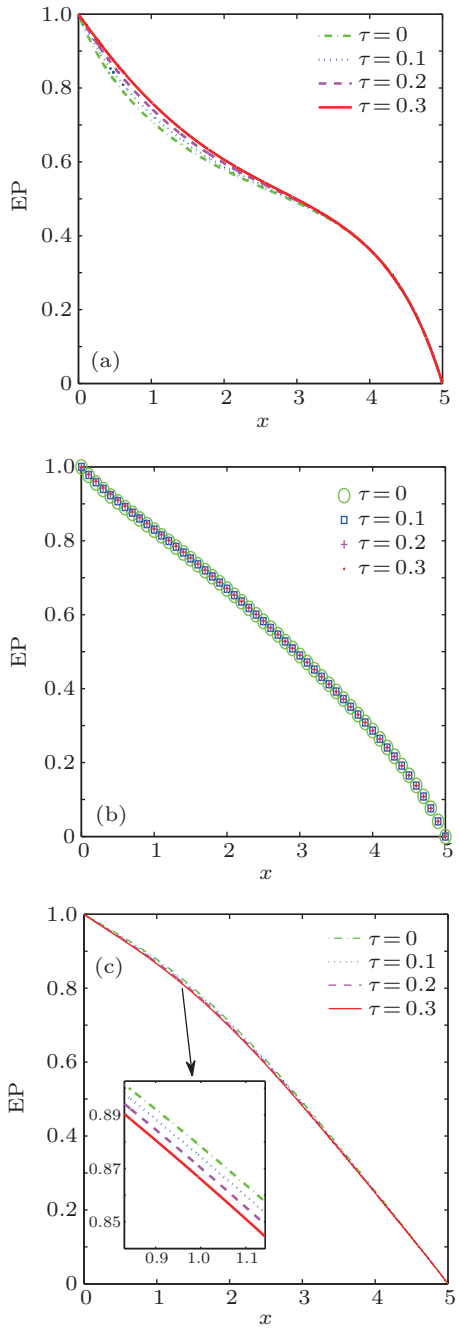


Fig. 5. (color online) Exit probability $p(x)$ for $d = 1.0, \varepsilon = 1.0$: (a) $\alpha = 0.1$; (b) $\alpha = 1.0$; (c) $\alpha = 1.9$.

To verify the validity of the proposed method, numerical simulations are performed by solving Eq. (5) directly. Figure 7 shows the comparison between the theoretical results and Monte–Carlo simulation results. Figure 7(a) plots the results without immune delay and figure 7(b) plots the results in the presence of immune delay. It is found that the theoretical results fit well with the Monte–Carlo simulation results. Therefore, the theoretical method can be used to estimate the extinction probability of tumor cells.

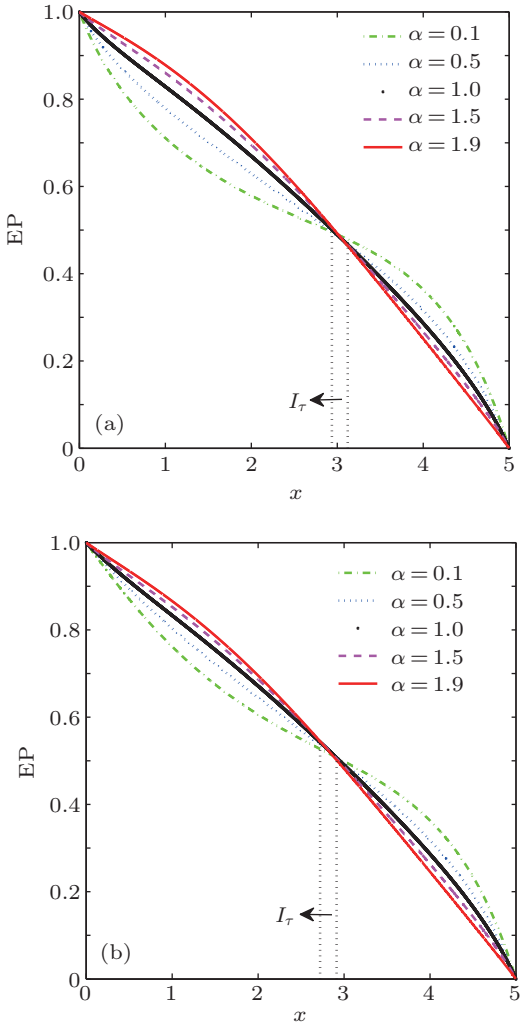


Fig. 6. (color online) Exit probability $p(x)$ for $d = 1.0, \varepsilon = 1.0$: (a) $\tau = 0.0$; (b) $\tau = 0.3$.

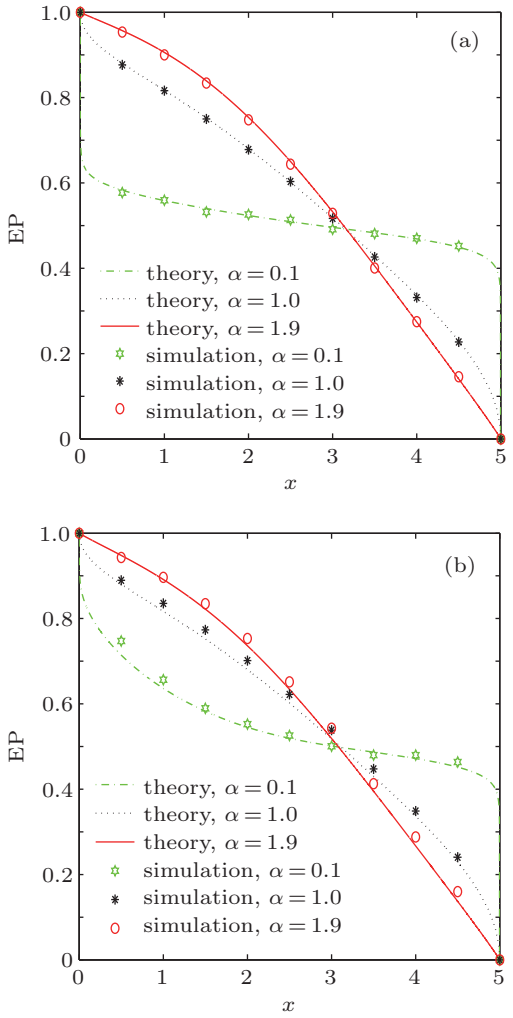


Fig. 7. (color online) Exit probability $p(x)$ for both theoretical results and Monte-Carlo simulation results when $d = 0.0$, $\varepsilon = 1.0$: (a) $\tau = 0$; (b) $\tau = 0.3$. The lines and the symbols represent the theoretical results and the Monte–Carlo simulation results, respectively.

5. Conclusions

In this work, we aim to explore the extinction probability induced by Lévy noise in a tumor growth model in the presence of immune delay. To describe the interactions between immune system and tumor issue more exactly, the model derived by the Michaelis–Menten mechanism is supplemented with immune delay, representing the time that immune system needs to identify a tumor and react fully, and Lévy noise, modeling environmental fluctuations. By means of the Taylor formula, the model described by a stochastic delay differential equation is transformed as a stochastic differential equation with multiplicative Lévy noise. Applying the infinitesimal generator theory, we obtain the equation that EP satisfies. By choosing proper escape interval, the EP is used to characterize the extinction probability of a tumor with certain density.

On the basis of numerical calculations, the influences of the immune delay and Lévy noise on the EP have been obtained. The results exhibit that the effects of the immune delay are related to the stability index α and $\alpha = 1$ is a critical value. The existence of the immune delay assists tumor extinction for $\alpha < 1$, but hinders tumor extinction for $\alpha > 1$. In addition, when the immune delay is fixed, larger stability index can effectively inhibit tumor proliferation for inchoate patients. While for the patients at advanced stage, smaller stability index plays a positive role in promoting tumor extinction. Furthermore, it is important to decrease the noise intensity to eliminate tumor. As is known that the likelihood that the spontaneous extinction of tumor with certain density caused by external environmental perturbations is a valuable research topic. We hope our study is helpful to design and ameliorate the treatment of tumor.

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