Asymmetric non-Gaussian effects in a tumor growth model with immunization

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Abstract

The dynamical evolution of a tumor growth model, under immune surveillance and subject to asymmetric non-Gaussian $\alpha$-stable Lévy noise, is explored. The lifetime of a tumor staying in the range between the tumor-free state and the stable tumor state, and the likelihood of noise-induced tumor extinction, are characterized by the mean residence time and the escape probability, respectively. For various initial densities of tumor cells, the mean residence time and the escape probability are computed with different noise parameters. It is observed that unlike the Gaussian noise or symmetric non-Gaussian noise, the asymmetric non-Gaussian noise plays a constructive role in the tumor evolution in this simple model. By adjusting the noise parameters, the mean residence time can be shortened and the escape probability can be increased, simultaneously. This suggests that a tumor may be mitigated with higher probability in a shorter time, under certain external environmental stimuli.

1. Introduction

In recent years, more and more facts have illustrated the important influences of noise on dynamical systems. It is often assumed that the external noise is Gaussian. This arises due to the assumption that the external perturbation is the result of a large number of independent interactions of bounded strength [1–5]. However, this assumption is not always suitable to adequately interpret real data. For instance, when the fluctuations are abrupt pulses or extreme events, the Gaussian assumption is obviously not proper. In this case, it may be more appropriate to model the fluctuations by a process with heavy tails and discontinuous sample paths. A class of this kind of processes is the asymmetric $\alpha$-stable Lévy motion. Noises following symmetric and asymmetric $\alpha$-stable laws are abundant in nature and have been observed in various fields of science [2,6,7].

Moreover, due to the increasing number of people with tumor, cancer research has become a major challenge in medicine and biology. Because surgeries, chemotherapies and radiotherapies could bring great pain to patients and adversely affect patients’ life, considerable attention has been paid to understanding immunotherapy, aiming to strengthen the body’s
own natural ability to combat cancer by enhancing the effectiveness of the immune system. One of the deterministic testbed models representing the interactions between tumor tissue and immune system is obtained by a “predator–prey” mechanism, in which tumor cells play the role of “preys” whereas the immune cells act as “predators” [1,4,8–12].

A lot of studies have been conducted on the dynamical behaviors of this model driven by different noises, such as Gaussian noise, colored noise and fractional Gaussian noise [3,5,9,11,13–18]. These research works have shown that environmental noises have great impact on the growth and extinction of tumor cells. Furthermore, the dynamical evolution behaves differently under different noises. Thus, it is important to gain deeper insight into the effects of various noises on this tumor evolution system.

In this paper, we focus on effects of the asymmetric $\alpha$-stable Lévy noise on the dynamical behaviors of a tumor cell growth model with immunization. We evaluate the evolution of the tumor cell density, including the lifetime in the range between the tumor-free state and the stable tumor state, as well as the likelihood that the tumor cells become extinct, by numerically examining the mean residence time and the escape probability.

This paper is organized as follows. In Section 2, we introduce the asymmetric $\alpha$-stable Lévy processes. Section 3 describes the tumor growth model with immunization, under the influence of asymmetric $\alpha$-stable Lévy noise. In Section 4, we recall the integro-differential equations satisfied by the mean residence time $u$ and the escape probability $p$, and give numerical algorithms for solving these equations. We present numerical results in Section 5, then finish with conclusions in the final section.

2. Asymmetric $\alpha$-stable Lévy motions

A scalar Lévy motion is characterized by a drift parameter $\mu$, a non-negative diffusion constant $d$, and a non-negative Borel measure $\nu$, defined on $(\mathbb{R}^1, B(\mathbb{R}^1))$ and concentrated on $\mathbb{R}^1 \setminus \{0\}$. The measure $\nu$ is called the Lévy jump measure and it has the following property:

$$\int_{\mathbb{R}^1 \setminus \{0\}} (y^2 \wedge 1) \nu(dy) < \infty,$$

where $a \wedge b = \min\{a, b\}$. We call $(\mu, d, \nu)$ the generating triplet of the Lévy motion $L_t$.

The generator $A$ of the Lévy motion $L_t$ is defined by $A\varphi = \lim_{\varepsilon \to 0} \frac{\varphi(x + \varepsilon) - \varphi(x)}{\varepsilon}$, where $\varphi$ is any function belonging to the domain of the operator $A$. Recall that the space $C_0^2(\mathbb{R}^1)$, consisting of $C^2$ functions with bounded derivatives up to order 2, is contained in the domain of $A$, and thus for every $\varphi \in C_0^2(\mathbb{R}^1)$ (see [19,20])

$$A\varphi(x) = \mu \varphi(x) + \frac{d}{2} \varphi''(x) + \int_{\mathbb{R}^1 \setminus \{0\}} \left[ \varphi(x + y) - \varphi(x) - 1_{\{y|<1\}} y \varphi'(x) \right] \nu(dy).$$

In this paper, we consider a special scalar Lévy motion $L_t$ with the generating triplet $(0, d, v_{x,\beta})$, for the diffusion coefficient $d \geq 0$, stability index $\alpha \in (0, 2)$, skewness parameter $\beta \in [-1, 1]$ and the Lévy jump measure $v_{x,\beta}$. More specifically, the jump measure is defined as [21,22]:

$$v_{x,\beta}(dy) = \begin{cases} \frac{C_1 dy}{y^{1+\alpha}}, & y > 0, \\ \frac{C_2 dy}{y^{1-\alpha}}, & y < 0, \end{cases}$$

with $C_1 = C_2 \frac{1+\beta}{\alpha}$ and $C_2 = C_1 \frac{1-\beta}{\alpha}$, where

$$C_2 = \begin{cases} \frac{\Gamma(1-x)}{\Gamma(2-x)}, & \alpha \neq 1, \\ \frac{\Gamma(1-x)}{\Gamma(2-x)}, & \alpha = 1. \end{cases}$$

Furthermore, $\beta = (C_1 - C_2)/(C_1 + C_2)$. This $L_t$ is a non-Gaussian process, although it has a Gaussian diffusion component described by the diffusion constant $d$. When $d = 0$, this is the well-known asymmetric $\alpha$-stable Lévy motion, and if additionally $\beta = 0$, it is the symmetric $\alpha$-stable Lévy motion.

Note that for a Lévy motion $L_t$, its characteristic function is [20]

$$E[e^{i\lambda \xi}] = e^{-|\lambda|^\alpha \Psi(\lambda)}, \quad t \geq 0, \ \lambda \in \mathbb{R}^1,$$

with $\Psi(\lambda)$ a function that does not depend on time $t$. In other words, $e^{-|\lambda|^\alpha \Psi(\lambda)}$ is the characteristic function for $L_t$. The characteristic function of $L_t$ (at time $t$) is just the $t^\alpha$ power of the characteristic function of $L_1$ (at time 1).

For the $\alpha$-stable Lévy motion considered here ($d = 0$), $L_t$ is an $\alpha$-stable random variable with distribution $S_x(1, \beta, 0)$; see [23, Ch. 1]. Fig. 1 shows the probability density function (PDF) for the $\alpha$-stable random variable $L_t$, with various stability indices $\alpha$ and skewness parameters $\beta$. The stability index $\alpha$ determines the rate at which the tails of the distribution taper off and controls the jump frequency or the jump size of the impulse. The small jumps with high frequency correspond to Lévy motion with the stability index closer to 2, while the large jumps with low frequency correspond to Lévy motion with the stability index closer to 0 (a highly impulsive process). The skewness parameter characterizes the degree of asymmetry of distribution function. The nonzero value of the skewness parameter implies the existence of a primary direction of the random pulses [24,25].
In this section, we consider a tumor growth model under immune surveillance. The reaction between the tumor tissues and the immune cells is based on a reaction scheme representative of the catalytic Michaelis–Menten scenario \[3\]. It can be

\[
S_a(x, \beta, 0)
\]

\[
\beta = -1.0
\]

\[
\beta = -0.5
\]

\[
\beta = 0.0
\]

\[
\beta = 0.5
\]

\[
\beta = 1.0
\]

**Fig. 1.** Probability density functions for \( L_1 \sim S_a(1, \beta, 0) \) for different values of \( x \) and \( \beta \): (a) \( x = 0.1 \), (b) \( x = 0.5 \), (c) \( x = 1 \), (d) \( x = 1.5 \), (e) \( x = 1.9 \), (f) \( x = 2 \).

3. Tumor growth model subject to an asymmetric Lévy noise

In this section, we consider a tumor growth model under immune surveillance. The reaction between the tumor tissues and the immune cells is based on a reaction scheme representative of the catalytic Michaelis–Menten scenario \[3\]. It can be
explained as follows: Firstly, the tumor cells denoted by \( X \) proliferate in two ways: one is the transformation of normal cells into neoplastic ones at a rate \( \kappa \); the other is the replication of the tumor cells at a rate \( i \). Then, the active cytotoxic cells (i.e., immune cells) \( Y \) bind the tumor cells to the complex \( Z \) with the kinetic constant \( k_1 \). Lastly, the complex \( Z \) dissociates into immune cells and the dead or non-replicating tumor cells \( P \) at a rate proportional to \( k_2 \). Schematically, the mechanisms above can be represented as follows:

\[
\text{Normal Cells} \xrightarrow{\kappa} X, \tag{4a}
\]

\[
X \xrightarrow{i} 2X, \tag{4b}
\]

\[
X + Y \xrightarrow{k_1} Z \xrightarrow{k_2} Y + P. \tag{4c}
\]

In order to construct a mathematical model, we can make the following assumptions based on biological principles. Firstly, because the transformation of normal cells into neoplastic ones originates from environmental carcinogenic agents rather than spontaneous endogenous somatic mutations, the average rate of this process is very low, compared with the rate of neoplastic cell replication. Typical experimental values are: \( \kappa \) the order of \( 10^{-17} - 10^{-18} \) transformed cell/normal cell/day, \( i = 0.2 - 1.5 \) day\(^{-1} \), \( k_1 = 0.1 - 18 \) day\(^{-1} \), \( k_2 = 0.2 - 18 \) day\(^{-1} \) as in \([13,26]\). Thus, we can ignore step (4a). Secondly, in the reaction process, \( Y \) behaves like the enzymes in the Michaelis-Menten reaction, so we consider a conserved mass of enzymes \( Y + Z = E = \text{const} \). Besides, in the limit case, the production of \( X \)-type cells inhibited by a hyperbolic activation is the slowest process. Therefore, by the assumptions and the quasi-steady-state approximation, the kinetics can be simplified to an equivalent single variable differential equation \([13,26]\):

\[
\frac{dx}{dt} = x(1 - \theta x) - \gamma x \frac{x}{x + 1}, \tag{5}
\]

with the potential function

\[
U(x) = -\frac{x^2}{2} + \frac{\theta x^3}{3} + \gamma x - \gamma \ln(x + 1), \tag{6}
\]

where \( x \) is the normalized molecular density of tumor cells with respect to the maximum tissue capacity. And we use the following scaling formulas in the process of nondimensionalization:

\[
x = \frac{k_1}{k_2} X, \quad \theta = \frac{k_2}{k_1}, \quad \gamma = \frac{k_1 E_1}{t}, \quad t = t'.
\]

Taking into account the biological significance and convenience of discussion, we choose the parameter ranges as follows: \( \theta < 1, 0 < \gamma < \left(\frac{1}{4\theta}\right)^2 \). In this case, the deterministic dynamical system Eq. (5) has two stable states and one unstable state (see \([5,26]\)). Namely, the potential function \( U(x) \) has two minima: \( x_1, x_3 \) and one maximum \( x_2 \) (see Fig. 2). That is to say, this system has three meaningful steady states:
\[ x_1 = 0, \]
\[ x_2 = \frac{1 - \theta - \sqrt{(1 + \theta)^2 - 4\gamma \theta}}{2\theta}, \]
\[ x_3 = \frac{1 - \theta + \sqrt{(1 + \theta)^2 - 4\gamma \theta}}{2\theta}. \]  

(7)

Without random initial fluctuations, for a given initial condition, the system state will eventually converge to one of the two stable states: (i) the stable state \( x_1 = 0 \), called the tumor-free state (or the state of tumor extinction), where no tumor cells exist, (ii) the stable state \( x_3 \), called the stable tumor state, where the tumor cell density does not increase but keeps at a certain constant level.

However, from a biological point of view, the growth rate of tumor tissue is inevitably influenced by many environmental factors, such as temperature, radiations, chemical agents, the degree of vascularization of tissue, the supply of nutrients, the immunological state of the host and so on \([13,26]\). Due to the limitations of the Gaussian noise, in this paper, we consider more general noise, an asymmetric Lévy noise to represent the environmental fluctuations. Our model is written as follows:

\[ dX_t = f(X_t)dt + dL_t, \quad X(0) = x, \]  

(8)

where

\[ f(X_t) = X_t(1 - \theta X_t) - \gamma \frac{X_t}{X_t + 1}, \]

and \( L_t \) is a Lévy process with the generating triplet \((0, d, v_{x,y})\), i.e., drift coefficient 0, diffusion coefficient \( d > 0 \) and the Lévy jump measure \( v_{x,y} \).

Under the effects of environmental fluctuations, the number of tumor cells may fluctuate in the range between the tumor-free state and the stable tumor state denoted by \( D = (x_1, x_3) \). In this paper, we concentrate on how the tumor density evolves in the range \( D \) and discuss the impacts of the asymmetric Lévy noise on the time that the density of tumor cells stays in the range \( D \) and the probability it exits \( D \) from the left side, i.e., becoming tumor-free.

4. Mean residence time, escape probability and numerical algorithms

In this section, we discuss mean residence time, escape probability and their numerical schemes in order to quantify the dynamics of the stochastic differential equation (8).

4.1. Mean residence time

First, we recall the definition of the first exit time from the bounded domain \( D = (x_1, x_3) \):

\[ \tau(\omega) = \inf\{ t > 0, X_t(\omega, x) \notin D \}. \]

The mean residence time \( u(x) = E\tau(\omega) \) then satisfies the following integro-differential equation [27] with an exterior boundary condition

\[ Au(x) = -1, \quad x \in D, \]
\[ u = 0, \quad x \in D^c. \]  

(9)

where the generator \( A \) of the solution process \( X(t) \) is

\[ Au = f(x)u'(x) + \frac{d}{2}u''(x) + \int_{B(1)} |u(x + y) - u(x) - 1_{\{y < 1\}}yu'(x)| \, v_{x,y}(dy). \]  

(10)

4.2. Escape probability

Now, we consider the escape probability of paths whose motion is described by Eq. (8). The likelihood that \( X(t) \), starting at a point \( x \), first exits from the domain \( D \) by landing in the subset \( E \) of \( D^c \) is called the escape probability and is denoted as \( p(x) \). This escape probability solves the following exterior Dirichlet problem [28,29]:

\[ Ap(x) = 0, \quad x \in D, \]
\[ p = h, \quad x \in D^c. \]  

(11)

where \( A \) is the generator defined in (10) and the function \( h \) is defined as:

\[ h = \begin{cases} 
1, & x \in E, \\
0, & x \in D^c \setminus E.
\end{cases} \]
We are concerned with how to enhance the likelihood of tumor extinction, so we choose $E = (-\infty, x_1]$, i.e., we examine the likelihood that the tumor state goes from $D = (x_1, x_2)$ (tumor) to $E = (-\infty, x_1]$ (tumor free).

### 4.3. Numerical algorithms

We only describe the numerical algorithms for Eq. (11), as the algorithm for Eq. (9) is similar. The algorithm below extends a numerical scheme in [30] for the case of symmetric Lévy noise to the case of asymmetric Lévy noise. For convenience, we use a general interval $D = (a, b)$, instead of $D = (x_1, x_3)$, in the following spatial discretization. Using (3), Eq. (11) can be rewritten as:

$$
\frac{d}{dx} p''(x) + f(x)p'(x) + \int_{B \setminus \{0\}} \left[ p(x+y) - p(x) - 1_{[y<1]}yp'(x) \right] \left[ \frac{C_1 1_{B(y>0)}(y)}{y^{1+\alpha}} + \frac{C_2 1_{B(y<0)}(y)}{y^{1+\beta}} \right] dy = 0,
$$

(12)

for $x \in (a, b)$: $p(x) = 1$ for $x \in (-\infty, a]$ and $p(x) = 0$ for $x \in [b, +\infty)$. Thus, we obtain:

$$
\frac{d}{dx} p''(x) + f(x)p'(x) + C_2 \int_{B \setminus \{0\}} \frac{p(x+y) - p(x) - 1_{[y<1]}yp'(x)}{|y|^{1+\alpha}} dy + (C_1 - C_2) \int_{B^{+1}} \frac{p(x+y) - p(x) - 1_{[y<1]}yp'(x)}{|y|^{1+\beta}} dy = 0.
$$

(13)

Because $\int_{B^{+1}(0)} 1_{B^+(a,

B^{+1}(0)} p'(x) dy = \int_{B^{+1}(0)} 1_{B^+(a,

B^{+1}(0)} p'(x) dy = 0$ for any $\delta > 0$, we can replace the former by the latter in (13). To take care of the external condition, we divide the integral as $\int_{B^+} = \int_{a-x}^{a+x} + \int_{x-b}^{x+b} + \int_{b-x}^{b+x}$ and choose $\delta = \min(\{a-x, b-x\})$, and then we get the following formula:

$$
\frac{d}{dx} p''(x) + f(x)p'(x) + C_2 \int_{a-x}^{a+x} \frac{p(x+y) - p(x) - 1_{[y<1]}yp'(x)}{|y|^{1+\alpha}} dy + C_2 \int_{b-x}^{b+x} \frac{p(x+y) - p(x) - 1_{[y<1]}yp'(x)}{|y|^{1+\alpha}} dy 
$$

$$
+ (C_1 - C_2) \int_{B^{+1}} \frac{p(x+y) - p(x) - 1_{[y<1]}yp'(x)}{|y|^{1+\beta}} dy = 0.
$$

(14)

By direct calculations, (14) can be further rewritten as:

$$
\frac{d}{dx} p''(x) + f(x)p'(x) - \frac{C_2}{x} \left[ \frac{1}{(x-a)^2} + \frac{1}{(b-x)^2} \right] p(x) + C_2 \int_{a-x}^{b-x} \frac{p(x+y) - p(x)}{|y|^{1+\alpha}} dy + C_2 \int_{b-x}^{a-x} \frac{p(x+y) - p(x)}{|y|^{1+\alpha}} dy 
$$

$$
+ (C_1 - C_2) \int_{B^{+1}} \frac{p(x+y) - p(x) - 1_{[y<1]}yp'(x)}{|y|^{1+\beta}} dy = -\frac{C_2}{x} \left[ \frac{1}{(x-a)^2} \right],
$$

(15)

for $x < \frac{a+b}{2}$, and

$$
\frac{d}{dx} p''(x) + f(x)p'(x) - \frac{C_2}{x} \left[ \frac{1}{(x-a)^2} + \frac{1}{(b-x)^2} \right] p(x) + C_2 \int_{a-x}^{b-x} \frac{p(x+y) - p(x)}{|y|^{1+\alpha}} dy + C_2 \int_{b-x}^{a-x} \frac{p(x+y) - p(x) - 1_{[y<1]}yp'(x)}{|y|^{1+\alpha}} dy 
$$

$$
+ (C_1 - C_2) \int_{B^{+1}} \frac{p(x+y) - p(x) - 1_{[y<1]}yp'(x)}{|y|^{1+\beta}} dy = -\frac{C_2}{x} \left[ \frac{1}{(x-a)^2} \right],
$$

(16)

for $x \geq \frac{a+b}{2}$.

For the last term on the left hand of Eq. (14), we have (Here, we omit the coefficient $(C_1 - C_2)$ and assume $b - a > 1$.)

$$
\int_{B^{+1}} \frac{p(x+y) - p(x) - 1_{[y<1]}yp'(x)}{|y|^{1+\beta}} dy = \int_{0}^{1} \frac{p(x+y) - p(x) - yp'(x)}{|y|^{1+\alpha}} dy + \int_{1}^{b-x} \frac{p(x+y) - p(x)}{|y|^{1+\alpha}} dy 
$$

$$
+ \int_{b-x}^{\infty} \frac{p(x+y) - p(x)}{|y|^{1+\alpha}} dy = \int_{0}^{1} \frac{p(x+y) - p(x) - yp'(x)}{|y|^{1+\beta}} dy + \int_{1}^{b-x} \frac{p(x+y) - p(x)}{|y|^{1+\alpha}} dy - \frac{p(x)}{\alpha} (b-x)^{\alpha},
$$

(17)

for $x \leq b - 1$, i.e., $b - x \geq 1$, and

$$
\int_{B^{+1}} \frac{p(x+y) - p(x) - 1_{[y<1]}yp'(x)}{|y|^{1+\beta}} dy = \int_{0}^{b-x} \frac{p(x+y) - p(x) - yp'(x)}{|y|^{1+\alpha}} dy - \int_{b-x}^{1} \frac{p(x+y) - p(x)}{|y|^{1+\alpha}} dy = \int_{0}^{b-x} \frac{p(x+y) - p(x) - yp'(x)}{|y|^{1+\beta}} dy - \frac{p(x)}{\alpha},
$$

(18)

for $x > b - 1$, i.e., $b - x < 1$. 

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Now, let us take the appropriate stepsize $h$, so that $\frac{1}{\alpha}, \frac{2}{\alpha}, \ldots, \frac{n_a}{\alpha} \in \mathbb{N}$ are integers, and define $x_i = jh$ for $\frac{n_a}{\alpha} < j < \frac{n_a+1}{\alpha}$. We use the notation $P_j$ to indicate the numerical solution of $p$ at $x_j$. Then, the first four terms on the left hand of Eqs. (15) and (16) can be discretized, respectively, by the central difference scheme for derivatives and “punched-hole” trapezoidal rule:

$$\frac{d P_j - 2P_j + P_{j+1}}{h^2} + f(x_j) \frac{P_{j+1} - P_{j-1}}{2h} = \frac{1}{\alpha} \left( \frac{1}{(x_j - a)^\alpha} + \frac{1}{(b - x_j)^\alpha} \right) P_j + C_2 \sum_{k=0}^{j-1} \frac{P_{j+k} - P_j - (P_{j+1} - P_j) \xi_k}{|x_k|^{1+\gamma}} + C_2 h \sum_{k=j}^{j+1} \frac{P_{j+k} - P_j - (P_{j+1} - P_j) \xi_k}{|x_k|^{1+\gamma}}/2h, \tag{19}$$

where $j = \frac{n_a}{\alpha} + 1, \frac{n_a}{\alpha} + 2, \ldots, \frac{n_a+1}{\alpha} - 1$. The meaning of the modified summation symbol $\sum'$ is that the quantities corresponding to the two endpoints of the integral interval should be multiplied by 1/2.

$$\frac{d P_j - 2P_j + P_{j+1}}{h^2} + f(x_j) \frac{P_{j+1} - P_{j-1}}{2h} = \frac{1}{\alpha} \left( \frac{1}{(x_j - a)^\alpha} + \frac{1}{(b - x_j)^\alpha} \right) P_j + C_2 h \sum_{k=j}^{j+1} \frac{P_{j+k} - P_j - (P_{j+1} - P_j) \xi_k}{|x_k|^{1+\gamma}}/2h, \tag{20}$$

where $j = \frac{n_a}{\alpha}, \frac{n_a}{\alpha} + 1, \ldots, \frac{n_a+1}{\alpha} - 1$.

For the last term on the left hand of Eqs. (15) and (16), we use the upwind finite difference scheme. That is, when $-(C_1 - C_2) \int_0^1 \frac{1}{|x|^{1+\gamma}} \, dy > 0$, we use the forward finite difference scheme to discretize $p'(x)$, while when $-(C_1 - C_2) \int_0^1 \frac{1}{|x|^{1+\gamma}} \, dy \leq 0$, we use the backward finite difference scheme to discretize $p'(x)$, i.e., as in [31],

$$p'(x) = \begin{cases} \frac{p(x+h) - p(x)}{h}, & -(C_1 - C_2) \int_0^1 \frac{1}{|x|^{1+\gamma}} \, dy > 0, \\ \frac{p(x) - p(x-h)}{h}, & -(C_1 - C_2) \int_0^1 \frac{1}{|x|^{1+\gamma}} \, dy \leq 0. \end{cases} \tag{21}$$

So the formula (17) can be discretized as:

$$-\frac{1}{\alpha (b - x_j)} P_j - h \sum_{k=0}^{\frac{j}{\alpha}} \frac{P_{j+k} - P_j}{|x_k|^{1+\gamma}} + h \sum_{k=0}^{\frac{j}{\alpha}} \frac{P_{j+k} - P_j - (P_{j+1} - P_j) \xi_k}{|x_k|^{1+\gamma}} h, \tag{22}$$

for $\beta < 0$, and

$$-\frac{1}{\alpha (b - x_j)} P_j - h \sum_{k=0}^{\frac{j}{\alpha}} \frac{P_{j+k} - P_j}{|x_k|^{1+\gamma}} + \sum_{k=0}^{h} \frac{P_{j+k} - P_j - (P_{j+1} - P_j) \xi_k}{|x_k|^{1+\gamma}} h, \tag{23}$$

for $\beta \geq 0$. By the same reason, we can get the discretization for the formula (18):

$$-\frac{1}{\alpha} P_j + h \sum_{k=0}^{\frac{j}{\alpha}} \frac{P_j - P_{j+1} - (P_{j+1} - P_j) \xi_k}{|x_k|^{1+\gamma}} + h \sum_{k=0}^{\frac{j}{\alpha}} \frac{P_{j+k} - P_j - (P_{j+1} - P_j) \xi_k}{|x_k|^{1+\gamma}} h, \tag{24}$$

for $\beta < 0$, and

$$-\frac{1}{\alpha} P_j + h \sum_{k=0}^{\frac{j}{\alpha}} \frac{P_j - P_{j+1} - (P_{j+1} - P_j) \xi_k}{|x_k|^{1+\gamma}} + \sum_{k=0}^{h} \frac{P_{j+k} - P_j - (P_{j+1} - P_j) \xi_k}{|x_k|^{1+\gamma}} h, \tag{25}$$

for $\beta \geq 0$. The boundary conditions require that $P_j = 1$ for $j = \frac{n_a}{\alpha}$ and $P_j = 0$ for $j \geq \frac{n_a}{\alpha}$.

The right hand of Eq. (15) can be discretized as:

$$-\frac{C_2}{\alpha} \left( \frac{1}{(x_j - a)^\alpha} \right). \tag{26}$$

Thus, we can obtain the escape probability $p(x)$, $x \in D$, by solving Eqs. (19)-(26).

The numerical scheme to solve Eq. (9) for mean residence time $u(x)$ is similar.

5. Numerical results

We fix the chemical system parameters $\theta = 0.1, \gamma = 3.0$ as suggested in [3], and focus on the impact of asymmetric Lévy noise on the mean residence time $u$ and the escape probability $p$, in order to gain understanding of the tumor evolution under uncertainty. With these parameters, the stable states of the deterministic tumor growth model are $x_1 = 0$ and $x_3 = 5$. The interval $D = (0, 5)$ encloses the tumor cell density from 0 (tumor-free state) to 5 (stable tumor state).
5.1. Mean residence time

We compute the mean residence time \( u(x) \) of the tumor density \( X_t \) from \( x \in D = (0, 5) \), between the tumor-free state and the stable tumor state. For example, \( u(3) \) is the mean time that the tumor cell density, starting at the initial density 3,
remains within the range $D$, before ‘exiting’ to outside $D$. It quantifies how long the tumor cell density stays between 0 (tumor-free state) and 5 (stable tumor state).

In Figs. 3 and 4, we observe that when the stability index $\alpha$ is fixed approximately below 1.77, for the inchoate patients, smaller skewness parameter $\beta$ leads to shorter mean residence time. While for the advanced patients, the situation becomes

Fig. 4. Mean residence time $u(x)$ when pure $\alpha$-stable Lévy noise is combined with Gaussian noise (i.e. $d = 1.0$): (a) $\alpha = 0.1$, (b) $\alpha = 0.5$, (c) $\alpha = 1.0$, (d) $\alpha = 1.5$; (e) $\alpha = 1.9$. 

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opposite. This suggests that asymmetry in the noise (described by $\beta$) plays a crucial role in the time span a patient remains in the tumor state, and this role is opposite for inchoate and advanced patients. Besides, when the stability index $\alpha \geq 1.77$, for all the patients, the mean residence time $u$ decreases as the skewness parameter $\beta$ decreases. From the Figs. 5 and 6, we find that when the skewness parameter $\beta$ is fixed, the behavior of the mean residence time under various stability indices $\alpha$ is

![Graphs showing mean residence time $u(x)$ with pure $\alpha$-stable Lévy noise](Fig. 5. Mean residence time $u(x)$ with pure $\alpha$-stable Lévy noise (i.e. $d = 0$): (a) $\beta = -1.0$, (b) $\beta = -0.5$, (c) $\beta = 0.0$, (d) $\beta = 0.5$, (e) $\beta = 1.0$.)
similar to the symmetric case (Figs. 5(c) and 6(c) for $\beta = 0$). That is, at the early ($x$ near 0) and advanced ($x$ close to 5) tumor stages, the mean residence time decreases as the stability index $\alpha$ increases, while in the middle tumor stage, this relationship becomes reversed. Moreover, comparing Fig. 3 with Fig. 4, and also Fig. 5 with Fig. 6, we notice that the input of the

Fig. 6. Mean residence time $u(x)$ when pure $\alpha$-stable Lévy noise is combined with Gaussian noise (i.e. $d = 1.0$): (a) $\beta = -1.0$, (b) $\beta = -0.5$, (c) $\beta = 0.0$, (d) $\beta = 0.5$, (e) $\beta = 1.0$. 
Gaussian noise component (i.e., the diffusion coefficient $d > 0$) just shortens the mean residence time, but appears not to change the evolution rules essentially.

Fig. 11 is a 3D plot of the above numerical results.

**Fig. 7.** Escape probability $p(x)$ with pure $\alpha$-stable Lévy noise (i.e. $d = 0$): (a) $\alpha = 0.1$, (b) $\alpha = 0.5$, (c) $\alpha = 1.0$, (d) $\alpha = 1.5$, (e) $\alpha = 1.9$. 
Fig. 8. Escape probability $p(x)$ when pure $\alpha$-stable Lévy noise is combined with Gaussian noise (i.e. $d = 1.0$): (a) $\alpha = 0.1$, (b) $\alpha = 0.5$, (c) $\alpha = 1.0$, (d) $\alpha = 1.5$, (e) $\alpha = 1.9$. 
5.2. Escape probability

We would like to do further investigation on the tumor evolution after the system exits the interval $D = (0, 5)$. Will it reach the tumor-free state (exit to the left of $D = (0, 5)$)? We compute the escape probability $p(x)$, i.e., the likelihood that

\[ p(x) \]

\[ \alpha = 0.1 \]
\[ \alpha = 0.5 \]
\[ \alpha = 1.0 \]
\[ \alpha = 1.5 \]
\[ \alpha = 1.9 \]

Fig. 9. Escape probability $p(x)$ with pure $\alpha$-stable Lévy noise (i.e., $d = 0$): (a) $\beta = -1.0$, (b) $\beta = -0.5$, (c) $\beta = 0.0$, (d) $\beta = 0.5$, (e) $\beta = 1.0$. 

5.2. Escape probability

We would like to do further investigation on the tumor evolution after the system exits the interval $D = (0, 5)$. Will it reach the tumor-free state (exit to the left of $D = (0, 5)$)? We compute the escape probability $p(x)$, i.e., the likelihood that
the tumor cell density $x \in (0.5)$ becomes tumor-free ($x = 0$). See Figs. 7–10. In these figures, high escape probability $p$ values indicate high likelihood for a tumor to become tumor-free.

In Figs. 7 and 8, we observe that when the stability index $\alpha$ is fixed, either with or without Gaussian noise component (i.e., diffusion coefficient $d = 0$ or $d = 1$), the escape probability $p$ increases as the skewness parameter $\beta$ decreases. Besides, the

Fig. 10. Escape probability $p(x)$ when pure $\alpha$-stable Lévy noise is combined with Gaussian noise (i.e. $d = 1.0$): (a) $\beta = -1.0$, (b) $\beta = -0.5$, (c) $\beta = 0.0$, (d) $\beta = 0.5$, (e) $\beta = 1.0$. 
smaller the stability index $\alpha$ is, the more effects the skewness parameter $\beta$ has on the escape probability. As the stability index $\alpha$ becomes larger (close to 2), for all the skewness parameter $\beta$, the escape probability tends to the symmetric case (i.e. $\beta = 0$). Especially, when $\alpha = 1.9$ (see Figs. 7(e) and 8(e)), the escape probability does not change much with the skewness parameter $\beta$.

As seen in Figs. 9 and 10, when the skewness parameter $\beta$ is near the extremes, the escape probability increases as the stability index $\alpha$ either decreases (in the $\beta \leq -0.99$ case) or increases (in the $\beta \geq 0.99$ case). However, when $-0.99 < \beta < 0.99$, due to the competition between the stability index $\alpha$ and the skewness parameter $\beta$, the behavior of the escape probability does not change monotonically with $\alpha$. Instead, they are similar to the symmetric case (see Figs. 9(c) and 10(c) for $\beta = 0$ case), in which case there exists a critical point. When the density of the tumor cells is less than the critical point, the escape probability increases with the increasing $\alpha$. While when the density of the tumor cells is more than the critical point, the escape probability shows an opposite trend with the increasing $\alpha$.

Fig. 11 is a 3D plot of the above numerical results.

In this biological setting, the escape probability means the likelihood of the tumor extinction, while the mean residence time quantifies the time that the density of tumor cells remains in the range between the tumor-free state and the stable tumor state. From the medical point of view, the clinicians focus primarily on the probability of tumor extinction, so high escape probability is preferred. With the high probability of tumor extinction, clinicians also want to shorten the mean residence time (during which patients endure the pain from medical treatment such as radiation or chemotherapy). By comparing these figures, we find that the smaller the stability index $\alpha$ and the skewness parameter $\beta$ are, the higher the

**Fig. 11.** Mean residence time $u(x)$ in 3-dimension plane: (a) $d = 0, \alpha = 0.1$, (b) $d = 1, \alpha = 0.1$.

**Fig. 12.** Escape probability $p(x)$ in 3-dimension plane: (a) $d = 0, \beta = -1.0$, (b) $d = 1.0, \beta = -1.0$. 
escape probability $p$ grows and simultaneously, the shorter the mean residence time $u$ becomes. Especially, when $\alpha = 0.1$ and $\beta = -1.0$, no matter at what tumor stage (either the early stage or the advanced stage) the patients are, the probability of curing the tumor is almost surely (see Fig. 7(a)). It implies that when the immunological state of the host is better ($\beta$ is close to $-1$), the therapy with the big stimulus such as radiotherapy and surgeries ($\alpha$ is close to 0) may be adopted to eliminate tumor in a shorter time. This is different from the symmetric noise case, which suggests that we should make the therapy strategy according to the stage of the patients (see Figs. 9(c) and 10(c)).

According to our results for this specific simple model and the roles of the stability index and the skewness parameter in modeling the environmental fluctuations (see Section 2), we find these two noise parameters play a constructive role in the tumor evolution. Thus, the environmental factors may be used to mitigate tumor [32,33].

6. Conclusions

In this paper, we have examined the impact of asymmetric non-Gaussian environmental fluctuations on the dynamical evolution of a tumor growth model with immunization. The mean residence time and the escape probability are computed to quantify the mean lifetime the tumor cells remain between the tumor-free state and the stable tumor state, and the likelihood that tumor with a certain initial density becomes extinct (i.e., tumor-free). These two quantities are described by exterior boundary value problems involving nonlocal operators. By the numerical experiments, we find that the parameters of asymmetric Lévy noise have significant influences on the mean residence time and the escape probability. Especially, the skewness parameter plays an important role in controlling the tumor cells evolution. By choosing the appropriate skewness parameter, we observe that it is likely to slow the tumor progression and at the same time, enhance the likelihood to induce tumor extinction.

Acknowledgment

We would like to thank Xiaofan Li and Ting Gao for helpful discussions on the numerical scheme.

References