SURVIVAL ANALYSIS FOR TUMOR GROWTH MODEL WITH STOCHASTIC PERTURBATION

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Abstract. In this paper, we investigate the dynamical behavior of extinction and survival in tumor growth model with immunization under stochastic perturbation. Firstly, the model describing the growth of cancer cells monitored by immune cells is established. Then, the steady probability distribution of tumor cells for different noise intensities and immune parameter intensities, and necessary conditions for extinction and different survival of cancer cells are obtained by numerical and theoretical method. Besides, it is found that the extinction and survival of cancer cells rely on the state of immunization and noise. Finally, stochastic simulations are taken to test the theoretical analytical results. The results of our work are beneficial to discover the evolution mechanism and design effective immunotherapy of tumor.

1. Introduction. Cancer is becoming a major death cause in our society. However, we still know little about the evolution mechanism of its survival and death. Although some effective therapies have been established, for example surgery, radiotherapy and chemotherapy, these traditional treatment can’t play good therapeutic effect, so some researchers start to investigate new therapies. Recently, evidence manifests that some kinds of immune cells could reveal and kill malignant tumor cells [27, 32], hence the immunotherapy [31] is presented and studied for cancer treatment. In order to improve the immunotherapy, it is important and significant to search the suitable growth law of tumors under the immune surveillance. Thus many mathematical models on tumor and immune system are put forward constantly [30, 2, 37]. For instance, R. Lefever [12, 15] proposed the model of tumor cells in the surveillance of immune cells based on Michaelis-Menten mechanism [38, 16].

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Besides, the immune response to destroy and eliminate tumor cells plays an important role in the process of immunotherapies. However, in the tumor tissue, the intensity of the immune response is influenced by the environment conditions [8], such as the ionic strength, the supply of oxygen and nutrients, chemicals, temperature, radiations, etc. So, it is necessary to study the probable influences of random perturbation in the process of cancer evolution. In fact, in recent years, many scholars have studied the influence of noise on some nonlinear systems [39, 40, 13, 41, 42, 43, 35]. Moreover, many works study the effect of noise on cancer dynamics analytically and numerically, and many stochastic characters have been discovered, such as stochastic bifurcation [4, 1], first extinction time [8, 25], noise induced extinction [17], stochastic resonance [9, 18, 44], resonant activation [36, 28, 26], noise enhanced stability [10, 29], and transient dynamics of biological systems [5, 11, 33, 3, 6, 34].

In this work, we mainly consider one kind of tumor growth model under stochastic perturbation and investigate the effect of noise on the progression of tumor evolution, especially extinction and persistence. The advantages of this paper are as follows. Firstly, we apply the theoretical approach of Ito calculus, instead of that related to the Fokker-Planck equation, to analyze the influence of noises in the tumor growth model. Secondly, we carry out the threshold for extinction and different kinds of persistence of cancer cells by mathematical proofs. In particular, the condition of extinction and survival is gained. Finally, we interpret the results and discuss the biological significance and application in cancer immunotherapy.

The work is organized below. In Section 2, the stochastic tumor-immune model is given. Section 3 analyzes the extinction and persistence of cancer cells under stochastic noise and proves the necessary conditions for extinction and different persistence. We verify and illustrate conclusions of Section 3 by numerical simulations in Section 4. Main conclusions and some future directions are shown in Section 5. In addition, some notations are introduced for convenience

\[ f^* = \limsup_{t \to +\infty} f(t); \quad f_* = \liminf_{t \to +\infty} f(t); \quad \langle f(t) \rangle = \frac{1}{t} \int_0^t f(s)ds; \]
\[ \hat{f} = \sup_{t \in \mathbb{R}_+} f(t); \quad \hat{f} = \inf_{t \in \mathbb{R}_+} f(t); \quad t \wedge \tau_k = \min\{t, \tau_k\}, \]

here \( f \) is a function of the time parameter \( t \) defined on \([0, \infty)\).

2. The model. The model on tumor cells under immune surveillance against cancer can be expressed by a Michaelis-Menten reaction [38]

\begin{align*}
X &\xrightarrow{\lambda} 2X \\
X + Y &\xrightarrow{k_1} Z \xrightarrow{k_2} Y + P,
\end{align*}

(1) \hspace{2cm} (2)

here \( X, Y, Z \) and \( P \) represent the population densities of tumor cells, immune cells, the compounds of tumor cells and immune cells and the dead or non-replicating tumor cells, respectively. \( \lambda, k_1 \) and \( k_2 \) are velocity coefficients. The biological interpretation of reactions can be represented that Equation (1) shows that the tumor cells duplicate at rate \( \lambda \), the former of Equation (2) means that the immune cells reveal and abolish cancer cells at rate \( k_1 \), and the latter of Equation (2) indicates that the compounds dissociate into immune cells and dead or non-replicating tumor cells at rate \( k_2 \). Besides, it is assumed that \( Y + Z = E = \text{constant} \). This reaction can be transformed to an equivalent single-variable deterministic dynamics.
differential equation \([37, 12]\),

\[
\frac{dx(t)}{dt} = x(t)(1 - \theta(t)x(t)) - \frac{\beta(t)x(t)}{1 + x(t)},
\]

here \(x(t) > 0\) represents the normalized tumor cells density. The proportional relationships are as follows:

\[x = \frac{k_1}{k_2}X, \quad \theta = \frac{k_2}{k_1}, \quad \beta = \frac{k_1E}{\lambda}, \quad t = \lambda t.\]

Moreover, the parameters \(\theta(t)\) and \(\beta(t)\) stand for the relative rate of compounds dissociation and the specific immune ratio, respectively. From Equation (3), it is seen that the growth of cancer relies on the parameters \(\theta(t)\) and \(\beta(t)\). Besides, stochastic factors influence the parameters in tumor micro–environment. So, it will be indispensable to study the tumor evolution in stochastic environment. In our work, the random perturbation is supposed to be Gaussian white noise \(\xi(t)\) satisfying \((\xi(t)) = 0\) and \((\xi(t)\xi(t')) = \delta(t - t')\). Then, the immune coefficient \(\beta(t)\) is subject to stochastic noise with \(\beta(t) \rightarrow \beta(t) - \sigma(t)\xi(t)\). Here \(\sigma(t)\) is the intensity of the noise. So, the equivalent Langevin equation of Formula (3) can be rewritten as,

\[
dx(t) = \{x(t)[1 - \theta(t)x(t)] - \frac{\beta(t)x(t)}{1 + x(t)}\}dt + \frac{\sigma(t)x(t)}{1 + x(t)}dB(t), \quad x(0) = x_0, \quad (4)\]

in which \(B(t)\) stands for standard Wiener process. Taking into account the biological significance, it is supposed that \(\theta(t), \beta(t)\) and \(\sigma(t)\) are bounded continuous function on \([0, \infty)\), and \(\theta(t)\) remains in the interval \((0, 1)\).

3. Analysis for steady probability distribution. The deterministic dynamics model (3) can be interpreted as an over damped motion in a potential [9] \(U(x)\)

\[
\frac{dx(t)}{dt} = -\frac{dU(x)}{dx}
\]

where \(U(x) = -\frac{x^2}{2} + \frac{\beta}{3}x^3 + \beta x - \beta \ln(x + 1)\). The potential \(U(x)\) exhibits at most three extremes:

\[x_0 = 0, \quad x_u = \frac{1 - \theta - \sqrt{(1 + \theta)^2 - 4\beta\theta}}{2\theta}, \quad x_s = \frac{1 - \theta + \sqrt{(1 + \theta)^2 - 4\beta\theta}}{2\theta}\]

Taking into account the biological significance and convenience of discussion, we fix the parameter \(\theta = 0.25\), the system is bistable and the bistable feature of system depends on the \(\beta\)(see FIGURE 1). Moreover, the model possesses one unstable state \(x_u\), and two stable states: the state of extinction \(x_0\), namely there is not tumor cells, and the state of stable tumor \(x_s\), namely the tumor exists and stays at a certain level. When \(\beta > 1.48\), the left potential barrier height \(\Delta V_2 = V(x_u) - V(x_0)\) is bigger than the right potential barrier height \(\Delta V_1 = V(x_u) - V(x_s)\), and while when \(\beta < 1.48\), the left potential barrier height \(\Delta V_2\) is smaller than the right potential barrier height \(\Delta V_1\). So, when \(\beta > 1.48\), the tumor cells are easier to experience extinction than recurrence, while the result is opposite when \(\beta < 1.48\).

Next, we simulate the steady probability distribution of tumor cells \(x(t)\) for different noise intensities \(\sigma^2\) and immune parameter intensities \(\beta\). In FIGURE 2,
the quasi-stationary probability distribution function is plotted. Here we choose parameter \( \theta = 0.25 \). For (a) and (b), the quasi steady state probability density as a function of \( x \) varying with immune parameter intensities are given. The results show clearly that if \( \beta = 1.46 \), the tumor cells are easier to experience recurrence, and the tumor cells are easier to experience extinction when \( \beta = 1.50 \). Meanwhile, in (c) and (d), we consider the influence of noise intensity on tumor when \( \beta = 1.48 \). We can observe that the probability in extinction state of tumor will increase with the increase of \( \sigma^2 \), while the probability of stable tumor state will decrease with the increase of \( \sigma^2 \), which indicates the increase of noise intensity makes the tumor cells more likely to experience extinction when \( \beta = 1.48 \).

4. Analysis for extinction and persistence under stochastic perturbation.

First, we need some appropriate definitions in order to analyze extinction and persistence. In the paper, we use the definition of strong persistence in the mean [19] and stochastic persistence [22]. Moreover, some proof methods are derived from the works red by Mao [23] and Liu [20, 21]. Some important definitions are expressed as followed:

1): If \( \lim_{t \to +\infty} x(t) = 0 \), then cancer cells are said to go extinction almost surely(a.s.)

2): If \( \langle x \rangle_* > 0 \), then the cancer cells are said to be strong persistence in the mean a.s.

3): If \( N > 0 \) and \( M > 0 \) so that \( P_*\{x(t) \geq N\} \geq 1-\varepsilon \) and \( P_*\{x(t) \leq M\} \geq 1-\varepsilon \), then the cancer cells size is said to be stochastic persistence a.s.

**Lemma 4.1.** For any given initial value \( x(0) = x_0 > 0 \), Equation (4) has a unique global solution \( x(t) \) on \( t \geq 0 \) and it will stay in \( \mathbb{R}_+ \) with probability one.
Proof. Because the coefficients of Equation (4) satisfy local Lipschitz continuous, for any initial value $x_0 \in R_+$, the equation has a unique local solution $x(t)$ on $t \in [0, \tau_e]$, where $\tau_e$ is the explosion time [24]. In order to prove that this solution is global, we have to prove $\tau_e = \infty$. Suppose that $n_0$ is so large that $x_0$ being in the interval $[1/n_0, n_0]$. For every integer $n > n_0$, we define the stopping times $\tau_n = \inf \{t \in [0, \tau_e] : x(t) \notin (\frac{1}{n}, n)\}$. According to the definition, $\tau_n$ is increasing as $n \to \infty$. Let $\tau_\infty = \lim_{n \to +\infty} \tau_n$, whence $\tau_\infty \leq \tau_e$ a.s. Next we only need to prove $\tau_\infty = \infty$. If $\tau_\infty < \infty$, there are a couple of constants $T > 0$ and $\varepsilon \in (0, 1)$, so that $P\{\tau_\infty < T\} > \varepsilon$. Consequently, there exists an integer $n_1 > n_0$ such that

$$P\{\tau_n < T\} > \varepsilon, \quad n > n_1.$$  \hfill (6)

To prove this statement, let $V(x)$ be the $C^2$-function defined by $V(x) = x - 1 - \ln x$. It is nonnegative on $x > 0$. Using Ito formula [7] to $V(x)$, we have

$$dV(x) = V'_x dx + 0.5V''_xx(dx)^2$$

$$= [-\theta(x)x^2 + (1 + \theta(t))x - 1 - x + \frac{1}{x + 1}\beta(t) + \frac{\sigma^2(t)}{2(1 + x)^2}]dt + \frac{x - 1}{x + 1}\sigma(t)dB(t)$$

$$\leq [-\hat{\theta}(t)x^2 + (\hat{\theta}(t) + 1)x - 1 + \hat{\beta}(t) + 0.5\hat{\sigma}^2(t)]dt + \sigma(t)dB(t).$$
It follows from \( \dot{\theta}(t) > 0 \) that a positive constant \( G \) exists and is not dependent of \( x \) and \( t \), so \( dV(x) \leq Gdt + \sigma(t)dB(t) \), which implies that

\[
\int_0^{\tau_n \wedge T} dV(x) \leq \int_0^{\tau_n \wedge T} Gdt + \int_0^{\tau_n \wedge T} \sigma(s)dB(s).
\]

Taking expectation of both sides gives

\[
E[V(x(\tau_n \wedge T))] \leq V(x_0) + G(\tau_n \wedge T) \leq V(x_0) + GT.
\]

(7)

Set \( \Omega_n = \{ \tau_n < T \} \), then according to Inequality (6), we have \( P(\Omega_n) > \varepsilon \). Note that for every \( \omega \in \Omega_n \), \( x(\tau_n, \omega) \) equals either \( n \) or \( 1/n \), hence \( V(x(\tau_n, \omega)) \) is no less than \( \min\{n - 1 - \ln n, 1/n - 1 + \ln n\} \). Then, it follows from Inequality (7) that

\[
V(x_0) + GT \geq E[1_{\Omega_n} V(x(\tau_n))] \geq \varepsilon \min\{n - 1 - \ln n, 1/n - 1 + \ln n\},
\]

here \( 1_{\Omega_n} \) is a indicator function of \( \Omega_n \). Letting \( n \to \infty \) leads to the contradiction \( \infty > V(x_0) + GT = \infty \). That is to say, Equation (4) has a unique global solution \( x(t) > 0 \) with any given initial state \( x_0 > 0 \).

\( \square \)

**Theorem 4.2.** If \( \langle \frac{(1+\theta(t)^2}{4\theta(t)} + \frac{1}{2} \sigma^2(t) - \beta(t) \rangle < 0 \), tumor cells \( x(t) \) will become extinction a.s.

**Proof.** Applying Ito rule to \( x + \ln x \) results in

\[
d(x + \ln x) = \frac{1 + x}{x} dx - \frac{1}{2x^2}(dx)^2
\]

\[
= [-\theta(t)x^2 + (1 - \theta(t))x + 1 - \beta(t)]dt + \sigma(t)dB(t) - \frac{\sigma^2(t)}{2(1 + x)^2} dt
\]

\[
\leq [\frac{(1 + \theta(t))^2}{4\theta(t)} - \beta(t)]dt + \sigma(t)dB(t) + \frac{1}{2} \sigma^2(t)dt.
\]

Integrating from 0 to \( t \) leads to

\[
x(t) + \ln x(t) - (x_0 + \ln x_0) \leq \int_0^t \left[ \frac{(1 + \theta(t))^2}{4\theta(t)} + \frac{1}{2} \sigma^2(s) - \beta(s) \right] ds + M(t),
\]

which means that

\[
\frac{x(t) + \ln x(t) - (x_0 + \ln x_0)}{t} \leq \langle \frac{(1 + \theta(t))^2}{4\theta(t)} + \frac{1}{2} \sigma^2(t) - \beta(t) \rangle + \frac{M(t)}{t},
\]

here \( M(t) = \int_0^t \sigma(s)dB(s) \). Here \( M(t) \) is a martingale.

\[
\langle M(t), M(t) \rangle = \int_0^t \sigma^2(s)ds \leq \varepsilon^2 t.
\]

By virtue of the strong law of large numbers for martingales [24], we can see

\[
\lim_{t \to +\infty} \frac{M(t)}{t} = 0.
\]

(8)

So, we can derive that

\[
\langle \frac{x(t) + \ln x(t)}{t} \rangle \leq \langle \frac{(1 + \theta(t))^2}{4\theta(t)} + \frac{1}{2} \sigma^2(t) - \beta(t) \rangle^*.
\]

That is to say, if \( \langle \frac{(1+\theta(t))^2}{4\theta(t)} + \frac{1}{2} \sigma^2(t) - \beta(t) \rangle^* < 0 \), we can see that \( \lim_{t \to +\infty} x(t) = 0 \). \( \square \)
Theorem 4.3. If \((1 - \frac{1}{2}\sigma^2(t) - \beta(t))_+ > 0\), then the cancer cells \(x(t)\) will be strongly persistent in the mean and the lower bound in the mean \(\langle x \rangle_* \geq (1 - \frac{1}{2}\sigma^2(t) - \beta(t))_+/\theta\) a.s.

Proof. According to Ito rule, we can obtain that
\[
d\ln x = \frac{1}{x}dx - \frac{1}{2x^2}(dx)^2 = (1 - \theta(t)x - \frac{\beta(t)}{1 + x})dt + \frac{\sigma(t)}{1 + x}dB(t) - \frac{\sigma^2(t)}{2(1 + x)^2}dt.
\]

Integrating both sides from 0 to \(t\), we get
\[
\ln x(t) - \ln x_0 \geq \int_0^t (1 - \beta(s) - \frac{1}{2}\sigma^2(s))ds - \theta \int_0^t x(s)ds - \int_0^t \sigma(s)dB(s).
\]

(9)

It follows from Equation (8) that for arbitrary \(\varepsilon > 0\), there is \(T_1 > 0\) such that \(t^{-1} \int_0^t \sigma(s)dB(s) < \varepsilon/2\) for all \(t > T_1\). In addition, for similar \(\varepsilon\), there exists \(T_2 > 0\) such that \(t^{-1} \int_0^t (1 - \beta(s) - \frac{1}{2}\sigma^2(s))ds > (1 - \frac{1}{2}\sigma^2(t) - \beta(t))_+ - \varepsilon/2\) for all \(t > T_2\). Substituting these inequalities into Inequality (9), we have
\[
\ln x(t) - \ln x_0 > vt - \theta \int_0^t x(s)ds - \int_0^t \sigma(s)dB(s), \quad t > T = \max\{T_1, T_2\},
\]

where \(v = (1 - \frac{1}{2}\sigma^2(t) - \beta(t))_+ - \varepsilon\). Set \(h(t) = \int_0^t x(s)ds\), then we can compute
\[
\ln (dh/dt) > vt - \theta h(t) + \ln x_0, \quad t > T.
\]

Consequently,
\[
\exp(\theta h(t))(dh/dt) > x_0 \exp(vt).
\]

Integrating both sides from \(T\) to \(t\) gives
\[
\theta^{-1}[\exp(\theta h(t)) - \exp(\theta h(T))] > x_0 v^{-1}[\exp(vt) - \exp(vT)].
\]

Rewriting this inequality, we obtain
\[
\exp(\theta h(t)) > \exp(\theta h(T)) + x_0 \theta v^{-1} \exp(vT) - x_0 \theta v^{-1} \exp(vT).
\]

Taking logarithm of both sides, we derive
\[
h(t) > \theta^{-1}\ln[x_0 \theta v^{-1} \exp(vT) + \exp(\theta h(T)) - x_0 \theta v^{-1} \exp(vT)].
\]

Namely,
\[
(\frac{1}{t} \int_0^t x(s)ds)_* \geq \theta^{-1}\{\ln[x_0 \theta v^{-1} \exp(vt)] + \exp(\theta h(T)) - x_0 \theta v^{-1} \exp(vT)/t\}_*.
\]

So, we can derive that
\[
\langle x \rangle_* \geq \theta^{-1}\{t^{-1}\ln[x_0 \theta v^{-1} \exp(vt)]\}_* = v/\theta = (1 - \frac{1}{2}\sigma^2(t) - \beta(t))_+ \varepsilon)/\theta.
\]

Since \(\varepsilon\) is arbitrary, we obtain \(\langle x \rangle_* \geq (1 - \frac{1}{2}\sigma^2(t) - \beta(t))_+/\theta > 0\).

Theorem 4.4. If \((1 - \sigma^2(t) - \beta(t))_+ > 0\), cancer cells \(x(t)\) will become stochastic permanent a.s.
Proof. Firstly, it is shown that for any given \( \varepsilon > 0 \), there is a number \( M > 0 \) such that \( P_x \{ x(t) \leq M \} \geq 1 - \varepsilon \). Define the function \( V(x) = x^q \) for \( x \in \mathbb{R}_+ \), where \( 0 < q < 1 \). By Ito rule, we get
\[
dV(x) = qx^{q-1}dx + \frac{1}{2}q(q-1)x^{q-2}(dx)^2
\]
\[
= qx^q[1 - \theta(t)x - \frac{\beta(t)}{1 + x} + \frac{(q-1)\sigma^2(t)}{2(1 + x)^2}]dt + \frac{q\sigma(t)x^q}{1 + x}dB(t).
\]
Applying Ito formula to \( \exp(t)V(x) \), it yields that
\[
d(\exp(t)V(x)) = \exp(t)V(x)dt + \exp(t)dV(x)
\]
\[
= \exp(t)\{x^q + qx^q[1 - \theta(t)x - \frac{\beta(t)}{1 + x} + \frac{(q-1)\sigma^2(t)}{2(1 + x)^2}]\}dt
\]
\[
+ \frac{\exp(t)q\sigma(t)x^q}{1 + x}dB(t)
\]
\[
\leq \exp(t)Kdt + \exp(t)q\sigma(t)x^qdB(t),
\]
(10)
in which \( K \) is a constant, which is positive and uncorrelated to \( x \) and \( t \). Let \( k_0 > 0 \) be sufficiently large so that \( \frac{1}{k_0} \leq x_0 \leq k_0 \). For every integer \( k > k_0 \), we define the stopping times \( \tau_k = \inf\{t \geq 0 : x(t) \notin (\frac{1}{k}, k)\} \). It is clear that \( \tau_k \) is increasing as \( k \rightarrow \infty \). We integrate Inequality (10) from 0 to \( \tau_k \), then we can derive
\[
\int_0^{t \wedge \tau_k} d(\exp(t)V(x)) \leq \int_0^{t \wedge \tau_k} K \exp(s)ds + \int_0^{t \wedge \tau_k} q\exp(s)\sigma(s)x^q(s)dB(s).
\]
In other words,
\[
\exp(t \wedge \tau_k)x^q(t \wedge \tau_k) - x^q_0 \leq \exp(t \wedge \tau_k) - K + \int_0^{t \wedge \tau_k} q\exp(s)\sigma(s)x^q(s)dB(s).
\]
Taking expectation to the inequality, we then see
\[
E[\exp(t \wedge \tau_k)x^q(t \wedge \tau_k)] - x^q_0 \leq E(\exp(t \wedge \tau_k) - K) \leq K(\exp(t) - 1).
\]
Letting \( k \rightarrow \infty \) obtains \( \exp(t)E(x^q(t)) \leq x^q_0 + K(\exp(t) - 1) \), which indicates that
\[
E(x^q(t)) \leq \exp(-t)x^q_0 + K(1 - \exp(-t)).
\]
(11)
Having \( t \rightarrow \infty \), we have already proved \( \limsup_{t \rightarrow +\infty} E(x^q(t)) \leq K \). Thus in view of Chebyshev inequality [24], we can see that for given \( \varepsilon > 0 \), there is \( M = (K^{1/q})/(\varepsilon^{1/q}) \) so that
\[
P\{x(t) > M\} = P\{x^q(t) > M^q\} \leq \frac{E(x^q(t))}{M^q}.
\]
Set \( t \rightarrow \infty \), then we can prove that \( P_x \{ x(t) > M \} \leq E(x^q(t))/M^q = \varepsilon \). That is to say, \( P_x \{ x(t) \leq M \} \geq 1 - \varepsilon \).

Next we need to demonstrate for any fixed \( \varepsilon > 0 \), there is a constant \( N > 0 \) so that \( P_x \{ x(t) \geq N \} \geq 1 - \varepsilon \). Define \( V_1(x) = x^{-1} \) for \( x \in \mathbb{R}_+ \). Using Ito rule to \( V_1(x) \) results in
\[
dV_1(x) = -x^{-2}dx + x^{-3}(dx)^2
\]
\[
= V_1(x)[\theta(t)x + \frac{\beta(t)}{1 + x} - 1 + \frac{\sigma^2(t)}{1 + x}]dt - \frac{\sigma(t)x^{-1}}{1 + x}dB(t)
\]
\[
\leq V_1(x)[\theta(t)x + \beta(t) - 1 + \sigma^2(t)]dt - \frac{\sigma(t)x^{-1}}{1 + x}dB(t).
\]
Set $V_2(x) = (1 + V_1(x))^\alpha$, for $\alpha \in (\frac{1}{4}, \frac{1}{2})$. Applying Ito rule to $V_2(x)$, we have
\[
dV_2(x) = \alpha(1 + V_1(x))^{\alpha-1}dV_1(x) + 0.5\alpha(\alpha - 1)(1 + V_1(x))^{\alpha-2}(dV_1(x))^2
\]
\[
\leq \alpha(1 + V_1(x))^{\alpha-2}\{\theta(t)x + \beta(t) + \sigma^2(t) - 1\}
+ 0.5(\alpha - 1)\sigma^2(t)x^{-2}(1 + x)dt - \frac{\alpha(1 + V_1(x))^{\alpha-1}\sigma(t)x^{-1}}{1 + x}dB(t)
\]
\[
\leq \alpha(1 + V_1(x))^{\alpha-2}\{1 - (1 - \sigma^2(t) - \beta(t))_\eta\}
\times \exp\{\alpha(1 + V_1(x))^{\alpha-1}\sigma(t)x^{-1}dB(t)\}
\]
for sufficiently large $t \geq T$ and $\epsilon > 0$. Next, let $V_3(x) = \exp(\eta t)V_2(x)$. By Ito rule to $V_3(x)$ for $t \geq T$, we have
\[
dV_3(x) = \eta \exp(\eta t)V_2(x)dt + \exp(\eta t)dV_2(x)
\]
\[
\leq \exp(\eta t)(1 + V_1(x))^{\alpha-2}\{1 - (1 - \sigma^2(t) - \beta(t))_\eta\}
- \exp(\eta t)(1 + V_1(x))^{\alpha-1}\sigma(t)x^{-1}(1 + x)^{-1}dB(t).
\]
Next suppose $\eta > 0$ is so small that $0 < \eta/\alpha < (1 - \sigma^2(t) - \beta(t))_\eta - \epsilon$. Hence there is the upper boundary $C_1$ so that
\[
dV_4(x) \leq C_1 \exp(\eta t)dt - \alpha \exp(\eta t)(1 + V_1(x))^{\alpha-1}\sigma(t)x^{-1}(1 + x)^{-1}dB(t),
\]
for $t \geq T$. That is to say,
\[
\int_T^t dV_5(x) \leq \int_T^t C_1 \exp(\eta s)ds - \int_T^t \alpha \exp(\eta s)(1 + V_1(x))^{\alpha-1}\sigma(s)(x + 1)^{-1}dB(s).
\]
Calculating expectation on both sides
\[
E(\exp(\eta t)(1 + V_1(x))^{\alpha} \leq \exp(\eta T)(1 + V_1(x(T)))^{\alpha} + \frac{C_1}{\eta} [\exp(\eta t) - \exp(\eta T)]
\]
\[-\alpha E \int_T^t \exp(\eta s)(1 + V_1(x))^{\alpha-1}\sigma(s)(x + 1)^{-1}dB(s).
\]
Compute that
\[
E \int_T^t \exp(\eta s)(1 + V_1(x))^{2\alpha-2}x^{-2}(s)\sigma(s)(x + 1)^{-2}ds
\]
\[
\leq E \int_T^t \exp(\eta s)(x^2 + x)^{2\alpha-2}x^{-4\alpha}(s)\sigma(s)ds
\]
\[
\leq \int_T^t \exp(\eta s)E(x^{2-4\alpha})\sigma(s)ds < \infty.
\]
The last inequality follows from the boundness of $\sigma^2(t)$, $\alpha \in (\frac{1}{4}, \frac{1}{2})$ and Inequality (11). Hence we have $\exp(\eta s)(1 + V_1(x))^{\alpha-1}x^{-1}(s)\sigma(s)(x + 1)^{-1} \in M^2([T, t]; R)$, where $M^2([T, t]; R)$ denotes the real-valued measurable spaces. Apply stochastic integral [10] yields
\[
E \int_T^t \exp(\eta s)(1 + V_1(x))^{\alpha-1}x^{-1}(s)\sigma(s)(x + 1)^{-1}dB(s) = 0.
\]
That is to say, we have already shown that
\[ \limsup_{t \to +\infty} E V^\alpha_1(x) \leq \limsup_{t \to +\infty} E (1 + V_1(x))^\alpha \leq \frac{C_1}{\eta}. \]
Namely, \( \limsup_{t \to +\infty} E (x^{-\alpha}(t)) \leq \frac{C_1}{\eta} = C \). Thus for any given \( \varepsilon > 0 \), let \( N = (\varepsilon^{1/\alpha})/(C^{1/\alpha}) \), by Chebyshev’s inequality,
\[ P\{x(t) < N\} = P\{x^{-\alpha/2} > N^{-\alpha/2}\} \leq \frac{E(x^{-\alpha}(t))}{N^{-\alpha}} = \varepsilon. \]
That is to say, \( P^*(x(t) < N) \leq \varepsilon \), whence \( P^*(x(t) \geq N) \geq 1 - \varepsilon. \)

5. **Numerical simulations.** For testing the theoretical results, we apply Milstein method [14] to carry out the stochastic simulations and illustrate the theoretical results. The iterative equation is as follows
\[
x_{k+1} = x_k + [x_k(1 - \theta(k\Delta t)x_k)]\Delta t - \frac{\beta(k\Delta t)x_k}{1 + x_k}\Delta t + \frac{\sigma(k\Delta t)x_k\sqrt{\Delta t}\xi_k}{1 + x_k} + 0.5\sigma^2(k\Delta t)x_k(\xi_k^2\Delta t - \Delta t),
\]
where \( \xi_k \) is i.i.d Gaussian random variable.

**Figure 3.** The valid regions as a function of \( \theta(t) \) and \( \beta(t) \).

Throughout this paper below, we choose the initial value \( x_0 = 0.5 \). According to the sufficient conditions in Theorem 4.2, the persistence and extinction of cancer cells rely on the parameters space \( \sigma(t) \) and \( \beta(t) \). The critical line of extinction and persistence is plotted in FIGURE 3. In view of Theorem 4.2, we can obtain that cancer cells will become extinct if the values of the parameters \( \sigma(t) \) and \( \beta(t) \) are in the region \( A \) of FIGURE 3. On the contrary, tumor will be persistent if the parameter belongs to the region \( B \).

FIGURE 4 gives the growth of tumor with different values of \( \beta(t) \) and \( \sigma(t) \). We fix \( \theta(t) = 0.9 + 0.01 \sin t \) and choose \( \sigma^2(t) = 0.02 + 0.004 \sin t \), \( \beta(t) = 3 + \sin t \) or
Figure 4. Solutions of extinction of tumor cells for (a): \( \sigma^2(t) = 0.02 + 0.004 \sin(t) \), \( \beta(t) = 3 + \sin(t) \); (b): \( \sigma^2(t) = 1 + 0.8 \sin(t) \), \( \beta(t) = 3 + \sin(t) \); (c): \( \sigma^2(t) = 1 + 0.8 \sin(t) \), \( \beta(t) = 6 + \sin(t) \), with the initial value \( x_0 = 0.5 \).

\[ \sigma^2(t) = 1 + 0.8 \sin(t) \), \( \beta(t) = 3 + \sin(t) \) or \( \sigma^2(t) = 1 + 0.8 \sin(t) \), \( \beta(t) = 6 + \sin(t) \), which are labeled as curves (a), (b) and (c) in the region A of FIGURE 3 respectively. It is quite clear that \( \langle (1+\theta(t))^2 + \frac{1}{2}\sigma^2(t) - \beta(t) \rangle^* < 0 \). According to Theorem 4.2, the tumor cells \( x(t) \) will become extinction. Figure 4 confirms this result. From FIGURE 4, we see that curves will decrease to zero. Besides, in comparison with the curves (a), (b) and (c) of FIGURE 4, it is seen that tumor cells will experience extinction faster when the immune strength \( \beta(t) \) and noise intensity \( \sigma(t) \) become greater. This behavior implies that the strength of immunization and the intensity of noise will help to speed up the extinction of tumor when the parameters meet the condition of Theorem 4.2. This result provides an idea that the extinction time of tumor could be decreased by increasing the immune coefficient and stochastic noise under given conditions.

In FIGURE 5, when we fix parameter \( \theta(t) = 0.9 + 0.01 \sin(t) \) and choose the following parameter (d) \( \sigma^2(t) = 0.002 + 0.001 \sin(t) \) and \( \beta(t) = 0.97 + 0.009 \sin(t) \) in the region of B of FIGURE 3, where it is satisfied the condition \( (1 - \frac{1}{2}\sigma^2(t) - \beta(t))_x^* > 0 \) in Theorem 4.3, we see that tumor cells will be strong persistent in the mean. Besides, we can observe that tumor cells will decrease firstly and then show randomness at low level, but don’t tend to zero. Meanwhile, the mean of tumor cells decreases firstly and ultimately reaches a limiting value and the lower bound in the mean is given by \( (x)_x^* \geq (1 - \frac{1}{2}\sigma^2(t) - \beta(t))_x^*/\hat{\theta} = 0.0227 \). This phenomenon is called strong persistence in the mean, which means that tumor cells can be controlled and remain at relatively low concentrations because of the immune coefficient with stochastic noise.
Figure 5. Solutions of strong persistence in the mean of tumor cells for (d): \( \sigma^2(t) = 0.002 + 0.001 \sin t, \beta(t) = 0.97 + 0.009 \sin t, \) with the initial value \( x_0 = 0.5. \)

Figure 6. Solutions of strong persistence in the mean of tumor for (e): \( \sigma^2(t) = 0.02 + 0.002 \sin t, \beta(t) = 0.8 + 0.008 \sin t, \) with the initial value \( x_0 = 0.5. \)
Figure 7. Mean time to extinction (MET) as a function of the noise intensity for different values of $\beta$ at $\theta = 0.25$.

Next, according to the condition of Theorem 4.4, we take $\sigma^2(t) = 0.02 + 0.002 \sin t$ and $\beta(t) = 0.8 + 0.008 \sin t$ in the curve (e) of the region $B$ of FIGURE 3 and choose $\theta(t) = 0.9 + 0.01 \sin t$. From FIGURE 6, the evolution of tumor cells exhibits randomness and unpredictability. This means that the tumor remains in an unstable state and the immune is insufficient to control the tumor. Here noise is not beneficial to the evolution of tumor. By comparing FIGURE 4, FIGURE 5 and FIGURE 6, we can deduce that the immune strength and stochastic noise play an important role in the progress of tumor treatment.

FIGURE 7 shows that the mean extinction time (MET) as a function of noise intensity for different values of $\beta$ at $\theta = 0.25$. We can see that the MET decreases as the parameter $\beta$ and noise intensity $\sigma^2$ increases. This indicates that the MET depends on the immune parameter of system, and the increase of immune parameter $\beta$ is conducive to tumor extinction. Under immune surveillance, a certain amount of noise is helpful to the extinction of tumor and treatment.

6. Conclusions. In our work, we mainly explore the stochastic behavior of extinction and survival of tumor cells under immunization. First, the model describing the tumor growth with immune surveillance is derived from the catalytic Michaelis-Menten reaction. The Gaussian white noise is adopted to simulate stochastic perturbation. Then, the steady probability distribution of tumor cells for different noise intensities and immune parameter intensities are investigated, and the sufficient conditions for extinction, strong persistence in the mean and stochastic persistence are deduced. The main results are expressed as followed:
(a): if \( \langle (1+\theta(t))^{2} + \frac{1}{2}\sigma^{2}(t) - \beta(t) \rangle^{*} < 0 \), then the cancer cells will go to extinction a.s.

(b): if \( (1 - \frac{1}{2}\sigma^{2}(t) - \beta(t))^{*} > 0 \), then the cancer cells will be strong persistence in the mean and the lower bound in the mean \( \langle x \rangle^{*} \geq (1 - \frac{1}{2}\sigma^{2}(t) - \beta(t))^{*}/\hat{\theta} \) a.s.

(c): if \( (1 - \sigma^{2}(t) - \beta(t))^{*} > 0 \), then the cancer cells will exhibit stochastic persistence a.s.

Based on theoretical and simulation results, we find that extinction and survival of tumor not only rely on the state of immunization but also the state of noise. Further, the critical line of extinction and persistence is plotted. When the tumor is under immune surveillance, stochastic noise could accelerate the extinction of tumor. When the tumor cells is not enough controlled by the immune surveillance, stochastic noise will enhance the randomness of tumor cells and is not beneficial in tumor therapy. So, it is very important to study the stochastic effect under immune surveillance in tumor treatment. In general, our theoretical results are beneficial to know the evolution mechanism and design effective immunotherapy of tumor.

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