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PERSISTENCE AND EXTINCTION OF THE TUMOR-IMMUNE STOCHASTIC MODEL WITH EFFECTOR CELLS AND CYTOKINES*

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Abstract To investigate the effects of microenvironment on the tumor growth and the loss rates of effector cells and cytokine, we present a stochastic tumor-immune model with the treatment response of effector cells assisted by cytokine to tumor growth. By using the comparison theorem, the Itô formula and the law of large numbers, we prove the existence of globally unique positive solution and obtain the sufficient conditions for the extinction and the persistence of tumor cells. Moreover, using our theoretical results, we perform some numerical simulations to show that different noise intensities lead to different states of tumor cells, including tumor extinction and tumor persistence, which confirms the obtained theoretical results and is useful for theoretical guidance of inhibiting tumor growth in clinical medicine.

Keywords Stochastic responses, Itô formula, tumor-immune model, extinction, persistent in mean.

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1. Introduction

With the rapid development and mutual penetration of oncology, immunology and molecular biology, immunological principles and methods have been applied to tumor immunotherapy. It becomes a new research direction in tumor immunotherapy to enhance anti-tumor immune response by using immune system supported external input drugs of activating effector cells and cytokines [1,3,11,13,17]. In order to explore tumor immunotherapy, scholars established many tumor-immune models to study the mechanism of tumor-immune [4–6,12,14,15,18,21,22].

Different immune cells have different ways to eliminate tumors. According to the characteristic of immune effector cells killing tumor cells under the support of some cytokines [1,3,17], Kirschner and Panetta [12] established an immunotherapy

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model of tumor-immune interaction. The specific form is as follows

$$\begin{cases} \dfrac{\mathrm{d}x}{\mathrm{d}t} = cy - \mu_2 x + \dfrac{p_1 xz}{g_1 + z} + s_1 \\ \dfrac{\mathrm{d}y}{\mathrm{d}t} = r_2 y(1 - by) - \dfrac{axy}{g_2 + y} \\ \dfrac{\mathrm{d}z}{\mathrm{d}t} = \dfrac{p_2 xy}{g_3 + y} - \mu_3 z + s_2 \end{cases} \tag{1.1}$$

where $x(t)$ represents the number of effector cells; $y(t)$ represents the number of tumor cells; $z(t)$ represents the number of cytokines (IL-2); c represents the antigenicity of the tumor; μ_2 represents the loss rate of effector cells; r_2 represents the growth rates of tumor cells ; μ_3 represents the loss rate of cytokines (IL-2); a represents the strength of the immune response,s_1 represents an external source of effector cells such as LAK or TIL cells; s_2 represents an external input of cytokines (IL-2) into the system; Michaelis-Menten function $\frac{p_1 x(t) z(t)}{g_1 + z(t)}, \frac{ax(t)y(t)}{g_2 + y(t)}, \frac{p_2 x(t) y(t)}{g_3 + y(t)}$ represent functional immune response functions. Authors [12] investigated the stability and bifurcations. In 2001, DePillis [5] established a tumor model with immune resistance and drug therapy, in which the functional response functions of immune response have two types, one is the Michaelis-Menten function, the other is the bilinear function.

In fact, the growth, the proliferation and the apoptosis of tumor cells are influenced by microenvironmental factors [2, 24, 25]. Hence, stochastic differential equations are introduced into modeling tumor-immune mechanisms. For example, the environmental noise and the time delay of tumor cell proliferation can lead to stochastic resonance of tumor growth to the immunotherapy [6]. Based on the theorem in tumor-immune system with periodic treatment, Li and Li [14] obtained that the extinction and survival of tumor cells rely on the intensity of periodic treatment. The microenvironment noise of tumor-immune system may affect the stochastic persistence of tumor cells and effector immune cells [15].

Recently, the role of cytokines (IL-21) in the treatment of malignancies has been widely investigated [3, 17]. In addition, many research results demonstrate that the inhibition of tumor angiogenesis and the destruction of the microenvironment depended on tumor survival may be attributed to direct effects on tumor cell proliferation. Therefore, in this paper, based on the immunotherapy of hepatocellular carcinomas, we replace two Michaelis-Menten functions of x and y with two bilinear functions of x and y, as follows

$$\frac{ax(t)y(t)}{g_2 + y(t)} \to ax(t)y(t), \quad \frac{p_2 x(t)y(t)}{g_3 + y(t)} \to p_2 x(t)y(t).$$

In addition, by considering the effect of microenvironment noise, we introduce stochastic perturbation into the loss rate of effector cells, the growth rate of tumor cells, the loss rate of cytokines in model (1.1), and assume that parameters μ_2, r_2, μ_3 are disturbed by $\mu_2 + \rho_1 \mathrm{d}B_1(t), r_2 + \rho_2 \mathrm{d}B_2(t), \mu_3 + \rho_3 \mathrm{d}B_3(t)$, respectively. Here ρ_1, ρ_2 and ρ_3 represent the intensities of environmental white noises for the loss rate of effector cells, the growth rate of tumor cells and the loss rate of cytokines, respectively. $B_i(t), i = 1, 2, 3, (B_i(0) = 0)$ are mutually independent standard Brownian motions defined on a complete probability space $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t \geq 0}, P)$ with a filtration $\{\mathcal{F}_t\}_{t \geq 0}$ satisfying the usual conditions(i.e., it is increasing and

right continuous while $\mathcal{F}_0$ contains all p-null sets), $\rho_i^2 > 0$. Therefore, our modified tumor-immune model with white noise is as follows

$$\begin{cases} \mathrm{d}x = (cy(t) - \mu_2 x(t) + \dfrac{p_1 x(t) z(t)}{g_1 + z(t)} + s_1)\mathrm{d}t - \rho_1 x(t)\mathrm{d}B_1(t) \\ \mathrm{d}y = (r_2 y(t) - \beta y^2(t) - a x(t) y(t))\mathrm{d}t + \rho_2 y(t)\mathrm{d}B_2(t) \\ \mathrm{d}z = (p_2 x(t) y(t) - \mu_3 z(t) + s_2)\mathrm{d}t - \rho_3 z(t)\mathrm{d}B_3(t) \end{cases} \tag{1.2}$$

where $\beta = r_2 b$ and $x(t), y(t), z(t)$ represent the number of effector cells, tumor cells(hepatocellular carcinomas), cytokines (IL-21), respectively. c, r_2, μ_2, p_1, g_1, s_1, r_2, b, a, p_2, μ_3, s_2 are the similar parameters in model (1.1).

The rest of the paper is organized as follows. In Section 2, we give some notations, definitions and the theory of stochastic differential equation. In Section 3, we prove that the tumor-immune solutions with the initial value in R_+^3 are globally positive and uniformly bounded in mean. In addition, we derive the sufficient conditions of the extinction and persistence of tumor cells. In Section 4, we perform numerical simulations to verify our obtained theorems and show the effects of stochastic intensity on tumor extinction and tumor survival. In section 5, we give some suggestions for the immunotherapy methods of inhibiting tumor growth, based on our obtained theoretical analysis and numerical results.

2. Theory of stochastic differential equation

For the convenience of investigation into the sufficient conditions of tumor cell extinction and tumor survival under the interference of microenvironment white noise, we introduce the following definitions [7–10, 15, 16] and theories [19, 20].

(i) The tumor cell $y(t)$ will go to extinction a.s. if $\lim_{t\to\infty} y(t) = 0$.

(ii) The tumor cell $y(t)$ will be strong persistent in the mean a.s. if

$$\langle y(t)\rangle_* = \lim_{t\to\infty} \inf \langle y(t)\rangle > 0.$$

(iii) $\langle y(t)\rangle = \frac{1}{t}\int_0^t y(s)\mathrm{d}s, \quad \langle y(t), y(t)\rangle = \frac{1}{t}\int_0^t y^2(s)\mathrm{d}s.$

Lemma 2.1 (Theorem 6.4, [19, 20]). *Let $X(t)$ be a d-dimensional Itô progress on $t \geq 0$ with the stochastic differential*

$$\mathrm{d}X(t) = \boldsymbol{f}(t)\mathrm{d}t + \boldsymbol{g}(t)\mathrm{d}B(t)$$

where $\boldsymbol{f}(t) \in \mathbb{L}^1(R_+, R^d)$ and $\boldsymbol{g}(t) \in \mathbb{L}^2(R_+, R^{d\times m})$. Let $V(X(t), t) \in C^{2,1}(R^d \times R_+, R)$. Then $V(X(t), t)$ is again an Itô progress with the stochastic differential given by

$$\mathrm{d}V(X(t), t) = LV(X(t), t)\mathrm{d}t + V_X(X(t), t)\boldsymbol{g}(t)\mathrm{d}B(t) \qquad a.s.$$

where $LV(X(t), t) = V_t(X(t), t) + V_X(X(t), t)\boldsymbol{f}(t) + \frac{1}{2}trace(\boldsymbol{g}^T(t)V_{XX}(X(t), t)\boldsymbol{g}(t))$.

Lemma 2.2 (Lemma 6.1, [19, 20]). *Let $f \in \mathbb{C}([0, \infty) \times \Omega, (0, \infty))$ and $F(t) \in \mathbb{C}([0, \infty) \times \Omega, R)$. Suppose there are constants λ_0, λ and T, such that for all $t \geq T$, the following condition holds*

$$\ln f(t) \geq \lambda t - \lambda_0 \int_0^t f(s)\mathrm{d}s - F(t) \tag{2.1}$$

where $\lim\limits_{t\to\infty}\frac{F(t)}{t}=0$ *a.s. , then the following conclusion holds*

$$\liminf_{t\to\infty}\frac{1}{t}\int_0^t f(s)\mathrm{d}s\geq\frac{\lambda}{\lambda_0}\quad a.s..$$

Lemma 2.3 (Chapter VI Theorem1.1*, [23]). *(comparison theorem): If the following one-dimensional stochastic differential equations*

$$\begin{aligned}\mathrm{d}x_1(t)=&f_1(x_1(t),t)\mathrm{d}t+g(x_1(t),t)\mathrm{d}B_1(t),x_1(0)=\tilde{x}_1\in\mathbb{R}\\ \mathrm{d}x_2(t)=&f_2(x_2(t),t)\mathrm{d}t+g(x_2(t),t)\mathrm{d}B_1(t),x_2(0)=\tilde{x}_2\in\mathbb{R}\end{aligned}$$

(where $f_i(x(t),t)\in\mathbb{C}([0,\infty)\times\mathbb{R}),g(x(t),t)\in\mathbb{C}([0,\infty)\times\mathbb{R})$*) both have solutions. Furthermore, if the pathwise uniqueness of solution holds for at least one of the above two stochastic differential equations and following conditions hold*

(i) $\rho(s)$ *is the function defined on* $[0,\infty)$, $\rho(0)=0$, $\int_{0^+}^{+\infty}\rho(s)\mathrm{d}s=\infty$ *and satisfies*

$$|g(x_1(t),t)-g(x_2(t),t)|\leq\rho\left(|x_1(t)-x_2(t)|\right),x_1(t),x_2(t)\in\mathbb{R},t\geq0;$$

(ii) $f_1(x(t),t)\leq f_2(x(t),t),\quad\forall t\geq0,x(t)\in\mathbb{R};$

(iii) $x_1(0)\leq x_2(0)$, *then* $x_1(t)\leq x_2(t),t\geq0$, *a.s., where* $x_i(t)(i=1,2)$ *are the solutions processes of the above two stochastic differential equations, respectively.*

3. Extinction and persistence of tumor cells

In this section, we use the method in published papers [8–10, 15, 16] to prove that there is a globally unique positive solution in model (1.2).

Theorem 3.1. *For any positive initial value* $(x_0,y_0,z_0)\in R_+^3$, *if* $\mu_2>p_1$, *then there is a unique solution* $(x(t),y(t),z(t))$ *in model* (1.2) *as* $t\geq0$, *and the solution will remain in* R_+^3 *with probability* 1.

Proof. Since the coefficients of model (1.2) satisfy the locally Lipschitz condition for any initial value $(x_0,y_0,z_0)\in R_+^3$, there is a unique local solution $(x(t),y(t),z(t))$ of model (1.2) on $t\in[0,\tau_e)$, where τ_e is the explosion time. To show that this solution is global, we only need to show $\tau_e=\infty$ a.s. Let $k_0\geq0$ be sufficiently large so that x_0,y_0,z_0 all lie within the interval $\left[\frac{1}{k_0},k_0\right]$. For each integer $k\geq k_0$, we define the stopping time

$$\tau_k=\inf\left\{t\in[0,\tau_e):\min\{x(t),y(t),z(t)\}\leq\frac{1}{k}\text{ or }\max\left\{x(t),y(t),z(t)\right\}\geq k\right\}.$$

By the definition of stopping time, we know that τ_k is increasing as $k\to\infty$. Set $\tau_\infty=\lim_{k\to\infty}\tau_k$. Since $\tau_\infty\leq\tau_e$ a.s., we know that if $\tau_\infty=\infty$ a.s., then $\tau_e=\infty$ a.s., that is to say, for all $t\geq0$, $(x(t),y(t),z(t))\in R_+^3$ a.s.

Next, we will prove $\tau_\infty=\infty$ a.s.by contradiction. Assuming the contrary, if τ_∞ cannot reach ∞, there exist constants $T>0$ and $\varepsilon\in(0,1)$ such that $P\left\{\tau_\infty\leq T\right\}>\varepsilon$. Thus there exists an integer $k_1\geq k_0$ such that

$$P\left\{\tau_k\leq T\right\}>\varepsilon,\quad k>k_1.\tag{3.1}$$

We define a C^3- function $V : R^3_+ \to \bar{R}_+$ by

$$V(x,y,z) = \theta\,(x - 1 - \ln x) + y - 1 - \ln y + \frac{a}{p_2}\,(z - 1 - \ln z) \tag{3.2}$$

where $\theta = a/(\mu_2 - p_1)$ is positive constant as $\mu_2 > p_1$. The nonnegativity of function $V(x,y,z)$ can be seen from the inequality $u - 1 - \ln u \geq 0$, $\forall u > 0$. Let $k \geq k_0$ and $\theta > 0$ be arbitrary. Applying the Itô formula, we have

$$\mathrm{d}V(x,y,z) = LV(x,y,z)\mathrm{d}t - \theta(x-1)\rho_1\mathrm{d}B_1(t) + (y-1)\rho_2\mathrm{d}B_2(t) - \frac{a}{p_2}(z-1)\rho_3 z\mathrm{d}B_3(t).$$

Here

$$\begin{aligned} LV(x,y,z) =& \theta(1-\frac{1}{x})(cy(t) - \mu_2 x(t) + \frac{p_1 x(t) z(t)}{g_1 + z(t)} + s_1) + (1 - \frac{1}{y})(r_2 y(t) - \beta y^2(t) \\ & - a x(t) y(t)) + \frac{a}{p_2}(1 - \frac{1}{z})(p_2 x(t) y(t) - \mu_3 z(t) + s_2) + \frac{1}{2}(\theta\rho_1^2 + \rho_2^2 + \frac{a\rho_3^2}{p_2}). \end{aligned}$$

By computing, we have

$$\begin{aligned} LV(x,y,z) =& \theta(s_1 + \mu_2) - r_2 + \frac{a(s_2 + \mu_3)}{p_2} + \frac{1}{2}(\theta\rho_1^2 + \rho_2^2 + \frac{a}{p_2}\rho_3^2) + (\theta c + r_2 + \beta)y \\ & - \beta y^2 + (a - \theta\mu_2)x + \frac{\theta p_1 x(t) z(t)}{g_1 + z(t)} - \frac{\theta(cy + s_1)}{x} - \frac{\theta z p_1}{g_1 + z} \\ & - \frac{a\mu_3}{p_2} z - \frac{a(p_2 xy + s_2)}{p_2 z}. \end{aligned} \tag{3.3}$$

Then we have inequality

$$\begin{aligned} LV(x,y,z) \leq& \theta(s_1 + \mu_2) - r_2 + \frac{a(s_2 + \mu_3)}{p_2} + \frac{1}{2}(\theta\rho_1^2 + \rho_2^2 + \frac{a}{p_2}\rho_3^2) + \frac{(\theta c + r_2 + \beta)^2}{4\beta} \\ & + (a - \theta(\mu_2 - \ p_1))x. \end{aligned} \tag{3.4}$$

Since $\theta = a/(\mu_2 - p_1)$, we obtain

$$LV(x,y,z) \leq K, \tag{3.5}$$

where $K = \theta(s_1 + \mu_2) - r_2 + \frac{a(s_2+\mu_3)}{p_2} + \frac{1}{2}(\theta\rho_1^2 + \rho_2^2 + \frac{a}{p_2}\rho_3^2) + \frac{(\theta c + r_2 + \beta)^2}{4\beta}$. K is a positive constant. Thus we obtain

$$\mathrm{d}V(x,y,z) \leq K\mathrm{d}t - \theta(x-1)\rho_1\mathrm{d}B_1(t) + (y-1)\rho_2\mathrm{d}B_2(t) - \frac{a}{p_2}(z-1)\rho_3\mathrm{d}B_3(t). \tag{3.6}$$

By integrating both sides of inequality (3.6) from 0 to $\tau_k \wedge T$ and taking expectation, we obtain

$$E\left[V\left(x\left(\tau_k \wedge T\right), y\left(\tau_k \wedge T\right), z\left(\tau_k \wedge T\right)\right)\right] \leq V\left(x_0, y_0, z_0\right) + E\left(\int_0^{\tau_k \wedge T} K\mathrm{d}t\right).$$

Then we have

$$E\left[V\left(x\left(\tau_k \wedge T\right), y\left(\tau_k \wedge T\right), z\left(\tau_k \wedge T\right)\right)\right] \leq V\left(x_0, y_0, z_0\right) + KT. \tag{3.7}$$

Let $\Omega_k = \{\tau_k \wedge T\}$ for $k \geq k_1$. By inequality (3.1), we have $P(\Omega_k) \geq \varepsilon$. Note that for every $\omega \in \Omega_k$, at least one of $x(\tau_k, \omega)$ or $y(\tau_k, \omega)$ or $z(\tau_k, \omega)$ equals either k or $\frac{1}{k}$, therefore

$$V(x(\tau_k), y(\tau_k), z(\tau_k)) \geq f(k)$$

where $f(k) = M\left[\left(\frac{1}{k} - 1 + \ln k\right) \wedge (k - 1 - \ln k)\right]$, $M = \max\{\theta, 1, a/p_2\}$. By inequality (3.7), we have

$$\begin{aligned} V(x_0, y_0, z_0) + KT &\geq E\left[I_{\Omega_k(\omega)} V(x(\tau_k), y(\tau_k), z(\tau_k))\right] \\ &\geq \varepsilon f(k), \end{aligned}$$

where $I_{\Omega_k(\omega)}$ is the indicator function of Ω_k. Let $k \to \infty$, which leads to $\infty > V(x_0, y_0, z_0) + KT = \infty$, which is contradiction. It is clear that the assumption that τ_∞ cannot reach ∞ does not hold. Therefore, we have $\tau_\infty = \infty$ a.s., and this means that $x(t)$, $y(t)$ and $z(t)$ will not cause a blast in any finite time with probability 1, that is to say, model (1.2) must have a unique globally positive solution $(x(t), y(t), z(t))$ for any given initial condition in R^3_+ a.s. This completes the proof. □

Lemma 3.1 (Lemma 2.2, [8]). *Let Φ is a solution of the following equation*

$$\mathrm{d}\Phi(t) = (r_2\Phi(t) - \beta\Phi^2(t))\mathrm{d}t + \rho_2\Phi(t)\mathrm{d}B_2(t). \tag{3.8}$$

Then

$$\limsup_{t\to\infty} E[\Phi(t)] \leq \frac{r_2}{\beta}. \tag{3.9}$$

Theorem 3.2. *If $\mu_2 > p_1$, then the solution $(x(t), y(t), z(t))$ of model (1.2) with any positive initial value $(x_0, y_0, z_0) \in R^+_3$ is uniformly bounded in mean. The specific form is as follows*

$$\begin{aligned} &\limsup_{t\to\infty} E[x(t)] \leq \frac{cr_2 + \beta s_1}{\beta(\mu_2 - p_1)}; \quad \limsup_{t\to\infty} E[y(t)] \leq \frac{r_2}{\beta}; \\ &\limsup_{t\to\infty} E[y(t) + \frac{a}{p_2} z(t)] \leq \frac{(r_2 + \mu_3)^2}{4\mu_3\beta} + \frac{as_2}{p_2\mu_3} \end{aligned} \tag{3.10}$$

Proof. By the second equation of model (1.2) and (3.8), we obtain $y(t) \leq \Phi(t)$. Since inequality (3.9) in Lemma 3.1 holds, it is easy to see that

$$\limsup_{t\to\infty} E[y(t)] \leq \frac{r_2}{\beta}. \tag{3.11}$$

Next, we show $x(t)$ is bounded in mean. By integrating the first equation of model (1.2) from 0 to t, we have

$$x(t) = x(0) + \int_0^t \left(cy(t) - \mu_2 x(t) + \frac{p_1 x(t) z(t)}{g_1 + z(t)} + s_1\right)\mathrm{d}t - \rho_1 \int_0^t x(t)\mathrm{d}B_1(t). \tag{3.12}$$

By taking expectation both sides of (3.12), we obtain

$$E[x(t)] = x(0) + c\int_0^t E[y(t)]\mathrm{d}t - \int_0^t E\left[\mu_2 x(t) - \frac{p_1 x(t) z(t)}{g_1 + z(t)} - s_1\right]\mathrm{d}t. \tag{3.13}$$

Differentiating both sides of (3.13) with respect to t, we obtain

$$\frac{\mathrm{d}E[x(t)]}{\mathrm{d}t} = cE[y(t)] - \mu_2 E[x(t)] + E\left[\frac{p_1 x(t) z(t)}{g_1 + z(t)}\right] + s_1. \tag{3.14}$$

For $x > 0$, $y > 0$ and $z > 0$, we obtain

$$\frac{\mathrm{d}E[x(t)]}{\mathrm{d}t} \leq cE[y(t)] + s_1 - \mu_2 E[x(t)] + p_1 E[x(t)]. \tag{3.15}$$

Thus, by (3.11) and the comparison theorem, if $\mu_2 > p_1$, then we obtain

$$\lim_{t\to\infty} \sup E[x(t)] \leq \frac{cr_2 + \beta s_1}{\beta(\mu_2 - p_1)}.$$

Next, we show $y(t) + \frac{a}{p_2} z(t)$is bounded in mean. Let

$$G(t) = y(t) + \frac{a}{p_2} z(t).$$

Calculating the time derivative of G(t) along model (1.2) , we obtain

$$\begin{aligned} \mathrm{d}G(t) = &\left((r_2 + \mu_3) y(t) - \beta y^2 - \mu_3 G(t) + \frac{a}{p_2} s_2\right) \mathrm{d}t \\ &+ \rho_2 y(t) \mathrm{d}B_2(t) - \frac{a}{p_2} \rho_3 z(t) \mathrm{d}B_3(t). \end{aligned} \tag{3.16}$$

By integrating (3.16) from 0 to t, we have

$$\begin{aligned} G(t) =& G(0) + \int_0^t ((r_2 + \mu_3) y(t) - \beta y^2 - \mu_3 G(t) + \frac{a}{p_2} s_2) \mathrm{d}t + \rho_2 \int_0^t y(t) \mathrm{d}B_2(t) \\ &- \frac{a}{p_2} \rho_3 \int_0^t z(t) \mathrm{d}B_3(t). \end{aligned} \tag{3.17}$$

By taking expectation both sides of (3.17), we obtain

$$E[G(t)] = G(0) + \int_0^t E[((r_2 + \mu_3) y(t) - \beta y^2 - \mu_3 G(t) + \frac{a}{p_2} s_2] \mathrm{d}t. \tag{3.18}$$

Differentiating both sides of (3.18) with respect to t, we obtain

$$\mathrm{d}E[G(t)] = E[(r_2 + \mu_3) y(t) - \beta y^2 + \frac{a}{p_2} s_2] - \mu_3 E[G(t))]. \tag{3.19}$$

By (3.19), we obtain

$$\mathrm{d}E[G(t)] \leq \frac{(r_2 + \mu_3)^2}{4\beta} + \frac{a}{p_2} s_2 - \mu_3 E[G(t))].$$

Thus, by the comparison theorem, we have

$$\lim_{t\to\infty} \sup E[G(t)] \leq \frac{(r_2 + \mu_3)^2}{4\mu_3 \beta} + \frac{a s_2}{p_2 \mu_3}$$

that is

$$\lim_{t\to\infty} \sup E[y(t) + \frac{a}{p_2} z(t)] \leq \frac{(r_2 + \mu_3)^2}{4\mu_3 \beta} + \frac{a s_2}{p_2 \mu_3}.$$

This completes the proof. □

Remark 3.1. Since the solution of model (1.2) is positive, from (3.10), it is clear that

$$\limsup_{t\to\infty} E[z(t)] \le \frac{p_2(r_2+\mu_3)^2}{4a\mu_3\beta} + \frac{s_2}{\mu_3}.$$

Theorem 3.2 shows that when the loss rate μ_2 of effector cells is greater than the rate p_1 of stimulated by cytokines (IL-2), effector cells,tumor cells and cytokines (IL-2) are all uniformly bounded in mean.

Lemma 3.2. *Let $(x(t), y(t), z(t))$ be a positive solution of model (1.2) with any positive initial value $(x_0, y_0, z_0) \in R_3^+$. If $2\mu_2 > c + 2p_1 + \rho_1^2$, then*

$$\limsup_{t\to\infty} E[x^2(t)] \le \frac{c(\frac{2r_2+\rho_2^2}{2\beta})^2 + \frac{2s_1(cr_2+\beta s_1)}{\beta(\mu_2-p_1)}}{2\mu_2 - c - 2p_1 - \rho_1^2}; \quad \limsup_{t\to\infty} E[y^2(t)] \le \left(\frac{2r_2+\rho_2^2}{2\beta}\right)^2. \tag{3.20}$$

Proof. Applying the Itô formula, we have

$$\mathrm{d}y^2(t) = 2y(t)(r_2y(t) - \beta y^2(t) - ax(t)y(t))\mathrm{d}t + \rho_2^2y^2\mathrm{d}t + 2\rho_2y^2(t)\mathrm{d}B_2(t). \tag{3.21}$$

Since $x(t) > 0$ and $y(t) > 0$, we have

$$\mathrm{d}y^2(t) \le ((2r_2+\rho_2^2)y^2(t) - 2\beta y^3(t))\mathrm{d}t + 2\rho_2y^2(t)\mathrm{d}B_2(t). \tag{3.22}$$

By integrating (3.22) from 0 to t, taking expectation and differentiating with respect to t, we obtain

$$\begin{aligned}\frac{\mathrm{d}E[y^2(t)]}{\mathrm{d}t} &\le (2r_2+\rho_2^2)E[y^2(t)] - 2\beta E[y^3(t)] \\ &\le (2r_2+\rho_2^2)E[y^2(t)] - 2\beta(E[y^2(t)])^{1+1/2}.\end{aligned} \tag{3.23}$$

Thus, we have

$$\limsup_{t\to\infty} E[y^2(t)] \le \left(\frac{2r_2+\rho_2^2}{2\beta}\right)^2. \tag{3.24}$$

Applying the Itô formula, we have

$$\mathrm{d}x^2(t) = 2x(t)\left(cy(t) - \mu_2x(t) + \frac{p_1x(t)z(t)}{g_1+z(t)} + s_1\right)\mathrm{d}t + \rho_1^2x^2\mathrm{d}t - 2\rho_1x^2(t)\mathrm{d}B_(t). \tag{3.25}$$

Since $z(t) > 0$, we have

$$\mathrm{d}x^2(t) \le (cx^2(t)+cy^2(t)-2\mu_2x^2(t)+2p_1x^2(t)+2s_1x+\rho_1^2x^2)\mathrm{d}t-2\rho_1x^2(t)\mathrm{d}B_1. \tag{3.26}$$

By integrating (3.26) from 0 to t, taking expectation and differentiating with respect to t, we obtain

$$\frac{\mathrm{d}E[x^2(t)]}{\mathrm{d}t} \le cE[y^2(t)] + 2s_1E[x(t)] - (2\mu_2 - c - 2p_1 - \rho_1^2)E[x^2(t)]. \tag{3.27}$$

By (3.10) and (3.24), if $2\mu_2 > c + 2p_1 + \rho_1^2$, then we obtain

$$\limsup_{t\to\infty} E[x^2(t)] \le \frac{c(\frac{2r_2+\rho_2^2}{2\beta})^2 + \frac{2s_1(cr_2+\beta s_1)}{\beta(\mu_2-p_1)}}{2\mu_2 - c - 2p_1 - \rho_1^2}.$$

This completes the proof. □

Theorem 3.3. *Let $(x(t), y(t), z(t))$ be the solution of model (1.2) with any positive initial value $(x_0, y_0, z_0) \in R_3^+$. If $\mu_2 > as_1/r_2$ and $\rho_2^2 > \frac{2(r_2\mu_2 - as_1)}{\mu_2}$, then we have*

$$\langle x(t)\rangle_* = \frac{s_1}{\mu_2}, \qquad \lim_{t\to\infty} y(t) = 0, \qquad \langle z(t)\rangle_* = \frac{s_2}{\mu_3}. \tag{3.28}$$

Proof. By integrating the first equation of model (1.2) from 0 to t and dividing it by t, we have

$$\frac{x(t) - x_0}{t} = c\langle y(t)\rangle - \mu_2\langle x(t)\rangle + p_1\left\langle \frac{x(t)z(t)}{g_1 + z(t)}\right\rangle + s_1 - \frac{1}{t}\int_0^t \rho_1 x(s)\mathrm{d}B_1(s).$$

By computing, we have

$$\begin{aligned}\langle x(t)\rangle &= \frac{c}{\mu_2}\langle y(t)\rangle + \frac{p_1}{\mu_2}\left\langle \frac{x(t)z(t)}{g_1 + z(t)}\right\rangle + \frac{s_1}{\mu_2} - \frac{1}{t\mu_2}\int_0^t \rho_1 x(s)\mathrm{d}B_1(s) - \frac{x(t) - x_0}{t\mu_2}\\ &\geq \frac{s_1}{\mu_2} - \frac{N_1(t)}{t} - \frac{x(t) - x_0}{t\mu_2}\end{aligned} \tag{3.29}$$

where

$$N_1(t) = \int_0^t \frac{\rho_1}{\mu_2} x(s)\mathrm{d}B_1(s)$$

which is a local continuous martingale and $N_1(0) = 0$. Based on the strong law of large numbers for local martingales in the method of [9], by (3.10) and (3.20), we obtain

$$\lim_{t\to\infty} \frac{N_1(t)}{t} = 0 \quad a.s.$$

By (3.29), we obtain

$$\langle x(t)\rangle_* = \lim_{t\to\infty} \inf\langle x(t)\rangle \geq \frac{s_1}{\mu_2} \quad a.s. \tag{3.30}$$

In addition, applying the Itô formula to the first equation of model (1.2), we obtain

$$\mathrm{d}\ln\frac{1}{x(t)} = \left(-\frac{cy(t)}{x(t)} + \mu_2 - \frac{p_1 z(t)}{g_1 + z(t)} - \frac{s_1}{x(t)} + \frac{1}{2}\rho_1^2\right)\mathrm{d}t + \rho_1\mathrm{d}B_1(t). \tag{3.31}$$

Then integrating both sides of (3.31) from 0 to t we have

$$\ln\frac{1}{x(t)} - \ln\frac{1}{x_0} = \left(\mu_2 + \frac{1}{2}\rho_1^2\right)t - \int_0^t \left(\frac{cy(s)}{x(s)} + \frac{p_1 z(s)}{g_1 + z(s)} + \frac{s_1}{x(s)}\right)\mathrm{d}s + \int_0^t \rho_1\mathrm{d}B_1(s). \tag{3.32}$$

By computing, (3.32) becomes

$$\ln\frac{1}{x(t)} \geq \mu_2 t - c\int_0^t \frac{y(s)}{x(s)}\mathrm{d}s - s_1\int_0^t \frac{1}{x(s)}\mathrm{d}s - p_1\int_0^t z(s)\mathrm{d}s. \tag{3.33}$$

Let

$$f(t) = \frac{1}{x(t)}, F(t) = c\int_0^t \frac{y(s)}{x(s)}\mathrm{d}s + p_1\int_0^t z(s)\mathrm{d}s.$$

It is clear that $\lim\limits_{t\to\infty}\frac{F(t)}{t}=0$, based on Lemma 2.2, let $\lambda=\mu_2$ and $\lambda_0=s_1$ in (3.2), we obtain

$$\liminf_{t\to\infty}\frac{1}{t}\int_0^t\frac{1}{x(s)}\mathrm{d}s\geq\frac{\mu_2}{s_1}\quad a.s.$$

which implies

$$\langle x(t)\rangle_*\leq\frac{s_1}{\mu_2}\quad a.s. \tag{3.34}$$

combining (3.30) and (3.34), we have

$$\langle x(t)\rangle_*=\lim_{t\to+\infty}\inf\langle x(t)\rangle=\frac{s_1}{\mu_2}\quad a.s.$$

Applying the Itô formula to the second equation of model (1.2), we get

$$\mathrm{d}\ln y(t)=(r_2-\beta y(t)-ax(t)-\frac{1}{2}\rho_2^2)\mathrm{d}t+\rho_2\mathrm{d}B_2(t). \tag{3.35}$$

By integrating (3.35) from 0 to t and dividing it by t, we have

$$\frac{\ln y(t)-\ln y_0}{t}=r_2-\beta\langle y(t)\rangle-a\langle x(t)\rangle-\frac{1}{2}\rho_2^2+\frac{N_2}{t} \tag{3.36}$$

where

$$N_2(t)=\int_0^t\rho_2\mathrm{d}B_2(s)$$

which is a local continuous martingale and $N_2(0)=0$ and

$$\lim_{t\to\infty}\frac{\langle N_2,N_2\rangle}{t}=\rho_2^2<\infty\quad a.s.$$

By the strong law of large numbers for local martingales, we obtain

$$\lim_{t\to\infty}\frac{N_2(t)}{t}=0\quad a.s.$$

Taking the superior limit on both sides of inequality (3.36), we have

$$\limsup_{t\to\infty}\frac{\ln y(t)}{t}\leq\frac{2(r_2\mu_2-as_1)-\mu_2\rho_2^2}{2\mu_2}\quad a.s.$$

If $\mu_2>as_1/r_2$ and $\rho_2^2>\frac{2(\mu_2r_2-as_1)}{\mu_2}$, then we obtain

$$\limsup_{t\to\infty}\frac{\ln y(t)}{t}\leq 0\quad a.s.$$

which implies

$$\lim_{t\to\infty}y(t)=0\qquad a.s.$$

By using same method of $\langle x(t)\rangle_*=\frac{s_1}{\mu_2}$, we can obtain that $\langle z(t)\rangle_*=\frac{s_2}{\mu_3}$, This completes the proof. □

Remark 3.2. Theorem 3.3 shows that when the effector cells loss rate μ_2 and noise intensity ρ_2 of tumors are both larger, tumor cells will go to extinction.

Theorem 3.4. *Suppose that* $(x(t), y(t), z(t))$ *is the solution of model* (1.2) *with any positive initial value* $(x_0, y_0, z_0) \in R_3^+$. *If* $\mu_2 > (r_2 p_1 + a s_1)/r_2$ *and* $\rho_2^2 < \frac{2(r_2(\mu_2 - p_1) - a s_1)}{\mu_2 - p_1}$, *then tumor cells will be strong persistent in mean* $\langle y(t)\rangle_* > 0$ *as* $t \to \infty$, *and*

$$\limsup_{t\to\infty} \langle x(t)\rangle < \frac{r_2 - \frac{1}{2}\rho_2^2}{a}, \qquad \liminf_{t\to\infty} \langle z(t)\rangle \geq \frac{s_2}{\mu_3}.$$

Proof. By integrating the first equation of model (1.2) from 0 to t and dividing it by t, we have

$$\frac{x(t) - x_0}{t} = c\langle y(t)\rangle - \mu_2 \langle x(t)\rangle + p_1 \left\langle \frac{x(t)z(t)}{g_1 + z(t)} \right\rangle + s_1 - \frac{1}{t}\int_0^t \rho x(s) \mathrm{d}B_1(s).$$

By computing, we have

$$\mu_2 \langle x(t)\rangle \leq c \langle y(t)\rangle + p_1 \langle x(t)\rangle + s_1 - \frac{1}{t}\int_0^t \rho_1 x(t) \mathrm{d}B_1(s) - \frac{x(t) - x_0}{t}. \tag{3.37}$$

Applying the Itô formula, we have

$$\mathrm{d}\ln y(t) = (r_2 - \beta y(t) - a x(t) - \frac{1}{2}\rho_2^2)\mathrm{d}t + \rho_2 \mathrm{d}B_2(t). \tag{3.38}$$

By integrating both sides of the equation (3.38) from 0 to t, we have

$$\frac{\ln y(t) - \ln y_0}{t} = r_2 - \beta \langle y(t)\rangle - a \langle x(t)\rangle - \frac{1}{2}\rho_2^2 + \frac{1}{t}\int_0^t \rho_2 \mathrm{d}B_2(s). \tag{3.39}$$

By (3.39), we obtain

$$\beta \langle y(t)\rangle = r_2 - \frac{1}{2}\rho_2^2 - a \langle x(t)\rangle + \frac{1}{t}\int_0^t \rho_2 \mathrm{d}B_2(s) - \frac{\ln y(t) - \ln y_0}{t}. \tag{3.40}$$

Submitting (3.37)into (3.40), if $\mu_2 > p_1$, then we obtain

$$\begin{aligned}\beta \langle y(t)\rangle \geq r_2 - \frac{1}{2}\rho_2^2 - \frac{ac}{\mu_2 - p_1}\langle y(t)\rangle - \frac{a s_1}{\mu_2 - p_1} + \frac{a}{(\mu_2 - p_1)t}\int_0^t \rho_1 x(t)\mathrm{d}B_1(s) \\ + \frac{a(x(t) - x_0)}{t(\mu_2 - p_1)} + \frac{1}{t}\int_0^t \rho_2 \mathrm{d}B_2(s) - \frac{\ln y(t) - \ln y_0}{t}.\end{aligned} \tag{3.41}$$

By (3.41) and $x(t), y(t), z(t)$ are all positive, we obtain

$$\langle y(t)\rangle \geq \frac{r_2(\mu_2 - p_1) - a s_1}{\beta(\mu_2 - p_1) + ac} - \frac{(\mu_2 - p_1)\rho_2^2}{2(\beta(\mu_2 - p_1) + ac)} - \frac{(\ln y(t) - \ln y_0)(\mu_2 - p_1)}{t(\beta(\mu_2 - p_1) + ac)}. \tag{3.42}$$

Taking the inferior limit on both sides of (3.42), if $\mu_2 > p_1$, we have

$$\liminf_{t\to\infty} \langle y(t)\rangle \geq \frac{r_2(\mu_2 - p_1) - a s_1}{\beta(\mu_2 - p_1) + ac} - \frac{(\mu_2 - p_1)\rho_2^2}{2(\beta(\mu_2 - p_1) + ac)}. \tag{3.43}$$

If $\mu_2 > (r_2 p_1 + a s_1)/r_2$ and $\rho_2^2 < \frac{2(r_2(\mu_2 - p_1) - a s_1)}{\mu_2 - p_1}$, then $\liminf_{t\to\infty} \langle y(t)\rangle > 0$,that is to say, tumor cells will be strong persistent $\langle y(t)\rangle_* > 0$. By (3.39) and $\langle y(t)\rangle_* > 0$, we have

$$\limsup_{t\to\infty} \langle x(t)\rangle < \frac{r_2 - \frac{1}{2}\rho_2^2}{a}.$$

In addition, by integrating the second equation of model (1.2) from 0 to t and dividing it by t, we have

$$\frac{z(t)-z_0}{t} = p_2\langle x(t)y(t)\rangle - \mu_3\langle z(t)\rangle + s_2 - \frac{1}{t}\int_0^t \rho_3 z(s)\mathrm{d}B_3(s).$$

By the strong law of large number for local martingales, we obtain

$$\liminf_{t\to\infty}\langle z(t)\rangle \geq \frac{s_2}{\mu_3}.$$

This completes the proof. □

Remark 3.3. Theorem 3.4 shows that when the effector cells loss rate μ_2 is larger and noise intensity ρ_2 of tumors is weak, tumor cells will be strong persistent in the mean. It is reveal that stochastic factors can control tumor growth. The various external stochastic disturbances are considered in many systems with external disturbances have been considered to study delayed dynamics [26–28]. Zhang et al [26] investigated Hybrid multi-delay impulsive control for synchronisation of multi-links stochastic delayed complex networks with semi-Markov jump. Zhai et al [27] investigated Stabilization of stochastic complex networks with delays based on completely aperiodically intermittent control. Zhou et al [28] investigated Stability of stochastic Lévy noise coupled systems with mixed delays.

4. Numerical simulations

In this section, we perform some numerical simulations to show the possible dynamics of effector cells, tumor cells and cytokines in Theorems 1-4. By referring to the value of parameters in paper [12], choosing parameters of model (1.2) as follows

$$\begin{aligned} c =& 0.05, \mu_2 = 0.28, p_1 = 0.1238, g_1 = 2\times 10^7, s_1 = 0.12, r_2 = 0.98, \beta = 0.98\times 10^{-8},\\ a =& 0.8, p_2 = 0.98, u_3 = 0.98, s_2 = 0.05 \end{aligned} \tag{4.1}$$

the initial value

$$(x_0, y_0, z_0) = (1, 1, 1) \tag{4.2}$$

and several different intensities of environmental white noises, we perform some numerical simulations and obtain Figs.1-4. With parameters (4.1) and initial value (4.2), in Figure 1, we observe that if the model (1.2) has no white noise, then there exists a unique interior equilibrium of model(1.2), which shows the persistent states of tumor cells, effector cells and cytokines of model (1.2) on the left of Figure 1; and if the model (1.2) with white noise $\rho_1 = 0.1, \rho_2 = 1.15$ and $\rho_1 = 0.1, \rho_2 = 1.15$ and $\rho_3 = 0.1$, then tumor cells of model (1.2) will go to extinction on the right of Figure 1, which shows that numerical simulations agree with analytic prediction of Theorem 3.3, at the same time, parameters meet the conditions $\rho_2^2 = 1.3225 > \frac{2(\mu_2 r_2 - a s_1)}{\mu_2} = 1.2743$ and $\langle x(t)\rangle_* = \frac{s_1}{\mu_2} = 0.4286, \langle z(t)\rangle_* = \frac{s_2}{\mu_3} = 0.0510$. With parameters (4.1) and initial value (4.2), Figures 2 and 3 shows the persistence state of tumor cells in model (1.2), it is clear that in which parameters of model (1.2) meet the condition $\rho_2^2 < \frac{2(r_2(u_2-p_1)-a s_1)}{\mu_2 - p_1} = 0.7308$ in Theorem 3.4. Figures 2 and show that Tumor cells are persistent, since parameters $\rho_2 = 0.1$ and $\rho_2 = 0.7$ of model (1.2) meet the persistence conditions $\rho_2^2 < 0.7308$.

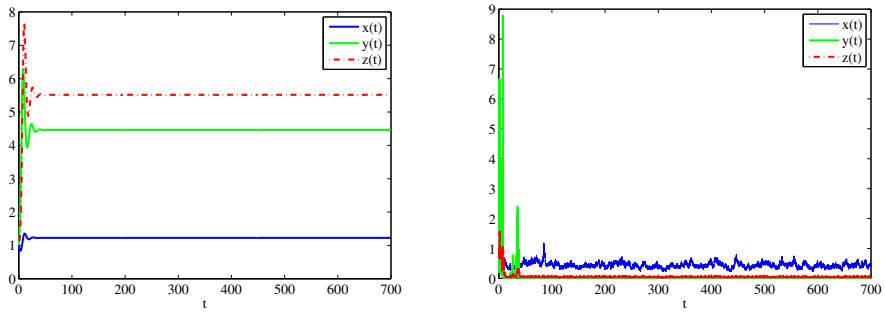

Figure 1. Waveform plots of effector cell $x(t)$, tumor cell $y(t)$ and cytokine $z(t)$ of model(1.2): Left is $\rho_i = 0, i = 1, 2, 3$; right is $\rho_1 = 0.1, \rho_2 = 1.15, \rho_3 = 0.1$

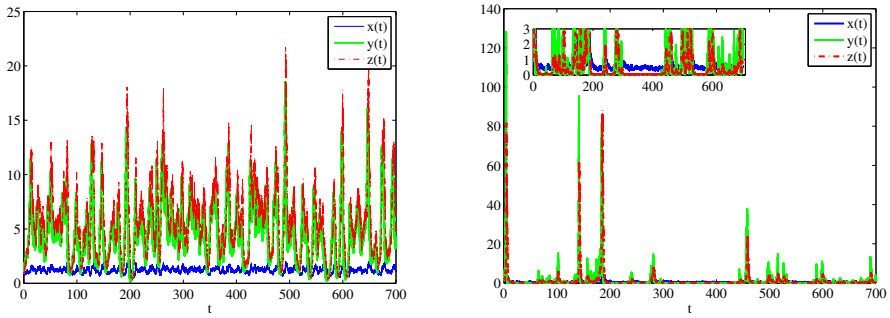

Figure 2. Waveform plots of effector cell $x(t)$, tumor cell $y(t)$ and cytokine $z(t)$ of model(1.2) with $\rho_1 = 0.1, \rho_3 = 0.1$: Left is $\rho_2 = 0.1$; right is $\rho_2 = 0.7$

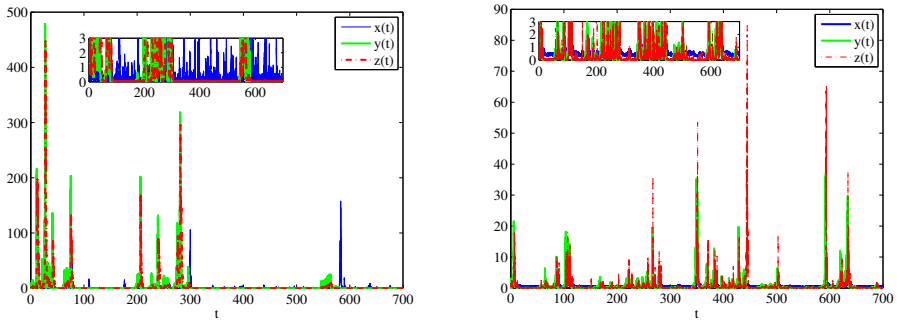

Figure 3. Waveform plots of effector cell $x(t)$, tumor cell $y(t)$ and cytokine $z(t)$ of model(1.2) with $\rho_2 = 0.7$: Left is $\rho_1 = 1.15, \rho_3 = 0.1$; right is $\rho_1 = 0.1, \rho_3 = 1.15$

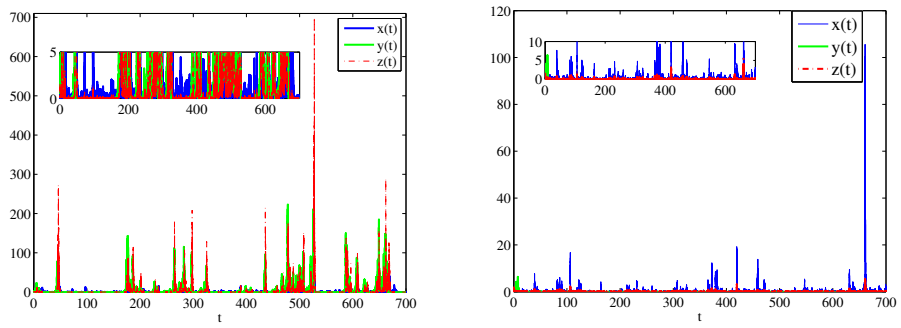

Figure 4. Waveform plots of effector cell $x(t)$, tumor cell $y(t)$ and cytokine $z(t)$ of model(1.2) with $\rho_1 = 1.15, \rho_3 = 1.15$: Left is $\rho_2 = 0.7$; right is $\rho_2 = 1.15$

In Figure 4, there exist two stronger intensities of microenvironment noises for the loss rates of effector cells and cytokines. In the left of Figure 4, $\rho_2 = 0.7$ of model (1.2) meets the persistence conditions $\rho_2^2 < 0.7308$; in the right of Figure 4, $\rho_2 = 1.15$ of model (1.2) meets the extinction condition $\rho_2^2 > 1.2743$, which indicate that the escape and survival of tumor cells are closely related to the intensity of the microenvironment noise for the tumor (hepatocellular carcinoma) growth but not the intensity of the microenvironment noise for the loss rates of effector cells and cytokines.

5. Conclusion

In this paper, through studying the dynamical behaviors of the stochastic tumor-immune model with the treatment response of effector cells assisted by cytokine to tumor growth, we obtain the existence of globally unique positive solution and sufficient conditions for tumor extinction and tumor persistence. In addition, theoretical analysis and numerical results show that the intensity of tumor microenvironmental noise is an important factor for inhibiting the growth of tumor cells. Numerical simulation results reveal that if the intensity of tumor microenvironmental noise is greater than the extinction critical value, then tumor cells will be extinct as $t \to \infty$. Therefore, according to the theoretical prediction and numerical simulation results, we suggest that hospitals should encourage experts, researchers and doctors to explore strategies to adjust the intensity of environmental fluctuation on tumor growth, such as finding new drugs which can inhibit tumor growth, and exploring minimally invasive ablation therapy to destroy the microenvironment of tumor growth. In addition, we suggest that patients should rationalize their sleep and diet habits together with mediating exercise to enhance human immunity.

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