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A Stochastic Immunotherapy Model for Breast Cancer with Pulsed Chemotherapy*

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Abstract In this paper, we consider an immunotherapy model for breast cancer with stochastic perturbations and pulsed chemotherapy. By using stochastic Lyapunov analysis and the strong law of large numbers, we first prove the existence, uniqueness and the stochastic ultimate boundedness of the global positive solution for the model. Then we obtain sufficient conditions for the extinction of tumor cells and the persistence of all three kinds of cells for this model. Finally, we use numerical simulations to verify the theoretical results which are obtained in the paper.

Keywords Breast cancer, persistence, extinction, white noise, impulsive effect

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1. Introduction

Breast cancer has become one of the malignant tumors that threaten women's lives and health in today's society and its mortality rate has already been the second highest among female tumors. Further, studies have shown that age, family history, reproductive factors, estrogen and lifestyle are the five important risk factors of breast cancer [26]. With the development of medical level and treatment method, survival rates and survival time of patients have increased. However, from the prevention of breast cancer to precise treatment, many problems remain to be explored. Therefore, it is very meaningful to study the mechanism of breast cancer. It is recorded that the immune system can recognize and eliminate cancer cells before they proliferate and grow, which is called immune surveillance [12, 29]. And the immune response to tumor cells is usually mediated by natural killer (NK) cells and cytotoxic T lymphocytes (CTLs) [1, 21, 31].

Mathematical models of tumor growth are powerful tools for understanding, predicting and improving treatment options. More and more scholars have further

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studied dynamical behaviors of tumor growth by establishing mathematical models containing NK cells and CTLs. For example, de Pillis et al. [5] set up a mathematical model to express tumor-immune interaction and they focused on the roles of NK cells and $CD8^+$ T cells in tumor monitoring. Further, Masaha et al. [20] presented a new model which involved various immune cell populations and tumor cell populations. Moreover, Wei [30] studied a four-dimensional tumor-immune model for breast cancer by comparing the results obtained from numerical simulation with those from clinical and experimental studies.

Up to now, the clinical treatment methods include surgery to remove cancerous tissue, chemotherapy, radiotherapy, immunotherapy and so on. Compared with other treatments, immunotherapy such as dendritic cell vaccine therapy [23] and HER2/neu(E75) peptide vaccine [2] has attracted more and more scholars' attention [13, 27]. Motivated by the above references, we consider the following model

$$\begin{cases} \mathrm{d}x(t) = \Big(ev - fx - p_2xz + \frac{p_3xz}{1+\alpha_3 z+\beta_3 x}\Big)\mathrm{d}t, \\ \mathrm{d}y(t) = \Big[\frac{p_5 Iy}{\alpha_4+I}\Big(1-\frac{y}{K_1}\Big)\frac{z}{\alpha_5+z} - dy + by\Big]\mathrm{d}t, \\ \mathrm{d}z(t) = \Big[z\Big(a + \frac{cE(t)z}{1+\alpha_1 E(t)+\beta_1 z^2}\Big)\Big(1-\frac{z}{K}\Big) - \frac{p_1x^2z}{1+\alpha_2 z+\beta_2 x^2} - \frac{p_6yz^2}{1+\alpha_6 z^2+\beta_6 y}\Big]\mathrm{d}t, \\ \mathrm{d}v(t) = (\alpha - \beta v)\mathrm{d}t, \\ x(0) = x_0,\ y(0) = y_0,\ z(0) = z_0,\ v(0) = v_0, \end{cases} \tag{1.1}$$

where $x(t)$, $y(t)$, $z(t)$ and $v(t)$ denote the NK cell population, the CTL population, the tumor cell population and the white blood cell (WBC) population, respectively, and $E(t)$ represents the circulating level of estradiol. Besides, $E(t)$ is a periodic function, namely, $E(t) = E(t - n\hat{\tau}), t \in [n\hat{\tau}, (n+1)\hat{\tau})$. Based on the realistic background, all parameters of system (1.1) are real and positive. Further, the significance of parameters and the schematic diagram of the interactions among four kinds of cells for system (1.1) are shown in Table 1 and Figure 1, respectively.

Table 1. The parameters and their interpretations in model (1.1).

Parameter	Description	Parameter	Description
e	Fraction of WBCs becoming NK cells	a	Tumor growth rate
f	NK cell death rate	c	Tumor growth rate induced by E_2
p_2	NK cell inactivation by tumor cells	α_1	Half saturation constant
p_3	NK cell recruitment rate	β_1	Half saturation constant
α_3	Half saturation constant	K	Tumor cell carrying capacity
β_3	Half saturation constant	p_1	NK induced tumor death
p_5	CTL growth rate induced by IL-2	α_2	Half saturation constant
I	IL-2 concentration	β_2	Half saturation constant
α_4	Half saturation constant	p_6	CTL induced tumor death
K_1	CTL carrying capacity	α_6	Half saturation constant
α_5	Half saturation constant	β_6	Half saturation constant
d	CTL death rate	α	WBC production rate
b	CTL growth rate by immunotherapy	β	WBC death rate

It is worth noting that the last equation is independent of the first three equations. Then we can derive $v(t) = \frac{\alpha}{\beta} + (v_0 - \frac{\alpha}{\beta})e^{-\beta t}$. Supposing that $v_0 > \frac{\alpha}{\beta}$, we

can easily know that $\frac{\alpha}{\beta} < v(t) \leq v_0$. Hence, system (1.1) can be reduced to the following differential equation

$$\begin{cases} \mathrm{d}x(t) = \Big(ev - fx - p_2xz + \frac{p_3xz}{1+\alpha_3 z+\beta_3 x}\Big)\mathrm{d}t, \\ \mathrm{d}y(t) = \Big[\frac{p_5Iy}{\alpha_4+I}\Big(1-\frac{y}{K_1}\Big)\frac{z}{\alpha_5+z} - dy + by\Big]\mathrm{d}t, \\ \mathrm{d}z(t) = \Big[z\Big(a + \frac{cE(t)z}{1+\alpha_1E(t)+\beta_1z^2}\Big)\Big(1-\frac{z}{K}\Big) - \frac{p_1x^2z}{1+\alpha_2z+\beta_2x^2} - \frac{p_6yz^2}{1+\alpha_6z^2+\beta_6y}\Big]\mathrm{d}t, \\ x(0) = x_0,\ y(0) = y_0,\ z(0) = z_0. \end{cases} \tag{1.2}$$

In the tumor tissue, the growth rate and cytotoxic parameters are always influenced by many environmental factors such as the supply of oxygen, temperature, radiation and gene expression [8]. As a consequence, it is very necessary to consider the impacts of the stochastic fluctuations of the environment. A widely used method is to assume that white noises may affect some parameters in a system [15, 32]. In this way, we assume that environmental fluctuations mainly affect the death rate of NK cells f, the death rate of CTLs d and the growth rate of tumor cells a, i.e.,

$$-f\mathrm{d}t \to -f\mathrm{d}t + \sigma_1\mathrm{d}B_1(t),\ \ -d\mathrm{d}t \to -d\mathrm{d}t + \sigma_2\mathrm{d}B_2(t),\ a\mathrm{d}t \to a\mathrm{d}t + \sigma_3\mathrm{d}B_3(t),$$

where $B_i(t)$ $(i = 1, 2, 3)$ are independent one-dimensional Brownian motions, and σ_i $(i = 1, 2, 3)$ are white noise intensities. Therefore, system (1.2) becomes the following SDE

$$\begin{cases} \mathrm{d}x(t) = \Big(ev - fx - p_2xz + \frac{p_3xz}{1+\alpha_3 z+\beta_3 x}\Big)\mathrm{d}t + \sigma_1x\mathrm{d}B_1(t), \\ \mathrm{d}y(t) = \Big[\frac{p_5Iy}{\alpha_4+I}\Big(1-\frac{y}{K_1}\Big)\frac{z}{\alpha_5+z} - dy + by\Big]\mathrm{d}t + \sigma_2y\mathrm{d}B_2(t), \\ \mathrm{d}z(t) = \Big[z\Big(a + \frac{cE(t)z}{1+\alpha_1E(t)+\beta_1z^2}\Big)\Big(1-\frac{z}{K}\Big) - \frac{p_1x^2z}{1+\alpha_2z+\beta_2x^2} - \frac{p_6yz^2}{1+\alpha_6z^2+\beta_6y}\Big]\mathrm{d}t + \sigma_3z\mathrm{d}B_3(t), \\ x(0) = x_0,\ y(0) = y_0,\ z(0) = z_0. \end{cases} \tag{1.3}$$

We can easily see that when $\sigma_1 = \sigma_2 = \sigma_3 = 0$, system (1.3) will degenerate into system (1.2).

In fact, the combination of chemotherapy and immunotherapy can undoubtedly achieve the best therapeutic effects [24, 25]. In experimental and clinical studies, chemotherapy and immunotherapy drugs are usually injected at a fixed time to treat cancer. This kind of pulsed therapy can be described by using impulsive differential equations [33]. For example, Yang et al. [33] investigated a stochastic tumor-immune system with impulse comprehensive therapy which can reduce the damage of therapy to the healthy cells. Consequently, inspired by the above references, we try to add pulsed chemotherapy to model (1.3). In order to be more realistic, we consider turning parameters of system (1.3) into time-dependent functions. Hence, we get the following stochastic immunotherapy model for breast cancer with pulsed

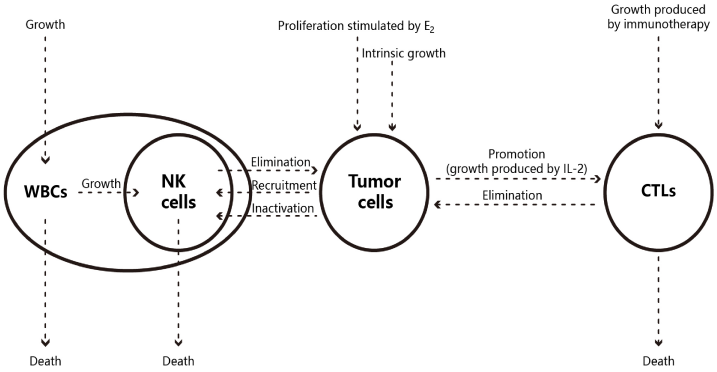

Figure 1. Schematic diagram of the interactions among NK cells, CTLs, tumor cells and WBCs for system (1.1).

chemotherapy

$$
\begin{cases}
\mathrm{d}x(t) = \Big(e(t)v - f(t)x - p_2(t)xz + \dfrac{p_3(t)xz}{1+\alpha_3(t)z+\beta_3(t)x}\Big)\mathrm{d}t \\
\qquad\quad + \sigma_1(t)x\mathrm{d}B_1(t),\ t \neq t_k,\ k \in \mathbb{N}, \\
\mathrm{d}y(t) = \Big[\dfrac{p_5(t)I(t)y}{\alpha_4(t)+I(t)}\Big(1-\dfrac{y}{K_1(t)}\Big)\dfrac{z}{\alpha_5(t)+z} - d(t)y + b(t)y\Big]\mathrm{d}t \\
\qquad\quad + \sigma_2(t)y\mathrm{d}B_2(t),\ t \neq t_k,\ k \in \mathbb{N}, \\
\mathrm{d}z(t) = \Big[z\Big(a(t) + \frac{c(t)E(t)z}{1+\alpha_1(t)E(t)+\beta_1(t)z^2}\Big)\Big(1-\frac{z}{K(t)}\Big) - \frac{p_1(t)x^2z}{1+\alpha_2(t)z+\beta_2(t)x^2} \\
\qquad\quad - \frac{p_6(t)yz^2}{1+\alpha_6(t)z^2+\beta_6(t)y}\Big]\mathrm{d}t + \sigma_3(t)z\mathrm{d}B_3(t),\ t \neq t_k,\ k \in \mathbb{N}, \\
x(t_k^+) = (1+d_{1k})x(t),\ t = t_k,\ k \in \mathbb{N}, \\
y(t_k^+) = (1+d_{2k})y(t),\ t = t_k,\ k \in \mathbb{N}, \\
z(t_k^+) = (1+d_{3k})z(t),\ t = t_k,\ k \in \mathbb{N},
\end{cases}
\tag{1.4}
$$

with initial values $x(0) = x_0$, $y(0) = y_0$ and $z(0) = z_0$. Moreover, the parameters of the first three equations for model (1.4) are all continuous bounded nonnegative functions on $[0, \infty)$; d_{1k}, d_{2k} and d_{3k} are all constants in the interval $(-1, 0)$ and $0 < t_1 < t_2 < \cdots < t_k < \cdots$ is a strictly increasing sequence satisfying $\lim\limits_{k\to\infty} t_k = +\infty$.

In this article, we will mainly study system (1.4) which not only involves the random perturbations but also simulates the comprehensive treatment including immunotherapy and pulsed chemotherapy. Further, using a suitable Lyapunov function, we get the existence and uniqueness of the global positive solution and obtain the sufficient condition for stochastic ultimate boundedness of the solution. Besides, by the strong law of large numbers, we prove the extinction of tumor cells and the persistence of all three kinds of cells under certain conditions. The results show that white noises do play an important role in the tumor treatment. What's more, the bounded impulsive effects do not affect some properties such as the existence, uniqueness and the stochastic ultimate boundedness of the global positive solution.

The structure of this paper is as follows: In Section 2, we give some preliminary knowledge. In Section 3, we prove the existence and uniqueness of the global positive

solution. In Section 4, we deduce the sufficient condition of the stochastic ultimate boundedness for the solution. In Section 5 and Section 6, we pay attention to the extinction of tumor cells and the persistence of all three kinds of cells. In Section 7, we use numerical simulations to verify the correctness of our theoretical results. Finally, our paper ends with a conclusion.

2. Preliminaries

In order to explore the above problems, firstly, we need to define some denotations. Throughout this paper, $\mathbb{R}^n$ represents the space of n-dimensional real column vectors and $\mathbb{R}^n_+$ is the set of n-dimensional real column vectors with positive elements, that is, $\mathbb{R}^n_+ = \{x \in \mathbb{R}^n \mid x_i > 0, 1 \le i \le n\}$, and we have $\bar{\mathbb{R}}^n_+ = \{x \in \mathbb{R}^n \mid x_i \ge 0, 1 \le i \le n\}$. Let $(\Omega, \{\mathcal{F}_t\}_{t\ge 0}, \mathbb{P})$ denote a complete probability space with a filtration $\{\mathcal{F}_t\}_{t\ge 0}$ satisfying the usual conditions and $\mathbb{E}$ be the probability expectation with respect to $\mathbb{P}$. For any $x \in \mathbb{R}^n$, we let $|x|$ denote the Euclidean norm of x on $\mathbb{R}^n$. $B_i(t)(i = 1, 2, \cdots, m)$ are mutually independent standard Brownian motions defined on this complete probability space.

Generally speaking, we consider the n-dimensional stochastic differential equation in reference [19]

$$\mathrm{d}x(t) = f\big(t, x(t)\big)\mathrm{d}t + g\big(t, x(t)\big)\mathrm{d}B(t), \tag{2.1}$$

where $x(t)$ is an n-dimensional vector valued function, $f\big(t, x(t)\big)$ is an n-dimensional vector valued function in $\mathbb{R}^n$ defined on $[0, +\infty) \times \mathbb{R}^n$, and $g\big(t, x(t)\big)$ is an $n \times m$ matrix valued function. f and g are locally Lipschitz functions in $x(t)$. $B(t)$ denotes an m-dimensional Brownian motion on the complete probability space $(\Omega, \{\mathcal{F}_t\}_{t\ge 0}, \mathbb{P})$. Furthermore, let $C^{1,2}([0, +\infty) \times \mathbb{R}^n; \mathbb{R})$ be the family of all nonnegative functions $V(t, x)$ defined on $[0, +\infty) \times \mathbb{R}^n$, which are continuously once differentiable in t and continuously twice differentiable in x. We define the differential operator $\mathcal{L}$ associated with equation (2.1) by

$$\mathcal{L} = \frac{\partial}{\partial t} + \sum_{i=1}^{n} f_i(t, x)\frac{\partial}{\partial x_i} + \frac{1}{2}\sum_{i,j=1}^{n} [g(t, x)g^T(t, x)]_{ij}\frac{\partial^2}{\partial x_i \partial x_j}.$$

Then for a function $V(t, x) \in C^{1,2}([0, +\infty) \times \mathbb{R}^n; \mathbb{R})$, we have

$$\mathcal{L}V(t, x) = V_t(t, x) + V_x(t, x)f(t, x) + \frac{1}{2}trace[g^T(t, x)V_{xx}(t, x)g(t, x)].$$

Here we set

$$V_t(t, x) = \frac{\partial V}{\partial t},\ V_x(t, x) = (\frac{\partial V}{\partial x_1}, \cdots, \frac{\partial V}{\partial x_n}),$$

$$V_{xx}(t, x) = (\frac{\partial^2 V}{\partial x_i \partial x_j})_{n\times n} = \begin{pmatrix} \frac{\partial^2 V}{\partial x_1 \partial x_1} & \cdots & \frac{\partial^2 V}{\partial x_1 \partial x_n} \\ \vdots & & \vdots \\ \frac{\partial^2 V}{\partial x_n \partial x_1} & \cdots & \frac{\partial^2 V}{\partial x_n \partial x_n} \end{pmatrix}.$$

For convenience, we set

$$\langle f(t)\rangle = \frac{1}{t}\int_0^t f(s)\mathrm{d}s,\ f_* = \liminf_{t\to\infty} f(t),\ f^* = \limsup_{t\to\infty} f(t),\ f^u = \sup_{t\ge 0} f(t),\ f^l = \inf_{t\ge 0} f(t),$$

where $f(t)$ is a continuous bounded function defined on $[0,\infty)$.

Assumption 2.1. Throughout this paper, we assume that there exist two constants m_1 and M_1 such that for all $t \geq 0$ and $i = 1, 2, 3$, $m_1 \leq \prod_{0<t_k<t}(1+d_{ik}) \leq M_1$.

Definition 2.1. [19] The population $x(t)$ is said to become extinct exponentially with probability one if $\limsup_{t\to\infty} \frac{\log x(t)}{t} < 0$ *a.s.*

Next, we give the definitions of weak persistence and persistence in the mean referring to the literature [16, 17].

Definition 2.2. The population $x(t)$ is said to be weakly persistent if $\limsup_{t\to\infty} x(t) > 0$ *a.s.*

Definition 2.3. The population $x(t)$ is said to be persistent in the mean if $\langle x(t)\rangle_* > 0$ *a.s.*

3. Existence and uniqueness of the global positive solution

From a biological point of view, we should ensure that system (1.4) has a unique global positive solution. First of all, we give the definition of solutions to impulsive stochastic differential equations (ISDEs).

Definition 3.1. ([17]) Consider the following ISDE

$$\begin{cases} \mathrm{d}X(t) = F\big(t, X(t)\big)\mathrm{d}t + G\big(t, X(t)\big)\mathrm{d}B(t), \ t \neq t_k, \ k \in \mathbb{N}, \\ X(t_k^+) - X(t_k) = B_k X(t_k), \ k \in \mathbb{N}, \end{cases} \tag{3.1}$$

with initial condition $X(0)$. A stochastic process $X(t) = \big(X_1(t), X_2(t), ...X_n(t)\big)^T$, $t \in \mathbb{R}_+$, is said to be a solution of ISDE (3.1) if

(i) $X(t)$ is $\mathcal{F}_t$-adapted and is continuous on $(0, t_1)$ and each interval $(t_k, t_{k+1}) \subset \mathbb{R}_+$, $k \in \mathbb{N}$; $F\big(t, X(t)\big) \in \mathcal{L}^1(\mathbb{R}_+; \mathbb{R}^n)$, $G\big(t, X(t)\big) \in \mathcal{L}^2(\mathbb{R}_+; \mathbb{R}^n)$, where $\mathcal{L}^k(\mathbb{R}_+; \mathbb{R}^n)$ is all $\mathbb{R}^n$ valued measurable $\{\mathcal{F}_t\}$-adapted processes $f(t)$ satisfying $\int_0^T |f(t)|^k \mathrm{d}t < \infty$ a.s. (almost surely) for every $T > 0$;

(ii) for each t_k, $k \in \mathbb{N}$, $X(t_k^+) = \lim_{t\to t_k^+} X(t)$ and $X(t_k^-) = \lim_{t\to t_k^-} X(t)$ exist and $X(t) = X(t_k^-)$ with probability one;

(iii) for almost all $t \in [0, t_1]$, $X(t)$ obeys the integral equation

$$X(t) = X(0) + \int_0^t F\big(s, X(s)\big)\mathrm{d}s + \int_0^t G\big(s, X(s)\big)\mathrm{d}B(s).$$

And for almost all $t \in (t_k, t_{k+1}]$, $k \in \mathbb{N}$, $X(t)$ obeys the integral equation

$$X(t) = X(t_k^+) + \int_{t_k}^t F\big(s, X(s)\big)\mathrm{d}s + \int_{t_k}^t G\big(s, X(s)\big)\mathrm{d}B(s).$$

Moreover, $X(t)$ satisfies the impulsive conditions at each $t = t_k$, $k \in \mathbb{N}$ with probability one.

Then we will prove the existence and uniqueness of the global positive solution for system (1.4).

Theorem 3.1. *System* (1.4) *has a unique global positive solution* $X(t) = \big(x(t), y(t), z(t)\big)$ *on* $t \geq 0$ *for any initial value* $X(0) = (x_0, y_0, z_0) \in \mathbb{R}^3_+$ *with probability one, that is to say,* $X(t) = \big(x(t), y(t), z(t)\big) \in \mathbb{R}^3_+$ *for all* $t \geq 0$ *almost surely.*

Proof. We first consider the following system without impulse

$$\begin{cases} \mathrm{d}x_1(t) = \Big(\dfrac{e(t)v}{D_1(t)} - f(t)x_1 - p_2(t)D_3(t)x_1z_1 + \dfrac{p_3(t)D_3(t)x_1z_1}{1+\alpha_3(t)D_3(t)z_1+\beta_3(t)D_1(t)x_1}\Big)\mathrm{d}t \\ \qquad\quad + \sigma_1(t)x_1\mathrm{d}B_1(t), \\ \mathrm{d}y_1(t) = \Big[\dfrac{p_5(t)I(t)y_1}{\alpha_4(t)+I(t)}\Big(1-\dfrac{D_2(t)y_1}{K_1(t)}\Big)\dfrac{D_3(t)z_1}{\alpha_5(t)+D_3(t)z_1} - d(t)y_1 + b(t)y_1\Big]\mathrm{d}t + \sigma_2(t)y_1\mathrm{d}B_2(t), \\ \mathrm{d}z_1(t) = \Big[z_1\Big(a(t) + \dfrac{c(t)E(t)D_3(t)z_1}{1+\alpha_1(t)E(t)+\beta_1(t)D_3^2(t)z_1^2}\Big)\Big(1-\dfrac{D_3(t)z_1}{K(t)}\Big) - \dfrac{p_1(t)D_1^2(t)x_1^2z_1}{1+\alpha_2(t)D_3(t)z_1+\beta_2(t)D_1^2(t)x_1^2} \\ \qquad\quad - \dfrac{p_6(t)D_2(t)D_3(t)y_1z_1^2}{1+\alpha_6(t)D_3^2(t)z_1^2+\beta_6(t)D_2(t)y_1}\Big]\mathrm{d}t + \sigma_3(t)z_1\mathrm{d}B_3(t), \end{cases} \tag{3.2}$$

where $v(t) = \frac{\alpha}{\beta} + (v_0 - \frac{\alpha}{\beta})e^{-\beta t}$. For any initial value $Y(0) = \big(x_1(0), y_1(0), z_1(0)\big) = X(0) \in \mathbb{R}^3_+$, where $D_i(t) = \prod\limits_{0<t_k<t}(1+d_{ik})$, $i = 1, 2, 3$, it is obvious that the coefficients of system (3.2) are locally Lipschitz continuous. So we see that system (3.2) has a unique local solution $\big(x_1(t), y_1(t), z_1(t)\big)$ on $t \in [0, \tau_e)$ and τ_e is the explosion time. To prove that the solution is global, we will show that $\tau_e = \infty$ *a.s.* Set $n_0 \in \mathbb{N}$ be sufficiently large such that $x_1(0) \in \left(\dfrac{1}{n_0}, n_0\right)$, $y_1(0) \in \left(\dfrac{1}{n_0}, n_0\right)$ and $z_1(0) \in \left(\dfrac{1}{n_0}, n_0\right)$. For $\forall\ n \geq n_0$, $n \in \mathbb{N}$, we define a stopping time as follows

$$\tau_n = \inf\left\{t \in [0, \tau_e) \mid \min\{x_1(t), y_1(t), z_1(t)\} \leq \frac{1}{n} \text{ or } \max\{x_1(t), y_1(t), z_1(t)\} \geq n\right\}, \tag{3.3}$$

where we define $\emptyset$ is the empty set and set $\inf\emptyset = \infty$. Thus, it is easy to see that τ_n is increasing as $n \to \infty$. We let $\tau_\infty = \lim\limits_{n\to\infty}\tau_n$, then $\tau_\infty \leq \tau_e$ *a.s.* Exactly, we just need to prove $\tau_\infty = \infty$ *a.s.* If this assertion is false, then there will exist two constants $T > 0$ and $\varepsilon \in (0, 1)$ such that $\mathbb{P}\{\tau_\infty \leq T\} \geq \varepsilon$. Then, there is an integer $n_1 \geq n_0$ such that

$$\mathbb{P}\{\tau_n \leq T\} \geq \varepsilon,\ \forall\ n \geq n_1. \tag{3.4}$$

Next, we define a C^2-function $V : \mathbb{R}^3_+ \to \bar{\mathbb{R}}_+$,

$$V(x_1, y_1, z_1) = (x_1 - 1 - \log x_1) + (y_1 - 1 - \log y_1) + (z_1 - 1 - \log z_1).$$

Using the Itô formula, we obtain that

$$\begin{aligned} \mathrm{d}V(x_1, y_1, z_1) = {} & \mathcal{L}V\mathrm{d}t + \sigma_1(t)(x_1 - 1)\mathrm{d}B_1(t) + \sigma_2(t)(y_1 - 1)\mathrm{d}B_2(t) \\ & + \sigma_3(t)(z_1 - 1)\mathrm{d}B_3(t), \end{aligned}$$

where

$$\mathcal{L}V = \left(1 - \frac{1}{x_1}\right)\left(\frac{e(t)v}{D_1(t)} - f(t)x_1 - p_2(t)D_3(t)x_1z_1 + \frac{p_3(t)D_3(t)x_1z_1}{1+\alpha_3(t)D_3(t)z_1+\beta_3(t)D_1(t)x_1}\right)$$

$$
\begin{aligned}
&+\left(1-\frac{1}{y_1}\right)\left[\frac{p_5(t)I(t)y_1}{\alpha_4(t)+I(t)}\left(1-\frac{D_2(t)y_1}{K_1(t)}\right)\frac{D_3(t)z_1}{\alpha_5(t)+D_3(t)z_1}-d(t)y_1+b(t)y_1\right]\\
&+\left(1-\frac{1}{z_1}\right)\cdot\left[z_1\left(a(t)+\frac{c(t)E(t)D_3(t)z_1}{1+\alpha_1(t)E(t)+\beta_1(t)D_3^2(t)z_1^2}\right)\left(1-\frac{D_3(t)z_1}{K(t)}\right)\right.\\
&\left.-\frac{p_1(t)D_1^2(t)x_1^2z_1}{1+\alpha_2(t)D_3(t)z_1+\beta_2(t)D_1^2(t)x_1^2}-\frac{p_6(t)D_2(t)D_3(t)y_1z_1^2}{1+\alpha_6(t)D_3^2(t)z_1^2+\beta_6(t)D_2(t)y_1}\right]\\
&+\frac{\sigma_1^2(t)}{2}+\frac{\sigma_2^2(t)}{2}+\frac{\sigma_3^2(t)}{2}\\
\le&\left(\frac{e(t)v}{D_1(t)}+f(t)+d(t)+\frac{c(t)E(t)}{\beta_1(t)D_3(t)}+\frac{c(t)E(t)}{K(t)\beta_1(t)}+\frac{p_1(t)}{\beta_2(t)}+\frac{\sigma_1^2(t)}{2}+\frac{\sigma_2^2(t)}{2}\right.\\
&\left.+\frac{\sigma_3^2(t)}{2}\right)+\frac{p_3(t)}{\alpha_3(t)}x_1+\left(p_5(t)+b(t)+\frac{p_5(t)D_2(t)}{K_1(t)}\right)y_1+\left(p_2(t)D_3(t)+a(t)\right.\\
&\left.+\frac{a(t)D_3(t)}{K}+\frac{p_6(t)D_3(t)}{\beta_6(t)}\right)z_1.
\end{aligned}
$$

Since for $\forall\ u>0$, the inequality $u\le 2(u+1-\log u)$ holds. Thus,

$$
\begin{aligned}
\mathcal{L}V\le&\left(\frac{e^uv_0}{m_1}+f^u+d^u+\frac{c^uE^u}{\beta_1^lm_1}+\frac{c^uE^u}{K^l\beta_1^l}+\frac{p_1^u}{\beta_2^l}+\frac{(\sigma_1^u)^2}{2}+\frac{(\sigma_2^u)^2}{2}+\frac{(\sigma_3^u)^2}{2}\right)\\
&+\frac{2p_3^u}{\alpha_3^l}(x_1+1-\log x_1)+2\left(p_5^u+b^u+\frac{p_5^uM_1}{K_1^l}\right)(y_1+1-\log y_1)\\
&+2\left(p_2^uM_1+a^u+\frac{a^uM_1}{K^l}+\frac{p_6^uM_1}{\beta_6^l}\right)(z_1+1-\log z_1).
\end{aligned}
$$

Then we define two positive constants $v_1:=\frac{e^uv_0}{m_1}+f^u+d^u+\frac{c^uE^u}{\beta_1^lm_1}+\frac{c^uE^u}{K^l\beta_1^l}+\frac{p_1^u}{\beta_2^l}+\frac{(\sigma_1^u)^2}{2}+\frac{(\sigma_2^u)^2}{2}+\frac{(\sigma_3^u)^2}{2}$, $v_2:=2\left(\frac{p_3^u}{\alpha_3^l}+p_5^u+b^u+\frac{p_5^uM_1}{K_1^l}+p_2^uM_1+a^u+\frac{a^uM_1}{K^l}+\frac{p_6^uM_1}{\beta_6^l}\right)$. Namely,

$$
\begin{aligned}
\mathcal{L}V\le\ & v_1+v_2(x_1+1-\log x_1)+v_2(y_1+1-\log y_1)+v_2(z_1+1-\log z_1)\\
=\ & v_1+v_2V(x_1,y_1,z_1).
\end{aligned}
$$

Further, we have

$$
\begin{aligned}
\mathrm{d}V(x_1,y_1,z_1)\le&[v_1+v_2V(x_1,y_1,z_1)]\mathrm{d}t+\sigma_1(t)(x_1-1)\mathrm{d}B_1(t)\\
&+\sigma_2(t)(y_1-1)\mathrm{d}B_2(t)+\sigma_3(t)(z_1-1)\mathrm{d}B_3(t).
\end{aligned}\tag{3.5}
$$

Integrating both sides of (3.5) from 0 to $T\wedge\tau_n$ and taking expectations, we then derive that

$$
\begin{aligned}
&\mathbb{E}\big[V\big(x_1(T\wedge\tau_n),y_1(T\wedge\tau_n),z_1(T\wedge\tau_n)\big)\big]\\
\le\ & V\big(x_1(0),y_1(0),z_1(0)\big)+v_1T+v_2\int_0^T\mathbb{E}\big[V\big(x_1(s\wedge\tau_n),y_1(s\wedge\tau_n),z_1(s\wedge\tau_n)\big)\big]\mathrm{d}s,
\end{aligned}
$$

where $a\wedge b=\min\{a,b\}$ and $\mathbf{I}_A(\cdot)$ is the indicate function of set A. Using the Gronwall inequality, then we have

$$
\mathbb{E}\big[V\big(x_1(T\wedge\tau_n),y_1(T\wedge\tau_n),z_1(T\wedge\tau_n)\big)\big]\le\Big(V\big(x_1(0),y_1(0),z_1(0)\big)+v_1T\Big)e^{v_2T}.\tag{3.6}
$$

Setting $\Omega_n = \{\omega \mid \tau_n \leq T\}$ for $n \geq n_1$, thus from (3.4) we get $\mathbb{P}(\Omega_n) \geq \varepsilon$. Consequently, for $\forall\ \omega \in \Omega_n$, at least one of $x(T \wedge \tau_n)$, $y(T \wedge \tau_n)$ and $z(T \wedge \tau_n)$ equals either n or $\dfrac{1}{n}$, which shows that

$$V\big(x_1(T \wedge \tau_n), y_1(T \wedge \tau_n), z_1(T \wedge \tau_n)\big) \geq \left(n + 1 - \log n\right) \wedge \left(\frac{1}{n} + 1 + \log n\right). \quad (3.7)$$

In view of (3.6) and (3.7), we get

$$\begin{aligned}
\Big(V\big(x_1(0), y_1(0), z_1(0)\big) + v_1 T\Big)e^{v_2 T} &\geq \mathbb{E}\big[V\big(x_1(T \wedge \tau_n), y_1(T \wedge \tau_n), z_1(T \wedge \tau_n)\big)\big] \\
&\geq \mathbb{E}\big[\mathbf{I}_{\Omega_n}(\omega) V\big(x_1(\tau_n, \omega), y_1(\tau_n, \omega), z_1(\tau_n, \omega)\big)\big] \\
&\geq \mathbb{P}(\Omega_n) \cdot \left[\left(n + 1 - \log n\right) \wedge \left(\frac{1}{n} + 1 + \log n\right)\right] \\
&\geq \varepsilon\left[\left(n + 1 - \log n\right) \wedge \left(\frac{1}{n} + 1 + \log n\right)\right].
\end{aligned}$$

Letting $n \to \infty$, it leads to $\left(n + 1 - \log n\right) \wedge \left(\dfrac{1}{n} + 1 + \log n\right) \to \infty$, and then we get a contradiction

$$\infty \geq \Big(V\big(x_1(0), y_1(0), z_1(0)\big) + v_1 T\Big)e^{v_2 T} = \infty.$$

Further, we obtain $\tau_\infty = \infty\ a.s.$ That is, system (3.2) has a unique global solution $\big(x_1(t), y_1(t),\ z_1(t)\big) \in \mathbb{R}^3_+$ with probability one for all $t \geq 0$. Setting $x(t) = D_1(t)x_1(t)$, $y(t) = D_2(t)y_1(t)$ and $z(t) = D_3(t)z_1(t)$, we can see that system (1.4) with initial value $X(0) = (x_0, y_0, z_0)$ has a unique global solution $X(t) = \big(x(t), y(t), z(t)\big) \in \mathbb{R}^3_+$. In fact, $x(t)$, $y(t)$ and $z(t)$ are continuous on $(0, t_1)$ and every interval $(t_k, t_{k+1}) \subset (0, \infty)$, $k \in \mathbb{N}$. If $t \neq t_k$, we have

$$\begin{aligned}
\mathrm{d}x(t) =&\ \mathrm{d}\big(D_1(t)x_1(t)\big) = D_1(t)\mathrm{d}x_1(t) \\
=&\ \left(e(t)v - f(t)x - p_2(t)xz + \frac{p_3(t)xz}{1 + \alpha_3(t)z + \beta_3(t)x}\right)\mathrm{d}t + \sigma_1(t)x\mathrm{d}B_1(t), \\
\mathrm{d}y(t) =&\ \mathrm{d}\big(D_2(t)y_1(t)\big) = D_2(t)\mathrm{d}y_1(t) \\
=&\ \left[\frac{p_5(t)I(t)y}{\alpha_4(t) + I(t)}\left(1 - \frac{y}{K_1(t)}\right)\frac{z}{\alpha_5(t) + z} - d(t)y + b(t)y\right]\mathrm{d}t + \sigma_2(t)y\mathrm{d}B_2(t), \\
\mathrm{d}z(t) =&\ \mathrm{d}\big(D_3(t)z_1(t)\big) = D_3(t)\mathrm{d}z_1(t) \\
=&\ \left[z\left(a(t) + \frac{c(t)E(t)z}{1 + \alpha_1(t)E(t) + \beta_1(t)z^2}\right)\left(1 - \frac{z}{K(t)}\right) - \frac{p_1(t)x^2z}{1 + \alpha_2(t)z + \beta_2(t)x^2}\right. \\
&\left. - \frac{p_6(t)yz^2}{1 + \alpha_6(t)z^2 + \beta_6(t)y}\right]\mathrm{d}t + \sigma_3(t)z\mathrm{d}B_3(t).
\end{aligned}$$

For any $k \in \mathbb{N}$, $t_k \in \mathbb{R}_+$, we observe

$$\begin{aligned}
x(t_k^+) =&\ \lim_{t \to t_k^+} x(t) = \prod_{0 < t_j \leq t_k} (1 + d_{1j})x_1(t_k^+) = (1 + d_{1k}) \prod_{0 < t_j < t_k} (1 + d_{1j})x_1(t_k) \\
=&\ (1 + d_{1k})x(t_k).
\end{aligned}$$

Similarly, we can obtain that $y(t_k^+) = (1 + d_{2k})y(t_k)$ and $z(t_k^+) = (1 + d_{3k})z(t_k)$. Therefore, $X(t) = \big(x(t), y(t), z(t)\big)$ is the unique global positive solution for system (1.4) with probability one. The proof is now complete. □

4. Stochastic ultimate boundedness

Theorem 3.1 allows us to further investigate how the solution of system (1.4) changes in $\mathbb{R}^3_+$. The following theorem gives a criterion for the stochastic ultimate boundedness (see the reference [18]) of the solution in system (1.4).

Theorem 4.1. *If $f^l - h^2 + \frac{(\sigma_1^u)^2}{2} > 0$, then the solution of system (1.4) is stochastically ultimately bounded for any initial value $X(0) = (x_0, y_0, z_0) \in \mathbb{R}^3_+$.*

Proof. Due to Theorem 3.1, we know that the solution $X(t) = \big(D_1(t)x_1(t),\ D_2(t)y_1(t),\ D_3(t)z_1(t)\big)$ of system (1.4) will remain in the positive cone $\mathbb{R}^3_+$ with probability one for all $t \geq 0$. Firstly, we will prove that for any initial value $Y(0) = \big(x_1(0),\ y_1(0),\ z_1(0)\big)$, the solution of system (3.2) is stochastically ultimately bounded. Then we define a function

$$g(z_1) = \frac{p_3^u M_1 z_1}{1 + \alpha_3^l m_1 z_1} - p_2^l m_1 z_1,\ z_1 > 0,$$

and obtain that

(i) If $p_3^u M_1 \leq p_2^l m_1$, then $g(z_1) < 0$, $\forall\ z_1 > 0$.

(ii) If $p_3^u M_1 > p_2^l m_1$, then $g(z_1) \leq \frac{\left(\sqrt{p_3^u M_1} - \sqrt{p_2^l m_1}\right)^2}{\alpha_3^l m_1}$, $\forall\ z_1 > 0$.

That is,

$$g(z_1) \leq \left[\frac{\sqrt{p_3^u M_1} - \sqrt{p_2^l m_1}}{\sqrt{\alpha_3^l m_1}} \vee 0\right]^2 =: h^2,\ \forall\ z_1 > 0, \tag{4.1}$$

where $a \vee b = \max\{a, b\}$. In view of $f^l - h^2 + \frac{(\sigma_1^u)^2}{2} > 0$, we get $1 + \frac{2(f^l - h^2)}{(\sigma_1^u)^2} > 0$. For any fixed $p \in \left(0, 1 + \frac{2(f^l - h^2)}{(\sigma_1^u)^2}\right)$, we define a function as follows

$$V_1 = (1 + x_1)^p,\ \forall\ x_1 \in \mathbb{R}_+.$$

By computing $\mathcal{L}V_1$, we derive that

$$\begin{aligned}\mathcal{L}V_1 =& p(1 + x_1)^{p-2}\bigg(\frac{e(t)v}{D_1(t)} - f(t)x_1 - p_2(t)D_3(t)x_1z_1 + -f(t)x_1^2 - p_2(t)D_3(t)x_1^2z_1 \\ & \frac{p_3(t)D_3(t)x_1z_1}{1+\alpha_3(t)D_3(t)z_1+\beta_3(t)D_1(t)x_1} + \frac{e(t)vx_1}{D_1(t)} + \frac{p_3(t)D_3(t)x_1^2z_1}{1 + \alpha_3(t)D_3(t)z_1 + \beta_3(t)D_1(t)x_1} \\ & + \frac{(p-1)\sigma_1^2(t)x_1^2}{2}\bigg).\end{aligned} \tag{4.2}$$

Based on the range of p, we obtain that $f^l - h^2 - \frac{(p-1)(\sigma_1^u)^2}{2} > 0$, and then we can choose a small enough positive constant κ such that

$$-\frac{\kappa}{p} + f^l - h^2 - \frac{(p-1)(\sigma_1^u)^2}{2} > 0. \tag{4.3}$$

By the Itô formula, it is easy to see that

$$M_{V_1}(t) := e^{\kappa t}V_1\big(x_1(t)\big) - V_1\big(x_1(0)\big) - \int_0^t \mathcal{L}\big[e^{\kappa s}V_1\big(x_1(s)\big)\big]\mathrm{d}s$$

is a local martingale. Next, we compute $\mathcal{L}[e^{\kappa t}V_1(x_1)]$. By (4.1) and (4.2), we have

$$\begin{aligned}
&\mathcal{L}\big[e^{\kappa t}V_1(x_1)\big]\\
\leq\ & pe^{\kappa t}(1+x_1)^{p-2}\bigg(\frac{\kappa}{p}+\frac{2\kappa}{p}x_1+\frac{\kappa}{p}x_1^2+\frac{e^u v_0}{m_1}-f^l x_1-p_2^l m_1 x_1 z_1+\frac{p_3^u M_1 x_1 z_1}{1+\alpha_3^l m_1 z_1}\\
&+\frac{e^u v_0 x_1}{m_1}-f^l x_1^2-p_2^l m_1 x_1^2 z_1+\frac{p_3^u M_1 x_1^2 z_1}{1+\alpha_3^l m_1 z_1}+\frac{(p-1)(\sigma_1^u)^2 x_1^2}{2}\bigg)\\
\leq\ & pe^{\kappa t}(1+x_1)^{p-2}W_1(x_1),
\end{aligned}$$

where

$$W_1(x_1)=\bigg(\frac{\kappa}{p}+\frac{e^u v_0}{m_1}\bigg)+\bigg(\frac{2\kappa}{p}-f^l+h^2+\frac{e^u v_0}{m_1}\bigg)x_1+\bigg(\frac{\kappa}{p}-f^l+h^2+\frac{(p-1)(\sigma_1^u)^2}{2}\bigg)x_1^2.$$

From (4.3), we can get

$$\lim_{x_1\to+\infty}(1+x_1)^{p-2}W_1(x_1) = -\infty.$$

This, together with the continuity of $(1+x_1)^{p-2}W_1(x_1)$ in $\mathbb{R}_+$, allow us to derive

$$H_1(p) := p\sup_{x_1\in\mathbb{R}_+}\big\{(1+x_1)^{p-2}W_1(x_1)\big\} < +\infty.$$

Hence,

$$\mathcal{L}[e^{\kappa t}V_1(x_1)] \leq H_1(p)e^{\kappa t}. \tag{4.4}$$

Then we will prove

$$\mathbb{E}\big[e^{\kappa t}V_1\big(x_1(t)\big)\big] = \mathbb{E}\big[V_1\big(x_1(0)\big)\big] + \mathbb{E}\int_0^t \mathcal{L}\big[e^{\kappa s}V_1\big(x_1(s)\big)\big]\mathrm{d}s.$$

In fact, we choose a sufficiently large constant r_0 such that $x_1(0), y_1(0)$ and $z_1(0)$ are all in the interval $\big(\frac{1}{r_0}, r_0\big)$. For $\forall\ r \geq r_0$, we define a stopping time as follows

$$\xi_r = \inf\{t\geq 0 \mid \max\{x_1(t), y_1(t), z_1(t)\} \geq r\}. \tag{4.5}$$

Noting that ξ_r is monotonically increasing, thus its limit exists and we define the limit as ξ_∞. According to the definition of τ_r in (3.3), we can know that $\xi_r \geq \tau_r$. By Theorem 3.1, we get $\tau_\infty = \infty\ a.s.$ Therefore, $\xi_\infty = \infty\ a.s.$ Because of the properties of local martingale, we easily obtain $\mathbb{E}[M_{V_1}(t\wedge\xi_r)] = 0$. Namely, for any $t \geq 0$, we deduce that

$$\mathbb{E}\big[e^{\kappa(t\wedge\xi_r)}V_1\big(x_1(t\wedge\xi_r)\big)\big] = \mathbb{E}\big[V_1\big(x_1(0)\big)\big] + \mathbb{E}\int_0^{t\wedge\xi_r} \mathcal{L}\big[e^{\kappa s}V_1\big(x_1(s)\big)\big]\mathrm{d}s. \tag{4.6}$$

Letting $r\to\infty$ and applying the monotonicity of ξ_r, then we have

$$e^{\kappa(t\wedge\xi_r)}\big(1+x_1(t\wedge\xi_r)\big)^p \to e^{\kappa t}\big(1+x_1(t)\big)^p \quad a.s.$$

Clearly,

$$\mathbb{E}\big[e^{\kappa(t\wedge\xi_r)}V_1\big(x_1(t\wedge\xi_r)\big)\big]\to\mathbb{E}\big[e^{\kappa t}V_1\big(x_1(t)\big)\big],\ as\ r\to\infty.$$

By (4.4) and the dominated convergence theorem, we derive that

$$\mathbb{E}\int_0^{t\wedge\xi_r}\mathcal{L}\big[e^{\kappa s}V_1\big(x_1(s)\big)\big]\mathrm{d}s\to\mathbb{E}\int_0^{t}\mathcal{L}\big[e^{\kappa s}V_1\big(x_1(s)\big)\big]\mathrm{d}s,\ as\ r\to\infty.$$

Letting $r\to\infty$ in (4.6), we obtain

$$\mathbb{E}\big[e^{\kappa t}V_1\big(x_1(t)\big)\big]=\mathbb{E}\big[V_1\big(x_1(0)\big)\big]+\mathbb{E}\int_0^t\mathcal{L}\big[e^{\kappa s}V_1\big(x_1(s)\big)\big]\mathrm{d}s. \tag{4.7}$$

Combining (4.4) with (4.7), we get

$$\begin{aligned}e^{\kappa t}\mathbb{E}\big[\big(1+x_1(t)\big)^p\big]&\le\ \mathbb{E}\big[\big(1+x_1(0)\big)^p\big]+\mathbb{E}\int_0^t H_1(p)e^{\kappa s}\mathrm{d}s\\&\le\ \mathbb{E}\big[\big(1+x_1(0)\big)^p\big]+\frac{H_1(p)}{\kappa}e^{\kappa t}.\end{aligned}$$

Then dividing $e^{\kappa t}$ and taking the upper limit on both sides, we arrive at

$$\limsup_{t\to\infty}\mathbb{E}\big[\big(1+x_1(t)\big)^p\big]\le\frac{H_1(p)}{\kappa}=:\hat{H}_1(p).$$

Consequently,

$$\limsup_{t\to\infty}\mathbb{E}\big[x_1^p(t)\big]<\hat{H}_1(p). \tag{4.8}$$

Next, we define

$$V_2=e^t y_1^p,\ \forall\ y_1\in\mathbb{R}_+.$$

Similarly, we have

$$\begin{aligned}\mathcal{L}V_2=&\,e^t y_1^p+pe^t y_1^{p-1}\left[\frac{p_5(t)I(t)y_1}{\alpha_4(t)+I(t)}\left(1-\frac{D_2(t)y_1}{K_1(t)}\right)\frac{D_3(t)z_1}{\alpha_5(t)+D_3(t)z_1}-d(t)y_1+b(t)y_1\right]\\&+\frac{p(p-1)}{2}e^t\sigma_2^2(t)y_1^p\\\le&\ e^t y_1^{p-1}\Big(y_1+pp_5^u y_1-\frac{pp_5^l I^l m_1^2 y_1^2 z_1}{K_1^u(\alpha_4^u+I^u)(\alpha_5^u+M_1z_1)}+pb^u y_1+\frac{p(p-1)}{2}(\sigma_2^u)^2y_1\Big)\\=&\ e^t y_1^{p-1}W_2(y_1,z_1),\end{aligned} \tag{4.9}$$

where

$$W_2(y_1,z_1)=\left(1+pp_5^u+pb^u+\frac{p(p-1)}{2}(\sigma_2^u)^2\right)y_1-\frac{pp_5^l I^l m_1^2 y_1^2 z_1}{K_1^u(\alpha_4^u+I^u)(\alpha_5^u+M_1z_1)}.$$

Obviously, we know

$$\lim_{y_1^2+z_1^2\to+\infty}y_1^{p-1}W_2(y_1,z_1)=-\infty.$$

Then combining the above formula with the continuity of $y_1^{p-1}W_2(y_1,z_1)$ in $\mathbb{R}^2_+$ leads to

$$H_2(p) := \sup_{(y_1,z_1)\in\mathbb{R}^2_+}\left\{y_1^{p-1}W_2(y_1,z_1)\right\} < +\infty.$$

Hence,

$$\mathcal{L}V_2 \le H_2(p)e^t. \tag{4.10}$$

According to the Itô formula again, we know that

$$M_{V_2}(t) := V_2\big(y_1(t)\big) - V_2\big(y_1(0)\big) - \int_0^t \mathcal{L}\big[V_2\big(y_1(s)\big)\big]\mathrm{d}s$$

is a local martingale. In the same way, $\mathbb{E}[M_{V_2}(t\wedge\xi_r)] = 0$, where ξ_r is defined by (4.5). Similar to the above proof, we can get

$$\mathbb{E}\big[V_2\big(y_1(t)\big)\big] = \mathbb{E}\big[V_2\big(y_1(0)\big)\big] + \mathbb{E}\int_0^t \mathcal{L}\big[V_2\big(y_1(s)\big)\big]\mathrm{d}s. \tag{4.11}$$

Combining (4.10) with (4.11), we have

$$e^t\mathbb{E}\big[y_1^p(t)\big] - y_1^p(0) \le H_2(p)e^t.$$

Therefore,

$$\limsup_{t\to\infty}\mathbb{E}\big[y_1^p(t)\big] \le H_2(p). \tag{4.12}$$

Setting q as a positive constant, we continue to define a function

$$V_3 = (1+qy_1+z_1)^p,\ \forall\ (y_1,z_1)\in\mathbb{R}^2_+.$$

Now, let's calculate $\mathcal{L}V_3$ as follows

$$\begin{aligned}\mathcal{L}V_3 =& p(1+qy_1+z_1)^{p-2}\bigg[(1+qy_1+z_1)\bigg(\frac{qp_5(t)I(t)D_3(t)y_1z_1}{\big(\alpha_4(t)+I(t)\big)\big(\alpha_5(t)+D_3(t)z_1\big)}\\
&-\frac{qp_5(t)I(t)D_2(t)D_3(t)y_1^2z_1}{K_1(t)\big(\alpha_4(t)+I(t)\big)\big(\alpha_5(t)+D_3(t)z_1\big)} - qd(t)y_1 + qb(t)y_1 + a(t)z_1 - \frac{a(t)D_3(t)z_1^2}{K(t)}\\
&+\frac{c(t)E(t)D_3(t)z_1^2}{1+\alpha_1(t)E(t)+\beta_1(t)D_3^2(t)z_1^2} - \frac{c(t)E(t)D_3^2(t)z_1^3}{K(t)\big(1+\alpha_1(t)E(t)+\beta_1(t)D_3^2(t)z_1^2\big)}\\
&-\frac{p_1(t)D_1^2(t)x_1^2z_1}{1+\alpha_2(t)D_3(t)z_1+\beta_2(t)D_1^2(t)x_1^2} - \frac{p_6(t)D_2(t)D_3(t)y_1z_1^2}{1+\alpha_6(t)D_3^2(t)z_1^2+\beta_6(t)D_2(t)y_1}\bigg)\\
&+\frac{p-1}{2}\sigma_2^2(t)q^2y_1^2 + \frac{p-1}{2}\sigma_3^2(t)z_1^2\bigg].\end{aligned} \tag{4.13}$$

Applying the Itô formula yields that

$$M_{V_3}(t) := V_3\big(y_1(t),z_1(t)\big) - V_3\big(y_1(0),z_1(0)\big) - \int_0^t \mathcal{L}\big[e^sV_3\big(y_1(s),z_1(s)\big)\big]\mathrm{d}s$$

is a local martingale. Similarly, $\mathbb{E}[M_{V_3}(t\wedge\xi_r)] = 0$, where ξ_r is defined by (4.5). Computing $\mathcal{L}[e^tV_3(y_1,z_1)]$ and according to (4.13), we deduce that

$$\mathcal{L}[e^tV_3(y_1,z_1)]$$

$$\begin{aligned}
&\leq\ e^t(1+qy_1+z_1)^{p-2}\bigg[1+q^2y_1^2+z_1^2+2qy_1+2z_1+2qy_1z_1+p(1+qy_1+z_1)\\
&\quad\bigg(qp_5(t)y_1+qb(t)y_1+a(t)z_1+\frac{c(t)E(t)}{\beta_1(t)D_3(t)}\bigg)-pz_1\cdot\frac{a(t)D_3(t)z_1^2}{K(t)}\\
&\quad-pqy_1\cdot\frac{qp_5(t)I(t)D_2(t)D_3(t)y_1^2z_1}{K_1(t)\big(\alpha_4(t)+I(t)\big)\big(\alpha_5(t)+D_3(t)z_1\big)}+\frac{p(p-1)}{2}\sigma_2^2(t)q^2y_1^2\\
&\quad+\frac{p(p-1)}{2}\sigma_3^2(t)z_1^2\bigg]\\
&\leq\ e^t(1+qy_1+z_1)^{p-2}W_3(y_1,z_1),
\end{aligned}$$

where

$$\begin{aligned}
W_3(y_1,z_1)=&\bigg(1+\frac{pc^uE^u}{\beta_1^lm_1}\bigg)+\bigg(2q+pqp_5^u+pqb^u+\frac{pqc^uE^u}{\beta_1^lm_1}\bigg)y_1+\bigg(2+pa^u\\
&+\frac{pc^uE^u}{\beta_1^lm_1}\bigg)z_1+\bigg(q^2+pq^2p_5^u+pq^2b^u+\frac{p(p-1)}{2}(\sigma_2^u)^2q^2\bigg)y_1^2\\
&+\bigg(2q+pqa^u+pqp_5^u+pqb^u\bigg)y_1z_1+\bigg(1+pa^u+\frac{p(p-1)}{2}(\sigma_3^u)^2\bigg)z_1^2\\
&-\frac{pa^lm_1}{K^u}z_1^3-\frac{pq^2p_5^lI^lm_1^2z_1}{K_1^u(\alpha_4^u+I^u)(\alpha_5^u+M_1z_1)}y_1^3.
\end{aligned}$$

It is obvious to see that

$$\lim_{y_1^2+z_1^2\to\infty}(1+qy_1+z_1)^{p-2}W_3(y_1,z_1)=-\infty.$$

Combining with the community of $(1+qy_1+z_1)^{p-2}W_3(y_1,z_1)$ in $\mathbb{R}^2_+$, we find that

$$H_3(p):=\sup_{(y_1,z_1)\in\mathbb{R}^2_+}\big\{(1+qy_1+z_1)^{p-2}W_3(y_1,z_1)\big\}\ <+\infty.$$

Consequently,

$$\mathcal{L}[e^tV_3]\leq H_3(p)e^t. \tag{4.14}$$

Similar to the above process, we arrive at

$$\mathbb{E}\big[e^tV_3\big(y_1(t),z_1(t)\big)\big]=\mathbb{E}\big[V_3\big(y_1(0),z_1(0)\big)\big]+\mathbb{E}\int_0^t\mathcal{L}\big[e^sV_3\big(y_1(s),z_1(s)\big)\big]\mathrm{d}s. \tag{4.15}$$

From (4.14) and (4.15), we obtain that

$$e^t\mathbb{E}\big[\big(1+qy_1(t)+z_1(t)\big)^p\big]\leq\mathbb{E}\big[\big(1+qy_1(0)+z_1(0)\big)^p\big]+H_3(p)e^t.$$

Dividing e^t and taking the upper limit on the both sides, then we know that

$$\limsup_{t\to\infty}\mathbb{E}\big[\big(1+qy_1(t)+z_1(t)\big)^p\big]\leq H_3(p).$$

Due to the positivity of $y_1(t)$ and the constant q, we can have

$$\limsup_{t\to\infty}\mathbb{E}\big[z_1^p(t)\big]\ <\ H_3(p). \tag{4.16}$$

For $X(t) = \big(x(t), y(t), z(t)\big) \in \mathbb{R}^3_+$, we derive that

$$|X|^p = \Big(x^2 + y^2 + z^2\Big)^{\frac{p}{2}} \leq 3^{\frac{p}{2}}\Big(x^p + y^p + z^p\Big).$$

By (4.8), (4.12), (4.16) and Assumption 2.1, we get

$$\begin{aligned}\limsup_{t\to\infty} \mathbb{E}[|X|^p] \leq\ & 3^{\frac{p}{2}}\Big(\limsup_{t\to\infty} \mathbb{E}\big[x^p\big] + \limsup_{t\to\infty} \mathbb{E}\big[y^p\big] + \limsup_{t\to\infty} \mathbb{E}\big[z^p\big]\Big)\\ \leq\ & 3^{\frac{p}{2}} M_1^p\Big(\limsup_{t\to\infty} \mathbb{E}\big[x_1^p\big] + \limsup_{t\to\infty} \mathbb{E}\big[y_1^p\big] + \limsup_{t\to\infty} \mathbb{E}\big[z_1^p\big]\Big)\\ <\ & 3^{\frac{p}{2}} M_1^p\Big(\hat{H}_1(p) + H_2(p) + H_3(p)\Big) < +\infty.\end{aligned}$$

Let $M(p) = 3^{\frac{p}{2}} M_1^p\Big(\hat{H}_1(p) + H_2(p) + H_3(p)\Big)$ and $\chi = \Big(\frac{2M(p)}{\varepsilon}\Big)^{\frac{1}{p}}$. Applying the Chebyshev inequality, we can obtain

$$\limsup_{t\to\infty} \mathbb{P}\left\{\omega : |X(\omega)| > \chi\right\} \leq \frac{\limsup\limits_{t\to\infty} \mathbb{E}[|X|^p]}{\chi^p} \leq \frac{M(p)}{\chi^p} = \frac{\varepsilon}{2} < \varepsilon. \tag{4.17}$$

The proof is therefore complete. □

5. Extinction

In this section, we shall consider the asymptotic behaviors of NK cells $x(t)$, CTLs $y(t)$ and tumor cells $z(t)$ under different noise intensities.

Lemma 5.1. *([17]) Suppose that $x(t) \in C[\Omega\times\mathbb{R}_+, \mathbb{R}^0_+]$, where $\mathbb{R}^0_+ = \{a \mid a > 0, a \in \mathbb{R}\}$. Let $B_i(t)(i = 1, 2, 3, ..., n)$ be independent Brownian motions defined on a complete probability space $(\Omega, \mathcal{F}, \mathbb{P})$.*

(i) If there are positive constants λ_0, T and $\lambda \geq 0$ such that

$$\log x(t) \leq \lambda t - \lambda_0 \int_0^t x(s)\mathrm{d}s + \sum_{i=1}^n \beta_i B_i(t)$$

for all $t \geq T$, where β_i is a constant, $1 \leq i \leq n$, then $\langle x(t)\rangle^* \leq \frac{\lambda}{\lambda_0}$ a.s.

(ii) If there are positive constants λ_0, T and $\lambda \geq 0$ such that

$$\log x(t) \geq \lambda t - \lambda_0 \int_0^t x(s)\mathrm{d}s + \sum_{i=1}^n \beta_i B_i(t)$$

for all $t \geq T$, where β_i is a constant, $1 \leq i \leq n$, then $\langle x(t)\rangle_* \geq \frac{\lambda}{\lambda_0}$ a.s.

Theorem 5.1. *If $\hat{\lambda}_2 < 0$, $\hat{\lambda}_3 < 0$ and $\frac{a^l}{K^u} - \frac{c^u}{\alpha_1^l} > 0$, then*

$$\begin{aligned}\limsup_{t\to\infty} x(t) >\ & 0 \quad a.s.\\ \limsup_{t\to\infty} \frac{\log y(t)}{t} \leq\ & \hat{\lambda}_2 < 0 \quad a.s.\\ \limsup_{t\to\infty} \frac{\log z(t)}{t} \leq\ & \hat{\lambda}_3 < 0 \quad a.s.\end{aligned}$$

where

$$\hat{\lambda}_2 := \limsup_{t\to\infty}\frac{1}{t}\left\{\sum_{0<t_k<t}\log(1+d_{2k}) - \int_0^t\left(d(s)-b(s)+\frac{\sigma_2^2(s)}{2}\right)\mathrm{d}s\right\},$$

$$\hat{\lambda}_3 := \limsup_{t\to\infty}\frac{1}{t}\left\{\sum_{0<t_k<t}\log(1+d_{3k}) + \int_0^t\left(a(s)-\frac{\sigma_3^2(s)}{2}\right)\mathrm{d}s\right\}.$$

That is, NK cells (x) will be weakly persistent while CTLs (y) and tumor cells (z) will become extinct exponentially with probability one.

Proof. Applying the Itô formula to $\log z_1$ leads to

$$\begin{aligned}
&\mathrm{d}(\log z_1)\\
=\ &\left[a(t)+\frac{c(t)E(t)D_3(t)z_1}{1+\alpha_1(t)E(t)+\beta_1(t)D_3^2(t)z_1^2}-\frac{a(t)D_3(t)z_1}{K(t)}\right.\\
&-\frac{c(t)E(t)D_3^2(t)z_1^2}{K(t)\big(1+\alpha_1(t)E(t)+\beta_1(t)D_3^2(t)z_1^2\big)}-\frac{p_1(t)D_1^2(t)x_1^2}{1+\alpha_2(t)D_3(t)z_1+\beta_2(t)D_1^2(t)x_1^2}\\
&\left.-\frac{p_6(t)D_2(t)D_3(t)y_1z_1}{1+\alpha_6(t)D_3^2(t)z_1^2+\beta_6(t)D_2(t)y_1}-\frac{\sigma_3^2(t)}{2}\right]\mathrm{d}t+\sigma_3(t)\mathrm{d}B_3(t).
\end{aligned}$$

According to $x(t)=D_1(t)x_1(t)$, $y(t)=D_2(t)y_1(t)$ and $z(t)=D_3(t)z_1(t)$, integrating both sides of the above equation from 0 to t and dividing both sides by t yield that

$$\begin{aligned}
\frac{\log z_1(t)-\log z_1(0)}{t} =\ &\frac{1}{t}\int_0^t\left(a(s)-\frac{\sigma_3^2(s)}{2}\right)\mathrm{d}s+\frac{1}{t}\int_0^t\frac{c(s)E(s)z(s)}{1+\alpha_1(s)E(s)+\beta_1(s)z^2(s)}\mathrm{d}s\\
&-\frac{1}{t}\int_0^t\frac{a(s)z(s)}{K(s)}\mathrm{d}s-\frac{1}{t}\int_0^t\left[\frac{c(s)E(s)z^2(s)}{K(s)\big(1+\alpha_1(s)E(s)+\beta_1(s)z^2(s)\big)}\right.\\
&\left.+\frac{p_1(s)x^2(s)}{1+\alpha_2(s)z(s)+\beta_2(s)x^2(s)}+\frac{p_6(s)y(s)z(s)}{1+\alpha_6(s)z^2(s)+\beta_6(s)y(s)}\right]\mathrm{d}s\\
&+\frac{1}{t}\int_0^t\sigma_3(s)\mathrm{d}B_3(s).
\end{aligned}\tag{5.1}$$

Because $z(t)=\prod_{0<t_k<t}(1+d_{3k})z_1(t)$ and $\frac{a^l}{K^u}-\frac{c^u}{\alpha_1^l}>0$, then we deduce that

$$\begin{aligned}
&\frac{\log z(t)-\log z(0)}{t}\\
=\ &\frac{\sum_{0<t_k<t}\log(1+d_{3k})}{t}+\frac{\log z_1(t)-\log z_1(0)}{t}\\
\le\ &\frac{\sum_{0<t_k<t}\log(1+d_{3k})}{t}+\frac{1}{t}\int_0^t\left(a(s)-\frac{\sigma_3^2(s)}{2}\right)\mathrm{d}s+\frac{1}{t}\int_0^t\sigma_3(s)\mathrm{d}B_3(s).
\end{aligned}\tag{5.2}$$

Taking the upper limit of both sides and using the strong law of large numbers, we arrive at

$$\limsup_{t\to\infty}\frac{\log z(t)}{t}\le\hat{\lambda}_3<0\quad a.s.\tag{5.3}$$

By the Itô formula, we can similarly calculate $\mathrm{d}(\log x_1)$ as follows

$$\mathrm{d}(\log x_1)=\bigg(\frac{e(t)v}{D_1(t)x_1}-f(t)-p_2(t)D_3(t)z_1+\frac{p_3(t)D_3(t)z_1}{1+\alpha_3(t)D_3(t)z_1+\beta_3(t)D_1(t)x_1} -\frac{\sigma_1^2(t)}{2}\bigg)\mathrm{d}t+\sigma_1(t)\mathrm{d}B_1(t).$$

Due to $x(t)=D_1(t)x_1(t)$ and $z(t)=D_3(t)z_1(t)$, integrating both sides of the above formula from 0 to t and dividing both sides by t, one derives

$$\begin{aligned}\frac{\log x_1(t)-\log x_1(0)}{t}=&\ \frac{1}{t}\int_0^t\frac{e(s)v(s)}{x(s)}\mathrm{d}s-\frac{1}{t}\int_0^t\bigg(f(s)+\frac{\sigma_1^2(s)}{2}\bigg)\mathrm{d}s\\&-\frac{1}{t}\int_0^t p_2(s)z(s)\mathrm{d}s+\frac{1}{t}\int_0^t\frac{p_3(s)z(s)}{1+\alpha_3(s)z(s)+\beta_3(s)x(s)}\mathrm{d}s\\&+\frac{1}{t}\int_0^t\sigma_1(s)\mathrm{d}B_1(s).\end{aligned}$$

Similarly by $x(t)=\prod\limits_{0<t_k<t}(1+d_{1k})x_1(t)$, we can have

$$\begin{aligned}\frac{\log x(t)-\log x(0)}{t}\geq&\frac{\sum\limits_{0<t_k<t}\log(1+d_{1k})}{t}+\frac{e^l\alpha}{\beta}\cdot\frac{1}{t}\int_0^t\frac{1}{x(s)}\mathrm{d}s\\&-\bigg(f^u+\frac{(\sigma_1^u)^2}{2}\bigg)-p_2^u\langle z(t)\rangle+\frac{1}{t}\int_0^t\sigma_1(s)\mathrm{d}B_1(s).\end{aligned}\tag{5.4}$$

Denote the set $S_1=\bigg\{\limsup\limits_{t\to\infty}x(t)=0\bigg\}$. If the first assertion of Theorem 5.1 does not hold, then $\mathbb{P}(S_1)>0$. Further, for any given $\omega\in S_1$, we derive $\lim\limits_{t\to\infty}x(t,\omega)=0$. And then for arbitrary small ε satisfying $0<\varepsilon<\min\bigg\{1,\frac{2e^l\alpha}{\big(2f^u+(\sigma_1^u)^2\big)\beta}\bigg\}$, there is a constant $T_1=T_1(\varepsilon,\omega)>0$ such that

$$x(t,\omega)\leq\varepsilon,\ \forall\ t\geq T_1(\varepsilon,\omega).$$

On the other hand, it follows from the continuity of $x(t)$ that there is a positive constant ρ such that

$$x(t,\omega)\leq\rho,\ \forall\ 0\leq t\leq T_1(\varepsilon,\omega).$$

Noting that the extinction of $z(t)$ implies that there exists a set $S_2\in\mathcal{F}$ satisfying $\mathbb{P}(S_2)=1$. Thus, for any $\omega\in S_2$, we have $\langle z(t,\omega)\rangle_*=0$. Moreover, using the strong law of large numbers shows that there exists a set $S_3\in\mathcal{F}$ with $\mathbb{P}(S_3)=1$, then for $\forall\ \omega\in S_3$, we obtain

$$\lim_{t\to\infty}\frac{1}{t}\int_0^t\sigma_1(s)\mathrm{d}B_1(s)=0.$$

It is easy to find that $S_1\cap S_2\cap S_3\neq\emptyset$, then for $\forall\ \omega\in S_1\cap S_2\cap S_3$, taking the

upper limit of both sides for (5.4) and by using $m_1 \leq \prod_{0<t_k<t}(1+d_{1k}) \leq M_1$, we get

$$\begin{aligned}\limsup_{t\to\infty}\frac{\log x(t)}{t} \geq\ & \frac{e^l\alpha}{\beta}\cdot\left(\limsup_{t\to\infty}\frac{1}{t}\int_0^{T_1}\frac{1}{\rho}\mathrm{d}s+\limsup_{t\to\infty}\frac{1}{t}\int_{T_1}^{t}\frac{1}{\varepsilon}\mathrm{d}s\right)-\left(f^u+\frac{(\sigma_1^u)^2}{2}\right)\\ =\ & \frac{e^l\alpha}{\beta}\cdot\limsup_{t\to\infty}\frac{1}{t}\int_{T_1}^{t}\frac{1}{\varepsilon}\mathrm{d}s-\left(f^u+\frac{(\sigma_1^u)^2}{2}\right).\end{aligned}$$

In view of $0<\varepsilon<\min\left\{1,\frac{2e^l\alpha}{(2f^u+(\sigma_1^u)^2)\beta}\right\}$, one may arrive

$$\limsup_{t\to\infty}\frac{\log x(t)}{t}>0. \tag{5.5}$$

However, for $\forall\ t\geq T_1(\varepsilon,\omega)$, we have

$$\frac{\log x(t)}{t}\leq\frac{\log\varepsilon}{t}<\frac{\log 1}{t}=0.$$

Hence, we can deduce the contradiction

$$0\geq\limsup_{t\to\infty}\frac{\log x(t)}{t}>0.$$

Then

$$\limsup_{t\to\infty}x(t)>0\quad a.s.$$

Finally, we will prove the extinction of $y(t)$. Computing $\mathrm{d}(\log y_1)$ by the Itô formula, we have

$$\begin{aligned}\mathrm{d}(\log y_1)=&\left[\frac{p_5(t)I(t)D_3(t)z_1}{\big(\alpha_4(t)+I(t)\big)\big(\alpha_5(t)+D_3(t)z_1\big)}-\frac{p_5(t)I(t)D_2(t)D_3(t)y_1z_1}{K_1(t)\big(\alpha_4(t)+I(t)\big)\big(\alpha_5(t)+D_3(t)z_1\big)}\right.\\&\left.-d(t)+b(t)-\frac{\sigma_2^2(t)}{2}\right]\mathrm{d}t+\sigma_2(t)\mathrm{d}B_2(t).\end{aligned}$$

By virtue of $y(t)=D_2(t)y_1(t)$ and $z(t)=D_3(t)z_1(t)$, integrating both sides of the above formula from 0 to t and dividing both sides by t, we can see that

$$\begin{aligned}\frac{\log y_1(t)-\log y_1(0)}{t}=&\frac{1}{t}\int_0^t\frac{p_5(s)I(s)z(s)}{\big(\alpha_4(s)+I(s)\big)\big(\alpha_5(s)+z(s)\big)}\mathrm{d}s\\&-\frac{1}{t}\int_0^t\frac{p_5(s)I(s)y(s)z(s)}{K_1(s)\big(\alpha_4(s)+I(s)\big)\big(\alpha_5(s)+z(s)\big)}\mathrm{d}s\\&-\frac{1}{t}\int_0^t\left(d(s)-b(s)+\frac{\sigma_2^2(s)}{2}\right)\mathrm{d}s\\&+\frac{1}{t}\int_0^t\sigma_2(s)\mathrm{d}B_2(s).\end{aligned}$$

Similarly, because $y(t)=\prod_{0<t_k<t}(1+d_{2k})y_1(t)$, we obtain

$$\frac{\log y(t)-\log y(0)}{t}$$

$$\leq \frac{\sum\limits_{0<t_k<t}\log(1+d_{2k})}{t}+\frac{1}{t}\int_0^t \frac{p_5(s)I(s)z(s)}{\big(\alpha_4(s)+I(s)\big)\big(\alpha_5(s)+z(s)\big)}\mathrm{d}s \tag{5.6}$$
$$-\frac{1}{t}\int_0^t\left(d(s)-b(s)+\frac{\sigma_2^2(s)}{2}\right)\mathrm{d}s+\frac{1}{t}\int_0^t\sigma_2(s)\mathrm{d}B_2(s).$$

Using the extinction of $z(t)$, we can see that for $\forall\ \varepsilon>0$, there exists a constant $T_2>0$ such that for any $t\geq T_2$, $z(t)<\varepsilon$ *a.s.* Consequently,

$$\begin{aligned}&\frac{\log y(t)-\log y(0)}{t}\\ \leq\ &\frac{\sum\limits_{0<t_k<t}\log(1+d_{2k})}{t}+\frac{1}{t}\int_0^{T_2}\frac{p_5(s)I(s)z(s)}{\big(\alpha_4(s)+I(s)\big)\big(\alpha_5(s)+z(s)\big)}\mathrm{d}s+\frac{t-T_2}{t}\cdot\frac{p_5^u\varepsilon}{\alpha_5^l}\\ &-\frac{1}{t}\int_0^t\left(d(s)-b(s)+\frac{\sigma_2^2(s)}{2}\right)\mathrm{d}s+\frac{1}{t}\int_0^t\sigma_2(s)\mathrm{d}B_2(s).\end{aligned}$$

By taking the upper limit on both sides of the above inequality and using the strong law of large numbers and the arbitrariness of ε, it follows that

$$\limsup_{t\to\infty}\frac{\log y(t)}{t}\leq\hat{\lambda}_2<0\quad a.s.$$

This completes the proof. □

Theorem 5.2. *If $\check{\lambda}_2>0$, $\hat{\lambda}_3<0$ and $\frac{a^l}{K^u}-\frac{c^u}{\alpha_1^l}>0$, then we can have that*

$$\limsup_{t\to\infty}x(t)>0\quad a.s. \tag{5.7}$$

$$\langle y(t)\rangle_*\geq\frac{K_1^l\check{\lambda}_2}{p_5^u}\quad a.s. \tag{5.8}$$

$$\limsup_{t\to\infty}\frac{\log z(t)}{t}\leq\hat{\lambda}_3<0\quad a.s. \tag{5.9}$$

where

$$\begin{aligned}\check{\lambda}_2:=\ &\liminf_{t\to\infty}\frac{1}{t}\left\{\sum_{0<t_k<t}\log(1+d_{2k})-\int_0^t\left(d(s)-b(s)+\frac{\sigma_2^2(s)}{2}\right)\mathrm{d}s\right\},\\ \hat{\lambda}_3:=\ &\limsup_{t\to\infty}\frac{1}{t}\left\{\sum_{0<t_k<t}\log(1+d_{3k})+\int_0^t\left(a(s)-\frac{\sigma_3^2(s)}{2}\right)\mathrm{d}s\right\}.\end{aligned}$$

That is, NK cells (x) will be weakly persistent and CTLs (y) will be persistent in the mean, while tumor cells (z) will become extinct exponentially with probability one.

Proof. The proof of (5.7) and (5.9) is the same as Theorem 5.1, hence it is omitted here. Next, we will prove (5.8). From (5.6), we get

$$\frac{\log y(t)-\log y(0)}{t}$$

$$\geq \frac{\sum\limits_{0<t_k<t}\log(1+d_{2k})}{t} - \frac{1}{t}\int_0^t \frac{p_5^u}{K_1^l}\cdot y(s)\mathrm{d}s - \frac{1}{t}\int_0^t \left(d(s)-b(s)+\frac{\sigma_2^2(s)}{2}\right)\mathrm{d}s + \frac{1}{t}\int_0^t \sigma_2(s)\mathrm{d}B_2(s).$$

Applying $\check{\lambda}_2 := \liminf\limits_{t\to\infty}\frac{1}{t}\left\{\sum\limits_{0<t_k<t}\log(1+d_{2k}) - \int_0^t\left(d(s)-b(s)+\frac{\sigma_2^2(s)}{2}\right)\mathrm{d}s\right\} > 0$, we can similarly obtain that for $\forall\ \varepsilon > 0$, there exists a constant $T_3 > 0$ such that for any $t \geq T_3$

$$\frac{1}{t}\left\{\sum_{0<t_k<t}\log(1+d_{2k}) - \int_0^t\left(d(s)-b(s)+\frac{\sigma_2^2(s)}{2}\right)\mathrm{d}s\right\} > \check{\lambda}_2 - \frac{\varepsilon}{2} \quad a.s. \tag{5.10}$$

Due to the strong law of large numbers, we easily know that there exists a set $\Omega_1 \in \mathcal{F}$ with $\mathbb{P}(\Omega_1) = 1$. For the above $\varepsilon > 0$, $\forall\ \omega \in \Omega_1$, there exists a constant $T_4 = T_4(\varepsilon,\omega) > 0$ such that for any $t \geq T_4$

$$-\frac{\varepsilon}{2} < \frac{1}{t}\int_0^t \sigma_2(s)\mathrm{d}B_2(s) < \frac{\varepsilon}{2}. \tag{5.11}$$

Consequently, by (5.10) and (5.11), for $t \geq \max\{T_3, T_4\}$, it is easy to get

$$\begin{aligned}\frac{\log y(t) - \log y(0)}{t} &\geq \check{\lambda}_2 - \frac{\varepsilon}{2} - \frac{p_5^u}{K_1^l}\cdot\frac{1}{t}\int_0^t y(s)\mathrm{d}s - \frac{\varepsilon}{2}\\ &= \check{\lambda}_2 - \frac{p_5^u}{K_1^l}\cdot\frac{1}{t}\int_0^t y(s)\mathrm{d}s - \varepsilon.\end{aligned}$$

Hence, using Lemma 5.1 and the arbitrariness of ε, we obviously have

$$\langle y(t)\rangle_* \geq \frac{K_1^l\check{\lambda}_2}{p_5^u} \quad a.s.$$

The proof is now complete. □

6. Persistence

In this section, we will find the conditions to guarantee the persistence of all three kinds of cells.

Theorem 6.1. *If* $\check{\lambda}_2 > 0$, $\check{\lambda}_3 - \frac{E^u\langle c(t)\rangle^*}{K^l\beta_1^l} - \frac{\langle p_1(t)\rangle^*}{\beta_2^l} > 0$ *and* $\frac{a^l}{K^u} - \frac{c^u}{\alpha_1^l} > 0$, *then we have*

$$\limsup_{t\to\infty} x(t) > 0 \quad a.s. \tag{6.1}$$

$$\langle y(t)\rangle_* \geq \frac{K_1^l\check{\lambda}_2}{p_5^u} \quad a.s. \tag{6.2}$$

$$\frac{\check{\lambda}_3 - \frac{E^u\langle c(t)\rangle^*}{K^l\beta_1^l} - \frac{\langle p_1(t)\rangle^*}{\beta_2^l}}{\frac{a^u}{K^l} + \frac{p_6^u}{\beta_6^l}} \leq \langle z(t)\rangle_* \leq \langle z(t)\rangle^* \leq \frac{\hat{\lambda}_3}{\frac{a^l}{K^u} - \frac{c^u}{\alpha_1^l}} \quad a.s. \tag{6.3}$$

where

$$\check{\lambda}_2 := \liminf_{t\to\infty}\frac{1}{t}\left\{\sum_{0<t_k<t}\log(1+d_{2k}) - \int_0^t\left(d(s)-b(s)+\frac{\sigma_2^2(s)}{2}\right)\mathrm{d}s\right\},$$

$$\check{\lambda}_3 := \liminf_{t\to\infty}\frac{1}{t}\left\{\sum_{0<t_k<t}\log(1+d_{3k}) + \int_0^t\left(a(s)-\frac{\sigma_3^2(s)}{2}\right)\mathrm{d}s\right\},$$

$$\hat{\lambda}_3 := \limsup_{t\to\infty}\frac{1}{t}\left\{\sum_{0<t_k<t}\log(1+d_{3k}) + \int_0^t\left(a(s)-\frac{\sigma_3^2(s)}{2}\right)\mathrm{d}s\right\}.$$

That is, NK cells (x) will be weakly persistent while CTLs (y) and tumor cells (z) will be persistent in the mean.

Proof. From (5.2), on one hand, we have

$$\begin{aligned}\frac{\log z(t)-\log z(0)}{t} \geq\ & \frac{\sum\limits_{0<t_k<t}\log(1+d_{3k})}{t} + \frac{1}{t}\int_0^t\left(a(s)-\frac{\sigma_3^2(s)}{2}\right)\mathrm{d}s\\ & - \frac{1}{t}\int_0^t\left(\frac{a^u}{K^l}+\frac{p_6^u}{\beta_6^l}\right)\cdot z(s)\mathrm{d}s - \frac{E^u\langle c(t)\rangle}{K^l\beta_1^l} - \frac{\langle p_1(t)\rangle}{\beta_2^l}\\ & + \frac{1}{t}\int_0^t\sigma_3(s)\mathrm{d}B_3(s).\end{aligned}$$

According to $\check{\lambda}_3 := \liminf\limits_{t\to\infty}\frac{1}{t}\left\{\sum\limits_{0<t_k<t}\log(1+d_{3k}) + \int_0^t\left(a(s)-\frac{\sigma_3^2(s)}{2}\right)\mathrm{d}s\right\}$, we know that for $\forall\ \varepsilon>0$, $\exists\ T_5>0$ such that for $\forall\ t\geq T_5$

$$\frac{1}{t}\left\{\sum_{0<t_k<t}\log(1+d_{3k}) + \int_0^t\left(a(s)-\frac{\sigma_3^2(s)}{2}\right)\mathrm{d}s\right\} > \check{\lambda}_3 - \frac{\varepsilon}{4}\quad a.s. \tag{6.4}$$

In view of the definition of upper limit, for the above $\varepsilon>0$, one can find two constants T_6, $T_7>0$ such that for $\forall\ t\geq\max\{T_6,T_7\}$

$$\langle c(t)\rangle < \langle c(t)\rangle^* + \frac{\varepsilon K^l\beta_1^l}{4E^u}\quad a.s. \qquad \langle p_1(t)\rangle < \langle p_1(t)\rangle^* + \frac{\varepsilon\beta_2^l}{4}\quad a.s. \tag{6.5}$$

Then, we use the strong law of large numbers again, and find that there exists a set $\Omega_2\in\mathcal{F}$ with $\mathbb{P}(\Omega_2)=1$. Thus, for the above $\varepsilon>0$, $\forall\ \omega\in\Omega_2$, there exists a constant $T_8=T_8(\varepsilon,\omega)>0$ such that for any $t\geq T_8$

$$-\frac{\varepsilon}{4} < \frac{1}{t}\int_0^t\sigma_3(s)\mathrm{d}B_3(s) < \frac{\varepsilon}{4}. \tag{6.6}$$

Combining (6.4), (6.5) and (6.6), we obviously get that $\exists\ \overline{T}=\max\{T_5,T_6,T_7,T_8\}$ such that for any $t\geq\overline{T}$

$$\begin{aligned}\frac{\log z(t)-\log z(0)}{t} \geq\ & \check{\lambda}_3 - \frac{\varepsilon}{4} - \frac{1}{t}\int_0^t\left(\frac{a^u}{K^l}+\frac{p_6^u}{\beta_6^l}\right)\cdot z(s)\mathrm{d}s - \frac{E^u\langle c(t)\rangle^*}{K^l\beta_1^l} - \frac{\varepsilon}{4}\\ & - \frac{\langle p_1(t)\rangle^*}{\beta_2^l} - \frac{\varepsilon}{4} - \frac{\varepsilon}{4}\\ =\ & \check{\lambda}_3 - \frac{1}{t}\int_0^t\left(\frac{a^u}{K^l}+\frac{p_6^u}{\beta_6^l}\right)\cdot z(s)\mathrm{d}s - \frac{E^u\langle c(t)\rangle^*}{K^l\beta_1^l} - \frac{\langle p_1(t)\rangle^*}{\beta_2^l} - \varepsilon.\end{aligned}$$

By $\check{\lambda}_3 - \frac{E^u\langle c(t)\rangle^*}{K^l\beta_1^l} - \frac{\langle p_1(t)\rangle^*}{\beta_2^l} > 0$, the arbitrariness of ε and Lemma 5.1, we have

$$\langle z(t)\rangle_* \geq \frac{\check{\lambda}_3 - \frac{E^u\langle c(t)\rangle^*}{K^l\beta_1^l} - \frac{\langle p_1(t)\rangle^*}{\beta_2^l}}{\frac{a^u}{K^l} + \frac{p_6^u}{\beta_6^l}} \quad a.s.$$

On the other hand, by (5.2) we can obtain

$$\begin{aligned}\frac{\log z(t) - \log z(0)}{t} \leq{}& \frac{\sum\limits_{0<t_k<t}\log(1+d_{3k})}{t} + \frac{1}{t}\int_0^t \left(a(s) - \frac{\sigma_3^2(s)}{2}\right)\mathrm{d}s \\ &+ \left(\frac{c^u}{\alpha_1^l} - \frac{a^l}{K^u}\right)\cdot\frac{1}{t}\int_0^t z(s)\mathrm{d}s \\ &+ \frac{1}{t}\int_0^t \sigma_3(s)\mathrm{d}B_3(s).\end{aligned}$$

Similarly, according to $\frac{a^l}{K^u} - \frac{c^u}{\alpha_1^l} > 0$ and using Lemma 5.1 we obtain

$$\langle z(t)\rangle^* \leq \frac{\hat{\lambda}_3}{\frac{a^l}{K^u} - \frac{c^u}{\alpha_1^l}} \quad a.s. \tag{6.7}$$

Finally, the proof of (6.1) and (6.2) is similar to (5.7) and (5.8) of Theorem 5.2, hence it is omitted here. □

7. Numerical simulation

In this section, we present some numerical simulations and examples to further illustrate our theoretical results. We use the Milstein method [10] to get the discretization equation for system (1.4) and discuss the influence of stochastic perturbations and pulsed chemotherapy. In the following examples, we choose the initial value $(x_0, y_0, z_0, v_0) = (4\times10^5, 10^5, 2\times10^5, 4\times10^5)$ and the parameter values are shown in Table 2. Besides, $E(t) = \widetilde{E}(t - n\hat{\tau})$, $t \in [n\hat{\tau}, (n+1)\hat{\tau})$, which is shown in Figure 2 [30], and $\hat{\tau} = 29$, which is a menstrual cycle.

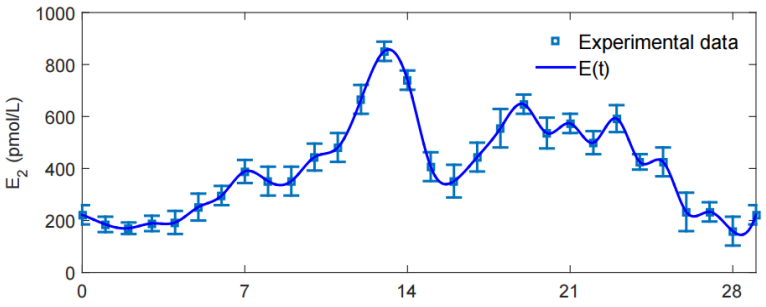

Figure 2. Estradiol levels across the menstrual cycle.

Example 7.1. Choose $\sigma_1(t) = \sqrt{0.04+0.02\sin t}$, $\sigma_2(t) = \sqrt{0.04+0.02\sin t}$, $\sigma_3(t) = \sqrt{0.04+0.02\sin t}$, $d_{1k} = d_{2k} = d_{3k} = e^{-\frac{1}{k^2}} - 1$ and $\tau = 30$.

By computing $h^2 = \left[\frac{\sqrt{p_3^u M_1}-\sqrt{p_2^l m_1}}{\sqrt{\alpha_3^l m_1}} \vee 0\right]^2 = 0$, we have $f^l - h^2 + \frac{(\sigma_1^u)^2}{2} = 0.0833 > 0$, which satisfies the condition of Theorem 4.1. Hence, the solution of system (1.4) is stochastically ultimately bounded. The results of numerical simulations are shown in Figure 3 and Figure 4. They reveal the sample path of $|X(t)| = \sqrt{x^2(t) + y^2(t) + z^2(t)}$ and the three-dimensional diagram of system (1.4), respectively. Obviously, both of the two figures verify the conclusion of Theorem 4.1.

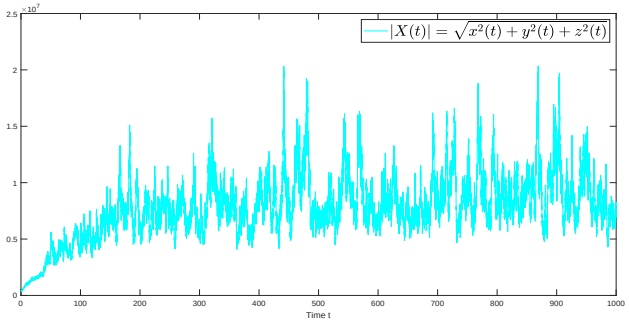

Figure 3. The sample path of $|X(t)| = \sqrt{x^2(t) + y^2(t) + z^2(t)}$ for system (1.4) with $\sigma_1(t) = \sqrt{0.04 + 0.02\sin t}$, $\sigma_2(t) = \sqrt{0.04 + 0.02\sin t}$ and $\sigma_3(t) = \sqrt{0.04 + 0.02\sin t}$.

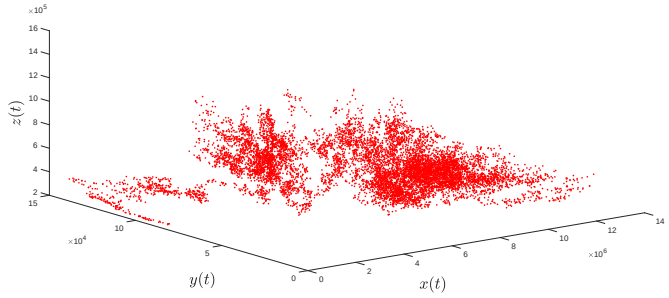

Figure 4. Three-dimensional diagram of system (1.4) with $\sigma_1(t) = \sqrt{0.04 + 0.02\sin t}$, $\sigma_2(t) = \sqrt{0.04 + 0.02\sin t}$ and $\sigma_3(t) = \sqrt{0.04 + 0.02\sin t}$.

Next, we choose $\sigma_1(t) = \sqrt{0.01+0.02\sin t}$, $\sigma_2(t) = \sqrt{0.25+0.01\sin t}$, $\sigma_3(t) = \sqrt{0.64+0.01\sin t}$, and other parameters keep unchanged. By calculating $\hat{\lambda}_2 = -0.115 < 0$, $\hat{\lambda}_3 = -0.02 < 0$ and $\frac{a^l}{K^u} - \frac{c^u}{\alpha_1^l} \approx 2.325 \times 10^{-7} > 0$, we can obtain that the conditions of Theorem 5.1 hold, namely, x is weakly persistent while y and z become extinct. And the numerical simulations are presented in Figure 5.

Further, we choose $\sigma_2(t) = \sqrt{0.01 + 0.02\sin t}$ and keep the other parameters unchanged. By computing $\check{\lambda}_2 = 0.005 > 0$, $\hat{\lambda}_3 = -0.02 < 0$ and $\frac{a^l}{K^u} - \frac{c^u}{\alpha_1^l} \approx 2.325 \times 10^{-7} > 0$, thus the conditions of Theorem 5.2 hold, that is, x will be weakly persistent and y will be persistent in the mean, while z goes to die out. The results of numerical simulations are shown in Figure 6, which confirms Theorem 5.2.

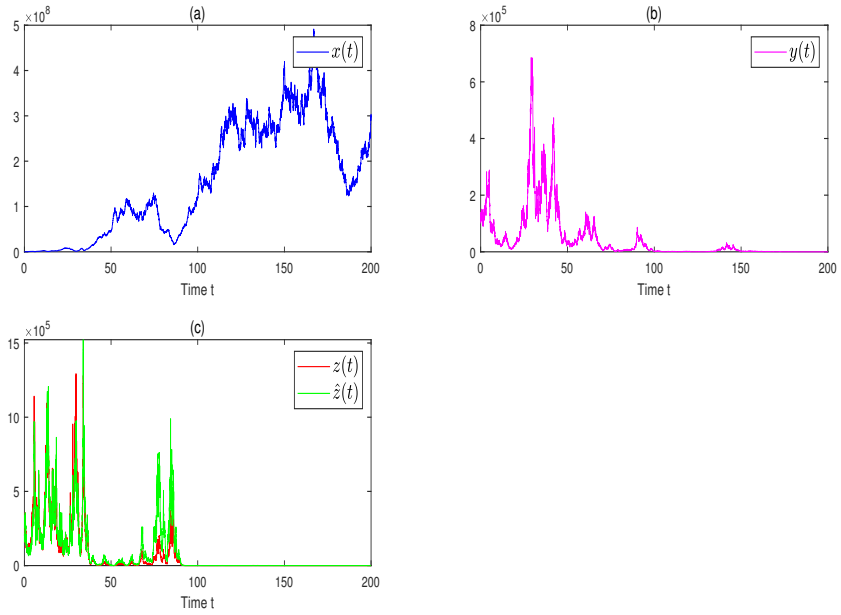

Figure 5. The sample path of $x(t)$, $y(t)$, $z(t)$ and $\hat{z}(t)$ with $\sigma_1(t) = \sqrt{0.01 + 0.02\sin t}$, $\sigma_2(t) = \sqrt{0.25 + 0.02\sin t}$ and $\sigma_3(t) = \sqrt{0.64 + 0.02\sin t}$, respectively.

Moreover, set $\sigma_3(t) = \sqrt{0.01 + 0.02\sin t}$ and the other parameters are the same as above. By computing $\check{\lambda}_2 = 0.005 > 0$, $\check{\lambda}_3 - \frac{E^u\langle c(t)\rangle^*}{K^l\beta_1^l} - \frac{\langle p_1(t)\rangle^*}{\beta_2^l} \approx 0.277 > 0$ and $\frac{a^l}{K^u} - \frac{c^u}{\alpha_1^l} \approx 2.325 \times 10^{-7} > 0$, we find that the conditions of Theorem 6.1 hold. Consequently, x will be weakly persistent as well as y and z will be persistent in the mean, as is shown in Figure 7.

Finally, in order to investigate the effects of pulsed chemotherapy on tumor cell extinction, we will compare the following SDE without impulse with system (1.4), where $\hat{v}(t) = v(t) = \frac{\alpha}{\beta} + (v_0 - \frac{\alpha}{\beta})e^{-\beta t}$.

$$\begin{cases} \mathrm{d}\hat{x}(t) = \Big(e(t)\hat{v} - f(t)\hat{x} - p_2(t)\hat{x}\hat{z} + \frac{p_3(t)\hat{x}\hat{z}}{1+\alpha_3(t)\hat{z}+\beta_3(t)\hat{x}}\Big)\mathrm{d}t + \sigma_1(t)\hat{x}\mathrm{d}B_1(t), \\ \mathrm{d}\hat{y}(t) = \Big(\frac{p_5(t)I(t)\hat{y}}{\alpha_4(t)+I(t)}\big(1 - \frac{\hat{y}}{K_1(t)}\big)\frac{\hat{z}}{\alpha_5(t)+\hat{y}} - d(t)\hat{y} + b(t)\hat{y}\Big)\mathrm{d}t + \sigma_2(t)\hat{y}\mathrm{d}B_2(t), \\ \mathrm{d}\hat{z}(t) = \Big(\hat{z}\big(a(t)+\frac{c(t)E(t)\hat{z}}{1+\alpha_1(t)E(t)+\beta_1(t)\hat{z}^2}\big)\big(1-\frac{\hat{z}}{K(t)}\big) - \frac{p_1(t)\hat{x}^2\hat{z}}{1+\alpha_2(t)\hat{z}+\beta_2(t)\hat{x}^2} \\ \qquad\qquad - \frac{p_6(t)\hat{y}\hat{z}^2}{1+\alpha_6(t)\hat{z}^2+\beta_6(t)\hat{y}}\Big)\mathrm{d}t + \sigma_3(t)\hat{z}\mathrm{d}B_3(t), \\ \hat{x}(0) = x_0,\ \hat{y}(0) = y_0,\ \hat{z}(0) = z_0. \end{cases} \tag{7.1}$$

The parameter values of system (7.1) are the same as model (1.4). We will take two sets of noise intensities as follows: $\sigma_1(t) = \sqrt{0.01 + 0.02\sin t}$, $\sigma_2(t) = \sqrt{0.25 + 0.01\sin t}$, $\sigma_3(t) = \sqrt{0.64 + 0.01\sin t}$, and $\sigma_2(t) = \sqrt{0.01 + 0.01\sin t}$, where $\sigma_1(t)$ and $\sigma_3(t)$ keep unchanged. Similarly, we can get the results that tumor cells will become extinct in both cases. Here, we only simulate the sample paths of tumor cells which are

shown in Figure 5(c) and Figure 6(c), respectively. Obviously, it is easy to find that pulsed chemotherapy can accelerate the extinction of tumor cells.

Table 2. Parameter values in model (1.4).

Parameter	Value	Reference
$e(t)$	$0.00486 + 0.0001\sin t$	Estimated from data [30, 34]
$a(t)$	$0.3 + 0.01\sin t$	Estimated from data [30]
$f(t)$	$0.0693 + 0.001\sin t$	Estimated from data [30, 34]
$c(t)$	$1.3 \times 10^{-7} + 10^{-8}\sin t$	Estimated
$p_2(t)$	$3.42 \times 10^{-6} + 10^{-7}\sin t$	Estimated from data [6, 7, 30]
$\alpha_1(t)$	$4.507 + 0.01\sin t$	Estimated
$p_3(t)$	$1.87 \times 10^{-8} + 10^{-9}\sin t$	Estimated from data [3, 30]
$\beta_1(t)$	$7.08 \times 10^{-8} + 10^{-9}\sin t$	Estimated from data [30]
$\alpha_3(t)$	$1.6 \times 10^{-5} + 10^{-6}\sin t$	Estimated from data [3, 30]
$K(t)$	$10^6 + 10^5\sin t$	Estimated
$\beta_3(t)$	$3.27 + 0.01\sin t$	Estimated from data [3, 30]
$p_1(t)$	$8.7 \times 10^{-7} + 10^{-8}\sin t$	Estimated
$p_5(t)$	$4.14 \times 10^{-3} + 10^{-4}\sin t$	Estimated from data [11, 30]
$\alpha_2(t)$	$7 \times 10^6 + 10^5\sin t$	Estimated from data [3, 30]
$I(t)$	$2.3 \times 10^{-11} + 10^{-12}\sin t$	Estimated from data [14, 22, 30]
$\beta_2(t)$	$5.4 \times 10^{-5} + 10^{-6}\sin t$	Estimated from data [3, 30]
$\alpha_4(t)$	$2.3 \times 10^{-11} + 10^{-12}\sin t$	Estimated from data [14, 22, 30]
$p_6(t)$	$2.04 \times 10^{-3} + 10^{-4}\sin t$	Estimated from data [3, 30]
$K_1(t)$	$8 \times 10^8 + 10^7\sin t$	Estimated from data [9, 30]
$\alpha_6(t)$	$0.268 + 0.01\sin t$	Estimated from data [3, 30]
$\alpha_5(t)$	$1000 + 100\sin t$	Estimated from data [30]
$\beta_6(t)$	$4343 + 100\sin t$	Estimated from data [3, 30]
$d(t)$	$0.41 + 0.01\sin t$	Estimated from data [4, 30]
α	3.6×10^7	[30]
$b(t)$	$0.42 + 0.01\sin t$	Estimated
β	6.3×10^{-3}	[28, 30]

Example 7.2. Choose $\sigma_1(t) = \sqrt{0.01+0.02\sin t}$, $\sigma_2(t) = \sqrt{0.25+0.01\sin t}$, $\sigma_3(t) = \sqrt{0.64+0.01\sin t}$, $\tau = 90$ and other parameters are the same as in Example 7.1.

By calculation, we can similarly obtain that tumor cells will die out. Moreover, our purpose is only to compare the effects of different pulsed chemotherapy cycles on tumor cell extinction, as shown in Figure 8. It is clear that shortening the pulsed period can keep the number of tumor cells lower until they become extinct.

Example 7.3. In order to illustrate the inhibitory effects of random disturbances on cell proliferation, we choose $\sigma_1(t) = \sqrt{0.2+0.02\sin t}$, $\sigma_2(t) = \sqrt{0.4+0.02\sin t}$ and $\sigma_3(t) = \sqrt{0.8+0.02\sin t}$, and other parameters are the same as in Example 7.1.

By similar calculation, we can easily observe that the parameters satisfy the conditions of Theorem 5.1. Hence, x will be weakly persistent while y and z will become extinct. The results of numerical simulations compared with Example 7.1 are shown in Figure 9. It can be seen that increasing the intensities of random disturbances will accelerate the extinction of tumor cells, that is, stochastic disturbances can inhabit the cell proliferation.

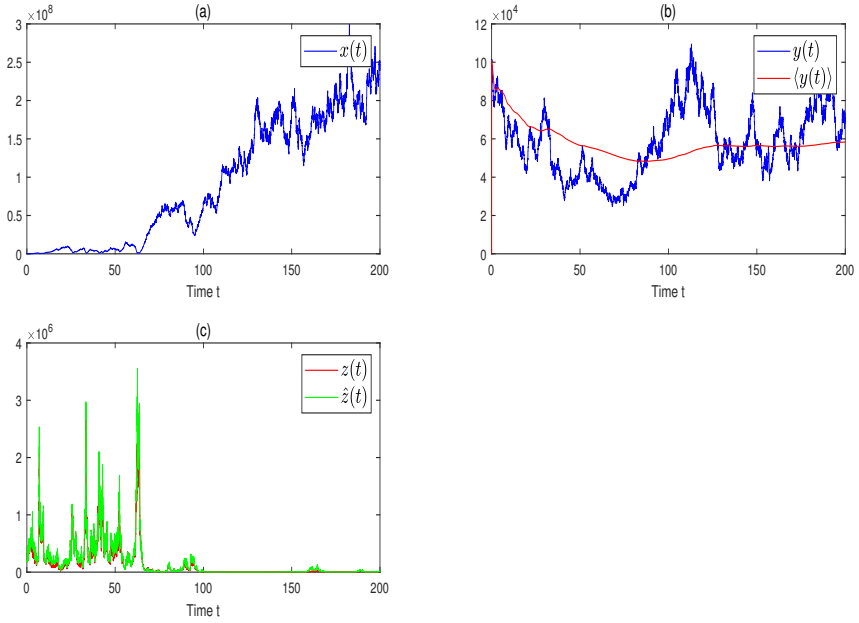

Figure 6. The sample path of $x(t)$, $y(t)$, $\langle y(t)\rangle$, $z(t)$ and $\hat{z}(t)$ with $\sigma_1(t) = \sqrt{0.01 + 0.02\sin t}$, $\sigma_2(t) = \sqrt{0.01 + 0.02\sin t}$ and $\sigma_3(t) = \sqrt{0.64 + 0.02\sin t}$, respectively.

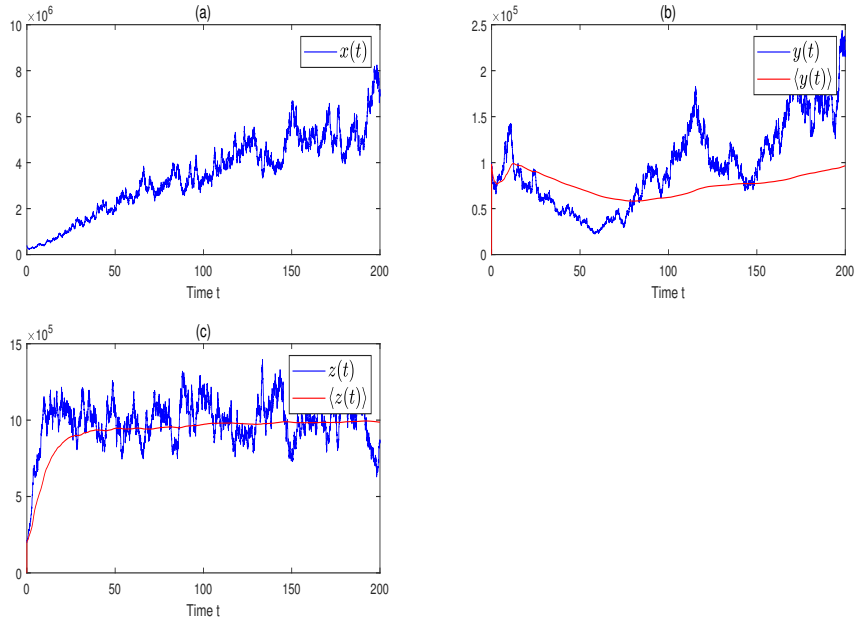

Figure 7. The sample path of $x(t)$, $y(t)$, $\langle y(t)\rangle$, $z(t)$ and $\langle z(t)\rangle$ with $\sigma_1(t) = \sqrt{0.01 + 0.02\sin t}$, $\sigma_2(t) = \sqrt{0.01 + 0.02\sin t}$ and $\sigma_3(t) = \sqrt{0.01 + 0.02\sin t}$, respectively.

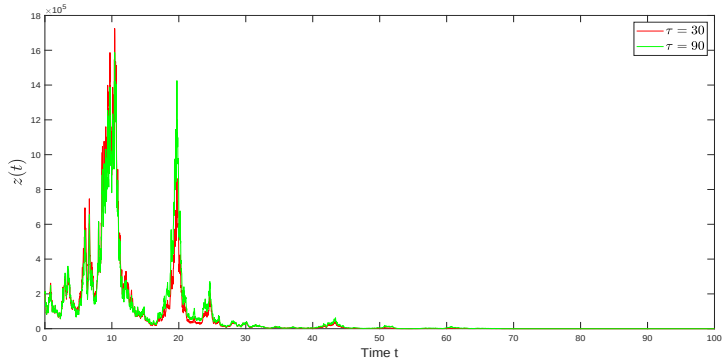

Figure 8. The sample path of $z(t)$ with different pulsed periods.

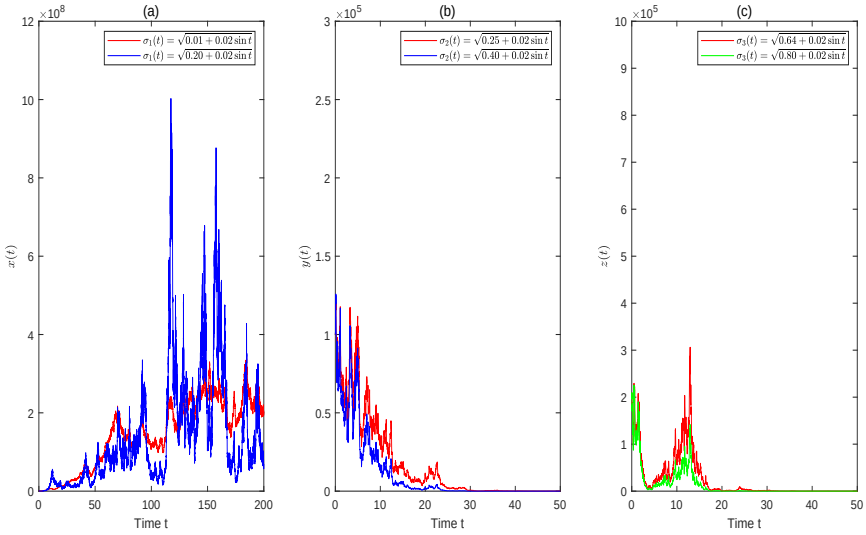

Figure 9. The sample paths of $x(t)$, $y(t)$ and $z(t)$ with different white noise intensities, respectively.

8. Conclusion

In this paper, we devote our main attention to studying stochastic model (1.4) which includes immunotherapy and pulsed chemotherapy. First, we prove the existence and uniqueness of the global positive solution for system (1.4) by the method of stochastic Lyapunov analysis, which lays a foundation for the following discussion. Next, the sufficient condition to guarantee the stochastic ultimate boundedness of the solution is obtained. Furthermore, we focus on the extinction of the tumor cells and the persistence of all three kinds of cells by using the strong law of large numbers. Specifically, when CTLs and tumor cells are subject to strong noises, both of them will become extinct exponentially with probability one. Moreover, tumor cells will be extinct when the perturbations to them are large enough while CTLs

will persist in the mean under weak noises. Besides, when both tumor cells and CTLs are subject to sufficiently weak noises, they will be persistent in the mean. In all the above three cases, NK cells are weakly persistent, and we can find that the stochastic perturbations play an important role in the elimination of tumor cells. At last, all of our theoretical results are illustrated by numerical simulations. The figures also imply that pulsed chemotherapy can accelerate the extinction of tumor cells and shortening the period of pulsed chemotherapy can keep tumor cells at a low level until they become extinct. In addition, stochastic disturbances can inhibit cell proliferation.

Therefore, one of the most commonly used methods in the clinical treatment of breast cancer is pulsed chemotherapy. This treatment is characterized by periodic dosing, that is, concentrated dosing over a period of time, followed by an intermittent period. This way of periodic administration can reduce the damage of the drug to normal cells, while improving the killing effect on tumor cells. In clinical treatment, appropriately shortening the cycle of pulse chemotherapy can also inhibit tumor cells at a lower level until extinction. In addition, in daily life, patients should maintain a reasonable rest to avoid the impact of environmental factors on cancer patients.

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