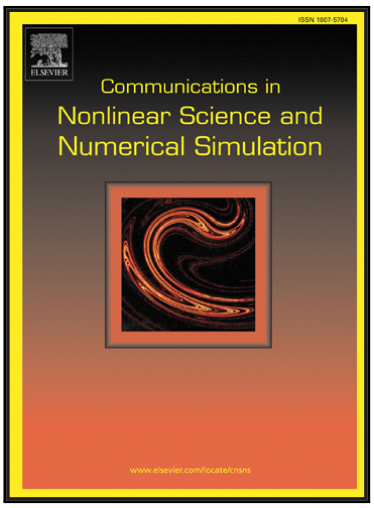

Thresholds for extinction and proliferation in a stochastic tumour-immune model with pulsed comprehensive therapy

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Highlights

- We developed a stochastic tumour-immune dynamical model concerning pulsed treatment.
- Conditions for the three phases of cancer immunoediting are provided.
- The results reveal that comprehensive therapy or noise can dominate evolution of tumours.
- Biological implications for cancer treatment are presented.

Thresholds for extinction and proliferation in a stochastic tumour-immune model with pulsed comprehensive therapy

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Abstract

Periodical applications of immunotherapy and chemotherapy play significant roles in cancer treatment and studies have shown that the evolution of tumour cells is subject to random events. In order to capture the effects of such noise we developed a stochastic tumour-immune dynamical model with pulsed treatment to describe combinations of immunotherapy with chemotherapy. By using theorems of the impulsive stochastic dynamical equation, the tumour free solution and the global positive solution of the proposed system were investigated. We then show that the expectations of the solutions are bounded. Furthermore, threshold conditions for extinction, non-persistence in the mean, weak persistence and stochastic persistence of tumour cells are provided. The results reveal that comprehensive therapy or noise can dominate the evolution of tumours. Finally, biological implications are addressed and a conclusion is presented.

Keywords:
Stochastic tumour-immune model, Pulsed therapy, Extinction and persistence, Lyapunov function

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1. Introduction

The malignant tumours of cancer result from the abnormal proliferation of cells. Cancer remains a worldwide aggressive disease and its treatment is still fraught with challenges. Traditional methods of treatment usually include surgery, radiotherapy and chemotherapy. However, these methods either cannot completely clear cancer cells or cause many negative side effects in the patients. To overcome these drawbacks, new treatments based on immunotherapy, intended to stimulate a strong immune response to its target tumours, has been used to cure cancer [1, 2]. Pre-clinical data and phased clinical studies have emphasized that immunotherapy may not only clear the tumour cells, but can also enhance the e□cacy of chemotherapy or radiotherapy [3-5].

Mathematical models have been used to study the interactions between tumor cells and immune cells [6-9]. In 1994, Kuznetsov constructed a novel tumour-immune dynamical model and the results showed how the tumour growth stimulated the immune response and how dormancy in tumours occurs [10]. The simple model consisted of two ordinary di□erential equations, where the e□ector cells (such as TIL or NK cells) act as role of predator, while the tumour cells play the role of the prey. Many phenomena were studied, such as immunostimulation of tumour growth, sneaking through of the tumour, and formation of a tumour dormant state. Later, Kirschner and Panetta extended this tumour-immune model by introducing immunotherapy [11]. The continuous injections of interleukin-2 (IL-2) were investigated and the conditions for short-term oscillations for tumour cells and for long-term tumour relapse were provided. Wei and Yang later studied pulsed tumour-immune models with immunotherapy and chemotherapy applied periodically [12, 13]. The conditions for the tumour free periodic solution were obtained and it was confirmed that Adoptive Cellular Immunotherapy (ACI) applied more frequently than inputs of IL-2 were a better way to cure cancer. Moreover, Tang and co-authors developed a series of tumour-immune models incorporating comprehensive therapy [14-16]. Surgery together with ACI and IL-2 were implemented once tumour cells or e□ector cells reached critical values. Periodic solutions and bifurcations were studied and the biological significance of the results for cancer treatment was also addressed.

A very important assumption in the above studies is that the growth of both tumour cells and e□ector cells follow deterministic laws. But most natural phenomena are influenced by stochastic processes rather than only

by strictly deterministic laws [17], and the tumour cells are no exception [18]. For instance, changes in the environment can lead to changes in the enzymatic activity of proteins, which will a□ect the growth of tumour cells [19]. Thus, it is more reasonable to describe the growth of tumour cells by using stochastic di□erential equations. Li and Cheng considered a stochastic tumour growth model and obtained conditions for extinction and persistence of tumour cells [19], and Caravagna investigated the e□ects of stochastic oscillations on tumour suppression [20]. Wang and co-authors studied how environmental fluctuations a□ected the dynamics of tumour cells [21].

However, there are few stochastic tumour-immune models with comprehensive therapy. In experimental and clinical studies, immunotherapeutic drugs and chemotherapy drugs are often injected at fixed periods to cure cancer [22, 23]. Such pulsed treatments, which can be described by impulsive di□erential equations [24, 25], have proved to be essential for governing whether the comprehensive treatment was successful or not [9]. Therefore, it is necessary to consider both environmental fluctuations and pulsed therapy in a tumour-immune model, and further to address how random noise and key factors (including the period of therapy, a clear rate representing the intensity of treatment and the growth rate stimulated by immunotherapy) a□ect the outcomes of the treatment. Thereby, we propose a stochastic tumour-immune model with pulsed comprehensive therapy to solve these problems. And such stochastic systems with pulsed control have been widely applied in many fields and sciences, such as in predator-prey systems [26-28], virus dynamical systems [29], and epidemic dynamical systems [30].

The structure of this paper is divided into the following sections: Some important definitions and lemmas about the impulsive stochastic dynamical equation are introduced in section 2. In section 3, the existence and uniqueness of a global positive solution for system (2.2) will be studied. In section 4, the conditions for the extinction and persistence of the tumour cells and e□ector cells are provided. Numerical investigations are carried out in section 5. In section 6, biological implications about the cancer treatment are addressed, followed by concluding remarks.

2. Mathematical Model

2.1. Model formation

Let $x(t)$ be the tumour cells and $y(t)$ be the e□ector cells include cytotoxic T-cells, macrophages, and natural killer cells that act on the tumour cells.

Assume that the tumour cell and effector cell play the role of the prey and predator, then the tumour-immune dynamical model proposed by Kuznetsov can be described by [10],

$$\begin{cases} \dfrac{dx(t)}{dt} = rx(t)(1-\eta x(t)) - ax(t)y(t), \\ \dfrac{dy(t)}{dt} = \dfrac{bx(t)y(t)}{1+wx(t)} - cx(t)y(t) - dy(t), \end{cases} \tag{2.1}$$

where r is the intrinsic growth rate of tumour cells, $1/\eta$ is the carrying capacity of tumour cells, a is the rate at which the effector cells bind to the tumour cells, c is the inactivation rate of effector cells, d is the death rate of effector cells, b denotes the maximum immune response rate due to the presence of tumour cells and w is the steepness of the immune response.

Based on system (2.1), we propose a stochastic tumour-immune dynamical model concerning pulsed treatment, so the extended model (2.1) is

$$\begin{cases} dx(t) = [rx(t)(1-\eta x(t)) - ax(t)y(t)]dt + \delta_1 x(t)dB_1(t), \\ dy(t) = \left[\frac{bx(t)y(t)}{1+wx(t)} - cx(t)y(t) - dy(t)\right]dt + \delta_2 y(t)dB_2(t), \end{cases} t \neq nT, \\ \begin{cases} x(nT^+) = (1-a(nT))x(nT), \\ y(nT^+) = (1+b(nT))y(nT), \end{cases} t = nT, \end{cases} \tag{2.2}$$

where δ_1^2 and δ_2^2 are the intensity of the noise on the tumour cells and effector cells, respectively, and $B_1(t)$ and $B_2(t)$ denote independent Brownian motions with $B_i(0) = 0$. T is the period for the pulsed therapy, n is a positive integer. In reality, the chemotherapy drug kills both the tumour cells and the effector cells, but although the killing rates for them will differ, we do not take this into account. $a(nT)$ is the killing rate of the chemotherapy, $b(nT)$ denotes the net growth rate of the effector cells stimulated by immunotherapy. $b - c > 0$ for biological significance.

2.2. Preliminaries

In the rest of the paper, let $(\Omega, F, \{F_t\}_{t\geq 0}, P)$ be a complete probability space with a filtration $\{F_t\}_{t\geq 0}$ which satisfies the usual conditions. We assume that the independent Brownian motion $B_i(t)$ is defined on this probability space. If the number of factors of a product is zero then we assume

that this produc equals unity. Now we introduce some useful definitions of the paper.

Definition 1. ([31]) $X(t) = (x(t), y(t))^T, t \in R_+ = [0, +\infty)$, is called a solution of ISDE (2.2) with initial condition $X(0) = X_0 \geq 0$ if the following holds:

(1) $X(t)$ is absolutely continuous on $(0, T]$ and $(nT, (n+1)T]$;

(2) for any nT, we have $X(nT^-) = \lim_{t \to nT^-} X(t)$ and $X(nT^+) = \lim_{t \to nT^+} X(t)$ and $X(nT) = X(nT^-)$;

(3) $X(t)$ obeys system (2.2) for every $t \in R_+ - nT$ and at pulsed point nT satisfies the pulse condition.

Definition 2. ([32, 33]) Let $X(t) = (x(t), y(t))^T$ be a solution of ISDE (2.2):

(1) $x(t)$ is called extinctive if $\lim_{t \to +\infty} x(t) = 0$;

(2) $x(t)$ is called non-persistent in the mean if $\lim_{t \to +\infty} \frac{1}{t} \int_0^t x(s)ds = 0$;

(3) $x(t)$ is called weakly persistent in the mean if $\lim_{t \to +\infty} \sup \frac{1}{t} \int_0^t x(s)ds > 0$;

(4) if for each $\varepsilon \in (0, 1)$, there exists $\beta > 0$ and $\delta > 0$ so that

$$\liminf_{t \to +\infty} P\{x(t) \geq \beta\} \geq 1 - \varepsilon, \liminf_{t \to +\infty} P\{x(t) \leq \delta\} \geq 1 - \varepsilon,$$

then $x(t)$ is called stochastically persistent.

Remark 1. Biologically, these definitions are very important to explain three phases of cancer immunoediting, i.e., the extinction, weakly persistence and stochastic persistence correspond to the phase of elimination, the phase of equilibrium and the phase of escape, respectively. Besides, extinction means non-persistence in the mean, but the reverse is not true.

Definition 3. Suppose that $X_1(t), X_2(t)$ are any two solutions of ISDE (2.2) with $X_1(0) > 0, X_2(0) > 0$, if $\lim_{t \to +\infty} | x_1(t) - x_2(t) | = 0$ and $\lim_{t \to +\infty} | y_1(t) - y_2(t) | = 0$, then ISDE (2.2) is called globally attractive.

Lemma 1 [34]. Let $f(t) \in C(\Omega \times R_+, R_+ - 0)$,

(1) if there are constants ζ_0, t_1 and $\zeta \geq 0$ such that $f(t)$ satisfies

$$\ln f(t) \leq \zeta t - \zeta_0 \int_0^t f(s)ds + \sum_{i=1}^{n} \beta_i B_i(t)$$

for any $t \geq t_1$, β_i is also a constant, then we have

$$\lim_{t \to +\infty} \sup \frac{1}{t} \int_0^t f(s)ds \leq \frac{\zeta}{\zeta_0}.$$

(2) if there are constants ζ_0, t_1 and $\zeta \geq 0$ such that $f(t)$ satisfies

$$\ln f(t) \geq \zeta t - \zeta_0 \int_0^t f(s)ds + \sum_{i=1}^{n} \beta_i B_i(t)$$

for any $t \geq t_1$, then we have

$$\limsup_{t \to +\infty} \frac{1}{t} \int_0^t f(s)ds \geq \frac{\zeta}{\zeta_0}.$$

3. Global positive solution

3.1. Tumour free solution

We first consider a special case. Suppose that chemotherapy and immunotherapy are very effective and that the tumour cells can then be eradicated by effector cells in a short time. Let $x(t) = 0$, then system (2.2) can be reduced to the following simple subsystem:

$$\begin{cases} dy(t) = -dy(t)dt + \delta_2 y(t)dB_2(t), & t = nT, \\ y(nT^+) = (1 + b(nT))y(nT), & t = nT. \end{cases} \tag{3.1}$$

We show that system (3.1) has a global positive solution based on reference [27].

Theorem 1. System (3.1) has a unique global positive solution $y(t)$ with initial value $y(0^+) = y(0)$ which can be expressed by

$$y(t) = \prod_{0<nT<t} (1 + b(nT))y(0) \exp[(-d - 0.5\delta_2^2)t + \delta_2 B_2(t)]. \tag{3.2}$$

Proof. Let $V(t) = \ln y(t)$ for any $t \in (nT, (n+1)T]$. By using Itô's formula we obtain

$$d\ln y(t) = (-d - 0.5\delta_2^2)dt + \delta_2 dB_2(t).$$

Integrating the above equation from nT to t yields

$$\ln y(t) - \ln y(nT) = (-d - 0.5\delta_2^2)(t - nT) + \delta_2(B_2(t) - B_2(nT)).$$

At time $t = nT^+$, immunotherapy is applied once and then

$$y(t) = (1 + b(nT))y(nT) \exp[(-d - 0.5\delta_2^2)(t - nT) + \delta_2(B_2(t) - B_2(nT))].$$

It follows by induction that we get the global positive solution $y(t)$ of system (3.1)

$$y(t) = \prod_{0<nT<t}(1 + b(nT))y(0)\exp[(-d - 0.5\delta_2^2)t + \delta_2 B_2(t)].$$

This completes the proof.

3.2. Global positive solution of system (2.2)

Now, we need to show that the solutions of system (2.2) should be non-negative, which are very useful for the rest of the paper.

Theorem 2. System (2.2) has a global unique positive solution $(x(t), y(t))$ for any initial point $(x(0), y(0)) \in R_+^2 = \{(x(t), y(t))|x(t) > 0, y(t) > 0\}$ and the solution $(x(t), y(t))$ will remain in R_+^2.

Proof. To show the existence of solutions of system (2.2), we focus on the following auxiliary SDE without pulsed effects:

$$\begin{cases} dx_1(t) = x_1[r - r\eta \prod_{0<nT<t}(1 - a(nT))x_1 - a \prod_{0<nT<t}(1 + b(nT))y_1]dt \\ \qquad +\delta_1 x_1 dB_1(t), \\ dy_1(t) = y_1 \left[\frac{b \prod_{0<nT<t}(1-a(nT))x_1}{1+w \prod_{0<nT<t}(1-a(nT))x_1} - c \prod_{0<nT<t}(1 - a(nT))x_1 - d\right]dt \\ \qquad +\delta_2 y_1 dB_2(t), \end{cases} \tag{3.3}$$

where the initial point is defined as $(x_1(0), y_1(0)) = (x(0), y(0))$. Note that Liu and Wang showed that system (3.3) has a unique global positive solution $(x_1(t), y_1(t))$ by using theories of SDEs [27]. Denote by $(x(t), y(t)) = (\prod_{0<nT<t}(1 - a(nT))x_1(t), \prod_{0<nT<t}(1 + b(nT))y_1(t))$ with $(x(0), y(0))$ as initial point, it follows from the absolute continuity of $(x_1(t), y_1(t))$ that $(x(t), y(t))$ is also absolutely continuous for any $t \in (nT, (n + 1)T] \subset [0, +\infty)$, $n \in N$. For $t = nT$, taking the derivatives of $(x(t), y(t))$ and combining model (3.3) yields

$$\begin{aligned} dx(t) &= \prod_{0<nT<t}(1 - a(nT))dx_1(t) \\ &= \prod_{0<nT<t}(1 - a(nT))x_1[r - r\eta \prod_{0<nT<t}(1 - a(nT))x_1 \\ &\quad -a \prod_{0<nT<t}(1 + b(nT))y_1]dt + \delta_1 x_1 dB_1(t) \\ &= [rx(t)(1 - \eta x(t)) - ax(t)y(t)]dt + \delta_1 x(t)dB_1(t), \\ dy(t) &= \prod_{0<nT<t}(1 + b(nT))dy_1(t) \\ &= y(t)[\frac{b \prod_{0<nT<t}(1-a(nT))x_1}{1+w \prod_{0<nT<t}(1-a(nT))x_1} - c \prod_{0<nT<t}(1 - a(nT))x_1 - d]dt \\ &\quad +\delta_2 y_1 dB_2(t) \\ &= [\frac{bx(t)y(t)}{1+wx(t)} - cx(t)y(t) - dy(t)]dt + \delta_2 y(t)dB_2(t). \end{aligned}$$

Moreover, for any $t = nT$, we obtain

$$\begin{aligned} x(nT^+) &= \lim_{t\to nT^+} \prod_{0<iT<t}(1-a(iT))x_1(t) = \prod_{0<iT\le nT}(1-a(iT))x_1(nT), \\ y(nT^+) &= \lim_{t\to nT^+} \prod_{0<iT<t}(1+b(iT))y_1(t) = \prod_{0<iT\le nT}(1+b(iT))y_1(nT), \end{aligned} \tag{3.4}$$

besides,

$$\begin{aligned} x(nT) &= \prod_{0<iT<t}(1-a(iT))x_1(nT), \\ y(nT) &= \prod_{0<iT<t}(1+b(iT))y_1(nT), \end{aligned} \tag{3.5}$$

From (3.4) and (3.5), we get

$$x(nT^+) = (1-a(nT)x(nT), y(nT^+) = (1+b(nT)y(nT),$$

Therefore, system (2.2) has a global unique positive solution which is defined as $(x(t), y(t)) = (\prod_{0<nT<t}(1-a(nT))x_1(t), \prod_{0<nT<t}(1+b(nT))y_1(t))$. This completes the proof.

Theorem 3. If $r\eta - b + c > 0$, then the solution of system (2.2) is globally attractive.

Proof. Without loss of generality, we assume that $(x_1(t), y_1(t))$ and $(x_2(t), y_2(t))$ be any two solutions of system (2.2) with initial conditions $x(0) > 0, y(0) > 0$. To show the global attractivity of the solution, we resort to constructing a Lyapunov function which is defined by the following equation:

$$V(t) = |\ln x_1(t) - \ln x_2(t)| + |\ln y_1(t) - \ln y_2(t)|,$$

where $t > 0$ and $t = nT$. On the one hand, we calculate the upper right derivative $d^+V(t)$ of $V(t)$ and then make use of Itô's formula along the solutions of system (2.2),

$$\begin{aligned} d^+V(t) &= sign(x_1(t)-x_2(t))d(\ln x_1(t) - \ln x_2(t)) \\ &\quad + sign(y_1(t)-y_2(t))d(\ln y_1(t) - \ln y_2(t)) \\ &= sign(x_1(t)-x_2(t))\Big(-r\eta(x_1(t)-x_2(t)) - a(y_1(t)-y_2(t))\Big)dt \\ &\quad + sign(y_1(t)-y_2(t))\ \frac{b(x_1(t)-x_2(t))}{(1+wx_1(t))(1+wx_2(t))} - c(x_1(t)-x_2(t))\ dt \\ &\le [-(r\eta - b + c)\,|\,x_1(t)-x_2(t)\,| - a\,|\,y_1(t)-y_2(t)\,|]dt \\ &\le -\rho(|\,x_1(t)-x_2(t)\,| + |\,y_1(t)-y_2(t)\,|)dt \doteq -\rho V(t)dt, \end{aligned} \tag{3.6}$$

where $\rho = \min\{r\eta - b + c, a\}$. On the other hand, for $t = nT$ we obtain

$$\begin{aligned} V(nT^+) &= |\ln x_1(nT^+) - \ln x_2(nT^+)| + |\ln y_1(nT^+) - \ln y_2(nT^+)| \\ &= |\ln(1-a(nT))x_1(nT) - \ln(1-a(nT))x_2(nT)| \\ &\quad + |\ln(1+b(nT))y_1(nT) - \ln(1+b(nT))y_2(nT)| \\ &= |\ln x_1(nT) - \ln x_2(nT)| + |\ln y_1(nT) - \ln y_2(nT)| = V(nT). \end{aligned}$$

Integrating equation (3.6) from 0 to t and taking expectation yields

$$V(t) \leq V(0) - \rho \int_0^t V(s)ds.$$

Thus,

$$V(t) + \rho \int_0^t V(s)ds \leq V(0) < \infty.$$

Moreover, $V(t) > 0$ always holds which leads to $\lim_{t \to +\infty} V(t) = 0$. In other words,

$$\lim_{t \to \infty} | x_1(t) - x_2(t) | = 0 \quad \text{and} \quad \lim_{t \to \infty} | y_1(t) - y_2(t) | = 0.$$

This completes the proof.

Theorem 4. For $0 \leq s < t$, if $\prod_{s \leq nT < t}(1 + b(nT)) \leq B$ $(B > 0)$ and $1 - d \leq 0$, then any solution $X(t) = (x(t), y(t))$ of system (2.2) satisfies the following inequality:

$$\lim_{t \to \infty} E | X(t) | \leq AB,$$

where $A = \frac{(b-c)(r+1)^2}{4r\eta}$.

Proof. We denote $V_1(t) = c_1 x(t) + c_2 y(t)$, here $c_1 = b - c > 0$ and $c_2 = a > 0$. For any $t \in ((n-1)T, nT]$, it follows from the Itô's formula for system (2.2) that we obtain

$$dV_1(t) = c_1 dx(t) + c_2 dy(t) = LV(t)dt + c_1\delta_1 x(t)dB_1(t) + c_2\delta_2 y(t)dB_2(t),$$

with

$$LV(t) = c_1[rx(t)(1 - \eta x(t)) - ax(t)y(t)] + c_2 \left[\frac{bx(t)y(t)}{1 + wx(t)} - cx(t)y(t) - dy(t) \right].$$

Furthermore, we consider another Lyapunov function $V_2(t) = e^t V_1(t)$ and the application of Itô's formula leads to

$$\begin{aligned} dV_2(t) &= e^t V_1(t)dt + e^t dV_1(t) \\ &= e^t V_1(t)dt + e^t\{LV(t)dt + c_1\delta_1 x(t)dB_1(t) + c_2\delta_2 y(t)dB_2(t)\}. \end{aligned}$$

Integrating the above equation from $(n-1)T$ to t and then calculating the corresponding expectations yields

$$Ee^t V_1(t) = e^{(n-1)T} V_1((n-1)T) + E \int_{(n-1)T}^t e^s[V_1(s) + LV(s)]ds. \qquad (3.7)$$

Note that

$$\begin{aligned} LV + V_1 &= c_1[rx(1-\eta x) - axy] + c_2\left(\frac{bxy}{1+wx} - cxy - dy\right) + c_1 x + c_2 y \\ &\le c_1(rx - r\eta x^2 + x) + (c_2(b-c) - c_1 a)xy + c_2(1-d)y \\ &\le c_1\frac{(r+1)^2}{4r\eta} = \frac{(b-c)(r+1)^2}{4r\eta} \doteq A. \end{aligned} \tag{3.8}$$

From equations (3.7) and (3.8) we obtain

$$e^t EV_1(t) \le e^{(n-1)T}(V_1((n-1)T) - A) + e^t A. \tag{3.9}$$

Using Itô's formula for (3.9) leads to

$$dEV_1(t) \le (A - EV_1(t))dt. \tag{3.10}$$

When $t = nT$,

$$\begin{aligned} EV_1(nT^+) &= c_1E(x(nT^+)) + c_2E(y(nT^+)) \\ &= c_1(1 - a(nT))E(x(nT)) + c_2(1 + b(nT))E(y(nT)) \\ &\le (1 + b(nT))(c_1E(x(nT)) + c_2E(y(nT))) \\ &= (1 + b(nT))EV_1(nT). \end{aligned} \tag{3.11}$$

Equations (3.10) and (3.11) can be rewritten as

$$\begin{cases} dEV_1(t) \le (A - EV_1(t))dt, & t = nT, \\ EV_1(nT^+) \le (1 + b(nT))EV_1(nT), & t = nT. \end{cases} \tag{3.12}$$

To show the boundedness of system (3.12), we need to consider the following new system:

$$\begin{cases} dz(t) = (A - z(t))dt, & t = nT, \\ z(nT^+) = (1 + b(nT))z(nT), & t = nT. \end{cases} \tag{3.13}$$

The unique solution of system (3.13) is given by

$$z(t) = z(0)m(t,0) + A\int_0^t m(t,s)ds,$$

where $m(t,s) = \prod_{s \le nT < t}(1+b(nT))\exp(-(t-s))$. Then we have $\lim_{t\to+\infty} z(t) = AB$. It follows from comparison theorems of impulsive differential equations [24, 25] that we obtain

$$\lim_{t\to+\infty} EV_1(t) \le \lim_{t\to+\infty} z(t) = AB.$$

This completes the proof.

Remark 2. Theorem 4 shows that the solutions of system (2.2) have upper bound in terms of expectations under certain conditions. Biologically, if pulsed perturbations are bounded or follow after finite pulse immunotherapy, then the tumour cells will be controlled and will not grow indefinitely.

4. Extinction and persistence

Since we have incorporated stochastic effects into model (2.2), we want to explore the conditions for the extinction and persistence of the tumour cells and the effector cells. To show these, we first need to give the following results by using Itô's formula. Defining a Lyapunov function $V(t) = \ln x_1(t)$ and noting that $x(t) = \prod_{0<nT<t}(1-a(nT))x_1(t), y(t) = \prod_{0<nT<t}(1+b(nT))y_1(t)$, then applying Itô's formula to the first equation of system (3.3),

$$\begin{aligned} d\ln x_1(t) &= [r - r\eta \prod_{0<nT<t}(1-a(nT))x_1 - a \prod_{0<nT<t}(1+b(nT))y_1 \\ &\quad -\tfrac{1}{2}\delta_1^2]dt + \delta_1 dB_1(t) \\ &= [r - r\eta x(t) - ay(t) - \tfrac{1}{2}\delta_1^2]dt + \delta_1 dB_1(t), \end{aligned} \tag{4.1}$$

integrating the above equation from 0 to t yields

$$\ln x_1(t) - \ln x_1(0) = \left(r - \tfrac{1}{2}\delta_1^2\right)t - r\eta \int_0^t x(s)ds - a\int_0^t y(s)ds + M_1(t), \tag{4.2}$$

where $M_i(t) = \int_0^t \delta_i dB_i(t) (i = 1, 2)$. Taking the pulsed effects of system (2.2) into equation (4.2) yields

$$\begin{aligned} &\prod_{0<nT<t}\ln(1-a(nT)) + \ln x_1(t) - \ln x_1(0) \\ &= \prod_{0<nT<t}\ln(1-a(nT)) + \left(r - \tfrac{1}{2}\delta_1^2\right)t - r\eta \int_0^t x(s)ds - a\int_0^t y(s)ds + M_1(t). \end{aligned} \tag{4.3}$$

Simplification of equation (4.3) yields following lemma.

Lemma 2. For system (2.2) the tumour $x(t)$ satisfies

$$\begin{aligned} \ln\frac{x(t)}{x(0)} &= \prod_{0<nT<t}\ln(1-a(nT)) + \left(r - \tfrac{1}{2}\delta_1^2\right)t - r\eta \int_0^t x(s)ds \\ &\quad -a\int_0^t y(s)ds + M_1(t). \end{aligned} \tag{4.4}$$

By applying the same methods we obtain

Lemma 3. For system (2.2) the effector cell $y(t)$ satisfies

$$\begin{aligned} \ln\frac{y(t)}{y(0)} &= \prod_{0<nT<t}\ln(1+b(nT)) - \left(d + \tfrac{1}{2}\delta_2^2\right)t - c\int_0^t x(s)ds \\ &\quad +b\int_0^t \frac{x(s)}{1+wx(s)}ds + M_2(t). \end{aligned} \tag{4.5}$$

Theorem 5. (1) If $\lim_{t\to+\infty}\sup\frac{\sum_{0<nT<t}\ln(1-a(nT))}{t}+r<\frac{1}{2}\delta_1^2$, then the tumour cells become extinct.

(2) If $\lim_{t\to+\infty}\sup\frac{\sum_{0<nT<t}\ln(1-a(nT))}{t}+r=\frac{1}{2}\delta_1^2$, then the tumour cells are non-persistent in the mean.

(3) If

$$\lim_{t\to+\infty}\sup\frac{\sum_{0<nT<t}\ln(1-a(nT))}{t}+r>\frac{1}{2}\delta_1^2$$

and

$$\lim_{t\to+\infty}\sup\frac{\sum_{0<nT<t}\ln(1+b(nT))}{t}<d+\frac{1}{2}\delta_2^2,$$

then the tumour cells become weakly persistent in the mean.

Proof. (1) It follows from (4.4) that we have

$$\begin{aligned}\frac{1}{t}\ln\frac{x(t)}{x(0)} &= \frac{\sum_{0<nT<t}\ln(1-a(nT))}{t}+\left[r-\frac{1}{2}\delta_1^2\right]-r\eta\frac{\int_0^t x(s)ds}{t}\\ &\quad -a\frac{\int_0^t y(s)ds}{t}+\frac{M_1(t)}{t}.\end{aligned}\tag{4.6}$$

Note that $<M_i(t),M_i(t)>=\int_0^t\delta_i^2ds$, because of the strong law of large numbers for local martingales we obtain

$$\lim_{t\to+\infty}\frac{M_i(t)}{t}=0.\tag{4.7}$$

Taking the superior limit of (4.6) gives

$$\begin{aligned}\lim_{t\to+\infty}\sup\frac{\ln x(t)}{t} &\le \lim_{t\to+\infty}\sup\frac{\sum_{0<nT<t}\ln(1-a(nT))}{t}+r-\frac{1}{2}\delta_1^2\\ &\quad -r\eta x(t)-ay(t)<0,\end{aligned}$$

where $x(t)=\lim_{t\to+\infty}\inf\frac{1}{t}\int_0^t x(s)ds$ and $y(t)=\lim_{t\to+\infty}\inf\frac{1}{t}\int_0^t y(s)ds$. It indicates that $\lim_{t\to+\infty}x(t)=0$, thereby the tumour cells becomes extinct.

(2) For any fixed $\varepsilon>0$, there exists a constant t_1 so that the following inequalities hold true for all $t\ge t_1$:

$$\frac{\sum_{0<nT<t}\ln(1-a(nT))}{t}\le\lim_{t\to+\infty}\sup\frac{\sum_{0<nT<t}\ln(1-a(nT))}{t}+\frac{\varepsilon}{2},\ \frac{M_1(t)}{t}\le\frac{\varepsilon}{2},$$

combining with (4.6) yields

$$\begin{aligned}\frac{1}{t}\ln\frac{x(t)}{x(0)} &= \frac{\sum_{0<nT<t}\ln(1-a(nT))}{t}+\left[r-\frac{1}{2}\delta_1^2\right]-r\eta\frac{\int_0^t x(s)ds}{t}\\ &\quad -a\frac{\int_0^t y(s)ds}{t}+\frac{M_1(t)}{t}\\ &\le \lim_{t\to+\infty}\sup\frac{\sum_{0<nT<t}\ln(1-a(nT))}{t}+\left[r-\frac{1}{2}\delta_1^2\right]\\ &\quad -r\eta\frac{1}{t}\int_0^t x(s)ds+\varepsilon.\end{aligned}$$

When ε is small enough, owing to Lemma 1 we have

$$\lim_{t\to+\infty}\sup\frac{1}{t}\int_0^t x(s)ds \le \frac{\lim_{t\to+\infty}\sup\frac{\sum_{0<nT<t}\ln(1-a(nT))}{t}+\left(r-\frac{1}{2}\delta_1^2\right)}{r\eta} = 0. \quad (4.8)$$

Notice that $x(t) \ge 0$ always holds and it implies that $\lim_{t\to+\infty}\sup\frac{1}{t}\int_0^t x(s)ds \ge 0$. Therefore, $\lim_{t\to+\infty}\sup\frac{1}{t}\int_0^t x(s)ds = 0$ and thus the tumour cells are non-persistent in the mean.

(3) Assume that $\lim_{t\to+\infty}\sup\frac{x(t)}{t} < 0$, by calculating the superior limit of (4.6) yields

$$\begin{aligned} r\eta x(t) + a y(t) \ge\ & \lim_{t\to+\infty}\sup\frac{\sum_{0<nT<t}\ln(1-a(nT))}{t} \\ & + r - \frac{1}{2}\delta_1^2 - \lim_{t\to+\infty}\sup\frac{\ln x(t)}{t} > 0, \end{aligned}$$

where $x(t) = \lim_{t\to+\infty}\sup\frac{1}{t}\int_0^t x(s)ds$ and $y(t) = \lim_{t\to+\infty}\sup\frac{1}{t}\int_0^t y(s)ds$. It implies $x(t) > 0$. Otherwise, for any $\tau \in \{x(t,\tau) = 0\}$, we obtain $y(t,\tau) > 0$. However, it follows from the superior limit of (4.5) and note that $x(t,\tau) = 0$ that one obtains

$$\lim_{t\to+\infty}\sup\frac{\ln y(t,\tau)}{t} \le \lim_{t\to+\infty}\sup\frac{\sum_{0<nT<t}\ln(1+b(nT))}{t} - \left(d+\frac{1}{2}\delta_2^2\right) < 0,$$

which means that $y(t,\tau) = 0$, which contradicts $y(t,\tau) > 0$. Therefore, $\lim_{t\to+\infty}\sup\frac{1}{t}\int_0^t x(t)dt > 0$. Thereby the tumour cells become weakly persistent in the mean. This completes the proof.

Theorem 6. (1) If

$$\begin{aligned} \lim_{t\to+\infty}\sup\frac{\sum_{0<nT<t}\ln(1-a(nT))}{t} + r &< \frac{1}{2}\delta_1^2, \\ \lim_{t\to+\infty}\sup\frac{\sum_{0<nT<t}\ln(1+b(nT))}{t} &< d+\frac{1}{2}\delta_2^2, \end{aligned}$$

then the e□ector cells become extinct.

(2) If $\lim_{t\to+\infty}\sup\frac{\sum_{0<nT<t}\ln(1-a(nT))}{t} + r = \frac{1}{2}\delta_1^2$, then the e□ector cells are non-persistent in the mean.

(3) If

$$\begin{aligned} &\lim_{t\to+\infty}\sup\frac{\sum_{0<nT<t}\ln(1+b(nT))}{t} - \left(d+\frac{1}{2}\delta_2^2\right) \\ &-\frac{b-c}{r\eta}\lim_{t\to+\infty}\sup\frac{\sum_{0<nT<t}\ln(1-a(nT))}{t} + \left(r-\frac{1}{2}\delta_1^2\right) > 0, \end{aligned}$$

then the e□ector cells become weakly persistent in the mean.

Proof. (1) It follows from (4.5) that we have

$$\frac{1}{t}\ln\frac{y(t)}{y(0)} = \frac{\sum_{0<nT<t}\ln(1+b(nT))}{t} - \left(d+\frac{1}{2}\delta_2^2\right) - c\frac{1}{t}\int_0^t x(s)ds + b\frac{1}{t}\int_0^t \frac{x(s)}{1+wx(s)}ds + \frac{M_2(t)}{t}. \tag{4.9}$$

Taking the superior limit of (4.9) gives

$$\limsup_{t\to+\infty}\frac{\ln y(t)}{t} \le \limsup_{t\to+\infty}\frac{\sum_{0<nT<t}\ln(1+b(nT))}{t} - \left(d+\frac{1}{2}\delta_2^2\right) + (b-c)x^*(t),$$

by (4.8) we have $x^*(t) < 0$, that is to say,

$$\limsup_{t\to+\infty}\frac{\ln y(t)}{t} \le 0.$$

Therefore, we have $\lim_{t\to+\infty} y(t) = 0$, which indicates that the vector cells become extinct.

(2) For any fixed $\varepsilon > 0$, there exists a t_2 such that for all $t \ge t_2$ we obtain:

$$\frac{\sum_{0<nT<t}\ln(1-a(nT))}{t} \le \limsup_{t\to+\infty}\frac{\sum_{0<nT<t}\ln(1-a(nT))}{t} + \frac{\varepsilon}{2}, \frac{M_1(t)}{t} \le \frac{\varepsilon}{2},$$

combining with (4.6) yields

$$\begin{aligned} a\frac{1}{t}\int_0^t y(s)ds &= -\frac{1}{t}\ln\frac{x(t)}{x(0)} + \frac{\sum_{0<nT<t}\ln(1-a(nT))}{t} + \left(r-\frac{1}{2}\delta_1^2\right) - r\eta\frac{\int_0^t x(s)ds}{t} \\ &\quad + \frac{M_1(t)}{t} \\ &\le \limsup_{t\to+\infty}\frac{\sum_{0<nT<t}\ln(1-a(nT))}{t} + \left(r-\frac{1}{2}\delta_1^2\right) + \varepsilon. \end{aligned}$$

When ε is small enough, taking the superior limit yields

$$\limsup_{t\to+\infty}\frac{1}{t}\int_0^t y(s)ds \le 0. \tag{4.10}$$

Therefore, $\limsup_{t\to+\infty}\frac{1}{t}\int_0^t y(s)ds = 0$ and thus the vector cells are non-persistent in the mean.

(3) From (4.9) we have

$$\frac{1}{t}\ln\frac{y(t)}{y(0)} \ge \frac{\sum_{0<nT<t}\ln(1+b(nT))}{t} - \left(d+\frac{1}{2}\delta_2^2\right) - (b+c)\frac{1}{t}\int_0^t x(s)ds + \frac{M_2(t)}{t}, \tag{4.11}$$

then (4.6) and (4.11) and taking the superior limit, there exists a $t_3 > 0$ such that

$$\begin{aligned} \frac{\ln y(t)}{t} \ge\ & \limsup_{t\to+\infty}\frac{\sum_{0<nT<t}\ln(1+b(nT))}{t} - \left(d+\frac{1}{2}\delta_2^2\right) \\ & + \limsup_{t\to+\infty}\frac{\sum_{0<nT<t}\ln(1-a(nT))}{t} + \left(r-\frac{1}{2}\delta_1^2\right) \\ & -(r\eta - b + c)x^*(t) - ay^*(t), \end{aligned}$$

and it follows from (4.8) that we obtain

$$\begin{aligned} ay(t) \geq\ & \limsup_{t\to+\infty} \frac{\sum_{0<nT<t}\ln(1+b(nT))}{t} - \left[d+\frac{1}{2}\delta_2^2\right] \\ & - \frac{b-c}{r\eta}\limsup_{t\to+\infty}\frac{\sum_{0<nT<t}\ln(1-a(nT))}{t} + \left[r-\frac{1}{2}\delta_1^2\right] > 0. \end{aligned}$$

which means that $y(t) = \limsup_{t\to+\infty}\frac{1}{t}\int_0^t y(s)ds > 0$. This completes the proof.

During the whole stages of treatment, the times of pulsed therapy are limited. So the following assumption is reasonable.

Assumption 1. There exist four positive constants m_1, m_2, M_1 and M_2 such that $m_1 \leq \prod_{0<nT<t}(1-a(nT)) \leq M_1$ and $m_2 \leq \prod_{0<nT<t}(1+b(nT)) \leq M_2$.

Theorem 7. Based on assumption 1, if $\tau = \min_{t\geq 0}[r-\frac{1}{2}\delta_1^2 - aM_2] > 0$, then the tumour cells are stochastically permanent.

Proof. We first need to prove that there exists two constants $\beta > 0$ and > 0 such that $\liminf_{t\to+\infty} P\{x(t) \geq \beta\} \geq 1-\varepsilon$ and $\liminf_{t\to+\infty} P\{x(t) \leq \} \geq 1-\varepsilon$ for any $\varepsilon \in (0,1)$, which will be addressed step by step.

For the former, defining a Lyapunov function $V^1(x) = 1/x_1$ $(x_1 > 0)$, and then applying Itô's formula to the first equation of system (3.3) yields

$$\begin{aligned} dV^1(x_1) =\ & -V^1(x_1)[r - r\eta\prod_{0<nT<t}(1-a(nT))x_1 \\ & -a\prod_{0<nT<t}(1+b(nT))y_1]dt + V^1(x_1)\delta_1^2 dt - V^1(x_1)\delta_1 dB_1(t). \end{aligned}$$

Choosing a positive constant ϑ which satisfies $\tau > 0.5\vartheta\delta_1^2$, we then define another Lyapunov function $V^2(x_1) = (1+V^1(x_1))^\vartheta$, again Itô's formula leads to

$$\begin{aligned} dV^2(x_1) &= \vartheta(1+V^1(x_1))^{\vartheta-1}dV^1(x_1) + 0.5\vartheta(\vartheta-1)(1+V^1(x_1))^{\vartheta-2}(dV^1(x_1))^2 \\ &= \vartheta(1+V^1(x_1))^{\vartheta-2}\{-V^1(x_1) - (V^1(x_1))^2[r - r\eta\prod_{0<nT<t}(1-a(nT))x_1 \\ &\quad -a\prod_{0<nT<t}(1+b(nT))y_1] + (V^1(x_1) + (V^1(x_1))^2)\delta_1^2 \\ &\quad +0.5(\vartheta-1)(V^1(x_1))^2\delta_1^2\}dt - \vartheta(1+V^1(x_1))^{\vartheta-1}V^1(x_1)\delta_1 dB_1(t) \\ &= \vartheta(1+V^1(x_1))^{\vartheta-2}\{-(V^1(x_1))^2[r - 0.5\delta_1^2 - 0.5\vartheta\delta_1^2 \\ &\quad -a\prod_{0<nT<t}(1+b(nT))y_1] \\ &\quad +V^1(x_1)[-r + r\eta\prod_{0<nT<t}(1-a(nT)) \\ &\quad +a\prod_{0<nT<t}(1+b(nT))y_1 + \delta_1^2] + r\eta\prod_{0<nT<t}(1-a(nT))\}dt \\ &\quad -\vartheta(1+V^1(x_1))^{\vartheta-1}V^1(x_1)\delta_1 dB_1(t) \\ &\leq \vartheta(1+V^1(x_1))^{\vartheta-2}\{-(V^1(x_1))^2[\tau - 0.5\vartheta\delta_1^2] + V^1(x_1)[r\eta M_1 \\ &\quad +aM_2 + \delta_1^2] + r\eta M_1\}dt - \vartheta(1+V^1(x_1))^{\vartheta-1}V^1(x_1)\delta_1 dB_1(t). \end{aligned}$$

Further, we choose a sufficiently small ξ which satisfies

$$\tau - 0.5\vartheta\delta_1^2 > \frac{\xi}{\vartheta} > 0. \tag{4.12}$$

And then define a Lyapunov function $V^3(x_1) = \exp(\xi t)V^2(x_1)$, using Itô's formula we have

$$\begin{aligned} dV^3(x_1) &= \xi\exp(\xi t)V^2(x_1)dt + \exp(\xi t)dV^2(x_1) \\ &\leq \vartheta\exp(\xi t)(1+V^1(x_1))^{\vartheta-2}\{\tfrac{\xi(1+V^1(x_1))^2}{\vartheta} - (V^1(x_1))^2[\tau - 0.5\vartheta\delta_1^2] \\ &\quad + V^1(x_1)[r\eta M_1 + aM_2y_0 + \delta_1^2] + r\eta M_1\}dt \\ &\quad - \vartheta\exp(\xi t)(1+V^1(x_1))^{\vartheta-1}V^1(x_1)\delta_1 dB_1(t) \\ &\doteq \exp(\xi t)f(x_1)dt - \vartheta\exp(\xi t)(1+V^1(x_1))^{\vartheta-1}V^1(x_1)\delta_1 dB_1(t), \end{aligned}$$

where

$$\begin{aligned} f(x_1) &= \vartheta(1+V^1(x_1))^{\vartheta-2}\{-[\tau - 0.5\vartheta\delta_1^2 - \tfrac{\xi}{\vartheta}](V^1(x_1))^2 \\ &\quad + [r\eta M_1 + aM_2y_0 + \delta_1^2 + \tfrac{2\xi}{\vartheta}]V^1(x_1) + r\eta M_1 + \tfrac{\xi}{\vartheta}\}. \end{aligned}$$

Let $C_1 = \tau - 0.5\vartheta\delta_1^2 - \frac{\xi}{\vartheta}$, $C_2 = r\eta M_1 + aM_2 + \delta_1^2 + \frac{2\xi}{\vartheta}$ and $C_3 = r\eta M_1 + \frac{\xi}{\vartheta}$, then $C_1 > 0$, $C_2 > 0$ and $C_3 > 0$ because all parameters are positive and (4.12) holds true. Thus, we can rewrite $f(x_1)$ as

$$f(x_1) = \vartheta(1+\frac{1}{x_1})^{\vartheta-2}\ -\frac{C_1}{x_1^2} + \frac{C_2}{x_1} + C_3\ \doteq f_1(x_1).$$

Next we show that $f(x_1)$ is upper bounded when $x_1 > 0$. If $\frac{1}{x_1} \geq \frac{C_2 + \sqrt{C_2^2 + 4C_1C_3}}{2C_1} \doteq \lambda_1$, then $f(x_1) \leq 0$. If $0 < \frac{1}{x_1} \leq \lambda_1$, then $f_1(x_1) \leq \frac{4C_1C_3 + C_2^2}{4C_1}$. Furthermore, if $\vartheta \geq 2$, then $\vartheta(1+\frac{1}{x_1})^{\vartheta-2} \leq \vartheta(1+\lambda_1)^{\vartheta-2}$; if $\vartheta < 2$, then $\vartheta(1+\frac{1}{x_1})^{\vartheta-2} \leq \vartheta$. Therefore, for $x_1 > 0$ we always have $f(x_1) \leq f_0 = \lambda_2\frac{4C_1C_3 + C_2^2}{4C_1}$, where $\lambda_2 = \max\{\vartheta, \vartheta(1+\lambda_1)^{\vartheta-2}\}$. In other words, $f(x_1)$ is always upper bounded. Moreover,

$$\begin{aligned} dV^3(x_1) &\leq \exp(\xi t)f(x_1)dt - \vartheta\exp(\xi t)(1+V^1(x_1))^{\vartheta-1}V^1(x_1)\delta_1 dB_1(t) \\ &\leq f_0\exp(\xi t)dt - \vartheta\exp(\xi t)(1+V^1(x_1))^{\vartheta-1}V^1(x_1)\delta_1 dB_1(t). \end{aligned}$$

We integrate the above equation from 0 to t and thereafter take the expectation, which yields

$$E[V^3(x_1(t))] \leq V^3(x_1(0)) + \frac{f_0}{\xi}\exp(\xi t),$$

note that $V^3(x_1(t)) = \exp(\xi t)(1+V^1(x_1(t)))^{\vartheta}$, thus we obtain

$$\begin{aligned} E[V^3(x_1(t))] &= E[\exp(\xi t)(1+V^1(x_1(t)))^{\vartheta}] \\ &\leq V^3(x_1(0)) + \tfrac{f_0}{\xi}\exp(\xi t) \\ &= (1+V^1(x_1(0)))^{\vartheta} + \tfrac{f_0}{\xi}\exp(\xi t). \end{aligned}$$

Taking the superior limit leads to

$$\begin{aligned}\limsup_{t\to+\infty} E[\tfrac{1}{x_1(t)^{\vartheta}}] &= \limsup_{t\to+\infty} E[(V^{1}(x_1(t)))^{\vartheta}] \\ &\le \limsup_{t\to+\infty} E[(1+V^{1}(x_1(t)))^{\vartheta}] \le \tfrac{f_0}{\xi}.\end{aligned}$$

Due to $x(t) = \prod_{0<nT<t}(1-a(nT))x_1(t)$, it is clear that

$$\limsup_{t\to+\infty} E[\tfrac{1}{x(t)^{\vartheta}}] = \limsup_{t\to+\infty} \frac{1}{[\prod_{0<nT<t}(1-a(nT))]^{\vartheta}} E[\tfrac{1}{x_1(t)^{\vartheta}}] \le \tfrac{f_0}{m_1^{\vartheta}\xi} \doteq f_M.$$

For arbitrary $\varepsilon > 0$, we denote $\beta = \varepsilon^{\frac{1}{\vartheta}} / f_M^{\frac{1}{\vartheta}}$. It follows from Chebyshev's inequality that one gets

$$\begin{aligned}\limsup_{t\to+\infty} \mathrm{P}\{x(t) < \beta\} &= \limsup_{t\to+\infty} \mathrm{P}\{\tfrac{1}{x^{\vartheta}(t)} > \tfrac{1}{\beta^{\vartheta}}\} \\ &\le \limsup_{t\to+\infty} \tfrac{E[\frac{1}{x^{\vartheta}(t)}]}{\beta^{-\vartheta}} \\ &= \limsup_{t\to+\infty} \beta^{\vartheta} E[\tfrac{1}{x^{\vartheta}(t)}] = \varepsilon.\end{aligned}$$

Therefore, $\liminf_{t\to+\infty} \mathrm{P}\{x(t) \ge \beta\} \ge 1-\varepsilon$.

For the latter, we also define a Lyapunov function $V_3(x_1(t)) = x_1^p(t)$ ($x_1 > 0$), and the application of Itô's formula to the first equation of system (3.3) yields

$$\begin{aligned}dV_3(x_1(t)) &= pV_3(x_1(t))[r - r\eta \prod_{0<nT<t}(1-a(nT))x_1(t) \\ &\quad - a\prod_{0<nT<t}(1+b(nT))y_1(t) + 0.5(p-1)\delta_1^2]dt \\ &\quad + p\delta_1 V_3(x_1(t))dB_1(t) \\ &\le pV_3(x_1(t))[r - r\eta m_1 x_1(t) + 0.5(p-1)\delta_1^2]dt \\ &\quad + p\delta_1 V_3(x_1(t))dB_1(t),\end{aligned}$$

integrating the above equation from 0 to t and then taking the expectation yields

$$E[V_3(x_1(t))] - E[V_3(x_1(0))] \le p\int_0^t E\{V_3(x_1(s))[r - r\eta m_1 x_1(s) + 0.5(p-1)\delta_1^2]\}ds,$$

the derivative of the upper formula gives

$$\frac{dE[V_3(x_1(t))]}{dt} \le pE[V_3(x_1(t))][r + 0.5(p-1)\delta_1^2] - pr\eta m_1 E[x_1^{p+1}(t)].$$

According to Hölder's inequality we obtain

$$\tfrac{dE[V_3(x_1(t))]}{dt} \le pE[V_3(x_1(t))][r + 0.5(p-1)\delta_1^2] - pr\eta m_1 E[x_1^{p}(t)]^{\frac{p+1}{p}}.$$

Let $h(t) = E[V_3(x_1(t))]$ we obtain

$$\begin{aligned} \frac{dh(t)}{dt} &\leq ph(t)[r + 0.5(p-1)\delta_1^2 - pr\eta m_1 h^{\frac{1}{p}}(t)] \\ &\leq ph(t)[r + 0.5p\delta_1^2 - pr\eta m_1 h^{\frac{1}{p}}(t)]. \end{aligned}$$

Making using of the standard comparison theorem yields

$$\begin{aligned} \limsup_{t\to+\infty} E[x_1^p(t)] &= \limsup_{t\to+\infty} E[V_3(x_1(t))] \\ &= \limsup_{t\to+\infty} h(t) \\ &\leq \frac{r+0.5p\delta_1^2}{pr\eta m_1}. \end{aligned}$$

Due to $x(t) = \prod_{0<nT<t}(1 - a(nT))x_1(t)$, thus

$$\begin{aligned} \limsup_{t\to+\infty} E[x^p(t)] &= \limsup_{t\to+\infty} \Big[\prod_{0<nT<t}(1 - a(nT))\Big]^p E[x_1^p(t)] \\ &\leq M_1^p \frac{r+0.5p\delta_1^2}{pr\eta m_1}. \end{aligned}$$

By using the same methods, it follows from Chebyshev's inequality that

$$\liminf_{t\to+\infty} \mathrm{P}\{x(t) \leq \} \geq 1 - \varepsilon.$$

Therefore, based on the definitions the tumour cells are stochastically permanent. This completes the proof.

5. Numerical results

Since we have investigated the extinction and persistence for tumours, to substantiate our results we carried out numerical simulations. In order to show approximate solutions of system (2.2) with initial conditions, we use the Milsteins higher order method [35], and then the discretization equations of system (2.2) are

$$\begin{aligned} x_{k+1} &= x_k + x_k[r(1 - \eta x_k) - ay_k]\Delta t + \delta_1 x_k \sqrt{\Delta t}\xi_k + \tfrac{\delta_1^2}{2} x_k(\xi_k^2 - 1)\Delta t, \\ y_{k+1} &= y_k + y_k \left[\frac{bx_k}{1+wx_k} - cx_k - d\right]\Delta t + \delta_2 y_k \sqrt{\Delta t}\eta_k + \tfrac{\delta_2^2}{2} y_k(\eta_k^2 - 1)\Delta t, \end{aligned} \tag{5.13}$$

and at the impulsive point series nT system (2.2) experiences pulsed therapies, i.e., if $mod(k, T) = 0$, then we have

$$\begin{aligned} x_{k+1} &= (1 - a_k)x_k, \\ y_{k+1} &= (1 + b_k)y_k, \end{aligned}$$

where ξ_k and $\eta_k (k = 1, 2, 3, \ldots)$ denote the independent Gaussian random variables with distribution $N(0, 1)$, we set time increment $\Delta t = 0.01$.

The baseline parameter values of the stochastic system (2.2) without pulses were chosen from the classical reference [10], because these values were not only obtained by parameter estimation based on experimental data, but also addressed the biological implications. Therefore, we fix $\eta = 0.002$, $a = 1$, $b = 1.131$, $w = 20.19$, $c = 0.00311$ and $d = 0.3$. To be convincing the logarithmic plots are carried out.

In Fig.1(a), we set $r = 1.85$, $\delta_1 = 2$, $\delta_2 = 0.5$, $n = 100$, $T = 100$, $a_k = 0.1$ and $b_k = 0.05$, the initial values were fixed as $(x(0), y(0)) = (0.1, 0.5)$ and $(x(0), y(0)) = (10, 0.5)$. By calculation we have $\lim_{t\to+\infty} \sup \frac{\sum_{0<nT<t} \ln(1-a(nT))}{t} \leq \frac{1}{T}\sum_{i=1}^{n} \ln(1 - a(iT)) + r - \frac{1}{2}\delta_1^2 \approx -0.149 < 0$, in the light of Theorem 5 we know that the tumours become extinct (Fig.1(a)). If we set $r = 2.5$ and fix all other parameters as shown in Fig.1(a), it was found that

$$\lim_{t\to+\infty} \sup \frac{\sum_{0<nT<t} \ln(1 - a(nT))}{t} + r - \frac{1}{2}\delta_1^2 \approx 0.5 > 0$$

and

$$\lim_{t\to+\infty} \sup \frac{\sum_{0<nT<t} \ln(1 + b(nT))}{t} - d - \frac{1}{2}\delta_2^2 \approx -0.424 < 0,$$

by Theorem 5 we know that the tumours become weakly persistent in the mean (Fig.1(b)).

In Fig. 2(a), we set $r = 3$, $\delta_1 = 1$, $\delta_2 = 0.5$, $n = 100$, $T = 100$, $a_k = 0.1$ and $b_k = 0.05$, the initial values were fixed as $(x(0), y(0)) = (0.1, 0.5)$ and $(x(0), y(0)) = (10, 0.5)$, then $\tau = \min_{t\geq 0}[r - \frac{1}{2}\delta_1^2 - aM_2] \approx 1.53 > 0$. It follows from Theorem 7 that the tumour cells are stochastically persistent (Fig. 2(a)). When $\delta_1 = 0$, the amplitude becomes smaller (Fig. 2(b)). In this case, periodical applications of immunotherapy could kill a certain amount of tumours, but the immune action is not strong enough to control the cancer cells and so they are in an unstable state.

In Fig.3(a), we set $r = 1.85$, $\delta_1 = 2$, $\delta_2 = 0.5$, $n = 100$, $T = 100$, $a_k = 0.1$ and $b_k = 0.05$, the initial values were fixed as $(x(0), y(0)) = (10, 5)$. By simple calculation we can show that

$$\lim_{t\to+\infty} \sup \frac{\sum_{0<nT<t} \ln(1-a(nT))}{t} + r - \frac{1}{2}\delta_1^2 \approx -0.149 < 0,$$
$$\lim_{t\to+\infty} \sup \frac{\sum_{0<nT<t} \ln(1+b(nT))}{t} - d + \frac{1}{2}\delta_2^2 \approx -0.424 < 0,$$

then by Theorem 6 the e□ector cells become extinct. Moreover, if we set b_k = 0.6 and fix others parameter values as shown in Fig.3(a), then we have

$$\lim_{t\to+\infty}\sup\frac{\sum_{0<nT<t}\ln(1+b(nT))}{t}-\left[d+\frac{1}{2}\delta_2^2\right]$$
$$-\frac{b-c}{r\eta}\lim_{t\to+\infty}\sup\frac{\sum_{0<nT<t}\ln(1-a(nT))}{t}+\left[r-\frac{1}{2}\delta_1^2\right]\approx 60.2>0,$$

by Theorem 6 the e□ector cells become weakly persistent in the mean (Fig.3(b)).

Under certain conditions, periodical applications of immunotherapy and chemotherapy could clear a certain number of tumour cells but cannot completely remove the tumours from the body, so the strength of treatment needs to be augmented in order to suppress the proliferation and mutation of tumours. For example, a feasible strategy can be implemented by adjusting the key parameters of the pulsed comprehensive therapy such as the dose of immunotherapy and chemotherapy, the period of treatment and the number of pulsed treatments. If we increase the dose of the chemotherapy, then the tumours can be eradicated (Fig. 4(a) and Fig. 4(b)). Similarly, increasing the dose of immunotherapy may also lead to the eradication of tumours and we omit it. While decreasing the periodicity of pulsed treatment may also control tumours (Fig. 4(c) and Fig. 4(d)).

6. Conclusions

It has been shown that the growth rate of tumours is inevitably a□ected by environmental noise [18-21] and that periodical applications of immunotherapy and chemotherapy are e□ective for treating tumours [9, 29, 30], with the latter confirmed by experimental and clinical studies [22, 23]. In this study, we have proposed a stochastic tumour-immune dynamical model with pulsed comprehensive treatment to investigate how stochastic fluctuations and combinations of immunotherapy with chemotherapy a□ect the evolution of tumours.

First of all, the explicit expression of the tumour free solution is given when tumour cells are eradicated, under certain conditions, and we show that for system (2.2) there exists a global unique positive solution which is globally attractive. Then the upper bound of the expectations of the solutions was estimated. Biologically, if pulsed perturbations are bounded or follow after finite pulse immunotherapy, then the tumour cells will be controlled and will not grow indefinitely. By using Itô's formula and defining Lyapunov functions, the su□cient conditions of extinction, non-persistece in

the mean and weak persistence in the mean for the tumour cells and e□ector cells were provided, and we also determine a condition for tumours being stochastically permanent. From a biological view of point, when the doses or frequencies of chemotherapy are large (i.e., the e□ect of chemotherapy is significant), then large stochastic disturbances will lead to extinction of tumours and small stochastic disturbances will result in weak persistence in the mean of the tumours. If the stochastic disturbances are fixed as being constant, then large doses or higher frequencies of chemotherapy will lead to extinction of tumours and vice versa. Moreover, if the stochastic disturbances are small or the initial density of e□ector cells is small or the doses (or frequencies) of immunotherapy are small, then the tumours will be stochastically permanent. Therefore, a feasible way to cure cancer is either to increase doses or frequencies of chemotherapy, or to increase the initial density of e□ector cells, or to augment the doses (or frequencies) of immunotherapy.

One of the drawbacks of periodical applications of chemotherapy is the emergence of drug resistance [36]. In the presence of drug resistance, it is necessary to divide tumour cells into drug sensitive strains and drug resistance strains [37], as alternate use of immunotherapy and chemotherapy drugs may delay the onset of resistance. Future work is required to combine pulsed treatment with a stochastic tumour-immune system to better prevent the evolution of drug resistance.

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Figure Legends

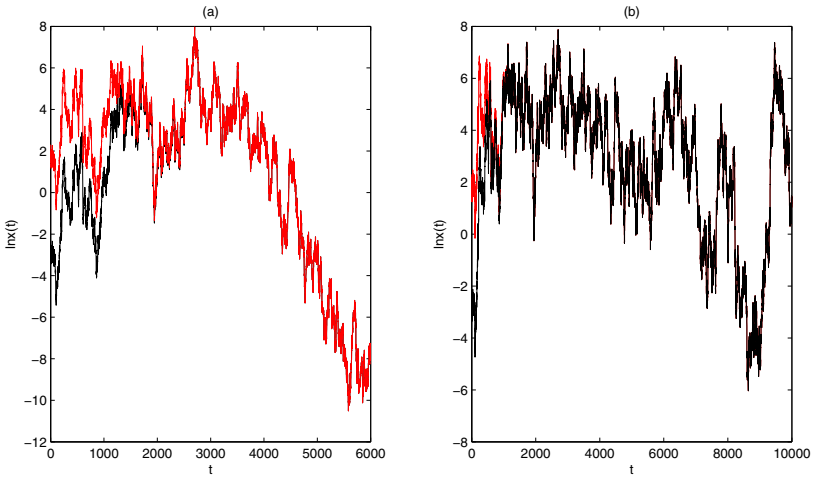

Figure 1: Extinction and weak persistence of tumours. (a) Time series of tumour cell $x(t)$ with $r = 1.85$; (b) Time series of tumour cells $x(t)$ with $r = 2.5$. The initial values of solution with black were fixed as $(x(0), y(0)) = (0.1, 0.5)$ and red for $(x(0), y(0)) = (10, 0.5)$, and all other parameters were fixed as: $\eta = 0.002$, $a = 1$, $b = 1.131$, $w = 20.19$, $c = 0.00311$, $d = 0.3$, $\delta_1 = 2$, $\delta_2 = 0.5$, $n = 100$, $T = 100$, $a(nT) = 0.1$ and $b(nT) = 0.05$.

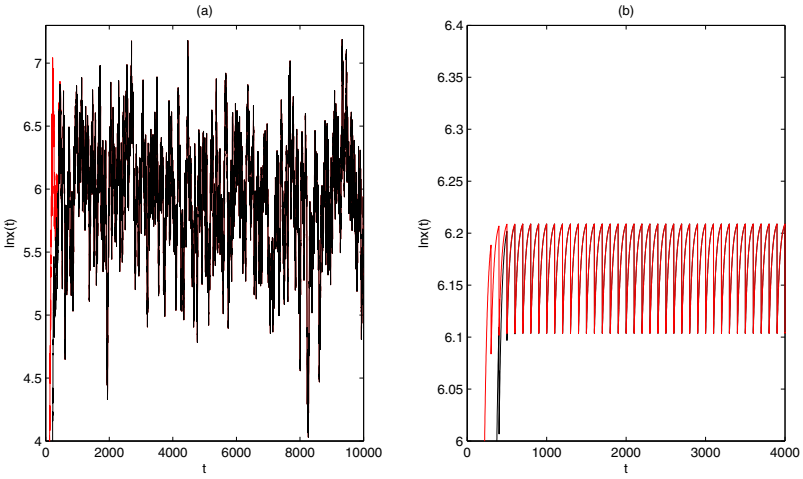

Figure 2: (a) Time series of tumour cells $x(t)$ with $\delta_1 = 1$; (b) Time series of tumour cells $x(t)$ with $\delta_1 = 0$. The initial values of solution with black were fixed as $(x(0), y(0)) = (0.1, 0.5)$ and red for $(x(0), y(0)) = (10, 0.5)$, and all other parameters were fixed as: $r = 3$, $\eta = 0.002$, $a = 1$, $b = 1.131$, $w = 20.19$, $c = 0.00311$, $d = 0.3$, $n = 100$, $\delta_2 = 0.5$, $T = 100$, $a(nT) = 0.1$ and $b(nT) = 0.05$.

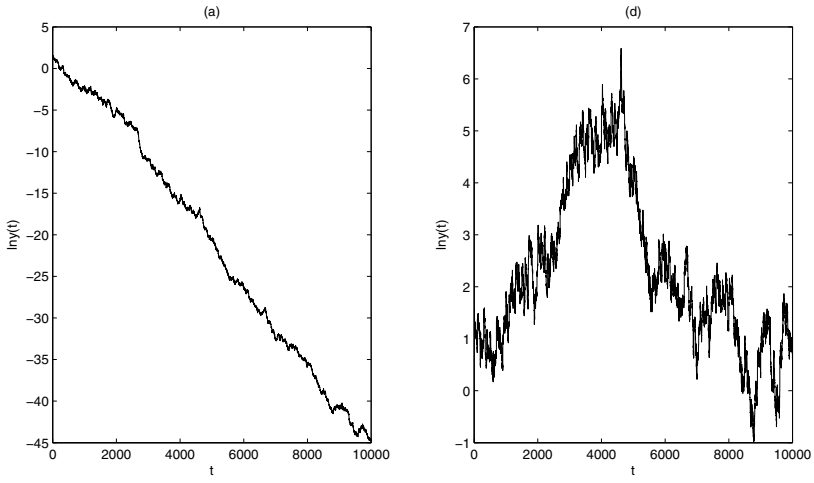

Figure 3: Extinction and weak persistence of e□ector cells. (a) Time series of e□ector cells $y(t)$ with $b(nT) = 0.05$; (b) Time series of e□ector cells $y(t)$ with $b(nT) = 0.6$. The initial values of solution were fixed as $(x(0), y(0)) = (10, 5)$, and all other parameters were fixed as: $r = 1.85$, $\eta = 0.002$, $a = 1$, $b = 1.131$, $w = 20.19$, $c = 0.00311$, $d = 0.3$, $\delta_1 = 2$, $\delta_2 = 0.5$, $n = 100$, $T = 100$ and $a(nT) = 0.1$.

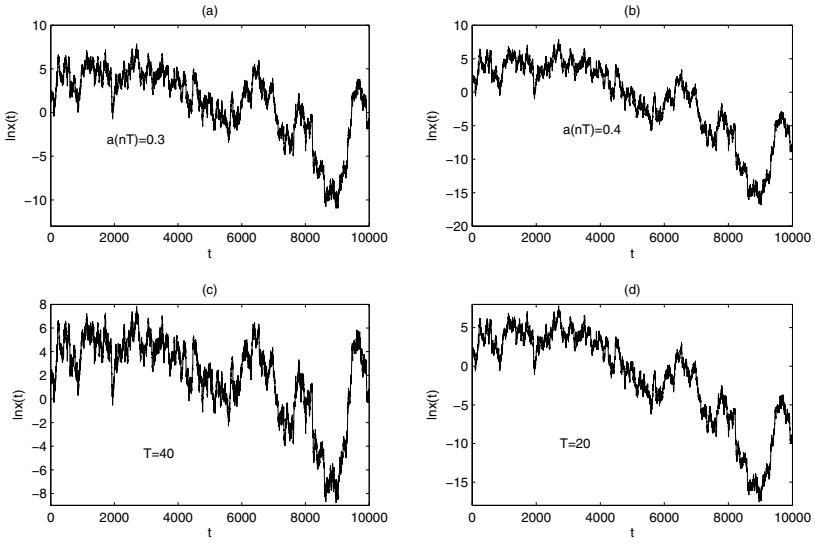

Figure 4: The effects of control parameters on the extinction of tumours. (a) Time series of tumour cells $x(t)$ with $a(nT) = 0.3$ and $T = 100$; (b) Time series of tumour cells $x(t)$ with $a(nT) = 0.4$ and $T = 100$; (c) Time series of tumour cells $x(t)$ with $a(nT) = 0.1$ and $T = 40$; (d) Time series of tumour cells $x(t)$ with $a(nT) = 0.1$ and $T = 25$. We set initial values as $(x(0), y(0)) = (0.1, 0.5)$ and all other parameters were fixed as: $r = 2.5$, $\eta = 0.002$, $a = 1$, $b = 1.131$, $w = 20.19$, $c = 0.00311$, $d = 0.3$, $\delta_1 = 2$, $\delta_2 = 0.5$, $n = 100$ and $b(nT) = 0.05$.