

Modelling chemotherapeutic dose response on a stochastic tumour-immune model

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Abstract

A stochastic tumour-immune dynamical system with pulse immunotherapy and chemotherapy is proposed to study how environmental noise affects the evolution of tumours. Firstly, the explicit expression of tumour free solution is obtained and then we show that the proposed system exists a globally asymptotically stable positive solution under certain conditions. Secondly, threshold criteria ensuring the eradication and persistence of tumours are provided. Moreover, numerical investigations are carried out to address the effects of key factors on the tumours. The results reveal that noises can dominate all dynamics of tumours, and the comprehensive therapy can not only accelerate the eradication of tumours, but also avoid the disadvantages of a single therapy.

Keywords:

Stochastic tumour-immune system, Comprehensive therapy, Eradication and persistence, Lyapunov function

1. Introduction

Cancer remains one of the fatal public health problems in the world [1], and traditional treatment like surgery, radiotherapy and chemotherapy usually can not result in the eradication of tumours. Immunotherapy, which

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aims at enhancing the effectiveness of the immune system, is quickly becoming a significant method to treat certain types of cancer [2-4]. Many studies have demonstrated that immunotherapy in combination with chemotherapy provides a more effective therapeutic protocol to treat cancer than a single therapy [5-7]. Thus, there are of great clinical significance to investigate the effects of comprehensive therapy on the prevention and treatment of tumours.

The aim of mathematical modelling of tumour-immune interactions is to provide better insight into the evolution of tumours from the view of qualitative and quantitative analysis, and try to give some advices on the treatment of tumours. The tumour-immune dynamical models with therapy have attracted a lot of attention [8-12]. A largely influential tumour-immune dynamical model proposed by Kuznetsov [13], consists two variables: tumour cells and effector cells, can be described by the following differential equations

$$\begin{cases} \frac{dx(t)}{dt} = rx(t)(1 - \eta x(t)) - ax(t)y(t), \\ \frac{dy(t)}{dt} = \frac{bx(t)y(t)}{1 + wx(t)} - cx(t)y(t) - dy(t), \end{cases} \quad (1.1)$$

where $x(t)$ and $y(t)$ represent densities of tumour cells and effector cells at time t . r denotes 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 denotes the death rate of effector cells, b is the maximum accumulated rate in the presence of tumours and w for the steepness of immune response.

For system (1.1), Kuznetsov studied the dynamics of immunogenic tumours, and the phenomena of oscillatory and dormancy of tumours were also examined [13]. Kirschner and Panetta investigated the effects of continuous injections of interleukin-2 (IL-2) on the dynamics of system (1.1), they also discussed the short-term oscillations and long-term relapse for tumour cells [14]. Tang and his coauthors extended system (1.1) that govern cancer growth with immunotherapy to include chemotherapy and surgery [15-20]. Particularly, pulsed comprehensive therapy was applied at fixed periods or once tumour cell (or effector cell) reached a threshold, conditions for the existence of periodic solutions and bifurcations were provided and they further showed how key parameters of treatment affected the outcomes of cancer treatment. These results were obtained based on the assumptions that the tumours are not affected by environmental random fluctuations.

However, all living things in nature are subject to the environment fluctuations including temperature, nutrition, oxygen and so on [21], and the tumours are also inevitably influenced by noise [22, 23]. Using stochastic differential equation to model evolution of tumours will not only seize the main features of tumour growth, but also provide the basis for the implementation of the treatment [23]. Based on these facts, Caravagna showed that the stochastic eradication of tumours was possible under certain conditions [23]. Aisu pointed that increasing the period would result in the eradication of tumours [22]. Li and Cheng studied one dimension tumour system with noise and gave sufficient conditions for tumours to be stochastically eradicated and persistent [24].

The experimental and clinical studies indicated that pulsed immunotherapy in combination with chemotherapy are often used to cure cancer than a single therapy [25, 26]. This raises several questions: (1) How to describe such pulsed treatment? (2) How do control parameters including noise, chemotherapeutic drug response, intensity of immunotherapy and impulsive period affect the outcomes of cancer treatment? (3) What is the best treatment strategy for patients? To conquer these questions, we develop a novel mathematical model based on system (1.1), in the form of a system of impulsive stochastic differential equations (ISDEs), governing the evolution of tumours with combination of immunotherapy and chemotherapy,

$$\left. \begin{array}{l} \left. \begin{array}{l} dx(t) = [rx(t)(1 - \eta x(t)) - ax(t)y(t) - k_1(t)x(t)]dt + \delta_1 x(t)dB_1(t), \\ dy(t) = \left[\frac{bx(t)y(t)}{1+wx(t)} - cx(t)y(t) - dy(t) - k_2(t)y(t) \right] dt + \delta_2 y(t)dB_2(t), \\ dD(t) = -\mu D(t), \end{array} \right\} t \neq nT, \\ \left. \begin{array}{l} x(nT^+) = x(nT), \\ y(nT^+) = (1 + R(nT))y(nT), \\ D(nT^+) = D(nT) + \tau, \end{array} \right\} t = nT, \end{array} \right\} \quad (1.2)$$

where $D(t)$ is the concentration of chemotherapeutic drug at time t , μ is the degradation rate. δ_1^2 and δ_2^2 are the intensity of the noise on the tumour cells and effector cells, $B_1(t)$ and $B_2(t)$ denote the independent Brownian motions with $E(B_i(t)) = 0$. T is the period of pulsed therapy, n is the positive integers. $R(nT)$ denotes the recruitment rate of effector cells when immunotherapy is initiated. τ is dosage of chemotherapeutic drugs injected at impulsive point series nT . $k_i(t) = d_i D(t)$ ($i = 1, 2$), d_i is the rate at which chemotherapeutic drug inhibits the tumour cells and effector cells with dif-

ferent clearance rate. The main object of this paper is to explore how pulsed comprehensive therapy and environmental fluctuation affect the evolution of tumours. Therefore, in order to carry out mathematical analyses and further provide biological implications of tumour treatment, the simple system (1.2) is employed. Such stochastic system with pulsed control has been widely applied in many fields and sciences, such as in predator-prey systems [27-29], virus dynamical systems [30], and epidemic dynamical systems [31].

The paper is organized as follows. In section 2, we introduce a series of useful definitions and lemmas of ISDEs. In section 3, we discuss the global positive solution of system (1.2). In section 4, we study the eradication and persistence of the tumours. In section 5, biological implications about the cancer treatment are addressed.

2. Preliminaries

Throughout the paper, $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t \geq 0}, \mathcal{P})$ is denoted as a complete probability space with a filtration $\{\mathcal{F}_t\}_{t \geq 0}$, and the independent Brownian motion $B_i(t)$ is defined on this probability space. If the number of factors is zero, then we call this product equals unity. The following definitions are very important in the rest of paper.

Definition 1. ([32]) $X(t) = (x(t), y(t))^T, t \in R_+ = [0, +\infty)$, is a solution of ISDE (1.2) with initial condition $X(0) = X_0 \geq 0$ provided

- (1) $X(t)$ is absolutely continuous on $(0, T]$ and $(nT, (n+1)T]$;
- (2) $X(nT^-) = \lim_{t \rightarrow nT^-} X(t)$ and $X(nT^+) = \lim_{t \rightarrow nT^+} X(t)$ and $X(nT) = X(nT^-)$ hold true for any nT ;
- (3) $X(t)$ obeys system (1.2) for every $t \in R_+ \setminus \{nT\}$ and the pulsed point nT satisfies the impulsive conditions.

Definition 2. ([33, 34]) Let $X(t) = (x(t), y(t))^T$ be a solution of ISDE (1.2):

- (1) if $\lim_{t \rightarrow +\infty} x(t) = 0$, then $x(t)$ becomes extinctive;
- (2) if $\lim_{t \rightarrow +\infty} t^- \int_0^t x(s) ds = 0$, then $x(t)$ becomes nonpersistent in the mean;
- (3) if $\limsup_{t \rightarrow +\infty} x(t) > 0$, then $x(t)$ becomes weakly persistent;
- (4) for any $\varepsilon \in (0, 1)$, there are two constants $\beta > 0$ and $\delta > 0$ such that

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

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

Definition 3. Let $X_1(t), X_2(t)$ be any two solutions of ISDE (1.2) with $X_1(0) > 0, X_2(0) > 0$, if $\lim_{t \rightarrow +\infty} |x_1(t) - x_2(t)| = 0$ and $\lim_{t \rightarrow +\infty} |y_1(t) - y_2(t)| = 0$, then ISDE (1.2) is globally attractive.

Lemma 1 [35]. 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 $\lim_{t \rightarrow +\infty} \sup \frac{1}{t} \int_0^t f(s)ds \leq \frac{\zeta}{\zeta_0}$.

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

3. Global positive solution

3.1. Tumour free solution

The dynamics of chemotherapeutic drug are given by

$$\begin{cases} dD(t) = -\mu D(t), & t \neq nT, \\ D(nT^+) = D(nT) + \tau, & t = nT. \end{cases} \quad (3.1)$$

By calculation we obtain the explicit expression of the T periodic solution $D^T(t)$ of (3.1) with

$$D^T(t) = \frac{\tau \exp(-\mu(t - nT))}{1 - \exp(-\mu T)},$$

where $t \in (nT, (n+1)T]$, $D^T(nT^+) = \tau/(1 - \exp(-\mu T))$.

Lemma 2 ([36, 37]) $D^T(t)$ is a unique positive periodic solution of system (3.1) which satisfies $\lim_{t \rightarrow \infty} D(t) = D^T(t)$, and for any $\epsilon > 0$ we have

$$D^T(t) - \epsilon < D(t) < D^T(t) + \epsilon \quad \text{and} \quad \lim_{t \rightarrow +\infty} \frac{1}{t} \int_0^t D^T(s)ds = \frac{\tau}{\mu T}. \quad (3.2)$$

An extreme case is considered and we study the tumour free solution of system (1.2). To do this, assume that the tumours will be eradicated during treatment, let $x(t) = 0$ and then system (1.2) is simplified as the following subsystem:

$$\begin{cases} \left. \begin{aligned} dy(t) &= [-dy(t) - d_2 D(t)y(t)] dt + \delta_2 y(t) dB_2(t), \\ dD(t) &= -\mu D(t), \end{aligned} \right\} t \neq nT, \\ \left. \begin{aligned} y(nT^+) &= (1 + R(nT))y(nT), \\ D(nT^+) &= D(nT) + \tau, \end{aligned} \right\} t = nT, \end{cases} \quad (3.3)$$

Since the explicit expression of $D(t)$ has been solved mathematically, system (3.3) can be reduced to the following system:

$$\begin{cases} dy(t) = [-dy(t) - d_2 D(t)y(t)] dt + \delta_2 y(t) dB_2(t), t \neq nT, \\ y(nT^+) = (1 + R(nT))y(nT), t = nT, \end{cases} \quad (3.4)$$

Theorem 1. For any initial value $y(0^+) = y(0)$, there is a unique global positive solution $y(t)$ of system (3.4), where

$$y(t) = \prod_{0 < nT < t} (1 + R(nT))y(0) \exp[(-d - d_2D(t) - 0.5\delta_2^2)t + \delta_2B_2(t)]. \quad (3.5)$$

Proof. For any $t \in (nT, (n+1)T]$, defining an Lyapunov function $V(t) = \ln y(t)$. Make using of the Itô's formula leads to

$$d \ln y(t) = (-d - d_2D(t) - 0.5\delta_2^2)dt + \delta_2dB_2(t).$$

From nT to t , the integral of the above equation yields

$$\ln y(t) - \ln y(nT) = (-d - d_2D(t) - 0.5\delta_2^2)(t - nT) + \delta_2(B_2(t) - B_2(nT)),$$

thus,

$$y(t) = y(nT) \exp[(-d - d_2D(t) - 0.5\delta_2^2)(t - nT) + \delta_2(B_2(t) - B_2(nT))].$$

At impulsive point $t = nT^+$, after one time immunotherapy we get

$$y(t) = (1 + R(nT))y(nT) \exp[(-d - d_2D(t) - 0.5\delta_2^2)(t - nT) + \delta_2(B_2(t) - B_2(nT))].$$

Mathematical induction leads to

$$y(t) = \prod_{0 < nT < t} (1 + R(nT))y(0) \exp[(-d - d_2D(t) - 0.5\delta_2^2)t + \delta_2B_2(t)].$$

This completes the proof.

3.2. Global positive solution of system (1.2)

To investigate the global dynamics of system (1.2), we just need to pay attention to the following equivalent subsystem (3.6) because the dynamics of the chemotherapy drugs are discussed,

$$\left\{ \begin{array}{l} dx(t) = [rx(t)(1 - \eta x(t)) - ax(t)y(t) - k_1(t)x(t)]dt + \delta_1x(t)dB_1(t), \\ dy(t) = \left[\frac{bx(t)y(t)}{1+wx(t)} - cx(t)y(t) - dy(t) - k_2(t)y(t) \right] dt + \delta_2y(t)dB_2(t), \\ x(nT^+) = x(nT), \\ y(nT^+) = (1 + R(nT))y(nT), \end{array} \right\} \begin{array}{l} t \neq nT, \\ t = nT, \end{array} \quad (3.6)$$

For simplicity, we define an SDE without pulsed immunotherapy according to system (3.6) which is very helpful for the rest of the paper.

$$\begin{cases} dx_1(t) &= x_1[r(1 - \eta x_1) - a \prod_{0 < nT < t} (1 + R(nT))y_1 - k_1(t)]dt \\ &\quad + \delta_1 x_1 dB_1(t), \\ dy_1(t) &= y_1 \left[\frac{bx_1}{1 + wx_1} - cx_1 - d - k_2(t) \right] dt + \delta_2 y_1 dB_2(t), \end{cases} \quad (3.7)$$

with $(x_1(0), y_1(0)) = (x(0), y(0)) \in R_+^2 = \{(x(t), y(t)) | x(t) > 0, y(t) > 0\}$.

Theorem 2. For any initial value $(x(0), y(0))$, a global unique positive solution $(x(t), y(t))$ of system (3.6) exists and it remains in R_+^2 .

Proof. By using the same methods as shown in [28], we can prove that the SDE (3.7) has a positive solution $(x_1(t), y_1(t))$ which is globally unique. Let

$$(x(t), y(t)) = \left(x_1(t), \prod_{0 < nT < t} (1 + R(nT))y_1(t) \right), \quad (3.8)$$

then the absolutely continuity of $(x_1(t), y_1(t))$ leads to the absolutely continuity of $(x(t), y(t))$ for any $t \in (nT, (n+1)T] \subset [0, +\infty)$, $n \in \mathcal{N}$. Once $t \neq nT$, the derivatives of (3.8) along SDE (3.7) yield

$$\begin{aligned} dx(t) &= dx_1(t) = x_1[r(1 - \eta x_1) - a \prod_{0 < nT < t} (1 + R(nT))y_1 - k_1(t)]dt \\ &\quad + \delta_1 x_1 dB_1(t) \\ &= [rx(t)(1 - \eta x(t)) - ax(t)y(t) - k_1(t)x(t)]dt + \delta_1 x(t)dB_1(t), \\ dy(t) &= \prod_{0 < nT < t} (1 + R(nT))dy_1(t) \\ &= y(t) \left[\frac{bx_1}{1 + wx_1} - cx_1 - d - k_2(t) \right] dt + \delta_2 y_1 dB_2(t) \\ &= \left[\frac{bx(t)y(t)}{1 + wx(t)} - cx(t)y(t) - dy(t) - k_2(t)y(t) \right] dt + \delta_2 y(t)dB_2(t). \end{aligned}$$

When $t = nT$,

$$\begin{aligned} x(nT^+) &= \lim_{t \rightarrow nT^+} x_1(t) = x_1(nT) \\ &= x(nT), \\ y(nT^+) &= \lim_{t \rightarrow nT^+} \prod_{0 < iT < t} (1 + R(iT))y_1(t) \\ &= (1 + R(nT)) \prod_{0 < iT < nT} (1 + R(iT))y_1(nT) \\ &= (1 + R(nT))y(nT), \end{aligned} \quad (3.9)$$

Therefore, there is a global unique positive solution of system (3.6). This completes the proof.

Theorem 3. The solution of system (1.2) is globally attractive provided $r\eta - b + c > 0$.

Proof. To show that the solution of system (1.2) is globally attractive, it is only necessary to discuss the global attractivity of the solution of equivalent system (3.6). To do this, chosen any two solutions $(x_1(t), y_1(t))$ and $(x_2(t), y_2(t))$ of system (3.6) with $x(0) > 0$ and $y(0) > 0$, a Lyapunov function is constructed to verify the global attractivity of the solutions of system (3.6), once $t \neq nT$ and for all $t > 0$, let

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

By taking the upper right derivative $d^+V(t)$ of $V(t)$ and employing Itô's formula, we obtain

$$\begin{aligned} d^+V(t) &= \text{sign}(x_1(t) - x_2(t))d(\ln x_1(t) - \ln x_2(t)) \\ &\quad + \text{sign}(y_1(t) - y_2(t))d(\ln y_1(t) - \ln y_2(t)) \\ &= \text{sign}(x_1(t) - x_2(t))(-r\eta(x_1(t) - x_2(t)) - a(y_1(t) - y_2(t)))dt \\ &\quad + \text{sign}(y_1(t) - y_2(t))\left(\frac{b(x_1(t) - x_2(t))}{(1+wx_1(t))(1+wx_2(t))} - c(x_1(t) - x_2(t))\right)dt \\ &\leq [-(r\eta - b + c)|x_1(t) - x_2(t)| - a|y_1(t) - y_2(t)|]dt \\ &\leq -\rho(|x_1(t) - x_2(t)| + |y_1(t) - y_2(t)|)dt \doteq -\rho\mathbb{V}(t)dt, \end{aligned} \tag{3.10}$$

where $\rho = \min\{r\eta - b + c, a\}$. If $t = nT$, then

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

Integrating the inequality (3.10) from 0 to t and then by calculating mathematical expectation we have

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

That is

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

Thus, $\lim_{t \rightarrow +\infty} \mathbb{V}(t) = 0$ because $V(t) \geq 0$ holds, it implies

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

According to Definition 3, the solution of system (1.2) is globally attractive. This completes the proof.

Theorem 4. For any $0 \leq s < t$, under the condition of $\prod_{s \leq nT < t} (1 + R(nT)) \leq \kappa_1$ ($\kappa_1 > 0$), the solution $X(t) = (x(t), y(t))$ of system (3.6) satisfies the following inequality:

$$\lim_{t \rightarrow \infty} E | X(t) | \leq \kappa_1 \kappa_2,$$

where $\kappa_2 = \frac{c_1}{4r\eta} \left(r + 1 - d_1 \frac{\tau \exp(-\mu T)}{1 - \exp(-\mu T)} \right)^2 + c_2 y_0 \left(1 - d - d_2 \frac{\tau \exp(-\mu T)}{1 - \exp(-\mu T)} \right)$.

Proof. Defining a Lyapunov function $V_1(t) = c_1 x(t) + c_2 y(t)$ with $c_1 = b - c > 0$ and $c_2 = a > 0$. In the light of system (3.6), when $t \in ((n-1)T, nT]$ we employ the Itô's formula

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

where

$$\begin{aligned} LV(t) = & c_1 [rx(t)(1 - \eta x(t)) - ax(t)y(t) - k_1(t)x(t)] \\ & + c_2 \left[\frac{bx(t)y(t)}{1 + wx(t)} - cx(t)y(t) - dy(t) - k_2(t)y(t) \right]. \end{aligned}$$

Defining another Lyapunov function $V_2(t) = e^t V_1(t)$ and making using of the Itô's formula follows

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

Integrating both sides of above equation from $(n-1)T$ to t and then calculating the expectations we obtain

$$E e^t V_1(t) = e^{(n-1)T} V_1((n-1)T) + E \int_{(n-1)T}^t e^s [V_1(s) + LV(s)] ds. \quad (3.11)$$

Once the tumours attack the effector cells, the effector cells in the course of treatment can not exceed a certain level, i.e., $y(t) \leq y_0$. Notice that

$$\begin{aligned} LV + V_1 &= c_1 [rx(1 - \eta x) - axy - k_1(t)x] + c_2 \left[\frac{bxy}{1 + wx} - cxy - dy - k_2(t)y \right] \\ &\quad + c_1 x + c_2 y \\ &\leq c_1 (rx - r\eta x^2 - k_1(t)x + x) \\ &\quad + (c_2(b - c) - c_1 a)xy + c_2 y(1 - d - k_2(t)) \\ &\leq \frac{c_1}{4r\eta} \left(r + 1 - d_1 \frac{\tau \exp(-\mu T)}{1 - \exp(-\mu T)} \right)^2 + c_2 y_0 \left(1 - d - d_2 \frac{\tau \exp(-\mu T)}{1 - \exp(-\mu T)} \right) \doteq \kappa_2. \end{aligned} \quad (3.12)$$

Based on equations (3.11) and (3.12) we have

$$e^t EV_1(t) \leq e^{(n-1)T} (V_1((n-1)T) - \kappa_2) + e^t \kappa_2. \quad (3.13)$$

By taking the derivative of (3.13), a simple calculation leads to

$$dEV_1(t) \leq (\kappa_2 - EV_1(t))dt. \quad (3.14)$$

For $t = nT$, by calculating mathematical expectation of $V_1(t)$,

$$\begin{aligned} EV_1(nT^+) &= c_1 E(x(nT^+)) + c_2 E(y(nT^+)) \\ &= c_1 E(x(nT)) + c_2 (1 + R(nT)) E(y(nT)) \\ &\leq (1 + R(nT)) (c_1 E(x(nT)) + c_2 E(y(nT))) \\ &= (1 + R(nT)) EV_1(nT). \end{aligned} \quad (3.15)$$

Combining equation (3.14) with (3.15), then

$$\begin{cases} dEV_1(t) \leq (\kappa_2 - EV_1(t))dt, & t \neq nT, \\ EV_1(nT^+) \leq (1 + R(nT)) EV_1(nT), & t = nT. \end{cases} \quad (3.16)$$

In order to determine the boundedness of $EV_1(t)$, we consider the following impulsive system:

$$\begin{cases} dz(t) = (\kappa_2 - z(t))dt, & t \neq nT, \\ z(nT^+) = (1 + R(nT))z(nT), & t = nT. \end{cases} \quad (3.17)$$

The unique solution of system (3.17) is obtained as follows

$$z(t) = z(0)m(t, 0) + \kappa_2 \int_0^t m(t, s)ds,$$

where $m(t, s) = \prod_{s \leq nT < t} (1 + R(nT)) \exp(-(t - s))$. Thus, $\lim_{t \rightarrow +\infty} z(t) = \kappa_1 \kappa_2$. In view of the comparison theorems of impulsive differential equations [38, 39],

$$\lim_{t \rightarrow +\infty} EV_1(t) \leq \lim_{t \rightarrow +\infty} z(t) = \kappa_1 \kappa_2.$$

This completes the proof.

4. The extinction and persistence of tumours

Since we have studied the uniqueness, global attractivity and boundedness for the solutions of stochastic model (1.2), the coming section will focus on how key parameters including the impulsive period, immune strength, doses of chemotherapy drugs and stochastic fluctuations affect the extinction and long-term survival of tumours. To this end, we denote $f_*(t) = \lim_{t \rightarrow +\infty} \inf \frac{1}{t} \int_0^t f(s) ds$ and $f^*(t) = \lim_{t \rightarrow +\infty} \sup \frac{1}{t} \int_0^t f(s) ds$ for simplicity, and then provide the following preparations by virtue of the Itô's formula. In the light of system (3.7), we define a Lyapunov function $V(t) = \ln x_1(t)$ and make using of the Itô's formula yields,

$$\begin{aligned} d \ln x_1(t) &= [r - r\eta x_1 - a \prod_{0 < nT < t} (1 + R(nT)) y_1 - d_1 D(t) \\ &\quad - \frac{1}{2} \delta_1^2] dt + \delta_1 dB_1(t) \\ &= [r - r\eta x(t) - ay(t) - d_1 D(t) - \frac{1}{2} \delta_1^2] dt + \delta_1 dB_1(t), \end{aligned} \quad (4.1)$$

by using mathematical integration method and notice that $x(t) = x_1(t)$ we obtain

$$\ln \frac{x(t)}{x(0)} = (r - \frac{1}{2} \delta_1^2) t - r\eta \int_0^t x(s) ds - d_1 \int_0^t D(s) ds - a \int_0^t y(s) ds + M_1(t), \quad (4.2)$$

denote $M_i(t) = \int_0^t \delta_i dB_i(t) (i = 1, 2)$. Similarly, we get

$$\begin{aligned} \ln \frac{y(t)}{y(0)} &= \sum_{0 < nT < t} \ln(1 + R(nT)) - (d + \frac{1}{2} \delta_2^2) t - c \int_0^t x(s) ds \\ &\quad - d_2 \int_0^t D(s) ds + b \int_0^t \frac{x(s)}{1+wx(s)} ds + M_2(t). \end{aligned} \quad (4.3)$$

Theorem 5. (1) If $r < \frac{1}{2} \delta_1^2 + \frac{d_1 \tau}{\mu T}$, then the tumour cells become extinct.
(2) If $r = \frac{1}{2} \delta_1^2 + \frac{d_1 \tau}{\mu T}$, then the tumour cells are nonpersistent in the mean.
(3) If $r > \frac{1}{2} \delta_1^2 + \frac{d_1 \tau}{\mu T}$ and $\lim_{t \rightarrow +\infty} \sup \frac{\sum_{0 < nT < t} \ln(1+R(nT))}{t} < d + \frac{1}{2} \delta_2^2 + \frac{d_2 \tau}{\mu T}$, then the tumour cells become weakly persistent in the mean.

Proof. (1) Based on (4.2),

$$\begin{aligned} \frac{1}{t} \ln \frac{x(t)}{x(0)} &= (r - \frac{1}{2} \delta_1^2) - r\eta \frac{\int_0^t x(s) ds}{t} - d_1 \frac{\int_0^t D(s) ds}{t} \\ &\quad - a \frac{\int_0^t y(s) ds}{t} + \frac{M_1(t)}{t}. \end{aligned} \quad (4.4)$$

Because of $\langle M_i(t), M_i(t) \rangle = \int_0^t \delta_i^2 ds$ and the strong law of large numbers for local martingales we obtain

$$\lim_{t \rightarrow +\infty} \frac{M_1(t)}{t} = 0. \quad (4.5)$$

When $t \rightarrow +\infty$, the superior limit of equation (4.4) yields

$$\lim_{t \rightarrow +\infty} \sup \frac{\ln x(t)}{t} \leq r - \frac{1}{2}\delta_1^2 - \frac{d_1\tau}{\mu T} - r\eta x_*(t) - ay_*(t) < 0.$$

Thus, $\lim_{t \rightarrow +\infty} x(t) = 0$ reveals that the tumour cells becomes extinct.

(2) For any small positive $\epsilon > 0$, there is a positive t_1 such that for all $t \geq t_1$ we have

$$d_1 \frac{\int_0^t D(s)ds}{t} > \frac{d_1\tau}{\mu T} - \frac{\epsilon}{2}, \quad \frac{M_1(t)}{t} \leq \frac{\epsilon}{2},$$

in view of equation (4.4),

$$\begin{aligned} \frac{1}{t} \ln \frac{x(t)}{x(0)} &= \left(r - \frac{1}{2}\delta_1^2 \right) - r\eta \frac{\int_0^t x(s)ds}{t} - d_1 \frac{\int_0^t D(s)ds}{t} \\ &\quad - a \frac{\int_0^t y(s)ds}{t} + \frac{M_1(t)}{t} \\ &\leq \left(r - \frac{1}{2}\delta_1^2 \right) - \frac{d_1\tau}{\mu T} - r\eta \frac{1}{t} \int_0^t x(s)ds + \frac{M_1(t)}{t} + \epsilon. \end{aligned}$$

According to Lemma 1, for a sufficiently small ϵ one gets

$$\lim_{t \rightarrow +\infty} \sup \frac{1}{t} \int_0^t x(s)ds \leq \frac{\left(r - \frac{1}{2}\delta_1^2 - \frac{d_1\tau}{\mu T} \right)}{r\eta} = 0. \quad (4.6)$$

Note that $x^*(t) \geq 0$ and so $\lim_{t \rightarrow +\infty} \sup \frac{1}{t} \int_0^t x(s)ds = 0$, i.e., the tumours are nonpersistent in the mean.

(3) If $\lim_{t \rightarrow +\infty} \sup \frac{x(t)}{t} < 0$, then the superior limit of (4.4) yields

$$r\eta x^*(t) + ay^*(t) \geq r - \frac{1}{2}\delta_1^2 - \frac{d_1\tau}{\mu T} - \lim_{t \rightarrow +\infty} \sup \frac{\ln x(t)}{t} > 0.$$

It means $x^*(t) > 0$, otherwise, for any $t^* \in \{x^*(t, t^*) = 0\}$ we have $y^*(t, t^*) > 0$. If $x^*(t, t^*) = 0$, then the superior limit of (4.3) leads to

$$\lim_{t \rightarrow +\infty} \sup \frac{\ln y(t, t^*)}{t} \leq \lim_{t \rightarrow +\infty} \sup \frac{\sum_{0 < nT < t} \ln(1+R(nT))}{t} - \left(d + \frac{1}{2}\delta_2^2 \right) - \frac{d_2\tau}{\mu T} < 0.$$

It indicates that $y^*(t, t^*) = 0$ which contradicts with $y^*(t, t^*) > 0$. Therefore, $\lim_{t \rightarrow +\infty} \sup \frac{x(t)}{t} > 0$, i.e., the tumour cells become weakly persistent in the mean. This completes the proof.

Theorem 6. (1) If

$$r < \frac{1}{2}\delta_1^2 + \frac{d_1\tau}{\mu T} \quad \text{and} \quad \lim_{t \rightarrow +\infty} \sup \frac{\sum_{0 < nT < t} \ln(1+R(nT))}{t} < d + \frac{1}{2}\delta_2^2 + \frac{d_2\tau}{\mu T},$$

then the effector cells become extinct.

(2) If $r = \frac{1}{2}\delta_1^2 + \frac{d_1\tau}{\mu T}$, then the effector cells are nonpersistent in the mean.

(3) If

$$\lim_{t \rightarrow +\infty} \sup \frac{\sum_{0 < nT < t} \ln(1+R(nT))}{t} - \left(d + \frac{1}{2}\delta_2^2 + \frac{d_2\tau}{\mu T} \right) - \frac{b-c}{r\eta} \left(r - \frac{1}{2}\delta_1^2 - \frac{d_1\tau}{\mu T} \right) > 0,$$

then the effector cells become weakly persistent in the mean.

Proof. (1) In the light of (4.3), we have

$$\begin{aligned} \frac{1}{t} \ln \frac{y(t)}{y(0)} &= \frac{\sum_{0 < nT < t} \ln(1+R(nT))}{t} - \left(d + \frac{1}{2}\delta_2^2 \right) - c \frac{1}{t} \int_0^t x(s) ds \\ &\quad - d_2 \frac{1}{t} \int_0^t D(s) ds + b \frac{1}{t} \int_0^t \frac{x(s)}{1+wx(s)} ds + \frac{M_2(t)}{t}. \end{aligned} \quad (4.7)$$

The superior limit of (4.7) leads to

$$\lim_{t \rightarrow +\infty} \sup \frac{\ln y(t)}{t} \leq \lim_{t \rightarrow +\infty} \sup \frac{\sum_{0 < nT < t} \ln(1+R(nT))}{t} - \left(d + \frac{1}{2}\delta_2^2 + \frac{d_2\tau}{\mu T} \right) + (b-c)x^*(t),$$

It follows from Theorem 5 that $x^*(t) < 0$, thus,

$$\lim_{t \rightarrow +\infty} \sup \frac{\ln y(t)}{t} \leq 0.$$

So we obtain $\lim_{t \rightarrow +\infty} y(t) = 0$, i.e., the effector cells become extinct.

(2) For any sufficiently small $\varepsilon > 0$, a t_2 exists and for any $t \geq t_2$ we obtain:

$$d_1 \frac{\int_0^t D(s) ds}{t} > \frac{d_1\tau}{\mu T} - \frac{\varepsilon}{2}, \quad \frac{M_1(t)}{t} \leq \frac{\varepsilon}{2},$$

in view of (4.4),

$$\begin{aligned} a \frac{1}{t} \int_0^t y(s) ds &= -\frac{1}{t} \ln \frac{x(t)}{x(0)} + \left(r - \frac{1}{2}\delta_1^2 \right) - r\eta \frac{\int_0^t x(s) ds}{t} - d_1 \frac{\int_0^t D(s) ds}{t} \\ &\quad + \frac{M_1(t)}{t} \\ &\leq \left(r - \frac{1}{2}\delta_1^2 - \frac{d_1\tau}{\mu T} \right) + \varepsilon. \end{aligned}$$

The superior limit of above equation gives

$$\lim_{t \rightarrow +\infty} \sup \frac{1}{t} \int_0^t y(s) ds \leq 0. \quad (4.8)$$

During the immunotherapy, $\lim_{t \rightarrow +\infty} \sup \frac{1}{t} \int_0^t y(s) ds \geq 0$ due to the recruitment of the effector cells. Therefore, we have $\lim_{t \rightarrow +\infty} \sup \frac{1}{t} \int_0^t y(s) ds = 0$ which reveals that the effector cells is nonpersistent in the mean.

(3) From (4.7) we have

$$\frac{1}{t} \ln \frac{y(t)}{y(0)} \geq \frac{\sum_{0 < nT < t} \ln(1+R(nT))}{t} - \left(d + \frac{1}{2}\delta_2^2\right) - (b+c)\frac{1}{t} \int_0^t x(s)ds - d_2 \frac{1}{t} \int_0^t D(s)ds + \frac{M_2(t)}{t}, \quad (4.9)$$

then (4.4)+(4.9) and the superior limit of the above inequality leads to

$$\frac{\ln y(t)}{t} \geq \lim_{t \rightarrow +\infty} \sup \frac{\sum_{0 < nT < t} \ln(1+R(nT))}{t} - \left(d + \frac{1}{2}\delta_2^2 + \frac{d_2\tau}{\mu T}\right) + \left(r - \frac{1}{2}\delta_1^2 - \frac{d_1\tau}{\mu T}\right) - (r\eta - b + c)x^*(t) - ay^*(t),$$

and it follows from (4.6) that we obtain

$$ay^*(t) \geq \lim_{t \rightarrow +\infty} \sup \frac{\sum_{0 < nT < t} \ln(1+R(nT))}{t} - \left(d + \frac{1}{2}\delta_2^2 + \frac{d_2\tau}{\mu T}\right) - \frac{b-c}{r\eta} \left(r - \frac{1}{2}\delta_1^2 - \frac{d_1\tau}{\mu T}\right) > 0.$$

which means that $y^*(t) = \lim_{t \rightarrow +\infty} \sup \frac{1}{t} \int_0^t y(s)ds \geq 0$. This completes the proof.

Assumption 1. There are two positive constants m_1 and M_1 such that $m_1 \leq \prod_{0 < nT < t} (1 + R(nT)) \leq M_1$.

Theorem 7. Based on assumption 1, if $\Phi = \min_{t \geq 0} [r - \frac{1}{2}\delta_1^2 - \frac{d_1\tau}{\mu T} - aM_1y_0] > 0$, then the tumour cells are stochastically permanent.

Proof. In the light of Definition 2, We first show that there exists a constants $\beta > 0$ such that $\liminf_{t \rightarrow +\infty} \mathbb{P}\{x(t) \geq \beta\} \geq 1 - \varepsilon$ when $\varepsilon \in (0, 1)$. To do this, we define a Lyapunov function $V^1(x) = 1/x_1$ ($x_1 > 0$) and the application of the Itô's formula to system (3.7) yields

$$dV^1(x_1) = -V^1(x_1)[r - r\eta x_1 - d_1D(t) - a \prod_{0 < nT < t} (1 + R(nT))y_1]dt + V^1(x_1)\delta_1^2 dt - V^1(x_1)\delta_1 dB_1(t).$$

For arbitrary positive constant ϑ so that $\Phi > 0.5\vartheta\delta_1^2$, we let $V^2(x_1) = (1 +$

$V^1(x_1)^\vartheta$ and make use of the Itô's formula results in

$$\begin{aligned}
dV^2(x_1) &= \vartheta(1 + V^1(x_1))^{\vartheta-1}dV^1(x_1) + 0.5\vartheta(\vartheta - 1)(1 + V^1(x_1))^{\vartheta-2}(dV^1(x_1))^2 \\
&= \vartheta(1 + V^1(x_1))^{\vartheta-2}\{-V^1(x_1) - (V^1(x_1))^2[r - r\eta x_1 - d_1D(t) \\
&\quad - a\prod_{0 < nT < t}(1 + R(nT))y_1] + (V^1(x_1) + (V^1(x_1))^2)\delta_1^2 \\
&\quad + 0.5(\vartheta - 1)(V^1(x_1))^2\delta_1^2\}dt - \vartheta(1 + V^1(x_1))^{\vartheta-1}V^1(x_1)\delta_1dB_1(t) \\
&= \vartheta(1 + V^1(x_1))^{\vartheta-2}\{-(V^1(x_1))^2[r - 0.5\delta_1^2 - d_1D(t) - 0.5\vartheta\delta_1^2 \\
&\quad - a\prod_{0 < nT < t}(1 + R(nT))y_1] \\
&\quad + V^1(x_1)[-r + r\eta + a\prod_{0 < nT < t}(1 + R(nT))y_1 + d_1D(t) + \delta_1^2] \\
&\quad + \eta\}dt - \vartheta(1 + V^1(x_1))^{\vartheta-1}V^1(x_1)\delta_1dB_1(t) \\
&\leq \vartheta(1 + V^1(x_1))^{\vartheta-2}\{-(V^1(x_1))^2[\Phi - 0.5\vartheta\delta_1^2] + V^1(x_1)[r\eta \\
&\quad + aM_1y_0 + \delta_1^2 + \frac{d_1\tau}{\mu T}] + r\eta\}dt - \vartheta(1 + V^1(x_1))^{\vartheta-1}V^1(x_1)\delta_1dB_1(t).
\end{aligned}$$

Subsequently, choosing a ξ small enough such that

$$\Phi - 0.5\vartheta\delta_1^2 > \frac{\xi}{\vartheta} > 0. \quad (4.10)$$

Again let $V^3(x_1) = \exp(\xi t)V^2(x_1)$ and by using the Itô's formula we obtain

$$\begin{aligned}
dV^3(x_1) &= \xi \exp(\xi t)V^2(x_1)dt + \exp(\xi t)dV^2(x_1) \\
&\leq \vartheta \exp(\xi t)(1 + V^1(x_1))^{\vartheta-2}\{\frac{\xi(1+V^1(x_1))^2}{\vartheta} - (V^1(x_1))^2[\Phi - 0.5\vartheta\delta_1^2] \\
&\quad + V^1(x_1)[r\eta + aM_1y_0 + \delta_1^2 + \frac{d_1\tau}{\mu T}] + r\eta\}dt \\
&\quad - \vartheta \exp(\xi t)(1 + V^1(x_1))^{\vartheta-1}V^1(x_1)\delta_1dB_1(t) \\
&\doteq \exp(\xi t)q(x_1)dt - \vartheta \exp(\xi t)(1 + V^1(x_1))^{\vartheta-1}V^1(x_1)\delta_1dB_1(t),
\end{aligned}$$

with

$$\begin{aligned}
q(x_1) &= \vartheta(1 + V^1(x_1))^{\vartheta-2}\{-[\Phi - 0.5\vartheta\delta_1^2 - \frac{\xi}{\vartheta}](V^1(x_1))^2 \\
&\quad + [r\eta + aM_1y_0 + \delta_1^2 + \frac{d_1\tau}{\mu T} + \frac{2\xi}{\vartheta}]V^1(x_1) + r\eta + \frac{\xi}{\vartheta}\}.
\end{aligned}$$

Let $C_1 = \Phi - 0.5\vartheta\delta_1^2 - \frac{\xi}{\vartheta}$, $C_2 = r\eta + aM_1y_0 + \delta_1^2 + \frac{d_1\tau}{\mu T} + \frac{2\xi}{\vartheta}$ and $C_3 = r\eta + \frac{\xi}{\vartheta}$, from (4.10) we know $C_1 > 0$, $C_2 > 0$ and $C_3 > 0$. Note that $V^1(x_1) = 1/x_1$ and $q(x_1)$ can be rewritten as

$$q(x_1) = \vartheta(1 + \frac{1}{x_1})^{\vartheta-2} \left\{ -\frac{C_1}{x_1^2} + \frac{C_2}{x_1} + C_3 \right\} \doteq q_1(x_1).$$

If $x_1 > 0$, then $f(x_1)$ is upper bounded. In fact, if $\frac{1}{x_1} \geq \frac{C_2 + \sqrt{C_2^2 + 4C_1C_3}}{2C_1} \doteq \lambda_1$, then $q(x_1) \leq 0$. If $0 < \frac{1}{x_1} \leq \lambda_1$, then $q_1(x_1) \leq \frac{4C_1C_3 + C_2^2}{4C_1}$. 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 any $x_1 > 0$ we have $q(x_1) \leq q_0 = \lambda_2 \frac{4C_1C_3+C_2^2}{4C_1}$ with $\lambda_2 = \max\{\vartheta, \vartheta(1 + \lambda_1)^{\vartheta-2}\}$, which means $q(x_1)$ is upper bounded. Furthermore,

$$\begin{aligned} dV^3(x_1) &\leq \exp(\xi t)q(x_1)dt - \vartheta \exp(\xi t)(1 + V^1(x_1))^{\vartheta-1}V^1(x_1)\delta_1 dB_1(t) \\ &\leq q_0 \exp(\xi t)dt - \vartheta \exp(\xi t)(1 + V^1(x_1))^{\vartheta-1}V^1(x_1)\delta_1 dB_1(t). \end{aligned}$$

From 0 to t integrating above equation and taking the expectation we obtain

$$E[V^3(x_1(t))] \leq V^3(x_1(0)) + \frac{q_0}{\xi} \exp(\xi t),$$

notice that $V^3(x_1(t)) = \exp(\xi t)(1 + V^1(x_1(t)))^\vartheta$,

$$\begin{aligned} E[V^3(x_1(t))] &= E[\exp(\xi t)(1 + V^1(x_1(t)))^\vartheta] \\ &\leq V^3(x_1(0)) + \frac{q_0}{\xi} \exp(\xi t) \\ &= (1 + V^1(x_1(0)))^\vartheta + \frac{q_0}{\xi} \exp(\xi t). \end{aligned}$$

The superior limit results in

$$\begin{aligned} \limsup_{t \rightarrow +\infty} E[\frac{1}{x_1(t)^\vartheta}] &= \limsup_{t \rightarrow +\infty} E[(V^1(x_1(t)))^\vartheta] \\ &\leq \limsup_{t \rightarrow +\infty} E[(1 + V^1(x_1(t)))^\vartheta] \leq \frac{q_0}{\xi}. \end{aligned}$$

It follows from (3.8) that we have $x(t) = x_1(t)$,

$$\limsup_{t \rightarrow +\infty} E[\frac{1}{x(t)^\vartheta}] = \limsup_{t \rightarrow +\infty} E[\frac{1}{x_1(t)^\vartheta}] \leq \frac{f_0}{\xi} \doteq q_M.$$

For any $\varepsilon > 0$, let $\beta = \varepsilon^{\frac{1}{\vartheta}}/q_M^{\frac{1}{\vartheta}}$, thus the Chebyshev's inequality leads to

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

Therefore, $\liminf_{t \rightarrow +\infty} \mathbb{P}\{x(t) \geq \beta\} \geq 1 - \varepsilon$.

Now, we only need to prove that there is a $\varrho > 0$ such that $\liminf_{t \rightarrow +\infty} \mathbb{P}\{x(t) \leq \varrho\} \geq 1 - \varepsilon$. To this end, defining another Lyapunov function $V_3(x_1(t)) = x_1^h(t)$ ($x_1 > 0$) and making use of the Itô's formula to system (3.7) yields

$$\begin{aligned} dV_3(x_1(t)) &= hV_3(x_1(t))[r - r\eta x_1(t) - d_1 D(t) - a \prod_{0 < nT < t} (1 + R(nT))y_1(t) \\ &\quad + 0.5(h-1)\delta_1^2]dt + h\delta_1 V_3(x_1(t))dB_1(t) \\ &\leq hV_3(x_1(t))[r - r\eta x_1(t) - \frac{d_1 T}{\mu T} + 0.5(h-1)\delta_1^2]dt \\ &\quad + h\delta_1 V_3(x_1(t))dB_1(t), \end{aligned}$$

integrating above equation from 0 to t and the expectation leads to

$$E[V_3(x_1(t))] - E[V_3(x_1(0))] \leq h \int_0^t E\{V_3(x_1(s)) [r - r\eta x_1(s) - \frac{d_1\tau}{\mu T} + 0.5(h-1)\delta_1^2]\} ds,$$

the derivative of the above formula yields

$$\frac{dE[V_3(x_1(t))]}{dt} \leq hE[V_3(x_1(t))] \left[r - \frac{d_1\tau}{\mu T} + 0.5(h-1)\delta_1^2 \right] - hr\eta E[x_1^{h+1}(t)].$$

Applying the Hölder's inequality results in

$$\frac{dE[V_3(x_1(t))]}{dt} \leq hE[V_3(x_1(t))] \left[r - \frac{d_1\tau}{\mu T} + 0.5(h-1)\delta_1^2 \right] - hr\eta E[x_1^h(t)]^{\frac{h+1}{h}}.$$

Denote $\phi(t) = E[V_3(x_1(t))]$,

$$\begin{aligned} \frac{d\phi(t)}{dt} &\leq h\phi(t) \left[r - \frac{d_1\tau}{\mu T} + 0.5(h-1)\delta_1^2 - hr\eta\phi^{\frac{1}{h}}(t) \right] \\ &\leq h\phi(t) \left[r - \frac{d_1\tau}{\mu T} + 0.5h\delta_1^2 - hr\eta\phi^{\frac{1}{h}}(t) \right]. \end{aligned}$$

It follows from the standard comparison theorem that we have

$$\begin{aligned} \limsup_{t \rightarrow +\infty} E[x_1^h(t)] &= \limsup_{t \rightarrow +\infty} E[V_3(x_1(t))] \\ &= \limsup_{t \rightarrow +\infty} \phi(t) \\ &\leq \left(\frac{r - \frac{d_1\tau}{\mu T} + 0.5h\delta_1^2}{hr\eta} \right)^h. \end{aligned}$$

Because $x(t) = x_1(t)$, thus

$$\begin{aligned} \limsup_{t \rightarrow +\infty} E[x^h(t)] &= \limsup_{t \rightarrow +\infty} E[x_1^h(t)] \\ &\leq \left(\frac{r - \frac{d_1\tau}{\mu T} + 0.5h\delta_1^2}{hr\eta} \right)^h. \end{aligned}$$

Again, the Chebyshev's inequality leads to

$$\liminf_{t \rightarrow +\infty} \mathbb{P}\{x(t) \leq \varrho\} \geq 1 - \varepsilon.$$

In conclusion, in the light of the definitions the tumour cells are stochastically permanent. This completes the proof.

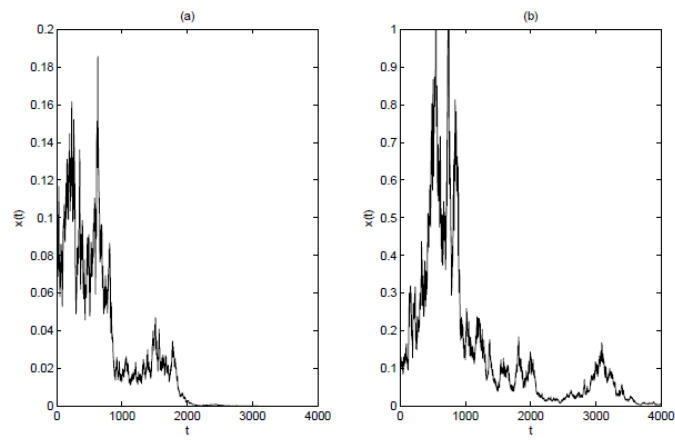


Figure 1: Extinction and weakly persistence of tumours. (a) Time series of tumour cell $x(t)$ with $r = 2$; (b) Time series of tumour cell $x(t)$ with $r = 2.2$. We set initial values as $(x(0), y(0)) = (0.1, 0.5)$ and all other parameters are fixed as: $\eta = 0.002$, $a = 1$, $b = 1.131$, $w = 20.19$, $c = 0.00311$, $d = 0.3$, $\delta_1 = 2$, $\delta_2 = 0.5$, $n = 80$, $T = 50$, $d_1 = d_2 = 0.5$, $\mu = 0.5$, $\tau = 0.2$ and $R(nT) = 0.05$.

5. Numerical results and biological implications

Since we have provided the conditions for the extinction and persistence of tumours, numerical studies will be carried out not only to substantiate theoretical results, but also to show how key parameters affect the evolution of tumours. The baseline parameters of the stochastic system (1.2) in the absence of periodical treatment can be found in the classical paper [13].

5.1. Numerical verifications of theoretical results

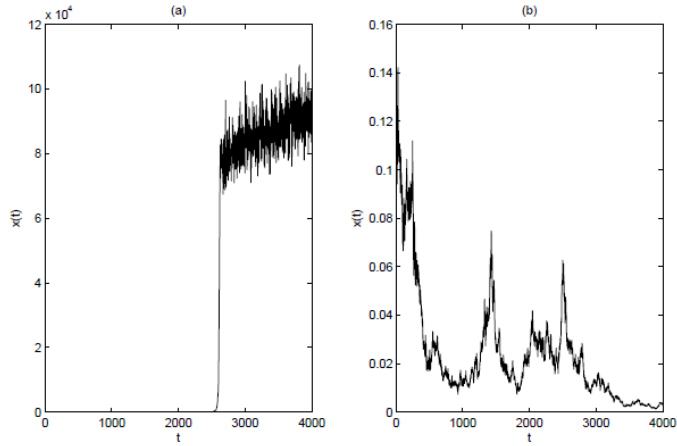


Figure 2: Stochastic persistence of tumours. (a) Time series of tumour cell $x(t)$ with $r = 3$; (b) Time series of tumour cell $x(t)$ with $r = 2$. We set initial values as $(x(0), y(0)) = (0.1, 0.5)$ and all other parameters are fixed as: $\eta = 0.002$, $a = 1$, $b = 1.131$, $w = 20.19$, $c = 0.00311$, $d = 0.3$, $\delta_1 = 1.5$, $\delta_2 = 0.5$, $n = 40$, $T = 100$, $d_1 = d_2 = 0.5$, $\mu = 0.5$, $\tau = 0.2$ and $R(nT) = 0.02$.

Fixed parameter values as shown in Fig.1(a) so that $r < \frac{1}{2}\delta_1^2 + \frac{d_1\tau}{\mu T}$, the tumours go extinct in the presence of pulsed treatment. It suggests to us that by using the stochastic tumour-immune model, periodical applications of immunotherapy and chemotherapy result in the eradication of tumours. However, increasing r such that $r > \frac{1}{2}\delta_1^2 + \frac{d_1\tau}{\mu T}$ and $\lim_{t \rightarrow +\infty} \sup \frac{\sum_{0 < nT < t} \ln(1+b(nT))}{t} < d + \frac{1}{2}\delta_2^2 + \frac{d_2\tau}{\mu T}$, then the tumours become weakly persistent in the mean (Fig.1(b)). Fixed parameters as shown in (Fig.2(a)), then $\Phi = \min_{t \geq 0} [r -$

$\frac{1}{2}\delta_1^2 - \frac{d_1\tau}{\mu T} - aM_1y_0] \approx 0.768 > 0$, it is noticed that the dynamical behaviour of system (1.2) is deeply different from Fig.1(b), the phenomenon of stochastically persistent for tumours can be observed. Otherwise, if we set $r = 2$ such that $\Phi \approx -0.232 < 0$, then the dynamic behavior of tumours changes from stochastically persistent to weak persistent in the mean (Fig.2(b)). These results confirm the correctness of the obtained conditions for the extinction and persistence of tumours.

5.2. The effects of noise on evolution of tumours

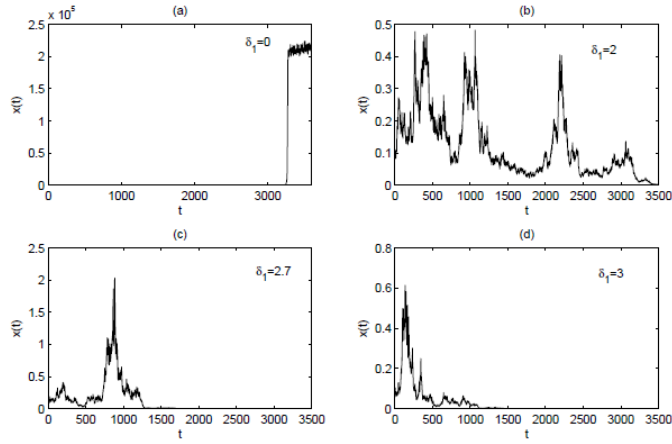


Figure 3: The effects of δ_1 on the evolution of tumours. (a) $\delta_1 = 0$; (b) $\delta_1 = 2$; (c) $\delta_1 = 2.7$; (d) $\delta_1 = 3$. We set initial values as $(x(0), y(0)) = (0.1, 0.5)$ and all other parameters are fixed as: $r = 2.5$, $\eta = 0.002$, $a = 1$, $b = 1.131$, $w = 20.19$, $c = 0.00311$, $d = 0.3$, $\delta_2 = 0.5$, $n = 80$, $T = 50$, $d_1 = d_2 = 0.5$, $\mu = 0.5$, $\tau = 0.2$ and $R(nT) = 0.05$.

Notice that the growth of tumour cells is influenced by many factors such as environmental noise [23, 24]. Inspired by this fact, we will perform a deeper analysis on what changes in the dynamics of tumour cells will be present as the noise term δ_1 changes. To this end, fixed all other parameters as shown in Fig .3 and a series of numerical simulations are carried out by varying δ_1 . When $\delta_1 = 0$, we found recurrence of the tumour cells and finally the tumours become stochastically persistent (Fig .3(a)). As δ_1 increases, the dynamical

behavior of tumours displayed dramatically changes. For example, if we set $\delta_1 = 2$, then the tumours become weak persistent (Fig .3(b)). As δ_1 further increases, the evolution of tumours changes from weak persistent to extinct (Fig .3(c)), and the larger the noise δ_1 , the shorter the extinction time for tumours (Fig .3(c) and Fig .3(d)). The results confirm that noise dominates all possible dynamics of tumours.

5.3. Chemotherapy alone or immunotherapy alone

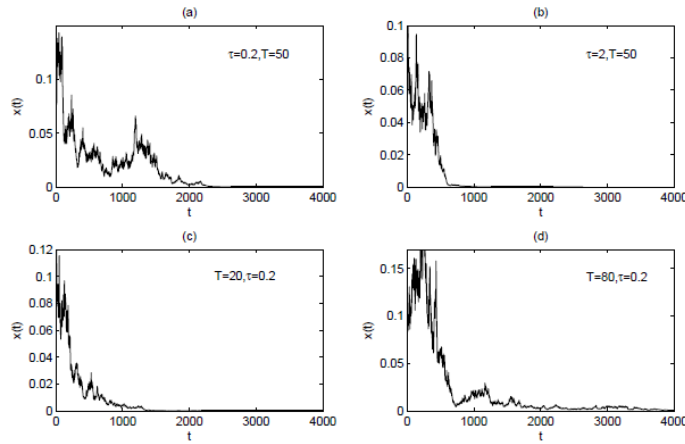


Figure 4: The effects of chemotherapy alone on the evolution of tumours. (a) $\tau = 0.2$ and $T = 50$; (b) $\tau = 2$ and $T = 50$; (c) $\tau = 0.2$ and $T = 20$; (d) $\tau = 0.2$ and $T = 80$. We set initial values as $(x(0), y(0)) = (0.1, 0.5)$ and all other parameters are fixed as: $r = 2.2$, $\eta = 0.002$, $a = 1$, $b = 1.131$, $w = 20.19$, $c = 0.00311$, $d = 0.3$, $\delta_1 = 2$, $\delta_2 = 0.5$, $n = 80$, $d_1 = d_2 = 0.5$, $\mu = 0.5$ and $R(nT) = 0$.

Theoretically, noise can determine all the dynamics of tumours (Fig.3), but in reality the changes in environment are limited so that the noise term is not strong enough to control cancer. Therefore, combinations of chemotherapy and immunotherapy are initiated to suppress the proliferation and mutation of tumours. If only chemotherapy is applied, then the eradication of tumours is observed (Fig.4). The feasible approaches to treat tumours include increasing the doses of chemotherapy (Fig.4 (a) and Fig.4 (b)) or increasing the frequencies of chemotherapy (Fig.4 (c) and Fig.4 (d)). Further,

a therapeutic regimen with smaller dose and more frequent deliveries is more effective (Fig.4 (a) and Fig.4 (c)).

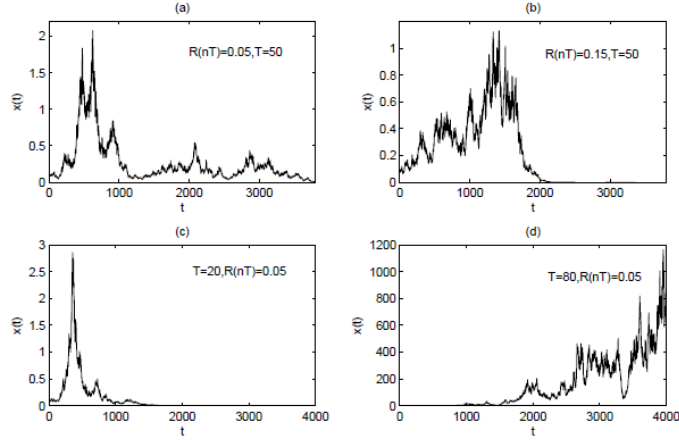


Figure 5: The effects of immunotherapy alone on the evolution of tumours. (a) $R(nT) = 0.05$ and $T = 50$; (b) $R(nT) = 0.15$ and $T = 50$; (c) $T = 20$ and $R(nT) = 0.05$; (d) $T = 80$ and $R(nT) = 0.05$. We set initial values as $(x(0), y(0)) = (0.1, 0.5)$ and all other parameters are fixed as: $r = 2.2$, $\eta = 0.002$, $a = 1$, $b = 1.131$, $w = 20.19$, $c = 0.00311$, $d = 0.3$, $\delta_1 = 2$, $\delta_2 = 0.5$, $n = 80$, $d_1 = d_2 = 0.5$, $\tau = 0$ and $\mu = 0.5$.

If only immunotherapy is initiated, then it is also possible to observe the outcome of the tumour's extinction (Fig. 5). For instance, we can achieve the goal of controlling tumours by increasing the doses of immunotherapy (Fig.5 (a) and Fig.5 (b)) or decreasing the periods of immunotherapy (Fig.5 (c) and Fig.5 (d)). A small increases of doses will result in the rapid eradication of tumours (Fig.5 (a) and Fig.5 (b)). While the effect of decreasing the periods of immunotherapy on treating tumours makes no different from chemotherapy (Fig.4 (c) and Fig.5 (c)).

5.4. Combinations of chemotherapy and immunotherapy

Under certain conditions, periodical applications of immunotherapy alone or chemotherapy alone could result in the eradication of tumours, but these two kinds of treatments have their drawbacks including resistance, toxic reaction and so on [25, 26]. To overcome these, immunotherapy is applied with

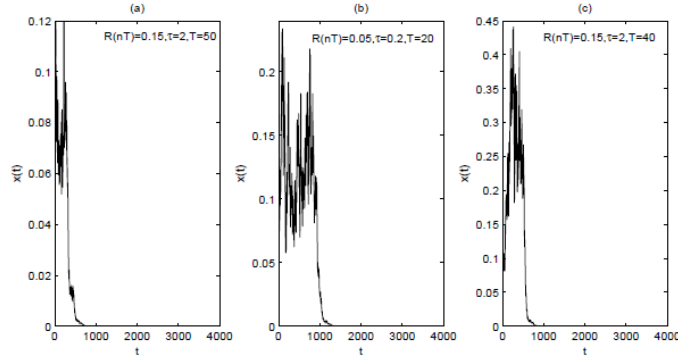


Figure 6: The effects of comprehensive therapy on the evolution of tumours. (a) $R(nT) = 0.15$, $\tau = 2$ and $T = 50$; (b) $R(nT) = 0.05$, $\tau = 0.2$ and $T = 20$; (c) $R(nT) = 0.15$, $\tau = 2$ and $T = 40$. We set initial values as $(x(0), y(0)) = (0.1, 0.5)$ and all other parameters are fixed as: $r = 2.2$, $\eta = 0.002$, $a = 1$, $b = 1.131$, $w = 20.19$, $c = 0.00311$, $d = 0.3$, $\delta_1 = 2$, $\delta_2 = 0.5$, $n = 80$, $d_1 = d_2 = 0.5$ and $\mu = 0.5$.

chemotherapy, such therapy can not only enhance the effect of chemotherapeutic agents, but also kill tumour cells with resistance. Compared to treatments with chemotherapy or immunotherapy alone, the eradication of tumours can be easily observed by applying comprehensive therapy. If we increase the dosages of immunotherapy and immunotherapy (Fig. 6(a)), or decrease the periods of comprehensive therapy (Fig. 6(b)), or increase the dosages and decrease the periods at the same time (Fig. 6(c)), then the tumours are quickly extinct. Compared to Fig. 4 and Fig. 5, we found that small changes in comprehensive therapy could accelerate the eradication of tumours.

From the above analysis, the simulation results can not only substantiate our theoretical works, but also confirm the effectiveness of comprehensive treatments. Biologically, we also study how changes of the key parameters affect the evolution of tumours, which is very helpful for treating cancer.

6. Conclusions

Recently, many works pointed out that the evolution of tumours is inevitably affected by environmental noise [23, 24]. Pulsed comprehensive therapy is one of the feasible methods to treat tumours [12, 18, 19, 30, 31]. Howev-

er, there are few studies about stochastic tumour-immune system with pulsed comprehensive therapy. In this paper, we construct a stochastic tumour-immune system with pulsed therapy to show how environmental noise and pulsed treatment affect the evolution of tumours.

We first study the pharmacokinetics of the chemotherapeutic drug and give the explicit expression of the tumour free solution. Under certain conditions, the solution of system (1.2) is not only unique and globally attractive, but also upper bounded in terms of expectation. It reveals that the tumours can not grow indefinitely when pulsed immunotherapy is introduced. By using theorems of ISDEs, we derive the sufficient conditions for tumours to be extinct, nonpersiste in the mean, weakly persistence in the mean and stochastically permanent almost surely. Then numerical simulations are carried out to confirm the correctness of our results.

Under the influence of environmental noise, biological implications of pulsed comprehensive treatment for the tumours are addressed. we found that large stochastic fluctuations will result in the eradication of tumours and small stochastic fluctuations will lead to stochastic permanence of tumours, and the larger the noise δ_1 , the shorter the time for tumours to be eradicated (Fig.3). In theory, noise can dominate the evolution of tumours. However, in reality, environment noise is usually restricted so that it is not strong enough to control cancer. Therefore, comprehensive therapy is introduced to inhibit proliferation and mutation of tumours. If a single chemotherapy is applied, then the eradication of tumours can be observed by means of increasing the dosages and frequencies of chemotherapy, the results also show that smaller dosages and more frequent deliveries are more effective for curing cancer (Fig. 4). If a single immunotherapy is implemented, then large dosages will result in the rapid eradication of tumours (Fig. 5). Though immunotherapy or chemotherapy alone could result in the eradication of tumours, many disadvantages result from these therapies are inevitable [25, 26]. Thus, the effects of combinations of chemotherapy and immunotherapy on the tumours are investigated. If we increase the dosages of comprehensive therapy, or decrease the periods of combined therapy, or increase the dosages and decrease the periods at the same time (Fig.6), then the eradication of tumours is easier to be observed than a single therapy. It is also concluded that the comprehensive therapy could accelerate the eradication of tumours.

Many interesting topics need to be investigate. For example, system (1.2) is proposed by autonomous differential equations, what happens if we take the nonautonomous case into account [32]? And what role does impulsive

comprehensive therapy play in tumor eradication? It is hoped that such research, planned for the near future and to be reported elsewhere, will be useful for cancer treatment.

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