

Threshold dynamics of a stochastic model of intermittent androgen deprivation therapy for prostate cancer

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Abstract

Intermittent androgen deprivation therapy is often used to treat prostate cancer, but there are few mathematical modelling studies of it. To explore the mechanisms of such therapy, we describe intermittent therapy with impulsive differential equations, then we propose a novel mathematical model of intermittent androgen deprivation therapy with white noise. We first studied the model's basic properties including the existence and uniqueness of the solution. By using the theory of stochastic differential equations, we investigated the thresholds for the extinction and persistence of prostate cancer cells, which are markedly affected by antigenicity of tumours and noise parameters. Moreover, sufficient conditions for the stationary distribution and ergodicity of the system are provided. The results show that reducing the period of pulsed interventions or increasing the dosages (or frequencies) of the therapy will be helpful for curing prostate cancer.

Keywords:

Prostate cancer, Stochastic dynamical model, Threshold dynamics, Stationary distribution

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1. Introduction

Prostate cancer is one of the most common cancers in the world [1], with its incidence ranking second of all male tumours worldwide in the latest survey [2]. The traditional treatment of prostate cancer mainly involves surgery, endocrine therapy and radiotherapy, but as these approaches were not always highly effective, androgen deprivation therapy (ADT) has become adopted in many cases. ADT is usually divided into two types: continuous androgen deprivation (CAD) therapy and intermittent androgen deprivation (IAD) therapy. Although CAD is the best endocrine therapy for advanced prostate cancer but, as the overall survival period can only be prolonged by 3-6 months at most, it is becoming less and less acceptable by patients. Therefore, IAD therapy has been proposed and has recently attracted the attention of the medical community. Serum prostate-specific antigen (PSA) which is produced by cells in the prostate gland is considered to be an important biomarker for detecting prostate cancer [3], with a high level of PSA indicating the presence of malignant tumours. According to their responses to androgen suppression, the tumour cells are divided into androgen dependent cells (AD) and androgen independent cells (AI). Many patients who have received CAD later suffered from tumour recurrence caused by emergence of AI cells [4].

Mathematically, IAD therapy was first proposed to prevent AI cells [5–7], and then IAD was studied to detect its therapeutic effect [8–10]. The results showed that IAD therapy not only improved the quality of a patient’s life, but also reduced adverse effects such as sexual dysfunction, osteoporosis and hot flushes during treatment. Ideta et. al. established an ordinary differential equation mathematical system to model the growth of prostate cancer with IAD therapy [11]. Their model fitted the concentration of androgen and the growth curves of AD and AI cells well, and mutation rates from AD to AI were also studied. Portz and Kuang then extended the previous studies by incorporating CAD therapy and immunotherapy into a model for advanced prostate cancer [12]. They pointed out that immunotherapy together with CAD therapy or IAD therapy can lead to eradication of cancer. Moreover, Rutter and Kuang later developed the model by taking the mutation of biphasic function into account [13], the global dynamics were investigated and the efficacy of of hormonal immunotherapy was discussed.

The above studies mainly focused on deterministic models [11–13], but all living organisms are influenced by environmental disturbances, such as tem-

perature, radiation, oxygen supply and nutrients, and cancer is no exception [14, 15], so a stochastic approach is more realistic. Tanaka and co-authors proposed a stochastic mathematical model concerning intermittent hormone therapy [4] and they not only considered personalized hormone therapy but also discussed optimal scheduling of hormone therapy. Zazoua and Wang considered different competition coefficients between AD and AI, established a mathematical model concerning CAD therapy with white noise, and focused on the effects of white noise and competition parameters on the dynamics of prostate cancer [16, 17].

In the above analyses, piece-wise functions were used to describe the I-AD therapy although details of how its dosage, period and frequency and of immunotherapy affect prostate cancer are still unknown. To investigate further we adopted Impulsive Differential Equations, widely used in many fields [18, 19], to describe IAD therapy, with which we can precisely adjust the concentration of androgen. For simplicity, we do not distinguish the types of prostate cancer cells, that is, we consider combinations of AD and AI cells as cancer cells. Since the antigenicity of the tumour always exists during the whole invasion process, pulsed immunotherapy and the antigenicity of the prostate cancer cells are also explored. Therefore, we develop a novel stochastic mathematical model concerning impulsive IAD therapy and immunotherapy, to answer the following questions: (1) How do the periods, dosages and frequencies of pulsed therapy affect the thresholds for extinction of prostate cancer cells? (2) When pulsed IAD therapy is considered, does the proposed system exist with an ergodic stationary distribution? (3) How can an optimal treatment scheme for prostate cancer be determined? The solutions to these problems would not only provide theoretical significance for cancer medication strategy, but also provide guidance for the treatment of other cancers.

The paper is divided into the following parts. In section 2, the model will be proposed and some important definitions and lemmas are introduced. In section 3, the main results are derived including the existence and uniqueness of the solution and the extinction and persistence of the solution. In section 4, we discuss the existence of the unique ergodic stationary distribution of the system. In section 5, numerical simulations are performed and the optimal treatment plan is obtained.

2. Model formation and preliminaries

2.1. Model formation

Recently, Ideta and co-authors proposed a mathematical model to explore the differences between CAD and IAD therapy, they also studied the effects of key factors on the androgen-independent relapse [11], the model can be described by the following equations,

$$\begin{cases} dA = \{-\gamma(A - a_0) - \gamma a_0 u(t)\}dt, \\ dX_1 = \{\alpha_1 p_1(A) - \beta_1 q_1(A) - m_1(A)\}X_1 dt, \\ dX_2 = \{m_1(A)X_1 + [\alpha_2 p_2(A) - \beta_2 q_2(A)]X_2\}dt, \end{cases} \quad (2.1)$$

where A is the serum androgen concentration, X_1 and X_2 represent the AD and AI cells at time t , respectively. γ is the clearance and production rate of androgen, a_0 represents the basic level of androgen concentration. $\alpha_1 p_1$ and $\beta_1 q_1$ are the proliferation and apoptosis rates of the AD cells, respectively. $\alpha_2 p_2$ and $\beta_2 q_2$ are the proliferation and apoptosis rates of the AI cells, respectively. m_1 is the irreversible mutation rate from AD to AI cells, and $u(t)$ is either 0 (if treatment off) or 1 (if treatment on).

In order to reduce the recurrence of the tumours and increase the survival rate of patients, immunotherapy was introduced for the treatment of the prostate cancer. Since dendritic cells are the most robust antigen-presenting cells and are capable of producing immature T cells to induce tumour immune responses, the dendritic cell vaccines are considered to be promising candidates for the treatment of cancer [20]. Notice that IL-2 is an important cytokine involved in the immune response. In fact, it can not only enhance the killing activity of the effector cells by enhancing dendritic cells, but also improve the efficacy of immunotherapy. Therefore, Rutter and Kuang extended system (2.1) by incorporating ADT (intermittent and continual) and dendritic cell vaccine immunotherapy into the model [13], which is described

as follows,

$$\left\{ \begin{array}{l} dX_1 = \{r_1(A, X_1, X_2)X_1 - m_1(A)X_1 + m_2(A)X_2 - X_1f_1(X_1, X_2, E)\}dt, \\ dX_2 = \{r_2(X_1, X_2)X_2 + m_1(A)X_1 - m_2(A)X_2 - X_2f_2(X_1, X_2, E)\}dt, \\ dE = \left\{ \frac{eD}{g + D} - \mu E + Ef_3(I_L, E) \right\}dt, \\ dI_L = \{Ef_4(X_1, X_2) - \omega I_L\}dt, \\ dA = \{\gamma(a_0 - A) - \gamma a_0 u(t)\}dt, \\ dD = -cDdt, \end{array} \right. \quad (2.2)$$

where E and I_L are the effector cells (such as cytotoxic T-cells, macrophages, and natural killer cells) and the concentration of IL-2, respectively. D is the number of dendritic cells. $r_1(A, X_1, X_2)X_1$ and $r_2(X_1, X_2)X_2$ are the growth and death rates of AD and AI cells. $m_1(A)X_1$ and $m_2(A)X_2$ represent the maximum mutation rates from AD to AI cells and from AI to AD cells. $f_1(X_1, X_2, E)$ and $f_2(X_1, X_2, E)$ are the death rates of AD and AI cells by E cells. $Ef_3(I_L, E)$ and $Ef_4(X_1, X_2)$ represent the activation of E cells by cytokines and the secretion by tumours, respectively. Besides, e is the max activation rate of E cells, g is the saturation level of dendritic cells activated by E cells. μ and c are the death rates of effector cells and the dendritic cells, respectively. ω denotes the clearance rate of IL-2. The effects of IL-2, ADT and dendritic cell vaccine immunotherapy on the AD to AI cells are discussed [13].

In the above analyses, IAD therapy was usually described by using a piecewise function, but the details of its dosages, period and frequencies, and how immunotherapy affects prostate cancer are still unclear. To explore these characteristics, the introduction of pulse therapy is meaningful. Since the antigenicity of the tumour remains throughout the invasion, the antigenicity of prostate cancer cells should be considered. For simplicity, we do not distinguish between the types of prostate cancer cells and ignore the term for cytokines (IL-2). Then impulsive differential equations are used to describe the IAD therapy and we take pulsed immunotherapy and the antigenicity of the prostate cancer cells into consideration [11, 13, 16, 21].

In reality, the growth rate rA and the antigenicity C are subjected to stochastic perturbations around some average value. Thus, rA and C can be random variables $\tilde{r}A$ and \tilde{C} , in $[t, t+dt)$, we have $\tilde{r}Adt = rAdt + \delta_1(X)dB_1(t)$

and $\tilde{C}dt = Cdt + \delta_2(E)dB_2(t)$, where $dB_i(t) = B_i(t+dt) - B_i(t)$ denotes the increment of a standard Brownian motion, but we still use the notations of rA and C instead of $r\tilde{A}$ and \tilde{C} for simplicity. Base on [11, 13], let X be the prostate cancer cells. All these modifications lead to the following extended model,

$$\left. \begin{cases} dX = [rA(1 - \frac{X}{K}) - d(1 - \frac{A}{a_0}) - \frac{aE}{g_1 + X}]Xdt + \delta_1XdB_1(t), \\ dE = [CE + \frac{eD}{g_2 + D} - \mu E]dt + \delta_2EdB_2(t), \\ \frac{dA}{dt} = -\gamma(A - a_0), \\ \frac{dD}{dt} = -cD, \\ A(nT^+) = (1 - \delta)A(nT), \\ D(nT^+) = D(nT) + \tau, \end{cases} \right\} \begin{array}{l} t \neq nT, \\ t = nT, \end{array} \quad (2.3)$$

where, r and d denote the growth rate and death rate of prostate cancer cells, respectively. K is the carrying capacity of these cells, a is the maximum killing rate of the effector cells, g_1 and g_2 are saturation constants of prostate cancer cells and dendritic cells, respectively, δ_1 and δ_2 denote the intensities of the white noise influencing X and E , respectively. δ is the treatment intensity of IAD, τ is the pulse injection dosage of dendritic cells at impulsive point series nT ($n = 1, 2, 3, \dots$), and we keep the meaning of other parameters consistent with (2.1) and (2.2). In addition, note that all the parameters in (2.1)-(2.3) are positive.

Moreover, the dynamics of the ADT and immunotherapeutic drugs are given by

$$\left. \begin{cases} \frac{dA}{dt} = -\gamma(A - a_0), \\ \frac{dD}{dt} = -cD, \\ A(nT^+) = (1 - \delta)A(nT), \\ D(nT^+) = D(nT) + \tau, \end{cases} \right\} \begin{array}{l} t \neq nT, \\ t = nT. \end{array}$$

By a simple calculation, we can derive the expression of the T periodic solu-

tion $A^T(t)$ and $D^T(t)$ of (2.3) with

$$\begin{cases} A^T(t) = a_0 - \frac{a_0 \delta e^{-\gamma(t-nT)}}{1 - (1-\delta)e^{-\gamma T}}, \\ D^T(t) = \frac{\tau e^{-c(t-nT)}}{1 - e^{-cT}}. \end{cases}$$

Replace A and D with $A^T(t)$ and $D^T(t)$, then we get the reduced system of system (2.3),

$$\begin{cases} dX = [rA^T(t)(1 - \frac{X}{K}) - d(1 - \frac{A^T(t)}{a_0}) - \frac{aE}{g_1 + X}]X dt + \delta_1 X dB_1(t), \\ dE = [CE + \frac{eD^T(t)}{g_2 + D^T(t)} - \mu E]dt + \delta_2 E dB_2(t). \end{cases} \quad (2.4)$$

Now, we will focus on the global dynamics of equivalent system (2.4). To this end, some important definitions and lemmas will be introduced first.

2.2. Preliminaries

Assume that $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t \geq 0}, \mathcal{P})$ is a complete probability space which has a filtration $\{\mathcal{F}_t\}_{t \geq 0}$, and it is right continuous and \mathcal{F}_0 contains all P -null sets. In this probability space, we define $B_i(t) (i = 1, \dots, n)$ as an independent Brownian motion. If the number of factors in a product is zero, then we assume that the product is equal to unity. Based on these assumptions, we introduce some useful definitions and lemmas [12].

Definition 2.1. For any $\varepsilon \in (0, 1)$, if there is a positive constant H such that any positive solution $Y(t) = (x(t), y(t))$ satisfies

$$\limsup_{t \rightarrow \infty} P\{|Y(t)| > H\} < \varepsilon,$$

then the positive solutions of system (2.4) are said to be stochastically ultimately bounded.

Definition 2.2. For any two solutions $X_1(t) = (x_1(t), y_1(t))$ and $X_2(t) = (x_2(t), y_2(t))$ of system (2.4) with $X_1(0) > 0, X_2(0) > 0$, system (2.4) is called globally attractive provided that

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

Lemma 2.3. Suppose that $N = \{N(t)\}_{t \geq 0}$ is a real-valued continuous local martingale vanishing at time zero. If

$$\limsup_{t \rightarrow \infty} \frac{\langle N, N \rangle_t}{t} < \infty \quad a.s.$$

then

$$\lim_{t \rightarrow \infty} \frac{N_t}{t} = 0 \quad a.s.$$

For simplicity, we introduce the following notation for any integrable function $x(t)$ on $[0, \infty)$, $\langle x \rangle_t = 1/t \int_0^t x(s) ds$ for $t > 0$, $\langle x \rangle^* = \limsup_{t \rightarrow \infty} 1/t \int_0^t x(s) ds$, and $\langle x \rangle_* = \liminf_{t \rightarrow \infty} 1/t \int_0^t x(s) ds$.

Definition 2.4. The solution $Y_i(t)$ is said to be extinctive if $\lim_{t \rightarrow \infty} Y_i(t) = 0$; and $Y_i(t)$ is said to be persistent in mean if $\langle Y_i(t) \rangle^* > 0$.

Definition 2.5. ([22, 23]). Let $Y(t) = (x(t), y(t))$ be a solution of system (2.4), if for any $\varepsilon \in (0, 1)$, there exist two positive constants $\beta > 0$ and $\delta > 0$ such that

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

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

Remark 1. Biologically, the definitions of extinction, weak persistence and stochastic permanence correspond to the phases of elimination, equilibrium and escape, respectively, which are just three phases of cancer immunoediting.

3. Analysis of stochastic system (2.4)

3.1. Existence and uniqueness of the solution

For simplicity, we denote $P_1 = rA^T(t) = ra_0 - \frac{ra_0\delta e^{-\gamma(t-nT)}}{1-(1-\delta)e^{-\gamma T}}$, $Q_1 = d(1 - \frac{A^T(t)}{a_0})$ and $S_1 = \frac{eD^T(t)}{g_2 + D^T(t)}$, then the system (2.4) can be simplified as

$$\begin{cases} dX = [P_1(1 - \frac{X}{K}) - Q_1 - \frac{aE}{g_1 + X}]X dt + \delta_1 X dB_1(t), \\ dE = [(C - \mu)E + S_1]dt + \delta_2 E dB_2(t). \end{cases} \quad (3.1)$$

Lemma 3.1. ([16, 24, 25]). For $(X(0), E(0)) \in \text{Int}\mathbb{R}_+^2$ and all $t \geq 0$, there exists with a unique positive solution $Y(t) = (X(t), E(t))$ for system (3.1) almost certainly.

Proof. The coefficients of system (3.1) are subjected to the local Lipschitz condition, then system (3.1) has a unique positive local solution. Then we want to show that the solution is global. Firstly, the process of the solution does not explode in finite time, defining the stopping times:

$$\tau_k = \inf \left\{ t \geq 0, \quad X(t) \notin \left(\frac{1}{k}, k\right) \quad \text{or} \quad E(t) \notin \left(\frac{1}{k}, k\right) \right\},$$

we just need to prove that $\tau_\infty = \lim_{k \rightarrow \infty} \tau_k = \infty$, where τ_∞ is the explosion time. Defining a C^2 -function $V : \text{Int}\mathbb{R}_+^2 \rightarrow \mathbb{R}_+$ as follows

$$V(X, E) = X - 1 - \ln X + E - 1 - \ln E.$$

By using Itô's formula,

$$dV = LVdt + \delta_1(X - 1)dB_1(t) + \delta_2(E - 1)dB_2(t),$$

where

$$\begin{aligned} LV &= (X - 1)\left(P_1\left(1 - \frac{X}{K}\right) - Q_1 - \frac{aE}{g_1 + X}\right) + (E - 1)(C - \mu) \\ &\quad + S_1 - \frac{S_1}{E} + \frac{1}{2}\delta_1^2 + \frac{1}{2}\delta_2^2 \\ &= (X - 1)\left(P_1\left(1 - \frac{X}{K}\right) - Q_1 - \frac{aE}{g_1 + X}\right) + CE + S_1 + \mu \\ &\quad - \mu E - C - \frac{S_1}{E} + \frac{1}{2}\delta_1^2 + \frac{1}{2}\delta_2^2. \end{aligned}$$

Furthermore,

$$\begin{aligned} LV &\leq -\frac{P_1 X^2}{K} + P_1\left(1 + \frac{1}{K}\right)X + Q_1 + \mu + S_1 \\ &\quad - \frac{(\mu - C - \frac{a}{g_1})E^2 + S_1}{E} + \frac{1}{2}\delta_1^2 + \frac{1}{2}\delta_2^2, \end{aligned}$$

It is easy to see that when $\mu - C - a/g_1 > 0$, and the right-hand side of the above inequality can be regarded as two quadratic functions with negative leading coefficients to judge the boundedness of LV . In terms of the extremum conditions of quadratic functions, LV is upper bounded. Then

$$LV \leq M,$$

where M is a positive constant. Then by a similar proof of Theorem 2.1 in literature [25] we can get the conclusion. This completes the proof.

Theorem 3.2. ([16, 26]). The positive solution $Y(t) = (X(t), E(t))$ of system (3.1) is stochastically ultimately bounded.

Proof. Let $V(t, X) = e^t X^p$ ($p > 1$). By using Itô's formula,

$$\begin{aligned}
dV(X) &= e^t \left(1 + p \left(P_1 \left(1 - \frac{X}{K} \right) - Q_1 - \frac{aE}{g_1 + X} + \frac{p-1}{2} \delta_1^2 \right) \right) X^p dt \\
&\quad + p e^t \delta_1 X^p dB_1(t) \\
&\leq e^t \left\{ \left(1 + p \left(P_1 + \frac{p-1}{2} \delta_1^2 \right) \right) X^p - p \frac{P_1}{K} X^{p+1} - \frac{paE}{g_1 + X} X^p \right\} dt \\
&\quad + p e^t \delta_1 X^p dB_1(t) \\
&= e^t X^{p-1} \left\{ \left(1 + p \left(P_1 + \frac{p-1}{2} \delta_1^2 \right) \right) X - p \frac{P_1}{K} X^2 - \frac{paEX}{g_1 + X} \right\} dt \\
&\quad + p e^t \delta_1 X^p dB_1(t) \\
&\leq M_1 e^t dt + p e^t \delta_1 X^p dB_1(t),
\end{aligned}$$

due to $-(paEX)/(g_1 + X) \leq 0$ and the maximum conditions for quadratic functions, we can get that M_1 is a positive constant. Integrating the above inequality from 0 to t and then the expectation of both sides leads to

$$E[e^t X^p(t)] \leq X^p(0) + M_1(e^t - 1).$$

Thus,

$$E[X^p(t)] \leq X^p(0)e^{-t} + M_1(1 - e^{-t}).$$

As a result,

$$\limsup_{t \rightarrow +\infty} E[X^p(t)] \leq M_1. \quad (3.2)$$

Similarly,

$$\begin{aligned}
dV(e^t E^p) &= e^t \left[1 + p \left(C - \mu + \frac{S_1}{E} + \frac{p-1}{2} \delta_2^2 \right) \right] E^p dt \\
&\quad + p e^t \delta_2 E^p dB_2(t) \\
&\leq e^t \left[1 + p \left(C + \frac{S_1}{E} + \frac{p-1}{2} \delta_2^2 \right) \right] E^p dt \\
&\quad + p e^t \delta_2 E^p dB_2(t) \\
&\leq M_2 e^t dt + p e^t \delta_2 E^p dB_2(t).
\end{aligned}$$

Using the same method as above,

$$\limsup_{t \rightarrow +\infty} E[E^p(t)] \leq M_2. \quad (3.3)$$

By a similar proof of Theorem 4.5 in literature [16], it follows from (3.2) and (3.3) that

$$\limsup_{t \rightarrow +\infty} E(|Y|^p) \leq 2^{p/2}[M_1 + M_2] < \infty.$$

The Chebychev's inequality gives rise to the desired result. The proof is completed.

Theorem 3.3. The solution of system (3.1) is globally attractive.

Proof. Assume that $(X_1(t), E_1(t))$ and $(X_2(t), E_2(t))$ be any two solutions of system (3.1) with initial values $X_1(0) > 0$, $E_1(0) > 0$, $X_2(0) > 0$ and $E_2(0) > 0$. In terms of Theorem 3.2, there exist three constants $M_3 > 0$, $c_1 > 0$ and $c_2 > 0$ such that $M_3 \geq X$, $M_3 \geq E$ hold almost surely, and we assume that $M_3 = c_1 X = c_2 E$. Defining the Lyapunov function as follows:

$$V(t) = |\ln X_1(t) - \ln X_2(t)| + |\ln E_1(t) - \ln E_2(t)|,$$

where $t > 0$ and $t \neq nT$. First of all, we calculate the upper right derivative $d^+V(t)$ of $V(t)$ and then an application of Itô's formula along the solutions

of system (3.1) leads to

$$\begin{aligned}
d^+V(t) &= \text{sign}(X_1(t) - X_2(t))d(\ln X_1(t) - \ln X_2(t)) \\
&\quad + \text{sign}(E_1(t) - E_2(t))d(\ln E_1(t) - \ln E_2(t)) \\
&\leq \text{sign}(X_1(t) - X_2(t))\left[-\frac{P_1}{K}(X_1(t) - X_2(t))\right. \\
&\quad \left.- \frac{a(E_1(t) - E_2(t))}{g_1 + M_3}\right]dt \\
&= \text{sign}(X_1(t) - X_2(t))\left[-\frac{P_1}{K}(X_1(t) - X_2(t))\right. \\
&\quad \left.- \frac{\frac{a}{g_1}(E_1(t) - E_2(t))}{(1 + \frac{c_2}{g_1}E_1(t))(1 + \frac{c_2}{g_1}E_2(t))}\right]dt \\
&\leq \text{sign}(X_1(t) - X_2(t))\left[-\frac{P_1}{K}(X_1(t) - X_2(t))\right. \\
&\quad \left.- \frac{\frac{a}{g_1}(E_1(t) - E_2(t))}{(1 + \frac{c_2}{g_1}M_3)^2}\right]dt \\
&= \left[-\frac{P_1}{K} | X_1(t) - X_2(t) | - \frac{\frac{a}{g_1}}{(1 + \frac{c_2}{g_1}M_3)^2} | E_1(t) - E_2(t) | \right]dt \\
&\leq -\rho(| X_1(t) - X_2(t) | + | E_1(t) - E_2(t) |)dt \\
&\doteq -\rho\mathbb{V}(t)dt,
\end{aligned} \tag{3.4}$$

where $\rho = \min\{P_1/K, (\frac{a}{g_1})/(1 + \frac{c_2}{g_1}M_3)^2\}$. Secondly, for $t = nT$ we have

$$\begin{aligned}
V(nT^+) &= | \ln X_1(nT^+) - \ln X_2(nT^+) | + | \ln E_1(nT^+) - \ln E_2(nT^+) | \\
&= | \ln X_1(nT) - \ln X_2(nT) | + | \ln E_1(nT) - \ln E_2(nT) | \\
&= V(nT).
\end{aligned}$$

From 0 to t , we integrate equation (3.4) and then take the expectation of both sides,

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

Hence,

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

In addition, $V(t) > 0$ is always valid which gives rise to $\lim_{t \rightarrow +\infty} \mathbb{V}(t) = 0$. That is to say,

$$\lim_{t \rightarrow \infty} | X_1(t) - X_2(t) | = 0 \quad \text{and} \quad \lim_{t \rightarrow \infty} | E_1(t) - E_2(t) | = 0.$$

This completes the proof.

3.2. Extinction and persistence in mean

Since we have studied the existence, uniqueness, global attractivity and stochastic ultimate boundedness of solutions of (3.1), in the following, the threshold conditions for the extinction and persistence of prostate cancer cells will be investigated which are important in their treatment.

Theorem 3.4. (i) If

$$P_1 - Q_1 - \frac{\delta_1^2}{2} < 0, \quad (3.5)$$

then prostate cancer cells X go to extinction.

(ii) If

$$C - \mu < \frac{1}{2}\delta_2^2 \quad \text{and} \quad P_1 - Q_1 - \frac{\delta_1^2}{2} > 0, \quad (3.6)$$

then prostate cancer cells X are persistent in the mean.

Proof. (i) For the positive solution of (2.4), we get

$$dX(t) \leq (P_1 - Q_1 - \frac{P_1}{K}X)Xdt + \delta_1XdB_1(t).$$

Let $\varphi(t)$ be the solution of

$$d\varphi(t) = (P_1 - Q_1 - \frac{P_1}{K}\varphi)\varphi dt + \delta_1\varphi dB_1(t), \quad \text{for all } t \geq 0,$$

with the initial value $\varphi(0) = X(0) > 0$. The comparison principle of stochastic differential equations [27] yields

$$X(t) \leq \varphi(t) \quad \text{for all } t \geq 0.$$

Applying the same methods as shown in [28, 29], we get

$$\lim_{t \rightarrow +\infty} \varphi(t) = 0 \quad a.s.$$

Therefore,

$$\lim_{t \rightarrow +\infty} X(t) = 0 \quad a.s.$$

That is to say, $P(\bar{\Omega}) = 1$ where

$$\bar{\Omega} = \{\omega \in \Omega : \lim_{t \rightarrow +\infty} X(\omega, t) = 0\}.$$

Consequently, for any $\omega \in \bar{\Omega}$ and any small $\epsilon > 0$, there exists a constant $T_2(\omega, \epsilon) > 0$ such that

$$X(\omega, t) < \epsilon \quad \text{for } t \geq T_2. \quad (3.7)$$

(ii) According to Lemma 3.1, $E(t) \geq 0$, for the positive solution of (2.4), one can see that

$$dE \leq [(C - \mu)E + S_1]Edt + \delta_2 EdB_2(t), \quad \text{for all } t \geq 0.$$

Let $\psi(t)$ be the solution of

$$d\psi(t) = [(C - \mu)\psi + S_1]\psi dt + \delta_2 \psi dB_2(t),$$

with the initial value $\psi(0) = E(0)$. Similarly,

$$E(t) \leq \psi(t) \quad \text{for all } t \geq 0.$$

Then

$$\lim_{t \rightarrow +\infty} \psi(t) = 0 \quad a.s.$$

Therefore,

$$\lim_{t \rightarrow +\infty} E(t) = 0 \quad a.s.$$

In other words, $P(\bar{\Theta}) = 1$ where

$$\bar{\Theta} = \{\omega \in \Theta : \lim_{t \rightarrow +\infty} E(\omega, t) = 0\}.$$

Thus, for any $\omega \in \bar{\Theta}$ and any small $\varepsilon > 0$, there exists a constant $T_3(\omega, \varepsilon) > 0$ such that

$$E(\omega, t) < \varepsilon \quad \text{for } t \geq T_3. \quad (3.8)$$

Let us consider the case that under (3.6), the inequality (3.8) conforms to $0 < \varepsilon < g_1(P_1 - Q_1 - \delta_1^2/2)/a$. As a consequence, for $t \geq T_3$ and $\omega \in \bar{\Theta}$, we have

$$dX(\omega, t) \geq [P_1 - Q_1 - \frac{a\varepsilon}{g_1} - \frac{P_1}{K}X]X(\omega, t)dt + \delta_1 X(\omega, t)dB_1(\omega, t).$$

Suppose φ be the solution of

$$d\varphi(t) = [P_1 - Q_1 - \frac{a\varepsilon}{g_1} - \frac{P_1}{K}\varphi]\varphi dt + \delta_1\varphi dB_1(\omega, t),$$

with the initial value $\varphi(0) = X(0)$. Hence,

$$\lim_{t \rightarrow +\infty} \frac{1}{t} \int_0^t \varphi(s) ds = \frac{K}{P_1} (P_1 - Q_1 - \frac{a\varepsilon}{g_1} - \frac{\delta_1^2}{2}) > 0.$$

With an application of the comparison principle, we have

$$\limsup_{t \rightarrow +\infty} \frac{1}{t} \int_0^t X(s, \omega) ds \geq \frac{K}{P_1} (P_1 - Q_1 - \frac{a\varepsilon}{g_1} - \frac{\delta_1^2}{2}) > 0 \quad \text{for all } \omega \in \bar{\Theta}.$$

Recalling that $P(\bar{\Theta}) = 1$, we obtain

$$\limsup_{t \rightarrow +\infty} \frac{1}{t} \int_0^t X(s) ds \geq \frac{K}{P_1} (P_1 - Q_1 - \frac{a\varepsilon}{g_1} - \frac{\delta_1^2}{2}) > 0 \quad a.s.$$

which is the required assertion. This completes the proof.

3.3. Stochastic permanence

Since X and E are stochastic ultimately bounded and the duration of pulse therapy throughout the treatment phase is limited, we can make the following assumptions.

Assumption 1. Theorem 3.2 shows that X and E are always bounded, and that there exist two positive constants J_1 and J_2 , such that $0 \leq X \leq J_1$ and $0 \leq E \leq J_2$. Therefore, there exist four positive constants $n_1 = 0$, $N_1 = J_1/K$, $n_2 = 0$, $N_2 = J_2/g_1$ such that $n_1 \leq X/K \leq N_1$ and $n_2 \leq E/(g_1 + X) \leq E/g_1 \leq N_2$.

Theorem 3.5. Under assumption 1, if $\tau = \min_{t \geq 0} [P_1 - Q_1 - \frac{1}{2}\delta_1^2 - aN_2] > 0$, then the prostate cancer cells are stochastically permanent.

Proof. We need to prove that there are two constants $\beta > 0$ and $\varrho > 0$ such that $\liminf_{t \rightarrow +\infty} \mathbb{P}\{X(t) \geq \beta\} \geq 1 - \varepsilon$ and $\liminf_{t \rightarrow +\infty} \mathbb{P}\{X(t) \leq \varrho\} \geq 1 - \varepsilon$ for any $\varepsilon \in (0, 1)$.

For the first inequality, define a Lyapunov function $V^1(x) = 1/X$ ($X > 0$), by using Itô's formula along the first equation of system (3.1), we get

$$\begin{aligned}
dV^1(X) &= -\frac{dX}{X^2} + \frac{dX^2}{X^3} \\
&= -\frac{1}{X} \left\{ [P_1(1 - \frac{X}{K}) - Q_1 - \frac{aE}{g_1 + X}] \right. \\
&\quad \left. + \delta_1 dB_1(t) \right\} + \frac{1}{X} \delta_1^2 dt \\
&= -V^1(X) \left(P_1 - Q_1 - \frac{P_1 X}{K} - \frac{aE}{g_1 + X} \right) dt + V^1(X) \delta_1^2 dt \\
&\quad - V^1(X) \delta_1 dB_1(t).
\end{aligned}$$

Then selecting a positive constant v such that $\tau > 0.5v\delta_1^2$. Define another Lyapunov function $V^2(X) = (1 + V^1(X))^v$, then application of Itô's formula leads to

$$\begin{aligned}
dV^2(X) &= v(1 + V^1(X))^{v-1} dV^1(X) + 0.5v(v-1)(1 + V^1(X))^{v-2} (dV^1(X))^2 \\
&= v(1 + V^1(X))^{v-2} \left\{ (-V^1(X) - (V^1(X))^2) [P_1 - Q_1 - \frac{P_1 X}{K} - \frac{aE}{g_1 + X}] \right. \\
&\quad \left. + (V^1(X) + (V^1(X))^2) \delta_1^2 + 0.5(v-1)(V^1(X))^2 \delta_1^2 \right\} dt \\
&\quad - v(1 + V^1(X))^{v-1} V^1(X) \delta_1 dB_1(t) \\
&= v(1 + V^1(X))^{v-2} \left\{ -(V^1(X))^2 [P_1 - Q_1 - \frac{aE}{g_1 + X} - 0.5\delta_1^2 - 0.5v\delta_1^2] \right. \\
&\quad \left. + V^1(X) \left\{ -(P_1 - Q_1 - \frac{P_1 X}{K} - \frac{aE}{g_1 + X}) + \delta_1^2 \right\} + \frac{P_1 X}{K} \right\} dt \\
&\quad - v(1 + V^1(X))^{v-1} V^1(X) \delta_1 dB_1(t) \\
&\leq v(1 + V^1(X))^{v-2} \left\{ -(V^1(X))^2 [\tau - 0.5v\delta_1^2] \right. \\
&\quad \left. + V^1(X) [Q_1 + \frac{P_1 N_1}{K} + aN_2 + \delta_1^2] + \frac{P_1 N_1}{K} \right\} dt \\
&\quad - v(1 + V^1(X))^{v-1} V^1(X) \delta_1 dB_1(t).
\end{aligned}$$

Further, we choose a sufficiently small ϵ which satisfies

$$\tau - 0.5v\delta_1^2 > \frac{\epsilon}{v} > 0. \quad (3.9)$$

Then define a Lyapunov function $V^3(X) = \exp(\epsilon t)V^2(X)$, and then Itô's

formula results in

$$\begin{aligned}
dV^3(X) &= \epsilon \exp(\epsilon t) V^2(X) dt + \exp(\epsilon t) dV^2(X) \\
&\leq v \exp(\epsilon t) (1 + V^1(X))^{v-2} \left\{ \frac{\epsilon(1+V^1(X))^2}{v} - (V^1(X))^2 [\tau - 0.5v\delta_1^2] \right. \\
&\quad \left. + V^1(X) [Q_1 + \frac{P_1 N_1}{K} + aN_2 + \delta_1^2] + \frac{P_1 N_1}{K} \right\} dt \\
&\quad - v \exp(\epsilon t) (1 + V^1(X))^{v-1} V^1(X) \delta_1 dB_1(t) \\
&\doteq \exp(\epsilon t) h(X) dt - v \exp(\epsilon t) (1 + V^1(X))^{v-1} V^1(X) \delta_1 dB_1(t),
\end{aligned}$$

where

$$\begin{aligned}
h(X) &= v(1 + V^1(X))^{v-2} \left\{ -[\tau - 0.5v\delta_1^2 - \frac{\epsilon}{v}] (V^1(X))^2 \right. \\
&\quad \left. + [Q_1 + \frac{P_1 N_1}{K} + aN_2 + \delta_1^2 + \frac{2\epsilon}{v}] V^1(X) + \frac{P_1 N_1}{K} + \frac{\epsilon}{v} \right\}.
\end{aligned}$$

Let $B_1 = \tau - 0.5v\delta_1^2 - \epsilon/v$, $B_2 = Q_1 + P_1 N_1/K + aN_2 + \delta_1^2 + 2\epsilon/v$ and $B_3 = P_1 N_1/K + \epsilon/v$. Because all parameters are positive, then $B_1 > 0$, $B_2 > 0$ and $B_3 > 0$ and (3.9) holds true. Therefore, $h(X)$ can be rewritten as

$$h(X) = v(1 + \frac{1}{X})^{v-2} \left\{ -\frac{B_1}{X^2} + \frac{B_2}{X} + B_3 \right\} \doteq h_1(X).$$

It is clear that $h(X)$ is upper bounded when $X > 0$. If $1/X \geq \{B_2 + \sqrt{B_2^2 + 4B_1 B_3}\}/2B_1 \doteq \Delta_1$, then $h_1(X) \leq 0$. If $0 < 1/X \leq \Delta_1$, then $h_1(X) \leq \{4B_1 B_3 + B_2^2\}/4B_1$. If $v \geq 2$, then $v(1 + 1/X)^{v-2} \leq v(1 + \Delta_1)^{v-2}$; if $v < 2$, then $v(1 + \frac{1}{X})^{v-2} \leq v$.

Therefore, when $X > 0$ we always have $h(X) \leq h_0 = \Delta_2(4B_1 B_3 + B_2^2)/(4B_1)$, where $\Delta_2 = \max\{v, v(1 + \Delta_1)^{v-2}\}$. That is, $h(X)$ is always upper bounded. Furthermore,

$$\begin{aligned}
dV^3(X) &\leq \exp(\epsilon t) h(X) dt - v \exp(\epsilon t) (1 + V^1(X))^{v-1} V^1(X) \delta_1 dB_1(t) \\
&\leq h_0 \exp(\epsilon t) dt - v \exp(\epsilon t) (1 + V^1(X))^{v-1} V^1(X) \delta_1 dB_1(t).
\end{aligned}$$

Integrating the above equation from 0 to t and then take the expectation, we have

$$E[V^3(X(t))] \leq V^3(X(0)) + \frac{h_0}{\epsilon} \exp(\epsilon t),$$

note that $V^3(X(t)) = \exp(\epsilon t)(1 + V^1(X(t)))^v$, thus,

$$\begin{aligned} E[V^3(X(t))] &= E[\exp(\epsilon t)(1 + V^1(X(t)))^v] \\ &\leq V^3(X(0)) + \frac{h_0}{\epsilon} \exp(\epsilon t) \\ &= (1 + V^1(X(0)))^v + \frac{h_0}{\epsilon} \exp(\epsilon t). \end{aligned}$$

By taking the upper limit of both sides, we get

$$\begin{aligned} \limsup_{t \rightarrow +\infty} E\left[\frac{1}{X(t)^v}\right] &= \limsup_{t \rightarrow +\infty} E[(V^1(X(t)))^v] \\ &\leq \limsup_{t \rightarrow +\infty} E[(1 + V^1(X(t)))^v] \leq \frac{h_0}{\epsilon} = h_N. \end{aligned}$$

For arbitrary $\varepsilon > 0$, let $\beta = \varepsilon^{\frac{1}{v}}/h_N^{\frac{1}{v}}$. From Chebyshev's inequality we have

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

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

For the second inequality, define a Lyapunov function $V_1(X(t)) = X^p(t)$ ($X > 0$), and by using Itô's formula along the first equation of system (3.1) yields

$$\begin{aligned} dV_1(X(t)) &= pX^{p-1}(t)dX(t) + 0.5p(p-1)X^{p-2}(t)(dX(t))^2 \\ &= pX^{p-1}(t)\left[\left(P_1 - Q_1 - \frac{P_1X}{K} - \frac{aE}{g_1 + X}\right)Xdt + \delta_1^2XdB_1(t)\right] \\ &\quad + 0.5p(p-1)X^{p-2}(t)\delta_1^2X^2dt \\ &= pV_1(X(t))\left[P_1 - Q_1 - \frac{P_1X}{K} - \frac{aE}{g_1 + X} + 0.5(p-1)\delta_1^2\right]dt \\ &\quad + p_1\delta_1^2V_1(X(t))dB_1(t) \\ &\leq pV_1(X(t))\left[P_1 - \frac{P_1X}{K} + 0.5(p-1)\delta_1^2\right]dt \\ &\quad + p\delta_1^2V_1(X(t))dB_1(t). \end{aligned}$$

Let us integrate both sides of the above inequality from 0 to t and then take the expectation,

$$E[V_1(X(t))] - E[V_1(X_1(0))] \leq p \int_0^t E\{V_1(X(s))\left[P_1 - \frac{P_1 X(s)}{K} + 0.5(p-1)\delta_1^2\right]\} ds,$$

taking the derivative of both sides of this inequality leads to

$$\frac{dE[V_1(X(t))]}{dt} \leq pE[V_1(X(t))][P_1 + 0.5(p-1)\delta_1^2] - \frac{pP_1}{K}E[X^{p+1}(t)].$$

In the light of Hölder's inequality, we have

$$\frac{dE[V_1(X(t))]}{dt} \leq pE[V_1(X(t))][P_1 + 0.5(p-1)\delta_1^2] - \frac{pP_1}{K}E[X^p(t)]^{\frac{p+1}{p}}.$$

Let $m(t) = E[V_1(X(t))]$, then

$$\begin{aligned} \frac{dm(t)}{dt} &\leq pm(t)[P_1 + 0.5(p-1)\delta_1^2] - \frac{P_1}{K}m^{\frac{1}{p}}(t) \\ &\leq pm(t)[P_1 + 0.5p\delta_1^2] - \frac{P_1}{K}m^{\frac{1}{p}}(t). \end{aligned}$$

It follows from the standard comparison theorem that

$$\begin{aligned} \limsup_{t \rightarrow +\infty} E[X^p(t)] &= \limsup_{t \rightarrow +\infty} E[V_1(X(t))] \\ &= \limsup_{t \rightarrow +\infty} m(t) \\ &\leq \left(\frac{(P_1 + 0.5p\delta_1^2)K}{P_1}\right)^p. \end{aligned}$$

Then the Chebyshev's inequality results in

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

Therefore, the prostate cancer cells are stochastically permanent. This completes the proof.

4. Stationary distribution and ergodicity of system (3.1)

In this section, we explore the existence of the stationary distribution and ergodicity of system (3.1), we need to show that the following two conditions are satisfied [26, 30–32],

- (i) There exists with a bounded domain $U \in \text{IntR}_+^2$ with regular boundary Γ such that its closure $\bar{U} \subset \text{IntR}_+^2$ and a non-negative C^2 - function $V(x)$ such that for any $x \in \text{IntR}_+^2 \setminus U$, LV is negative;
- (ii) For any bounded domain $\hat{U} \in \text{IntR}_+^2$, there is a positive constant ζ such that the diffusion matrix for system (3.1) given by

$$b(Y) = \begin{pmatrix} \delta_1^2 X^2 & 0 \\ 0 & \delta_2^2 E^2 \end{pmatrix}$$

satisfies $\sum_{i,j=1}^2 b_{ij}(Y)\xi_i\xi_j > \zeta\|\xi\|^2$ for all $Y = (X, E) \in \hat{U}$, and $\xi = (\xi_1, \xi_2) \in \mathbb{R}^2$.

Theorem 4.1. If

$$\left\{ \begin{array}{l} Z_1 : = P_1 - Q_1 - \frac{1}{2}\delta_1^2 > 0, \\ Z_2 : = \mu - C > 0, \\ Z_3 : = |P_1 - Q_1 - \frac{1}{2}\delta_1^2| - |C - \mu - \frac{\delta_2^2}{2}| > 0, \\ \Delta : = S_1^2 - 4(\mu - C)S_1 < 0, \end{array} \right. \quad (4.1)$$

then system (3.1) has a unique ergodic stationary distribution.

Proof. Let

$$V(X, E) = X + E - \ln X - \ln E.$$

Making use of Itô's formula yields

$$dV = LVdt + \delta_1(X - 1)dB_1(t) + \delta_2(E - 1)dB_2(t),$$

where

$$\begin{aligned} LV(X, E) &= X(P_1 - Q_1 - \frac{P_1 X}{K} - \frac{aE}{g_1 + X}) - (P_1 - Q_1 - \frac{\delta_1^2}{2}) + \frac{P_1 X}{K} \\ &\quad + \frac{aE}{g_1 + X} + E(C - \mu) - (C - \mu - \frac{\delta_2^2}{2}) - \frac{S_1}{E} + S_1. \end{aligned}$$

Then

$$LV(X, E) \leq \varphi(X) + \varphi(E) + \frac{aE}{g_1 + X},$$

where

$$\begin{aligned}\varphi(X) &= -\frac{P_1}{K}X^2 + (P_1 - Q_1 + \frac{P_1}{K})X, \\ \varphi(E) &= \frac{1}{E}(-(\mu - C)E^2 + S_1E - S_1) - (P_1 - Q_1 - \frac{\delta_1^2}{2}) - (C - \mu - \frac{\delta_2^2}{2}).\end{aligned}$$

It is worth noting that the leading coefficients of the quadratic functions $\varphi(X)$ and $\varphi(E)$ are negative, so $\varphi(X)$ has an upper bound $O_1 = \sup \varphi(X) = K(P_1 - Q_1 + \frac{P_1}{K})^2/4P_1$. Moreover, it follows from (4.1) that $\varphi(E)$ has a negative upper bound $O_2 = \sup \varphi(E)$.

Now let us find a bounded domain

$$U = [\epsilon_1, 1/\epsilon_2] \times [\sigma_1, 1/\sigma_2] \subset \text{IntR}_+^2,$$

such that $LV(X, E)$ is negative for all $(X, E) \in \text{IntR}_+^2 \setminus U$. Because $O_2 < 0$, we can choose sufficiently small $\epsilon_1, \sigma_1, \epsilon_2$ and σ_2 which satisfy the following conditions:

$$\begin{aligned}(P_1 - Q_1 + \frac{P_1}{K})\frac{-(a\sigma_1 + O_1g_1 + g_1)}{O_1 + 1} + O_2 &< 0, \\ \epsilon_1 &= \frac{-(a\sigma_1 + O_1g_1 + g_1)}{O_1 + 1},\end{aligned}\tag{4.2}$$

and

$$O_1 - \frac{P_1}{2K} \frac{1}{\epsilon_2^2} < -1, \quad O_2 - \frac{\mu - C}{2\sigma_2^2} < -1.\tag{4.3}$$

It is clear that $\text{IntR}_+^2 \setminus U = U_1 \cup U_2 \cup U_3 \cup U_4$, where

$$\begin{aligned}U_1 &= \{(X, E) \in \text{IntR}_+^2, X \geq \epsilon_1, E < \sigma_1\}, & U_2 &= \{(X, E) \in \text{IntR}_+^2, X < \epsilon_1\}, \\ U_3 &= \{(X, E) \in \text{IntR}_+^2, X > \frac{1}{\epsilon_2}\}, & U_4 &= \{(X, E) \in \text{IntR}_+^2, E > \frac{1}{\sigma_2}\}.\end{aligned}$$

Hence, from (4.2) we obtain

$$LV(X, E) \leq O_1 + \frac{aE}{g_1 + X} < -1 \quad \text{if } (X, E) \in U_1,$$

and

$$LV \leq (P_1 - Q_1 + \frac{P_1}{K})\epsilon_1 + O_2 < 0 \quad \text{if } (X, E) \in U_2.$$

In the same way, from (4.3) we get

$$LV \leq -1 \quad \text{when} \quad (X, E) \in U_3 \quad \text{or} \quad (X, E) \in U_4.$$

As a result, under (4.1) we conclude that

$$LV(X, E) < 0 \quad \text{for} \quad \text{all} \quad (X, E) \in \text{IntR}_+^2 \setminus U.$$

Moreover,

$$\begin{aligned} \sum_{i,j=1}^2 b_{ij}(X, E)\xi_i\xi_j &= \delta_1^2 E^2 \xi_1^2 + \delta_2^2 X^2 \xi_2^2 \\ &\geq \min_{(X,E) \in E} \{\delta_1^2 X^2, \delta_2^2 E^2\} \|\xi\|^2 \end{aligned}$$

for all $(X, E) \in U$, $(\xi_1, \xi_2) \in \mathbb{R}^2$.

It means that the necessary conditions have been satisfied. Therefore, system (3.1) has a unique ergodic stationary distribution. This completes the proof.

5. Numerical simulations

In this section, we describe numerical simulations to verify our results and to be convincing, we used logarithmic plots. By adopting the Milstein higher order method [33], we get the approximate solution of system (2.3) under initial conditions and the discretization equations of system (2.3) are as follows:

$$\left\{ \begin{array}{l} A_{k+1} = A_k - \gamma(A_k - a_0)\Delta t, \\ D_{k+1} = D_k - cD_k\Delta t, \\ X_{k+1} = X_k + [rA_k(1 - \frac{X_k}{K}) - d(1 - \frac{A_k}{a_0}) - \frac{aE_k}{g_1 + X_k}]X_k\Delta t \\ \quad + \delta_1 X_k \sqrt{\Delta t} \xi_k + \frac{\delta_1^2}{2} X_k (\xi_k^2 - 1) \Delta t, \\ E_{k+1} = E_k + [(C - \mu)E_k + \frac{eD_k}{g_2 + D_k}] \Delta t \\ \quad + \delta_2 E_k \sqrt{\Delta t} \eta_k + \frac{\delta_2^2}{2} E_k (\eta_k^2 - 1) \Delta t, \end{array} \right. \quad (5.1)$$

at the impulsive point series $t = nT$, system (2.3) performed pulsed therapies, i.e., if $\text{mod}(k, T) = 0$, then

$$\begin{cases} A_{i+1} = (1 - \delta)A_i, \\ D_{i+1} = D_i + \tau, \end{cases} \quad (5.2)$$

where ξ_k and η_k ($k = 1, 2, 3, \dots$) represent independent Gaussian random variables with a distribution $N(0, 1)$, and we let the time increment $\Delta t = 0.01$. For simplification, we take the maximum values of periodic solution A^* and D^* instead of $A^T(t)$ and $D^T(t)$, where $A^* = \frac{a_0(1-\delta)(1-e^{-\gamma T})}{1-(1-\delta)e^{-\gamma T}}$ and $D^* = \frac{\tau}{1-e^{-cT}}$.

5.1. Effects of random perturbation on the evolution of prostate cancer cells

The parameter values were taken as the same as those shown in the papers [11–13, 16, 21, 34], as these values are not only based on parameter estimates from experimental data, but also are of biological significance. Because the growth of prostate cancer cells is affected by random disturbances such as temperature, oxygen supply, nutrients, radiation and so on, we will show how the changes of δ_1 affect the evolution of prostate cancer cells. As above, logarithmic plots are displayed.

In Fig.1(a), we set $r = 1.4$, $\delta_1 = 3$, $\delta_2 = 1$, $T = 100$, $n = 100$, the initial values were fixed as $(X(0), E(0)) = (0.1, 0.5)$ and $(X(0), E(0)) = (10, 0.5)$. Simple calculation indicates that $P_1 - Q_1 - \frac{1}{2}\delta_1^2 \approx -1.15 < 0$, from Theorem 3.4, the prostate cancer cells become extinct (Fig.1(a)). If we set $r = 1.85$, $\delta_1 = 1$ and fix others as shown in Fig.1(a), then $C - \mu = 0.17 < \frac{\delta_2^2}{2} = 0.5$, and $P_1 - Q_1 - \frac{1}{2}\delta_1^2 \approx 3.97 > 0$. Theorem 3.4 implies that the prostate cancer cells become persistent in the mean (Fig.1(b)). If we set $C = 0.81$ and fix others as shown in Fig.1(b), then we have $C - \mu = 0.51 > \frac{\delta_2^2}{2} = 0.5$, by Theorem 3.4 we know that the prostate cancer cells also become persistent in the mean (Fig.1(c)).

From Fig.1(a) and Fig.1(b), the dynamic behaviours of prostate cancer cells gradually changed from extinction to persistence in the mean when the white noise decreased. This reveals that random interference has a relatively large impact on the prostate cancer cells. In addition, from Fig.1(c) we know that tumour antigenicity also affects population dynamics.

In Fig.2(a), we set $r = 3$, $\delta_1 = 0.5$, $\delta_2 = 1$, $T = 100$, $n = 100$ and the initial values were fixed as $(X(0), E(0)) = (800, 100)$ and $(X(0), E(0)) =$

(500, 50), then

$$\tau = \min_{t \geq 0} [P_1 - Q_1 - \frac{1}{2}\delta_1^2 - aN_2] \approx 3.225 > 0.$$

It is concluded from Theorem 3.5 that the prostate cancer cells became stochastically permanent (Fig.2(a)). When $\delta_1 = 0$, the amplitude becomes smaller (Fig.2(b)).

5.2. Combinations of ADT and immunotherapy

Theoretically, environmental noise can determine all possible dynamical behaviours of prostate cancer cells (Fig.3), but in practice it is so limited that prostate cancer cannot be controlled by adjusting the noise term alone. Therefore, we also need to study how ADT and immunotherapy affect the evolution of the prostate cancer. In Fig.4, when a single ADT is applied, increasing the intensity of ADT (Fig.4(a),Fig.4(b)) or reducing the impulsive period (Fig.4(c),Fig.4(d)) will lead to the extinction of the tumours.

It is observed that a single ADT with large dosages or long periods could result in the eradication of prostate cancer cells (Fig.4(b),Fig.4(c)), but many drawbacks including resistance or toxic reactions will be found [35]. Therefore, it is very important to address how the tumours will be affected if ADT is applied together with immunotherapy. Compared to treatments with ADT alone, the eradication of prostate cancer cells can be more easily achieved by combining ADT and immunotherapy (Fig.5). For example, if we increase the dosages of ADT and immunotherapy (Fig.5(a)), or decrease the periods of impulsive therapy (Fig.5(b)), or increase the dosages and decrease the periods simultaneously (Fig.5(c)), then the prostate cancer cells become extinct. It can be seen that increasing the dosages of ADT and immunotherapy or increasing the dosages and decreasing the periods simultaneously can reduce the time to tumour extinction (Fig.5(a),Fig.5(c)).

5.3. Stationary distribution of the system

With the parameter values as shown in Fig.6, the initial values are fixed as $(X(0), E(0)) = (300, 5)$ and $(X(0), E(0)) = (600, 10)$, then it is found that all conditions of Theorem 4.1 are satisfied. By simple calculation, we have

$$P_1 - Q_1 - \frac{1}{2}\delta_1^2 \approx 5.9369 > 0, \mu - C = 0.1 > 0,$$

$$|P_1 - Q_1 - \frac{1}{2}\delta_1^2| - |C - \mu - \frac{\delta_2^2}{2}| \approx 5.8367 > 0,$$

and

$$S_1^2 - 4(\mu - C)S_1 \approx -0.0039 < 0,$$

it follows from Theorem 4.1 that system (3.1) exists with a unique stationary distribution.

6. Discussion

Many studies pointed out that random disturbances such as variations in nutrients, oxygen supply, chemical products, radiation and temperature have impacts on the growth rate of tumours [36–39]. However, periodical applications of immunotherapy and chemotherapy are effective for treating tumours [21] and intermittent androgen deprivation therapy is often used to treat prostate cancer. In this paper, by using impulsive differential equations, we proposed and analyzed a novel mathematical model with intermittent androgen deprivation therapy taking account of white noise.

We first studied the existence and uniqueness of global positive solutions. Then the ultimate boundedness of the system was analysed, with results suggesting that prostate cancer cells can be controlled and will not grow indefinitely. Further, threshold conditions for the extinction and persistence in the mean of prostate cancer cells were provided by using Itô's formula, the strong law of large numbers for local martingales and Lyapunov functions. We also derived sufficient conditions for the stochastic permanence of the system. Moreover, the system exists with an ergodic steady-state distribution under certain conditions. Numerical simulations were carried out to verify our theoretical results. The results showed that combinations of ADT and immunotherapy can reduce the time of tumour extinction more than a single ADT (Fig.4 and Fig.5). Increasing the dosages of ADT and immunotherapy or increasing the dosages and decreasing the periods simultaneously is more effective than decreasing the periods of impulsive therapy (Fig.5).

Compared to the results of [16], the differences are listed as follows: (1) In this paper, we consider combinations of AD and AI cells as cancer cells and do not distinguish this two types of cells for simplicity. Since the antigenicity of the tumour always exists during the whole invasion process, a combination of immunotherapy and IAD therapy and the antigenicity of the prostate cancer cells are explored. (2) The global attractivity of the system and the sufficient

conditions for stochastic permanence of tumour cells are studied. (3) It is shown that both random interference and tumour antigenicity can affect the dynamic behaviours of prostate cancer cells. Reducing the period of pulsed interventions or increasing the dosages (or frequencies) of the therapy will be helpful for curing prostate cancer. Moreover, immunotherapy and ADT are also discussed, which suggesting that the comprehensive therapy is more effective than ADT alone.

There are still many interesting questions deserving future investigation. Cytokines can enhance the effect of immunotherapy by promoting dendritic cells, so how could injections of cytokines affect the evolution of tumours in the proposed model? It is also worthwhile to investigate the effects of chemotherapy, immunotherapy and impulsive ADT on the evolution of prostate cancer cells, and we leave these questions for the future.

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Figure Legends

Figure 1: Extinction and persistence in the mean of prostate cancer cells. (a) $r = 1.4$, $\delta_1 = 3$, $C = 0.47$; (b) $r = 1.85$, $\delta_1 = 1$, $C = 0.47$; (c) $C = 0.81$, $r = 1.85$, $\delta_1 = 1$. The initial values of the solution were fixed as $X((0), E(0)) = (800, 100)$ and red for $(X(0), E(0)) = (10, 0.5)$, and all other parameters were fixed as: $K = 1000$, $d = 0.3$, $a_0 = 5$, $a = 0.4$, $T = 100$, $g_1 = 10$, $g_2 = 10$, $J_2 = 100$, $N_2 = 10$, $\gamma = 0.08$, $\mu = 0.3$, $e = 10$, $c = 0.2$, $\delta = 0.5$, $\tau = 0.2$, $D(1) = 100$, $A(1) = 15$ and $\delta_2 = 1$.

Figure 2: Stochastic permanence of prostate cancer cells. (a) $\delta_1 = 0.5$; (b) $\delta_1 = 0$. We set initial values of the solution were fixed as $(X(0), E(0)) = (800, 100)$ and red for $(X(0), E(0)) = (500, 50)$, and all other parameters were fixed as: $r = 3$, $K = 1000$, $d = 0.3$, $a_0 = 5$, $a = 0.4$, $T = 100$, $g_1 = 10$, $g_2 = 10$, $J_2 = 100$, $N_2 = 10$, $\gamma = 0.08$, $\mu = 0.3$, $e = 10$, $c = 0.2$, $C = 0.47$, $\delta = 0.5$, $D(1) = 100$, $A(1) = 15$, $\tau = 0.2$ and $\delta_2 = 1$.

Figure 3: The effects of white noise on the evolution of prostate cancer cells. (a) $\delta_1 = 0.5$; (b) $\delta_1 = 1$; (c) $\delta_1 = 1.5$; (d) $\delta_1 = 2$; the initial values of solution were fixed as $(X(0), E(0)) = (300, 5)$, and all other parameters were fixed as: $r = 3$, $K = 1000$, $d = 0.3$, $a_0 = 5$, $a = 0.4$, $T = 100$, $g_1 = 10$, $g_2 = 10$, $J_2 = 100$, $N_2 = 10$, $\gamma = 0.08$, $\mu = 0.3$, $e = 10$, $c = 0.2$, $C = 0.47$, $\delta = 0.5$, $D(1) = 100$, $A(1) = 15$, $\tau = 0.2$ and $\delta_2 = 1$.

Figure 4: The effects of ADT alone on the evolution of prostate cancer cells. (a) $T = 50$, $\delta = 0.2$; (b) $T = 50$, $\delta = 0.9$; (c) $T = 20$, $\delta = 0.2$; (d) $T = 80$, $\delta = 0.2$. We set initial values of the solution were fixed as $(X(0), E(0)) = (10, 0.5)$, and all other parameters were fixed as: $r = 1.85$, $K = 1000$, $d = 0.3$, $a_0 = 5$, $a = 0.4$, $g_1 = 10$, $g_2 = 10$, $J_2 = 100$, $N_2 = 10$, $\gamma = 0.08$, $\mu = 0.3$, $e = 10$, $c = 0.2$, $C = 0.47$, $A(1) = 15$, $D(1) = 100$, $\delta_2 = 1$, $\delta_1 = 1$ and $\tau = 0$.

Figure 5: The effects of comprehensive therapy on the evolution of prostate cancer cells. (Time series of prostate cancer cells $X(t)$) (a) $T = 50$, $\tau = 2$ and $\delta = 0.9$; (b) $T = 20$, $\tau = 0.2$ and $\delta = 0.2$; (c) $T = 40$, $\tau = 2$ and $\delta = 0.9$. We set initial values of the solution were fixed as $(X(0), E(0)) = (10, 0.5)$, and all other parameters were fixed as: $r = 1.85$, $K = 1000$, $d = 0.3$, $a_0 = 5$, $a = 0.4$, $g_1 = 10$, $g_2 = 10$, $J_2 = 100$, $N_2 = 10$, $\gamma = 0.08$, $\mu = 0.3$, $e = 10$, $c = 0.2$, $C = 0.47$, $A(1) = 15$, $D(1) = 100$, $\delta_2 = 1$ and $\delta_1 = 1$.

Figure 6: Stationary distribution of deterministic model and stochastic model (The specific parameter values of each curve are shown in the figure above). (a) We set initial values as $(X(0), E(0)) = (300, 5)$. (b) We set initial values as $(X(0), E(0)) = (600, 10)$. Furthermore, all other parameters were fixed as: $r = 1.2$, $K = 1000$, $d = 0.3$, $a_0 = 5$, $a = 0.4$, $g_1 = 10$, $g_2 = 10$, $J_2 = 100$, $N_2 = 10$, $\gamma = 0.08$, $\mu = 0.3$, $e = 10$, $c = 0.2$, $C = 0.2$, $D(1) = 100$ and $A(1) = 1$.