Stationary distribution and persistence of a stochastic mathematical model for prostate cancer with pulsed therapy

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Abstract

Intermittent androgen deprivation therapy is one of the most commonly used therapeutic regimens for treating prostate cancer. Immunotherapy with dendritic cells, which act as the most robust antigen-presenting cells, are regarded as an effective method for the treatment of advanced prostate cancer. This paper utilizes impulsive differential equations to describe the combinations of a dendritic cell vaccine and intermittent androgen therapy with white noise. The tumour-free solution is obtained and the unique global positive solution of the system is explored. Then it is proved that the solutions of the system are stochastic ultimately bounded and stochastically permanent. In addition, threshold conditions for the extinction and persistence of prostate cancer cells are derived, and the stationary distribution and ergodicity of the system are investigated. Finally, numerical studies and the biological significance of the results are discussed.

Keywords:
Cancer model, Pulsed therapy, Extinction and permanence, Stationary distribution

1. Introduction

Prostate cancer is one of the most common types of cancer affecting men. It has a high incidence rate [1] and is especially dangerous since it may take a long time to develop and become detectable [2]. Androgens of testosterone and 5α-dihydrotestosterone (5α-dihytesterone) have significant impacts on the growth of prostate cells, but both are beneficial to the proliferation of prostate cancer cells and can stop them from dying so, clinically, androgen concentration is usually suppressed to inhibit them [3, 4]. Thus, androgen deprivation therapy (ADT) has become the major therapeutic regimen for reducing the proliferation rate and increasing the mortality rate of prostate cancer cells [5]. Prostate cancer cells usually contain androgen dependent (AD) cells and androgen independent (AI) cells. ADT reduces AD cells by inhibiting the growth of cancer cells and then inducing their apoptosis [2]. ADT is often realized by continuous androgen deprivation (CAD) therapy (the treatment is administered continuously) and intermittent androgen deprivation (IAD) therapy (the treatment is administered intermittently). In previous studies, IAD therapy was performed before the patient reached a certain

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threshold of prostate specific antigen (PSA), which is a biomarker for the disease. After reaching this threshold, the patients will be cancelled until their PSA level rises above the second threshold, and then they will receive androgen deprivation therapy again. CAD therapy refers to continuous injection of drugs. Generally speaking, the efficacy of CAD therapy is expressed as a constant, while the efficacy of IAD therapy is described as a function [3, 4]. Although ADT is effective initially, AD will eventually develop into AI cells, both of which lead to fatal consequences [6, 7]. It has been shown that CAD plays a significant role in the treatment of advanced prostate cancer, but the overall survival interval is less than 6 months [8]. Therefore, IAD, which improves the quality of life of an individual patient and reduces the adverse side effects of ADT, has been proposed and has attracted the attention of the medical community [3, 9–13].

Initiation of additional therapies is still necessary to prevent production of AI cells and treat existing AI cells. Since immunotherapy can stimulate the body's immunity to fight against cancer cells, it has been widely used to treat hormone-resistant prostate cancer cells and advanced prostate cancer [14–17]. In particular, dendritic cells have been proved to be the most robust antigen-presenting cells to promote immunotherapy, by means of inducing a tumour immune response, such as the production of immature T cells and the destruction of peripheral tolerance [18–20]. By extracting a patient's dendritic cells, then loading them with antigens and injecting them back into the patients, a dendritic cell vaccine may become possible. Trials have shown that because different patients have different immune response abilities, for some patients, PSA levels dropped significantly, while the disease progressed steadily in others [3, 21]. Consequently, dendritic cells are considered to be promising candidates for cancer vaccine therapy due to their multiple anti-tumour effects [18].

In order to explore the combined mechanisms of ADT and immunotherapy, mathematical models with therapy for prostate cancer have attracted a lot of attention [4, 21–26]. Ideta et. al. established a mathematical model with IAD for prostate cancer, proposing a new perspective on optimal intermittent regulation to avoid the recurrence of AD cells [25]. Jain and Friedman discussed the response of prostate cancer to CAD and IAD therapy [26]. Portz and Kuang studied the effectiveness of dendritic cell vaccines on CAD or IAD therapy and their results revealed that immunotherapy can successfully stabilize the disease through continuous and intermittent ADT [21]. Moreover, Rutter and Kuang developed a new mathematical model incorporating ADT combined with dendritic cell vaccines. From the analysis for their whole model and its limit cases, the necessary conditions for global stability of the disease-free equilibria were determined [3].

For simplicity, these studies were carried out with deterministic dynamical systems so the influence of random elements were often ignored [3, 21, 25–27]. However, changes in external environment factors may have impacts on the activities of proteins and enzymes, which in turn affect the growth of tumours [4, 28–31]. To explore the influence of these uncertainties on deterministic models of prostate cancer and its treatment, it is necessary to develop new stochastic differential equation models [1, 30, 32–34]. Zazoua and Wang constructed a stochastic mathematical model with competition for prostate cancer to investigate the effects of CAD therapy, and proved that the intensities of white noise can determine the dynamics of the tumours [4]. Yang and collaborators pointed out that noise can alter the final states of tumours [29], but only a few studies have considered the effects of random perturbations on prostate cancer. In addition, Yang established a tumour immune model with pulse comprehensive treatment under random disturbance. Their results show that random disturbance can

inhibit the growth of tumour cells, and the combination of chemotherapy and immunotherapy can reduce the damage of treatment to healthy cells [35]. Later, Yang utilized a stochastic impulsive tumour model combining ADT and immunotherapy to analyze the elimination of AD and AI cells. It is proved that high intensity noise interference is unfavorable to the evolution of prostate cancer cells [36].

Piece-wise functions are usually employed to describe IAD therapy. Injections or use of drugs are usually applied at fixed intervals, and Yang verified that frequent vaccination can improve the survival time of patients with ADT [36], so they can be characterized by impulsive differential equations. Hence, we make use of impulsive differential equations to capture the characteristics of IAD therapy. In addition, there is competition between AD and AI cells, so the equivalent of a competition coefficient in interspecific competition equations has been studied [3, 21]. But different shapes, genes and functions of AD and AI cells will result in different abilities for them to compete for resources, such as nutrients and oxygen [1, 4, 37]. Moreover, the antigenicity of tumours exists throughout the life of tumours, so taking into account the influence of the antigenicity on tumour growth will make a model more realistic. Based on these assumptions, we have extended previous stochastic models of prostate cancer by introducing combinations of antigenicity and impulsive immunotherapy with different competition coefficients. The main objectives of this paper are to investigate how white noise, IAD and different competition coefficients affect the global dynamics of tumours.

The paper is arranged as follows. In section 2, the model is derived and some important definitions and lemmas are presented. In section 3, the tumour-free periodic solution is obtained, and it is proved that the solution is globally attractive. In section 4, we first show that the solution is stochastically ultimately bounded and stochastic permanent. Then thresholds for extinction, persistence and stochastic permanence for both AD and AI cells are derived. In section 5, the stationary distribution and ergodicity of the system are explored. In section 6, numerical simulations are performed to verify our theoretical results. Finally, the biological significance of the model is discussed and conclusions are drawn.

2. Model formation and preliminaries

2.1. Model formation

Recently, Rutter and Kuang constructed a mathematical model to investigate the effects of ADT and immunotherapy with dendritic cell vaccines on prostate cancer [3]. Their model is a population-style model of the interaction between the number of AD cells (X_1), number of AI cells (X_2), number of effector cells (Y) (such as natural killer cells, cytotoxic T cells and macrophages) that act on the tumour cells, concentration of cytokine IL-2 (I_L), concentration of androgen (A) in serum and number of dendritic cells (D) at time t. Their model can be

written as follows:

$$\begin{cases} dX_1 = \{r_1(A, X_1, X_2)X_1 - m_1(A)X_1 + m_2(A)X_2 - X_1 f_1(X_1, X_2, Y)\}dt, \\ dX_2 = \{r_2(X_1, X_2)X_2 + m_1(A)X_1 - m_2(A)X_2 - X_2 f_2(X_1, X_2, Y)\}dt, \\ dY = \{\dfrac{eD}{g+D} - \mu Y + Y f_3(I_L, Y)\}dt, \\ dI_L = \{Y f_4(X_1, X_2) - \omega I_L\}dt, \\ dA = \{\gamma(a_0 - A) - \gamma a_0 u(t)\}dt, \\ dD = -cDdt, \end{cases} \tag{2.1}$$

where γ and a_0 denote the clearance and production rate of androgen and the basic level of androgen concentration, respectively. μ and c are the death rates of effector cells and dendritic cells, respectively. e and ω are the maximum activation rates of Y cells and the clearance rate of IL-2, respectively. g is the saturation level of dendritic cells activated by Y cells. $r_1(A, X_1, X_2)X_1$ and $r_2(X_1, X_2)X_2$ are the reproductive rates of AD and AI cells, respectively. In general, $f_1(X_1, X_2, Y)$, $f_2(X_1, X_2, Y)$, $f_3(I_L, Y)$ and $f_4(X_1, X_2)$ are nonlinear functions. $f_1(X_1, X_2, Y)$ and $f_2(X_1, X_2, Y)$ represent the death rate functions to simulate the number of AD and AI cells killed by Y cells, respectively. $f_3(I_L, Y)$ represents the activation rate function of Y cells by cytokines. $f_4(X_1, X_2)$ denotes the activation rate function of tumour secretion on IL-2. $m_1(A)X_1$ denotes the maximum mutation rate from AD to AI cells and $m_2(A)X_2$ is the maximum mutation rate from AI to AD cells. The androgen concentration is controlled by the function $u(t)$. $u(t)$ is either 0 (if treatment is off) or 1 (if treatment is on). For details see [3].

Model (2.1) is a mathematical model describing the growth of prostate cancer under IAD therapy based on the monitoring of PSA in serum. The administration switching based on the observation of serum PSA level can be regarded as the feedback control of the observable output of the system. The intermittent administration included in the model will be described as a hybrid dynamic system [3]. The IAD therapy of the model (2.1) is described by piecewise function, but the details of its period, frequencies and dosages, and the effect of immunotherapy on prostate cancer are still unclear. To explore these characteristics, it is meaningful to use impulsive differential equations to describe IAD therapy and immunotherapy [38]. On the one hand, in order to explore the dynamic behaviours of AD and AI cells to develop more specific treatment regimens for prostate cancer, we will distinguish the types of prostate cancer cells and expand the mathematical model in reference [38]. On the other hand, competition between AD cells and AI cells may alter the fate of tumour cells, then the interspecific competition between AD and AI cells should be considered [4].

Besides, the growth rate $r_1 A$ of AD cells depends on androgen, the growth rate of AI cells r_2 and the antigenicity C are perturbed randomly around some average value [38]. Thus, $r_1 A$, r_2 and C can be random variables $\tilde{r_1 A}$, $\tilde{r_2}$ and $\tilde{C}$, in $[t, t+dt)$, then $\tilde{r_1 A}dt = r_1 A dt + \delta_1(X_1)dB_1(t)$, $\tilde{r_2}dt = r_2 dt + \delta_2(X_2)dB_2(t)$ and $\tilde{C}dt = Cdt + \delta_3(Y)dB_3(t)$, where $dB_i(t) = B_i(t+dt) - B_i(t)(i = 1, 2, 3)$ denotes the increment of a standard Brownian motion. Here we retain the notation of $r_1 A$, r_2 and C instead of $\tilde{r_1 A}$, $\tilde{r_2}$ and $\tilde{C}$. Based on [3, 38], we do not consider the effects of mutation m_2 from AI to AD cells and cytokines I_L. Then we develop model (2.1) with different competition coefficients by introducing combinations of the stochastic perturbations

and impulsive immunotherapy, leading to the following extended model:

$$\left\{\begin{array}{l} dX_1 = \{[r_1A(1-\frac{X_1+\alpha X_2}{K}) - (d_1+m_1)(1-\frac{A}{a_0}) - \frac{a_1Y}{g_1+X_1+X_2}]dt + \delta_1 dB_1(t)\}X_1, \\ dX_2 = [r_2(1-\frac{\beta X_1+X_2}{K})X_2 + m_1(1-\frac{A}{a_0})X_1 - \frac{a_2X_2Y}{g_2+X_1+X_2}]dt + \delta_2 X_2 dB_2(t), \\ dY = [(C-\mu)Y + \frac{eD}{g_3+D}]dt + \delta_3 Y dB_3(t), \\ \dfrac{dA}{dt} = -\gamma(A-a_0), \\ \dfrac{dD}{dt} = -cD, \end{array}\right\} t \neq nT,$$

$$\left\{\begin{array}{l} A(nT^+) = (1-\delta)A(nT), \\ D(nT^+) = D(nT) + \tau, \end{array}\right\} \quad t = nT, \tag{2.2}$$

where, K is the carrying capacity of prostate cancer cells. α and β are the competition coefficients between two types of prostate cancer cells. m_1 is the irreversible mutation rate from AD cells to AI cells. g_1 and g_2 are the killing rates of effector cells at saturation level of AD and AI cells. g_3 is the saturation concentration of dendritic cells activated by effector cells, d_1 denotes the death rate of AD cells. a_1 and a_2 are the maximum killing rates of effector cells due to AD and AI cells. τ is the dosage of immunotherapy drugs injected at impulsive point series $nT(n = 1, 2, 3, \cdots)$. δ is the treatment intensity of IAD therapy. δ_1^2, δ_2^2 and δ_3^2 denote the intensities of the white noise. Note that X_1, X_2, Y, A and D have the same biological significance as model (2.1).

From above, AD cells are controlled by their proliferation and death, dependent of androgen, their mutation to AI cells and the number killed by Y cells. AI cells are controlled by proliferation, independent of androgen, their mutation from AD cells and the number killed by Y cells. The number of Y cells is determined by the number of dendritic cells activated, their natural death and the linear growth of effector cells induced by tumour antigenicity. The concentration of androgen in the blood is described by homeostasis term and deprivation therapy term [3]. Dendritic cells are controlled by their mortality. ADT and immunotherapy with dendritic cells are achieved by pulsed and periodic medication.

The dynamics of the immunotherapeutic drug and ADT are given by the last four lines of (2.2), i.e.:

$$\left\{\begin{array}{l} \dfrac{dA}{dt} = -\gamma(A-a_0), \\ \dfrac{dD}{dt} = -cD, \end{array}\right\} t \neq nT,$$

$$\left\{\begin{array}{l} A(nT^+) = (1-\delta)A(nT), \\ D(nT^+) = D(nT) + \tau, \end{array}\right\} \quad t = nT. \tag{2.3}$$

By simple calculation, we obtained the explicit expressions of the T periodic solution $A^T(t)$ and $D^T(t)$ of (2.3) with

$$\left\{\begin{array}{l} A^T(t) = a_0 + (A^* - a_0)e^{-\gamma(t-nT)} = a_0 - \dfrac{a_0\delta e^{-\gamma(t-nT)}}{1-(1-\delta)e^{-\gamma T}}, \\ D^T(t) = \dfrac{\tau e^{-c(t-nT)}}{1-e^{-cT}}, \end{array}\right.$$

where $t \in (nT, (n+1)T]$, and

$$A^T(nT^+) = \frac{a_0(1-\delta)\left(1-\mathrm{e}^{-\gamma T}\right)}{1-(1-\delta)\mathrm{e}^{-\gamma T}}, D^T(nT^+) = \frac{\tau}{1-\exp(-cT)}.$$

In the following parts, the global dynamic behaviour of system (2.2) will be studied, so we first introduce some useful definitions and lemmas.

2.2. Preliminaries

Assume $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t\geq 0}, \mathcal{P})$ is a complete probability space with conditions (right continuous and $\mathcal{F}_0$ contains all $\mathcal{P}$-null sets), which has a filtration $\{\mathcal{F}_t\}_{t\geq 0}$. Let $B_i(t)(i = 1, \ldots, n)$ be an independent Brownian motion which is defined on this probability space [21].

Definition 2.1. For any positive solution $Z(t) = (y_1(t), y_2(t), y_3(t))$ with initial condition $Z(0) = Z_0 \in \mathrm{R}^3_+$, if for any $\varepsilon \in (0, 1)$, there exists a solution with a positive constant H such that

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

then the positive solutions of system (2.2) are stochastically ultimately bounded.

Definition 2.2. For any solutions $Z_1(t) = (y_{11}(t), y_{12}(t), y_{13}(t)), Z_2(t) = (y_{21}(t), y_{22}(t), y_{23}(t))$ of system (2.2) with $Z_1(0) > 0, Z_2(0) > 0$, if

$$\lim_{t\to+\infty} \mid y_{11}(t) - y_{21}(t) \mid = 0, \lim_{t\to+\infty} \mid y_{12}(t) - y_{22}(t) \mid = 0 \text{ and } \lim_{t\to+\infty} \mid y_{13}(t) - y_{23}(t) \mid = 0,$$

then system (2.2) is said to be globally attractive.

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

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

then

$$\lim_{t\to\infty} \frac{M_t}{t} = 0 \quad a.s.$$

Besides, for an integrable function $y(t)$ on $[0, \infty)$, we give the following notations,

$$< x >_t = \frac{1}{t}\int_0^t y(s)ds \quad \text{for} \quad t > 0,$$

$$< x >^* = \limsup_{t\to\infty} \frac{1}{t}\int_0^t y(s)ds,$$

$$< x >_* = \liminf_{t\to\infty} \frac{1}{t}\int_0^t y(s)ds.$$

Definition 2.4. If $\lim_{t\to\infty} Z_i(t) = 0$, then the population $Z_i(t)$ is said to go to extinction; if $< Z_i(t) >^* > 0$, then the population $Z_i(t)$ is said to be persistent in mean.

Definition 2.5. ([39, 40]) Let $Z(t) = (y_1(t), y_2(t), y_3(t))^T$ be any solution of system (2.2), $y_i(t)$ is called stochastically permanent if for any $\varepsilon \in (0, 1)$, there exists a solution with $\beta > 0$ and $\delta > 0$ such that for all $i = 1, 2, 3$

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

Lemma 2.6. ([41–43]) Assume that
(1) (Minorization condition) for a compact set $\Gamma_1 \subset \mathrm{R}^3_+$, there are $S, \beta > 0$ and a probability measure m on R^3_+ with $m(\Gamma_1) > 0$ such that

$$P_S(Y_0, D) \geq \beta m(D), \quad \forall\, Y_0 \in \Gamma_1, \quad \forall\, D \in C(\mathrm{R}^3_+).$$

(2) (Lyapunov condition) defining a function $V : \mathrm{R}^3_+ \to [1, \infty)$ satisfies $\lim_{|Y(t)|\to\infty} V(Y) = \infty$, for any real numbers $\alpha_1, \alpha_2 \in (0, \infty)$ yield

$$LV(Y) \leq \alpha_1 - \alpha_2 V(Y),$$

where $LV(Y)$ is a function of Y.
If there exists a state with an unique stationary distribution Λ such that for constants $B, \chi > 0$,

$$|Ef(Y(t)) - \Lambda(f)| \leq BV(Y_0)e^{-\chi t}, \quad \forall\, Y(0) = Y_0 \in \mathrm{R}^3_+,$$

for all measurable function $f \in \Im := \{\text{measurable f} : \mathrm{R}^3_+ \to \mathrm{R}^3 \text{ with } |\mathrm{f(Y)}| \leq \mathrm{V(Y)}\}$, then the Markov process $Y(t)$ is V-geometrically ergodic.

More details of Lemma 2.6 are shown in ([41], Theorem 16.0.1) or ([42], Theorem 2.5). In what follows, unless otherwise specified, the function $V(\cdot)$ represents different variables in different places.

Remark 1. ([43, 44]) Let $Z(t) = (y_1(t), y_2(t), y_3(t))^T$ be the solution of system (2.2) with initial value $y(0) \in \mathrm{R}^3_+$. For any $0 < \epsilon < 1$, if there exists a positive constant $\Upsilon = \Upsilon(\epsilon)$ such that for all $i = 1, 2, 3$,

$$\liminf_{t\to\infty} P\{y_i(t) \geq \Upsilon\} \geq 1 - \epsilon,$$

then the stochastic model (2.2) is stochastically persistent; if there exists a positive constant $\delta = \delta(\epsilon)$ such that for all $i = 1, 2, 3$,

$$\liminf_{t\to\infty} P\{y_i(t) \leq \delta\} \geq 1 - \epsilon,$$

then the stochastic model (2.2) is stochastically bounded from above. A stochastic system is stochastic permanent if it is both stochastic persistent and stochastic bounded.

3. Global positive solution

The dynamics of the immunotherapeutic drug can be described by

$$\begin{cases} \dfrac{dD}{dt} = -cD, & t \neq nT, \\ D(nT^+) = D(nT) + \tau, & t = nT. \end{cases} \tag{3.1}$$

Lemma 3.1. $D^T(t)$ is a unique positive periodic solution of system (3.1) and satisfies $\lim_{t\to\infty} D(t) = D^T(t)$. Besides, for any $\epsilon > 0$ we get

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

Now we study the tumour-free solution of the system, assume that the prostate cancer cells can be eliminated. Let $X_1(t) = X_2(t) = 0$, the system (2.2) becomes

$$\left\{\begin{array}{l} dY = [(C-\mu)Y + \dfrac{eD}{g_3+D}]dt + \delta_3 Y dB_3(t), \\ dD = -cDdt, \\ D(nT^+) = D(nT) + \tau, \quad t = nT. \end{array}\right\} t \neq nT, \tag{3.3}$$

Replacing D with $D^T(t)$, then system (3.3) can be reduced to

$$dY = [(C-\mu)Y + \frac{eD^T(t)}{g_3 + D^T(t)}]dt + \delta_3 Y dB_3(t). \tag{3.4}$$

Theorem 3.2. For any initial value $Y(0^+) = Y(0)$, there exists a state with a unique global positive solution $Y(t)$ of system (3.4), where

$$\begin{array}{rcl} Y(t) & = & Y(0)\exp[(C-\mu-\frac{\delta_3^2}{2})t + \delta_3 B_3(t)] \\ & & + \int_0^t \frac{eD^T(s)}{g_3+D^T(s)} \exp[(C-\mu-\frac{\delta_3^2}{2})(t-s) + \delta_3(B_3(t)-B_3(s))]ds. \end{array} \tag{3.5}$$

Proof. For the homogeneous linear stochastic differential equation, let

$$d\tilde{Y} = (C-\mu)\tilde{Y}dt + \delta_3 \tilde{Y} dB_3(t).$$

Then, we define a Lyapunov function $V(t) = \ln \tilde{Y}(t)$ by using Itô's formula which leads to

$$\begin{array}{rcl} d\ln\tilde{Y}(t) & = & \frac{d\tilde{Y}}{\tilde{Y}} - \frac{(d\tilde{Y})^2}{2\tilde{Y}^2} \\ & = & \left(C-\mu-\frac{\delta_3^2}{2}\right)dt + \delta_3 dB_3(t). \end{array}$$

From 0 to t, integrating the above equation yields

$$\begin{array}{rcl} \ln\tilde{Y}(t) - \ln\tilde{Y}(0) & = & \int_0^t (C-\mu-\frac{\delta_3^2}{2})ds \\ & & + \int_0^t \delta_3 B_3(t)ds. \end{array}$$

Hence,

$$\tilde{Y}(t) = \tilde{Y}(0)\exp[(C-\mu-\frac{\delta_3^2}{2})t + \delta_3 B_3(t)].$$

Now writing the solution of the nonhomogeneous linear stochastic differential equation (3.4) as $Y(t) = P(t)Y_0(t)$, this problem is to determine $P(t)$.

$$P(t) = Y_0^{-1}(t)Y(t),$$

where

$$Y_0^{-1}(t) = \exp\left\{-\int_0^t (C-\mu-\frac{\delta_3^2}{2})ds - \int_0^t \delta_3 dB_3(s)\right\}.$$

Applying the preceding result for linear homogeneous equation $d\tilde{Y}(t)$ gives

$$dY_0^{-1}(t) = Y_0^{-1}(t)\{[-(C-\mu)+\delta_3^2]dt - \delta_3 dB_3(t)\}.$$

From the above we can see that

$$\begin{aligned} dP(t) &= Y_0^{-1}(t)dY(t) + Y(t)dY_0^{-1}(t) - \delta_3 Y(t)Y_0^{-1}(t)\delta_3 dt \\ &= Y_0^{-1}(t)\Big\{[\tfrac{eD^T(t)}{g_3+D^T(t)} + (C-\mu)Y(t)]dt + \delta_3 Y(t)dB_3(t)\Big\} \\ &\quad + Y(t)Y_0^{-1}(t)\Big\{[-(C-\mu)+\delta_3^2]dt - \delta_3 dB_3(t)\Big\} - \delta_3 Y(t)Y_0^{-1}(t)\delta_3 dt \\ &= Y_0^{-1}(t)\Big\{\tfrac{eD^T(t)}{g_3+D^T(t)}\Big\}dt. \end{aligned}$$

Therefore,

$$P(t) = P(0) + \int_0^t Y_0^{-1}(s)\frac{eD^T(s)}{g_3 + D^T(s)}ds.$$

Consequently, by combining $\tilde{Y}$ and $P(t)$, the solution of equation (3.4) is as follows:

$$Y(t) = Y_0(t)\Big\{Y(0) + \int_0^t Y_0^{-1}(s)\frac{eD^T(s)}{g_3 + D^T(s)}ds\Big\},$$

where $Y_0(t) = \exp[(C-\mu-\frac{\delta_3^2}{2})t+\delta_3 B_3(t)]$. After sorting out the above equations, it is concluded that

$$\begin{aligned} Y(t) &= Y(0)\exp[(C-\mu-\tfrac{\delta_3^2}{2})t + \delta_3 B_3(t)] \\ &\quad + \int_0^t \frac{eD^T(s)}{g_3 + D^T(s)}\exp[(C-\mu-\frac{\delta_3^2}{2})(t-s) + \delta_3(B_3(t) - B_3(s))]ds. \end{aligned}$$

Hence, this completes the proof.

For the global dynamics of system (2.2), replacing A and D with $A^T(t)$ and $D^T(t)$, then we get the equivalent system (3.6) for system (2.2),

$$\begin{cases} dX_1 = [r_1 A^T(t)(1-\frac{X_1+\alpha X_2}{K}) - (d_1+m_1)(1-\frac{A^T(t)}{a_0}) - \frac{a_1 Y}{g_1+X_1+X_2}]X_1 dt + \delta_1 X_1 dB_1(t), \\ dX_2 = [r_2(1-\frac{\beta X_1+X_2}{K})X_2 + m_1(1-\frac{A^T(t)}{a_0})X_1 - \frac{a_2 XY}{g_2+X_1+X_2}]dt + \delta_2 X_2 dB_2(t), \\ dY = [(C-\mu)Y + \frac{eD^T(t)}{g_3+D^T(t)}]dt + \delta_3 Y dB_3(t). \end{cases} \tag{3.6}$$

For convenience, let

$$W_1 = r_1 A^T(t) = r_1 a_0 - \frac{r_1 a_0 \delta e^{-\gamma(t-nT)}}{1-(1-\delta)e^{-\gamma T}}, H_1 = (d_1+m_1)(1-\frac{A^T(t)}{a_0}),$$

$S_1 = m_1(1-A^T(t)/a_0)$ and $S_2 = eD^T(t)/(g_3+D^T(t))$, then system (2.2) becomes

$$\begin{cases} dX_1 = [W_1(1-\dfrac{X_1+\alpha X_2}{K}) - H_1 - \dfrac{a_1 Y}{g_1+X_1+X_2}]X_1 dt + \delta_1 X_1 dB_1(t), \\ dX_2 = [r_2(1-\dfrac{\beta X_1+X_2}{K})X_2 + S_1 X_1 - \dfrac{a_2 X_2 Y}{g_2+X_1+X_2}]dt + \delta_2 X_2 dB_2(t), \\ dY = [(C-\mu)Y + S_2]dt + \delta_3 Y dB_3(t). \end{cases} \tag{3.7}$$

4. Dynamics of stochastic model

4.1. Existence and uniqueness of the solution

This part mainly focuses on the existence and uniqueness of the solution for system (3.7).

Theorem 4.1. If $\mu - C - a_1/g_1 - a_2/g_2 > 0$, then for any initial value $(X_1(0), X_2(0), Y(0)) \in \text{Int}\mathbb{R}^3_+$, system (3.7) has a unique positive solution $Z(t) = (X_1(t), X_2(t), Y(t))$ for all $t \geq 0$ almost surely.

Proof. Notice that the coefficients of system (3.7) satisfy the local Lipschitz condition, for any $(X_1(0), X_2(0), Y(0)) \in \text{Int}\mathbb{R}^3_+$, there exists with a unique positive local solution on $[0, \tau_e)$, where τ_e represents the explosion time. If $\tau_e = \infty$, then the solution is global. Choose $k_0 > 0$ such that $X_1(0)$, $X_2(0)$ and $Y(0)$ all lie within the interval $(1/k_0, k_0)$. For each $k \geq k_0$, the stopping time can be defined as

$$\tau_k = \inf\{t \in [0, \tau_e), \quad X_1(t) \notin (\frac{1}{k}, k) \quad \text{or} \quad X_2(t) \notin (\frac{1}{k}, k) \quad \text{or} \quad Y(t) \notin (\frac{1}{k}, k)\},$$

where τ_k is increasing as $k \to \infty$. Denote $\tau_\infty := \lim_{k\to\infty} \tau_k$. Then, $\tau_\infty \leq \tau_e$ a.s. If $\tau_\infty = \infty$ a.s., then $\tau_e = \infty$ a.s. and the solution $(X_1(t), X_2(t), Y(t)) \in \text{Int}\mathbb{R}^3_+$ for $t \geq 0$ a.s. Otherwise, if $\tau_\infty \neq \infty$, then there are two constants $T_1 > 0$ and $\varepsilon \in (0, 1)$ such that $\mathcal{P}\{\tau_\infty \leq T_1\} > \varepsilon$. Thus, for an integer $k_1 \geq k_0$ we have

$$P\{\tau_k \leq T_1\} \geq \varepsilon \quad \text{for} \quad k \geq k_1. \tag{4.1}$$

Constructing a C^2- function V: $\text{Int}\mathbb{R}^3_+ \to \mathbb{R}_+$ as

$$V(X_1, X_2, Y) = X_1 - 1 - \ln X_1 + X_2 - 1 - \ln X_2 + Y - 1 - \ln Y,$$

Applying Itô's formula gives

$$dV = LVdt + \delta_1(X_1 - 1)dB_1(t) + \delta_2(X_2 - 1)dB_2(t) + \delta_3(Y - 1)dB_3(t),$$

where

$$\begin{aligned} LV &= (X_1 - 1)(W_1(1 - \tfrac{X_1+\alpha X_2}{K}) - H_1 - \tfrac{a_1 Y}{g_1+X_1+X_2}) + (X_2 - 1)(r_2(1 - \tfrac{\beta X_1+X_2}{K}) \\ &\quad + \tfrac{S_1 X_1}{X_2} - \tfrac{a_2 Y}{g_2+X_1+X_2}) + (Y - 1)(C - \mu) + S_2 - \tfrac{S_2}{Y} + \tfrac{1}{2}\delta_1^2 + \tfrac{1}{2}\delta_2^2 + \tfrac{1}{2}\delta_3^2 \\ &= X_1 W_1 - \tfrac{W_1}{K}X_1^2 - \tfrac{W_1 \alpha X_1 X_2}{K} - H_1 X_1 - \tfrac{a_1 Y X_1}{g_1+X_1+X_2} - W_1 + \tfrac{W_1 X_1}{K} + \tfrac{\alpha W_1 X_2}{K} + H_1 \\ &\quad + \tfrac{a_1 Y}{g_1+X_1+X_2} + r_2 X_2 - \tfrac{r_2 \beta X_1 X_2}{K} - \tfrac{r_2 \beta}{K}X_2^2 + S_1 X_1 - \tfrac{a_2 Y X_2}{g_2+X_1+X_2} - r_2 + \tfrac{r_2 \beta}{K}X_1 \\ &\quad + \tfrac{r_2 X_2}{K} - \tfrac{S_1 X_1}{X_2} - \tfrac{a_2 Y}{g_2+X_1+X_2} + CY - \mu Y - C + \mu + S_2 - \tfrac{S_2}{Y} + \tfrac{1}{2}\delta_1^2 + \tfrac{1}{2}\delta_2^2 + \tfrac{1}{2}\delta_3^2. \end{aligned}$$

Then

$$\begin{aligned} LV &\leq -\frac{W_1}{K}X_1^2 + (W_1 + \frac{W_1}{K} + S_1 + \frac{r_2\beta}{K})X_1 \\ &\quad -\frac{r_2}{K}X_2^2 + (\frac{W_1\alpha}{K} + r_2 + \frac{r_2}{K})X_2 \\ &\quad +\frac{1}{Y}(-(\mu - C - \frac{a_1}{g_1} - \frac{a_2}{g_2})Y^2 + S_2) \\ &\quad +H_1 + S_2 + \mu + \frac{1}{2}\delta_1^2 + \frac{1}{2}\delta_2^2 + \frac{1}{2}\delta_3^2, \end{aligned}$$

where

$$\varphi(X_1) = -\frac{W_1}{K}X_1^2 + (W_1 + \frac{W_1}{K} + S_1 + \frac{r_2\beta}{K})X_1,$$
$$\varphi(X_2) = -\frac{r_2}{K}X_2^2 + (\frac{W_1\alpha}{K} + r_2 + \frac{r_2}{K})X_2,$$
$$\varphi(Y) = -(\mu - C - \frac{a_1}{g_1} - \frac{a_2}{g_2})Y^2 + S_2.$$

Clearly, $\varphi(X_1)$ and $\varphi(X_2)$ are both quadratic functions with negative leading coefficients, which indicates that they are upper bounded. Similarly, $\varphi(Y)$ is also upper bounded if $\mu - C - a_1/g_1 - a_2/g_2 > 0$. Consequently, $\varphi(X_1) + \varphi(X_2) + \varphi(Y)$ is always upper bounded, i.e., we have

$$LV \leq M,$$

where

$$M = \varphi(X_1)_{\max} + \varphi(X_2)_{\max} + \varphi(Y)_{\max} + H_1 + S_2 + \mu + \frac{1}{2}\delta_1^2 + \frac{1}{2}\delta_2^2 + \frac{1}{2}\delta_3^2,$$

with M being positive. Thus,

$$dV \leq Mdt + \delta_1(X_1 - 1)dB_1(t) + \delta_2(X_2 - 1)dB_2(t) + \delta_3(Y - 1)dB_3(t). \tag{4.2}$$

Integrating both sides of this inequality from 0 to $\tau_k \wedge T_1$ and taking the expectation on both sides, then

$$E(V(X_1(\tau_k \wedge T_1), X_2(\tau_k \wedge T_1), Y(\tau_k \wedge T_1))) \leq V(X_1(0), X_2(0), Y(0)) + MT_1. \tag{4.3}$$

Let $\Omega_k = \{\tau_k \leq T_1\}$ at this moment with $k \geq k_1$. The inequality (4.1) leads to $P(\Omega_k) \geq \varepsilon$. Note that each of $\omega \in \Omega_k$, $X_1(\tau_k, \omega)$ or $X_2(\tau_k, \omega)$ or $Y(\tau_k, \omega)$ equals either k or $1/k$,

$$V(X_1(\tau_k \wedge T_1, \omega), X_2(\tau_k \wedge T_1, \omega), Y(\tau_k \wedge T_1, \omega)) \geq \min\{k - 1 - \ln k, \frac{1}{k} - 1 + \ln k\}. \tag{4.4}$$

From (4.3) and (4.4),

$$\begin{aligned} V(X_1(0), X_2(0), Y(0)) + MT_1 &\geq E(1_{\Omega_k}(\omega)V(X_1(\tau_k, \omega), X_2(\tau_k, \omega), Y(\tau_k, \omega))) \\ &\geq \varepsilon \min\{k - 1 - \ln k, \frac{1}{k} - 1 + \ln k\}, \end{aligned}$$

where 1_{Ω_k} is the indicator function of Ω_k. If $k \to \infty$, then

$$\infty > V(X_1(0), X_2(0), Y(0)) + MT_1 = \infty,$$

which is a contradiction. Therefore, $\tau_\infty = \infty \quad a.s.$ This completes the proof.

Theorem 4.1 indicates that system (3.7) exists with a unique global positive solution $Z(t) = (X_1(t), X_2(t), Y(t))$ for all $t \geq 0$ almost surely, which is the precondition to study other properties of the solution of system (3.7).

Theorem 4.2. If $\mu - C > 0$, then the positive solutions $Z(t) = (X_1(t), X_2(t), Y(t))$ of system (3.7) are stochastically ultimately bounded.

Proof. Let $V(t,X)=e^tX^p$ with $p>1$, then the application of Itô's formula leads to

$$\begin{aligned}
dV(X_1) &= e^tX_1^pdt+e^tpX_1^{p-1}[(W_1(1-\tfrac{X_1+\alpha X_2}{K})-H_1-\tfrac{a_1Y}{g_1+X_1+X_2})X_1dt\\
&\quad +\delta_1X_1dB_1(t)]+\tfrac{p(p-1)}{2}e^tX_1^{p-2}X_1^2dt\\
&= e^tX_1^p+e^tpX_1^p((W_1-\tfrac{W_1X_1}{K}-\tfrac{W_1\alpha X_2}{K}-H_1-\tfrac{a_1Y}{g_1+X_1+X_2})\\
&\quad +\tfrac{p-1}{2}\delta_1^2)dt+pe^t\delta_1X_1^pdB_1(t)\\
&\leq e^tX_1^{p-1}\{(1+p(W_1+\tfrac{p-1}{2}\delta_1^2))X_1-p\tfrac{W_1}{K}X_1^2\}dt\\
&\quad +pe^t\delta_1X_1^pdB_1(t).
\end{aligned}$$

Denote

$$g(X_1)=(1+p(W_1+\frac{p-1}{2}\delta_1^2))X_1-p\frac{W_1}{K}X_1^2.$$

Let $A_1=pP_1/K>0$ and $A_2=1+p(W_1+(p-1)\delta_1^2/2)>0$, then

$$g(X_1)=-A_1X_1^2+A_2X_1.$$

Apparently, $g(X_1)$ is always upper bounded and let M_1 be its upper bound, thus,

$$dV(X_1)\leq M_1e^tdt+pe^t\delta_1X_1^pdB_1(t).$$

Integrating the above inequality from 0 to t and taking the expectation yields

$$E[e^tX_1^p(t)]\leq X_1^p(0)+M_1(e^t-1),$$

then

$$E[X_1^p(t)]\leq X_1^p(0)e^{-t}+M_1(1-e^{-t}).$$

As a result,

$$\limsup_{t\to+\infty}E[X_1^p(t)]\leq M_1. \tag{4.5}$$

By using the same methods,

$$\begin{aligned}
dV(e^tX_2^p) &= e^t\{(1+p(r_2(1-\tfrac{\beta X_1+X_2}{K})+\tfrac{p-1}{2}))X_2^p+pS_1X_1X_2^{p-1}\\
&\quad -\tfrac{pa_2YX_2^p}{g_2+X_1+X_2})\}dt+pe^t\delta_2X_2^pdB_2(t)\\
&\leq e^t\{(1+p(r_2+\tfrac{p-1}{2}\delta_2^2))X_2^p+pS_1X_1X_2^{p-1}-\tfrac{pr_2}{K}X_2^{p+1}\\
&\quad -\tfrac{pa_2YX_2^p}{g_2+X_1+X_2}\}dt+pe^t\delta_2X_2^pdB_2(t)\\
&\leq M_2e^t+pe^t\delta_2X_2^pdB_2(t),
\end{aligned}$$

where M_2 is a positive constant. Integrating the above inequality from 0 to t and taking the expectation from both sides, then

$$E[e^tX_2^p(t)]\leq X_2^p(0)+M_2(e^t-1),$$

which implies

$$E[X_2^p(t)]\leq X_2^p(0)e^{-t}+M_2(1-e^{-t}).$$

Thereby,

$$\limsup_{t\to+\infty} E[X_2^p(t)] \leq M_2. \tag{4.6}$$

Using the same method,

$$\begin{aligned} dV(e^tY^p) &= e^t[1+p(C-\mu+\tfrac{S_2}{Y}+\tfrac{p-1}{2}\delta_3^2)]Y^p dt \\ &\quad +pe^t\delta_3 Y^p dB_3(t) \\ &\leq e^t[1+p(\tfrac{-(\mu-C)Y^2+S_2Y}{Y^2}+\tfrac{p-1}{2}\delta_3^2)]Y^p dt \\ &\quad +pe^t\delta_3 Y^p dB_3(t) \\ &\leq M_3 e^t dt + pe^t\delta_3 Y^p dB_3(t), \end{aligned}$$

where M_3 is a positive constant.
Thus,

$$\limsup_{t\to+\infty} E[Y^p(t)] \leq M_3. \tag{4.7}$$

Notice that

$$(X_1(t)^2+X_2(t)^2+Y(t)^2)^{p/2} \leq 3^{p/2}(X_1(t)^p+X_2(t)^p+Y(t)^p).$$

If follows from (4.5), (4.6) and (4.7) that

$$\limsup_{t\to+\infty} E(|Z|^p) \leq 3^{p/2}[M_1+M_2+M_3] < \infty.$$

By Chebychev's inequality, the solutions of system (3.7) are stochastically ultimately bounded. The proof is completed.

Remark 2. Theorem 4.2 implies that the number of prostate cancer cells will be controlled and they will not grow indefinitely.

Next we show that the Markov process $Z(t) = (X_1(t), X_2(t), Y(t))$ is V-geometrically ergodic [43].

Theorem 4.3. For $Z_0 \in \mathbb{R}^3_+$, if $\delta_1 > 0$, $\delta_2 > 0$, $\delta_3 > 0$ and $\mu - C > 0$, then Markov process $Z(t) = (X_1(t), X_2(t), Y(t))$ is V-geometrically ergodic.

Proof. Denote $N = X_1 + X_2 + Y$, defining a Lyapunov function $V(Z(t))$ such that $V(Z(t)) \to \infty$ as $\mid Z(t) \mid \to \infty$ for $Z(t) \in \mathbb{R}^3_+$, where

$$V(Z(t)) = N + \frac{1}{N}. \tag{4.8}$$

Applying Itô's formula yields

$$\begin{aligned}
LV(Z(t)) &= (1-\tfrac{1}{N^2})dN + \tfrac{\delta_1^2X_1^2+\delta_2^2X_2^2+\delta_3^2Y^2}{N^3} \\
&= (W_1-H_1)X_1 - \tfrac{W_1X_1^2}{K} - \tfrac{W_1\alpha X_1X_2}{K} - \tfrac{X_1Y}{g_1+X_1+X_2} + r_2X_2 \\
&\quad -\tfrac{r_2\beta X_1X_2}{K} - \tfrac{r_2X_2^2}{K} + S_1X_1 - \tfrac{a_2X_2Y}{g_2+X_1+X_2} + (C-\mu)Y \\
&\quad +S_2 - \tfrac{dN}{N^2} + \tfrac{\delta_1^2X_1^2+\delta_2^2X_2^2+\delta_3^2Y^2}{N^3} \\
&\leq -\tfrac{W_1X_1^2}{K} + (W_1+S_1)X_1 - \tfrac{r_2X_2^2}{K} + (r_2+1)X_2 - H_1X_1 - X_2 \\
&\quad +(C-\mu)Y + S_2 - \tfrac{dN}{N^2} + \tfrac{\delta_1^2X_1^2+\delta_2^2X_2^2+\delta_3^2Y^2}{N^3} \qquad (4.9) \\
&\leq \tfrac{K(W_1+S_1)^2}{4W_1} + \tfrac{K(r_2+1)^2}{4r_2} - \rho N + S_2 - \tfrac{\rho N-2\rho N}{N^2} + \tfrac{\delta_1^2X_1^2+\delta_2^2X_2^2+\delta_3^2Y^2}{N^3} \\
&= \tfrac{K(W_1+S_1)^2}{4W_1} + \tfrac{K(r_2+1)^2}{4r_2} - \rho V(Z) + S_2 + \tfrac{2\rho N}{N^2} + \tfrac{\delta_1^2X_1^2+\delta_2^2X_2^2+\delta_3^2Y^2}{N^3} \\
&\leq (\tfrac{K(W_1+S_1)^2}{4W_1} + \tfrac{K(r_2+1)^2}{4r_2} + S_2 + 2\rho) + \tfrac{\delta_1^2+\delta_2^2+\delta_3^2}{N} - \rho V(Z) \\
&\leq (\tfrac{K(W_1+S_1)^2}{4W_1} + \tfrac{K(r_2+1)^2}{4r_2} + S_2 + 2\rho + \delta_1^2 + \delta_2^2 + \delta_3^2) - \rho V(Z) \\
&= D^* - \rho V(Z),
\end{aligned}$$

where

$$D^* = \frac{K(W_1+S_1)^2}{4W_1} + \frac{K(r_2+1)^2}{4r_2} + S_2 + 2\rho + \delta_1^2 + \delta_2^2 + \delta_3^2, \quad \rho = \min\{H_1, 1, \mu - C\}.$$

It implies that condition (2) (Lyapunov condition) of Lemma 2.6 holds.

If $\delta_1 > 0$, $\delta_2 > 0$ and $\delta_3 > 0$, then SDE (3.7) is uniformly elliptic [45]. Defining a jointly continuous function as $q : \mathbb{R}_+ \times \mathbb{R}_+^3 \times \mathbb{R}_+^3 \to (0, \infty)$. For each (t, Z_0, P), $q_t(Z_0, P)$ is strictly positive and for all measure sets B we obtain

$$q_t(Z_0, B) = \int_B q_t(Z_0, P)dP.$$

For any $\varpi > 0$, there is a positive constant $b = b(\varpi, t) > 0$ such that $\inf\{q_t(Z_0, P) : Z_0, P \in \mathbb{R}_+^3, \mid Z_0 \mid, \mid P \mid \leq \varpi\} \geq b$. So for any measurable set B,

$$q_t(Z, B) = \textstyle\int_B q_t(Z_0, P)dP \geq b\text{Leb}(B \cap \mathcal{B}_\varpi(0)) = b\text{Leb}(\mathcal{B}_\varpi(0))m(B),$$

where $m(B) = \text{Leb}(B \cap \mathcal{B}_\varpi(0))/\text{Leb}(\mathcal{B}_\varpi(0))$ and Leb is the Lebesgue measure. It indicates that condition (1) (Minorization condition) of Lemma 2.6 holds true. Therefore, the Markov process $Z(t) = (X_1(t), X_2(t), Y(t))$ is V-geometrically ergodic. This completes the proof.

Theorem 4.4. The solution of system (3.7) is globally attractive.

Proof. Without loss of generality, we assume that $Z_1(t) = (x_1(t), y_1(t), z_1(t))$ and $Z_2(t) = (x_2(t), y_2(t), z_2(t))$ be any two solutions of system (3.7) with initial values $Z_1(0) > 0$ and $Z_2(0) > 0$. Since $(X_1(t), X_2(t), Y(t))$ is stochastically ultimately bounded, then there are four positive constants $N_1 > 0, c_1 > 0, c_2 > 0, c_3 > 0$ such that $X_1 \leq N_1, X_2 \leq N_1$ and $Y \leq N_1$ almost surely for all $t \geq T_0$, and we assume that $N_1 = c_1X_1 = c_2X_2 = c_3Y$. Defining the following Lyapunov function:

$$V(t) = \mid \ln x_1(t) - \ln x_2(t) \mid + \mid \ln y_1(t) - \ln y_2(t) \mid + \mid \ln z_1(t) - \ln z_2(t) \mid,$$

where $t > 0$ and $t \neq nT$. By calculating the upper right derivative $d^+V(t)$ of $V(t)$ and employing the Itô's formula on (3.7), we get

$$\begin{aligned}
d^+V(t) &= sign(x_1(t)-x_2(t))d(\ln x_1(t)-\ln x_2(t)) \\
&\quad +sign(y_1(t)-y_2(t))d(\ln y_1(t)-\ln y_2(t)) \\
&\quad +sign(z_1(t)-z_2(t))d(\ln z_1(t)-\ln z_2(t)) \\
&\leq sign(x_1(t)-x_2(t))[-\tfrac{W_1}{K}(x_1(t)-x_2(t))-\tfrac{W_1\alpha}{K}(y_1(t)-y_2(t)) \\
&\quad +\tfrac{-\frac{a_1}{g_1}(z_1(t)-z_2(t))}{(1+\frac{c_3}{g_1}z_1(t))(1+\frac{c_3}{g_1}z_2(t))}]dt \\
&\quad +sign(y_1(t)-y_2(t))[-\tfrac{r_2}{K}(y_1(t)-y_2(t))-\tfrac{r_2\beta}{K}(x_1(t)-x_2(t)) \\
&\quad +\tfrac{-\frac{a_2}{g_2}(z_1(t)-z_2(t))}{(1+\frac{c_3}{g_2}z_1(t))(1+\frac{c_3}{g_2}z_2(t))}]dt \\
&\leq [-(\tfrac{W_1}{K}+\tfrac{r_2\beta}{K}) \mid x_1(t)-x_2(t) \mid -(\tfrac{W_1\alpha}{K}+\tfrac{r_2}{K}) \mid y_1(t)-y_2(t) \mid \\
&\quad -(\tfrac{a_1}{g_1(1+\frac{c_3}{g_1}N_1)^2}+\tfrac{a_2}{g_2(1+\frac{c_3}{g_2}N_1)^2}) \mid z_1(t)-z_2(t) \mid]dt \\
&\leq -\rho(\mid x_1(t)-x_2(t) \mid + \mid y_1(t)-y_2(t) \mid + \mid z_1(t)-z_2(t) \mid)dt \\
&\doteq -\rho\mathbb{V}(t)dt,
\end{aligned} \tag{4.10}$$

where $\rho = \min\{W_1/K + r_2\beta/K, W_1\alpha/K + r_2/K, a_1/g_1(1+\frac{c_3}{g_1}N_1)^2 + a_2/(g_2(1+\frac{c_3}{g_2}N_1)^2)\}$. When $t = nT$,

$$\begin{aligned}
V(nT^+) &= \mid \ln x_1(nT^+)-\ln x_2(nT^+) \mid + \mid \ln y_1(nT^+)-\ln y_2(nT^+) \\
&\quad + \mid \ln z_1(nT^+)-\ln z_2(nT^+) \mid \\
&= \mid \ln x_1(nT)-\ln x_2(nT) \mid + \mid \ln y_1(nT)-\ln y_2(nT) \mid \\
&\quad + \mid \ln z_1(nT)-\ln z_2(nT) \mid \\
&= V(nT).
\end{aligned}$$

Integrating equation (4.10) from 0 to t and taking expectation of both sides gives

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

Hence,

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

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

$$\lim_{t\to\infty} \mid x_1(t)-x_2(t) \mid = 0 \quad \text{and} \quad \lim_{t\to\infty} \mid y_1(t)-y_2(t) \mid = 0 \quad \text{and} \quad \lim_{t\to\infty} \mid z_1(t)-z_2(t) \mid = 0.$$

This completes the proof.

4.2. Extinction and persistence in mean

In this subsection, the threshold conditions for the extinction and persistence of prostate cancer cells will be studied.

Theorem 4.5. (i) Assume that

$$W_1 - H_1 < \frac{1}{2}\delta_1^2, \tag{4.11}$$

(a) then AD cells X_1 go to extinction;
(b) if

$$r_2 - \frac{\delta_2^2}{2} < 0, \tag{4.12}$$

then AI cells X_2 go to extinction;
(c) if

$$C - \mu < \frac{\delta_3^2}{2} \quad \text{and} \quad r_2 - r_2\beta - \frac{\delta_2^2}{2} > 0, \tag{4.13}$$

then AI cells X_2 are persistent in mean.
(ii) If

$$C - \mu < \frac{\delta_3^2}{2} \quad \text{and} \quad W_1 - H_1 - W_1\alpha - \frac{1}{2}\delta_1^2 > 0, \tag{4.14}$$

then AD cells X_1 are persistent in mean.

Proof. (i)(a) For a positive solution of (2.2), we get

$$dX_1(t) \leq (W_1 - H_1 - \frac{W_1}{K}X_1)X_1dt + \delta_1 X_1 dB_1(t).$$

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

$$d\varphi(t) = (W_1 - H_1 - \frac{W_1}{K}\varphi)\varphi dt + \delta_1\varphi dB_1(t), \quad \varphi(0) = X_1(0), \quad \text{for} \quad \text{all} \quad t \geq 0.$$

The comparison principle of stochastic differential equations [46] leads to

$$X_1(t) \leq \varphi(t) \quad \text{for} \quad \text{all} \quad t \geq 0.$$

A simple calculation yields

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

Therefore,

$$\lim_{t\to+\infty} X_1(t) = 0 \quad a.s.$$

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

$$\bar{\Omega} = \{\omega \in \Omega : \lim_{t\to+\infty} X_1(\omega, t) = 0\}.$$

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

$$X_1(\omega, t) < \varepsilon \quad \text{for} \quad t \geq T_2. \tag{4.15}$$

(i)(b) Now let us prove the extinction of X_2 under (4.11) and (4.12). From (4.15),

$$dX_2(\omega,t) \leq (r_2 X_2(\omega,t) + S_1\varepsilon)dt + \delta_2 X_2(\omega,t)dB_2(\omega,t)$$

for all $t \geq T_2$ and $\omega \in \bar{\Omega}$.
Notice that

$$\phi(t,\omega) = \phi(0,\omega)e^{t(r_2 - \frac{\delta_2^2}{2} + \sigma_2 \frac{B_2(t,\omega)}{t})} + S_1\varepsilon \int_0^t e^{(t-s)(r_2 - \frac{\delta_2^2}{2} + \delta_2 \frac{B_2(t,\omega) - B_2(s,\omega)}{t-s})} ds, \tag{4.16}$$

and it satisfies the following equation

$$d\phi = (r_2\phi + S_1\varepsilon)dt + \delta_2 \phi dB_2(t). \tag{4.17}$$

According to Lemma 2.3, for any $\epsilon \in (0,1)$, there exists a state with a large T_3 such that

$$\left| \frac{B_2(t,\omega) - B_2(s,\omega)}{t-s} \right| < \epsilon \quad \text{for} \quad \text{all} \quad t - s > T_3 \tag{4.18}$$

almost surely. Without loss of generality, for any $\omega \in \bar{\Omega}$ we assume (4.18) is true. Choosing ϵ such that $2(r_2 + \delta_2\epsilon) - \delta_2^2 < 0$. For $t \geq T_3$,

$$\phi(t,\omega) \leq \phi(0,\omega)e^{t(r_2 - \frac{\delta_2^2}{2} + \delta_2\epsilon)} + \varepsilon\left(S_1 D_1 + \int_{T_3}^t S_1 e^{v(r_2 - \frac{\delta_2^2}{2} + \delta_2\epsilon)} dv \right), \tag{4.19}$$

where

$$D_1 = \int_0^{T_3} e^{v(r_2 - \frac{\delta_2^2}{2}) + \delta_2(B_2(t,\omega) - B_2(t-v,\omega))} dv.$$

It follows from the Kolmogrov Theorem [47] that there is a positive constant M_4 such that

$$D_1 \leq M_4, \quad \text{for} \quad \text{all} \quad t \geq T_3.$$

Because of (4.19),

$$\limsup_{t \to +\infty} \phi(t,\omega) \leq S_1\varepsilon(M_4 - \frac{e^{L_1 T_3}}{L_1}),$$

where

$$L_1 = r_2 - \frac{\delta_2^2}{2} + \delta_2\epsilon < 0.$$

As a result of the arbitrariness of ε,

$$\limsup_{t \to +\infty} \phi(t,\omega) = 0.$$

If $\phi(0) = X_2(0)$, then according to the comparison principle we have

$$\limsup_{t \to +\infty} X_2(t,\omega) = 0, \quad \text{for} \quad \text{all} \quad \omega \in \bar{\Omega}.$$

While $P(\bar{\Omega}) = 1$, so

$$\lim_{t \to +\infty} X_2(t) = 0 \quad a.s.$$

(i)(c) Now let us prove the persistence in mean of X_2 under (4.11) and (4.13). By (4.15) and Theorem 3.2, we obtain

$$\begin{aligned} Y(t,\omega) &= Y(0,\omega)\exp[(C-\mu-\tfrac{\delta_3^2}{2})t+\delta_3 B_3(t)] \\ &\quad + \int_0^t S_2 \exp[(C-\mu-\frac{\delta_3^2}{2})(t-s)+\delta_3(B_3(t)-B_3(s))]ds \end{aligned}$$

for all $t \geq 0$, and $\omega \in \bar{\Omega}$. According to Lemma 2.3, for any $\epsilon_1 \in (0,1)$, there exists a state with a large T_4 such that

$$\left|\frac{B_3(t,\omega)-B_3(s,\omega)}{t-s}\right| < \epsilon_1 \quad \text{for} \quad \text{all} \quad t-s > T_4 \tag{4.20}$$

almost surely. Similarly, for any $\omega \in \bar{\Omega}$ we assume (4.20) is true. Choosing ϵ_1 such that $2(C-\mu+\delta_3\epsilon_1)-\delta_3^2 < 0$. For $t \geq T_4$,

$$\begin{aligned} Y(t,\omega) &= Y(0,\omega)\exp(C-\mu-\tfrac{\delta_3^2}{2}+\delta_3\epsilon_1)t \\ &\quad + \left(E_1 S_2 + \textstyle\int_{T_4}^t S_2 e^{u(C-\mu-\frac{\delta_3^2}{2}+\delta_3\epsilon_1)}du\right), \end{aligned} \tag{4.21}$$

where

$$E_1 = \int_0^{T_4} e^{u(C-\mu-\frac{\delta_3^2}{2})+\delta_3(B_3(t,\omega)-B_3(t-u,\omega))}du.$$

By the Kolmogrov Theorem [47], there is a positive constant M_5 such that

$$E_1 \leq M_5, \quad \text{for} \quad \text{all} \quad t \geq T_4.$$

Because of (4.21), for any $\omega \in \bar{\Omega}$, there exist two constants $\varepsilon_1 > 0$ and $T_4(\omega,\varepsilon_1) > 0$ such that

$$\limsup_{t\to+\infty} Y(t,\omega) \leq S_2(M_5 - \frac{e^{L_2 T_4}}{L_2}) < \varepsilon_1,$$

where

$$L_2 = C-\mu-\frac{\delta_3^2}{2}+\delta_3\epsilon_1 < 0.$$

Thus,

$$Y(\omega,t) < \varepsilon_1 \quad \text{for} \quad t \geq T_4. \tag{4.22}$$

Assume that (4.11) and (4.13) are satisfied. Because of (4.11), the (4.22) are satisfied for $0 < \varepsilon_1 < g_2(r_2 - r_2\beta - \delta_2^2/2)/a_2$. Hence, for $t \geq T_4$ and $\omega \in \bar{\Omega}$, we have

$$dX_2(\omega,t) \geq r_2\left(1-\beta-\frac{X_2(\omega,t)}{K}-\frac{a_2\varepsilon_1}{r_2 g_2}\right)X_2(\omega,t)dt + \delta_2 X_2(\omega,t)dB_2(\omega,t).$$

Let φ be the solution of

$$d\varphi(t) = r_2(1-\beta-\frac{\varphi}{K}-\frac{a_2\varepsilon_1}{r_2 g_2})\varphi dt + \delta_2\varphi dB_2(t), \quad \varphi(0) = X_2(0).$$

Then

$$\lim_{t\to+\infty}\frac{1}{t}\int_0^t\varphi(s)ds=\frac{K}{r_2}(r_2(1-\beta-\frac{a_2\varepsilon_1}{r_2g_2})-\frac{1}{2}\delta_2^2)>0.$$

By the comparison principle, we obtain

$$\limsup_{t\to+\infty}\frac{1}{t}\int_0^t X_2(s,\omega_1)ds\geq\frac{K}{r_2}\left(r_2(1-\beta-\frac{a_2\varepsilon_1}{r_2g_2})-\frac{1}{2}\delta_2^2\right)>0\quad\text{for}\quad\text{all}\quad\omega\in\bar{\Omega}.$$

In view of $P(\bar{\Omega})=1$, thus

$$\limsup_{t\to+\infty}\frac{1}{t}\int_0^t X_2(s)ds\geq\frac{K}{r_2}\left(r_2(1-\beta-\frac{a_2\varepsilon_1}{r_2g_2})-\frac{1}{2}\delta_2^2\right)>0\quad a.s.$$

(ii) Similarly, consider the inequality (4.22) conforms to $0<\varepsilon_1<g_1(W_1-H_1-W_1\alpha-\delta_1^2/2)/a_1$ under (4.14). For $t\geq T_4$ and $\omega\in\bar{\Omega}$, we get

$$dX_1(\omega,t)\geq[W_1-H_1-W_1\alpha-\frac{a_1\varepsilon_1}{g_1}-\frac{W_1}{K}X_1]X_1(\omega,t)dt+\delta_1X_1(\omega,t)dB_1(\omega,t).$$

Let φ be the solution of

$$d\varphi(t)=[W_1-H_1-W_1\alpha-\frac{a_1\varepsilon_1}{g_1}-\frac{W_1}{K}\varphi]\varphi dt+\delta_1\varphi dB_1(\omega,t),\quad\varphi(0)=X(0).$$

Hence,

$$\lim_{t\to+\infty}\frac{1}{t}\int_0^t\varphi(s)ds=\frac{K}{W_1}(W_1-H_1-W_1\alpha-\frac{a_1\varepsilon_1}{g_1}-\frac{\delta_1^2}{2})>0.$$

Applying the comparison principle,

$$\limsup_{t\to+\infty}\frac{1}{t}\int_0^t X_1(s,\omega)ds\geq\frac{K}{W_1}(W_1-H_1-W_1\alpha-\frac{a_1\varepsilon_1}{g_1}-\frac{\delta_1^2}{2})>0\quad\text{for}\quad\text{all}\quad\omega\in\bar{\Omega}.$$

Notice that $P(\bar{\Omega})=1$, then

$$\limsup_{t\to+\infty}\frac{1}{t}\int_0^t X_1(s)ds\geq\frac{K}{W_1}(W_1-H_1-W_1\alpha-\frac{a_1\varepsilon_1}{g_1}-\frac{\delta_1^2}{2})>0\quad a.s.$$

This completes the proof.

Assumption 1. Theorem 4.2 reveals that X_1, X_2 and Y are always bounded, existing with three positive constants J_1, J_2 and J_3 such that $0\leq X_1\leq J_1$, $0\leq X_2\leq J_2$ and $0\leq Y\leq J_3$. Moreover, $0\leq\frac{a_1Y}{g_1+X_1+X_2}\leq\frac{a_1K}{g_1+2K}\doteq G_1$ and $0\leq\frac{a_2Y}{g_1+X_1+X_2}\leq\frac{a_2K}{g_2+2K}\doteq G_2$.

Theorem 4.6. Under assumption 1, if $\kappa_1=\min_{t\geq0}[W_1-H_1-W_1\alpha-\frac{1}{2}\delta_1^2-a_1G_1]>0$ and $\kappa_2=\min_{t\geq0}[r_2-r_2\beta-\frac{1}{2}\delta_2^2-a_2G_2]>0$, then the AD and AI cells are stochastically permanent, respectively.

Proof. We only need to prove that there are four constants $\beta_i>0$ and $\varrho_i>0$ such that $\liminf_{t\to+\infty}\mathbb{P}\{X_i(t)\geq\beta_i\}\geq1-\varepsilon$ and $\liminf_{t\to+\infty}\mathbb{P}\{X_i(t)\leq\varrho_i\}\geq1-\varepsilon$ for any $\varepsilon\in(0,1)$, where $i=1,2$.

For the first inequality, defining Lyapunov function $V^1(X_i) = 1/X_i$ $(i = 1, 2, X_i > 0)$ and applying Itô's formula to the first two equations of system (3.7), we have

$$\begin{aligned} dV^1(X_1) &= -\tfrac{dX_1}{X_1^2} + \tfrac{{dX_1}^2}{X_1^3} \\ &= -\tfrac{1}{X_1}\{[W_1(1 - \tfrac{X_1+\alpha X_2}{K}) - H_1 - \tfrac{a_1 Y}{g_1+X_1+X_2}] \\ &\quad +\delta_1 dB_1(t)\} + \tfrac{1}{X_1}\delta_1^2 dt \\ &= -V^1(X_1)(W_1 - H_1 - \tfrac{W_1 X_1}{K} - \tfrac{W_1\alpha X_2}{K} - \tfrac{a_1 Y}{g_1+X_1+X_2})dt + V^1(X_1)\delta_1^2 dt \\ &\quad -V^1(X_1)\delta_1 dB_1(t), \end{aligned}$$

and

$$\begin{aligned} dV^1(X_2) &= -\tfrac{dX_2}{X_2^2} + \tfrac{{dX_2}^2}{X_2^3} \\ &= -\tfrac{1}{X_2}\{[r_2(1 - \tfrac{\beta X_1+X_2}{K}) + S_1 X_1 X_2 - \tfrac{a_2 Y}{g_2+X_1+X_2}] \\ &\quad +\delta_2 dB_2(t)\} + \tfrac{1}{X_2}\delta_2^2 dt \\ &= -V^1(X_2)(r_2 - \tfrac{r_2 X_2}{K} - \tfrac{r_2\beta X_1}{K} + S_1 X_1 X_2 - \tfrac{a_2 Y}{g_2+X_1+X_2})dt + V^1(X_2)\delta_2^2 dt \\ &\quad -V^1(X_2)\delta_2 dB_2(t). \end{aligned}$$

Selecting two positive constants ϑ_1 and ϑ_2 such that $\kappa_i > 0.5\vartheta_i\delta_i^2$ $(i = 1, 2)$, then we define another Lyapunov function $V^2(X_i) = (1 + V^1(X_i))^{\vartheta_i} (i = 1, 2)$, by using Itô's formula gives

$$\begin{aligned} dV^2(X_1) &= \vartheta_1(1 + V^1(X_1))^{\vartheta_1 - 1} dV^1(X_1) + 0.5\vartheta_1(\vartheta_1 - 1)(1 + V^1(X_1))^{\vartheta_1 - 2}(dV^1(X_1))^2 \\ &= \vartheta_1(1 + V^1(X_1))^{\vartheta_1 - 2}\{(-V^1(X_1) - (V^1(X_1))^2)[W_1 - H_1 - \tfrac{W_1 X_1}{K} - \tfrac{W_1\alpha X_2}{K} \\ &\quad -\tfrac{a_1 Y}{g_1+X_1+X_2}] + (V^1(X_1) + (V^1(X_1))^2)\delta_1^2 + 0.5(\vartheta_1 - 1)(V^1(X_1))^2\delta_1^2\}dt \\ &\quad -\vartheta_1(1 + V^1(X_1))^{\vartheta_1 - 1} V^1(X_1)\delta_1 dB_1(t) \\ &= \vartheta_1(1 + V^1(X_1))^{\vartheta_1 - 2}\{-(V^1(X_1))^2[W_1 - H_1 - \tfrac{W_1\alpha X_2}{K} - \tfrac{a_1 Y}{g_1+X_1+X_2} - 0.5\delta_1^2 \\ &\quad -0.5\vartheta_1\delta_1^2] + V^1(X_1)\{[-(W_1 - H_1 - \tfrac{W_1 X_1}{K} - \tfrac{a_1 Y}{g_1+X_1+X_2}) + \delta_1^2] + \tfrac{W_1 X_1}{K}\}dt \\ &\quad -\vartheta_1(1 + V^1(X_1))^{\vartheta_1 - 1} V^1(X_1)\delta_1 dB_1(t) \\ &\leq \vartheta_1(1 + V^1(X_1))^{\vartheta_1 - 2}\{-(V^1(X_1))^2[\kappa_1 - 0.5\vartheta_1\delta_1^2] \\ &\quad +V^1(X_1)[H_1 + \tfrac{W_1 J_1}{K} + a_1 G_1 + \delta_1^2] + \tfrac{W_1 G_1}{K}\}dt \\ &\quad -\vartheta_1(1 + V^1(X_1)^{\vartheta_1 - 1} V^1(X_1)\delta_1 dB_1(t), \end{aligned}$$

and

$$\begin{aligned}
dV^2(X_2) &= \vartheta_2(1+V^1(X_2))^{\vartheta_2-1}dV^1(X_2) + 0.5\vartheta_2(\vartheta_2-1)(1+V^1(X_1))^{\vartheta_2-2}(dV^1(X_1))^2 \\
&= \vartheta_2(1+V^1(X_2))^{\vartheta_2-2}\{(-V^1(X_2)-(V^1(X_2))^2)[r_2 - \tfrac{r_2X_2}{K} - \tfrac{r_2\beta X_1}{K} + S_1X_1X_2 \\
&\quad -\tfrac{a_2Y}{g_2+X_1+X_2}] + (V^1(X_2)+(V^1(X_2))^2)\delta_2^2 + 0.5(\vartheta_2-1)(V^1(X_2))^2\delta_2^2\}dt \\
&\quad -\vartheta_2(1+V^1(X_2))^{\vartheta_2-1}V^1(X_2)\delta_2 dB_2(t) \\
&= \vartheta_2(1+V^1(X_2))^{\vartheta_2-2}\{-(V^1(X_2))^2[r_2 - \tfrac{r_2\beta X_1}{K} + S_1X_1X_2 - \tfrac{a_2Y}{g_2+X_1+X_2} - 0.5\delta_2^2 \\
&\quad -0.5\vartheta_2\delta_2^2] + V^1(X_2)\{[-(r_2 - \tfrac{r_2\beta X_2}{K} + S_1X_1X_2 - \tfrac{a_2Y}{g_2+X_1+X_2}) + \delta_2^2] + \tfrac{r_2X_2}{K}\}dt \\
&\quad -\vartheta_2(1+V^1(X_2))^{\vartheta_2-1}V^1(X_2)\delta_2 dB_2(t) \\
&\le \vartheta_2(1+V^1(X_2))^{\vartheta_2-2}\{-(V^1(X_2))^2[\kappa_2 - 0.5\vartheta_2\delta_2^2] \\
&\quad +V^1(X_2)[\tfrac{r_2J_2}{K} + a_2G_2 + \delta_2^2] + \tfrac{r_2G_2}{K}\}dt \\
&\quad -\vartheta_2(1+V^1(X_2)^{\vartheta_2-1}V^1(X_2)\delta_2 dB_2(t).
\end{aligned}$$

Choosing sufficiently small $\xi_i (i=1,2)$, then

$$\kappa_i - 0.5\vartheta_i\delta_i^2 > \tfrac{\xi_i}{\vartheta_i} > 0. \tag{4.23}$$

Defining another two Lyapunov functions $V^3(X_i) = \exp(\xi_i t)V^2(X_i))(i=1,2)$, an application of Itô's formula leads to

$$\begin{aligned}
dV^3(X_1) &= \xi_1\exp(\xi_1 t)V^2(X_1)dt + \exp(\xi_1 t)dV^2(X_1) \\
&\le \vartheta_1\exp(\xi_1 t)(1+V^1(X_1))^{\vartheta_1-2}\{\tfrac{\xi_1(1+V^1(X_1))^2}{\vartheta_1} - (V^1(X_1))^2[\kappa_1 - 0.5\vartheta_1\delta_1^2] \\
&\quad +V^1(X_1)[H_1 + \tfrac{W_1J_1}{K} + a_1G_1 + \delta_1^2] + \tfrac{W_1G_1}{K}\}dt \\
&\quad -\vartheta_1\exp(\xi_1 t)(1+V^1(X_1))^{\vartheta_1-1}V^1(X_1)\delta_1 dB_1(t) \\
&\doteq \exp(\xi_1 t)h(X_1)dt - \vartheta_1\exp(\xi_1 t)(1+V^1(X_1))^{\vartheta_1-1}V^1(X_1)\delta_1 dB_1(t),
\end{aligned}$$

and

$$\begin{aligned}
dV^3(X_2) &= \xi_2\exp(\xi_2 t)V^2(X_2)dt + \exp(\xi_2 t)dV^2(X_2) \\
&\le \vartheta_2\exp(\xi_2 t)(1+V^1(X_2))^{\vartheta_2-2}\{\tfrac{\xi_2(1+V^1(X_2))^2}{\vartheta_2} - (V^1(X_2))^2[\kappa_2 - 0.5\vartheta_2\delta_2^2] \\
&\quad +V^1(X_2)[\tfrac{r_2J_2}{K} + a_2G_2 + \delta_2^2] + \tfrac{r_2G_2}{K}\}dt \\
&\quad -\vartheta_2\exp(\xi_2 t)(1+V^1(X_2))^{\vartheta_2-1}V^1(X_2)\delta_2 dB_2(t) \\
&\doteq \exp(\xi_2 t)h(X_2)dt - \vartheta_2\exp(\xi_2 t)(1+V^1(X_2))^{\vartheta_2-1}V^1(X_2)\delta_2 dB_2(t),
\end{aligned}$$

where

$$\begin{aligned}
h(X_1) &= \vartheta_1(1+V^1(X_1))^{\vartheta_1-2}\{-[\kappa_1 - 0.5\vartheta_1\delta_1^2 - \tfrac{\xi_1}{\vartheta_1}](V^1(X_1))^2 \\
&\quad +[H_1 + \tfrac{W_1J_1}{K} + a_1G_1 + \delta_1^2 + \tfrac{2\xi_1}{\vartheta_1}]V^1(X_1) + \tfrac{W_1J_1}{K} + \tfrac{\xi_1}{\vartheta_1}\},
\end{aligned}$$

and

$$\begin{aligned}
h(X_2) &= \vartheta_2(1+V^1(X_2))^{\vartheta_2-2}\{-[\kappa_2 - 0.5\vartheta_2\delta_2^2 - \tfrac{\xi_2}{\vartheta_2}](V^1(X_2))^2 \\
&\quad +[\tfrac{r_2J_2}{K} + a_2G_2 + \delta_2^2 + \tfrac{2\xi_2}{\vartheta_2}]V^1(X_2) + \tfrac{r_2J_2}{K} + \tfrac{\xi_2}{\vartheta_2}\}.
\end{aligned}$$

Let $B_1 = \kappa_1 - 0.5\vartheta_1\delta_1^2 - \frac{\xi_1}{\vartheta_1}$, $B_2 = H_1 + W_1J_1/K + a_1G_1 + \delta_1^2 + 2\xi_1/\vartheta_1$, $B_3 = W_1J_1/K + \xi_1/\vartheta_1$, $C_1 = \kappa_2 - 0.5\vartheta_2\delta_2^2 - \frac{\xi_2}{\vartheta_2}$, $C_2 = r_2J_2/K + a_2G_2 + \delta_2^2 + 2\xi_2/\vartheta_2$ and $C_3 = r_2J_2/K + \xi_2/\vartheta_2$. It is found that $B_j > 0$ and $C_j > 0 (j = 1, 2, 3)$ and (4.23) holds true. Therefore, we can define $h(X_1)$ and $h(X_2)$ as

$$h(X_1) = \vartheta_1(1 + \frac{1}{X_1})^{\vartheta_1 - 2}\Big\{ - \frac{B_1}{X_1^2} + \frac{B_2}{X_1} + B_3\Big\},$$

and

$$h(X_2) = \vartheta_2(1 + \frac{1}{X_2})^{\vartheta_2 - 2}\Big\{ - \frac{C_1}{X_2^2} + \frac{C_2}{X_2} + C_3\Big\}.$$

Obviously, $h(X_1)$ is upper bounded when $X_1 > 0$. If $1/X_1 \geq \{B_2 + \sqrt{B_2^2 + 4B_1B_3}\}/2B_1 \doteq \Delta_1$, then $h(X_1) \leq 0$. If $0 < 1/X_1 \leq \Delta_1$, then $h(X_1) \leq \{4B_1B_3 + B_2^2\}/4B_1$. Furthermore, if $\vartheta_1 \geq 2$, then $\vartheta_1(1+1/X_1)^{\vartheta_1-2} \leq \vartheta_1(1+\Delta_1)^{\vartheta_1-2}$; if $\vartheta_1 < 2$, then $\vartheta_1(1+\frac{1}{X_1})^{\vartheta_1-2} \leq \vartheta_1$. Thus, for $X_1 > 0$ we always have $h(X_1) \leq h^0 = \Delta_2(4B_1B_3 + B_2^2)/(4B_1)$, where $\Delta_2 = \max\{\vartheta_1, \vartheta_1(1 + \Delta_1)^{\vartheta_1 - 2}\}$. In short, $h(X_1)$ is always upper bounded. Similarly, $h(X_2)$ is also upper bounded.

From $dV^3(X_1)$ and $dV^3(X_2)$ we have

$$\begin{aligned} dV^3(X_i) &\leq \exp(\xi_i t)h(X_i)dt - \vartheta_i \exp(\xi_i t)(1 + V^1(X_i))^{\vartheta_i - 1}V^1(X_i)\delta_i dB_i(t) \\ &\leq h^0 \exp(\xi_i t)dt - \vartheta_i \exp(\xi_i t)(1 + V^1(X_i))^{\vartheta_i - 1}V^1(X_i)\delta_i dB_i(t). \end{aligned}$$

Integrating the above equation from 0 to t and taking the expectation,

$$E[V^3(X_i(t))] \leq V^3(X_i(0)) + \frac{h_i^0}{\xi_i}\exp(\xi_i t),$$

notice that $V^3(X_i(t)) = \exp(\xi_i t)(1 + V^1(X_i(t)))^{\vartheta_i}$,

$$\begin{aligned} E[V^3(X_i(t))] &= E[\exp(\xi_i t)(1 + V^1X_i(t)))^{\vartheta_1}] \\ &\leq V^3(X_i(0)) + \tfrac{h_i^0}{\xi_1}\exp(\xi_i t) \\ &= (1 + V^1(X_i(0)))^{\vartheta_i} + \tfrac{h_i^0}{\xi_i}\exp(\xi_i t). \end{aligned}$$

Taking the upper limit of both sides yields

$$\begin{aligned} \limsup_{t\to+\infty} E[\tfrac{1}{X_i(t)^{\vartheta_i}}] &= \limsup_{t\to+\infty} E[(V^1(X_i(t)))^{\vartheta_i}] \\ &\leq \limsup_{t\to+\infty} E[(1 + V^1(X_i(t)))^{\vartheta_i}] \leq \tfrac{h_i^0}{\xi_i} = h_{iN_i}. \end{aligned}$$

For arbitrary $\varepsilon_i > 0$, let $\beta_i = \varepsilon_i^{\frac{1}{\vartheta_i}}/h_{iN_i}^{\frac{1}{\vartheta_i}}$, by Chebyshev's inequality

$$\begin{aligned} \limsup_{t\to+\infty} \mathbb{P}\{X_i(t) < \beta_i\} &= \limsup_{t\to+\infty} \mathbb{P}\{\tfrac{1}{X_i^{\vartheta_i}(t)} > \tfrac{1}{\beta_i^{\vartheta_i}}\} \\ &\leq \limsup_{t\to+\infty} \frac{E[\frac{1}{X_i^{\vartheta_i}(t)}]}{\beta_i^{-\vartheta_i}} \\ &= \limsup_{t\to+\infty} \beta_i^{\vartheta_i} E[\tfrac{1}{X_i^{\vartheta_i}(t)}] = \varepsilon_i. \end{aligned}$$

Thus, $\liminf_{t\to+\infty}\mathbb{P}\{X_i(t)\geq\beta_i\}\geq 1-\varepsilon_i$.

Now, defining another Lyapunov function $V_1(X_i(t))=X_i^p(t)(X_i>0,i=1,2)$, and applying Itô's formula to the equations of system (3.7) yields

$$\begin{aligned}
dV_1(X_1(t)) &= pX_1^{p-1}(t)dX_1(t)+\tfrac{p(p-1)}{2}X_1^{p-2}(t)(dX_1(t))^2\\
&= pX_1^{p-1}(t)[(W_1-H_1-\tfrac{W_1X_1}{K}-\tfrac{W_1\alpha X_2}{K}-\tfrac{a_1Y}{g_1+X_1+X_2})X_1dt+\delta_1^2X_1dB_1(t)]\\
&\quad +0.5p(p-1)X_1^{p-2}(t)\delta_1^2X_1^2dt\\
&= pV_1(X_1(t))[W_1-H_1-\tfrac{W_1X_1}{K}-\tfrac{W_1\alpha X_2}{K}-\tfrac{a_1Y}{g_1+X_1+X_2}+0.5(p-1)\delta_1^2]dt\\
&\quad +p\delta_1^2V_1(X_1(t))dB_1(t)\\
&\leq pV_1(X_1(t))[W_1-\tfrac{W_1X_1}{K}+0.5(p-1)\delta_1^2]dt\\
&\quad +p\delta_1^2V_1(X_1(t))dB_1(t),
\end{aligned}$$

and

$$\begin{aligned}
dV_1(X_2(t)) &= pX_2^{p-1}(t)dX_2(t)+\tfrac{p(p-1)}{2}X_2^{p-2}(t)(dX_2(t))^2\\
&= pX_2^{p-1}(t)[(r_2-\tfrac{r_2X_2}{K}-\tfrac{r_2\beta X_1}{K}+S_1\tfrac{X_1}{X_2}-\tfrac{a_2Y}{g_2+X_1+X_2})X_2dt+\delta_2^2X_2dB_2(t)]\\
&\quad +0.5p(p-1)X_2^{p-2}(t)\delta_2^2X_2^2dt\\
&= pV_1(X_2(t))[r_2-\tfrac{r_2X_2}{K}-\tfrac{r_2\beta X_1}{K}+S_1\tfrac{X_1}{X_2}-\tfrac{a_2Y}{g_2+X_1+X_2}+0.5(p-1)\delta_1^2]dt\\
&\quad +p\delta_2^2V_1(X_2(t))dB_1(t)\\
&\leq pV_1(X_2(t))[r_2-\tfrac{r_2X_2}{K}+S_1J_1+0.5(p-1)\delta_2^2]dt\\
&\quad +p\delta_2^2V_2(X_2(t))dB_1(t).
\end{aligned}$$

For $dV_1(X_1(t))$, let us integrate both sides of the above inequality from 0 to t and then taking the expectation yields

$$E[V_1(X_1(t))]-E[V_1(X_1(0))]\leq p\int_0^t E\Big\{V_1(X_1(s))[W_1-\frac{W_1X_1(s)}{K}+0.5(p-1)\delta_1^2]\Big\}ds,$$

Taking the derivative of both sides of this inequality, then

$$\frac{dE[V_1(X_1(t))]}{dt}\leq pE[V_1(X_1(t))][W_1+0.5(p-1)\delta_1^2]-\frac{pP_1}{K}E[X_1^{p+1}(t)].$$

In the light of Hölder's inequality,

$$\frac{dE[V_1(X_1(t))]}{dt}\leq pE[V_1(X_1(t))][W_1+0.5(p-1)\delta_1^2]-\frac{pP_1}{K}E[X_1^p(t)]^{\frac{p+1}{p}}.$$

Let $n(t)=E[V_1(X_1(t))]$, we get

$$\begin{aligned}
\frac{dn(t)}{dt} &\leq pn(t)[W_1+0.5(p-1)\delta_1^2-\tfrac{W_1}{K}m^{\frac{1}{p}}(t)]\\
&\leq pn(t)[W_1+0.5p\delta_1^2-\tfrac{W_1}{K}m^{\frac{1}{p}}(t)].
\end{aligned}$$

An application of the standard comparison theorem yields

$$\begin{aligned}\limsup_{t\to+\infty} E[X_1^p(t)] &= \limsup_{t\to+\infty} E[V_1(X_1(t))]\\ &= \limsup_{t\to+\infty} n(t)\\ &\leq \left(\frac{(W_1+0.5p\delta_1^2)K}{W_1}\right)^p.\end{aligned}$$

Similarly, the Chebyshev's inequality results in

$$\liminf_{t\to+\infty} \mathbb{P}\{X_1(t) \leq \varrho_1\} \geq 1-\varepsilon_1.$$

For $dV_2(X_1(t))$, by using the same methods as $dV_1(X_1(t))$,

$$\begin{aligned}\limsup_{t\to+\infty} E[X_2^p(t)] &= \limsup_{t\to+\infty} E[V_1(X_2(t))]\\ &= \limsup_{t\to+\infty} n(t)\\ &\leq \left(\frac{(r_2+S_1J_1+0.5p\delta_1^2)K}{r_2}\right)^p,\end{aligned}$$

we also have

$$\liminf_{t\to+\infty} \mathbb{P}\{X_2(t) \leq \varrho_2\} \geq 1-\varepsilon_2.$$

Therefore, the AD and AI cells are stochastically persistent, respectively. This completes the proof.

5. Stationary distribution and ergodicity of the system

In this section, by using the same methods as shown in [1, 4, 32, 34, 48, 49], we will explore the existence of a unique ergodic steady state distribution of the system (3.7).

Lemma 5.1 ([48]) If there is a bounded domain $U \in \mathrm{IntR}_+^3$ with regular boundary Γ and (i) there exists a state with a positive ζ such that $\sum_{i,j=1}^3 b_{ij}(Z)\xi_i\xi_j > \zeta\|\xi\|^2$, $Z \in \bar{U}$, $\xi \in \mathrm{R}^3$. ˙(ii) there exists a state with a non-negative C^2- function V such that LV is negative for any $\mathrm{IntR}_+^3 \setminus U$. Then

$$P_z\{\lim_{T\to\infty}\frac{1}{T}\int_0^T g(Z(t))dt = \int g(z)\mu(dz)\} = 1,$$

for all $z \in \bar{U}$, where $g(\cdot)$ is a function integrable with respect to the measure μ, then the Markov process $Z(t)$ has a unique ergodic stationary distribution $\mu(\cdot)$.

Theorem 5.2. If

$$\begin{cases} Z_1: &= W_1 - H_1 - \frac{1}{2}\delta_1^2 > 0,\\ Z_2: &= \mu - C - \frac{2a_1}{g_1} - \frac{a_2}{g_2} > 0,\\ Z_3: &= r_2 - \frac{1}{2}\delta_2^2 > 0,\\ Z_4: &= \mid W_1 - H_1 - \frac{1}{2}\delta_1^2 \mid - \mid C - \mu - \frac{\delta_3^2}{2} \mid > 0,\\ \Delta_1: &= S_2^2 - 4(\mu - C - \frac{2a_1}{g_1} - \frac{a_2}{g_2})S_2 \leq 0,\end{cases} \tag{5.1}$$

then system (3.7) has a unique ergodic stationary distribution.

Proof. For simplicity, denote $X_1(t)$, $X_2(t)$ and $Y(t)$ as X_1, X_2 and Y. The diffusion matrix for system (3.7) is given by

$$b(Z) = \begin{pmatrix} \delta_1^2 X_1^2 & 0 & 0 \\ 0 & \delta_2^2 X_2^2 & 0 \\ 0 & 0 & \delta_3^2 Y^2 \end{pmatrix}.$$

Selecting $\xi = \min_{(X_1,X_2,Y)\in \bar{U}_\delta \subset \mathrm{R}^3_+} \{\delta_1^2 X_1^2, \delta_2^2 X_2^2, \delta_3^2 Y^2\}$, then

$$\begin{aligned} \sum_{i,j=1}^{3} b_{ij}(Z)\xi_i\xi_j = \sum_{i,j=1}^{3} b_{ij}(X_1,X_2,Y)\xi_i\xi_j &= \delta_1^2 X_1^2\xi_1^2 + \delta_2^2 X_2^2\xi_2^2 + \delta_3^2 Y^2\xi_3^2 \\ &\geq \min_{(X_1,X_2,Y)\in\bar{U}} \{\delta_1^2 X_1^2, \delta_2^2 X_2^2, \delta_3^2 Y^2\}\|\xi\|^2 \end{aligned}$$

for all $Z = (X_1, X_2, Y) \in \bar{U}, \xi = (\xi_1, \xi_2, \xi_3) \in \mathrm{R}^3$. This indicates that condition (i) in Lemma 5.1 holds.

Let

$$V(X_1, X_2, X_3) = X_1 - \ln X_1 + \frac{1}{X_1} + X_2 - \ln X_2 + Y - \ln Y.$$

Making use of Itô's formula yields

$$dV = LVdt + \delta_1(X_1 - 1 - \frac{1}{X_1})dB_1(t) + \delta_2(X_2 - 1)dB_2(t) + \delta_3(Y - 1)dB_3(t),$$

where

$$\begin{aligned} LV(X_1,X_2,Y) \;=\; & X_1(W_1 - H_1 - \tfrac{W_1X_1}{K} - \tfrac{W_1\alpha X_2}{K} - \tfrac{a_1Y}{g_1+X_1+X_2}) - (W_1 - H_1 - \tfrac{\delta_1^2}{2}) \\ & -\tfrac{1}{X_1}(W_1 - H_1 - \tfrac{W_1X_1}{K} - \tfrac{W_1\alpha X_2}{K} - \tfrac{a_1Y}{g_1+X_1+X_2}) + \tfrac{\delta_1^2}{X_1} \\ & +\tfrac{W_1X_1}{K} + \tfrac{W_1\alpha}{K}X_2 + \tfrac{a_1Y}{g_1+X_1+X_2} + X_2(r_2 - \tfrac{r_2\beta X_1}{K} - \tfrac{r_2}{K}X_2 \\ & +S_1\tfrac{X_1}{X_2} - \tfrac{a_2Y}{g_2+X_1+X_2}) - (r_2 - \tfrac{\delta_2^2}{2}) + \tfrac{r_2\beta X_1}{K} + \tfrac{r_2}{K}X_2 - S_1\tfrac{X_1}{X_2} \\ & +\tfrac{a_2Y}{g_2+X_1+X_2} - (C - \mu - \tfrac{\delta_3^2}{2}) + \tfrac{-(\mu-C)Y^2+S_2Y-S_2}{Y}. \end{aligned}$$

Then

$$LV(X_1,X_2,Y) \leq \psi(X_1) + \psi(X_2) + \psi(Y) - S_1\frac{X_1}{X_2},$$

where

$$\begin{aligned} \psi(X_1) &= -\frac{W_1}{K}X_1^2 + (W_1 - H_1 + \frac{W_1}{K} + S_1 + \frac{r_2\beta}{K})X_1 + \frac{H_1 - W_1}{X_1} + \frac{W_1\alpha}{X_1} + \frac{\delta_1^2}{X_1} + \frac{W_1}{K}, \\ \psi(X_2) &= -\frac{r_2}{K}X_2^2 + (r_2 + \frac{r_2}{K} + \frac{W_1\alpha}{K})X_2 - (W_1 - H_1 - \frac{\delta_1^2}{2}) - (r_2 - \frac{\delta_2^2}{2}) - (C - \mu - \frac{\delta_3^2}{2}), \\ \psi(Y) &= \frac{-(\mu - C - \frac{2a_1}{g_1} - \frac{a_2}{g_2})Y^2 + S_2Y - S_2}{Y}. \end{aligned}$$

Notice that $\psi(Y)$ has a negative upper bound. Now we construct subset U such that the condition (ii) in Lemma 5.1 holds. To this end, defining the following bounded domain

$$U = [\epsilon, 1/\epsilon] \times [\epsilon, 1/\epsilon] \times [\epsilon, 1/\epsilon] \subset \mathrm{IntR}^3_+,$$

implies that $LV(X_1, X_2, Y)$ is negative for all $(X_1, X_2, Y) \in \mathrm{IntR}^3_+ \setminus U$. One can choose sufficiently small ϵ which satisfies the following conditions:

$$(W_1 - H_1 + \frac{W_1}{K} + S_1 + \frac{r_2\beta}{K})\epsilon + \frac{W_1\alpha + \delta_1^2 + H_1 - W_1}{\epsilon} + \frac{W_1}{K} + A_1 \leq -1, \tag{5.2}$$

$$(r_2 + \frac{r_2}{K} + \frac{W_1\alpha}{K})\epsilon - \frac{S_1}{\epsilon} + A_2 \leq -1, \tag{5.3}$$

$$-\frac{S_2}{\epsilon} + A_3 \leq -1, \tag{5.4}$$

$$-\frac{W_1}{2K\epsilon^2} + \frac{W_1 - H_1 + \frac{W_1}{K} + S_1 + \frac{r_2\beta}{K}}{\epsilon} + \frac{W_1}{K} + A_4 \leq -1, \tag{5.5}$$

$$-\frac{r_2}{2K\epsilon^2} + \frac{r_2 + \frac{r_2}{K} + \frac{W_1\alpha}{K}}{\epsilon} + A_5 \leq -1, \tag{5.6}$$

$$-\frac{\mu - C - \frac{2a_1}{g_1} - \frac{a_2}{g_2}}{\epsilon} + A_6 \leq -1, \tag{5.7}$$

where A_1, A_2, A_3, A_4, A_5 and A_6 are positive constants which are defined in the following inequalities (5.8)-(5.13). It is clear that $\mathrm{IntR}^3_+ \setminus U = U_1 \cup U_2 \cup U_3 \cup U_4 \cup U_5 \cup U_6$, where

$$\begin{aligned} U_1 &= \{0 < X_1 < \epsilon\}, & U_2 &= \{X_1 \geq \epsilon, 0 < X_2 < \epsilon, Y \geq \epsilon\}, \\ U_3 &= \{0 < Y < \epsilon\}, & U_4 &= \{X_1 > \frac{1}{\epsilon}\}, \\ U_5 &= \{X_2 > \frac{1}{\epsilon}\}, & U_6 &= \{Y > \frac{1}{\epsilon}\}. \end{aligned}$$

Next we will show that $LV(X_1, X_2, Y) \leq -1$ on $U^C = U_1 \cup \ldots \cup U_6$.

Case 1, if $(X_1, X_2, Y) \in U_1$, then

$$\begin{aligned} LV &\leq -\tfrac{W_1}{K}X_1^2 + (W_1 - H_1 + \tfrac{W_1}{K} + S_1 + \tfrac{r_2\beta}{K})X_1 + \tfrac{H_1 - W_1}{X_1} + \tfrac{W_1\alpha}{X_1} + \tfrac{\delta_1^2}{X_1} \\ &\quad + \tfrac{W_1}{K} + \psi(X_2) + \psi(Y) \\ &\leq (W_1 - H_1 + \tfrac{W_1}{K} + S_1 + \tfrac{r_2\beta}{K})\epsilon + \tfrac{W_1\alpha + \delta_1^2 + H_1 - W_1}{\epsilon} + \tfrac{W_1}{K} + A_1, \end{aligned} \tag{5.8}$$

where

$$A_1 = \sup_{(X_1, X_2, Y) \in \mathrm{R}^3_+} \{\psi(X_2) + \psi(Y)\}.$$

According to (5.2), we know that $LV \leq -1$ on U_1.

Case 2, if $(X_1, X_2, Y) \in U_2$, we have

$$\begin{aligned} LV &\leq (r_2 + \tfrac{r_2}{K} + \tfrac{W_1\alpha}{K})X_2 + \psi(X_1) + \psi(Y) - \tfrac{S_1X_1}{X_2} \\ &\leq (r_2 + \tfrac{r_2}{K} + \tfrac{W_1\alpha}{K})\epsilon - \tfrac{S_1}{\epsilon} + A_2, \end{aligned} \tag{5.9}$$

where

$$A_2 = \sup_{(X_1,X_2,Y)\in \mathrm{R}^3_+} \{\psi(X_1) + \psi(Y)\}.$$

In terms of (5.3), on can get that $LV \leq -1$ on U_2.

Case 3, if $(X_1, X_2, Y) \in U_3$, then

$$\begin{aligned} LV &\leq S_2 - \tfrac{S_2}{Y} + \psi(X_1) + \psi(X_2) - \tfrac{S_1 X_1}{X_2} \\ &\leq -\tfrac{S_2}{\epsilon} + A_3, \end{aligned} \tag{5.10}$$

where

$$A_3 = \sup_{(X_1,X_2,Y)\in \mathrm{R}^3_+} \{S_2 + \psi(X_1) + \psi(X_2)\}.$$

In the light of (5.4) that $LV \leq -1$ on U_3.

Case 4, if $(X_1, X_2, Y) \in U_4$, we obtain

$$\begin{aligned} LV &\leq -\tfrac{W_1}{2K}X_1^2 + (W_1 - H_1 + \tfrac{W_1}{K} + S_1 + \tfrac{r_2\beta}{K})X_1 + \tfrac{W_1}{K} + \psi(X_2) + \psi(Y) \\ &\leq -\tfrac{W_1}{2K\epsilon^2} + \tfrac{W_1 - H_1 + \frac{W_1}{K} + S_1 + \frac{r_2\beta}{K}}{\epsilon} + \tfrac{W_1}{K} + A_4, \end{aligned} \tag{5.11}$$

where

$$A_4 = \sup_{(X_1,X_2,Y)\in \mathrm{R}^3_+} \{-\frac{W_1}{2K}X_1^2 + \psi(X_2) + \psi(Y)\}.$$

By (5.5), we have $LV \leq -1$ on U_4.

Case 5, if $(X_1, X_2, Y) \in U_5$, we can get that

$$\begin{aligned} LV &\leq -\tfrac{r_2}{2K}X_2^2 + (r_2 + \tfrac{r_2}{K} + \tfrac{W_1\alpha}{K})X_2 + \psi(X_1) + \psi(Y) \\ &\leq -\tfrac{r_2}{2K\epsilon^2} + \tfrac{r_2 + \frac{r_2}{K} + \frac{W_1\alpha}{K}}{\epsilon} + A_5, \end{aligned} \tag{5.12}$$

where

$$A_5 = \sup_{(X_1,X_2,Y)\in \mathrm{R}^3_+} \{-\frac{r_2}{2K}X_2^2 + \psi(X_1) + \psi(Y)\}.$$

From (5.6), we can conclude that $LV \leq -1$ on U_5.

Case 6, if $(X_1, X_2, Y) \in U_6$, we have

$$\begin{aligned} LV &\leq -(\mu - C - \tfrac{2a_1}{g_1} - \tfrac{a_2}{g_2})Y + \psi(X_1) + \psi(X_2) - \tfrac{S_1 X_1}{X_2} \\ &\leq -\tfrac{\mu - C - \frac{2a_1}{g_1} - \frac{a_2}{g_2}}{\epsilon} + A_6, \end{aligned} \tag{5.13}$$

where

$$A_6 = \sup_{(X_1,X_2,Y)\in \mathrm{R}^3_+} \{\psi(X_1) + \psi(X_2)\}.$$

It follows from (5.7) that $LV \leq -1$ on U_6.

Obviously, it follows from (5.8)-(5.13) that for a sufficient small ϵ,

$$LV \leq -1 \quad \text{for} \quad \text{all} \quad (X_1, X_2, Y) \in \mathrm{R}^3_+ \setminus U.$$

It means that condition (ii) of Lemma 5.1 holds true. Therefore, system (5.1) is ergodic and has a unique stationary distribution. This completes the proof.

6. Numerical simulations

In what follows, we carry out numerical simulations by adopting the Milsteins higher order method [50] to get the approximate solution system (2.2) with initial conditions. System (2.2) of the discretization equations are as shown in the following,

$$\begin{cases} A_{k+1} &= A_k - \gamma(A_k - a_0)\Delta t, \\ D_{k+1} &= D_k - cD_k\Delta t, \\ X_{1k+1} &= X_{1k} + [r_1A_k(1 - \dfrac{X_{1k} + \alpha X_{2k}}{K}) - (d_1 + m_1)(1 - \dfrac{A_k}{a_0}) \\ & \quad - \dfrac{a_1Y_k}{g_1 + X_{1k} + X_{2k}}]X_{1k}\Delta t + \delta_1X_{1k}\sqrt{\Delta t}\xi_k + \dfrac{\delta_1^2}{2}X_{1k}(\xi_k^2 - 1)\Delta t, \\ X_{2k+1} &= X_{2k} + [r_2(1 - \dfrac{\beta X_{1k} + X_{2k}}{K})X_{2k} + m_1(1 - \dfrac{A_k}{a_0})X_{1k} \\ & \quad - \dfrac{a_2X_{2k}Y_k}{g_2 + X_{1k} + X_{2k}}]\Delta t + \delta_2X_{2k}\sqrt{\Delta t}\zeta_k + \dfrac{\delta_2^2}{2}X_{2k}(\zeta_k^2 - 1)\Delta t, \\ Y_{k+1} &= Y_k + [(C - \mu)Y_k + \dfrac{eD_k}{g_3 + D_k}]\Delta t \\ & \quad + \delta_3Y_k\sqrt{\Delta t}\eta_k + \dfrac{\delta_3^2}{2}Y_k(\eta_k^2 - 1)\Delta t, \end{cases} \tag{6.1}$$

when $t = nT$, the system (2.2) executed pulsed therapies, i.e., there is a time step h, if $mod(hk, T)$=0, then

$$\begin{cases} A_{k+1} = (1 - \delta)A_k, \\ D_{k+1} = D_k + \tau, \end{cases} \tag{6.2}$$

where ξ_k, ζ_k and $\eta_k (k = 1, 2, 3, \cdots)$ represent independent Gaussian random variables with a distribution $N(0, 1)$, and let the time increment $\Delta t = h = 0.01$.

6.1. Effects of random perturbations on the evolution of AD and AI cells

The baseline parameter values of system (2.2) were fixed as shown in references [3, 4, 21, 25, 28, 51]. Since tumour growth is sensitive to environmental variables such as temperature, radiation, nutrients and oxygen supply [4, 30, 52–54], we will show how the changes of δ_1 and δ_2 affect the evolution of AD and AI cells, respectively.

We fixed the parameter values as shown in Fig.1. Simple calculations indicate that $W_1 - H_1 - \frac{1}{2}\delta_1^2 \approx -0.751 < 0$, from Theorem 4.5 the AD cells become extinct (Fig.1(a)). If we set $\delta_1 = 0.5$, $C = 0.47$, then we have $C - \mu - \frac{\delta_3^2}{2} = -0.33 < 0$ and $W_1 - H_1 - W_1\alpha - \frac{1}{2}\delta_1^2 \approx 0.222 > 0$, the results of Theorem 4.5 imply that the AD cells become persistent in the mean (Fig.1(b)). If we set $C = 0.81$ and fix others as shown in (Fig.1(c)), thus $C - \mu - \frac{\delta_3^2}{2} = 0.01 > 0$, it is found that AD cells eventually become extinct (Fig.1(c)).

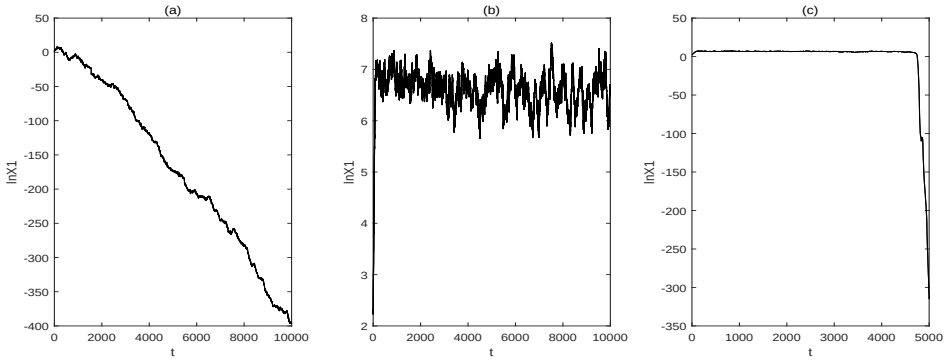

Figure 1: Extinction and persistence in mean of AD cells. (a) $C = 0.47$, $\delta_1 = 3$; (b) $C = 0.47$, $\delta_1 = 0.5$; (c) $C = 0.81$, $\delta_1 = 0.5$. The initial values of the solution illustrated in black were fixed as $(X_1(0), X_2(0), Y(0)) = (10, 10, 0.5)$, and all other parameters were fixed as: $r_1 = 1.2$, $r_2 = 0.4$, $d_1 = 0.3$, $m_1 = 0.01$, $K = 1000$, $a_0 = 3.5$, $\gamma = 0.08$, $a_1 = 0.2$, $a_2 = 0.2$, $T = 100$, $g_1 = 10$, $g_2 = 10$, $g_3 = 10$, $\mu = 0.3$, $e = 10$, $c = 0.00311$, $d = 0.3$, $\delta_2 = 1$, $\delta_3 = 1$, $\tau = 0.1$, $\delta = 0.1$, $\alpha = 0.9$ and $\beta = 0.8$.

By keeping all other parameters as shown in Fig.2, from the results in Fig.2(a), it is found that $W_1 - H_1 - \frac{1}{2}\delta_1^2 \approx -0.751 < 0$ and $r_2 - \frac{1}{2}\delta_2^2 \approx -0.1 < 0$, so from Theorem 4.5 the AI cells become extinct (Fig.2(a)). If we set $\delta_2 = 0.1$, then $W_1 - H_1 - W_1\alpha - \frac{1}{2}\delta_1^2 \approx -0.751 < 0$, $C - \mu - \frac{\delta_3^2}{2} = -0.33 < 0$ and $r_2 - r_2\beta - \frac{1}{2}\delta_2^2 = 0.075 > 0$, Theorem 4.5 suggests that the AI cells become persistent in the mean (Fig.1(b)). If we set $C = 0.81$, then $C - \mu - \frac{\delta_3^2}{2} = 0.01 > 0$, it is observed that AI cells become extinct (Fig.2(c)).

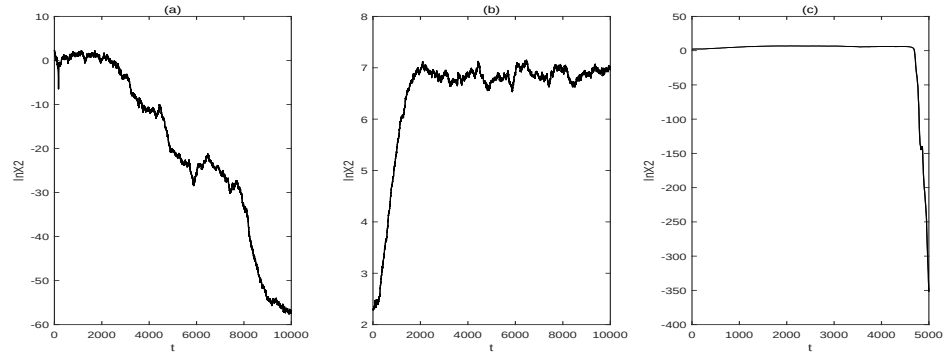

Figure 2: Extinction and persistence in mean of AI cells. (a) $C = 0.47$, $\delta_2 = 1$; (b) $C = 0.47$, $\delta_2 = 0.1$; (c) $C = 0.81$, $\delta_2 = 0.1$. The initial values of solution with black were fixed as $(X_1(0), X_2(0), Y(0)) = (10, 10, 0.5)$, and all other parameters were fixed as: $r_1 = 1.2$, $r_2 = 0.4$, $d_1 = 0.3$, $m_1 = 0.01$, $K = 1000$, $a_0 = 3.5$, $\gamma = 0.08$, $a_1 = 0.2$, $a_2 = 0.2$, $T = 100$, $g_1 = 10$, $g_2 = 10$, $g_3 = 10$, $\mu = 0.3$, $e = 10$, $c = 0.00311$, $d = 0.3$, $\delta_1 = 3$, $\delta_3 = 1$, $\tau = 0.1$, $\delta = 0.1$, $\alpha = 0.9$ and $\beta = 0.8$.

From Fig.1(a) to Fig.2(a)) or from Fig.1(b) to Fig.2(b), with the decrease of white noise, the dynamic behaviour of the two types of prostate cancer cells gradually changed from the state of extinction to persistence in the mean. This reveals that random interference has a relatively important impact on both AD and AI cells. From Fig.1(b) to Fig.1(c), the antigenicity of the tumours also affects the dynamics of both AD and AI cells.

With the other parameter values as shown in Fig.3, in Fig.3(a), we set $\delta_1 = 0.5$ and

$\delta_2 = 0.3$, then

$$\kappa_1 = \min_{t\geq 0}[W_1 - H_1 - W_1\alpha - \frac{1}{2}\delta_1^2 - a_1 G_1] \approx 0.1225 > 0.$$

It follows from Theorem 4.6 that the AD cells become stochastically permanent (Fig.3(a)). Similarly, in Fig.4(a), we set $r_2 = 0.8$, $\delta_1 = 0.3$ and $\delta_2 = 0.3$, then

$$\kappa_2 = \min_{t\geq 0}[r_2 - r_2\beta - \frac{1}{2}\delta_2^2 - a_2 G_2] \approx 0.0155 > 0.$$

From Theorem 4.6, the AI cells become stochastically permanent (Fig.4(a)). Increasing the white noise will lead both AD and AI cells to extinction (Fig.5 and Fig.6), showing that white noise can determine the dynamic behaviour of AD and AI cells.

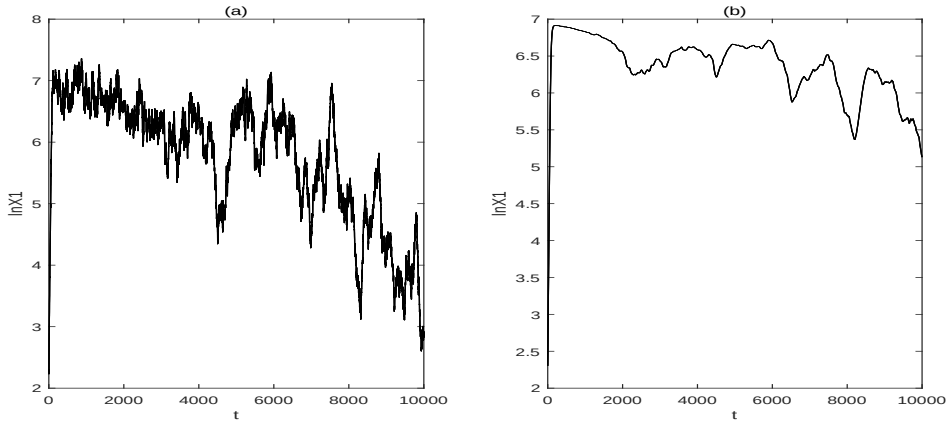

Figure 3: Stochastic permanence of AD cells. (a) $\delta_1 = 0.5$; (b) $\delta_1 = 0$. The initial values of the solution illustrated in black were fixed as $(X_1(0), X_2(0), Y(0)) = (10, 10, 0.5)$, and all other parameters were fixed as: $r_1 = 1.2$, $r_2 = 0.4$, $d_1 = 0.3$, $m_1 = 0.01$, $K = 1000$, $a_0 = 3.5$, $\gamma = 0.08$, $C = 0.47$, $a_1 = 0.2$, $a_2 = 0.2$, $T = 100$, $g_1 = 10$, $g_2 = 10$, $g_3 = 10$, $\mu = 0.3$, $e = 10$, $c = 0.00311$, $d = 0.3$, $\delta_2 = 0.3$, $\delta_3 = 1$, $\tau = 0.1$, $\delta = 0.1$, $\alpha = 0.9$ and $\beta = 0.8$.

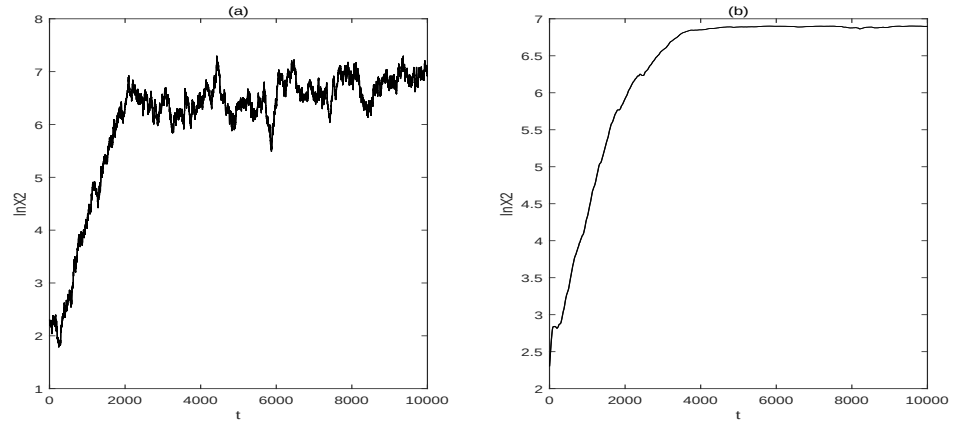

Figure 4: Stochastic permanence of AI cells. (a) $\delta_2 = 0.3$; (b) $\delta_2 = 0$. The initial values of the solution illustrated in black were fixed as $(X_1(0), X_2(0), Y(0)) = (10, 10, 0.5)$, and all other parameters were fixed as: $r_1 = 1.2$, $r_2 = 0.8$, $d_1 = 0.3$, $m_1 = 0.01$, $K = 1000$, $a_0 = 3.5$, $\gamma = 0.08$, $C = 0.47$, $a_1 = 0.2$, $a_2 = 0.2$, $T = 100$, $g_1 = 10$, $g_2 = 10$, $g_3 = 10$, $\mu = 0.3$, $e = 10$, $c = 0.00311$, $d = 0.3$, $\delta_1 = 0.3$, $\delta_3 = 1$, $\tau = 0.1$, $\delta = 0.1$, $\alpha = 0.9$ and $\beta = 0.8$.

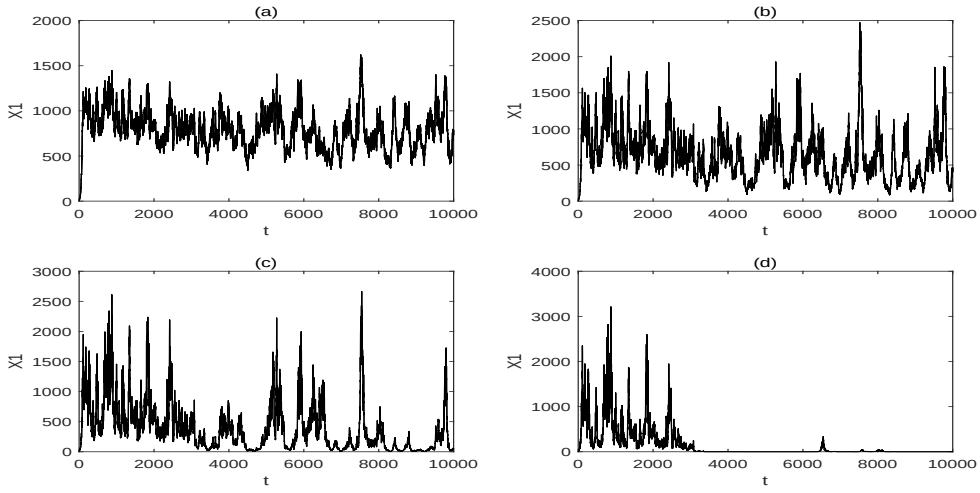

Figure 5: The effects of noise on the evolution of AD cells. (a) $\delta_1 = 0.4$; (b) $\delta_1 = 0.8$; (c) $\delta_1 = 1.2$; (d) $\delta_1 = 1.6$. The initial values of the solution illustrated in black were fixed as $(X_1(0), X_2(0), Y(0)) = (10, 10, 0.5)$, and all other parameters were fixed as: $r_1 = 1.2$, $r_2 = 0.8$, $d_1 = 0.3$, $m_1 = 0.01$, $K = 1000$, $a_0 = 3.5$, $\gamma = 0.08$, $C = 0.47$, $a_1 = 0.2$, $a_2 = 0.2$, $T = 100$, $g_1 = 10$, $g_2 = 10$, $g_3 = 10$, $\mu = 0.3$, $e = 10$, $c = 0.00311$, $d = 0.3$, $\delta_2 = 1$, $\delta_3 = 1$, $\tau = 0.1$, $\delta = 0.1$, $\alpha = 0.9$ and $\beta = 0.8$.

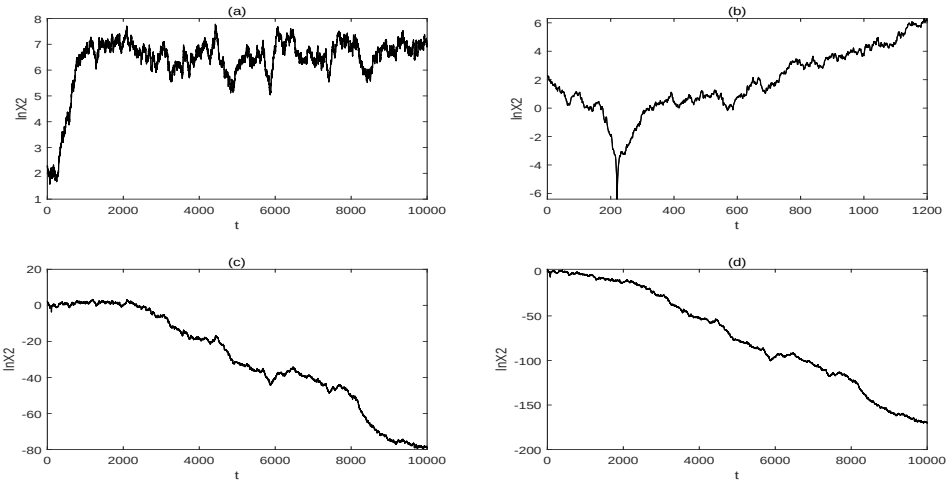

Figure 6: The effects of noise on the evolution of AI cells. (a) $\delta_2 = 0.5$; (b) $\delta_2 = 1$; (c) $\delta_2 = 1.5$; (d) $\delta_2 = 2$. The initial values of the solution illustrated in black were fixed as $(X_1(0), X_2(0), Y(0)) = (10, 10, 0.5)$, and all other parameters were fixed as: $r_1 = 1.2$, $r_2 = 0.8$, $d_1 = 0.3$, $m_1 = 0.01$, $K = 1000$, $a_0 = 3.5$, $\gamma = 0.08$, $C = 0.47$, $a_1 = 0.2$, $a_2 = 0.2$, $T = 100$, $g_1 = 10$, $g_2 = 10$, $g_3 = 10$, $\mu = 0.3$, $e = 10$, $c = 0.00311$, $d = 0.3$, $\delta_1 = 3$, $\delta_3 = 1$, $\tau = 0.1$, $\delta = 0.1$, $\alpha = 0.9$ and $\beta = 0.8$.

6.2. Monotherapy and comprehensive therapy

Theoretically, environmental noise can determine all the kinetic behaviour of tumour cells, but environmental interference is limited in practice and not strong enough to control the progression of cancer cells. The experiment verified that AI cells show stronger drug resistance than AD cells at low dosages, but large dosages of drugs are likely to cause harm and side effects (Fig.7) [3, 29, 55–62]. Therefore, we need an additional treatment to assist IAD, namely

immunotherapy. Next, we will show how combination therapy of immunotherapy together with IAD affects the evolution of AD and AI cells.

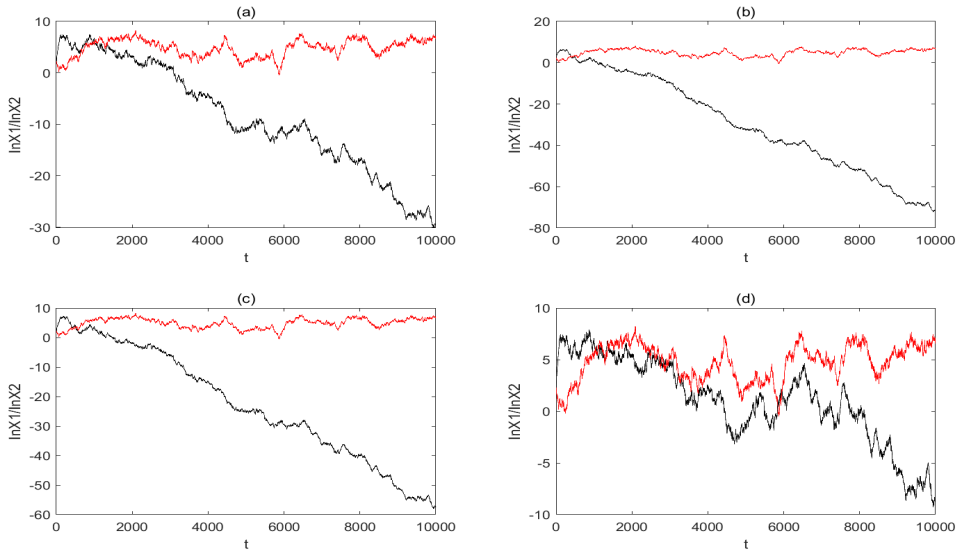

Figure 7: The effects of IAD alone on the evolution of AD and AI cells, where black is for AD cells ($\delta_1 = 1$), and red is for AI cells ($\delta_1 = 3$). (a) $\delta = 0.2$, $T = 50$; (b) $\delta = 0.9$, $T = 50$; (c) $\delta = 0.2$, $T = 20$; (d) $\delta = 0.2$, $T = 80$. The initial values were fixed as $(X_1(0), X_2(0), Y(0)) = (10, 10, 0.5)$, and all other parameters were fixed as: $r_1 = 1.2$, $r_2 = 0.8$, $d_1 = 0.3$, $m_1 = 0.01$, $K = 1000$, $a_0 = 3.5$, $\gamma = 0.08$, $C = 0.47$, $a_1 = 0.2$, $a_2 = 0.2$, , $g_1 = 10$, $g_2 = 10$, $g_3 = 10$, $\mu = 0.3$, $e = 10$, $c = 0.00311$, $d = 0.3$, $\delta_2 = 1$, $\delta_3 = 1$, $\tau = 0$, $\alpha = 0.9$ and $\beta = 0.8$.

Compared to treatments with IAD alone, comprehensive therapy has greater advantages than application of IAD alone. It is revealed that both AD and AI cells can be removed in a shorter time under combined treatment (Fig.8). If we increase the dosages of immunotherapy and IAD therapy (Fig.8(a)), or increase the frequencies of the comprehensive treatment (Fig.8(b)), or increase the frequencies and increase the dosages of comprehensive treatment (Fig.8(c)), it can be seen that AD and AI cells go extinct very quickly compared to IAD alone.

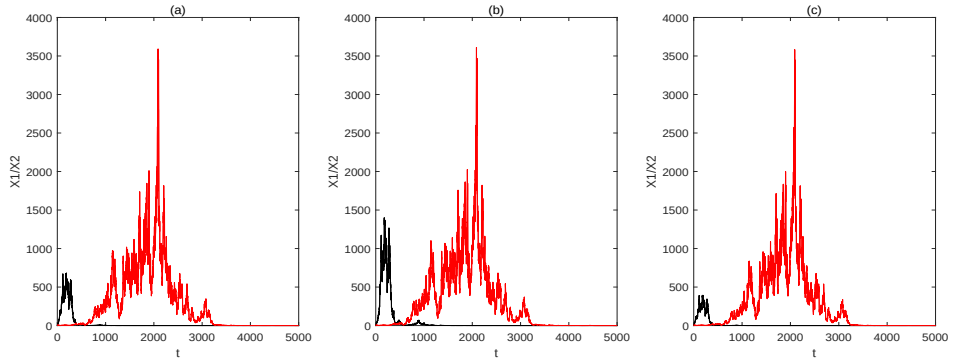

Figure 8: The effects of comprehensive therapy on the evolution of AD ($\delta_1 = 1$), and red for AI cells ($\delta_1 = 3$). (a) $\delta = 0.9$, $\tau = 0.9$, $T = 50$; (b) $\delta = 0.2$, $\tau = 0.2$, $T = 20$; (c) $\delta = 0.9$, $\tau = 0.9$, $T = 40$. The initial values were fixed as $(X_1(0), X_2(0), Y(0)) = (10, 10, 0.5)$, and all other parameters were fixed as: $r_1 = 1.2$, $r_2 = 0.8$, $d_1 = 0.3$, $m_1 = 0.01$, $K = 1000$, $a_0 = 3.5$, $\gamma = 0.08$, $C = 0.47$, $a_1 = 0.2$, $a_2 = 0.2$, $g_1 = 10$, $g_2 = 10$, $g_3 = 10$, $\mu = 0.3$, $e = 10$, $c = 0.00311$, $d = 0.3$, $\delta_2 = 1$, $\delta_3 = 1$, $\alpha = 0.9$ and $\beta = 0.8$.

6.3. Stationary distribution of the system

With the parameter values fixed as shown in Fig.9, it is found that all conditions of Theorem 5.2 are satisfied, i.e.,

$$W_1 - H_1 - \frac{1}{2}\delta_1^2 \approx 3.749 > 0, \quad \mu - C - \frac{2a_1}{g_1} - \frac{a_2}{g_2} = 0.04 > 0, \quad r_2 - \frac{1}{2}\delta_2^2 \approx 0.8 > 0,$$

$$Z_4 = \mid W_1 - H_1 - \frac{1}{2}\delta_1^2 \mid - \mid C - \mu - \frac{\delta_3^2}{2} \mid \approx 3.649 > 0,$$

and

$$S_2^2 - 4(\mu - C - \frac{2a_1}{g_1} - \frac{a_2}{g_2})S_2 \approx -0.191 \leq 0,$$

it follows from Theorem 5.2 that system (3.7) exists with a unique stationary distribution.

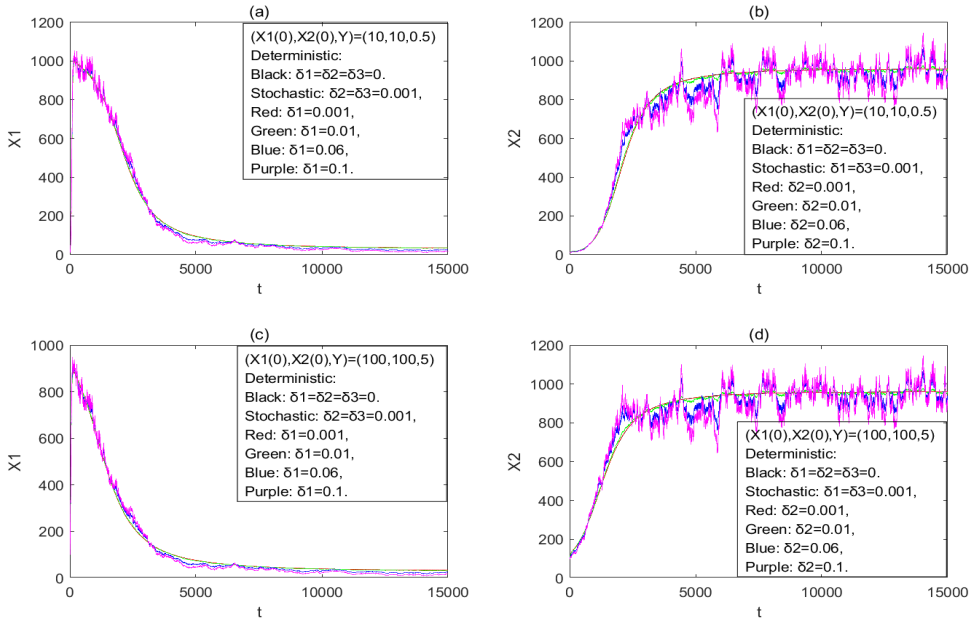

Figure 9: Stationary distribution of AD and AI cells in deterministic and stochastic models. (a) and (b) The initial values were fixed as $(X_1(0), X_2(0), Y(0)) = (10, 10, 0.5)$. (c) and (d) The initial values were fixed as $(X_1(0), X_2(0), Y(0)) = (100, 100, 5)$. All other parameters were fixed as: $r_1 = 1.2$, $r_2 = 0.8$, $d_1 = 0.3$, $m_1 = 0.01$, $K = 1000$, $a_0 = 3.5$, $\gamma = 0.08$, $C = 0.2$, $a_1 = 0.2$, $a_2 = 0.2$, $g_1 = 10$, $g_2 = 10$, $g_3 = 10$, $\mu = 0.3$, $e = 10$, $c = 0.00311$, $d = 0.3$, $\tau = 0.1$, $\delta = 0.1$, $\alpha = 0.9$ and $\beta = 0.8$.

7. Discussion

In recent years, IAD therapy has been much discussed by the medical community and has also been studied by many scholars [3, 21, 25, 30, 63]. It has been shown that IAD therapy can improve the quality of life of patients and delay the development of drug resistance. To prevent the production of new AI cells and treat the existing AI cells, immunotherapy is considered to stop AI cells by enhancing the immunity of patients to cancer cells, thereby improving the survival rate of patients with advanced prostate cancer [14–16]. Besides, the evolution of tumours is inevitably affected by environmental disturbances such as temperature, oxygen supply, nutrition, etc [4, 28–30]. The competition between the two types of

tumour cells will affect their evolution, so it is necessary to consider white noise and different competition coefficients. Based on these considerations, we extended the previous stochastic models of prostate cancer by introducing combinations of tumour antigenicity and impulsive immunotherapy with different competition coefficients.

We first examined the pharmacokinetics of immunotherapy and provided the expression of the tumour-free periodic solution, indicating that there is a unique global positive solution for the system. Then Itô's formula, Lyapunov functions, the law of strong numbers, the comparison theorem and relevant theorems of stochastic differential equations were used to show that the solutions of the system are stochastically ultimately bounded and stochastic persistent. The global attractivity of the solutions of the system was also proved. Furthermore, we derived the threshold conditions for the extinction and persistence of tumours, and the sufficient conditions for stochastic permanence of tumours and the stationary distribution and ergodicity of the stochastic system were also obtained.

Numerical simulations were also carried out to support our theoretical results. The results showed that both white noise and the antigenicity of the tumours have marked influences on the survival of tumours. It was observed that AI cells are more resistant than AD cells, requiring larger perturbations to make AI cells extinct. The results also indicate that the combined therapy is more effective than IAD alone, which can not only completely eliminate the two kinds of prostate cancer cells in a shorter time, but can also make up for the deficiency of the single therapy (Fig.7 and Fig.8). Moreover, it was also verified that white noise can affect the stationary distribution of prostate cancer cells (Fig.9).

Biologically, the results revealed that white noise can determine the dynamics of prostate cancer cells. Specifically, we observed that low amounts of white noise can make tumour cells present stochastic persistence, while large quantities of white noise lead to the extinction of tumour cells, that is, white noise had a negative effect on the survival of prostate cancer cells. However, environmental interference alone is not enough to control the progression of prostate cancer cells, thus we must introduce a combination of IAD therapy and immunotherapy to control the development of prostate cancer cells. The results showed that increasing the dosages of immunotherapy (or IAD therapy) or shortening the treatment period of immunotherapy (or IAD therapy) is a feasible treatment for prostate cancer.

Compare with reference [36], the differences are listed as follows: (1) It is critical for ADT to control androgen concentration, then we consider not only the dendritic cell vaccine, but also the pulse effect of periodic injection of androgen. Since the antigenicity of tumours always exists in the whole process of invasion, the antigenicity of prostate cancer cells is also considered. (2) In addition to calculating the extinction and persistence of tumour cells, we also explore the sufficient conditions for the existence of stationary distribution of the system. (3) The experiments have confirmed that AI cells show stronger drug resistance than AD cells at low dosages of androgen, but high dosages of drugs may cause side effects, and the periodic injection of androgen can better control the growth of tumour cells [1, 32–34, 61, 62]. Besides, the tumour antigenicity also affects the evolution of prostate cancer cells.

åThere are still many meaningful studies deserving future investigation. On the one hand, bifurcation analysis of the model in this paper is an interesting research topic. On the other hand, since cytokines have a good promoting effect on dendritic cells, the effects of pulse injections of cytokines on the dynamic behaviour of prostate cancer cells is worth exploring. We leave these questions for future work.

Competing interests: We declare we have no conflict of interest.

Authors' contributions: Lin Chen: Methodology, Software, Writing Original draft preparation; Jin Yang: Conceptualization, Revising the original draft preparation; Yuanshun Tan: Visualization, Investigation; Zijian Liu: Software; Robert A. Cheke: Reviewing and Editing.

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