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ORIGINAL PAPER

Dynamic behavior of prostate cancer cells under antitumor immunity and pulse vaccination in a random environment

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Abstract Advanced prostate cancer (PCa) is usually treated with androgen deprivation therapy (ADT), which is initially effective but can lead to metastatic castration-resistant prostate cancer. The dendritic cell vaccine immunotherapy can enhance the antitumor immune responses to help fight cancer and has been shown to be effective. A stochastic impulsive PCa model incorporating ADT and immunotherapy is developed in this article to analyze the elimination of androgen-dependent and androgen-independent cancer cells under the noise interference. Besides the existence, uniqueness and boundedness of global positive solution of the model, some sufficient conditions of extinction and persistence in mean of PCa cells are also obtained by using the Itô's formula and the comparison theorem of stochastic differential equation. Our study illustrates that high-intensity noise perturbation can inhibit the development of PCa and verifies theoretically and numerically that frequent vaccination can improve the survival time of the patient with ADT.

Keywords Pulse vaccination · Antitumor immunity · Stochastic disturbance · Dynamic behavior

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1 Introduction

Prostate cancer (PCa) is the second most common cancer in male cancer patients, and the fifth leading cause of death [1]. Beginning as early as the second decade of life, the development of PCa can require over 50 years to reach a detectable state. Due to the slow growth rate of PCa, chemotherapy has a limited effect on the disease. Instead, treatment focuses on surgery and radiotherapy for localized disease and hormone therapy for metastatic cancer [2,3].

The growth of PCa is highly dependent on androgen, such as testosterone and dihydrotestosterone, mainly produced by testis. Therefore, for metastatic cancer, the standard hormone therapy is androgen deprivation therapy (ADT) [3–6]. Although androgen suppression initially succeeds in reducing PCa in most patients, almost all patients with metastatic disease relapse within a few years, known as metastatic castration-resistant prostate cancer (mCRPC). At this hormone refractory stage, the androgen-dependent (AD) cancer cells have mutated into the androgen-independent (AI) cancer cells, and the AI cancer cells are not sensitive to androgen inhibition and able to sustain growth even in androgen deficient environment and may be resistant to the apoptosis effect of this environment [2,6–9]. During the development of AD to AI cancer cells, most differentially expressed genes and signal networks are downregulated, which indicates that the performance of AD cancer cells in proliferation, apoptosis and movement

is different from that of AI cancer cells. Therefore, when AD and AI cancer cells compete for nutrition resources, the competition intensity should be different [10–12]. Jackson proves for the first time through mathematical modeling that the relapse following positive responses to hormonal castration is because PCa is composed of different cell subpopulations, and each has different dependence on androgen [13]. Ideta et al. establish a model of ADT considering the mutation from AD to AI cancer cells and investigate the factors affecting an AI relapse [14]. However, Jackson's and Ideta et al. models do not directly incorporate the competitive effect of the two populations. To address this limitation, Shimada, Aihara and Yang propose models to directly explain the competition between two kinds of cancer, and both of their numerical simulation show that the competition between two kinds of cancer cells can prevent the recurrence of PCa [15,16]. Zhang et al. utilize a three-population Lotka–Volterra type model to investigate solely the competition aspect of cancer sub-populations, and their results show that AD cells are likely to have a significant competitive advantage over AI cells when treatment is not applied [17].

For the treatment of asymptomatic or minimally symptomatic mCRPC, sipuleucel-T is the only immunotherapy currently approved by the United States Food and Drug Administration. The sipuleucel-T, a type of dendritic cell (DC) vaccine immunotherapy, is manufactured by extracting DCs from the patient, loading antigen in DCs, and injecting DCs into the patient's body. DCs are the most powerful antigen-presenting cells in the human body, and they ingest antigens and present antigen substances to the naive and memory T-cells, which then clear specific antigens [18–20]. The sipuleucel-T stimulates the anti-tumor immune response against PCa cells carrying prostatic-acid phosphatase (PAP) antigen and has shown evidence of efficacy in reducing the risk of death among men with asymptomatic or minimally symptomatic mCRPC [9,21]. Therefore, researchers began to pay attention to the application of mathematical model in the vaccine immunotherapy of PCa. Peng et al. construct a differential equation system composed of two kinds of PCa cells and immune microenvironment. Their study shows the potential of a system biology type approach in the modeling of PCa [22]. Kirschner and Panetta explore the effects of immunotherapy on the tumor-immune system taking T-cells, cytokine interleukin-2 and tumor cells into consideration [23]. By combining the models of [14] and [23], Portz and Kuang study a system of ordinary differential equations of PCa treatment with ADT and DC vaccine immunotherapy [4]. They simulate the injections of DC vaccine numerically, and the result illustrates that the DC vaccination can successfully stabilize the disease with ADT. Rutter and Kuang appropriately modify Portz and Kuang's model and further research the effect of DC vaccine injection frequency on relapse time of cancer by simulating [18].

Great progress has been made in the mathematical modeling of ADT and immunotherapy for PCa. However, it should be noted that these models above are deterministic systems, while actually the therapeutic effect is usually affected due to the sensitivity of tumor microenvironment. d'Onofrio points out that the extremely complex interaction between tumor cells and immune effectors justifies the inclusion of noise on a deterministic model of tumor-immune system in order to take into account a plethora of relevant phenomena, such as the variable intensity of neoantigen that stimulate the immune response, the expression or absence of expression of molecules needed for T-cell activation [24]. Therefore, random perturbation should be included in deterministic models in order to consider more related phenomena [25–30]. By taking the effect of white noise into the model of ordinary differential equations in [18], Zazoua and Wang investigate the dynamic behaviors of AD and AI cancer cells with ADT and reveal the impacts of random disturbance and tumor cancer competitiveness on the recurrence of cancer [12].

For modeling the DC vaccination, in fact, after each injection of DC vaccine, the number of DCs increases transiently, which is one of the key factors to activate T-cells and stimulate antitumor immunity. In [4], the vaccinations are administered every 30 days in model simulations, and the numerical simulations suggest that immunotherapy can promote the stabilization of PCa treated by ADT. In [18], Rutter and Kuang run a series of simulations varying only the dosage level and frequency of the DC immunotherapy. They illustrate that increasing the frequency of the injections but keeping the total dosage identical can vast improve the survival time of the patient. However, in the existing studies on vaccine immunotherapy of PCa model, the pulse effect of vaccine injection is only simulated by computer, while there is lack of theoretical research on the elimination of PCa cells by immunotherapy. Therefore,

in our model, we introduce an impulsive equation to depict the pulse effect of DC vaccination and theoretically investigate the extinction and persistence of PCa cells with ADT and vaccine immunotherapy. In addition, our model considering the incorporation of ADT and DC vaccination is the extension of the reference [12] that considering two kinds of PCa cells under ADT alone.

The structure of the article is as follows: In Sect. 2, the mathematical model is formulated and some preliminaries for the study are given. Section 3 focuses on the analysis of the dynamic behaviors of cells and obtains the sufficient conditions for cancer cell extinction and persistence in mean. In Sect. 4, numerical simulations are implemented to demonstrate our results. Our main conclusions are recalled in Sect. 5. Section 6 presents the general discussions of this paper.

2 Mathematical model

2.1 Model formation

Zazoua and Wang [12] investigate the following stochastic model of ADT considering androgen, AD and AI cancer cells,

$$\begin{cases} \mathrm{d}A = \Big[-\gamma\Big(A - a_0\Big) - \gamma a_0 u\Big]\mathrm{d}t, \\ \mathrm{d}X_1(t) = \Big\{ r_1 A\Big(1 - \dfrac{X_1 + \alpha X_2}{K}\Big) \\ \quad - \Big(d_1 + m_1\Big)\Big(1 - \dfrac{A}{a_0}\Big)\Big\} X_1 \mathrm{d}t + \sigma_1 X_1 \mathrm{d}B_1(t), \\ \mathrm{d}X_2(t) = \Big\{ r_2\Big(1 - \dfrac{\beta X_1 + X_2}{K}\Big) X_2 \\ \quad + m_1\Big(1 - \dfrac{A}{a_0}\Big) X_1 \Big\}\mathrm{d}t + \sigma_2 X_2 \mathrm{d}B_2(t), \end{cases} \tag{1}$$

where X_1 and X_2 are the concentrations of AD and AI cancer cells, respectively, A is the concentration of androgen, r_1 and d_1 are the AD cancer cell proliferation and death rate, respectively, r_2 is the AI cancer cell net proliferation rate, a_0 is the normal androgen concentration, α and β are the positive rivalry intensity of the two cancer cells, m_1 is the maximum mutation rate from AD to AI cancer cells, u is the ADT efficacy, K is the carrying capacity of these cells, γ is the clearance and production rate of androgen, $B_i(t)$ $(i = 1, 2)$ are independent one-dimensional standard Brownian motions defined on a given complete probability space $\big(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t\geq 0}, \mathcal{P}\big)$, and σ_i^2 $(i = 1, 2)$ are the intensities of white noise.

Now, we introduce immunotherapy of DC vaccines into model (1). When the DC vaccine is injected into the body, a large number of DCs increase suddenly in vivo and then activate T-cells to induce antitumor immunity. Therefore, we utilize an impulse differential equation to describe the change of DC number with DC vaccination and add the description of anti-tumor immune responses in the model as follows:

$$\begin{cases} \mathrm{d}X_1(t) = \Big\{\Big[r_1 A\Big(1 - \dfrac{X_1 + \alpha X_2}{K}\Big) \\ \quad - \Big(d_1 + m_1\Big)\Big(1 - \dfrac{A}{a_0}\Big)\Big] X_1 - \dfrac{e_1 T X_1}{g_1 + X_1 + X_2}\Big\}\mathrm{d}t \\ \quad + \sigma_1 X_1 \mathrm{d}B_1(t), \\ \mathrm{d}X_2(t) = \Big\{ r_2\Big(1 - \dfrac{\beta X_1 + X_2}{K}\Big) X_2 \\ \quad + m_1\Big(1 - \dfrac{A}{a_0}\Big) X_1 - \dfrac{e_2 T X_2}{g_2 + X_1 + X_2}\Big\}\mathrm{d}t \\ \quad + \sigma_2 X_2 \mathrm{d}B_2(t), \\ \mathrm{d}T(t) = \Big(\dfrac{e_3 D}{g_3 + D} - \mu T\Big)\mathrm{d}t, \\ \mathrm{d}A(t) = \Big[\gamma\Big(a_0 - A\Big) - \gamma a_0 u\Big]\mathrm{d}t, \\ \mathrm{d}D(t) = -cD\mathrm{d}t, \quad t \neq n\tau, n \in \mathbb{Z}^+, \\ \triangle X_1(t) = \triangle X_2(t) = \triangle T(t) = \triangle A(t) = 0, \\ \triangle D(t) = D(n\tau^+) - D(n\tau) = h, \quad t = n\tau, n \in \mathbb{Z}^+, \end{cases} \tag{2}$$

where T is the concentration of T-cell, μ is T-cell death rate, c is the decay rate of DCs, e_1 and e_2 are the max killing rate of T-cells to AD and AI cancer cells, respectively, g_1 and g_2 are the AD and the AI cancer cell saturation level for T-cell kill rate, respectively, e_3 is maximum activation rate of DCs to T-cells, g_3 is DC saturation level for T-cell activation, h is the number of DCs injected with vaccination, τ is the period of the DC vaccination.

2.2 Preliminaries

We list some notations, lemmas and definitions of the paper here. For convenience, we give some notations,

$$\begin{aligned} &f(t)^* = \limsup_{t\to+\infty} f(t), \quad f(t)_* = \liminf_{t\to+\infty} f(t),\\ &\langle f(t)\rangle = \frac{1}{t}\int_0^t f(s)\mathrm{d}s,\\ &H_0 = \frac{e_3 h}{\mu[g_3(e^{c\tau}-1)+h]}, \quad H = \frac{e_3 h}{\mu[g_3(1-e^{-c\tau})+h]},\\ &\mathbb{R}^n_+ = \left\{\boldsymbol{x} = \left(x_1,\ldots,x_n\right) \in \mathbb{R}^n : x_i > 0, i = 1,\ldots n\right\}, \end{aligned} \tag{3}$$

where $f(t)$ is an integrable function on $[0,+\infty)$.

For the following subsystem of system (2),

$$\begin{cases} \mathrm{d}D(t) = -cD\mathrm{d}t, & t \neq n\tau, n \in \mathbb{Z}^+,\\ D(n\tau^+) = D(n\tau) + h, & t = n\tau, n \in \mathbb{Z}^+, \end{cases} \tag{4}$$

the following Lemma 1 gives its solution.

Lemma 1 [31] *System* (4) *has a unique* τ*-periodic solution* $\widetilde{D}(t)$*, where*

$$\begin{cases} \widetilde{D}(t) = \dfrac{he^{-c(t-n\tau)}}{1-e^{-c\tau}},\\ \widetilde{D}(0) = \dfrac{h}{1-e^{-c\tau}}, \end{cases}$$

for any $t \in \left(n\tau,(n+1)\tau\right]$ *and* $n \in \mathbb{Z}^+$*. For each solution* $D(t)$*, we have that* $\lim_{t\to+\infty} D(t) = \widetilde{D}(t)$*.*

From the periodic solution of $D(t)$, it is easy to obtain its boundedness that

$$D(t)_* \doteq \frac{he^{-c\tau}}{1-e^{-c\tau}} \le D(t) \le \frac{h}{1-e^{-c\tau}} \doteq D(t)^*,$$

and other basic properties. It is noted that androgen dynamics evolves much faster than cancer cell dynamics and androgen concentration can reach equilibrium in a relatively short time. So, we consider the steady state of androgen concentration, $A^* = a_0(1-u)$, and in the sequent research, we focus on the following system:

$$\begin{cases} \mathrm{d}X_1(t) = \left\{R\left(1-\dfrac{X_1+\alpha X_2}{K}\right) - U\right.\\ \qquad \left. - \dfrac{e_1 T}{g_1+X_1+X_2}\right\}X_1\mathrm{d}t + \sigma_1 X_1\mathrm{d}B_1(t),\\ \mathrm{d}X_2(t) = \left\{r_2\left(1-\dfrac{\beta X_1+X_2}{K}\right)X_2\right.\\ \qquad \left. + m_1 u X_1 - \dfrac{e_2 T X_2}{g_2+X_1+X_2}\right\}\mathrm{d}t + \sigma_2 X_2\mathrm{d}B_2(t),\\ \mathrm{d}T(t) = \left(\dfrac{e_3 D(t)}{g_3+D(t)} - \mu T\right)\mathrm{d}t, \end{cases} \tag{5}$$

where $R = r_1 a_0(1-u)$, $U = (d_1+m_1)u$.

Lemma 2 [32] *Suppose* $f(t) \in \mathbb{C}\left(\Omega\times[0,+\infty),\mathbb{R}_+\right)$.

1. *If there are constants* $\lambda_0 > 0, t_1 > 0$ *and* $\lambda \ge 0$ *such that*

$$\ln f(t) \le \lambda t - \lambda_0\int_0^t f(s)\mathrm{d}s + \sum_{i=1}^n \sigma_i \mathrm{d}B_i(t)$$

for any $t > t_1$*, where* σ_i *is a constant,* $1 \le i \le n$*, then* $\langle f(t)\rangle^* \le \dfrac{\lambda}{\lambda_0}$ *a.s.*

2. *If there are constants* $\lambda_0 > 0, t_1 > 0$ *and* $\lambda \ge 0$ *such that*

$$\ln f(t) \ge \lambda t - \lambda_0\int_0^t f(s)\mathrm{d}s + \sum_{i=1}^n \sigma_i \mathrm{d}B_i(t)$$

for any $t > t_1$*, where* σ_i *is a constant,* $1 \le i \le n$*, then* $\langle f(t)\rangle_* \ge \dfrac{\lambda}{\lambda_0}$ *a.s.*

Lemma 3 [12] *Let* $M = \{M_t\}_{t\ge0}$ *be 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

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

The Brownian motion $B(t)$ is a continuous square integrable martingale, and its quadratic variation is $\langle B(t),B(t)\rangle_t = t\,(t \ge 0)$. Therefore, from Lemma 3,

$$\lim_{t\to+\infty} \frac{B(t)}{t} = 0 \quad a.s. \tag{6}$$

and for any small $\epsilon \in (0, 1)$, there exists a $\bar{T}$ such that

$$\left|\frac{B(t)-B(s)}{t-s}\right| < \epsilon, \quad t-s > \bar{T} \quad a.s. \tag{7}$$

Definition 1 [12]

1. The population $X_i(t)$ becomes extinct if
$$\lim_{t\to+\infty} X_i(t) = 0 \quad a.s.$$
2. The population $X_i(t)$ becomes persistent in mean if
$$\langle X_i(t)\rangle^* > 0 \quad a.s.$$

Definition 2 [12] The system (5) is stochastically ultimately bounded in the sense that for any $\epsilon \in (0, 1)$, there is a positive constant M such that for any initial value $X(0) = (X_1(0), X_2(0), T(0)) \in \mathbb{R}^3_+$, the solution of system (5) satisfies

$$\limsup_{t\to+\infty} P\left\{|X(t)| > M\right\} < \epsilon.$$

3 The dynamical analysis of system (5)

The following two theorems will show the existence, uniqueness and boundedness of global positive solutions $\left(X_1(t), X_2(t), T(t)\right)$ of system (5).

Theorem 1 *For any initial value* $\left(X_1(0), X_2(0), T(0)\right) \in \mathbb{R}^3_+$, *model* (5) *has a unique global solution* $\left(X_1(t), X_2(t), T(t)\right) \in \mathbb{R}^3_+$ *a.s.*

Proof This proof is inspired by reference [33]. We firstly show the existence of unique local positive solution of model (5). For the following equations:

$$\begin{cases} \mathrm{d}x(t) = \left\{R\left(1-\dfrac{e^{x(t)}+\alpha e^{y(t)}}{K}\right) - U \right. \\ \qquad \left. -\dfrac{1}{2}\sigma_1^2 - \dfrac{e_1 e^{z(t)}}{g_1+e^{x(t)}+e^{y(t)}}\right\}\mathrm{d}t + \sigma_1 \mathrm{d}B_1(t), \\ \mathrm{d}y(t) = \left\{r_2\left(1-\dfrac{\beta e^{x(t)}+e^{y(t)}}{K}\right) + \dfrac{m_1 u e^{x(t)}}{e^{y(t)}} \right. \\ \qquad \left. -\dfrac{1}{2}\sigma_2^2 - \dfrac{e_2 e^{z(t)}}{g_2+e^{x(t)}+e^{y(t)}}\right\}\mathrm{d}t + \sigma_2 \mathrm{d}B_2(t), \\ \mathrm{d}z(t) = \left(\dfrac{e_3 D(t)}{(g_3+D(t))e^{z(t)}} - \mu\right)\mathrm{d}t, \end{cases} \tag{8}$$

with initial data $\left(x(0), y(0), z(0)\right) = \left(\ln X_1(0), \ln X_2(0), \ln T(0)\right)$, model (8) has a unique local solution $\left(x(t), y(t), z(t)\right)$ on $[0, t_e)$ under the local Lipschitz condition, where t_e is the explosion time. It is from Itô's formula that $\left(X_1(t), X_2(t), T(t)\right) = \left(e^{x(t)}, e^{y(t)}, e^{z(t)}\right)$ is the unique local positive solution of model (5).

Now, it suffices to prove $t_e = +\infty$. Consider the following auxiliary equations:

$$\mathrm{d}\phi(t) = \left(\frac{e_3 D(t)_*}{g_3+D(t)_*} - \mu\phi(t)\right)\mathrm{d}t, \tag{9}$$

$$\mathrm{d}\Phi(t) = \left(\frac{e_3 D(t)^*}{g_3+D(t)^*} - \mu\Phi(t)\right)\mathrm{d}t, \tag{10}$$

$$\mathrm{d}N(t) = N(t)\left(R-U-\frac{R}{K}N(t)\right)\mathrm{d}t + \sigma_1 N(t)\mathrm{d}B_1(t), \tag{11}$$

$$\mathrm{d}m(t) = m(t)\left(r_2 - \frac{\beta r_2 N(t)}{K} - \frac{e_2\Phi(t)}{g_2} - \frac{r_2}{K}m(t)\right)\mathrm{d}t + \sigma_2 m(t)\mathrm{d}B_2(t), \tag{12}$$

$$\mathrm{d}M(t) = M(t)\left(r_2 + \frac{m_1 u N(t)}{m(t)} - \frac{r_2}{K}M(t)\right)\mathrm{d}t + \sigma_2 M(t)\mathrm{d}B_2(t), \tag{13}$$

$$\mathrm{d}n(t) = n(t)\left(R-U-\frac{\alpha R M(t)}{K} - \frac{e_1\Phi(t)}{g_1} - \frac{R}{K}n(t)\right)\mathrm{d}t + \sigma_1 n(t)\mathrm{d}B_1(t), \tag{14}$$

with $\Phi(0) = \phi(0) = T(0), N(0) = n(0) = X_1(0), M(0) = m(0) = X_2(0)$. According to the comparison theorem for stochastic differential equations [34], for $t \in [0, t_e)$,

$$\phi(t) \le T(t) \le \Phi(t), m(t) \le X_2(t) \le M(t), n(t) \le X_1(t) \le N(t) \quad a.s.$$

We can compute equations from (9) to (14) and get their solutions as follows:

$$\phi(t) = e^{-\mu t}\phi(0) + H_0\left(1 - e^{-\mu t}\right),$$

$$\Phi(t) = e^{-\mu t}\Phi(0) + H\left(1 - e^{-\mu t}\right),$$

$$N(t) = \frac{\exp\left\{\left[R - U - \frac{1}{2}\sigma_1^2\right]t + \sigma_1 B_1(t)\right\}}{\frac{1}{N(0)} + \frac{R}{K}\int_0^t \exp\left\{\left[R - U - \frac{1}{2}\sigma_1^2\right]s + \sigma_1 B_1(s)\right\}\mathrm{d}s},$$

$$m(t) = \frac{\exp\left\{\int_0^t \left[r_2 - \frac{1}{2}\sigma_2^2 - \frac{\beta r_2 N(s)}{K} - \frac{e_2\Phi(s)}{g_2}\right]\mathrm{d}s + \sigma_2 B_2(t)\right\}}{\frac{1}{m(0)} + \frac{r_2}{K}\int_0^t \exp\left\{\int_0^v \left[r_2 - \frac{1}{2}\sigma_2^2 - \frac{\beta r_2 N(s)}{K} - \frac{e_2\Phi(s)}{g_2}\right]\mathrm{d}s + \sigma_2 B_2(v)\right\}\mathrm{d}v},$$

$$M(t) = \frac{\exp\left\{\int_0^t \left[r_2 - \frac{1}{2}\sigma_2^2 + \frac{m_1 u N(s)}{m(s)}\right]\mathrm{d}s + \sigma_2 B_2(t)\right\}}{\frac{1}{M(0)} + \frac{r_2}{K}\int_0^t \exp\left\{\int_0^v \left[r_2 - \frac{1}{2}\sigma_2^2 + \frac{m_1 u N(s)}{m(s)}\right]\mathrm{d}s + \sigma_2 B_2(v)\right\}\mathrm{d}v},$$

$$n(t) = \frac{\exp\left\{\int_0^t \left[R - U - \frac{1}{2}\sigma_1^2 - \frac{\alpha R M(s)}{K} - \frac{e_1\Phi(s)}{g_1}\right]\mathrm{d}s + \sigma_1 B_1(t)\right\}}{\frac{1}{n(0)} + \frac{R}{K}\int_0^t \exp\left\{\int_0^v \left[R - U - \frac{1}{2}\sigma_1^2 - \frac{\alpha R M(s)}{K} - \frac{e_1\Phi(s)}{g_1}\right]\mathrm{d}s + \sigma_1 B_1(v)\right\}\mathrm{d}v},$$

where H_0 and H are given in (3). Note that $\phi(t) > 0, \Phi(t) > 0, N(t) > 0, m(t) > 0, M(t) > 0, m(t) > 0$ hold for all $t \ge 0$, therefore $t_e = +\infty$. □

Theorem 2 *The system* (5) *is stochastically ultimately bounded.*

Proof Define the function $V\left(t, X_1, X_2, T\right) = e^t\left(X_1^p + X_2^p + T^p\right)$, where $p > 1$. Applying Itô's formula to $V\left(t, X_1, X_2, T\right)$ yields

$$
\begin{aligned}
&\mathrm{d}V\Big(t, X_1, X_2, T\Big) = e^t\Big(X_1^p + X_2^p + T^p\Big)\mathrm{d}t + pe^t\Big(X_1^{p-1}\mathrm{d}X_1 + X_2^{p-1}\mathrm{d}X_2 + T^{p-1}\mathrm{d}T\Big)\\
&+ \frac{1}{2}p(p-1)e^t\Big[X_1^{p-2}\Big(\mathrm{d}X_1\Big)^2 + X_2^{p-2}\Big(\mathrm{d}X_2\Big)^2\Big]\\
&= pe^t\Big\{X_1^p\Big[R\big(1-\frac{X_1+\alpha X_2}{K}\big) - U - \frac{e_1 T}{g_1+X_1+X_2}\Big]\mathrm{d}t + \sigma_1 X_1^p\mathrm{d}B_1(t)\Big\}\\
&+ pe^t\Big\{X_2^{p-1}\Big[r_2\big(1-\frac{\beta X_1+X_2}{K}\big)X_2 + m_1 u X_1 - \frac{e_2 T X_2}{g_2+X_1+X_2}\Big]\mathrm{d}t + \sigma_2 X_2^p\mathrm{d}B_2(t)\Big\}\\
&+ pe^t T^{p-1}\Big[\frac{e_3 D}{g_3+D} - \mu T\Big]\mathrm{d}t + e^t\Big(X_1^p + X_2^p + T^p\Big)\mathrm{d}t + \frac{1}{2}e^t p(p-1)\Big(\sigma_1^2 X_1^p + \sigma_2^2 X_2^p\Big)\mathrm{d}t\\
&\le e^t\Big\{\Big[1 + p\big(R + \frac{1}{2}(p-1)\sigma_1^2\big)\Big]X_1^p - \frac{pR}{K}X_1^{p+1}\Big\}\mathrm{d}t\\
&+ e^t\Big\{pm_1 u X_1 X_2^{p-1} + \Big(1 + p(r_2 + \frac{1}{2}(p-1)\sigma_2^2)\Big)X_2^p - \frac{pr_2}{K}X_2^{p+1}\Big\}\mathrm{d}t\\
&+ e^t\Big\{\frac{pe_3 D}{g_3+D}T^{p-1} + \big(1-p\mu\big)T^p\Big\}\mathrm{d}t + pe^t\sum_{i=1}^{2}\sigma_i X_i^p\mathrm{d}B_i(t)
\end{aligned}
$$

$$
\le e^t\Big(Q_1 + Q_2 + Q_3\Big)\mathrm{d}t + pe^t\sum_{i=1}^{2}\sigma_i X_i^p\mathrm{d}B_i(t), \tag{15}
$$

where constants $Q_1, Q_2, Q_3 > 0$. Write $Q = Q_1 + Q_2 + Q_3$. Integrating both sides of (15) from 0 to t and calculating the expectation of both sides leads to

$$
\begin{aligned}
&E\Big[e^t\Big(X_1^p(t) + X_2^p(t) + T^p(t)\Big)\Big]\\
&\quad\le X_1^p(0) + X_2^p(0) + T^p(0) + Q\Big(e^t - 1\Big),
\end{aligned}
$$

and then

$$
\begin{aligned}
&E\Big[X_1^p(t) + X_2^p(t) + T^p(t)\Big]\\
&\quad\le e^{-t}\Big(X_1^p(0) + X_2^p(0) + T^p(0)\Big) + Q\Big(1 - e^{-t}\Big).
\end{aligned}
$$

Therefore,

$$
\limsup_{t\to+\infty} E\Big[X_1^p(t) + X_2^p(t) + T^p(t)\Big] \le Q. \tag{16}
$$

Note that

$$
|X|^p = \Big(X_1^2 + X_2^2 + T^2\Big)^{p/2} < 3^{p/2}\Big(X_1^p + X_2^p + T^p\Big). \tag{17}
$$

Hence, from (16) and (17), we get

$$
\limsup_{t\to+\infty} E\Big[|X|^p\Big] < 3^{p/2}Q.
$$

For any $\epsilon \in (0,1)$, let $\chi = \sqrt{3}\big(Q/\epsilon\big)^{1/p}$. According to the Chebyshev inequality,

$$
\begin{aligned}
\limsup_{t\to+\infty} P\Big\{|X| > \chi\Big\} &= \limsup_{t\to+\infty} P\Big\{|X|^p > \chi^p\Big\}\\
&< \frac{3^{p/2}Q}{\Big[\sqrt{3}\big(Q/\epsilon\big)^{1/p}\Big]^p} = \epsilon.
\end{aligned}
$$

So the solutions of the model are stochastically ultimately bounded. □

Theorem 3 *Assume that*

$$
R - U - \frac{1}{2}\sigma_1^2 < 0, \tag{18}
$$

then there are the following assertions:

(i) *Androgen-dependent cells X_1 will be extinct.*

(ii) *If*

$$r_2 - \frac{1}{2}\sigma_2^2 < 0, \tag{19}$$

then androgen-independent cells X_2 will be extinct.

(iii) *If*

$$r_2 - \frac{1}{2}\sigma_2^2 - \frac{e_2}{g_2}H > 0, \tag{20}$$

then androgen-independent cells X_2 are persistent in mean.

Proof i) Let us prove the extinction of androgen-dependent cells X_1 under condition (18). Applying Itô's formula to $\ln X_1(t)$ and integrating from 0 to t lead to

$$\begin{aligned}\ln\frac{X_1(t)}{X_1(0)} &= \Big(R - U - \frac{1}{2}\sigma_1^2\Big)t - \frac{R}{K}\int_0^t X_1(s)\mathrm{d}s - \frac{\alpha R}{K}\int_0^t X_2(s)\mathrm{d}s\\ &\quad - \int_0^t \frac{e_1 T(s)}{g_1 + X_1(s) + X_2(s)}\mathrm{d}s + \sigma_1 B_1(t),\end{aligned}$$

then,

$$\begin{aligned}\frac{1}{t}\ln\frac{X_1(t)}{X_1(0)} &= R - U - \frac{1}{2}\sigma_1^2 - \frac{R}{K}\Big\langle X_1(t)\Big\rangle - \frac{\alpha R}{K}\Big\langle X_2(t)\Big\rangle\\ &\quad - \Big\langle\frac{e_1 T(t)}{g_1 + X_1(t) + X_2(t)}\Big\rangle + \sigma_1\frac{B_1(t)}{t}.\end{aligned} \tag{21}$$

Taking the superior limit of (21) and then using (6) and (18) yields

$$\limsup_{t\to+\infty}\frac{1}{t}\ln\frac{X_1(t)}{X_1(0)} \le R - U - \frac{1}{2}\sigma_1^2 < 0 \quad a.s.$$

Therefore,

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

That is to say, for $\Omega_1 = \Big\{\omega\in\Omega : \lim_{t\to+\infty} X_1(t,\omega) = 0\Big\}$, $P(\Omega_1) = 1$ holds. In view of $\omega\in\Omega_1$, for any $\varepsilon_1 > 0$, there is a large $T_1(\varepsilon_1,\omega) > 0$ such that for all $t > T_1$, we have

$$X_1(t,\omega) < \varepsilon_1. \tag{22}$$

(ii) Next, the extinction of androgen-independent cells X_2 under conditions (18) and (19) will be proved.

It is clear that

$$\begin{aligned}\mathrm{d}X_2(t) &= \Big\{r_2\Big(1 - \frac{\beta X_1 + X_2}{K}\Big)X_2 + m_1 u X_1\\ &\quad - \frac{e_2 T X_2}{g_2 + X_1 + X_2}\Big\}\mathrm{d}t + \sigma_2 X_2\mathrm{d}B_2(t)\\ &\le \Big(m_1 u X_1 + r_2 X_2\Big)\mathrm{d}t + \sigma_2 X_2\mathrm{d}B_2(t).\end{aligned}$$

In view of (22), for all $t > T_1$ and $\omega\in\Omega_1$,

$$\mathrm{d}X_2(t,\omega) \le \Big(m_1 u\varepsilon_1 + r_2 X_2(t,\omega)\Big)\mathrm{d}t + \sigma_2 X_2(t,\omega)\mathrm{d}B_2(t,\omega).$$

Consider this following stochastic differential equation

$$\varphi(t,\omega) = \Big(m_1 u\varepsilon_1 + r_2\varphi(t,\omega)\Big)\mathrm{d}t + \sigma_2\varphi(t,\omega)\mathrm{d}B_2(t,\omega) \tag{23}$$

with initial value $\varphi(0,\omega) = X_2(0,\omega)$. The solution of (23) is

$$\begin{aligned}\varphi(t,\omega) &= \varphi(0,\omega)\exp\Big\{\Big(r_2 - \frac{1}{2}\sigma_2^2 + \sigma_2\frac{B_2(t,\omega)}{t}\Big)t\Big\}\\ &\quad + m_1 u\varepsilon_1\int_0^t \exp\Big\{\Big(r_2 - \frac{1}{2}\sigma_2^2 + \sigma_2\frac{B_2(t,\omega) - B_2(s,\omega)}{t-s}\Big)(t-s)\Big\}\mathrm{d}s.\end{aligned}$$

By virtue of (7), we see that there is a constant $T_2 > 0$ such that

$$\left|\frac{B_2(t,\omega) - B_2(s,\omega)}{t-s}\right| < \varepsilon_1, \quad t - s > T_2 \quad a.s. \tag{24}$$

Without losing generality, it is assumed that (24) holds for any $\omega\in\Omega_1$. Hence, for all $t > T_2$,

$$\varphi(t,\omega) \le \varphi(0,\omega)e^{L_1 t} + m_1 u\varepsilon_1\Big(I_1 + \frac{e^{L_1 t} - e^{L_1 T_2}}{L_1}\Big), \tag{25}$$

where

$$\begin{aligned}I_1 &= \int_0^{T_2}\exp\Big\{\Big(r_2 - \frac{1}{2}\sigma_2^2\Big)v\\ &\quad + \sigma_2\Big(B_2(t,\omega) - B_2(t-v,\omega)\Big)\Big\}\mathrm{d}v,\\ L_1 &= r_2 - \frac{1}{2}\sigma_2^2 + \sigma_2\varepsilon_1 < 0.\end{aligned} \tag{26}$$

From the Kolmogorov Theorem [35], for all $t \geq T_2$, there is a positive constant M_1 such that

$$I_1 \leq M_1. \tag{27}$$

Therefore, taking the superior limit of (25) and according to (26) and (27), we get

$$\limsup_{t\to+\infty} \varphi(t,\omega) \leq m_1 u \varepsilon_1 \left(M_1 - \frac{e^{L_1 T_2}}{L_1} \right).$$

From the arbitrariness of ε_1 and the comparison theorem, we obtain that for all $\omega \in \Omega_1$

$$\limsup_{t\to+\infty} X_2(t,\omega) = 0.$$

According to $P(\Omega_1) = 1$, we conclude that

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

(iii) Now, let us show that androgen-independent cells X_2 will be persistent in mean when (18) and (20) occur. Applying Itô's formula to $\ln X_2(t)$ and then integrating from 0 to t yields

$$\begin{aligned} \ln \frac{X_2(t)}{X_2(0)} = {} & \left(r_2 - \frac{1}{2}\sigma_2^2\right)t - \frac{r_2\beta}{K}\int_0^t X_1(s)\mathrm{d}s \\ & - \frac{r_2}{K}\int_0^t X_2(s)\mathrm{d}s + m_1 u \int_0^t \frac{X_1(s)}{X_2(s)}\mathrm{d}s \\ & - \int_0^t \frac{e_2 T(s)}{g_2 + X_1(s) + X_2(s)}\mathrm{d}s + \sigma_2 B_2(t). \end{aligned} \tag{28}$$

Theorem 1 implies that there exists $t_0 > 0$ such that $T(t) \leq H$ for all $t > t_0$, where H is given in (3). It is from (22) that for any $\omega \in \Omega_1$ and $t > T^1 := T_1 \vee t_0$,

$$\begin{aligned} \ln \frac{X_2(t,\omega)}{X_2(0,\omega)} \geq {} & \left\{ r_2\left(1 - \frac{\beta\varepsilon_1}{K}\right) - \frac{1}{2}\sigma_2^2 - \frac{e_2}{g_2}H \right\} t \\ & - \frac{r_2}{K}\int_0^t X_2(s,\omega)\mathrm{d}s + \sigma_2 B_2(t). \end{aligned}$$

By Lemma 2 and (20), we can obtain that for all $\omega \in \Omega_1$

$$\liminf_{t\to+\infty} \frac{1}{t}\int_0^t X_2(s,\omega)\mathrm{d}s \geq \frac{r_2\left(1 - \frac{\beta\varepsilon_1}{K}\right) - \frac{1}{2}\sigma_2^2 - \frac{e_2}{g_2}H}{\frac{r_2}{K}}.$$

Due to the arbitrariness of ε_1 and $P(\Omega_1) = 1$, we get

$$\limsup_{t\to+\infty} \frac{1}{t}\int_0^t X_2(s)\mathrm{d}s > 0 \quad a.s.$$

This completes the proof. □

Theorem 4 *If the following condition is satisfied,*

$$R - U - \frac{1}{2}\sigma_1^2 - \frac{e_1}{g_1}H > 0,$$

then androgen-independent cells X_2 are persistent in mean.

Proof We will complete the proof by contradiction. Suppose that X_2 are not persistent in mean, that is to say, for $\Omega_2 = \left\{\omega \in \Omega : \langle X_2(\omega)\rangle^* = 0\right\}$, $P(\Omega_2) > 0$ holds. Therefore, in view of $\omega \in \Omega_2$, for any small ε_2, there is a $T_3 > 0$ such that

$$\langle X_2(\omega)\rangle < \varepsilon_2, \quad t > T_3. \tag{29}$$

Notice that

$$\begin{aligned} \mathrm{d}X_1 \geq {} & \left\{ R - U - \frac{e_1}{g_1}T - \frac{\alpha R}{K}X_2 - \frac{R}{K}X_1 \right\} X_1 \mathrm{d}t \\ & + \sigma_1 X_1 \mathrm{d}B_1(t) \quad a.s. \end{aligned}$$

According to the comparison theorem for stochastic differential equations,

$$X_1(t,\omega) \geq \frac{\exp\left\{ t\left(R - U - \frac{1}{2}\sigma_1^2 - \frac{e_1}{g_1}\langle T(t)\rangle - \frac{\alpha R}{K}\langle X_2(t)\rangle + \sigma_1 \frac{B_1(t)}{t} \right) \right\}}{\frac{1}{X_1(0)} + \frac{R}{K}\int_0^t \exp\left\{ s\left(R - U - \frac{1}{2}\sigma_1^2 \right) - \frac{e_1}{g_1}\int_0^s T(\theta)\mathrm{d}\theta - \frac{\alpha R}{K}\int_0^s X_2(\theta)\mathrm{d}\theta + \sigma_1 B_1(s) \right\}\mathrm{d}s},$$

almost surely, and then we have

$$\begin{aligned}\frac{1}{X_1(t,\omega)} \le \frac{1}{X_1(0)} \exp\Big\{ -t\Big(R - U - \frac{1}{2}\sigma_1^2 - \frac{e_1}{g_1}\langle T(t)\rangle \\ - \frac{\alpha R}{K}\Big\langle X_2(t)\Big\rangle + \sigma_1 \frac{B_1(t)}{t}\Big)\Big\} \\ + \frac{R}{K}\int_0^t \exp\Big\{\Big(t-s\Big) \\ \Big(-R + U + \frac{1}{2}\sigma_1^2 + \sigma_1 \frac{B_1(s,\omega) - B_1(t,\omega)}{t-s}\Big) \\ + \frac{e_1}{g_1}\int_s^t T(\xi_1)\mathrm{d}\xi_1 + \frac{\alpha R}{K}\int_s^t X_2(\xi_1)\mathrm{d}\xi_1 \end{aligned} \tag{30}$$

almost surely. It follows from (7) that for the ε_2, there exists a large $T_4 > 0$ such that

$$\left|\frac{B_1(t,\omega) - B_1(s,\omega)}{t-s}\right| < \varepsilon_2, \quad t - s > T_4 \quad a.s. \tag{31}$$

It is general to suppose that (31) is valid for any $\omega \in \Omega_2$.

Substituting (29) and (31) into (30), we see that for all $t > T^2 := t_0 \vee T_3 \vee T_4$ and $\omega \in \Omega_2$,

$$\frac{1}{X_1(t,\omega)} \le \frac{1}{X_1(0)} e^{L_2 t} + \frac{R}{K}\left\{ I_2 + \frac{e^{L_2 t} - e^{L_2 T^2}}{L_2}\right\},$$

where

$$\begin{aligned} L_2 &= -R + U + \frac{1}{2}\sigma_1^2 + \frac{e_1}{g_1}H + (\sigma_1 + \frac{\alpha R}{K})\varepsilon_2 < 0, \\ I_2 &= \int_0^{T^2} \exp\Big\{ v\Big(-R + U + \frac{1}{2}\sigma_1^2\Big) \\ &\quad + \sigma_1\Big(B_1(t-v,\omega) - B_1(t,\omega)\Big) \\ &\quad + \frac{e_1}{g_1}\int_0^v T(\xi_2)\mathrm{d}\xi_2 + \frac{\alpha R}{K}\int_0^v X_2(\xi_2,\omega)\mathrm{d}\xi_2\Big\}\mathrm{d}v. \end{aligned}$$

From the Kolmogorov Theorem, we obtain that there exists a constant $M_2 > 0$ such that

$$I_2 \le M_2, \quad t > T^2,$$

and then for all $\omega \in \Omega_2$,

$$\limsup_{t\to+\infty} \frac{1}{X_1(t,\omega)} \le \frac{R}{K}\left(M_2 - \frac{e^{L_2 T^2}}{L_2}\right).$$

Thus, there exists a positive constant κ_1 such that

$$X_1(t,\omega) \ge \kappa_1, \quad t > T^2. \tag{32}$$

In view of Theorem 2, we have that there exists positive constants M_3 and T_5 such that for all $t > T_5$,

$$X_1(t) \le M_3 \quad a.s. \quad \text{and} \quad X_2(t) \le M_3 \quad a.s.$$

Therefore, for all $t > T^3 := t_0 \vee T_5 \vee T^2$ and $\omega \in \Omega_2$, we get

$$\begin{aligned}\mathrm{d}X_2(t,\omega) \ge \Big\{\Big(r_2(1 - \frac{\beta M_3 + M_3}{K}) - \frac{e_2}{g_2}H\Big)X_2 + m_1 u\kappa_1\Big\}\mathrm{d}t \\ + \sigma_2 X_2 \mathrm{d}B_2(t),\end{aligned}$$

thus,

$$\begin{aligned} X_2(t) \ge X_2(0)\exp\Big\{t\Big(r_2(1 - \frac{\beta M_3 + M_3}{K}) - \frac{e_2}{g_2}H \\ - \frac{1}{2}\sigma_2^2 + \sigma_2\frac{B_2(t)}{t}\Big)\Big\} \\ + m_1 u\kappa_1 \int_0^t \exp\Big\{\Big(t-s\Big)\Big(r_2(1 - \frac{\beta M_3 + M_3}{K}) \\ - \frac{e_2}{g_2}H - \frac{1}{2}\sigma_2^2 + \sigma_2\frac{B_2(t,\omega) - B_2(s,\omega)}{t-s}\Big)\Big\}\mathrm{d}s. \end{aligned}$$

According to (7), we have that for the ε_2, there is a T_6 such that

$$\left|\frac{B_2(t,\omega) - B_2(s,\omega)}{t-s}\right| < \varepsilon_2, \quad t - s > T_6 \quad a.s. \tag{33}$$

In general, it is assumed that (33) is valid for any $\omega \in \Omega_2$. Therefore, for all $t > T^4 := T_6 \vee T^3$ and $\omega \in \Omega_2$,

$$X_2(t) \ge m_1 u\kappa_1 \int_{T^4}^t e^{L_3 v}\mathrm{d}v,$$

where

$$L_3 := r_2(1 - \frac{\beta M_3 + M_3}{K}) - \frac{e_2}{g_2}H - \frac{1}{2}\sigma_2^2 + \sigma_2\varepsilon_2.$$

If $L_3 = 0$, then for all $t > T^4$

$$X_2(t,\omega) \ge m_1 u\kappa_1 (t - T^4).$$

If $L_3 \ne 0$, then for all $t > T^4$,

$$X_2(t,\omega) \ge \frac{m_1 u\kappa_1}{L_3}\Big(e^{L_3 t} - e^{L_3 T^4}\Big).$$

As a result, if $L_3 \ge 0$, then

$$\liminf_{t\to+\infty} X_2(t,\omega) = +\infty,$$

and if $L_3 < 0$, then

$$\liminf_{t\to+\infty} X_2(t,\omega) \ge -\frac{m_1 u\kappa_1}{L_3} e^{L_3 T^4},$$

which contradicts the previous hypothesis. So X_2 are persistent in mean. □

Theorem 5 *The androgen-dependent cells X_1 will become extinct if one of the following two conditions is satisfied,*

(i) $R-U-\frac{1}{2}\sigma_1^2-\frac{\alpha R}{r_2}\left(r_2-\frac{1}{2}\sigma_2^2-\frac{e_2}{g_2}H\right)<0$ *and* $\alpha\beta\le 1$.

(ii) $R-U-\frac{1}{2}\sigma_1^2-\frac{R}{r_2\beta}\left(r_2-\frac{1}{2}\sigma_2^2-\frac{e_2}{g_2}H\right)<0$ *and* $\alpha\beta>1$.

Proof Divide both sides of (28) by t to get

$$\begin{aligned}\frac{1}{t}\ln\frac{X_2(t)}{X_2(0)}&=r_2-\frac{1}{2}\sigma_2^2-\frac{r_2\beta}{K}\left\langle X_1(t)\right\rangle-\frac{r_2}{K}\left\langle X_2(t)\right\rangle\\&\quad+m_1u\left\langle\frac{X_1(t)}{X_2(t)}\right\rangle\\&\quad-\left\langle\frac{e_2T(t)}{g_2+X_1(t)+X_2(t)}\right\rangle+\sigma_2\frac{B_2(t)}{t}.\end{aligned}\tag{34}$$

For case (i), computing (21)$-\frac{\alpha R}{r_2}$(34) yields

$$\begin{aligned}&t^{-1}\ln\left(\frac{X_1(t)}{X_2(t)^{\alpha R/r_2}}\right)\\&=t^{-1}\left(\ln X_1(0)-\frac{\alpha R}{r_2}\ln X_2(0)\right)\\&\quad+\left(R-U-\frac{1}{2}\sigma_1^2\right)-\frac{\alpha R}{r_2}\left(r_2-\frac{1}{2}\sigma_2^2\right)\\&\quad-\frac{R}{K}\left(1-\alpha\beta\right)\left\langle X_1(t)\right\rangle-\frac{\alpha Rm_1u}{r_2}\left\langle\frac{X_1(t)}{X_2(t)}\right\rangle\\&\quad-\left\langle\frac{e_1T(t)}{g_1+X_1(t)+X_2(t)}\right\rangle\\&\quad+\frac{\alpha R}{r_2}\left\langle\frac{e_2T(t)}{g_2+X_1(t)+X_2(t)}\right\rangle+\sigma_1\frac{B_1(t)}{t}-\sigma_2\frac{\alpha R}{r_2}\frac{B_2(t)}{t},\end{aligned}\tag{35}$$

and then,

$$\begin{aligned}&t^{-1}\ln\left(\frac{X_1(t)}{X_2(t)^{\alpha R/r_2}}\right)\\&\le t^{-1}\left(\ln X_1(0)-\frac{\alpha R}{r_2}\ln X_2(0)\right)+R\\&\quad-U-\frac{1}{2}\sigma_1^2-\frac{\alpha R}{r_2}\left(r_2-\frac{1}{2}\sigma_2^2\right)\\&\quad+\frac{\alpha R}{r_2}\frac{e_2}{g_2}\left\langle T(t)\right\rangle-\frac{R}{K}(1-\alpha\beta)\left\langle X_1(t)\right\rangle+\sigma_1\frac{B_1(t)}{t}\\&\quad-\sigma_2\frac{\alpha R}{r_2}\frac{B_2(t)}{t}.\end{aligned}\tag{36}$$

Taking the superior limit on both sides of (36), and then according to (6) and the conditions of (i), we get

$$\begin{aligned}&\limsup_{t\to+\infty}\left(t^{-1}\ln\left(\frac{X_1(t)}{X_2(t)^{\alpha R/r_2}}\right)\right)\le R-U\\&\quad-\frac{1}{2}\sigma_1^2-\frac{\alpha R}{r_2}\left(r_2-\frac{1}{2}\sigma_2^2-\frac{e_2}{g_2}H\right)<0\quad a.s.\end{aligned}$$

Hence,

$$\limsup_{t\to+\infty}\frac{X_1(t)}{X_2(t)^{\alpha R/r_2}}=0\quad a.s.$$

Theorem 2 indicates that there exists a upper bound M_3 of $X_2(t)$, therefore,

$$0\le\frac{X_1(t)}{M_3^{\alpha R/r_2}}\le\frac{X_1(t)}{X_2(t)^{\alpha R/r_2}}\quad a.s.\tag{37}$$

Taking the superior limit on both side of (37) yields

$$\limsup_{t\to+\infty}\frac{X_1(t)}{M_3^{\alpha R/r_2}}=0\quad a.s.\tag{38}$$

For case (ii), computing (21)$-\frac{R}{r_2\beta}$(34) yields

$$\begin{aligned}&t^{-1}\ln\left(\frac{X_1(t)}{X_2(t)^{R/(r_2\beta)}}\right)\\&\le t^{-1}\left(\ln X_1(0)-\frac{R}{r_2\beta}\ln X_2(0)\right)+R\\&\quad-U-\frac{1}{2}\sigma_1^2-\frac{R}{r_2\beta}\left(r_2-\frac{1}{2}\sigma_2^2\right)\\&\quad+\frac{R}{r_2\beta}\frac{e_2}{g_2}\left\langle T(t)\right\rangle-\frac{R}{K\beta}\left(\alpha\beta-1\right)\left\langle X_2(t)\right\rangle\\&\quad+\sigma_1\frac{B_1(t)}{t}-\sigma_2\frac{R}{r_2\beta}\frac{B_2(t)}{t}.\end{aligned}\tag{39}$$

Taking the superior limit on both sides of (39), and applying (6) and the conditions of (ii) gets

$$\begin{aligned}&\limsup_{t\to+\infty}\left(t^{-1}\ln\left(\frac{X_1(t)}{X_2(t)^{R/(r_2\beta)}}\right)\right)\\&\le R-U-\frac{1}{2}\sigma_1^2-\frac{R}{r_2\beta}\left(r_2-\frac{1}{2}\sigma_2^2-\frac{e_2}{g_2}H\right)<0\quad a.s.\end{aligned}$$

Using the same method as in case (i), we obtain

$$\limsup_{t\to+\infty}\frac{X_1(t)}{M_3^{R/(r_2\beta)}}=0\quad a.s.\tag{40}$$

According to (38) and (40), in both cases (i) and (ii),

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

This completes the proof. □

Theorem 6 *If the following conditions are satisfied,*

$$R-U-\frac{1}{2}\sigma_1^2-\frac{e_1}{g_1}H-\frac{\alpha R}{r_2}(r_2-\frac{1}{2}\sigma_2^2)>0,\quad r_2-\frac{1}{2}\sigma_2^2-\frac{e_2}{g_2}H>0, \tag{41}$$

then androgen-dependent cells X_1 are persistent in mean.

Proof We make use of reduction to absurdity in the following proof process. Supposing that the androgen-dependent cells are not persistent in mean, then we have that $P(\Omega_3) > 0$ holds for $\Omega_3 = \Big\{\omega \in \Omega : \langle X_1(\omega)\rangle^* = 0\Big\}$. Thus, in view of $\omega \in \Omega_3$, for any small ε_3, there is a $T_7 > 0$ such that

$$\langle X_1(\omega)\rangle < \varepsilon_3, \quad t > T_7. \tag{42}$$

Noting that

$$\begin{aligned} \mathrm{d}X_2(t) \geq &\Big\{r_2 - \frac{r_2\beta}{K}X_1 - \frac{e_2}{g_2}T - \frac{r_2}{K}X_2\Big\}X_2(t)\mathrm{d}t \\ &+\sigma_2 X_2 \mathrm{d}B_2(t) \quad a.s., \end{aligned}$$

we obtain

$$\begin{aligned} X_2(t,\omega) \geq \frac{\exp\Big\{t\Big(r_2 - \frac{1}{2}\sigma_2^2 - \frac{r_2\beta}{K}\Big\langle X_1(t)\Big\rangle - \frac{e_2}{g_2}\Big\langle T(t)\Big\rangle + \sigma_2\frac{B_2(t)}{t}\Big)\Big\}}{\frac{1}{X_2(0)} + \frac{r_2}{K}\int_0^t \exp\Big\{\int_0^s [r_2 - \frac{1}{2}\sigma_2^2 - \frac{r_2\beta}{K}X_1(\theta) - \frac{e_2}{g_2}T(\theta)]\mathrm{d}\theta + \sigma_2 B_2(s)\Big\}\mathrm{d}s} \end{aligned}$$

almost surely, thus,

$$\begin{aligned} \frac{1}{X_2(t,\omega)} \leq &\frac{1}{X_2(0)}\exp\Big\{-t\Big(r_2 - \frac{1}{2}\sigma_2^2 - \frac{r_2\beta}{K}\Big\langle X_1(t)\Big\rangle \\ &- \frac{e_2}{g_2}\Big\langle T(t)\Big\rangle + \sigma_2\frac{B_2(t)}{t}\Big)\Big\} \\ &+ \frac{r_2}{K}\int_0^t \exp\Big\{\Big(t-s\Big)\Big(-r_2 + \frac{1}{2}\sigma_2^2 \\ &+ \sigma_2\frac{B_2(s,\omega)-B_2(t,\omega)}{t-s}\Big) \\ &+ \frac{e_2}{g_2}\int_s^t T(\xi_3)\mathrm{d}\xi_3 + \frac{r_2\beta}{K}\int_s^t X_1(\xi_3)\mathrm{d}\xi_3\Big\}\mathrm{d}s \end{aligned} \tag{43}$$

almost surely. It follows from (7) that for the ε_3, there exists a large $T_8 > 0$ such that

$$\left|\frac{B_2(t,\omega)-B_2(s,\omega)}{t-s}\right| < \varepsilon_3, \quad t-s > T_8 \quad a.s. \tag{44}$$

It is supposed that (44) is valid for any $\omega \in \Omega_3$ in general. Substituting (42) and (44) into (43), we see that for all $t > T^5 := t_0 \vee T_7 \vee T_8$ and $\omega \in \Omega_3$,

$$\frac{1}{X_2(t,\omega)} \leq \frac{1}{X_2(0)}e^{L_4 t} + \frac{r_2}{K}\Big\{I_3 + \frac{e^{L_4 t} - e^{L_4 T^5}}{L_4}\Big\}, \tag{45}$$

where

$$\begin{aligned} L_4 &= -r_2 + \frac{1}{2}\sigma_2^2 + \frac{e_2}{g_2}H + (\sigma_2 + \frac{r_2\beta}{K})\varepsilon_3 < 0, \\ I_3 &= \int_0^{T^5} \exp\Big\{v\Big(-r_2 + \frac{1}{2}\sigma_2^2 + \sigma_2\frac{B_2(t-v,\omega)-B_2(t,\omega)}{v}\Big) \\ &\quad + \frac{e_2}{g_2}\int_0^v T(\xi_4)\mathrm{d}\xi_4 + \frac{r_2\beta}{K}\int_0^v X_1(\xi_4,\omega)\mathrm{d}\xi_4\Big\}\mathrm{d}v. \end{aligned}$$

According to the Kolmogorov Theorem, there exists a constant $M_4 > 0$ such that

$$I_3 \leq M_4, \quad t > T^5,$$

and then for all $\omega \in \Omega_3$,

$$\limsup_{t\to+\infty} \frac{1}{X_2(t,\omega)} \leq \frac{r_2}{K}\Big(M_4 - \frac{e^{L_4 T^5}}{L_4}\Big).$$

Therefore, there exists a positive constant κ_2 such that

$$X_2(t,\omega) \geq \kappa_2, \quad t > T^5. \tag{46}$$

Substituting (46) into (35) yields that for all $t > T^5$ and $\omega \in \Omega_3$,

$$\begin{aligned}
&\frac{1}{t}\ln X_1(t,\omega) - \frac{\alpha R}{r_2}\frac{1}{t}\ln X_2(t,\omega)\\
&\quad\geq \frac{1}{t}\Big(\ln X_1(0) - \frac{\alpha R}{r_2}\ln X_2(0)\Big) + \Big(R - U - \frac{1}{2}\sigma_1^2\\
&\quad - \frac{e_1}{g_1}H\Big) - \frac{\alpha R}{r_2}\Big(r_2 - \frac{1}{2}\sigma_2^2\Big)\\
&\qquad - \Big(\frac{R}{K} - \frac{\alpha\beta R}{K} + \frac{\alpha R m_1 u}{r_2\kappa_2}\Big)\Big\langle X_1(t)\Big\rangle + \sigma_1\frac{B_1(t,\omega)}{t}\\
&\qquad - \sigma_2\frac{\alpha R}{r_2}\frac{B_2(t,\omega)}{t}. \qquad (47)
\end{aligned}$$

From (46) and boundedness of $X_2(t)$, we get that

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

Notice that

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

As a consequence, taking the limit on both sides of (47) leads to

$$0 \geq R - U - \frac{1}{2}\sigma_1^2 - \frac{e_1}{g_1}H - \frac{\alpha R}{r_2}\Big(r_2 - \frac{1}{2}\sigma_2^2\Big) > 0,$$

where a contradiction occurs. So the androgen-dependent cells $X_1(t)$ are persistent in mean. □

Remark 1 In model (2), when the parameters e_1 and e_2 are equal to zero and there is no pulse DC vaccination, model (2) becomes model (1), and Theorem 4.8, (i) and (iii) of Theorem 4.9 in reference [12] become the special cases of Theorem 3, Theorem 4 and Theorem 5 of this article, respectively. Therefore, our model is an extension of reference [12].

4 Numerical simulations

In this section, we use numerical simulations for model (2) to show the effects of intercellular competition, random disturbance and the cancer treatment combining ADT and immunotherapy on tumor dynamics. In order to show approximate solutions with initial conditions, we use the Milstein's higher order method [36].

Rewrite (X_1, X_2, T, A, D) as (x, y, z, p, q) for convenience and get the discretization equations of model (2) as follows:

$$\begin{cases}
x_{k+1} = x_k + \Big[r_1 p_k\Big(1 - \dfrac{x_k + \alpha y_k}{K}\Big)\\
\qquad - \Big(d_1 + m_1\Big)\Big(1 - \dfrac{p_k}{a_0}\Big) - \dfrac{e_1 z_k}{g_1 + x_k + y_k}\Big]x_k\triangle t\\
\qquad + \sigma_1 x_k\sqrt{\triangle t}\zeta_k + \dfrac{1}{2}\sigma_1^2 x_k(\zeta_k^2 - 1)\triangle t,\\
y_{k+1} = y_k + \Big[r_2\Big(1 - \dfrac{\beta x_k + y_k}{K}\Big)y_k\\
\qquad + m_1\Big(1 - \dfrac{p_k}{a_0}\Big)x_k - \dfrac{e_2 z_k y_k}{g_2 + x_k + y_k}\Big]\triangle t\\
\qquad + \sigma_2 y_k\sqrt{\triangle t}\xi_k + \dfrac{1}{2}\sigma_2^2 y_k(\xi_k^2 - 1)\triangle t,\\
z_{k+1} = z_k + \Big(\dfrac{e_3 q_k}{g_3 + q_k} - \mu z_k\Big)\triangle t,\\
p_{k+1} = p_k + \Big(\gamma(a_0 - p_k) - \gamma a_0 u\Big)\triangle t,\\
q_{k+1} = q_k - c q_k\triangle t,
\end{cases}$$

where the step size $\triangle t = 0.01$. At the impulsive point series $\{n\tau\}_{n\in\mathbb{Z}^+}$, the corresponding program is $x_{k+1} = x_{k+1}$, $y_{k+1} = y_{k+1}$, $z_{k+1} = z_{k+1}$, $p_{k+1} = p_{k+1}$ and $q_{k+1} = q_{k+1} + h$.

The parameter values are shown in Table 1, and the initial values are set as $X_1(0) = 15 \times 10^6$ cells, $X_2(0) = 0.1 \times 10^6$ cells, $T(0) = 0$ cells, $A(0) = 30$ nmol/L, $D(0) = 0$ cells [18,20]. Making use of the numerical simulation method given above and applying parameters in Table 1, we verify the main results in Sect. 3 and get some interesting conclusions.

Firstly, the inhibitory effect of stochastic perturbation on cell proliferation is indicated by Fig. 1. We fix $u = 0.5$, $\alpha = 0.9$, $\beta = 0.8$, $h = 40 \times 10^6$ (unit: cells) and $\tau = 30$ (unit: days), and the values of σ_1 and σ_2 are labeled at the top of each subgraph. For each subgraph, we calculate that the following conditions hold,

(a) $R - U - \frac{1}{2}\sigma_1^2 - \frac{e_1}{g_1}H - \frac{\alpha R}{r_2}(r_2 - \frac{1}{2}\sigma_2^2) = 0.0152 > 0$, $r_2 - \frac{1}{2}\sigma_2^2 - \frac{e_2}{g_2}H = 1.4172 \times 10^{-4} > 0$. Theorem 6 indicates the persistence of AD cancer cells;

(b) $R - U - \frac{1}{2}\sigma_1^2 = -0.027 < 0$, $r_2 - \frac{1}{2}\sigma_2^2 - \frac{e_2}{g_2}H = 1.4172 \times 10^{-4} > 0$. The conditions (iii) of Theorem 3 show that AI cancer cells are persistent;

(c) $R - U - \frac{1}{2}\sigma_1^2 = -0.027 < 0$. The condition (i) of Theorem 3 illustrates the extinction of AD cells;

Table 1 Parameter values

Parameters	Biological Meaning	Value	Source
r_1	Proliferation rate of AD cancer cells	0.025/day	[18]
r_2	Net proliferation rate of AI cancer cells	0.006/day	[18]
d_1	AD cancer cell proliferation rate	0.064/day	[18]
m_1	Maximum mutation rate from AD to AI cancer cells	0.00005/day	[18]
K	Tissue capacity for cancer cells	11×10^9 cells	[18]
e_1	Max killing rate of T-cells to AD cancer cells	0.75/day	[18]
e_2	Max killing rate of T-cells to AI cancer cells	0.75/day	[18]
e_3	T-cell max activation rate	20×10^6cells/day	[18]
g_1	AD cancer cell saturation level for T-cell kill rate	10×10^9cells	[18]
g_2	AI cancer cell saturation level for T-cell kill rate	10×10^9cells	[18]
g_3	DC saturation level for T-cell activation	400×10^6cells	[18]
μ	T-cell death rate	0.03/day	[18]
γ	Androgen clearance and production rate	0.08/day	[18]
a_0	Base level androgen concentration	20 nmol/L	[14]
u	The efficacy of ADT	0–1	[12]
c	DC death rate	0.14/day	[18]

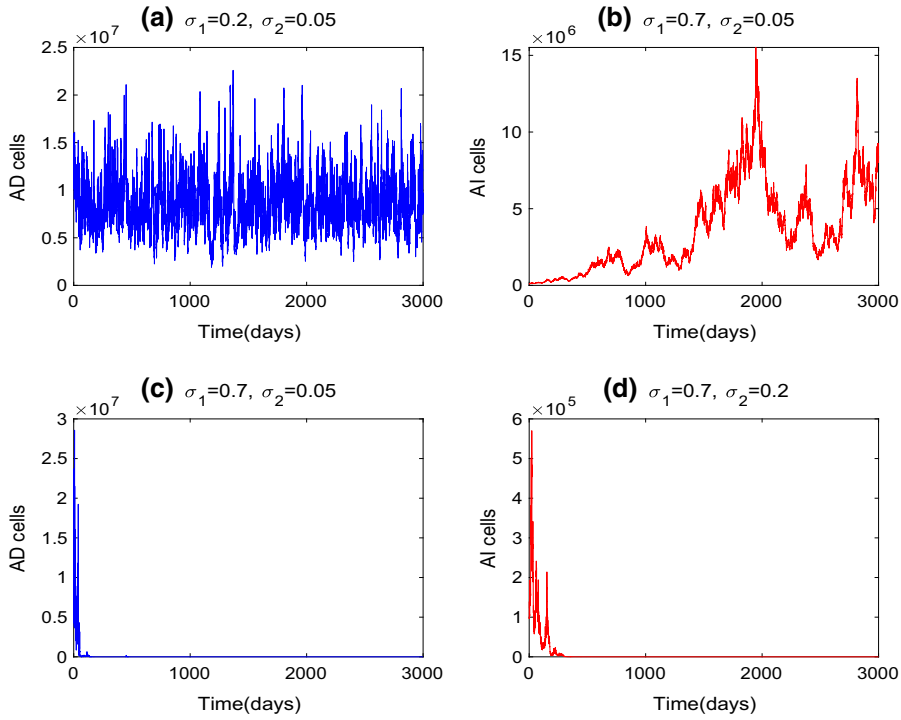

Fig. 1 Inhibitory effect of random disturbance of environment on proliferation of PCa

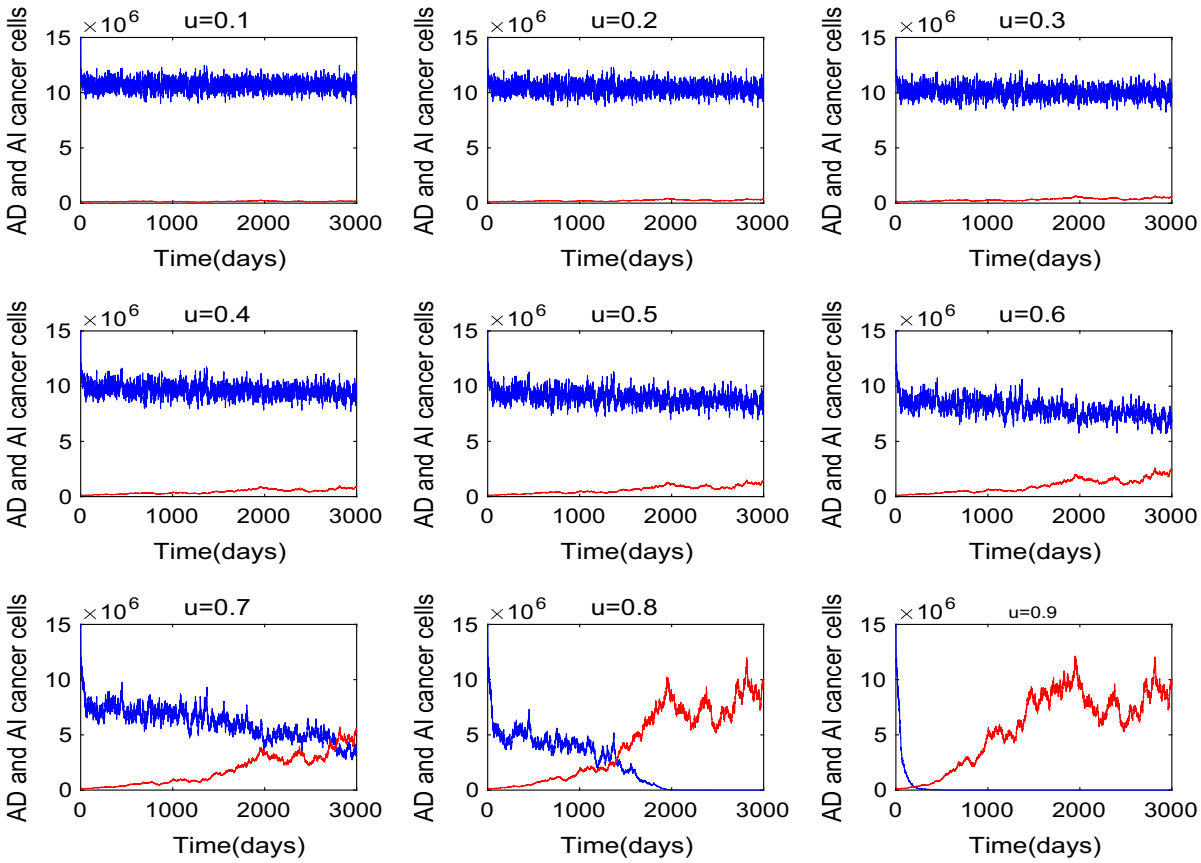

Fig. 2 Treatment effect under different efficacy of ADT

(d) $R - U - \frac{1}{2}\sigma_1^2 = -0.027 < 0, r_2 - \frac{1}{2}\sigma_2^2 = -0.014 < 0$. The conditions (ii) of Theorem 3 demonstrate that AI cells go to extinction.

By comparing subfigures (a) and (c), subfigures (b) and (d) of Fig. 1, it is obvious that random disturbance can inhibit two types cancer cell proliferation, and when the stochastic perturbation reaches a certain intensity, it will even lead to the complete elimination of cancer cells.

Secondly, Fig. 2 illustrates the influence of efficacy of ADT on the development of cancer. We fix $\alpha = 0.9$, $\beta = 0.8$, $h = 40 \times 10^6$ (unit: cells), $\tau = 30$ (unit: days), $\sigma_1 = 0.04$ and $\sigma_2 = 0.02$, change the value of u to explore the efficacy of ADT on the development of cancer. When $0.1 \leq u \leq 0.5$, the graph shows the persistence of AD and AI cancer cells, and that the AI cancer cells are at a controllable level. However, as the value of u continues to increase from 0.5, the AD cancer cells tend to be extinct, while the AI cancer cells increase rapidly, which means that cancer has developed into more fatal metastatic castration-resistant prostate cancer (mCRPC). Therefore, in this simulation, $u = 0.5$ is the approximate optimal value to control both AD and AI cancer cells, and AI cancer cells cannot turn over AD cancer cells until more than 8 years when $u \leq 0.5$.

Next, Fig. 3 implies the therapeutic effect of different frequency of DC vaccination. We fix $u = 0.5$, $h = 500 \times 10^6$ (unit: cells), $\alpha = 0.9, \beta = 0.8, \sigma_1 = 0.7$ and $\sigma_2 = 0.05$ such that the condition (i) of Theorem 3 is satisfied ($R - U - 1/2\sigma_1^2 = -0.027 < 0$) and the AD cancer cells go to extinction. We change the value of τ to observe how the number of AI cancer cells would evolve under different injection frequencies. It is clear from Fig. 3 that more frequent DC vaccination leads to the extinction trend of AI cancer cells. On the other hand, by calculation, we gain that the value of $r_2 - 1/2\sigma_2^2$ equals 0.0047 in the three subfigures (a),

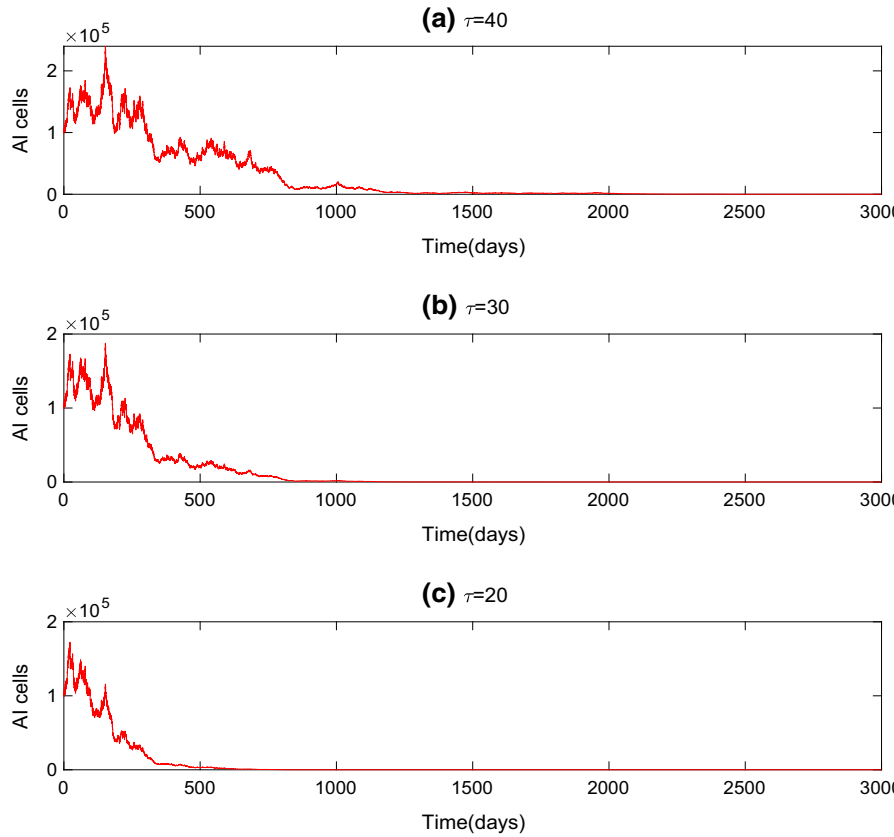

Fig. 3 Treatment effect under different frequency of the DC vaccine injection

(b) and (c) and the values of $r_2 - 1/2\sigma_2^2 - e_2 H/g_2$ are -0.0231, -0.0232 and -0.0238, respectively. Therefore, this simulation shows that when the case $0 \leq r_2 - 1/2\sigma_2^2 \leq e_2 H/g_2$ occurs, the AI cancer cells may eventually become extinct.

Finally, through the comprehensive analysis of Figs. 4, 5 and 6, we will obtain the effects of α and β for the remission of mCRPC. Here, we fix $u = 0.5$, $h = 40 \times 10^6$ (unit: cells), $\tau = 30$ (unit: days), $\sigma_1 = 0.6$ and $\sigma_2 = 0.05$. It is obvious from Fig. 4 that larger α and smaller β can promote the reduction in AD cancer cell number. However, at the stage of mCPRC, the extinction of AD cancer cells would mean the more fatal androgen independent cancer. In order to more clearly get how the number of AI cancer cells changes when α and β vary, respectively, in according to Fig. 5, we draw the AI cancer cell quantity differences between different situations as in Fig. 6, which indicates that in the process of decreasing the value of α (see the subfigures (a) and (c)) or increasing the value of β (see the subfigures (b) and (d)), the number of AI cancer cells always tends to decrease. From Figs. 4, 5 and 6, it is apparent that smaller α and larger β may play a role in delaying the occurrence of mCRPC and improving the quality of life of patients.

5 Conclusion

In this paper, we study an impulsive stochastic model for prostate cancer (PCa) with androgen deprivation therapy (ADT) and dendritic cell (DC) vaccine immunotherapy. In addition to the effects of different competition intensities and random interference on the proliferation of PCa cells are considered, the pulse effect of periodic injection of DC vaccine is also taken into consideration. The sufficient conditions of extinction and persistence in mean for cancer cells are derived by using the Itô's formula and the comparison theorem of stochastic differential equation.

According to the sufficient conditions of cancer cell extinction and persistence and Fig. 1 in numerical simulation, we can obtain that the higher the intensity of environmental disturbance, the greater the inhibitory

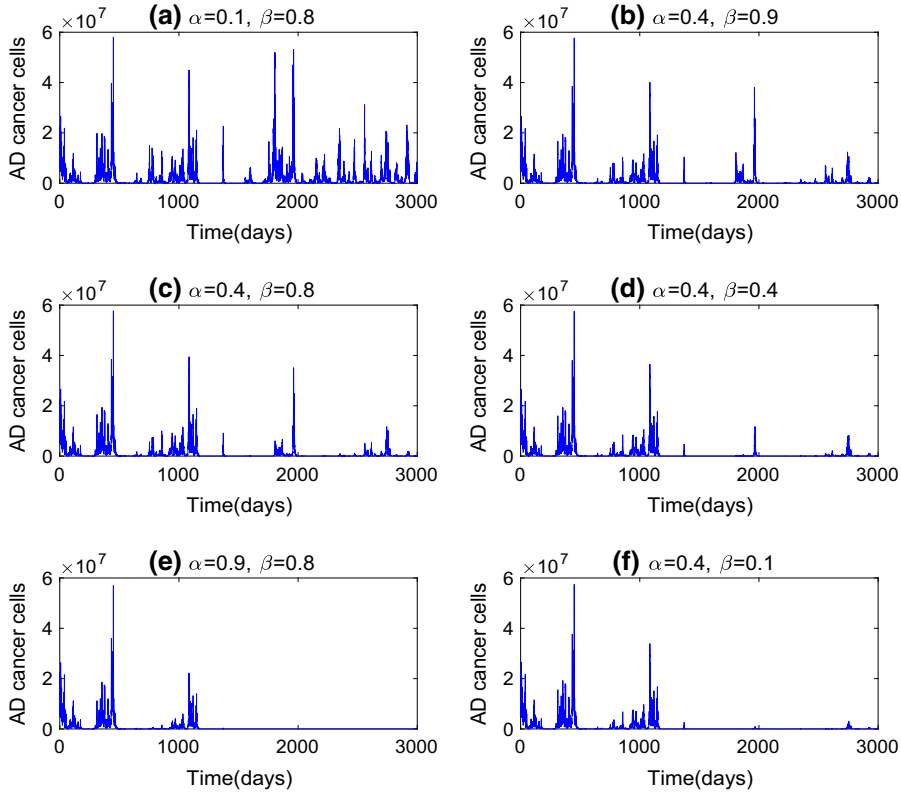

Fig. 4 AD cancer cell densities versus time in days under different values of α and β

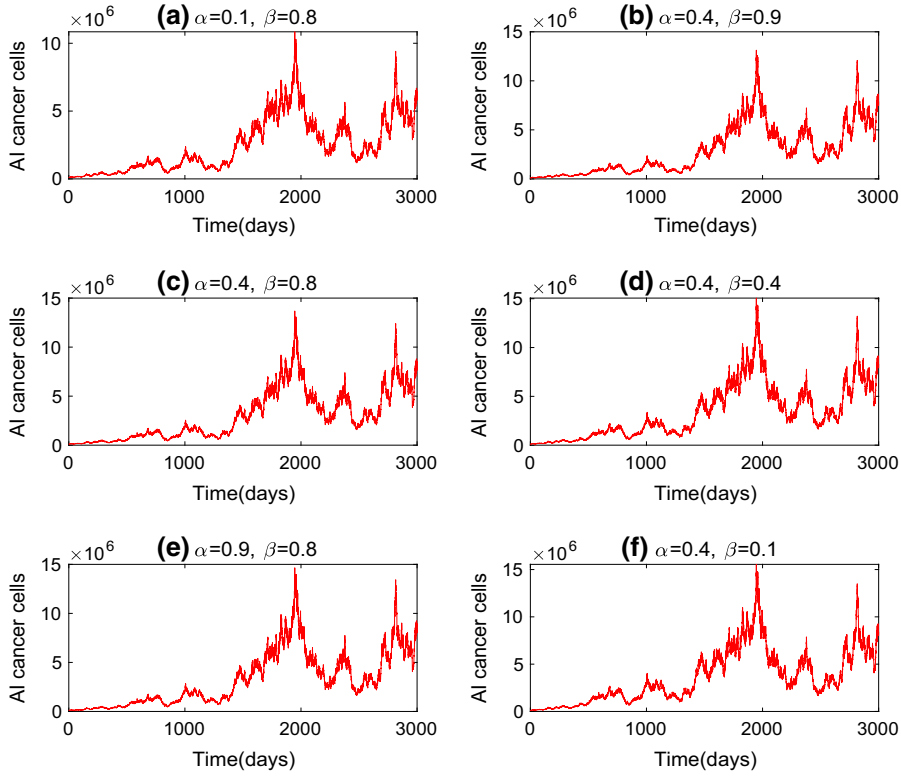

Fig. 5 AI cancer cell densities versus time in days under different values of α and β

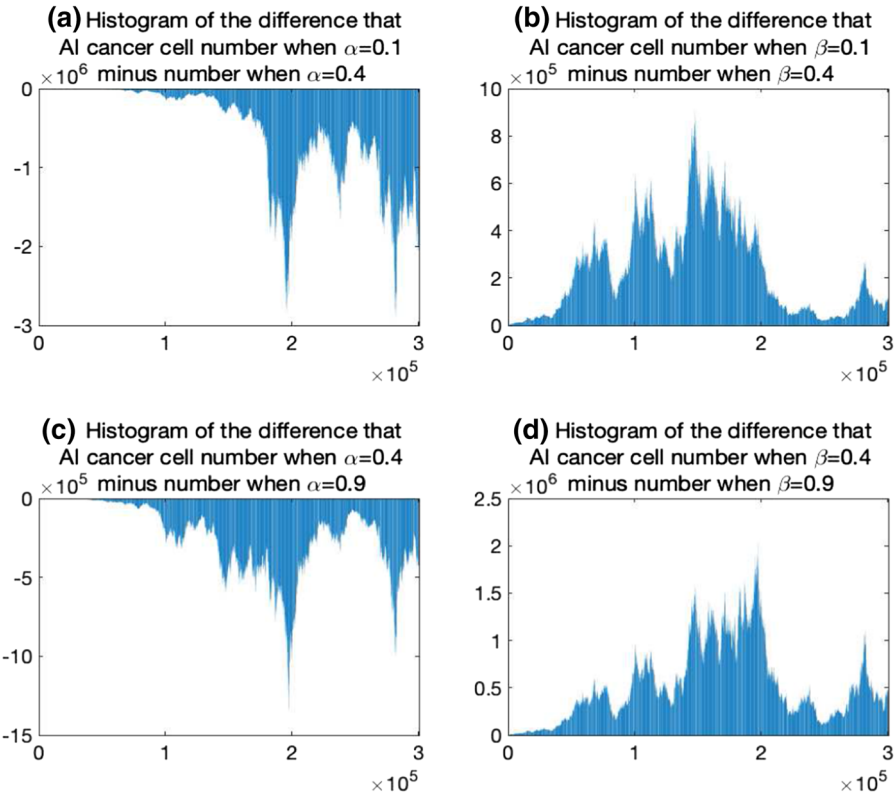

Fig. 6 Smaller α and larger β can promote the reduction in AI cancer cells in the treatment of mCRPC

effect on the development of PCa. Then, from Fig. 2, there is an optimal treatment efficacy of ADT, which makes AD and AI cancer cells be well controlled and prevents cancer from developing into a more terrifying resistant cancer. Moreover, by combining the definition of $H = e_3h/\mu[g_3(1-e^{-c\tau})+h]$ in theoretical results and Fig. 3 in numerical simulation, we can illustrate that more frequent injections of the DC vaccine can prolong the survival time of the patient with ADT. Finally, the time series diagrams of Figs. 4 and 5 and the histogram of Fig. 6 show that the greater the competitiveness β of AD cancer cells or the smaller the competitiveness α of AI cancer cells may delay the occurrence of metastatic castration-resistant prostate cancer.

6 Discussion

Here are some discussions of our model and results by comparing with some existing research and putting forward the future work worthy of study. Firstly, our model considers the DC vaccination by constructing an impulsive differential equation to describe the pulse effect of cell transient increase after vaccine injection, which makes up for the lack of modeling the pulse vaccination of PCa in current research.

Secondly, our theoretical results show that when the parameters representing the lethality of T-cells to both AD and AI cancer cells are equal to 0, the corresponding conclusions about the extinction and persistence of PCa cells in [12] can be obtained obviously. In addition, from the sufficient conditions of extinction and persistence of AD and AI cancer cells and the definition of $H = e_3h/\mu[g_3(1-e^{-c\tau})+h]$, one can see that a small τ means the possibility of cancer cell extinction, which is in accordance with the assert obtained by numeration simulation in reference [18] that the more frequent injections improve the survival time of the patient.

Thirdly, Theorem 3 shows that under the assumption that $R-U-1/2\sigma_1^2 < 0$, the AI cancer cells go to extinction when $r_2-1/2\sigma_2^2 < 0$ while will be persistent in mean when $r_2-1/2\sigma_2^2-e_2H/g_2 > 0$. Our theoretical analysis does not get the dynamic behavior of AI cancer cells under the case $0 \le r_2-1/2\sigma_2^2 \le e_2H/g_2$ due to the complexity of tumor immune response with pulse effect. But Fig. 3 shows that the AI cancer cells will eventually become extinct in a certain period of

time when $0 \leq r_2 - 1/2\sigma_2^2 \leq e_2 H/g_2$. The corresponding theoretical analysis and more detailed numerical simulation are remained for our future research.

Finally, another issue worth discussing is that besides the small disturbances in the internal environment, there are some large perturbations that can also affect the cancer cell proliferation. For example, if a patient's mood suddenly collapses due to certain stimulation, it may lead to faster growth and spread of cancer cells, correspondingly, the parameters in model will switch from the original value to another. Liu and his coauthors point out that such switch can be described by the region-switching system and investigate the effects of regional switch on cancer cell growth [37,38]. Therefore, it is interesting to extend our model by introducing region-switching system and observe how the similar fluctuations influence cancer cell growth with ADT and pulse immunotherapy.

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Data availability statement All data analyzed during this study are included in this published article.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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