Hindawi
Discrete Dynamics in Nature and Society
Volume 2023, Article ID 6887913, 28 pages
https://doi.org/10.1155/2023/6887913

Research Article

Modeling the Effects of Chemotherapeutic Dose Response on a Stochastic Tumor-Immune Model of Prostate Cancer with Androgen Deprivation Therapy

Lin Chen and Jin Yang

College of Mathematics and Statistics, Chongqing Jiaotong University, Chongqing 400074, China

Correspondence should be addressed to Jin Yang; seehom@126.com

Received 28 June 2022; Revised 8 November 2022; Accepted 30 January 2023; Published 9 March 2023

Academic Editor: Ya Jia

The periodical application of androgen deprivation therapy, immunotherapy, or chemotherapy is an effective method for cancer treatment, but few studies combine them. To explore such comprehensive treatment mechanisms, this paper establishes a pulsed stochastic hybrid dynamics model considering tumor antigenicity and density-dependent mortality. In addition to analyzing the basic properties of solutions such as the tumor-free periodic solution and global attraction of the model, the threshold conditions for the persistence and extinction of prostate cancer cells and effector cells are obtained by using stochastic differential equation theory. Besides, sufficient conditions for the existence of stationary distribution of the system are established. The results reveal that comprehensive therapy or white noise can determine tumor dynamics and suggest that the treatment of prostate cancer should be individualized according to the state of tumor development. Finally, biological significance is discussed and conclusions are given.

1. Introduction

Prostate cancer is the second leading cause of cancer death and the most common type of cancer in American men [1, 2]. Prostate specific antigen (PSA) is a protein secreted by prostate cells. It is the main index to detect the presence of malignant tumors [3–5]. Prostate cancer is a hormone-dependent cancer [6]. Prostate cancer cells include androgen dependent (AD) and androgen independent (AI) cells during evolution. Surgery, chemotherapy, and radiotherapy are traditional methods, but these treatments often cannot eliminate cancer cells completely and may have side effects [7]. To this end, androgen deprivation therapy (ADT) and immunotherapy came into being. ADT has become the main treatment for prostate cancer because it affects the proliferation rate and mortality of tumor cells [8, 9]. Besides, ADT includes intermittent androgen deprivation (IAD) and continuous androgen deprivation (CAD) therapy [3]. However, ADT is often accompanied by the emergence of drug-resistant cells, then, an additional treatment is needed to introduce. Since immunotherapy has become the most effective method for the treatment of prostate cancer by stimulating a massive immune response in the target tumor and enhancing the immune system of patients [1, 7, 10–12]. It is reasonable and effective to add immunotherapy to ADT to treat prostate cancer. Moreover, CAD therapy is one of the endocrine therapies for advanced prostate cancer, and there is no clear medical evidence that IAD is better than CAD therapy [3, 13].

Mathematical modeling and analysis of ADT and immunotherapy have devoted to the development of mechanisms for tumor progression [1, 8, 9, 14–20]. Ideta et al. established a deterministic model of IAD therapy, illustrating that how the net growth rate of AI cells affects tumor growth and recurrence [16]. Jain and Friedman proposed a mathematical model to simulate prostate cancer response to ADT [17]. In addition, the interaction between tumors and immune cells has been studied by many mathematical

models [7, 10–12, 21–24]. Since many studies have shown that single chemotherapy or immunotherapy is far less effective than comprehensive therapy, the therapeutic effect of single chemotherapy is also very limited [1, 10, 25, 26]. Yang et al. pointed out that tumor cells can be eradicated or controlled with comprehensive therapy [11]. Hence, the mathematical model of the combination of ADT and immunotherapy has been studied. Portz and Kuang then developed a model of advanced prostate cancer to test the efficacy of immunotherapy combined with ADT. Their results suggest that comprehensive treatment can stabilize the disease [1]. Moreover, Rutter and Kuang confirmed that IAD therapy can delay the occurrence of drug resistance and improve the quality of life of patients [20].

Nevertheless, most of these models are all deterministic [1, 11, 16, 17, 20], but the growth of cancer cells is easily affected by temperature, nutrition, radiation, and other environmental interferences [3, 7, 10, 27–33]. Naturally, the deterministic system of Ideta et al. was developed into the stochastic system of Tanaka and collaborators [16, 27]. In 2018, Hening and Nguyen studied the coexistence and extinction of stochastic Kolmogorov systems and gave sharp conditions under which populations converge exponentially to their unique stationary distributions [32]. Benaim investigated the stochastic persistence and extinction of populations, and the results greatly generalized the results of various stochastic models of population dynamics given by stochastic differential equations or pure jump processes [33]. Zazoua and Wang introduced the stochastic model of prostate cancer and showed the stability of the system that can be determined by white noise [3]. Furthermore, clinical data have shown that immunotherapy can promote chemotherapy [7, 25, 26, 34]. Thereafter, Yang established random tumor-immune models combining immunotherapy and chemotherapy, and observed that all dynamic processes of tumors can be realized by changing environmental noise [7, 10]. In 2021, Chen et al. proposed a mathematical model describing the threshold dynamics of tumors under random interference of tumor antigenicity and white noise [35]. Yang et al. studied stochastic impulsive tumor models combining ADT and immunotherapy to analyze the elimination and persistence of tumor cells [23, 24]. Moreover, Rihan and Alsakaji proposed a stochastic epidemic model with time delay. It is proved that the stochastic delay model is consistent with the physical sensitivity and volatility of the actual observation [29]. Rihan and Rajivganthi introduced a stochastic tumor-immune model with random noise in epidemiology and immunology, and concluded that white noise is a key factor in treating infectious diseases [28]. In 2022, Alsakaji et al. expanded the SEIR epidemic model by combining stochastic perturbation with time delay, established a mathematical model considering vaccination, time delay and random noise, and studied the dynamics of COVID-19 in the UAE [30]. Furthermore, the dynamics of delayed differential model of tumor-immune system with random noise was investigated by Rihan and Alsakaji. Their results showed that in some cases, random noise can completely inhibit the growth of tumors [31]. In addition, the idea of randomness is also widely used in numerical calculation, which is of great significance for the development of stochastic computing procedure [36–42].

As our knowledge, immunotherapy combined with chemotherapy or ADT has been widely studied, but there are few scholars combining these three therapies to establish models [1, 7, 10, 20, 34]. Actually, it is necessary to consider the influence of tumor antigenicity on its growth, because it always exists in the whole life cycle of the tumors [11]. In addition, some cancer cells will die due to limited living space and insufficient resources and nutrition [14]. For the purpose, considering both antigenicity and density-dependent mortality of tumors, we propose a pulsed stochastic model combining CAD therapy, immunotherapy, and chemotherapy to explore hybrid dynamics and cancer therapy strategies. We mainly answered the following questions: (1) How do the periods, dosages, and frequencies of in pulse comprehensive therapy affect tumor dynamics? (2) Does the system have a unique ergodic stationary distribution? (3) What is the difference between comprehensive treatment and single treatment and what are the medication strategies for clinical medicine?

The rest of this paper is arranged as follows. In Section 2, a pulsed stochastic model is proposed and some useful basic knowledge of ISDEs (Impulsive stochastic differential equations) is presented. In Section 3, the expression of a tumor-free solution and the global attraction and boundness of the system are showed. In Section 4, threshold conditions for persistence and extinction of prostate cancer cells and effector cells are obtained. In Section 5, the existence of a unique ergodic stationary distribution of the hybrid system is analyzed. The numerical simulations are given out to verify the theoretical results in Section 6. Finally, this paper is concluded in Section 7.

2. Preliminaries and Mathematical Model

2.1. Model Formation. In 2017, Rutter and Kuang developed a deterministic model of prostate cancer dendritic cell vaccine combined with hormone therapy to explore its global dynamics [20]. To separate the influence of stochastic noise from immune response, Zazoua and Wang did not include the state variables of effector cells and cytokines related to immunotherapy. Inspired by Tanaka et al. [27], they proposed a stochastic mathematical model to explore the evolution of prostate cancer cells [3, 20]. Let A be the concentration of androgen in the blood. Z_1 and Z_2 are AD and AI cells, respectively. Their model is as follows:

$$\begin{cases} \dfrac{\mathrm{d}A}{\mathrm{d}t} = [-\gamma(A - a_0) - \gamma a_0 u], \\ \mathrm{d}Z_1 = \left\{ r_1 A\left(1 - \dfrac{Z_1 + \alpha Z_2}{K}\right) - (p_1 + m_1)\left(1 - \dfrac{A}{a_0}\right)\right\} Z_1 \mathrm{d}t + \sigma_1 Z_1 \mathrm{d}B_1(t), \\ \mathrm{d}Z_2 = \left\{ r_2\left(1 - \dfrac{\beta Z_1 + Z_2}{K}\right) Z_2 + m_1\left(1 - \dfrac{A}{a_0}\right) Z_1 \right\} \mathrm{d}t + \sigma_2 Z_2 \mathrm{d}B_2(t). \end{cases} \tag{1}$$

Since the single treatment can easily make prostate cancer cells develop drug resistance, and AD cells eventually develop into AI cells. It is particularly critical to add new treatments to reduce drug resistance [25, 26]. In 1994, Kuznetsov et al. developed an influential deterministic tumor-immune model [43]. Moreover, some experimental and clinical studies have shown that pulsed immunotherapy combined with chemotherapy is more practical than single therapy for treating cancer [44, 45]. Based on the above-mentioned considerations, Yang incorporated the white noise into the model of Kuznetsov et al. [43], and studied a stochastic model of chemotherapy combined with immunotherapy, which showed that the larger white noise can lead to the extinction of tumors and the combination therapy could avoid the shortcomings of a single therapy [34, 43–45]. Then, taking immunotherapy as an auxiliary treatment to prevent drug resistance is reasonable. Let $X(t)$ and $Y(t)$ be the prostate cancer cells and effector cells, respectively. H is the concentration of a chemotherapeutic drug at time t. The system is written as follows [10]:

$$\begin{cases} \left.\begin{aligned} &\mathrm{d}X = [r(1 - \eta X)X - aXY - k_1 H(t)X]\mathrm{d}t + \delta_1 X \mathrm{d}B_1(t), \\ &\mathrm{d}Y = \left[\dfrac{bXY}{1 + \upsilon X} - cXY - \mathrm{d}Y - k_2 H(t)Y\right]\mathrm{d}t + \delta_2 Y dB_2(t), \\ &\mathrm{d}H = -\mu H \mathrm{d}t, \end{aligned}\right\} t \neq nT, \\ \left.\begin{aligned} &H(nT^+) = H(nT) + \iota, \\ &Y(nT^+) = (1 + e(nT))Y(nT), \end{aligned}\right\} t = nT. \end{cases} \tag{2}$$

However, few scholars have explored the dynamic behaviors of complex dynamical systems that combine ADT with immunotherapy and chemotherapy. It is very meaningful to study how dosages, periods (or frequencies) of drug use under pulse comprehensive treatment affect tumor dynamics and provide theoretical guidance for clinical treatment. Inspired by CAD in system (1) and immunotherapy and chemotherapy in system (2), we take tumor antigenicity and white noise into consideration to investigate the evolution of prostate cancer cells under comprehensive treatment [3, 7, 10, 11, 14, 35]. Then, our model is described by

$$\begin{cases} \left.\begin{aligned} &\mathrm{d}X = [r]A\left(1 - \frac{X}{K}\right)X - \left(d_1\left(1 - \frac{A}{a_0}\right) + d_2\right)X - k_1 H(t)X \\ &-aX(Y]\,dt + \delta_1 X dB_1(t), \\ &\mathrm{d}Y = [(C - d)Y - k_2 H(t)Y - cXY]\mathrm{d}t + \delta_2 Y \mathrm{d}B_2(t), \\ &\mathrm{d}A = [-\gamma(A - a_0) - \gamma a_0 u]\mathrm{d}t, \\ &\mathrm{d}H = -\mu H \mathrm{d}t, \end{aligned}\right\} t \neq nT, \\ \left.\begin{aligned} &H(nT^+) = H(nT) + \iota, \\ &Y(nT^+) = (1 + e(nT))Y(nT), \end{aligned}\right\} t = nT, \end{cases} \tag{3}$$

where $B_i(t)(i = 1, 2)$ is an independent Brownian motion. The biological meanings of other parameters are the same as systems (1) and (2), and all of these parameters in system (3) are positive. The biological meanings of other parameters from system (1) to system (3) are shown in Table 1.

The evolution of androgen dynamics takes less time to reach equilibrium than cancer cells because androgen dynamics is faster than prostate cancer cells [3]. Thus, we let androgen go into equilibrium $A^* = a_0(1 - u)$, and let $R_1 = rA^* = ra_0(1 - u), U_1 = d_1u + d_2$, then system (3) becomes

$$\left\{\begin{array}{l} \left.\begin{array}{l} \mathrm{d}X = \left[R_1X\left(1 - \dfrac{X}{K}\right) - U_1X - k_1H(t)X - aXY\right]\mathrm{d}t \\ +\delta_1 X dB_1(t), \\ \mathrm{d}Y = \left[(C - d)Y - k_2H(t)Y - cXY\right]\mathrm{d}t + \delta_2 Y\mathrm{d}B_2(t), \\ \mathrm{d}H = -\mu H\mathrm{d}t, \end{array}\right\} t \neq nT, \\ \left.\begin{array}{l} H\left(nT^+\right) = H(nT) + \iota, \\ Y\left(nT^+\right) = (1 + e(nT))Y(nT), \end{array}\right\} t = nT. \end{array}\right. \tag{4}$$

Next, we first give the biological meaning and source of the parameters involved in this paper, and then, give the basic knowledge for further research.

2.2. Preliminaries. Let $(\Omega, \mathscr{F}, \{\mathscr{F}_t\}_{t\geq 0}, \mathscr{P})$ be a complete probability space ($B_i(t)$ is defined on this), which conforms to the usual conditions and has a filtration $\{\mathscr{F}_t\}_{t\geq 0}$, where $B_i(t)$ is the independent Brownian motion [7, 10, 47]. Then, we introduce some basic knowledge of the paper.

Definition 1 (see [7, 10, 48]). $Z(t) = (P)(t), Q(t)^T$ is a solution of ISDE (4) with initial values $P(0) \geq 0$ and $Q(0) \geq 0$, $t \in R_+$, if

(1) $Z(t)$ is absolutely continuous on $(0, \mathrm{T}]$ *and* $(nT, (n) + 1)T]$
(2) *For any* nT, $Z(nT^-) = \lim_{t \longrightarrow nT^-} Z(t)$ *and* $Z(nT^+) = \lim_{t \longrightarrow nT^+} Z(t)$ *and* $Z(nT) = Z(nT^-)$ *hold true*
(3) $Z(t)$ *follows system* (4) *for all* $t \in \mathrm{R}_+/\{nT\}$ *and satisfies the impulsive condition at the impulse point* nT

Definition 2. For the solution $Z(t) = (P)(t), Q(t)^T$ with initial conditions $P(0) \in R_+^2$ and $Q(0) \in \mathrm{R}_+^2$, if for any $\epsilon \in (0, 1)$, there is a solution with a positive constant S such that

$$\limsup_{t\longrightarrow\infty} P\{|Z(t)| > S\} < \epsilon. \tag{5}$$

Then, the solutions of ISDE (4) are stochastically ultimately bounded.

Definition 3 (see [7, 49]). *Let* $Z(t) = (P)(t), Q(t)^T$ be a solution of ISDE (4):

(1) When $\lim_{t\longrightarrow+\infty} Q(t) = 0$, $Q(t)$ is extinctive.
(2) When $\lim_{t\longrightarrow+\infty} 1/t \int_0^t Q(s)\mathrm{d}s = 0$, $Q(t)$ is non-persistent in the mean.
(3) When $\lim_{t\longrightarrow+\infty} \sup 1/t \int_0^t Q(s)\mathrm{d}s > 0$, $Q(t)$ is weakly persistent in the mean.
(4) If for each $\varepsilon \in (0, 1)$, there exist $\beta > 0$ and $\delta > 0$ so that

$$\liminf_{t\longrightarrow+\infty} \mathscr{P}\{Q(t) \geq \beta\} \geq 1 - \varepsilon, \liminf_{t\longrightarrow+\infty} \mathscr{P}\{Q(t) \leq \delta\} \geq 1 - \varepsilon. \tag{6}$$

then $Y(t)$ is stochastically persistent.

Definition 4 (see [7]). Assume $Z_1(t) = (P_1(t), Q_1(t))$ and $Z_2(t) = (P_2(t), Q_2(t))$ are any two solutions of system (4) with $P_i(0) > 0$, $Q_i(0) > 0$, $i = 1, 2$, if

$$\lim_{t\longrightarrow+\infty} \left|P_1(t) - P_2(t)\right| = 0, \tag{7}$$

and

$$\lim_{t\longrightarrow+\infty} \left|Q_1(t) - Q_2(t)\right| = 0. \tag{8}$$

Then, ISDE (4) is called globally attractive.

Definition 5 (see [3]). If

$$g(t) = \frac{1}{t}\int_0^t g(s)\mathrm{d}s \text{ for } t > 0, \tag{9}$$

then

$$g_*(t) = \liminf_{t\longrightarrow\infty} \frac{1}{t}\int_0^t g(s)\mathrm{d}s \text{ for } t > 0, \tag{10}$$

and

Table 1: Biological meaning and source of parameters.

Parameters	Biological meaning	Source
γ	The clearance and production rate of androgen	[3]
u	The efficacy of CAD therapy	[3]
r_1	The proliferation rate of AD cells	[3]
r_2	The proliferation rate of AI cells	[3]
α	The competition coefficient of AD cells	[3]
β	The competition coefficient of AI cells	[3]
p_1	The mortality of AD cells	[3]
a_0	The normal androgen concentration	[3]
T	The periods of therapy	[3]
K	The carrying capacity of cancer cells	[3]
m_1	The mutation rate from AD to AI cells	[3]
σ_1^2	The intensities of white noise on the AD cells	[3]
σ_2^2	The intensities of white noise on the AI cells	[3]
$1/\eta$	Carrying capacity of the tumor cells	[10]
d	The mortality of effector cells	[10]
b	The maximum accumulation rate of tumors	[10]
v	The steepness of effector cells	[10]
c	The inactivation rate of effector cells	[10]
a	The rate at which the effector cells bind to the tumor cells	[10]
$e(nT)$	The net growth rate of effector cells stimulated by immunotherapy	[10]
μ	The degradation rate of chemotherapy	[10]
ι	The dosages at impulsive point series $nT\,(n = 1, 2, 3, \cdots)$	[10]
r	The growth rate of cancer cells	[10]
d_1	The death rate of prostate cancer cells	[3]
d_2	The density-dependent mortality of prostate cancer cells	[46]
δ_1^2	The intensities of white noise on prostate cancer cells	[3]
δ_2^2	The intensities of white noise on effector cells	[10]
k_1	The inhibitory rate of chemotherapy drugs on prostate cancer cells	[10]
k_2	The inhibitory rate of chemotherapy drugs on effector cells	[10]

$$g^*(t) = \limsup_{t\longrightarrow\infty} \frac{1}{t}\int_0^t g(s)\mathrm{d}s \text{ for } t > 0. \tag{11}$$

Lemma 1 (see [7, 10]). *Let* $g(t) \in C(\Omega \times \mathrm{R}_+, \mathrm{R}_+ - 0)$.

(1) If there exist η_0, t_1 and $\eta \geq 0$ such that $g(t)$ satisfies

$$\ln g(t) \leq \eta t - \eta_0 \int_0^t g(s)\mathrm{d}s + \sum_{i=1}^{n} \beta_i B_i(t), \tag{12}$$

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

$$\limsup_{t\longrightarrow+\infty} \frac{1}{t}\int_0^t g(s)\mathrm{d}s \leq \frac{\eta}{\eta_0}. \tag{13}$$

(2) If there exist η_0, t_1 and $\eta \geq 0$ such that $g(t)$ satisfies

$$\ln g(t) \geq \eta t - \eta_0 \int_0^t g(s)\mathrm{d}s + \sum_{i=1}^{n} \beta_i B_i(t), \tag{14}$$

for any $t \geq t_1$, then

$$\limsup_{t\longrightarrow+\infty} \frac{1}{t}\int_0^t g(s)\mathrm{d}s \geq \frac{\eta}{\eta_0}. \tag{15}$$

Lemma 2 (see [3]). *Assume* $F = F(t)_{t\geq 0}$ *is a real-valued continuous local martingale vanishing at time zero. If*

$$\limsup_{t\longrightarrow+\infty} \frac{\langle F, F\rangle_t}{t} < \infty a.s., \tag{16}$$

then,

$$\limsup_{t\longrightarrow+\infty} \frac{\langle F_t\rangle}{t} = 0. \tag{17}$$

3. Global Positive Solution

3.1. Tumor-free Solution. It is obvious that the dynamics of chemotherapeutic drugs can be described by

$$\begin{cases} \mathrm{d}H(t) = -\mu H, t \neq nT, \\ H(nT^+) = H(nT) + \iota, t = nT. \end{cases} \tag{18}$$

Let us compute the expression for the T periodic solution $H^T(t)$ as the following:

$$H^T(t) = \frac{\iota e^{-\mu(t-nT)}}{1 - e^{-\mu T}}, \tag{19}$$

where $t \in (nT, (n+1)T]$, $H^T(nT^+) = \iota/(1 - e^{-\mu T})$.

Lemma 3 (see [10, 50, 51]). *A unique positive periodic solution of system (5) can be expressed by* $\mathrm{H^T(t)}$, *and it holds that* $\lim_{t\longrightarrow\infty} H(t) = H^T(t)$, *then for any* $\epsilon > 0$ *yields*

$$H^T(t) - \epsilon < H(t) < H^T(t) + \epsilon \text{ and } \lim_{t \longrightarrow \infty} \frac{1}{t} \int_0^t H^T(s)\mathrm{d}s = \frac{\iota}{\mu T}. \tag{20}$$

For the convenience of writing, we use $H(t)$ instead of $H^T(t)$. Suppose that the prostate cancer cells can be eradicated, then let $X(t) = 0$, and system (4) becomes

$$\begin{cases} \mathrm{d}Y = [(C-d)Y - k_2 H(t)Y]\mathrm{d}t + \delta_2 Y \mathrm{d}B_2(t), \\ \mathrm{d}H = -\mu H, \end{cases} \Big\} t \neq nT,$$
$$\begin{cases} H(nT^+) = H(nT) + \iota, \\ Y(nT^+) = (1 + e(nT))Y(nT), \end{cases} \Big\} t = nT. \tag{21}$$

Since the explicit expression of $H(t)$ is given, then

$$\begin{cases} \mathrm{d}Y = [(C-d)Y - k_2 H(t)Y]\mathrm{d}t + \delta_2 Y \mathrm{d}B_2(t), t \neq nT, \\ Y(nT^+) = (1 + e(nT))Y(nT), t = nT. \end{cases} \tag{22}$$

Theorem 1. *There exists a unique global positive solution $Y(t)$ of system (8) for any initial value $Y(0^+) = Y(0)$, where*

$$Y(t) = \prod_{0<nT<t} (1 + e(nT))Y(0) \exp\left[\left(C - d - k_2 H(t) - \frac{\delta_2^2}{2}\right)t + \delta_2 B_2(t)\right]. \tag{23}$$

Proof. For any $t \in (nT, (n+1)T]$, define a Lyapunov function $V(t) = \ln Y(t)$. Applying Itô's formula gives

$$\mathrm{dl\,n}Y(t) = \left(C - d - k_2 H(t) - 0.5\delta_2^2\right)dt + \delta_2 dB_2(t). \tag{24}$$

We integrate the above equation from nT to t, then

$$\ln Y(t) - \ln Y(nT) = \left(C - d - k_2 H(t) - 0.5\delta_2^2\right)(t - nT) + \delta_2\left(B_2(t) - B_2(nT)\right). \tag{25}$$

Therefore,

$$Y(t) = Y(nT)\exp\left[\left(C - d - k_2 H(t) - 0.5\delta_2^2\right)(t - nT) + \delta_2\left(B_2(t) - B_2(nT)\right)\right]. \tag{26}$$

When $t = nT^+$, after a single immunotherapy, we have

$$Y(t) = \prod_{0<nT<t} (1 + e(nT))Y(nT) \exp\left[\left(C - d - k_2 H(t) - \frac{\delta_2^2}{2}\right)(t - nT) + \delta_2\left(B_2(t) - B_2(nT)\right)\right]. \tag{27}$$

An application of mathematical induction yields

$$Y(t) = \prod_{0<nT<t} (1 + e(nT))Y(0) \exp\left[\left(C - d - k_2 H(t) - \frac{\delta_2^2}{2}\right)t + \delta_2 B_2(t)\right]. \tag{28}$$

This completes the proof. □

3.2. Global Positive Solution of System (4). Now, we will study the global dynamics of ISDE (4). Based on reference [7], we just need to explore the following system (29), which is equivalent to the original system (4). Since the dynamics of CAD drugs and chemotherapy drugs have been studied, then

$$\begin{cases} \left.\begin{array}{l} dX = \left[R_1 X\left(1-\dfrac{X}{K}\right) - k_1 H(t)X - aXY - U_1 X\right]dt \\ \\ +\delta_1 X dB_1(t), \end{array}\right\} t \neq nT, \\ dY = \left[(C-d)Y - k_2 H(t)Y - cXY\right]dt + \delta_2 Y dB_2(t), \\ Y\left(nT^+\right) = (1+e(nT))Y(nT), t = nT. \end{cases} \tag{29}$$

It is expedient to define a SDE (Stochastic Differential Equation) without pulsed effects:

$$\begin{cases} dX_1 = X_1\left[R_1\left(1-\dfrac{X_1}{K}\right) - \left(k_1 H(t) + U_1\right)\right. \\ \\ \left. -a\prod\limits_{0<nT<t}(1+e(nT))Y_1\right]dt + \delta_1 X_1 dB_1(t), dY_1 = Y_1\left[C-d-k_2 H(t) - cX_1\right]dt + \delta_2 Y_1 dB_2(t), \end{cases} \tag{30}$$

with $(X_1(0), Y_1(0)) = (X(0), Y(0)) \in \mathrm{R}_+^2$.

Theorem 2. *For any initial value* $(\mathrm{X}(0), \mathrm{Y}(0))$*, system (9) has a unique positive solution* $(\mathrm{X}(\mathrm{t}), \mathrm{Y}(\mathrm{t}))$ *and the solution* $(\mathrm{X}(\mathrm{t}), \mathrm{Y}(\mathrm{t}))$ *will remain in* R_+^2.

Proof. According to Yang et al. [10, 52], system (10) has a unique global positive solution $(X_1(t), Y_1(t))$. Setting

$$(X(t), Y(t)) = \left(X_1(t), \prod_{0<nT<t}(1+e(nT))Y_1(t)\right), \tag{31}$$

thereafter, since $(X_1(t), Y_1(t))$ is absolute continuous, which results in the absolute continuity of $(X(t), Y(t))$ for any $t \in (nT, (n+1)(T] \subset [0, +\infty), n \in \aleph$.

When $t \neq nT$, the derivatives of (31) with respect to (30) lead to the following:

$$\begin{aligned} dX(t) = dX_1(t) &= X_1\left[R_1\left(1-\frac{X}{K}\right) - a\prod_{0<nT<t}(1+e(nT))Y_1(t)\right. \\ &\quad \left. -\left(k_1 H(t) + U_1\right)\right]dt + \delta_1 X_1 dB_1(t), \\ dY(t) &= \prod_{0<nT<t}(1+e(nT))dY_1(t) \\ &= Y\left[-cX_1 + C - d - k_2 H(t)\right]dt + \delta_2 Y_1 dB_2(t) \\ &= \left[-cXY + (C-d)Y - k_2 H(t)Y\right]dt + \delta_2 Y dB_2(t). \end{aligned} \tag{32}$$

Once $t = nT$,

$$\begin{aligned} X(nT^{+}) &= \lim_{t \longrightarrow nT^{+}} X_1(t) = X_1(nT) = X(nT), \\ Y(nT^{+}) &= \lim_{t \longrightarrow nT^{+}} \prod_{0<iT<t} (1 + a(iT))Y_1(t) \\ &= (1 + e(nT)) \prod_{0<iT<nT} (1 + a(iT))Y_1(n)T \\ &= (1 + e(nT))Y(nT). \end{aligned} \tag{33}$$

Consequently, system (29) has a global unique positive solution. This completes the proof of Theorem 2. □

Theorem 3. *If $C - d - k_2 H(t) < 0$, then the positive solutions $Z(t) = (X(t), Y(t))$ of system (4) are stochastically ultimately bounded.*

Proof. We also define equations without respect to the pulsed immunotherapy, then

$$\begin{cases} dX_1 = \left[R_1\left(1 - \dfrac{X_1}{K}\right) - k_1 H(t) - a \prod_{0<nT<t} (1 + e(nT))Y_1 - U_1 \right] X_1 \mathrm{d}t \\ \quad + \delta_1 X dB_1(t), \\ dY_1 = [(C - d)Y_1 - k_2 H(t)Y_1 - cX_1 Y_1]dt + \delta_2 Y_1 dB_2(t). \end{cases} \tag{34}$$

To prove the boundedness of the solutions of system (4), we just need to illustrate that the solutions of system (34) are stochastically ultimately bounded.

For X_1, we let $V(t, X_1) = e^t X_1^q$ where $q > 0$. Applying Itô's formula yields

$$\begin{aligned} dV(X_1) &= e^t \left(1 + q\left(R_1\left(1 - \frac{X_1 R_1 + Ka\prod_{0<nT<t}(1 + e(nT))Y_1}{R_1 K} \right) \right.\right. \\ &\quad \left.\left. -(k_1 H(t) + U_1) + \frac{q-1}{2}\delta_1^2 \right) \right) X_1^q dt + qe^t \delta_1 X_1^q \mathrm{d}B_1(t) \\ &\le e^t \left\{ \left(1 + q\left(R_1 + \frac{q-1}{2}\delta_1^2 \right) \right) X_1^q - q\frac{R_1}{K} X_1^{q+1} \right\} \mathrm{d}t \\ &\quad + qe^t \delta_1 X^q \mathrm{d}B_1(t) \\ &\le e^t X_1^{q-1} \left\{ \left(1 + q\left(R_1 + \frac{q-1}{2}\delta_1^2 \right) \right) X_1 - q\frac{R_1}{K} X_1^2 \right\} \mathrm{d}t \\ &\quad + qe^t \delta_1 X_1^q dB_1(t) \\ &\le M_1 e^t dt + qe^t \delta_1 X_1^q \mathrm{d}B_1(t), \end{aligned} \tag{35}$$

where M_1 is a positive constant. By some calculations,

$$E\left[e^t X_1^q(t)\right] \le X_1^q(0) + M_1\left(e^t - 1\right). \tag{36}$$

Then,

$$E\left[X_1^q(t)\right] \le \frac{X_1^q(0)}{e^t} + M_1\left(1 - e^{-t}\right). \tag{37}$$

Consequently,

$$\limsup_{t \longrightarrow +\infty} E\left[X_1^q(t)\right] \le M_1. \tag{38}$$

For Y_1, note that

$$dY_1 \le [C - d - k_2 H(t)]Y_1 \mathrm{d}t + \delta_2 Y_1 dB_2(t). \tag{39}$$

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

$$d\varphi(t) = [C - d - k_2 H(t)]\varphi \mathrm{d}t + \delta_2 \varphi \mathrm{d}B_2(t), \text{ for all } t \ge 0. \tag{40}$$

Then, for $\varphi(t)$, using the same method as previous yields

$$E[\varphi(t)] = \varphi(0) + \frac{1}{2}E\left[(C - d - k_2H(t))Y^2\right]. \quad (41)$$

Due to $C - d - k_2H(t) < 0$,

$$E[Y_1] \le E[\varphi(t)] \le \varphi(0) \le N_1, \quad (42)$$

where N_1 is a positive constant, and then

$$E[Y_1] \le E[\varphi(t)] \le \varphi(0) \le N_1. \quad (43)$$

That is to say,

$$\limsup_{t\longrightarrow+\infty} E[Y_1^q(t)] \le N_1^p \doteq M_2, \quad (44)$$

where M_2 is a positive constant. Note that

$$\left(X_1(t)^2 + Y_1(t)^{2q/2} \le 2^{q/2}\left(X_1(t^q + Y_1(t^q\right). \quad (45)$$

It follows from systems (38) and (44) that

$$\limsup_{t\longrightarrow+\infty} E(\mid Z \mid^q) \le 2^{q/2}[M_1 + M_2] < \infty. \quad (46)$$

From Chebychev's inequality, this proof is completed. □

Theorem 4. *The solution of system (4) is globally attractive.*

Proof. Without loss of generality, we let $Z_1(t) = (P_1(t), Q_1(t))$ and $Z_2(t) = (P_2(t), Q_2(t))$ be any two solutions of system (9), which have initial values $P_i(0) > 0$, $Q_i(0) > 0$, $i = 1, 2$. First of all, define the Lyapunov function as follows:

$$V(t) = \left|\ln P_1(t) - \ln P_2(t)\right| + \left|\ln Q_1(t) - \ln Y_2(t)\right|, \quad (47)$$

where $t > 0$ and $t \ne nT$. Then, we compute the upper right derivative $d^+V(t)$ of $V(t)$ and apply the Itô's formula to system (29),

$$\begin{aligned} d^+V(t) &= \operatorname{sign}(P_1(t) - P_2(t))d(\ln P_1(t) - \ln P_2(t)) \\ &\quad + \operatorname{sign}(Q_1(t) - Q_2(t))d(\ln Q_1(t) - \ln Q_2(t)) \\ &= \operatorname{sign}(P_1(t) - P_2(t))\left(-\frac{R_1}{K}(P_1(t) - P_2(t)) - a(Q_1(t) - Q_2(t))\right) \\ &\quad dt + \operatorname{sign}(Q_1(t) - Q_2(t))(-c(P_1(t) - P_2(t)))dt \\ &= \left[-\left(\frac{R_1}{K} + c\right)\left|P_1(t) - P_2(t)\right| - a\left|Q_1(t) - Q_2(t)\right|\right]dt \\ &\le -\pi\left(\left|P_1(t) - \left|P_2(t) + \left|Q_1(t) - Q_2(t)\right|\right)dt \\ &\doteq -\pi\mathbb{V}(t)dt, \end{aligned} \quad (48)$$

where $\pi = \min\{R_1/K + c, a\}$. Second, when $t = nT$,

$$\begin{aligned} V(nT^+) &= \left|\ln P_1(nT^+) - \ln P_2(nT^+)\right| + \left|\ln Q_1(nT^+) - \ln Q_2(nT^+)\right| \\ &= \left|\ln P_1(nT) - \ln P_2(nT)\right| + \left|\ln(1 + e(nT))Q_1(nT)\right. \\ &\quad \left. - \ln(1 + e(nT))Q_2(nT)\right| \\ &= \left|\ln X_1(nT) - \ln P_2(nT)\right| + \left|\ln Q_1(nT) - \ln Q_2(nT)\right| \\ &= V(nT). \end{aligned} \quad (49)$$

From 0 to t, we integrate system (48) and compute the expectation of both sides, and we have

$$V(t) \le V(0) - \pi\int_0^t \mathbb{V}(s)ds. \quad (50)$$

Hence,

$$V(t) + \pi\int_0^t \mathbb{V}(s)ds \le V(0) < \infty. \quad (51)$$

$V(t) > 0$ is always valid which gives rise to $\lim_{t\longrightarrow+\infty}\mathbb{V}(t) = 0$.

That is to say,

$$\lim_{t\longrightarrow\infty}\left|P_1(t) - P_2(t)\right| = 0 \text{ and } \lim_{t\longrightarrow\infty}\left|Q_1(t) - Q_2(t)\right| = 0. \quad (52)$$

This completes the proof. □

Theorem 5. *For* $0 \le s < t$, *if* $\prod_{s \le nT < t}(1 + e(nT)) \le M$ $(M > 0)$ *and* $1 + C - d - k_2(\iota e^{-\mu T})/(1 - e^{-\mu T}) \le 0$, *then, the solution* $x(t) = (X(t), Y(t))$ *of system (9) satisfies*

$$\lim_{t \longrightarrow \infty} E|X(t)| \le MN, \tag{53}$$

where $N = cK/4R_1(R_1 + 1 - k_1\iota e^{-\mu T}/1 - e^{-\mu T})^2$.

Proof. Define $V_1(t) = e_1X(t) + e_2Y(t)$, here $e_1 = c > 0$ and $e_2 = -a < 0$. For any $t \in ((n-1)T, nT]$, by use of Itô's formula for system (9), we have

$$dV_1(t) = e_1dX + e_2dY = LV(t)dt + e_1\delta_1 X dB_1(t) + e_2\delta_2 Y dB_2(t), \tag{54}$$

with

$$LV(t) = e_1X\left[R_1\left(1 - \frac{X}{K}\right) - aY - k_1H(t) - U_1\right] + e_2Y[-cX + C - d - k_2H(t)]. \tag{55}$$

Moreover, we define Lyapunov function $V_2(t) = e^tV_1(t)$ and employ Itô's formula, so one can get that

$$\begin{aligned} dV_2(t) &= e^tV_1(t)dt + e^tdV_1(t) \\ &= e^tV_1(t)dt + e^t\{LV(t)dt + e_1\delta_1X(t)dB_1(t) + e_2\delta_2Y(t)dB_2(t)\}. \end{aligned} \tag{56}$$

Integrating the abovementioned equation from $(n-1)T$ to t and computing the expectations,

$$E\left[e^tV_1(t)\right] = e^{(n-1)T}V_1((n-1)T) + E\int_{(n-1)T}^{t} e^s[V_1(s) + LV(s)]ds. \tag{57}$$

Note that

$$\begin{aligned} LV + V_1 &= e_1\left[R_1X\left(1 - \frac{X}{K}\right) - U_1X - aXY - k_1H(t)X\right] \\ &\quad + e_2[(C-d)Y - cXY - k_2H(t)Y] + e_1X + e_2Y \\ &\le e_1\left[R_1X - \frac{R_1X^2}{K} - k_1H(t)X + X\right] + (-ae_1 - ce_2)XY \\ &\quad + e_2Y[1 + C - d - k_2H(t)] \\ &\le \frac{cK}{4R_1}\left(R + 1 - \frac{k_1\iota e^{-\mu T}}{1 - e^{-\mu T}}\right)^2 - aY\left(1 + C - d - \frac{k_2\iota e^{-\mu T}}{1 - e^{-\mu T}}\right) \\ &\le N. \end{aligned} \tag{58}$$

From systems (57) and (58), we deduce that

$$e^t EV_1(t) \le e^{(n-1)T}\left(V_1((n-1)T) - N\right) + e^t N. \tag{59}$$

Taking both sides of the derivative of system (59) leads to the following:

$$\mathrm{dEV}_1(t) \le \left(N - EV_1(t)\right)\mathrm{d}t. \tag{60}$$

When $t = nT$,

$$\begin{aligned} EV_1(nT^+) &= e_1E(X(nT^+)) + e_2E(Y(nT^+)) \\ &= e_1E(X(nT)) + e_2(1 + e(nT))E(Y(nT)) \\ &\le (1 + e(nT))\left(e_1E(X(nT)) + e_2E(Y(nT))\right) \\ &= (1 + e(nT))EV_1(nT). \end{aligned} \tag{61}$$

By systems (60) and (61),

$$\begin{cases} dEV_1(t) \le \left(N - EV_1(t)\right)dt, t \ne nT, \\ EV_1(nT^+) \le (1 + e(nT))EV_1(nT), t = nT. \end{cases} \tag{62}$$

To prove $EV_1(t)$ is bounded, consider the following impulsive system:

$$\begin{cases} dw(t) = (N - w(t))dt, t \ne nT, \\ w(nT^+) = (1 + e(nT))w(nT), t = nT. \end{cases} \tag{63}$$

The unique solution of system (63) is deduced by

$$w(t) = w(0)n(t,0) + N\int_0^t n(t,s)\mathrm{d}s, \tag{64}$$

where $n(t,s) = \prod_{s \le nT < t}(1 + e(n)(T))e^{-(t-s)}$. The methods of references [7, 10] give rise to $\lim_{t \longrightarrow +\infty} w(t) = MN$. Based on the comparison theorem of impulsive differential equations [7, 10, 53, 54],

$$\lim_{t \longrightarrow +\infty} EV_1(t) \le \lim_{t \longrightarrow +\infty} w(t) = MN. \tag{65}$$

This completes the proof. □

Remark 1. Under certain conditions, Theorem 5 indicates that there is an upper bound on the expectation of the solution of ISDE (4). Biologically, when the pulse immunotherapy or pulsed perturbations are bounded, the number of prostate cancer cells is controllable.

4. Extinction and Persistence

To investigate the threshold conditions for extinction and persistence of effector cells and prostate cancer cells. Let $V(t) = \ln X_1(t)$ and set $X(t) = X_1(t), Y(t) = \prod_{0<nT<t}(1 + e(n)(T))Y_1(t)$, then using Itô's formula to the first equation of system (30) gives

$$\begin{aligned} d\ln X_1(t) &= [R_1 - \frac{R_1}{K}X_1 - a\prod_{0<nT<t}(1 + e(n)(T))Y_1 \\ &\quad - k_1H(t) - U_1 - \frac{\delta_1^2}{2}]\,dt + \delta_1 dB_1(t) \\ &= [R_1 - \frac{R_1}{K}X - aY - k_1H(t) \\ &\quad - U_1 - \frac{\delta_1^2}{2}]\,dt + \delta_1 dB_1(t). \end{aligned} \tag{66}$$

Lemma 4. *Define $M_i(t) = \int_0^t \delta_i dB_i(t)\,(i = 1, 2)$, then integrating the abovementioned equation from 0 to t yields*

$$\begin{aligned} \ln X(t) - \ln X(0) &= \left(R_1 - U_1 - \frac{1}{2}\delta_1^2\right)t - \frac{R_1}{K}\int_0^t X(s)\mathrm{d}s \\ &\quad - k_1\int_0^t H(s)ds - a\int_0^t Y(s)ds + M_1(t). \end{aligned} \tag{67}$$

Similarly,

$$\begin{aligned} \ln Y(t) - \ln Y(0) &= \sum_{0<nT<t}\ln(1 + e(nT)) - \left(d - C + \frac{1}{2}\delta_2^2\right)t \\ &\quad - c\int_0^t X(s)ds - k_2\int_0^t H(s)ds + M_2(t). \end{aligned} \tag{68}$$

Theorem 6

(1) If

$$R_1 - U_1 - \frac{1}{2}\delta_1^2 - \frac{k_1\iota}{\mu T} < 0, \tag{69}$$

then the prostate cancer cells $X(t)$ are extinct.

(2) If

$$R_1 - U_1 - \frac{1}{2}\delta_1^2 - \frac{k_1\iota}{\mu T} = 0, \tag{70}$$

then the prostate cancer cells $X(t)$ become nonpersistent in the mean.

(3) If

$$R_1 - U_1 - \frac{1}{2}\delta_1^2 - \frac{k_1\iota}{\mu T} > 0, \tag{71}$$

$$\lim_{t\longrightarrow+\infty}\sup\frac{\sum_{0<nT<t}\ln\left(1+e\left(nT\right)\right)}{t} < d - C + \frac{1}{2}\delta_2^2 + \frac{k_2\iota}{\mu T}, \tag{72}$$

then the prostate cancer cells $X(t)$ are weakly persistent in the mean.

Proof

(1) From system (25),

$$\frac{1}{t}\ln\frac{X(t)}{X(0)} = \left(R_1 - U_1 - \frac{1}{2}\delta_1^2\right) - \frac{R_1}{K}\frac{\int_0^t X(s)ds}{t} - k_1\frac{\int_0^t H(s)ds}{t} - a\frac{\int_0^t Y(s)ds}{t} + \frac{M_1(t)}{t}. \tag{73}$$

Due to $<M_i(t), M_i(t)> = \int_0^t \delta_i^2 ds$, and in the light of Lemma 2, we have

$$\lim_{t\longrightarrow+\infty}\frac{M_i(t)}{t} = 0. \tag{74}$$

Taking the superior limit of equality (27) yields

$$\lim_{t\longrightarrow+\infty}\sup\frac{\ln X(t)}{t} \le R_1 - U_1 - \frac{1}{2}\delta_1^2 - \frac{k_1\iota}{\mu T} - \frac{R_1}{K}X_*(t) - aY_*(t) < 0. \tag{75}$$

It indicates that $\lim_{t\longrightarrow+\infty}X(t) = 0$, and the prostate cancer cells become extinct.

(2) For any fixed $\varepsilon > 0$, there is a constant t_1 so that for all $t \ge t_1$,

$$k_1\frac{\int_0^t H(s)ds}{t} > \frac{k_1\iota}{\mu T} - \frac{\varepsilon}{2}, \frac{M_1(t)}{t} \le \frac{\varepsilon}{2}. \tag{76}$$

Based on system (73),

$$\begin{aligned}\frac{1}{t}\ln\frac{X(t)}{X(0)} &= \left(R_1 - U - \frac{1}{2}\delta_1^2\right) - \frac{R_1}{K}\frac{\int_0^t X(s)ds}{t} - k_1\frac{\int_0^t H(s)ds}{t} \\ &\quad - a\frac{\int_0^t Y(s)ds}{t} + \frac{M_1(t)}{t} \\ &\le \left(R_1 - U - \frac{1}{2}\delta_1^2\right) - \frac{k_1\iota}{\mu T} \\ &\quad - \frac{R}{K}\frac{\int_0^t X(s)ds}{t} + \frac{M_1(t)}{t} + \varepsilon.\end{aligned} \tag{77}$$

Owing to Lemma 1, if ε is small enough, then

$$\limsup_{t\longrightarrow+\infty}\frac{1}{t}\int_0^t X(s)ds \le \frac{K\left(R_1 - U_1 - 1/2\delta_1^2 - k_1\iota/\mu T\right)}{R} = 0. \tag{78}$$

Since $X^*(t) \ge 0$, it indicates that $\lim_{t\longrightarrow+\infty}\sup 1/t\int_0^t X(s)ds \ge 0$.

Then, $\lim_{t\longrightarrow\infty}\sup 1/t\int_0^t X(s)ds = 0$; thus, the prostate cancer cells become nonpersistent in the mean.

(3) When $\lim_{t\longrightarrow\infty}\sup X(t)/t < 0$, the superior limit of system (27) gives rise to

$$\frac{R_1}{K}X^*(t) + aY^*(t) \ge R_1 - U_1 - \frac{1}{2}\delta_1^2 - \frac{k_1\iota}{\mu T} - \limsup_{t\longrightarrow\infty}\frac{\ln X(t)}{t} > 0. \tag{79}$$

As a result, $X^*(t) \ge 0$. Else, for any $t^* \in \{X^*(t, t^*) = 0\}$, then $Y^*(t, t^*) > 0$. If $X^*(t, t^*) = 0$, we use the same method mentioned previously,

$$\limsup_{t\longrightarrow+\infty}\frac{\ln Y(t,t^*)}{t}\le\limsup_{t\longrightarrow+\infty}\frac{\sum_{0<nT<t}\ln(1+e(nT))}{t}-\left(d-C+\frac{1}{2}\delta_2^2\right)-\frac{k_2\iota}{\mu T}<0, \tag{80}$$

which means that $Y^*(t,t^*)=0$; it is a contradiction that $Y^*(t,t^*)>0$, i.e., $\lim_{t\longrightarrow\infty}X(t)/t>0$. Then, the prostate cancer cells are weakly persistent in the mean. This completes the proof. □

Theorem 7

(1) If

$$R_1-U_1-\frac{1}{2}\delta_1^2-\frac{k_1\iota}{\mu T}<0 \tag{81}$$

$$\limsup_{t\longrightarrow\infty}\frac{\sum_{0<nT<t}\ln(1+e(nT))}{t}<d-C+\frac{1}{2}\delta_2^2+\frac{k_2\iota}{\mu T}, \tag{82}$$

then the effector cells $Y(t)$ are extinct.

(2) If

$$R_1-U_1-\frac{1}{2}\delta_1^2-\frac{k_1\iota}{\mu T}=0, \tag{83}$$

then the effector cells $Y(t)$ become nonpersistent in the mean.

(3) If

$$\limsup_{t\longrightarrow+\infty}\frac{\sum_{0<nT<t}\ln(1+e(nT))}{t}-\left(d-C+\frac{1}{2}\delta_2^2+\frac{k_2\iota}{\mu T}\right)-\frac{cK}{R_1}\left(R_1-U_1-\frac{1}{2}\delta_1^2-\frac{k_1\iota}{\mu T}\right)>0, \tag{84}$$

then the effector cells $Y(t)$ are weakly persistent in the mean.

Proof

(1) According to system (26), we can deduce

$$\frac{1}{t}\ln\frac{Y(t)}{Y(0)}=\frac{\sum_{0<nT<t}\ln(1+e(nT))}{t}-\left(d-C+\frac{1}{2}\delta_2^2\right)-c\frac{1}{t}\int_0^t X(s)ds-k_2\frac{1}{t}\int_0^t H(s)ds+\frac{M_2(t)}{t}. \tag{85}$$

Taking the superior limit of system (85) gives

$$\limsup_{t\longrightarrow+\infty}\frac{\ln Y(t)}{t}\le\limsup_{t\longrightarrow\infty}\frac{\sum_{0<nT<t}\ln(1+e(nT))}{t}-\left(d-C+\frac{1}{2}\delta_2^2+\frac{k_2\iota}{\mu T}\right)-cX_*(t). \tag{86}$$

Then,

$$\limsup_{t\longrightarrow\infty}\frac{\ln Y(t)}{t}\le 0. \tag{87}$$

Hence, $\lim_{t\longrightarrow+\infty}Y(t)=0$; then, the effector cells are extinct.

(2) For any fixed $\varepsilon>0$, there is a t_2 so that for all $t\ge t_2$, one can obtain

$$k_1\frac{\int_0^t H(s)ds}{t}>\frac{k_1\iota}{\mu T}-\frac{\varepsilon}{2},\frac{M_1(t)}{t}\le\frac{\varepsilon}{2}, \tag{88}$$

in the light of system (73) yields

$$a\frac{1}{t}\int_0^t Y(s)ds=-\frac{1}{t}\ln\frac{X(t)}{X(0)}+\left(R_1-U_1-\frac{1}{2}\delta_1^2\right)-\frac{R_1}{K}\frac{\int_0^t X(s)ds}{t}-k_1\frac{\int_0^t H(s)ds}{t}+\frac{M_1(t)}{t}\le\left(R_1-U_1-\frac{1}{2}\delta_1^2-\frac{k_1\iota}{\mu T}\right)+\varepsilon. \tag{89}$$

As ε is small enough, we take the superior limit that leads to the following:

$$\limsup_{t\longrightarrow+\infty}\frac{1}{t}\int_0^t Y(s)\mathrm{d}s\le 0. \tag{90}$$

Thus, $\limsup_{t\longrightarrow\infty}1/t\int_0^t Y(s)\mathrm{d}s=0$; then, the effector cells become nonpersistent in the mean.

(3) From system (30), we know

$$\frac{1}{t}\ln\frac{Y(t)}{Y(0)}=\frac{\sum_{0<nT<t}\ln(1+e(nT))}{t}-\left(d-C+\frac{1}{2}\delta_2^2\right)-c\frac{1}{t}\int_0^t X(s)\mathrm{d}s-k_2\frac{1}{t}\int_0^t H(s)ds+\frac{M_2(t)}{t}. \tag{91}$$

Adding systems (73) and (85) and taking the superior limit, there is a $t_3>0$ so that

$$\frac{\ln Y(t)}{t} \geq \lim_{t\longrightarrow+\infty}\sup\frac{\sum_{0<nT<t}\ln\left(1+e(nT)\right)}{t} - \left(d - C + \frac{1}{2}\delta_2^2 + \frac{k_2\iota}{\mu T}\right) + \left(R_1 - U_1 - \frac{1}{2}\delta_1^2 - \frac{k_1\iota}{\mu T}\right) - \left(\frac{R_1}{K} + c\right)X^*(t) - aY^*(t). \tag{92}$$

It follows from system (78), and then

$$aY^*(t) \geq \lim_{t\longrightarrow+\infty}\sup\frac{\sum_{0<nT<t}\ln\left(1+e(nT)\right)}{t} - \left(d - C + \frac{1}{2}\delta_2^2 + \frac{k_2\iota}{\mu T}\right) - \frac{cK}{R_1}\left(R_1 - U_1 - \frac{1}{2}\delta_1^2 - \frac{k_1\iota}{\mu T}\right) > 0. \tag{93}$$

Hence, $Y^*(t) = \text{limsup}_{t\longrightarrow+\infty} 1/t\int_0^t Y(s)ds \geq 0$; then, the effector cells are weakly persistent in the mean. This completes the proof. □

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

Theorem 8. *Based on Assumption 1, if* $\varsigma = \min_{t\geq 0}[R_1 - U_1 - 0.5\delta_1^2 - k_1\iota/\mu T - aM_1y_0] > 0$, *the prostate cancer cells become stochastically permanent.*

Proof. First, we want to show that there are two constants $\beta > 0$ and $\varrho > 0$ so that $\liminf_{t\longrightarrow+\infty}\mathbb{P}\{X(t) \geq \beta\} \geq 1 - \varepsilon$ and $\liminf_{t\longrightarrow+\infty}\mathbb{P}\{X(t) \leq \varrho\} \geq 1 - \varepsilon$ for any $\varepsilon \in (0,1)$. For one thing, defining a Lyapunov function $V^1(x) = 1/X_1\,(X_1 > 0)$ and using Itô's formula to the first equation of system (10) lead to the following:

$$dV^1(X_1) = -V^1(X_1)\left[R_1 - U_1 - \frac{R_1}{K}X_1 - k_1H(t) - a\prod_{0<nT<t}(1+e(n)(T))Y_1\right]dt + V^1(X_1)\delta_1^2dt - V^1(X_1)\delta_1dB_1(t). \tag{94}$$

Select a constant $\omega > 0$ which satisfies $\varsigma > 0.5\omega\delta_1^2$ and establish $V^2(X_1) = (1 + V^1(X_1)^\omega$. An application of Itô's formula yields

$$\begin{aligned} dV^2(X_1) &= \omega\left(1+V^1(X_1)\right)^{\omega-1}dV^1(X_1) \\ &\quad + 0.5\omega(\omega-1)\left(1+V^1(X_1)\right)^{\omega-2}\left(dV^1(X_1)\right)^2 \\ &= \omega\left(1+V^1(X_1)\right)^{\omega-2}\left\{-V^1(X_1) - \left(V^1(X_1)\right)\left[R_1 - U_1 - \frac{R_1}{K}X_1\right.\right. \\ &\quad \left.\left. - k_1H(t) - a\prod_{0<nT<t}(1+e(nT))Y_1\right] + \left(V^1(X_1) + \left(V^1(X_1)\right)^2\right)\delta_1^2\right. \end{aligned}$$

$$
\begin{aligned}
&+0.5(\omega-1)\left(V^1(X_1)\right)^2\delta_1^2\Big\}\mathrm{d}t-\omega\left(1+V^1(X_1)\right)^{\omega-1}V^1(X_1)\delta_1 dB_1(t)\\
&=\omega\left(1+V^1(X_1)\right)^{\omega-2}\Big\{-\left(V^1(X_1)\right)^2\left[R_1-U_1-0.5\delta_1^2-k_1H(t)\right.\\
&\left.-0.5\omega\delta_1^2-a\prod_{0<nT<t}(1+e(nT))Y_1\right]+V^1(X_1)\Big[-R_1+U_1+\frac{R_1}{K}\\
&+a\prod_{0<nT<t}(1+e(nT))Y_1+k_1H(t)+\delta_1^2\Big]+\frac{R_1}{K}\Big\}\mathrm{d}t\\
&-\omega\left(1+V^1(X_1)\right)^{\omega-1}V^1(X_1)\delta_1 dB_1(t)\\
&\le\omega\left(1+V^1(X_1)\right)^{\omega-2}\Big\{-\left(V^1(X_1)\right)^2\left[\varsigma-0.5\omega\delta_1^2\right]+V^1(X_1)\left[U_1\right.\\
&\left.+\frac{R_1}{K}+aM_1Y_0+\delta_1^2+\frac{k_1\iota}{\mu T}\right]+\frac{R_1}{K}\Big\}\mathrm{d}t\\
&-\omega\left(1+V^1(X_1)\right)^{\omega-1}V^1(X_1)\delta_1 dB_1(t).
\end{aligned}
\tag{95}
$$

Thereafter, choose a sufficiently small ϱ such that

$$
\varsigma-0.5\omega\delta_1^2>\frac{\varrho}{\omega}>0. \tag{96}
$$

Defining $V^3(X_1)=\exp(\varrho t)V^2(X_1)$ and employing Itô's formula give

$$
\begin{aligned}
dV^3(X_1)&=\varrho\exp(\varrho t)V^2(X_1)dt+\exp(\varrho t)dV^2(X_1)\\
&\le\omega\exp(\varrho)t)(1+V^1(X_1)^{\omega-2}\Big\{\frac{\varrho(1+V^1(X_1)^2}{\omega}\\
&-\left(V^1(X_1)^2\left[\varsigma-0.5\omega\delta_1^2\right]\right.\\
&\left.+V^1(X_1)\Big[U_1+\frac{R_1}{K}+aM_1Y_0+\delta_1^2+\frac{k_1\iota}{\mu T}\Big]+\frac{R_1}{K}\Big\}\mathrm{d}t\right.\\
&-\omega\exp(\varrho t)(1+V^1(X_1)^{\omega-1}V^1(X_1)\delta_1 dB_1(t)\Big)\\
&\doteq\exp(\varrho t)P(X_1)\mathrm{d}t\\
&-\omega\exp(\varrho t)(1+V^1(X_1)^{\omega-1}V^1(X_1)\delta_1 dB_1(t),
\end{aligned}
\tag{97}
$$

where

$$
P(X_1)=\omega\left(1+V^1(X_1)\right)^{\omega-2}\Big\{-\Big[\varsigma-0.5\omega\delta_1^2-\frac{\varrho}{\omega}\Big]\left(V^1(X_1)^2+\Big[U_1+\frac{R_1}{K}+aM_1Y_0+\delta_1^2+\frac{k_1\iota}{\mu T}+\frac{2\varrho}{\omega}\Big]V^1(X_1)+\frac{R_1}{K}+\frac{\varrho}{\omega}\right\}. \tag{98}
$$

Let $E_1=\varsigma-0.5\omega\delta_1^2-\varrho/\omega$, $E_2=U_1+R_1/K+aM_1Y_0+\delta_1^2+k_1\iota/\mu T+2\varrho/\omega$, and $E_3=R_1/K+\varrho/\omega$; from (96), we know that $E_1>0$, $E_2>0$, and $E_3>0$. Thus, we can rewrite $P(X_1)$ as follows:

$$
P(X_1)=\omega\left(1+\frac{1}{X_1}\right)^{\omega-2}\left\{-\frac{E_1}{X_1^2}+\frac{E_2}{X_1}+E_3\right\}\doteq P_1(X_1). \tag{99}
$$

We show that $P(X_1)$ is upper bounded when $X_1 > 0$. If $1/X_1 \geq (E_2 + \sqrt{E_2^2 + 4E_1E_3})/2E_1 \doteq \lambda_1$, then $P(X_1) \leq 0$. If $0 < 1/X_1 \leq \lambda_1$, then $P_1(X_1) \leq (4E_1E_3 + E_2^2)/4E_1$. Besides, if $\omega \geq 2$, then $\omega(1 + 1/X_1)^{\omega-2} \leq \omega(1 + \lambda_1)^{\omega-2}$; if $\omega < 2$, then $\omega(1 + 1/X_1)^{\omega-2} \leq \omega$. Therefore, for $X_1 > 0$, we always have $P(X_1) \leq P_0 = \lambda_2(4E_1E_3 + E_2^2)/4E_1$, where $\lambda_2 = \max\{\omega, \omega(1 + \lambda_1)^{\omega-2}\}$. Clearly, $P(X_1)$ is always upper bounded. Furthermore,

$$\begin{aligned} dV^3(X_1) &\leq \exp(\varrho t)P(X_1)\,dt - \omega\exp(\varrho t)(1 + V^1(X_1)^{\omega-1}V^1(X_1)\delta_1 dB_1(t)) \\ &\leq P_0\exp(\varrho t)\,dt - \omega\exp(\varrho t)(1 + V^1(X_1)^{\omega-1}V^1(X_1)\delta_1 dB_1(t). \end{aligned} \tag{100}$$

From 0 to t, integrating the previous inequality and taking the expectation,

$$E\left[V^3(X_1(t))\right] \leq V^3(X_1(0)) + \frac{P_0}{\varrho}\exp(\varrho t). \tag{101}$$

Since $V^3(X_1(t)) = \exp(\varrho(t)(1 + V^1(X_1(t))^\omega$, then we have

$$\begin{aligned} E\left[V^3(X_1(t))\right] &= E\left[\exp(\varrho t)(1 + V^1(X_1(t))^\omega\right] \\ &\leq V^3(X_1(0)) + \frac{P_0}{\varrho}\exp(\varrho t) \\ &= (1 + V^1(X_1(0))^\omega + \frac{P_0}{\varrho}\exp(\varrho t). \end{aligned} \tag{102}$$

Taking the superior limit, then

$$\limsup_{t\longrightarrow+\infty} E\left[\frac{1}{X_1(t)^\omega}\right] = \limsup_{t\longrightarrow+\infty} E\left[\left(V^1(X_1(t))^\omega\right] \leq \limsup_{t\longrightarrow+\infty} E\left[\left(1 + V^1(X_1(t))^\omega\right] \leq \frac{P_0}{\varrho}. \tag{103}$$

From system (31), one can obtain $X(t) = X_1(t)$,

$$\limsup_{t\longrightarrow+\infty} E\left[\frac{1}{X(t)^\omega}\right] = \limsup_{t\longrightarrow+\infty} E\left[\frac{1}{X_1(t)^\omega}\right] \leq \frac{P_0}{\varrho} \doteq P_M. \tag{104}$$

Furthermore, using the same method as in references [7, 10], then

$$\limsup_{t\longrightarrow+\infty} E\left[\frac{1}{X(t)^\omega}\right] \leq \frac{P_0}{\varrho} \doteq P_M. \tag{105}$$

For arbitrary $\varepsilon > 0$, we denote $\beta = \varepsilon^{1/\omega}/P_M^{1/\omega}$. Making use of Chebyshev's inequality gives

$$\begin{aligned} \limsup_{t\longrightarrow+\infty} \mathbb{P}\{X(t) < \beta\} &= \limsup_{t\longrightarrow+\infty} \mathbb{P}\left\{\frac{1}{X^\omega(t)} > \frac{1}{\beta^\omega}\right\} \\ &\leq \limsup_{t\longrightarrow+\infty} \frac{E\left[1/X^\omega(t)\right]}{\beta^{-\omega}} \\ &= \limsup_{t\longrightarrow+\infty} \beta^\omega E\left[\frac{1}{X^\omega(t)}\right] = \varepsilon. \end{aligned} \tag{106}$$

Thus,

$$\liminf_{t\longrightarrow+\infty} \mathbb{P}\{X(t) \geq \beta\} \geq 1 - \varepsilon. \tag{107}$$

For another, defining a Lyapunov function $V_3(X_1(t)) = X_1^q(t)(X_1 > 0)$ and in terms of Itô's formula with the first equation of system (30), it indicates that

$$\begin{aligned} dV_3(X_1(t)) &= qV_3(X_1(t))\Big[R_1 - U_1 - \frac{R_1}{K}X_1 - k_1H(t) \\ &\quad - a\prod_{0<nT<t}(1 + e(n)(T))Y_1(t) \\ &\quad + 0.5(q-1)\delta_1^2\Big]dt + q\delta_1V_3(X_1(t))\mathrm{d}B_1(t) \\ &\leq qV_3(X_1(t)) \\ &\quad \left[R_1 - U_1 - \frac{R_1}{K}X_1 - \frac{k_1\iota}{\mu T} + 0.5(q-1)\delta_1^2\right]\mathrm{d}t \\ &\quad + q\delta_1V_3(X_1(t))\mathrm{d}B_1(t). \end{aligned} \tag{108}$$

Integrating it from 0 to t and then taking the expectation lead to

$$E[V_3(X_1(t))] - E[V_3(X_1(0))] \le q\int_0^t E\left\{V_3(X_1(s))\left[R_1 - U_1 - \frac{R_1}{K}X_1 - \frac{k_1\iota}{\mu T} + 0.5(q-1)\delta_1^2\right]\right\}ds. \tag{109}$$

The derivative of the upper formula gives

$$\begin{aligned}\frac{dE[V_3(X_1(t))]}{dt} &\le qE[V_3(X_1(t))]\left[R_1 - U_1 - \frac{k_1\iota}{\mu T} + 0.5(q-1)\delta_1^2\right]\\ &\quad - q\frac{R_1}{K}E\left[X_1^{q+1}(t)\right].\end{aligned} \tag{110}$$

On account of Hölder's inequality, it can be obtained that

$$\begin{aligned}\frac{dE[V_3(X_1(t))]}{dt} &\le qE[V_3(X_1(t))]\left[R_1 - U_1 - \frac{k_1\iota}{\mu T} + 0.5(q-1)\delta_1^2\right]\\ &\quad - q\frac{R_1}{K}E[X_1^q(t)]^{\frac{q+1}{q}}.\end{aligned} \tag{111}$$

Let $m(t) = E[V_3(X_1(t))]$, one can obtain that

$$\begin{aligned}\frac{dm(t)}{dt} &\le qm(t)\left[R_1 - U_1 - \frac{k_1\iota}{\mu T} + 0.5(q-1)\delta_1^2 - \frac{R_1}{K}m^{\frac{1}{q}}(t)\right]\\ &\le qm(t)\left[R_1 - U_1 - \frac{k_1\iota}{\mu T} + 0.5q\delta_1^2 - \frac{R_1}{K}m^{\frac{1}{q}}(t)\right].\end{aligned} \tag{112}$$

From the standard comparison theorem, we conclude that

$$\begin{aligned}\limsup_{t\longrightarrow+\infty} E\left[X_1^q(t)\right] &= \limsup_{t\longrightarrow+\infty} E\left[V_3(X_1(t))\right]\\ &= \limsup_{t\longrightarrow+\infty} m(t)\\ &\le \left(\frac{R_1 - U_1 - k_1\iota/\mu T + 0.5q\delta_1^2}{R_1/K}\right)^q.\end{aligned} \tag{113}$$

Since $X(t) = X_1(t)$,

$$\begin{aligned}\limsup_{t\longrightarrow+\infty} E\left[X^q(t)\right] &= \limsup_{t\longrightarrow+\infty} E\left[X_1^q(t)\right]\\ &\le \left(\frac{K\left(R_1 - U_1 - k_1\iota/\mu T + 0.5q\delta_1^2\right)}{R_1}\right)^q.\end{aligned} \tag{114}$$

Similarly, it follows from Chebyshev's inequality that

$$\liminf_{t\longrightarrow+\infty} \mathbb{P}\{X(t) \le \varrho\} \ge 1 - \varepsilon. \tag{115}$$

As a consequence, it follows from system (4) of Definition 3. This completes the proof of Theorem 8. □

5. Stationary Distribution and Ergodicity of System (4)

Here, we wonder the existence of a unique ergodic stationary distribution of ISDE (4). If g is a bounded function on R_+, we define $g^u = \sup_{t\in R_+} g(t)$. For more details, readers can refer to references [3, 46, 55].

Define a SDE that equivalents to the original system (4) without pulsed effects:

$$\begin{cases} dX = X\left[R_1\left(1-\dfrac{X_1}{K}\right)-\left(k_1H(t)+U_1\right)\right. \\ \left.-a\displaystyle\prod_{0<nT<t}(1+e(n)(T))Y\right]dt+\delta_1 X dB_1(t), \\ dY = Y\left[C-d-k_2H(t)-cX\right]dt+\delta_2 Y dB_2(t). \end{cases} \tag{116}$$

With $(X(t),Y(t))\in \mathrm{R}_+^2$.

Theorem 9. *Assume*

$$\begin{cases} R_1-U_1-k_1H(t)-\dfrac{1}{2}\delta_1^2>0, \\ C-d-k_2H(t)-\dfrac{1}{2}\delta_2^2>0. \end{cases} \tag{117}$$

Then, system (4) has a unique ergodic stationary distribution.

Proof. Let

$$V_1(X,Y)=\ln X+\ln Y. \tag{118}$$

Then,

$$\begin{aligned} LV_1(X,Y) &= R_1-U_1-k_1H(t)-\frac{1}{2}\delta_1^2-\frac{R_1X}{K} \\ &\quad -a\prod_{0<nT<t}(1+e((n)T)Y \\ &\quad +C-d-k_2H(t)-\frac{1}{2}\delta_2^2-cX. \end{aligned} \tag{119}$$

Define

$$V_2(X,Y)=\frac{1}{X^\theta}+\frac{1}{Y^\theta},\ 0<\theta<1. \tag{120}$$

By some calculations, we obtain

$$\begin{aligned} LV_2(X,Y) &= -\theta X^{-\theta}\left[R_1-U_1-k_1H(t)-a\prod_{0<nT<t}(1+e(n)(T))Y\right. \\ &\quad \left.-\frac{\theta+1}{2}\delta_1^2\right]+\frac{R_1\theta}{K}X^{1-\theta}-\theta Y^{-\theta}\left[C-d-k_2H(t)-cX-\frac{\theta+1}{2}\delta_2^2\right] \\ &\le -\theta X^{-\theta}\left[R_1-U_1-k_1H(t)-\frac{\theta+1}{2}\delta_1^2\right]+\frac{R_1\theta}{K}X^{1-\theta} \\ &\quad -\theta Y^{-\theta}\left[C-d-k_2H(t)-\frac{\theta+1}{2}\delta_2^2\right]. \end{aligned} \tag{121}$$

Let

$$V(X,Y)=V_1(X,Y)+V_2(X,Y)=\ln X+\ln Y+\frac{1}{X^\theta}+\frac{1}{Y^\theta}. \tag{122}$$

We obtain

$$\begin{aligned} LV(X,Y) &= LV_1+LV_2 \\ &\le -\left(\frac{R_1}{K}+c\right)X+R_1-U_1-k_1H(t)-\frac{1}{2}\delta_1^2 \\ &\quad -a\prod_{0<nT<t}(1+e(n)(T))Y+C-d-k_2H(t)-\frac{1}{2}\delta_2^2 \\ &\le -\theta X^{-\theta}\left[R_1-U_1-k_1H(t)-\frac{\theta+1}{2}\delta_1^2\right]+\frac{R_1\theta}{K}X^{1-\theta} \\ &\quad -\theta Y^{-\theta}\left[C-d-k_2H(t)-\frac{\theta+1}{2}\delta_2^2\right]. \end{aligned} \tag{123}$$

It is easy to obtain that

$$LV(X,Y) \le \phi_1(X) + \phi_2(Y), \tag{124}$$

where

$$\begin{aligned}\phi_1(X) &= -\left(\frac{R_1}{K} + c\right)X + R_1 - U_1 - k_1 H(t) - \frac{1}{2}\delta_1^2 \\ &\quad - \theta X^{-\theta}\left[R_1 - U_1 - k_1 H(t) - \frac{\theta+1}{2}\delta_1^2\right] + \frac{R_1\theta}{K}X^{1-\theta}, \\ \phi_2(Y) &= -a\prod_{0<nT<t}(1+e(n)(T))Y + C - d - k_2 H(t) - \frac{1}{2}\delta_2^2 \\ &\quad - \theta Y^{-\theta}\left[C - d - k_2 H(t) - \frac{\theta+1}{2}\delta_2^2\right].\end{aligned} \tag{125}$$

□

Case 1. If $X \longrightarrow 0^+$, then

$$LV = \phi_1(X) + \phi_2(Y) \le \phi_1(X) + \phi_2^u \longrightarrow -\infty. \tag{126}$$

If $Y \longrightarrow 0^+$, then

$$LV = \phi_1(X) + \phi_2(Y) \le \phi_1^u + \phi_2(Y) \longrightarrow -\infty. \tag{127}$$

Case 2. If $X \longrightarrow +\infty$, then

$$LV = \phi_1(X) + \phi_2(Y) \le \phi_1(X) + \phi_2^u \longrightarrow -\infty. \tag{128}$$

If $Y \longrightarrow +\infty$, then

$$LV = \phi_1(X) + \phi_2(Y) \le \phi_1^u + \phi_2(Y) \longrightarrow -\infty. \tag{129}$$

Using the analysis method of Theorem 5.1 in reference [46], we conclude that when $X \longrightarrow 0^+$ or $Y \longrightarrow 0^+$ or $X \longrightarrow +\infty$ or $Y \longrightarrow +\infty$, we can get $LV \longrightarrow -\infty$. Hence, we take sufficiently small $\nu > 0$ and let $U := [\nu, 1/\nu] \times [\nu, 1/\nu]$, then

$$LV(X,Y) \le -1 \text{ for all } (X,Y) \in \frac{\mathrm{IntR}_+^2}{U}. \tag{130}$$

Moreover,

$$\begin{aligned}\sum_{i,j=1}^{2} b_{ij}(X,Y)\xi_i\xi_j &= \delta_1^2 X^2\xi_1^2 + \delta_2^2 Y^2\xi_2^2 \\ &\ge \min_{(X,Y)\in U}\left\{\delta_1^2 X^2, \delta_2^2 Y^2\right\}\|\xi\|^2 \\ &\quad \text{for all } (X,Y) \in U, (\xi_1,\xi_2) \in \mathrm{R}^2.\end{aligned} \tag{131}$$

It follows from Theorem 9, which completes the proof.

6. Numerical Simulations

Next, numerical simulations are conducted to verify our results by the Milstein higher order method [7, 35, 56]. The approximate solution system (4) is obtained and the discretization equations of system (4) are as follows:

$$\begin{cases} dX_{k+1} = X_k + X_k\left[rA_k\left(1 - \dfrac{X_k}{K}\right) - \left(d_1\left(1 - \dfrac{A_k}{a_0}\right) + d_2\right) - k_1 H_k - aY_k\right]\Delta t \\ \quad + \delta_1 X_k\sqrt{\Delta t\xi_k} + \dfrac{\delta_1^2}{2}X_k\left(\xi_k^2 - 1\right)\Delta t, \\ dY_{k+1} = Y_k + Y_k[(C-d) - k_2 H_k - cX_k]\Delta t + \delta_2 Y_k\sqrt{\Delta t\eta_k} \\ \quad + \dfrac{\delta_2^2}{2}Y_k\left(\eta_k^2 - 1\right)\Delta t, \\ dA_{k+1} = A_k + [-\gamma(A_k - a_0) - \gamma a_0 u]\Delta t, \\ dH_{k+1} = H_k - \mu H_k\Delta t, \end{cases} \tag{132}$$

and when $t = nT$ system (4) implements pulsed therapy, i.e., when mod $(k, T) = 0$, then

$$\begin{cases} Y_{k+1} = (1 + a_k)Y_k, \\ H_{k+1} = H_k + b_k, \end{cases} \tag{133}$$

where ξ_k and $\eta_k\,(k = 1, 2, 3, \cdots)$ have a distribution $N(0,1)$, which represents independent Gaussian random variables. We set time increment $\Delta t = 0.01$. We replace the periodic solution $D^T(t)$ with the maximum D^*, where $D^* = \iota/1 - e^{-\mu T}$.

6.1. Extinction and Persistence of Tumor Cells and Effector Cells. The standard parameter values of the pulseless random system are selected from the classical references [3, 7, 10, 20], which are scientific and reliable to a certain extent.

In Figure 1(a), we fix parameters as in Figure 1(a). By a simple calculation,

$$R_1 - U_1 - \frac{1}{2}\delta_1^2 - \frac{k_1\iota}{\mu T} = -0.926 < 0, \tag{134}$$

and by Theorem 6, the prostate cancer cells are extinct (Figure 1(a)). Set $r = 1.663$, and keep other parameters as in Figure 1(a); it is easy to see

$$\limsup_{t\longrightarrow\infty} \frac{\sum_{0<nT<t} \ln\,(1 + e(nT))}{t} \approx 0.01 < d - C + \frac{1}{2}\delta_2^2 + \frac{k_2\iota}{\mu T} = 0.026. \tag{137}$$

From Theorem 6, the prostate cancer cells are weakly persistent in the mean (Figure 1(c)). It is easy to see that as the growth rate increases, the dynamic behaviors of prostate cancer cells changes from extinction to persistence, which means that the growth rate of tumors is positively correlated with their persistence under certain conditions (Figures 1(a)–1(c)).

According to Theorem 7, the effector cells are extinct. In Figure 1(e), we set $C = 0.7$ and $a_k = 0.3$ and keep all other parameters as shown in Figure 1(b). One can get that

$$R_1 - U_1 - \frac{1}{2}\delta_1^2 - \frac{k_1\iota}{\mu T} = 0. \tag{140}$$

From Theorem 7, the effector cells become nonpersistent in the mean. In Figure 1(f), $r = 1.663, \delta_1 = 3$, and $a_k = 0.3$; keeping all other parameters as shown in Figure 1(a), we obtain

$$\lim_{t\longrightarrow+\infty} \sup \frac{\sum_{0<nT<t} \ln\,(1 + e(nT))}{t} - \left(d - C + \frac{1}{2}\delta_2^2 + \frac{k_2\iota}{\mu T}\right) - \frac{cK}{R_1}\left(R_1 - U_1 - \frac{1}{2}\delta_1^2 - \frac{k_1\iota}{\mu T}\right) \approx 1.3297 > 0. \tag{141}$$

Theorem 7 suggests that the effector cells are weakly persistent in the mean.

In Figure 2(a), setting $r = 3$ and $\delta_1 = 2$ and keeping all other parameters as shown in Figure 1(c), then

$$\varsigma = \min_{t\geq 0}\left[R_1 - U_1 - \frac{1}{2}\delta_1^2 - \frac{k_1\iota}{\mu T} - aM_1 y_0\right] = 2.694 > 0. \tag{142}$$

$$R_1 - U_1 - \frac{1}{2}\delta_1^2 - \frac{k_1\iota}{\mu T} = 0. \tag{135}$$

In terms of Theorem 6, the prostate cancer cells are nonpersistent in the mean (Figure 1(b)). Let $r = 1.85$ and $C = 0.4$, then

$$R_1 - U_1 - \frac{1}{2}\delta_1^2 - \frac{k_1\iota}{\mu T} = 0.374 > 0, \tag{136}$$

and

In Figure 1(d), set $C = 0.4$, by computing,

$$R_1 - U_1 - \frac{1}{2}\delta_1^2 - \frac{k_1\iota}{\mu T} = -0.926 < 0, \tag{138}$$

and

$$\limsup_{t\longrightarrow\infty} \frac{\sum_{0<nT<t} \ln\,(1 + e(nT))}{t} \approx 0.01 < d - C + \frac{1}{2}\delta_2^2 + \frac{k_2\iota}{\mu T} = 0.026. \tag{139}$$

Theorem 8 means that the prostate cancer cells become stochastically permanent (Figure 2(a)). In Figure 2(b), let $\delta_1 = 0.5$ and it is easy to see that the amplitude becomes smaller (Figure 2(b)), and then

$$\varsigma = \min_{t\geq 0}\left[R_1 - U_1 - \frac{1}{2}\delta_1^2 - \frac{k_1\iota}{\mu T} - aM_1 y_0\right] = 4.569. \tag{143}$$

It is concluded that with the increase of ς, the stronger the random persistence, the smaller the corresponding amplitude (Figure 2).

6.2. Effects of Random Perturbation on the Dynamics of Tumor Cells. To investigate how these disturbances affect the dynamical behaviors of prostate cancer cells, we do the following things.

In Figure 3(a), we set $\delta_1 = 1$ and fix all other parameters as Figure 1(b) and then

$$\iota = \min_{t\geq 0}\left[R_1 - U_1 - \frac{1}{2}\delta_1^2 - \frac{k_1\iota}{\mu T} - aM_1 y_0\right] = 1.52 > 0. \tag{144}$$

By Theorem 8, the prostate cancer cells are stochastically persistent (Figure 3(a)). If we set $\delta_1 = 2.2$, by some computations,

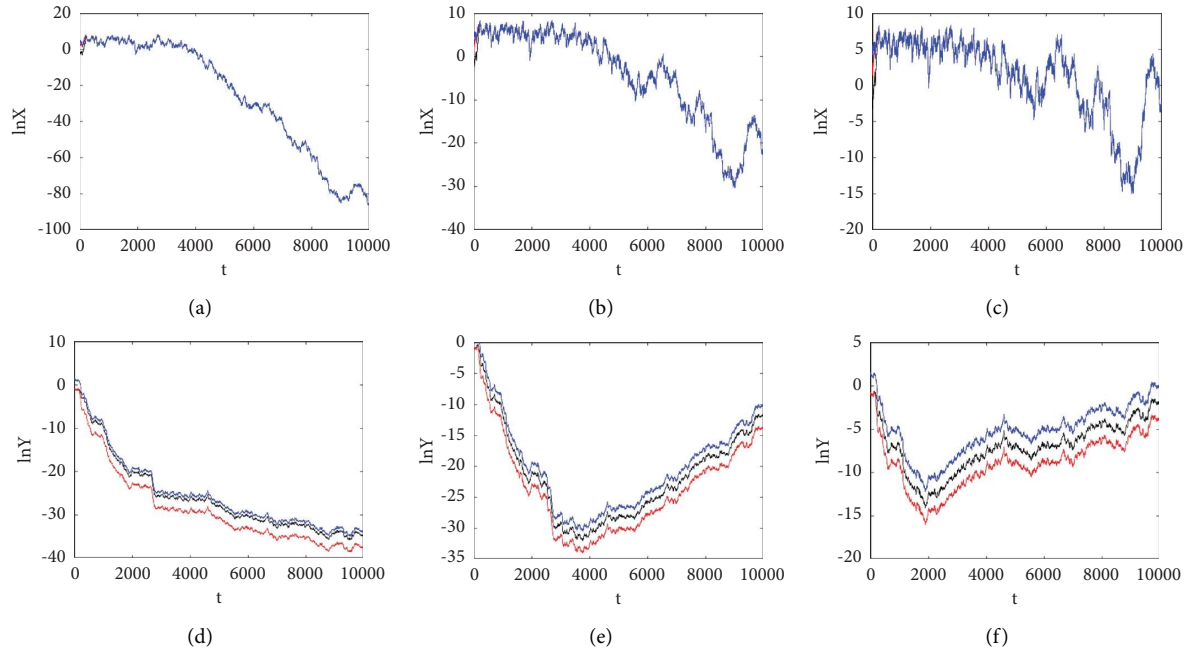

Figure 1: (a–c) The extinction, nonpersistence in the mean, and weakly persistence in the mean of prostate cancer cells. (d–f) The extinction, nonpersistence in the mean, and weakly persistence in the mean of effector cells. (a) $r = 1.2, C = 0.47, \delta_1 = 2.5$, and $e(nT) = 0.05$; (b) $C = 0.47$, $\delta_1 = 2.5$, and $e(nT) = 0.05$; (c) $\delta_1 = 2.5$ and $e(nT) = 0.05$; (d) $r = 1.2$, $\delta_1 = 2.5$, and $e(nT) = 0.1$; (e) $r = 1.663$, $\delta_1 = 2.5$, and $e(nT) = 0.3$; (f) $C = 0.47$ and $e(nT) = 0.3$. The initial values were fixed as $(X(0), Y(0)) = (0.1, 0.5)$, red for $(X(0), Y(0)) = (10, 0.5)$ and blue for $(X(0), Y(0)) = (300, 5)$, and other parameters were fixed as $\delta_2 = 0.5$, $u = 0.5$, $\iota = 0.1$, $T = 100$, $A(0) = 5$, $H(0) = 0.2$, $a_0 = 4$, $a = 1$, $d_1 = 0.2$, $d_2 = 0.1$, $d = 0.3$, $k_1 = 0.5$, $k_2 = 0.5$, $\gamma = 0.08$, $\mu = 0.5$, $K = 1000$, and $c = 0.00311$.

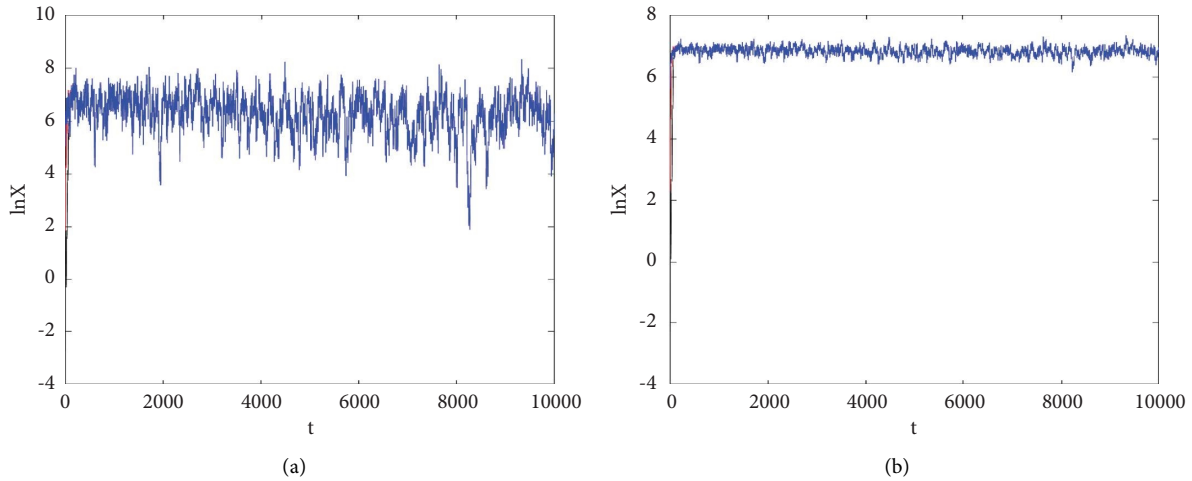

Figure 2: Stochastic permanence of prostate cancer cells. (a) $r = 3$ and $\delta_1 = 2$; (b) $r = 3$ and $\delta_1 = 0.5$. Other parameters were fixed as $\delta_2 = 0.5$, $u = 0.5$, $\iota = 0.1$, $C = 0.4$, $e(nT) = 0.05$, and $T = 100$.

$$\iota = \min_{t \geq 0} \left[R_1 - U_1 - \frac{1}{2}\delta_1^2 - \frac{k_1 \iota}{\mu T} - aM_1 y_0 \right] = -0.4 < 0, \tag{145}$$

$$R_1 - U_1 - \frac{1}{2}\delta_1^2 - \frac{k_1 \iota}{\mu T} = 0.705 > 0, \tag{146}$$

and

$$\begin{aligned} \limsup_{t \longrightarrow \infty} \frac{\sum_{0<nT<t} \ln(1 + e(nT))}{t} \\ \approx 0.01 < d - C + \frac{1}{2}\delta_2^2 + \frac{k_2 \iota}{\mu T} = 0.026. \end{aligned} \tag{147}$$

In the light of Theorem 6, the dynamics of prostate cancer cells changes from stochastically persistent to weakly

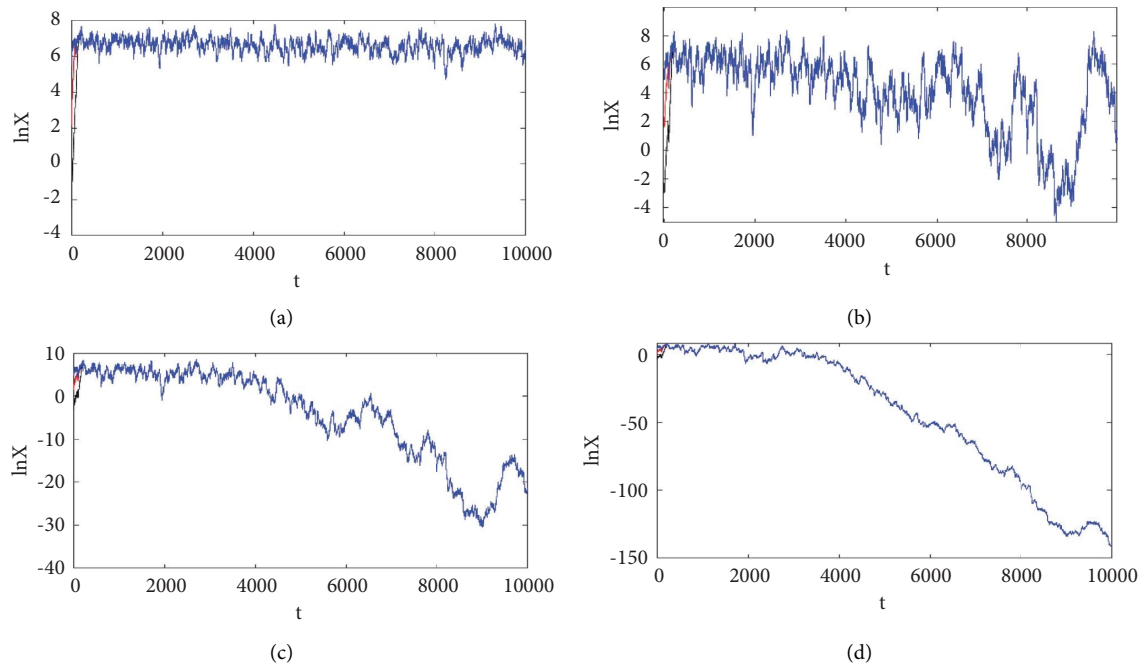

FIGURE 3: The effects of white noise on the evolution of prostate cancer cells. (a) $r = 1.663$ and $\delta_1 = 1$; (b) $r = 1.663$ and $\delta_1 = 2.2$; (c) $r = 1.663$ and $\delta_1 = 2.5$; (d) $r = 1.663$ and $\delta_1 = 3$. Other parameters were fixed as $\delta_2 = 0.5$, $u = 0.5$, $\iota = 0.1$, $C = 0.47$, $e(nT) = 0.05$, and $T = 100$.

persistent in the mean (Figure 3(b)). If we set $\delta_1 = 2.5$, we have

$$R_1 - U_1 - \frac{1}{2}\delta_1^2 - \frac{k_1\iota}{\mu T} = 0. \tag{148}$$

Theorem 6 explains that the dynamic behaviors of prostate cancer cells change from weakly persistent in the mean to nonpersistent in the mean (Figure 3(c)). If we set $\delta_1 = 3$, then

$$R_1 - U_1 - \frac{1}{2}\delta_1^2 - \frac{k_1\iota}{\mu T} = -1.375 < 0. \tag{149}$$

By Theorem 6, the dynamics of prostate cancer cells change from nonpersistent in the mean to extinct (Figure 3(d)). It can be seen that white noise can determine all the dynamic behaviors of prostate cancer cells. Increasing the intensities of white noise can accelerate the death of cancer cells, which indicates that white noise has a great influence on the evolution of tumors.

6.3. Monotherapy and Comprehensive Therapy. In this subsection, the initial values were fixed as $(X(0), Y(0)) = (10, 0.5)$, and other parameters are fixed as shown in (Figure 1(c)).

If only CAD therapy is used, we just need to adjust the value of u, and the feasible method of this therapy is to increase its intensities (Figure 4). If only chemotherapy is applied (Figures 5), the feasible methods of chemotherapy include increasing the dosages of chemotherapy (Figures 5(a) and 5(b)) and decreasing the pulsed periods (Figures 5(c) and 5(d)). If only immunotherapy is initiated, the feasible options of immunotherapy are to increase the dosages of immunotherapy (Figures 6(a) and 6(b)) or reduce the duration of immunotherapy (Figures 6(c) and 6(d)).

From (Figures 4–6), it has been observed that although the extinction of prostate cancer cells can be achieved by any of the previous single treatments under large stochastic fluctuations, these three kinds of treatments have their drawbacks such as resistance and toxic reaction [44, 45]. Hence, we will show how combination therapy of immunotherapy and chemotherapy together with CAD affects the evolution of prostate cancer cells. It can be seen from (Figures 4–6) that appropriately increasing the intensities of CAD therapy (or chemotherapy), increasing the dosages of chemotherapy (or immunotherapy), or shortening the treatment periods of immunotherapy (or increasing the frequencies of treatment) is more conducive to cancer treatment. Furthermore, compared with (Figures 4–7), we found that the tiny changes in hybrid therapy may cause big changes, such as to shorten the death time of prostate cancer cells (Figure 7).

Next, we will explore the development of prostate cancer cells with different initial values under the same parameters, we set $a_k = 1.3$, $u = 0.5$, $b_k = 0.1$, and $T = 30$, and other parameters were fixed as shown in Figure 1(c).

In Figure 8, it is revealed that the treatment of prostate cancer is associated with the initial tumor state of each patient. Therefore, the medical profession should formulate corresponding treatment strategies according to the development of patients' condition.

6.4. Existence of Stationary Distribution of System (4). With the parameters as shown in Figure 9, one can see that all conditions of Theorem 9 are satisfied. If we set

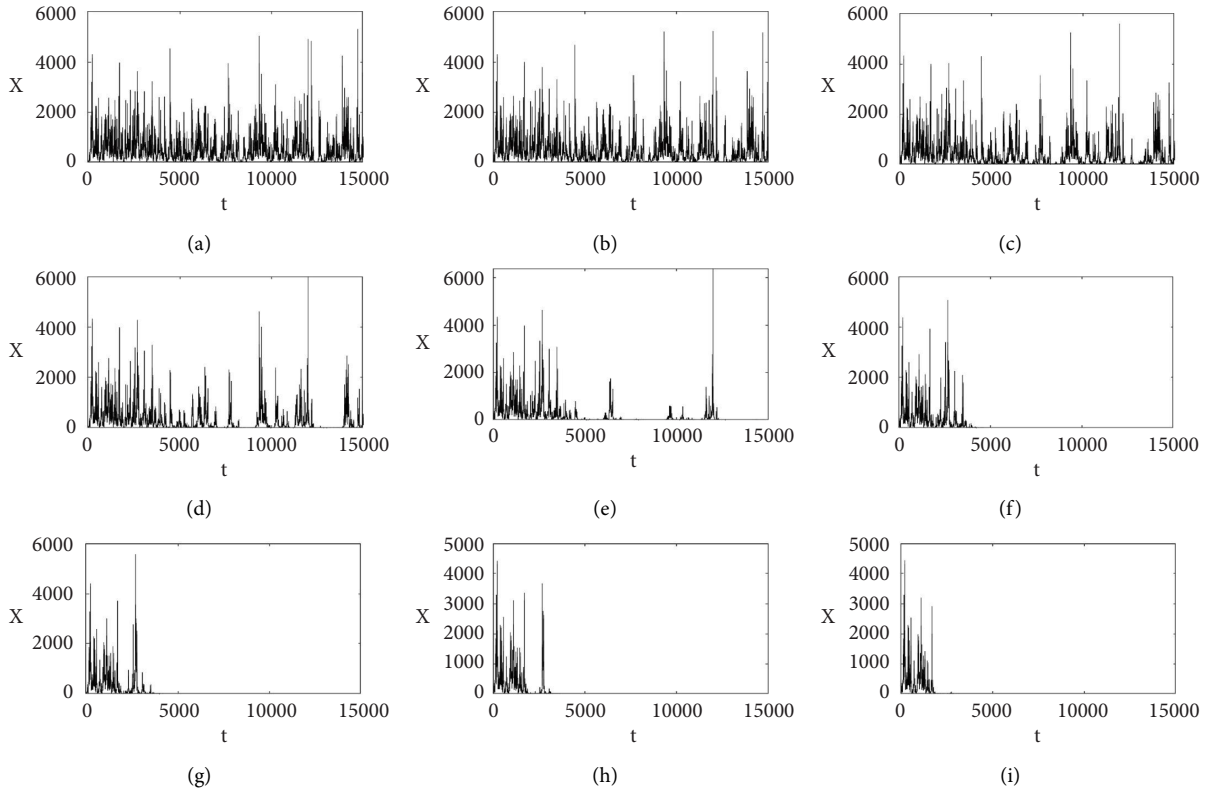

Figure 4: The effects of CAD alone on the evolution of prostate cancer cells. (a) $u = 0.1$; (b) $u = 0.2$; (c) $u = 0.3$; (d) $u = 0.4$; (e) $u = 0.5$; (f) $u = 0.6$; (g) $u = 0.7$; (h) $u = 0.8$; (i) $u = 0.9$. Other parameters were fixed as $r = 1.85$, $\delta_1 = 2.5$, $\delta_2 = 0.5$, $T = 100$, $\iota = 0$, $C = 0.4$, and $e(nT) = 0$.

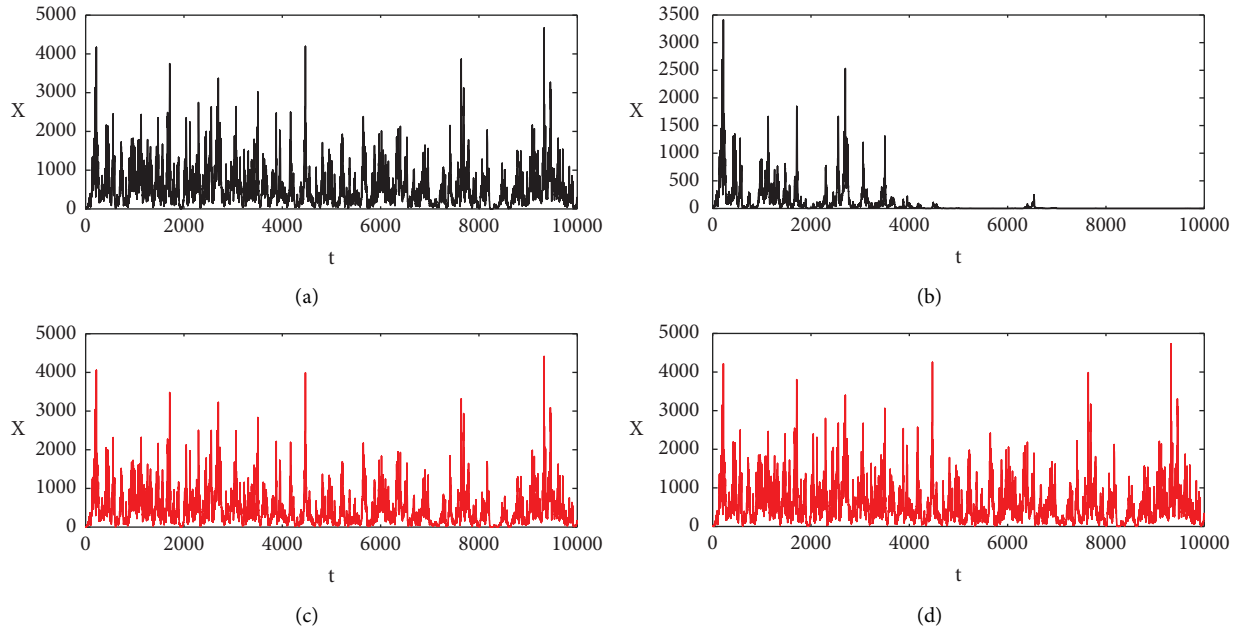

Figure 5: The effects of chemotherapy alone on the evolution of prostate cancer cells. (a) $\iota = 0.2, T = 50$; (b) $\iota = 2, T = 50$; (c) $\iota = 0.2, T = 20$; (d) $\iota = 0.2, T = 80$ (red for (c), (d)). Other parameters were fixed as $r = 1.85$, $\delta_1 = 2.5$, $\delta_2 = 0.5$, $u = 0$, $C = 0.4$, and $e(nT) = 0$.

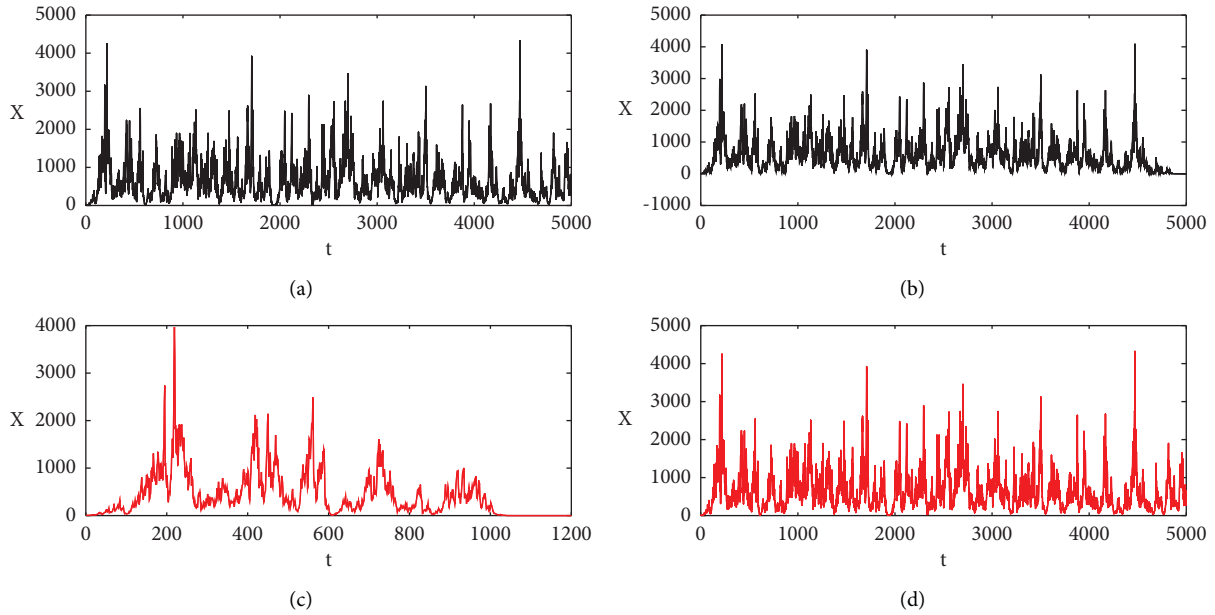

Figure 6: The effects of immunotherapy alone on the evolution of prostate cancer cells. (a) $e(nT) = 0.5, T = 50$; (b) $e(nT) = 1.7, T = 50$; (c) $e(nT) = 0.5, T = 20$; (d) $e(nT) = 0.5, T = 80$ (red for (c), (d)). Other parameters were fixed as $r = 1.85$, $\delta_1 = 2.5$, $\delta_2 = 0.5$, $\iota = 0$, $C = 0.4$, and $u = 0$.

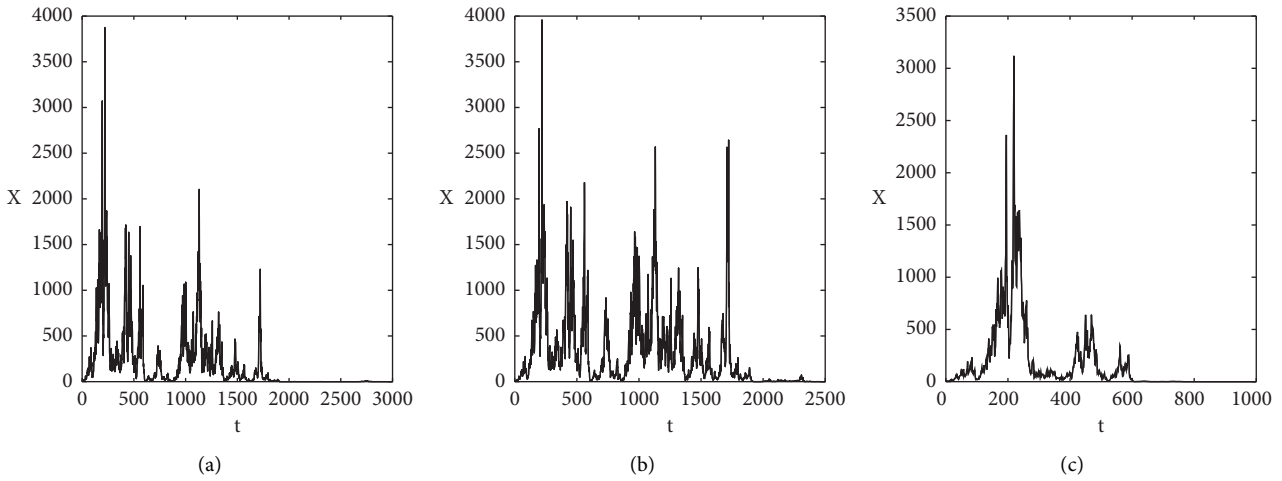

Figure 7: The effects of comprehensive therapy on the evolution of prostate cancer cells. (a) $T = 50, \iota = 2, e(nT) = 1.7$, and $u = 0.6$; (b) $T = 20, \iota = 0.2, e(nT) = 0.5$, and $u = 0.2$; (c) $T = 40, \iota = 2, e(nT) = 1.7$, and $u = 0.6$. Other parameters were fixed as $r = 1.85$, $\delta_1 = 2.5$, $\delta_2 = 0.5$, and $C = 0.4$.

$\delta_1 = 0.1, \delta_2 = 0.1, u = 0.1, a_k = 0.1, b_k = 0.1$, by a calculation, then

$$R_1 - U_1 - k_1 H(t) - \frac{1}{2}\delta_1^2 \approx 6.485 > 0, C - d - k_2 H(t) - \frac{1}{2}\delta_2^2 \approx 0.045 > 0. \tag{150}$$

By Theorem 9, system (4) has a unique stationary distribution (Figure 9). The existence of stationary distribution shows that the dynamic behaviors of prostate cancer cells fluctuate within a certain range when the white noise is small.

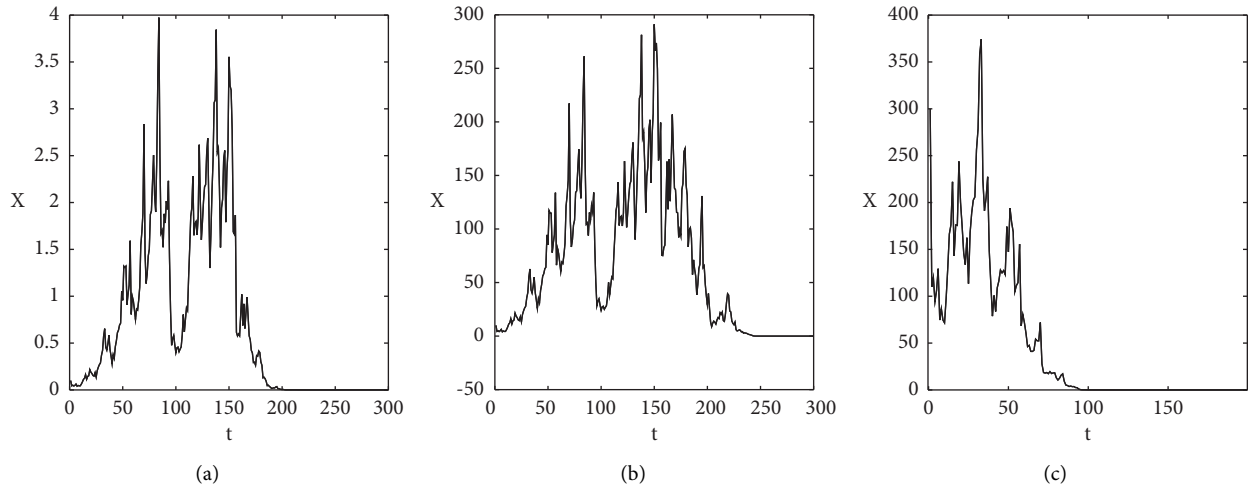

Figure 8: The dynamics of prostate cancer cells with different initial values under optimal strategy. (a) $(X(0), Y(0)) = (0.1, 0.5)$; (b) $(X(0), Y(0)) = (10, 0.5)$; (c) $(X(0), Y(0)) = (300, 5)$; other parameters were fixed as $r = 1.85$, $\delta_1 = 2.5$, $\delta_2 = 0.5$, $T = 30$, $\iota = 0.1$, $C = 0.4$, $u = 0.5$, and $e(nT) = 1.3$.

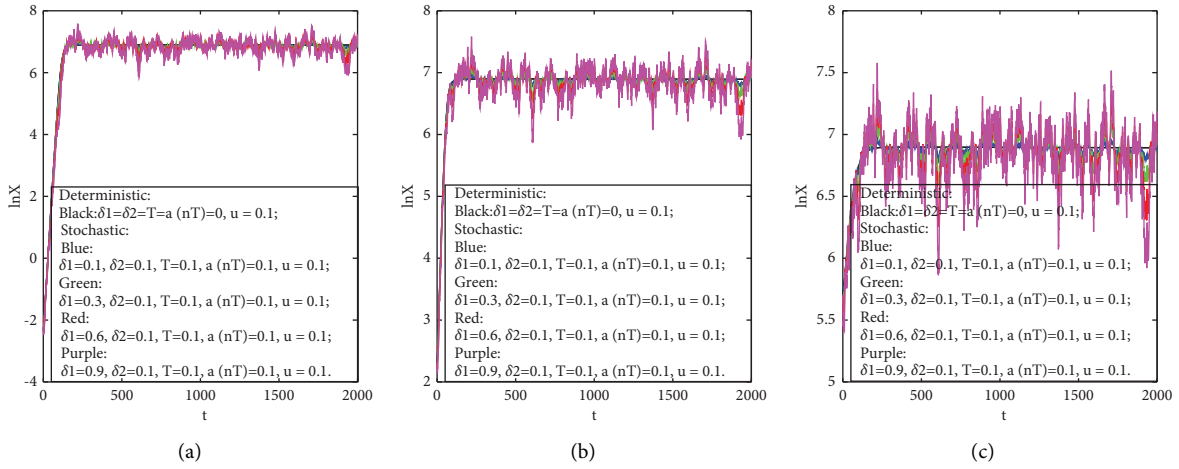

Figure 9: Stationary distribution of deterministic model and stochastic model. (a) $(X(0), Y(0)) = (0.1, 0.5)$; (b) $(X(0), Y(0)) = (10, 0.5)$; (c) $(X(0), Y(0)) = (300, 5)$; other parameters were fixed as $r = 1.85$, $C = 0.4$, and $T = 100$.

Table 2: The main theoretical results and corresponding conditions.

Conditions	Theoretical results
$R_1 - U_1 - 1/2\delta_1^2 - k_1\iota/\mu T < 0$	$X(t)$: extinct
$R_1 - U_1 - 1/2\delta_1^2 - k_1\iota/\mu T = 0$	$X(t)$: nonpersistent in the mean
$R_1 - U_1 - 1/2\delta_1^2 - k_1\iota/\mu T > 0$ and $\lim_{t\longrightarrow+\infty}\sup\sum_{0<nT<t}\ln(1+e(nT))/t < d - C + 1/2\delta_2^2 + k_2\iota/\mu T$	$X(t)$: weakly persistent in the mean
$R_1 - U_1 - 1/2\delta_1^2 - k_1\iota/\mu T < 0$ and $\lim_{t\longrightarrow\infty}\sup\sum_{0<nT<t}\ln(1+e(nT))/t < d - C + 1/2\delta_2^2 + k_2\iota/\mu T$	$Y(t)$: extinct
$R_1 - U_1 - 1/2\delta_1^2 - k_1\iota/\mu T = 0$	$Y(t)$: nonpersistent in the mean
$\lim_{t\longrightarrow+\infty}\sup\sum_{0<nT<t}\ln(1+e(nT))/t - (d - C + 1/2\delta_2^2 + k_2\iota/\mu T) - cK/R_1(R_1 - U_1 - 1/2\delta_1^2 - k_1\iota/\mu T) > 0$	$Y(t)$: weakly persistent in the mean
$\varsigma = \min_{t\geq0}[R_1 - U_1 - 0.5\delta_1^2 - k_1\iota/\mu T - aM_1 y_0] > 0$	$X(t)$: stochastically permanent
$R_1 - U_1 - k_1 H(t) - 1/2\delta_1^2 > 0$ and $C - d - k_2 H(t) - 1/2\delta_2^2 > 0$	$X(t)$: stationary distribution

7. Conclusions

Many studies have pointed out that the development of prostate cancer cells is inevitably affected by environmental disturbances such as nutrients and temperature [3, 7, 10, 27]. To our knowledge, there is no conclusive evidence in the medical field that IAD therapy is better than CAD therapy, and experiments have shown that immunotherapy can promote chemotherapy [3, 7, 10, 13]. However, there are few studies that combine CAD, immunotherapy and chemotherapy to study the dynamics of prostate cancer. Based on these considerations, we proposed a pulsed stochastic model, which combined the three treatments mentioned previously by incorporating tumor antigenicity and density-dependent mortality.

We first explore the pharmacokinetics of chemotherapy and obtain the expression of the tumor-free solution, indicating that the system has a unique global positive solution. Then, the global attraction of solution and the boundness of expectation are proved, which indicates that prostate cancer cells cannot grow indefinitely and can be controlled under limited pulse immunotherapy. Furthermore, the threshold conditions of extinction and persistence for prostate cancer cells and effector cells are provided by using the theorems of ISDEs and Itô's formula. Moreover, the sufficient conditions of stochastically permanence of prostate cancer cells and the existence of ergodic stationary distribution of the system are established. Finally, numerical simulations are carried out to confirm the theoretical results and provide guidance for treatment. The details of the theoretical results are shown in Table 2.

Biologically, we obtain the following conclusions: (1) White noise can change tumor dynamics and has a negative effect on the evolution of prostate cancer cells. (2) Compared with single treatment, comprehensive therapy can significantly reduce the time of tumor regression and prevent tumor recurrence. The results show that increasing the intensities of CAD therapy (or chemotherapy), increasing the dosages of chemotherapy (or immunotherapy), or shortening the treatment periods of immunotherapy (or increasing the frequencies of treatment) are feasible treatments for prostate cancer (Figures 4–7). (3) This paper investigates the development of prostate cancer cells with different initial values under the same parameter conditions, declaring that the treatment of prostate cancer can be adjusted according to the initial tumor state (Figure 8). (4) The existence of stationary distribution shows that small noise means stochastic stability, while large noise is destructive to stability of the system and leads to cure (Figure 9).

Some interesting questions deserve further investigation, and more effective but complex models can be studied. Firstly, without using the traditional Lyapunov function method, how to analyze the properties of impulsive-free boundary stochastic differential systems [32, 33]? Secondly, Markov chain is often used to simulate random factors in ecosystems. Based on the original model, what is the dynamic behaviours after considering such random factors? Besides, it is interesting to investigate IAD with pulses. We leave these questions for future work.

Data Availability

The data used for this research are from the respective published articles that are cited.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (NSFC: 11801047), the Natural Science Foundation of Chongqing (cstc2\\017jcyjAX0131), the Group Building Scientific Innovation Project for Universities in Chongqing (CXQT21021), the Team Building Project for Graduate Tutors in Chongqing (JDDSTD201802), and the Graduate Research and Innovation Project of Chongqing (CYS21370).

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