Journal of Nonlinear Modeling and Analysis
Volume 7, Number 6, December 2025, 2261–2284
https://journal.global-sci.org/jnma
DOI:10.12150/jnma.2025.2261

Dynamical Properties of a Stochastic Tumor-Immune Model with Pulsed Chemotherapeutic Dose Response*

N. Bajja[1,2,†,*] and D. Seghir[1,2]

Abstract Comprehensive pulsed chemotherapy and immunotherapy are widely employed in clinical tumor treatment. Given the periodically pulsed nature of this approach, we propose a stochastic tumor-immune dynamical model with a pulsed chemotherapeutic dose response. The model accounts for the combined effects of pulsed chemotherapy and pulsed immunotherapy, as well as the influence of environmental random disturbances. We prove the existence and uniqueness of a global positive solution to the proposed model. By using comparison theorems for impulsive differential equations, we show the boundedness of the solution's expectation. Furthermore, we derive sufficient conditions for the extinction and non-persistence in the mean of tumor cells, hunting T-cells, and helper T-cells, as well as for the weak persistence in the mean of tumor cells and helper T-cells, and the stochastic persistence of tumor cells. The results of our study, supported by numerical simulations, demonstrate that random disturbances can effectively inhibit tumor cell growth.

Keywords Tumor-immune model, chemotherapeutic dose response, random disturbances, Itô's formula, impulsive stochastic differential equation

MSC(2010) 97M60, 93E03, 93E15

1. Introduction

Malignant tumors in cancer arise from the uncontrolled and abnormal proliferation of cells. Cancer continues to be a pervasive and aggressive global disease,with its treatment posing significant and persistent challenges. Traditional treatment methods, such as surgery, radiotherapy, and chemotherapy, are commonly employed. However, these approaches often fail to completely eradicate cancer cells and may result in numerous adverse side effects for patients. To address these challenges, which aim to enhance the immune system's response to target tumors, have been developed as promising cancer therapies [1, 2]. Preclinical data and staged clinical trials have demonstrated that immunotherapy has the potential not only to

†the corresponding author.
Email address: n.bajja@edu.umi.ac.ma. (N. Bajja), d.seghir@umi.ac.ma. (D. Seghir)
[1]Department of Mathematics,Faculty of Sciences, Moulay Ismail University, Zitoune, 11201 Meknes, Morocco.
[2]Laboratory of Mathematics and their Interactions, Faculty of Sciences, Moulay Ismail University, Zitoune, 11201 Meknes, Morocco.
*The author was supported by the National center for Scientific and Technical Research (CNRST) under the PhD-ASsociate Scholarship Program-PASS.

eradicate tumor cells but also to enhance the effectiveness of chemotherapy and radiotherapy [3–5].

Mathematical modeling has broad applications in ecological, epidemiological, and tumor fields [6–12, 17, 19, 38]. Samanta and co-authors established a system of impulsive ordinary differential equations to model the interactions between tumor, normal, and immune cells, incorporating the effects of periodically pulsed chemotherapy [15]. Their study identified the necessary parametric conditions to prevent relapse after tumor or metastasis removal. Additionally, the research explored the effects of resistant tumor sub-populations and proposed strategies to prevent recurrence. The authors developed and analyzed a nonlinear mathematical model for tumor-immune interactions with drug treatment [16]. They formulated an optimal control problem to reduce cancer cells, enhance the immune response, and minimize drug side effects. They conducted sensitivity and cost-effectiveness analyses, and the results confirmed the effectiveness of combination therapy in reducing the tumor. A bifurcation analysis of a tumor-immune model subjected to periodically pulsed immunotherapy revealed that when the immune response is weak, increasing its intensity can yield positive therapeutic effects [17]. However, if the immune response intensity exceeds a certain threshold, it may lead to treatment failure. Tang utilized a pulsed differential system to model the interactions between pulsed chemotherapy and immunotherapy, demonstrating the substantial benefits of combining low-dose chemotherapy with high-dose immunotherapy in treating solid tumors [18]. This study highlighted the hormetic effects of chemotherapy and immune response curves, affirming the synergistic advantages of this combined therapeutic approach in reducing side effects and enhancing tumor suppression. Similarly, Sharma developed a system of ordinary differential equations to examine the interactions among tumor cells, cytotoxic T lymphocytes (CTLs), and helper T-cells within the tumor-immune system under chemotherapy [19], further analyzing the dynamic behavior of this system.

Li and Cheng emphasized that in natural biochemical systems, the enzymatic activity of proteins is highly sensitive to environmental factors such as temperature, nutrition, oxygen, and pH levels [20]. Consequently, it is imperative to consider the effects of stochastic noise on cellular evolution.d'Onofrio argued that the complex interactions between tumor cells and immune effectors necessitate the inclusion of noise in deterministic models of the tumor-immune system [21]. The influence of noise on cancer dynamics has been extensively studied, including its role in stochastic fluctuations leading to extinction and recurrence, stochastic resonance [22], and the extinction and persistence of tumor cells [25, 28, 35]. These findings underscore the complexity of tumor behavior and the necessity of integrating stochastic elements into mathematical models to better reflect biological realities.

Yang developed a stochastic tumor-immune model under the influence of immunotherapy and chemotherapy [24], deriving sufficient conditions for the extinction and persistence of both tumor cells and effector cells. However, this model did not account for the role of helper T-cells, which are crucial for stimulating effector cells. In contrast, Wang analyzed a stochastic tumor-immune system using a system of stochastic differential equations [23]. Wang also derived sufficient conditions for the extinction and persistence of tumor cells. This study extends previous models by incorporating pulse treatment, which combines chemotherapy and immunotherapy, and by examining the effects of random disturbances in the internal environment on tumor cells and two types of immune cells. The mathematical modeling of com-

prehensive cancer therapies, considering fluctuations in homeostasis, coupled with research on the extinction and persistence of cells, provides significant insights for the development of specific treatment strategies, including treatment cycles and intensity. These findings are expected to contribute to the optimization of therapeutic approaches in oncology.

The paper is organized as follows: In Section (2) we describe the construction of the stochastic model and present important definitions and lemmas about impulsive stochastic differential equations (ISDEs). In Section (3), we discuss the global positive solution of the system. Section (4) focuses on the extinction and persistence of tumor cells, hunting T-cells, and helper T-cells. Section (5) presents numerical investigations. Finally, Section (6) provides general conclusions.

2. Mathematical model

We start by defining the mathematical model and highlighting its key components.

2.1. Model formation

Wang et al. [23] investigated the following stochastic prey-predator like tumor-immune system, incorporating interactions between tumor cells, hunting T-cells and helper T-cells:

$$\begin{cases} dT(t) = [\alpha_1 T(1 - \frac{T}{K_1}) - \beta_1 TH]dt + \sigma_1 T dB_1(t), \\ dH(t) = [\gamma HR - \delta_1 H - \beta_2 HT]\, dt + \sigma_2 H dB_2(t), \\ dR(t) = [\alpha_2 R(1 - \frac{R}{K_2}) - \gamma RH - \delta_2 R + \frac{kTR}{T+\eta}]dt + \sigma_3 R dB_3(t), \end{cases} \tag{2.1}$$

with initial conditions $T(0) > 0$, $H(0) > 0$, $R(0) > 0$, where $T(t)$, $H(t)$ and $R(t)$ denote the populations of tumor cells, hunting T-cells and helper T-cells, respectively. α_i $(i = 1, 2)$ represent the intrinsic growth rates of tumor cells and helper T-cells, respectively. K_i $(i = 1, 2)$ represent the maximum carrying capacity of the environment for tumor cells and helper T-cells, respectively. β_i $(i = 1, 2)$ denote the rate at which hunting T-cells kill tumor cells and the rate at which tumor cells reduce hunting T-cells, respectively. Additionally, δ_i $(i = 1, 2)$ indicate the death rates of hunting T-cells and helper T-cells, respectively. γ represents the activation rate of helper T-cells to hunting T-cells. The parameter k represents the proliferation rate of helper T-cells, while η indicates the half-saturation coefficient of proliferation term. $B_i(t)$ $(i = 1, 2, 3)$ are independent one-dimensional standard Brownian motions defined on a given complete filtered probability space $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t\geq 0}, \mathbb{P})$ with a filtration $\{\mathcal{F}_t\}_{t\geq 0}$ satisfying the usual condition (i.e, it is right continuous and $\mathcal{F}_0$ contains all $\mathbb{P}$-null sets). σ_i^2 $(i = 1, 2, 3)$ represent the intensities of the corresponding white noise terms.

Experimental and clinical studies have demonstrated that pulsed immunotherapy, when combined with chemotherapy, is more frequently utilized for cancer treatment compared to monotherapy [13, 14]. Motivated by this, we propose a novel mathematical model based on the system (2.1), formulated as a system of impulsive stochastic differential equations (ISDEs), to describe the dynamics of tumor evolution under the combined effects of immunotherapy and chemotherapy. This

model is expressed as follows:

$$\begin{cases} dT(t) = [\alpha_1 T(1-\frac{T}{K_1}) - \beta_1 TH - d_1 DT]dt + \sigma_1 T dB_1(t), & t \neq \tau_n, \\ dH(t) = [\gamma HR - \delta_1 H - \beta_2 HT - d_2 DH]\,dt + \sigma_2 H dB_2(t), & t \neq \tau_n, \\ dR(t) = [\alpha_2 R(1-\frac{R}{K_2}) - \gamma RH - \delta_2 R - d_3 DR + \frac{kTR}{T+\eta}]dt + \sigma_3 R dB_3(t), & t \neq \tau_n, \\ dD(t) = -\mu D dt, & t \neq \tau_n, \\ T(\tau_n^+) = T(\tau_n), \quad R(\tau_n^+) = R(\tau_n), & t = \tau_n, \\ H(\tau_n^+) = (1+R_n)H(\tau_n), & t = \tau_n, \\ D(\tau_n^+) = D(\tau_n) + u, & t = \tau_n, \end{cases} \tag{2.2}$$

with initial conditions $T(0) > 0$, $H(0) > 0$, $R(0) > 0$, $D(0) > 0$, where $D(t)$ is the concentration of a chemotherapeutic drug at time t, μ is its degradation rate and u is the dosage of chemotherapeutic administered at the impulsive points, denoted by the series τ_n. Specifically, $\tau_n = n\tau$ $(n \in \mathbb{N})$, where τ is a time interval between two pulse therapy. Additionally, R_n represents the recruitment rate of the hunting T-cells in the n-th immunotherapy.

The subsequent subsection presents specific notations to aid expression and provides definitions and lemmas to analyze the properties of the model's solution.

2.2. Preliminaries

In this subsection, we present several definitions, notations, and preliminary lemmas that are essential for the clarification and development of our main results.

We will now present some fundamental properties of the dynamics of chemotherapeutic drug.

$$\begin{cases} dD(t) = -\mu D dt, & t \neq \tau_n, \\ D(\tau_n^+) = D(\tau_n) + u, & t = \tau_n. \end{cases} \tag{2.3}$$

Through a detailed calculation, we derive the explicit form of the τ-periodic solution $D^\tau(t)$ to the subsystem (2.3), which is given by

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

where $t \in (\tau_n, \tau_{n+1}]$, and the initial condition is specified as $D^\tau(\tau_n^+) = \frac{u}{1-\exp\{-\mu\tau\}}$.

Lemma 2.1 ([24]). *$D^\tau(t)$ is a unique positive τ-periodic solution of system (2.3) which satisfies $\lim\limits_{t\to+\infty} D(t) - D^\tau(t) = 0$ and for any $\epsilon > 0$, we have*

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

To simplify the expression, we give the following notations:

$$\langle T(t)\rangle = \frac{1}{t}\int_0^t T(s)ds, \quad \langle T(t)\rangle^* = \limsup_{t\to+\infty} \frac{1}{t}\int_0^t T(s)ds,$$
$$\langle T(t)\rangle_* = \liminf_{t\to+\infty} \frac{1}{t}\int_0^t T(s)ds, \quad \kappa_1 = \alpha_1 - \frac{d_1 u}{\mu\tau} - \frac{\sigma_1^2}{2},$$

$$\kappa_2 = \limsup_{t\to+\infty} \frac{1}{t} \sum_{0<\tau_n<t} \ln(1+R_n) - \delta_1 - \frac{d_2 u}{\mu\tau} - \frac{\sigma_2^2}{2},$$

$$\kappa_3 = \alpha_2 - \delta_2 - \frac{d_3 u}{\mu\tau} - \frac{\sigma_3^2}{2} + k, \quad \mathbb{R}^3_+ = \{(x,y,z) : x>0, y>0, z>0\}.$$

Definition 2.1 ([25, 26]). $X(t) = (T(t), H(t), R(t))^T$, $t \in \mathbb{R}_+ := [0, +\infty)$, is a solution of ISDE (2.2) with initial condition $X(0) \geq 0$, if the following holds:

1. $X(t)$ is absolutely continuous on $(0, \tau]$ and $(\tau_n, \tau_{n+1}]$, $n \in \mathbb{N}$.
2. For any pulsed point τ_n, $X(\tau_n^+) = \lim_{t\to\tau_n^+} X(t)$, $X(\tau_n^-) = \lim_{t\to\tau_n^-} X(t)$ exist and $X(\tau_n^-) = X(\tau_n)$ a.s.
3. $X(t)$ follows system (2.2) for every $t \in \mathbb{R}_+ - \{\tau_n\}$ and satisfies the pulse condition at pulsed point τ_n.

Definition 2.2 ([28,29]). For any solutions $(x_1(t), x_2(t), x_3(t))$ of the system (2.2),

1. If $\lim\limits_{t\to+\infty} x_i(t) = 0$ a.s, then $x_i(t)$ is said to go to extinction, $i = 1, 2, 3$.
2. If $\lim\limits_{t\to+\infty} \langle x_i(t)\rangle = 0$ a.s, then $x_i(t)$ is said to be non-persistent in the mean, $i = 1, 2, 3$.
3. If $\langle x_i(t)\rangle^* > 0$ a.s, then $x_i(t)$ is said to be weak persistent in the mean, $i = 1, 2, 3$.
4. For each $\epsilon \in (0, 1)$, there are two positive constants η_1 and η_2 such that

$$\liminf_{t\to+\infty} \mathbb{P}\{x_i(t) \geq \eta_1\} \geq 1-\epsilon, \quad \liminf_{t\to+\infty} \mathbb{P}\{x_i(t) \leq \eta_2\} \geq 1-\epsilon,$$

then $x_i(t)$ is called stochastically persistent, $i = 1, 2, 3$.

Remark 2.1. In biological terms, extinction, weak persistence, and stochastic persistence correspond to the three phases of cancer immunoediting: the elimination phase, the equilibrium phase, and the escape phase, respectively. Cancer immunoediting is a dynamic process that describes the interaction between tumor cells and the immune system, consisting of these three distinct phases. While extinction implies non-persistence on average, the converse is not necessarily true.

Definition 2.3 ([30]). Assume $X_1(t) = (T_1(t), H_1(t), R_1(t))$ and $X_2(t) = (T_2(t), H_2(t), R_2(t))$ are two any solutions of ISDE (2.2) with $X_1(0) \geq 0$, $X_2(0) \geq 0$, if $\lim_{t\to+\infty} |T_1(t)-T_2(t)| = 0$ a.s, $\lim_{t\to+\infty} |H_1(t)-H_2(t)| = 0$ a.s and $\lim_{t\to+\infty} |R_1(t)-R_2(t)| = 0$ a.s. Then ISDEs (2.2) is called globally attractive.

Lemma 2.2 ([31]). *Let* $\zeta \in C(\Omega \times \mathbb{R}_+, (0, +\infty))$.

1. *If there are constants* $\xi \geq 0$, $\xi_0 > 0$ *and* $t_1 > 0$ *such that* ζ *satisfies*

$$\ln\zeta(t) \leq \xi t - \xi_0 \int_0^t \zeta(s)ds + \sum_{i=1}^n \sigma_i B_i(t),$$

for any $t \geq t_1$, σ_i $(i = 1, 2, \ldots, n)$ *are constants, then* $\langle\zeta(t)\rangle^* \leq \frac{\xi}{\xi_0}$ *with probability one.*

2. If there are constants $\xi \geq 0$, $\xi_0 > 0$ and $t_2 > 0$ such that ζ satisfies

$$\ln \zeta(t) \geq \xi t - \xi_0 \int_0^t \zeta(s)ds + \sum_{i=1}^{n} \sigma_i B_i(t),$$

for any $t \geq t_2$, then $\langle \zeta(t) \rangle^* \geq \frac{\xi}{\xi_0}$ with probability one.

Lemma 2.3 ([27,35]). *For system (2.2), we have identified the following properties:*

$$\limsup_{t\to+\infty} \frac{\ln T(t)}{t} \leq 0 \quad a.s, \quad \limsup_{t\to+\infty} \frac{\ln H(t)}{t} \leq 0 \quad a.s, \quad \limsup_{t\to+\infty} \frac{\ln R(t)}{t} \leq 0 \quad a.s.$$

Next, we shall examine the properties of the solution of model (2.2).

3. Global positive solution

In this section, it is imperative to assert that the solutions of system (2.2) must be positive, as this condition is crucial for the ultimate analysis presented in this paper. To analyze the global dynamics of system (2.2), it suffices to focus on the following equivalent subsystem (3.1), as the dynamics of the chemotherapy drugs have already been addressed.

$$\begin{cases} dT(t) = [\alpha_1 T(1 - \frac{T}{K_1}) - \beta_1 TH - d_1(t)T]dt + \sigma_1 T dB_1(t), & t \neq \tau_n, \\ dH(t) = [\gamma HR - \delta_1 H - \beta_2 HT - d_2(t)H]\, dt + \sigma_2 H dB_2(t), & t \neq \tau_n, \\ dR(t) = [\alpha_2 R(1 - \frac{R}{K_2}) - \gamma RH - \delta_2 R - d_3(t)R + \frac{kTR}{T+\eta}]dt + \sigma_3 R dB_3(t), & t \neq \tau_n, \\ T(\tau_n^+) = T(\tau_n), \quad R(\tau_n^+) = R(\tau_n), & t = \tau_n, \\ H(\tau_n^+) = (1 + R_n)H(\tau_n), & t = \tau_n, \end{cases} \tag{3.1}$$

with $d_i(t) = d_i D(t)$ for $i = 1, 2, 3$.

Theorem 3.1. *System (3.1) has a global unique positive solution $X(t) = (T(t), H(t), R(t))$ for any initial value $(T(0), H(0), R(0)) \in \mathbb{R}^3_+$ and the solution $X(t)$ will remain in $\mathbb{R}^3_+$ a.s.*

Proof. Consider the following stochastic system without impulse:

$$\begin{cases} dx(t) = [\alpha_1 x(1 - \frac{x}{K_1}) - \beta_1 \prod_{0<\tau_n<t}(1 + R_n)xy - d_1(t)x]dt + \sigma_1 x dB_1(t), \\ dy(t) = [\gamma yz - \delta_1 y - \beta_2 xy - d_2(t)y]\, dt + \sigma_2 y dB_2(t), \\ dz(t) = [\alpha_2 z(1 - \frac{z}{K_2}) - \gamma \prod_{0<\tau_n<t}(1 + R_n)yz - \delta_2 z - d_3(t)z + \frac{kxz}{x+\eta}]dt + \sigma_3 z dB_3(t), \end{cases} \tag{3.2}$$

where the initial value is defined as $(x(0), y(0), z(0)) = (T(0), H(0), R(0))$. By using the same methods as shown in [23], we can prove that the SDEs (3.2) has a positive solution $(x(t), y(t), z(t))$ which is globally unique. Let $(T(t), H(t), R(t)) = (x(t), \prod_{0<\tau_n<t}(1 + R_n)y(t), z(t))$, then the absolute continuity of $(x(t), y(t), z(t))$) leads to the absolutely continuity of $(T(t), H(t), R(t))$ for $t \in (\tau_n, \tau_{n+1}] \subset [0, +\infty)$, $n \in \mathbb{N}$.

For $t \neq \tau_n$, Itô's formula is applied to $(T(t), H(t), R(t))$, yielding

$$dT(t) = dx(t), \qquad dR(t) = dz(t),$$
$$dH(t) = \prod_{0<\tau_n<t} (1 + R_n)dy(t)$$

$$= \prod_{0<\tau_n<t} (1+R_n)[\gamma yz - \delta_1 y - \beta_2 xy - d_2(t)y]dt + \sigma_2 \prod_{0<\tau_n<t} (1+R_n) y dB_2(t)$$
$$= [\gamma HR - \delta_1 H - \beta_2 HT - d_2(t)H]\, dt + \sigma_2 H dB_2(t).$$

For $t = \tau_n$, we get

$$T(\tau_n^+) = T(\tau_n), \qquad R(\tau_n^+) = R(\tau_n),$$
$$H(\tau_n^+) = \lim_{t\to\tau_n^+} \prod_{0<\tau_i<t} (1+R_i)y(t) = \prod_{0<\tau_i\le\tau_n} (1+R_i)y(\tau_n)$$
$$= (1+R_n) \prod_{0<\tau_i<\tau_n} (1+R_i)y(\tau_n) = (1+R_n)H(\tau_n).$$

Moreover,

$$T(\tau_n^-) = T(\tau_n), \qquad R(\tau_n^-) = R(\tau_n),$$
$$H(\tau_n^-) = \lim_{t\to\tau_n^-} \prod_{0<\tau_i<t} (1+R_i)y(t) = \prod_{0<\tau_i<\tau_n} (1+R_i)y(\tau_n)$$
$$= H(\tau_n).$$

Therefore, there is a globally unique positive solution of system (3.1). □

Theorem 3.2. *If* $\min\{\frac{\alpha_1}{K_1} + \beta_2 - \frac{k}{\eta}, \frac{\alpha_2}{K_2} - \gamma\} > 0$, *then the solution of system* (3.1) *is globally attractive.*

Proof. Let $(T_1(t), H_1(t), R_1(t))$ and $(T_2(t), H_2(t), R_2(t))$ be two arbitrary solutions of system (3.1) with initial conditions $T(0) > 0$, $H(0)$ and $R(0) > 0$. Define

$$V(t) = |\ln T_1(t) - \ln T_2(t)| + |\ln H_1(t) - \ln H_2(t)| + |\ln R_1(t) - \ln R_2(t)|.$$

Then $V(t)$ is continuous and positive on $t \ge 0$. A calculation of the right differential $d^+V(t)$ of $V(t)$ and making use of Itô's formula for all $t \ne \tau_n$, we obtain

$$\begin{aligned}
&d^+V(t)\\
=&sign(T_1(t)-T_2(t))d(\ln T_1(t)-\ln T_2(t))+sign(H_1(t)-H_2(t))d(\ln H_1(t)-\ln H_2(t))\\
&+ sign(R_1(t)-R_2(t))d(\ln R_1(t)-\ln R_2(t))\\
=&sign(T_1(t)-T_2(t))[-\frac{\alpha_1}{K_1}(T_1(t)-T_2(t)) - \beta_1(H_1(t)-H_2(t))]dt\\
&+ sign(H_1(t)-H_2(t))[\gamma(R_1(t)-R_2(t)) - \beta_2(T_1(t)-T_2(t))]dt\\
&+ sign(R_1(t)-R_2(t))[-\frac{\alpha_2}{K_2}(R_1(t)-R_2(t)) - \gamma(H_1(t)-H_2(t))\\
&+ \frac{k\eta(T_1(t)-T_2(t))}{(T_1(t)+\eta)(T_2(t)+\eta)}]dt\\
\le&[-(\frac{\alpha_1}{K_1}+\beta_2-\frac{k}{\eta})|T_1(t)-T_2(t)| - (\beta_1+\gamma)|H_1(t)-H_2(t)|\\
&-(\frac{\alpha_2}{K_2}-\gamma)|R_1(t)-R_2(t)|]dt\\
\le&-\rho[|T_1(t)-T_2(t)| + |H_1(t)-H_2(t)| + |R_1(t)-R_2(t)|]dt = -\rho\mathbb{V}dt,
\end{aligned} \tag{3.3}$$

where $\rho = \min\{\frac{\alpha_1}{K_1} + \beta_2 - \frac{k}{\eta}, \beta_1 + \gamma, \frac{\alpha_2}{K_2} - \gamma\}$. Moreover, for $t = \tau_n$ we obtain

$$\begin{aligned}
V(\tau_n^+) =& |\ln T_1(\tau_n^+) - \ln T_2(\tau_n^+)| + |\ln H_1(\tau_n^+) - \ln H_2(\tau_n^+)| + |\ln R_1(\tau_n^+) - \ln R_2(\tau_n^+)| \\
=& |\ln T_1(\tau_n) - \ln T_2(\tau_n)| + |\ln(1+R_n)H_1(\tau_n) - \ln(1+R_n)H_2(\tau_n)| \\
&+ |\ln R_1(\tau_n) - \ln R_2(\tau_n)| \\
=& |\ln T_1(\tau_n) - \ln T_2(\tau_n)| + |\ln H_1(\tau_n) - \ln H_2(\tau_n)| + |\ln R_1(\tau_n) - \ln R_2(\tau_n)| \\
=& V(\tau_n).
\end{aligned}$$

Integrating both sides of (3.3) on $[0, t]$ and taking expectation yields

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

Consequently,

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

Moreover, $V(t) \geq 0$ always holds for all t, which leads to $\lim_{t\to+\infty} \mathbb{V}(t) = 0$. Consequently, $\lim_{t\to+\infty} |T_1(t) - T_2(t)| = 0$ a.s, $\lim_{t\to+\infty} |H_1(t) - H_2(t)| = 0$ a.s and $\lim_{t\to+\infty} |R_1(t) - R_2(t)| = 0$ a.s. Therefore, according to Definition (2.3), system (3.1) is globally attractive. □

Theorem 3.3. *For any $0 \leq s < t$, if $\prod_{s\leq\tau_n<t}(1+R_n) \leq M_1$ $(M_1 > 0)$ and if $1 - \delta_1 - d_2\tau \exp\{-\mu\tau\}/(1 - \exp\{-\mu\tau\}) \leq 0$, then the solution $(T(t), H(t), R(t))$ of system* (3.1) *satisfies the following inequality*

$$\lim_{t\to+\infty} \mathbb{E}[T(t) + H(t) + R(t)] \leq M_1 M_2,$$

where $M_2 = \frac{K_1(\alpha_1+1)^2}{4\alpha_1} + \frac{K_2(1+\alpha_2+k)^2}{4\alpha_2}$.

Proof. Applying Itô's formula to $V(t) = T(t) + H(t) + R(t)$, for $t \in (\tau_n, \tau_{n+1}]$, we get

$$dV(t) = LV(t)dt + \sigma_1 T dB_1(t) + \sigma_2 H dB_2(t) + \sigma_3 R dB_3(t),$$

with

$$\begin{aligned}
LV =& T[\alpha_1(1 - \frac{T}{K_1}) - \beta_1 H - d_1(t)] + H[\gamma R - \delta_1 - \beta_2 T - d_2(t)] \\
&+ R[\alpha_2(1 - \frac{R}{K_2}) - \gamma H - \delta_2 - d_3(t) + \frac{kT}{T+\eta}] \\
\leq& (-\frac{\alpha_1}{K_1}T^2 + \alpha_1 T) - H(\delta_1 + d_2(t)) + (-\frac{\alpha_2}{K_2}R^2 + (\alpha_2 + k)H).
\end{aligned}$$

Furthermore, by applying Itô's formula to $e^t V(t)$, we obtain

$$d(e^t V(t)) = [e^t V(t) + e^t LV(t)]dt + e^t[\sigma_1 T dB_1(t) + \sigma_2 H dB_2(t) + \sigma_3 R dB_3(t)],$$

integrating the above equation on $(\tau_n, t]$ and taking the expectation yields

$$\mathbb{E}[e^t V(t)] = e^{\tau_n} V(\tau_n^+) + \int_{\tau_n}^t e^s [V(s) + LV(s)]ds. \tag{3.4}$$

In the other words,

$$\begin{aligned} V(t)+LV(t) \leq & (-\frac{\alpha_1}{K_1}T^2+(\alpha_1+1)T)+H(1-\delta_1-d_2\frac{u\exp\{-\mu\tau\}}{1-\exp\{-\mu\tau\}}) \\ & +(-\frac{\alpha_2}{K_2}R^2+(\alpha_2+k+1)H) \\ \leq & \frac{K_1(\alpha_1+1)^2}{4\alpha_1}+\frac{K_2(1+\alpha_2+k)^2}{4\alpha_2}=:M_2. \end{aligned} \tag{3.5}$$

Therefore, from equations (3.4) and (3.5) we get

$$\mathbb{E}[e^tV(t)] \leq e^{\tau_n}(\mathbb{E}V(\tau_n^+)-M_2)+M_2e^t.$$

An easy calculation yields

$$d\mathbb{E}V(t) \leq (M_2-\mathbb{E}V(t))dt. \tag{3.6}$$

When $t=\tau_n$, we have

$$\begin{aligned} \mathbb{E}V(\tau_n^+) &= \mathbb{E}[T(\tau_n^+)]+\mathbb{E}[H(\tau_n^+)]+\mathbb{E}[R(\tau_n^+)] \\ &= \mathbb{E}[T(\tau_n)]+(1+R_n)\mathbb{E}[H(\tau_n)]+\mathbb{E}[R(\tau_n)] \\ &\leq (1+R_n)\mathbb{E}V(\tau_n). \end{aligned} \tag{3.7}$$

Therefore, from equations (3.6) and (3.7) we can write the following system

$$\begin{cases} d\mathbb{E}V(t) \leq (M_2-\mathbb{E}V(t))dt, & t\neq\tau_n, \\ \mathbb{E}V(\tau_n^+) \leq (1+R_n)\mathbb{E}V(\tau_n), & t=\tau_n. \end{cases}$$

Based on [33], the solution of system

$$\begin{cases} d\phi(t)=(M_2-\phi(t))dt, & t\neq\tau_n, \\ \phi(\tau_n^+)=(1+R_n)\phi(\tau_n), & t=\tau_n, \end{cases}$$

is given by

$$\phi(t)=\phi(0)m(0,t)+M_2\int_0^t m(s,t)ds,$$

with $m(s,t)=\prod_{s\leq\tau_n<t}(1+R_n)e^{-(t-s)}$. Then we have $\lim_{t\to+\infty}\phi(t) \leq M_1M_2$. According to the impulsive differential equations theorem [34], it follows that

$$\lim_{t\to+\infty}\mathbb{E}V(t) \leq \lim_{t\to+\infty}\phi(t) \leq M_1M_2.$$

□

Remark 3.1. In Theorem (3.3), the condition $\prod_{s\leq\tau_n<t}(1+R_n) \leq M_1$ represents the administration of pulse immunotherapy at a specific intensity. Furthermore, the condition $1-\delta_1-d_2\tau\exp\{-\mu\tau\}/(1-\exp\{-\mu\tau\}) \leq 0$ quantifies the efficacy of the chemotherapy. From a biological perspective, these conditions indicate that, with an appropriate combination of immunotherapy and chemotherapy, tumor growth can be effectively controlled and will not proceed unchecked.

The following section derives the sufficient conditions for the extinction and persistence of the model (3.1).

4. The extinction and persistence of system (3.1)

Since we have examined the uniqueness, global attractivity and boundedness of the solutions for stochastic model (3.1), the upcoming section will concentrate on the influence of key parameters including the impulsive period, doses of chemotherapy drugs, immune strength and stochastic fluctuations on the extinction and long-term survival of tumor cells, hunting T-cells and helper T-cells.

For system (3.2), we define a Lyapunov function $\ln x(t)$. Making use the Itô's formula we get

$$\begin{aligned} d\ln x(t) &= (\alpha_1 - \frac{\alpha_1}{K_1}x - \beta_1 \prod_{0<\tau_n<t}(1+R_n)y - d_1(t) - \frac{\sigma_1^2}{2})dt + \sigma_1 dB_1(t) \\ &= (\alpha_1 - \frac{\alpha_1}{K_1}T(t) - \beta_1 H(t) - d_1(t) - \frac{\sigma_1^2}{2})dt + \sigma_1 dB_1(t). \end{aligned}$$

Integrating from 0 to t and noticing that $T(t) = x(t)$ we obtain the following results.

Lemma 4.1. *Denote $M_i(t) = \int_0^t \sigma_i dB_i(s)$ $(i = 1, 2, 3)$. Then*

$$\ln\frac{T(t)}{T(0)} = (\alpha_1 - \frac{\sigma_1^2}{2})t - \int_0^t d_1(s)ds - \frac{\alpha_1}{K_1}\int_0^t T(s)ds - \beta_1\int_0^t H(s)ds + M_1(t), \quad (4.1)$$

and similarly, we get

$$\begin{aligned} \ln\frac{H(t)}{H(0)} =& \sum_{0<\tau_n<t}\ln(1+R_n) - (\delta_1 + \frac{\sigma_2^2}{2})t - \int_0^t d_2(s)ds - \beta_2\int_0^t T(s)ds \\ &+ \gamma\int_0^t R(s)ds + M_2(t), \end{aligned} \quad (4.2)$$

$$\begin{aligned} \ln\frac{R(t)}{R(0)} =& (\alpha_2 - \delta_2 - \frac{\sigma_3^2}{2})t - \int_0^t d_3(s)ds - \frac{\alpha_2}{K_2}\int_0^t R(s)ds - \gamma\int_0^t H(s)ds \\ &+ \int_0^t \frac{kT(s)}{T(s)+\eta}ds + M_3(t). \end{aligned} \quad (4.3)$$

Theorem 4.1. *For the tumor cells $T(t)$ and helper T-cells $R(t)$, it holds that*

1. *If $\kappa_1 < 0$, then the tumor cells will become extinct; if $\kappa_1 = 0$, then the tumor cells are non-persistent in the mean.*
2. *If $\kappa_3 < 0$, then the helper T-cells will become extinct; if $\kappa_3 = 0$, then the helper T-cells are non-persistent in the mean.*

Proof. Based on (4.1), we have the following inequality

$$\frac{1}{t}\ln\frac{T(t)}{T(0)} \le \alpha_1 - \frac{\sigma_1^2}{2} - \frac{d_1 u}{\mu\tau} + d_1\epsilon + \frac{M_1(t)}{t}.$$

By applying the strong law of large numbers for local martingales [32], it follows that

$$\limsup_{t\to+\infty}\frac{M_i(t)}{t} = 0 \quad \text{a.s,} \quad i = 1, 2, 3.$$

Consequently, for ϵ small enough, we obtain

$$\limsup_{t\to+\infty}\frac{1}{t}\ln T(t)\le\alpha_1-\frac{\sigma_1^2}{2}-\frac{d_1u}{\mu\tau}=\kappa_1<0.\qquad\text{a.s,}$$

thus $\lim_{t\to+\infty}T(t)=0$ almost surely.

For any $\epsilon>0$, there exists a $t_1>0$ such that for all $t\ge t_1$ we have $\frac{1}{t}\int_0^t d_1(s)ds>\frac{d_1u}{\mu\tau}-\frac{\epsilon}{2}$, $\frac{M_1(t)}{t}\le\frac{\epsilon}{2}$. In view of equation (4.1)

$$\frac{1}{t}\ln\frac{T(t)}{T(0)}=(\alpha_1-\frac{\sigma_1^2}{2})-\langle d_1(t)\rangle-\frac{\alpha_1}{K_1}\langle T(t)\rangle-\beta_1\langle H(t)\rangle+\frac{M_1(t)}{t}\tag{4.4}$$

$$\le(\alpha_1-\frac{d_1u}{\mu\tau}-\frac{\sigma_1^2}{2})+\epsilon-\frac{\alpha_1}{K_1}\langle T(t)\rangle.\tag{4.5}$$

According to Lemma (2.2) and $\kappa_1\ge0$, for a sufficiently small ϵ, we get

$$\langle T(t)\rangle^*\le\frac{K_1}{\alpha_1}(\alpha_1-\frac{d_1u}{\mu\tau}-\frac{\sigma_1^2}{2})=\frac{K_1}{\alpha_1}\kappa_1\qquad\text{a.s.}\tag{4.6}$$

When $\kappa_1=0$, we have $\langle T(t)\rangle^*\le0$ a.s. It is always true that $T(t)\ge0$, which leads to $\langle T(t)\rangle_*\ge0$ a.s. Therefore $\lim_{t\to+\infty}\langle T(t)\rangle=0$ a.s.

Similarly, the extinction and non-persistence of the helper T-cells $R(t)$ under the conditions can be proved. □

Theorem 4.2. *1. If one of the following conditions is satisfied:*

- $\kappa_3\ge0$ *and* $\kappa_2+\frac{\gamma K_2}{\alpha_2}\kappa_3<0$,
- $\kappa_3<0$ *and* $\kappa_2<0$,

then the hunting T-cells $H(t)$ will become extinct.

2. If $\kappa_1=0$, then the hunting T-cells $H(t)$ are non-persistent in the mean.

Proof.

1. Based on (4.3), we have the following inequality

$$\ln\frac{R(t)}{R(0)}\le(\alpha_2+k-\delta_2-\frac{\sigma_3^2}{2}-\frac{d_3u}{\mu\tau}+d_3\epsilon)t-\frac{\alpha_2}{K_2}\int_0^tR(s)ds+M_3(t),$$

when $\kappa_3\ge0$, from Lemma (2.2) we conclude that

$$\langle R(t)\rangle^*\le\frac{K_2}{\alpha_2}\kappa_3.$$

From equation (4.2), we get

$$\ln\frac{H(t)}{H(0)}\le\sum_{0<\tau_n<t}\ln(1+R_n)-(\delta_1+\frac{\sigma_2^2}{2}+\frac{d_2u}{\mu\tau})t+d_2\epsilon t+\gamma\int_0^tR(s)ds+M_2(t).\tag{4.7}$$

Dividing both sides by t and taking the superior limit, we obtain

$$\limsup_{t\to+\infty}\frac{\ln H(t)}{t}\le\kappa_2+\frac{\gamma K_2}{\alpha_2}\kappa_3<0\qquad\text{a.s.}$$

Therefore $\lim_{t\to+\infty} H(t) = 0$ almost surely.
When $\kappa_3 < 0$, Theorem (4.1) shows that the helper T-cells become extinct. While extinction implies non-persistent in the mean, then for any $\epsilon > 0$ we have $\langle R(t)\rangle^* \leq \epsilon$. From inequality (4.7), we get

$$\frac{1}{t}\ln\frac{H(t)}{H(0)} \leq \frac{1}{t}\sum_{0<\tau_n<t}\ln(1+R_n) - \delta_1 - \frac{\sigma_2^2}{2} - \frac{d_2 u}{\mu\tau} + (d_2+\gamma)\epsilon + \frac{M_2(t)}{t}.$$

Taking the superior limit both side gives

$$\limsup_{t\to+\infty}\frac{\ln H(t)}{t} \leq \kappa_2 < 0 \qquad \text{a.s,}$$

thus $\lim_{t\to+\infty} H(t) = 0$ almost surely.

2. For any $\epsilon > 0$, there exists a $t_2 > 0$ such that for all $t \geq t_2$ we have $\frac{1}{t}\int_0^t d_1(s)ds > \frac{d_1 u}{\mu\tau} - \frac{\epsilon}{2}$, $\frac{M_1(t)}{t} \leq \frac{\epsilon}{2}$. In view of equation (4.4)

$$\begin{aligned}\beta_1\langle H(t)\rangle &= -\frac{1}{t}\ln\frac{T(t)}{T(0)} + \alpha_1 - \frac{\sigma_1^2}{2} - \langle d_1(t)\rangle - \frac{\alpha_1}{K_1}\langle T(t)\rangle + \frac{M_1(t)}{t}\\ &\leq \alpha_1 - \frac{d_1 u}{\mu\tau} - \frac{\sigma_1^2}{2} + \epsilon.\end{aligned}$$

Calculating the superior limit of the above equation yields $\langle H(t)\rangle^* \leq \kappa_1 = 0$ a.s. Since $H(t) \geq 0$ for all $t \geq 0$ a.s, then $\langle H(t)\rangle_* \geq 0$ a.s. Therefore $\lim_{t\to+\infty}\langle H(t)\rangle = 0$ a.s.

□

Theorem 4.3. *1. Assume $\kappa_1 > 0$. If one of the following conditions is satisfied:*

- *$\kappa_3 \geq 0$ and $\kappa_2 + \frac{\gamma K_2}{\alpha_2}\kappa_3 < 0$,*
- *$\kappa_2 < 0$ and $\kappa_3 < 0$,*

then the tumor cells $T(t)$ become weakly persistent in the mean.

2. If $\kappa_3 > k$ and $\kappa_2 + \frac{\gamma K_2}{\alpha_2}\kappa_3 < 0$, then the helper T-cells $R(t)$ become weakly persistent in the mean.

Proof.

1. Theorem (4.2) shows that the hunting T-cells $H(t)$ become extinct, then for any $\epsilon > 0$, we obtain $\langle H(t)\rangle^* \leq \epsilon$ almost surely.
From equation (4.1), we get

$$\limsup_{t\to+\infty}\frac{\ln T(t)}{t} \geq \kappa_1 - d_1\epsilon - \frac{\alpha_1}{K_1}\langle T(t)\rangle_* - \beta_1\epsilon \quad \text{a.s.}$$

According to Lemma (2.3), for sufficiently small values of ϵ, one obtains

$$\langle T(t)\rangle^* \geq \frac{K_1}{\alpha_1}\kappa_1 > 0 \quad \text{a.s.}$$

That is, the tumor cells $T(t)$ become weakly persistent in the mean.

2. From the last equation of system (3.1)

$$dR(t) \geq [\alpha_2 R(1-\frac{R}{K_2}) - \gamma RH - \delta_2 R - d_3(t)R]dt + \sigma_3 R dB_3(t), \qquad \text{for all } t > 0.$$

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

$$d\psi(t) = [\alpha_2 \psi(1-\frac{\psi}{K_2}) - \gamma \psi H - \delta_2 \psi - d_3(t)\psi]dt + \sigma_3 \psi dB_3(t), \qquad \text{for all } t > 0$$

with initial value $\psi(0) = R(0)$. An application of the comparison theorem for stochastic differential equations, as presented in [36], leads to the following results

$$\psi(t) \leq R(t), \qquad \text{for all } t > 0.$$

Applying Itô's formula to $\ln \psi(t)$, we obtain

$$\begin{aligned} d\ln\psi(t) &= [\alpha_2(1-\frac{\psi}{K_2}) - \gamma H - \delta_2 - d_3(t) - \frac{\sigma_3^2}{2}]dt + \sigma_3 dB_3(t) \\ &\geq [\alpha_2 - \delta_2 - \frac{d_3 u}{\mu\tau} - \frac{\sigma_3^2}{2} - \gamma H - d_3\epsilon - \frac{\alpha_2}{K_2}\psi]dt + \sigma_3 dB_3(t). \end{aligned}$$

Integrating both sides on $[0, t]$ and dividing by t, we obtain

$$\frac{1}{t}\ln\frac{\psi(t)}{\psi(0)} \geq \alpha_2 - \delta_2 - \frac{d_3 u}{\mu\tau} - \frac{\sigma_3^2}{2} - \gamma\langle H(t)\rangle - d_3\epsilon - \frac{\alpha_2}{K_2}\langle\psi(t)\rangle + \frac{M_3(t)}{t}.$$

Theorem (4.2) shows for any $\epsilon > 0$, $\langle H(t)\rangle^* \leq \epsilon$. Taking the superior limit, we obtain

$$\langle\psi(t)\rangle^* \geq \frac{K_2}{\alpha_2}(\alpha_2 - \delta_2 - \frac{d_3 u}{\mu\tau} - \frac{\sigma_3^2}{2}), \qquad \text{a.s.}$$

Thus

$$\langle R(t)\rangle^* \geq \frac{K_2}{\alpha_2}(\kappa_3 - k) > 0, \qquad \text{a.s.}$$

In other words, the helper T-cells become persistent in the mean.

□

Throughout all stages of treatment, the times of pulsed therapy are limited. Therefore, the assumption in the following theorem is reasonable.

Theorem 4.4. *Assume that* $\prod_{0<\tau_n<t}(1+R_n) \leq M$ *where* $M > 0$. *If* $\kappa_1 - \beta_1 M H(0) > 0$, *then the tumor cells* $T(t)$ *are stochastically persistent.*

Proof. First, we will demonstrate that for any $\epsilon \in (0,1)$, there is a positive constant η_1 such that

$$\liminf_{t\to+\infty} \mathbb{P}\{T(t) \geq \eta_1\} \geq 1 - \epsilon.$$

To attain this aim. For any $p > 1$, by applying Itô's formula to the first equation of system (3.1), we obtain

$$\begin{aligned} d(e^t x^p(t)) &= e^t x^p(t)\,dt + e^t\,dx^p(t) \\ &= e^t[x^p(t) + px^{p-1}(t)\,dx(t) + 0.5p(p-1)x^{p-2}(t)(dx(t))^2] \end{aligned}$$

$$= e^t x^p(t)(1 + p[\alpha_1 - d_1(t) - \frac{\alpha_1}{K_1}x(t) - \beta_1 \prod_{0<\tau_n<t}(1+R_n)y(t) + 0.5(p-1)\sigma_1^2])dt + pe^t\sigma_1 x^p(t)\, dB_1(t),$$

which results in

$$\begin{aligned} &d(e^t x^p(t)) \\ \leq &e^t x^p(t)[1 + p(\alpha_1 - \frac{d_1 u}{\mu\tau}) - p\frac{\alpha_1}{K_1}x(t) + 0.5p(p-1)\sigma_1^2]dt + p\sigma_1 e^t x^p(t)dB_1(t). \end{aligned}$$

Integrating both sides on the interval $[0,t]$ yields,

$$\begin{aligned} e^t x^p(t) - x(0) \leq &\int_0^t e^s x^p(s)[1 + p(\alpha_1 - \frac{d_1 u}{\mu\tau}) - p\frac{\alpha_1}{K_1}x(s) + 0.5p(p-1)\sigma_1^2]ds \\ &+ p\int_0^t e^s \sigma_1 x^p(s)dB_1(s). \end{aligned}$$

Taking expectation on both sides, we obtain

$$\mathbb{E}[e^t x^p(t)] \leq x^p(0) + \mathbb{E}\int_0^t e^s x^p(s)[1 + p(\alpha_1 - \frac{d_1 u}{\mu\tau}) - p\frac{\alpha_1}{K_1}x(s) + 0.5p(p-1)\sigma_1^2]ds.$$

Note that $f(x) = x^p[1 + p(\alpha_1 - \frac{d_1 u}{\mu\tau}) - p\frac{\alpha_1}{K_1}x + 0.5p(p-1)\sigma_1^2]$. Then

$$\begin{aligned} f^{'}(x_1) &= p[1 + p(\alpha_1 - \frac{d_1 u}{\mu\tau}) - (p+1)\frac{\alpha_1}{K_1}x + 0.5p(p-1)\sigma_1^2]x^{p-1}, \\ f^{''}(x_1) &= p[(p-1)(1 + p(\alpha_1 - \frac{d_1 u}{\mu\tau}) + 0.5p(p-1)\sigma_1^2) - p(p+1)\frac{\alpha_1}{K_1}x]x^{p-2}. \end{aligned}$$

It can be readily established that $f(x)$ has a unique maximum $x^* = K_1\dfrac{1 + p(\alpha_1 - \frac{d_1 u}{\mu\tau}) + 0.5p(p-1)\sigma_1^2}{(p+1)\alpha_1}$ since $f^{''}(x^*) = -p[1 + p(\alpha_1 - \frac{d_1 u}{\mu\tau}) + 0.5p(p-1)\sigma_1^2](x^*)^{p-2}$. That is $f(x) \leq f(x^*) =: C_1$. This implies

$$\mathbb{E}[e^t x^p(t)] \leq x^p(0) + C_1(e^t - 1).$$

It is easy to obtain

$$\limsup_{t\to+\infty} \mathbb{E}[x^p(t)] \leq C_1.$$

Therefore

$$\limsup_{t\to+\infty} \mathbb{E}[T^p(t)] = \limsup_{t\to+\infty} \mathbb{E}\left[x^p(t)\right] \leq C_1.$$

For any $\epsilon > 0$, we define $\eta_1 = C_1^{1/p}/\epsilon^{1/p}$. It follows from Chebyshev's inequality that

$$\begin{aligned} \limsup_{t\to+\infty} \mathbb{P}\{T(t) > \eta_1\} &= \limsup_{t\to+\infty} \mathbb{P}\{T^p(t) > \eta_1^p\} \\ &\leq \limsup_{t\to+\infty} \frac{\mathbb{E}[T^p(t)]}{\eta_1^p} \\ &\leq \frac{C_1}{\eta_1^p} = \epsilon. \end{aligned}$$

Therefore, $\liminf_{t\to+\infty}\mathbb{P}\{T(t)\le\eta_1\}\ge 1-\epsilon$.

Now, we will prove that for any $\epsilon>0$, there is a positive constant η_2 such that $\liminf_{t\to+\infty}\mathbb{P}\{T(t)\ge\eta_2\}\ge 1-\epsilon$.

We define the Lyapunouv function as follows $V(x)=\frac{1}{x}$ $(x>0)$. By Itô's formula, we obtain

$$\begin{aligned}&dV(x)\\=&-V(x)[\alpha_1-d_1(t)-\frac{\alpha_1}{K_1}x(t)-\beta_1\prod_{0<\tau_n<t}(1+R_n)y(t)+V(x)\sigma_1]dt-V(x)\sigma_1dB_1(t).\end{aligned}$$

According to Lemma (2.3), we can find a constant $t^*>0$ such that $y(t)\le H(0)$ for all $t>t^*$. Choosing a positive constant θ such that $\kappa_1-\beta_1MH(0)>0.5\theta\sigma_1^2$. We define another Lyapunouv function $W(x)=(1+V(x))^\theta$. Applying Itô's formula for all $t>t^*$ gives

$$\begin{aligned}dW(x)=&\theta(1+V(x))^{\theta-1}dV(x)+\frac{\theta(\theta-1)}{2}(1+V(x))^{\theta-2}(dV(x))^2\\=&\theta(1+V(x))^{\theta-2}\{dV(x)+V(x)dV(x)+\frac{\theta-1}{2}(dV(x))^2\}\\=&\theta(1+V(x))^{\theta-2}\{-V(x)^2[\alpha_1-d_1(t)-\frac{\alpha_1}{K_1}x(t)-\beta_1\prod_{0<\tau_n<t}(1+R_n))y(t)-0.5\sigma_1^2\\&-0.5\theta\sigma_1^2]+V(x)[-\alpha_1+\frac{\alpha_1}{K_1}+\beta_1\prod_{0<\tau_n<t}(1+R_n)y(t)+\sigma_1^2]+\frac{\alpha_1}{K_1}\}dt\\&-\theta(1+V(x))^{\theta-1}V(x)\sigma_1dB_1(t)\\\le&\theta(1+V(x))^{\theta-2}\{-V(x)^2[\kappa_1-\beta_1MH(0)-0.5\theta\sigma_1^2]+V(x)[\frac{\alpha_1}{K_1}+\beta_1MH(0)\\&+\sigma_1^2]+\frac{\alpha_1}{K_1}\}dt-\theta(1+V(x))^{\theta-1}V(x)\sigma_1dB_1(t).\end{aligned}\tag{4.8}$$

Next, select a ξ small enough such that $\kappa_1-\beta_1MH(0)-0.5\theta\sigma_1^2>\frac{\xi}{\theta}>0$. Using Itô's formula to $\exp(\xi t)W(x)$, we get

$$\begin{aligned}&d(\exp(\xi t)W(x))\\=&\xi\exp(\xi t)W(x)dt+\exp(\xi t)dW(x)\\\le&\theta\exp(\xi t)(1+V(x))^{\theta-2}\{\frac{\xi(1+V(x))^2}{\theta}-(V(x))^2[\kappa_1-\beta_1H(0)-0.5\theta\sigma_1^2]\\&+V(x)[\frac{\alpha_1}{K_1}+\beta_1MH(0)+\sigma_1^2]+\frac{\alpha_1}{K_1}\}dt\\&-\theta\exp(\xi t)(1+V(x))^{\theta-1}V(x)\sigma_1dB_1\\\le&\exp(\xi t)g(x)dt-\theta\exp(\xi t)(1+V(x))^{\theta-1}V(x)\sigma_1(t)dB_1(t),\end{aligned}$$

with

$$\begin{aligned}g(x)=&\theta(1+V(x))^{\theta-2}\{-[\kappa_1-\beta_1H(0)-0.5\theta\sigma_1^2-\frac{\xi}{\theta}](V(x_1))^2\\&+[\frac{\alpha_1}{K_1}+\beta_1MH(0)+\sigma_1^2+\frac{2\xi}{\theta}]V(x)+\frac{\alpha_1}{K_1}+\frac{\xi}{\theta}\}.\end{aligned}$$

Let $\mu_1=\kappa_1-\beta_1H(0)-0.5\theta\sigma_1^2-\frac{\xi}{\theta}$, $\mu_2=\frac{\alpha_1}{K_1}+\beta_1MH(0)+\sigma_1^2+\frac{2\xi}{\theta}$ and $\mu_3=\frac{\alpha_1}{K_1}+\frac{\xi}{\theta}$.

Then $\mu_1 > 0$, $\mu_2 > 0$ and $\mu_3 > 0$. Thus

$$g(x) = \theta \left(1 + \frac{1}{x}\right)^{\theta-2} \left\{-\frac{\mu_1}{x^2} + \frac{\mu_2}{x} + \mu_3\right\}.$$

We will next show that $g(x)$ is bounded when $x > 0$. If $\frac{1}{x} \geq \frac{\mu_2+\sqrt{\mu_2^2+4\mu_1\mu_3}}{2\mu_1} =: \nu_1$, then $g(x) \leq 0$. If $0 < \frac{1}{x} \leq \nu_1$, then $g(x) \leq \dfrac{4\mu_1\mu_2 + \mu_2^2}{4\mu_1}$. Furthermore, if $\theta \geq 2$, then $\theta \left(1 + \frac{1}{x}\right)^{\theta-2} \leq \theta \left(1 + \nu_1\right)^{\theta-2}$; if $\theta < 2$, then $\theta \left(1 + \frac{1}{x}\right)^{\theta-2} \leq \theta$. Thus, for any $x > 0$ we always have $g(x) \leq \nu_2 \frac{4\mu_1\mu_3+\mu_2^2}{4\mu_1} =: C_2$ with $\nu_2 = \max\{\theta, \theta(1 + \nu_1)^{\theta-2}\}$, which means that $g(x)$ is upper bounded. Consequently,

$$\begin{aligned} d(\exp(\xi t)W(x)) &\leq \exp(\xi t)g(x)dt - \theta \exp(\xi t)(1 + V(x))^{\theta-1}V(x)\sigma_1 dB_1(t) \\ &\leq C_2 \exp(\xi t)dt - \theta \exp(\xi t)(1 + V(x))^{\theta-1}V(x)\sigma_1 dB_1(t). \end{aligned}$$

Integrating and taking expectations, we can get that

$$\mathbb{E}[\exp(\xi t)W(x(t))] \leq \exp(\xi t^*)W(x(t^*)) + \frac{C_2}{\xi}(\exp(\xi t) - \exp(\xi t^*)).$$

Taking the superior limit yields

$$\begin{aligned} \limsup_{t\to+\infty} \mathbb{E}\left[\frac{1}{x(t)^\theta}\right] &= \limsup_{t\to+\infty} \mathbb{E}\left[(V(x(t)))^\theta\right] \\ &\leq \limsup_{t\to+\infty} \mathbb{E}\left[W(x(t))^\theta\right] \leq \frac{C_2}{\xi}. \end{aligned} \tag{4.9}$$

Since $T(t) = x(t)$, it follows that

$$\limsup_{t\to+\infty} \mathbb{E}\left[\frac{1}{T(t)^\theta}\right] = \limsup_{t\to+\infty} \mathbb{E}\left[\frac{1}{x(t)^\theta}\right] \leq \frac{C_2}{\xi} =: C_3.$$

For any arbitrary $\epsilon > 0$, we define $\eta_2 = \epsilon^{1/\theta}/C_3^{1/\theta}$. By Chebyshev's inequality, we get

$$\begin{aligned} \limsup_{t\to+\infty} \mathbb{P}\{T(t) < \eta_2\} &= \limsup_{t\to+\infty} \mathbb{P}\{\frac{1}{T(t)^\theta} > \frac{1}{\eta_2^\theta}\} \\ &\leq \limsup_{t\to+\infty} \frac{\mathbb{E}\left[\frac{1}{T(t)^\theta}\right]}{\eta_2^{-\theta}} \\ &= \limsup_{t\to+\infty} \eta_2^\theta \mathbb{E}\left[\frac{1}{T(t)^\theta}\right] = \epsilon. \end{aligned}$$

Therefore, $\liminf_{t\to+\infty} \mathbb{P}\{T(t) \geq \eta_2\} \geq 1 - \epsilon$. □

Next, we numerically investigate extinction, persistence and stochastic persistence.

5. Numerical simulations

We conducted numerical simulations to validate the theoretical results regarding the extinction and persistence of tumor under comprehensive pulse therapy and

stochastic disturbances. To approximate the solutions of system (2.2) based on initial conditions, we employed the Milstein higher-order method [37]. The discretized equations for system (2.2) are as follows:

$$\begin{aligned}
T_{i+1} &= T_i + [\alpha_1 T_i(1-\frac{T_i}{K_1}) - \beta_1 T_i H_i - d_1 D_i T_i]\Delta t + \sigma_1 T_i\sqrt{\Delta t}\Delta B_{1i} \\
&\quad + \frac{\sigma_1^2}{2} T_i\left(\Delta B_{1i}^2 - 1\right)\Delta t, \\
H_{i+1} &= H_i + [\gamma H_i R_i - \delta_1 H_i - \beta_2 H_i T_i - d_2 D_i H_i]\Delta t + \sigma_2 H_i\sqrt{\Delta t}\Delta B_{2i} \\
&\quad + \frac{\sigma_2^2}{2} H_i\left(\Delta B_{2i}^2 - 1\right)\Delta t, \\
R_{i+1} &= R_i + [\alpha_2 R_i(1-\frac{R_i}{K_2}) - \gamma R_i H_i - d_3 D_i R_i + \frac{kT_i R_i}{T_i+\eta}]\Delta t + \sigma_3 R_i\sqrt{\Delta t}\Delta B_{3i} \\
&\quad + \frac{\sigma_3^2}{2} Y_i\left(\Delta B_{3i}^2 - 1\right)\Delta t, \\
D_{i+1} &= D_i - \mu D_i \Delta t,
\end{aligned}$$

and at the impulsive points corresponding to the series τ_n, system (2.2) is subjected to pulsed therapies, which occurs when $mod(k,\tau) = 0$. Therefore, we obtain:

$$\begin{aligned}
H_{i+1} &= (1+R_i)H_i, \\
D_{i+1} &= D_i + u.
\end{aligned}$$

We define a time increment of $\Delta t = 0.01$, with ΔB_{1i}, ΔB_{2i} and ΔB_{3i} $(i = 1, 2, 3, \ldots)$ denoting independent Gaussian random variables that follow a normal distribution $\mathcal{N}(0,1)$.

The values of the parameters in the system (2.2) are presented in Table 1. These values were obtained through parameter estimation based on experimental data. Additionally, the initial conditions are set as $(T(0), H(0), R(0), D(0)) = (10^3, 3\times 10^3, 5.5\times 10^3, 0.05)$ and $(T(0), H(0), R(0), D(0)) = (6\times 10^3, 8\times 10^3, 9\times 10^3, 0.05)$.

The baseline parameter values u, R_n, and τ were taken from references [24, 30], as these values were derived not only through parameter estimation based on experimental data but also with consideration of their biological implications.

First, we examine the extinction of tumor cells, hunting T-cells, and helper T-cells. Set $u = 0.1$, $R_i = 0.55$, $\tau = 100$, $\sigma_1 = 1.2$, $\sigma_2 = 0.5$, and $\sigma_3 = 0.75$, the resulting value of $\kappa_1 = \alpha_1 - \frac{d_1 u}{\mu\tau} - \frac{\sigma_1^2}{2} \approx -0.548 < 0$, $\kappa_2 = \limsup_{t\to+\infty} \frac{1}{t}\sum_{0<\tau_n<t} \ln(1+R_n) - \delta_1 - \frac{d_2 u}{\mu\tau} - \frac{\sigma_2^2}{2} \approx -0.1223745 < 0$ and $\kappa_3 = \alpha_2 - \delta_2 - \frac{d_3 u}{\mu\tau} - \frac{\sigma_3^2}{2} + k \approx -0.134251 < 0$. Based on Theorem (4.1) and Theorem (4.2), it follows that the tumor cells $T(t)$, the hunting T-cells $H(t)$ and the helper T-cells $R(t)$ will become extinct and the curves in Figure 1 clearly demonstrate the tendency toward extinction.

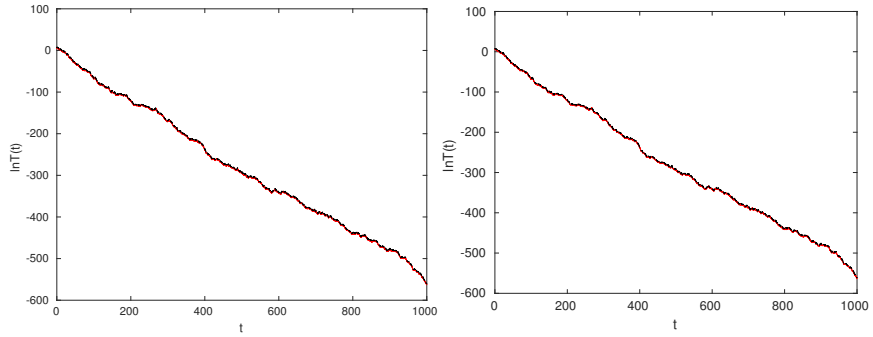
Next, we verify the weak persistence in the mean of the tumor cells and helper T-cells. When setting $u = 0.1$, $R_i = 0.55$, $\tau = 100$, $\sigma_1 = 0.4$, $\sigma_2 = 0.5$, and $\sigma_3 = 0.75$, the resulting value of $\kappa_1 = 0.127 > 0$. According to the result in Theorem (4.3) the tumor cells become weakly persistent in the mean. Similarly, when setting $\sigma_1 = 1.2$, $\sigma_2 = 2.5$, and $\sigma_3 = 0.17$, the resulting value of $\kappa_3 = 0.132549 > k = 0.1245$ and $\kappa_2 + \frac{\gamma K_2}{\alpha_2}\kappa_1 \approx -1.085 < 0$. Based on the findings in Theorem (4.3) the helper T-cells become weakly persistent in the mean. Figure 2 (a) and (b) illustrate the time evolution of the logarithmic solution for the tumor cells and helper T-cells,

respectively. It is observed that the logarithmic solution accurately reflects the behavior of weak persistence.

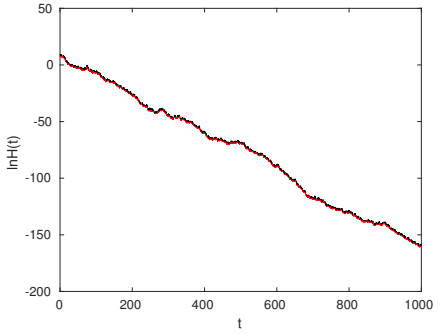
Parameter	Value	Source
α_1	0.18 /day	[38]
α_2	0.0245 /day	[39]
K_1	5×10^8 cells	[38]
K_2	10^9 cells	[39]
β_1	1.101×10^{-7} /cells/day	[39]
β_2	3.422×10^{-10} /cells/day	[39]
δ_1	0.0412 /day	[39]
δ_2	0.002 /day	[23]
γ	6.2×10^{-9} /cells/day	[39]
k	0.1245 /day	[38]
η	2.019×10^7 cells	[38]
μ	0.01 /day	[19]
d_1	0.08 /mg/day	[19]
d_2	2×10^{-11} /mg/day	[19]
d_3	10^{-5} /mg/day	[19]

Table 1. Parameters values used for numerical simulations.

In Figure 3, we set $u = 0.1$, $R_n = 0.55$, $\tau = 30$, $\sigma_1 = 0.5$, $\sigma_2 = 0.1$, $\sigma_3 = 0.5$ and initial values $(10^3, 3 \times 10^3, 5.5 \times 10^3, 0.05)$ and $(10^3, 5 \times 10^5, 5.5 \times 10^3, 0.05)$. When $H(0) = 3 \times 10^3$, then $\kappa_1 - \beta_1 M H(0) \approx 1.9 \times 10^{-2} > 0$. Based on the criteria established in Theorem (4.4), the tumor cells $T(t)$ exhibit stochastic persistence. When $H(0) = 5 \times 10^5$, then $\kappa_1 - \beta_1 M H(0) \approx -4.37 < 0$. Consequently, the dynamic behavior of tumor cells changes from stochastically persistent to weak persistent in the mean or non-persistent in the mean as shown in Figure 3.

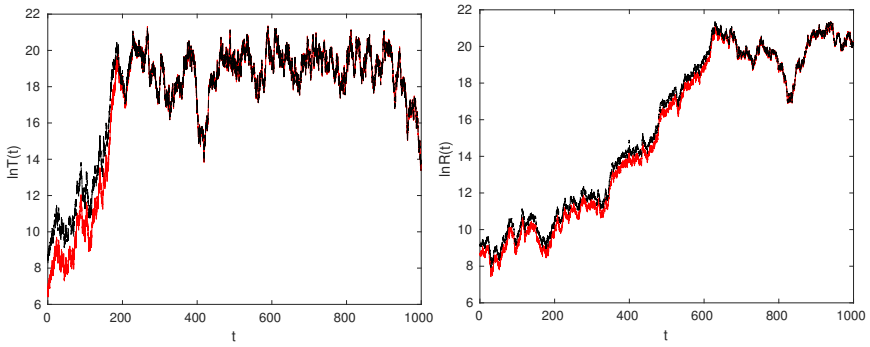


(a) The extinction of tumor cells (b) The extinction of hunting cells



(c) The extinction of helper T-cells

Figure 1. The extinction of tumor cells $T(t)$, hunting T-cells $H(t)$ and helper T-cells $R(t)$. The initial values of solution with red are fixed as $(10^3, 3\times10^3, 5.5\times10^3, 0.05)$ and black for $(6\times10^3, 8\times10^3, 9\times10^3, 0.05)$.



(a) The weak persistence in the mean of tumor cells.

(b) The weak persistence in the mean of helper T-cells.

Figure 2. The weak persistence in the mean of tumor cells $T(t)$ and helper T-cells $R(t)$. The initial values of solution with red are fixed as $(10^3, 3\times10^3, 5.5\times10^3, 0.05)$ and black for $(6\times10^3, 8\times10^3, 9\times10^3, 0.05)$.

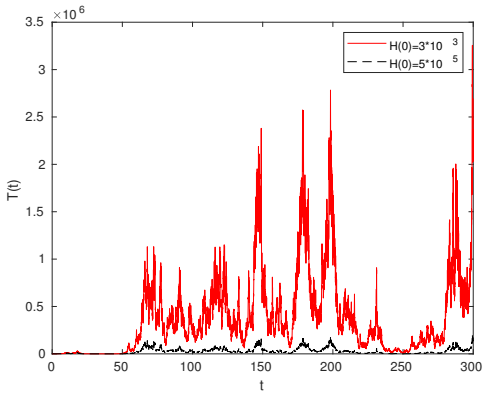


Figure 3. Stochastic persistence of tumor cells $T(t)$.

We manipulate the key parameters, u, R_n and τ, which correspond to the dosage of chemical drugs, the recruitment rate of hunting T-cells upon the initiation of immunotherapy, and the interval of pulse therapy, respectively, to model the effects of different treatments on cancer therapy. We modify the values of u, R_n and τ. It is evident that increasing the dosage of both immunotherapy and chemotherapy, while reducing the treatment periodicity, enhances the elimination of tumor cells and the maintenance of hunting T-cells, in line with the simulation results presented in Figures 4 and 5.

6. Conclusion

Numerous studies have highlighted that the evolution of tumors is inevitably influenced by environmental noise [20, 23, 28, 35, 39]. Pulsed comprehensive therapy is a viable approach for tumor treatment [4, 15–17, 19, 40]. However, there is limited research on stochastic tumor-immune systems with pulsed comprehensive therapy.

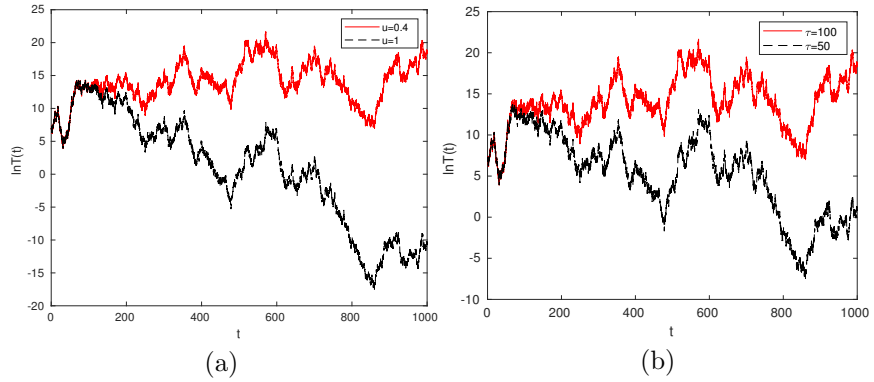


Figure 4. Simulation of key parameter control. Red curve: $u = 0.4$, $\tau = 100$. black curve: (a) $u = 1$, $\tau = 100$; (b) $u = 0.4$, $\tau = 50$. We set initial value $(10^3, 3 \times 10^3, 5.5 \times 10^3, 0.05)$ and all other parameters were fixed as: $R_n = 0.55$, $\sigma_1 = 0.5$, $\sigma_2 = 0.05$, and $\sigma_3 = 0.3$.

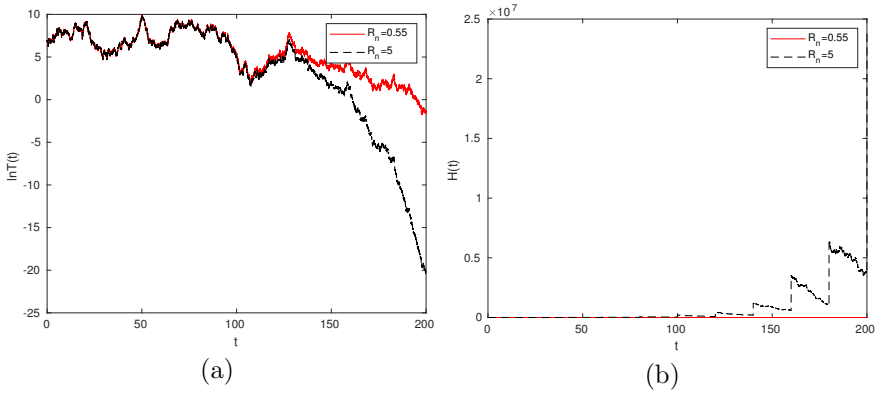


Figure 5. Simulation of key parameter control. Red curve: $R_n = 0.55$. Black curve: $R_n = 5$. We set initial value $(10^3, 3 \times 10^3, 5.5 \times 10^3, 0.05)$ and all other parameters are fixed as: $u = 0.4$, $\tau = 20$, $\sigma_1 = 0.5$, $\sigma_2 = 0.05$, and $\sigma_3 = 0.3$.

In this paper, we develop a stochastic tumor-immune system with pulsed therapy to investigate how environmental noise and pulsed treatment impact tumor evolution.

Firstly, we prove the existence and uniqueness of the global positive solution in the stochastic tumor-immune model. Next, we estimate an upper bound for the expected value of the solution. From a biological perspective, under constrained pulsed immunotherapy, if the tumor cell response rate to chemotherapy exceeds a critical threshold, tumor growth can be regulated, preventing uncontrolled proliferation. After that, we derive the sufficient conditions for tumor extinction, as well as for non-persistence in the mean sense of the three cell populations. We then establish the conditions of the weak persistence of tumor cells and helper T-cells, along with stochastic persistence of tumor cells. Finally, the numerical Milstein method is employed to validate the theoretical results, and both the numerical and theoretical findings demonstrate strong agreement.

Under the influence of environmental noise, the biological impact of pulsed comprehensive treatment for tumor cells is examined. It was found that large stochastic fluctuations lead to the eradication of tumor cells, while small fluctuations result in the stochastic persistence of tumor cells. Furthermore, higher noise levels shorten

the time required for tumor eradication (Figure 1). Although noise can theoretically dominate the evolution of tumor cells, environmental noise in practice is typically constrained and insufficient to control cancer. Therefore, pulsed comprehensive therapy is introduced to inhibit tumor proliferation and mutation. The effects of combinations of chemotherapy and immunotherapy on tumors are investigated. Increasing the doses of comprehensive therapy or reducing the treatment periods (Figures 4 and 5) facilitates the eradication of tumor cells. It is concluded that comprehensive therapy accelerates tumor cell eradication and can reduce the damage to healthy cells caused by chemotherapy.

Several important topics warrant further investigation. For instance, while system (2.2) has been proposed for autonomous differential equations, a crucial question arises: what occurs when the non-autonomous case is considered? Additionally, the role of impulsive comprehensive therapy in tumor eradication remains an open and compelling area of study. It is expected that future research will provide valuable insights into cancer treatment and make meaningful contributions to advancements in this field.

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