Nonlinear Dyn
https://doi.org/10.1007/s11071-024-09768-5

RESEARCH

Stochastic dynamics of a nonlinear tumor-immune competitive system

Mrinmoy Sardar · Subhas Khajanchi · Santosh Biswas

Received: 17 January 2024 / Accepted: 14 May 2024

Abstract The paper uses nine coupled ordinary differential equations (ODEs) to describe a tumor-immune competitive system. The model is then reduced to four nonlinear coupled ODEs, encompassing tumor cells, cytotoxic T-lymphocytes, macrophages, and dendritic cells by utilizing quasi-steady-state approximations. We explore the dynamics of biologically feasible steady states and their local stability analysis. We introduce stochastic fluctuation terms into the deterministic system to account for uncertainty and variability in the tumor-immune interaction system. The uniqueness and existence of our stochastic system is established by applying Itô's lemma. Additionally, it is demonstrated that the solution of the stochastic system is both stochastically ultimately bounded and permanent. We established the criteria for determining the extinction of tumor cell population, and conditions under which our stochastic system exhibits asymptotic stability in a mean square sense are derived. Numerical illustrations are performed to validate both deterministic and stochastic models under different intensities of population fluctuation. Our model explores that in the absence of intensity fluctuations, the deterministic model remains stable around a high tumor-presence steady state. Additionally, the tumor cell population quickly approaches zero for sufficiently small values of intensity fluctuation parameters. If the intensity value of population fluctuations is increased, then the cell populations are more fluctuated. Moreover, the stochastic mean solution confirms the influence of stochastic noise on the cell population.

Keywords Standard Wiener process · Gaussian white noise · Itô's lemma · Stochastically permanence · Mean square stable

1 Introduction

Over the past few decades, malignant tumors or cancers have emerged as one of the deadliest global health challenges. The tumors consist of uncontrolled growth of abnormal tissues and cells, leading to the invasion of nearby body parts and the spread to surrounding organs. Various risk factors, such as obesity, unhealthy lifestyle, alcohol consumption, and smoking have been linked to the increased incidence of cancer [1]. In the field of medical science, a pivotal question in oncology revolves around understanding how our immune system can effectively combat tumor proliferation [2,3]. Immune responses play a crucial role in regulating tumor growth and progression, posing a significant challenge in the quest for effective cancer treatment strategies.

M. Sardar · S. Biswas
Department of Mathematics, Jadavpur University, 188 Raja S.C. Mallik Road, Kolkata 700032, India

S. Khajanchi (✉)
Department of Mathematics, Presidency University, 86/1 College Street, Kolkata 700073, India
e-mail: subhaskhajanchi@gmail.com

Published online: 03 June 2024

Our immune system is an intricate network comprising various types of cells, proteins, and cytokines that work collaboratively to safeguard our body against external invaders. The primary components of our immune system consist of cytotoxic T-lymphocytes (CD8+ T cells), B cells, NK cells or natural killer cells, Helper T cells, macrophages, and specific immune-stimulatory cytokines such as IL-10 or interleukin-10, IL-12 or interleukin-12 and IFN-γ or interferon-gamma, etc. Macrophages, NK cells, and CD8+ T cells are commonly referred to as effector cells [4]. Their main function is to eliminate or destroy tumor cells, thereby playing pivotal roles in the immune response against cancer cells [5]. On the other hand, immuno-stimulatory cytokines, while unable to directly eliminate tumor cells, play an important role in enhancing the functions of effector cells. They stimulate these cells to inhibit the proliferation of tumor cells. A vital link between the innate and adaptive immune system is formed by antigen-presenting dendritic cells. These specialized cells act as messengers and are responsible for producing IL-12, a cytokine that plays a crucial role in promoting CD8+ T cells. Regulatory T-cells or Tregs and transforming growth factor-β (TGF-β) play critical role in the tumor-immune interaction system, primarily contributing to the immuno-suppressive component. However, in the tumor-immune interaction system, the dynamics are more complex. This interplay between the tumor cells and immune system can be likened to a prey-predator relationship, where tumor cells act as prey and effector cells take on the role of predators [6,7].

The balance between effector cells (like cytotoxic T cells, macrophages and natural killer cells) and immune-suppressive components such as regulatory T cells (Tregs) and TGF-β plays a crucial role in shaping the outcome of the 'prey-predator' relationship between tumor cells and effector cells. When there are more effector cells than immune-suppressive components, they can effectively identify and remove tumor cells, resulting in tumor control or regression. In this situation, the immune systems like a predator, effectively managing the population of tumor cells. On the other hand, when immune-suppressive components dominate the immune cells, they can suppress the activity of effector cells. This allows tumor cells to evade immune surveillance. In this scenario, the imbalance favors tumor cells, resembling a 'prey-predator' dynamic where the tumor cells act as predators, taking advantage of the weakened immune response. An excessive presence of immune-suppressive components can also promote tumor progression. Tregs and TGF-β have the capability to suppress effector cell function, which diminishes the immune response against the tumor cells. In summary, the balance between effector cells and immune-suppressive components significantly impacts the outcome of the interaction between the immune system and tumor cells.

Biologically, our deterministic system faces certain limitations. The parameters governing the system such as activation rate, growth rate, death rate, and carrying capacity are subject to fluctuations induced by various environmental factors including body weight, air pollution, temperature, etc. Environmental fluctuations are a crucial phenomena in the tumor-immune interaction model. In most of the cases, equilibrium points of the deterministic system oscillate randomly and deterministic equilibrium points are no longer in a fixed state. As a result, the deterministic system may not accurately predict the future of the biological system. To address these challenges and achieve a more realistic representation of natural phenomena, stochastic systems offer a promising alternative. Unlike deterministic systems, stochastic models consider randomness and uncertainty observed in biological systems. Two approaches exist for developing stochastic models that correspond to deterministic systems. The first method involves introducing stochastic perturbation terms of Gaussian white noise type into important parameters, thereby formulating the system as an Itô stochastic differential equation. In the second approach, random fluctuating terms are directly added into the deterministic system without changing any parameters. In this manuscript, we explain the impact of randomly fluctuating terms on our system and investigate its effects around the interior fixed point of the deterministic system. As a result, the stochastic system offers a valuable framework for studying and understanding the dynamic behavior of biological populations in response to environmental fluctuations and uncertainties.

The introduction of stochastic perturbation terms can enhance the accuracy of predictions about the future of a biological system by accounting for environmental fluctuations and uncertainties. These perturbation terms simulate the inherent randomness and variability in biological processes, allowing models to capture the unpredictable nature of environmental influences. By incorporating stochasticity, predictions

can better reflect real-world dynamics, where environmental factors can vary widely and unpredictably over time. In the absence of stochastic fluctuations, the system may still exhibit stability under certain conditions. While stability may be observed in the absence of fluctuations, incorporating stochasticity provides a more accurate representation of the system's dynamics and enhances the predictive capability of the model in the face of environmental uncertainties. In many cases, random environmental fluctuations can indeed contribute to the stability of competitive systems. The introduction of stochastic perturbation terms may not necessarily lead to enhanced stability. Random fluctuations in our system can perturb the balance by disturbing the interactions between tumor cells, immune cells, and other components of the microenvironment. In simply, although random fluctuations can sometimes help stabilize competitive systems, their effects on biological systems such as tumor-immune interactions are more complex. They can lead to unpredictable outcomes, unlike the stabilizing effects seen in other competitive systems. Therefore, we need to thoroughly study and understand the impact of stochastic perturbations in this context, as they may not always produce the same stabilizing effects.

Introducing stochastic fluctuations into a mathematical model of tumor-immune interactions can help understand the role of lifestyle factors such as obesity and smoking in tumor proliferation by accounting for the inherent randomness and variability in biological systems. Lifestyle factors like obesity and smoking can influence the immune response and tumor growth through various mechanisms, including inflammation, oxidative stress, and immune suppression. By incorporating stochastic fluctuations into the model, researchers can simulate the unpredictable nature of these lifestyle factors' effects on immune cell dynamics, tumor growth rates, and treatment responses. This stochastic approach allows for a more realistic representation of the complex interplay between lifestyle factors, immune function, and tumor development, helping to identify critical points where interventions may be most effective in preventing or treating malignant tumors in individuals with specific lifestyle risk factors.

Many research articles on the tumor-immune competitive system can be found in [4–6,8–19], but there are few articles published on stochastic cancer models. Kloeden & Platen [20] introduced a stochastic system to study the limitations of appropriate overlap in a randomly fluctuating environment. Li et al. [21] studied a cancer growth model using a stochastic system and observed extinction in the presence of the immune system. Lefever et al. [22] explored that when the variance of population fluctuations is increased around a mean value, a transition exists in the bifurcation diagram, which eventually disappears. Li et al. [23] observed stochastic fluctuation-induced tumor extinction and recurrence in a tumor growth model based on a catalytic Michaelis-Menten reaction. The authors found that at a certain level, environmental fluctuations facilitate tumor extinction. Oroji et al. [24] introduced a stochastic cancer model and this model has been categorized into three subpopulations for radiotherapy. They calculated the entire lifespan of tumor cells and observed the behavior of tumor cells under the application of two different treatment strategies. A tumor-immune interaction system was considered as a deterministic prey-predator system in [25]. In this paper, the authors tried to control the tumor cells by applying stochastic fluctuations in their deterministic system. Sardar et al. [26] introduced a deterministic model of tumor cell growth with the Allee effect. The authors extended the deterministic system into a stochastic system by applying the parameter perturbation method. Additionally, they conducted numerical simulations of the stochastic system corresponding to the Allee effect, weak Allee effect, and strong Allee effect. Kim et al. [27] developed a stochastic tumor model with virotherapy. To determine the probability of tumor extinction, the authors altered the parameter values. Additionally, they revealed that high infection rate viruses and optimal cytotoxicity are more effective for cancer treatment. Caravanga et al. [28] presented a hybrid-stochastic version of the tumor-immune interaction model in presence of cytokine IL-2, which is introduced by Kirschner and Panetta [4]. In their study, the researchers demonstrated that tumor growth can be reduced through random environmental fluctuations. Tumor-immune competitive systems with immunotherapeutic drug has played an important role to eradicate the tumor cell population [29,30].

Parameter perturbation methods involve systematically varying model parameters to observe their impact on tumor growth and response to treatment. This approach allows researchers to identify critical parameters that strongly influence tumor dynamics and treatment outcomes. By perturbing parameters related to factors such as tumor growth rate, immune cell activ-

ity, and treatment efficacy, researchers can gain insights into which factors are most important in determining tumor behavior and response to therapy. Additionally, studying phenomena like the Allee effect, which describes how populations may struggle to grow or survive at low densities, can provide valuable insights into tumor growth dynamics. In the context of cancer, the Allee effect suggests that tumors may face challenges in proliferating and spreading when their population density is low. Understanding how the Allee effect influences tumor growth dynamics can help predict the likelihood of tumor eradication and inform the design of more effective treatment strategies. Overall, the combined use of parameter perturbation methods and the examination of phenomena like the Allee effect can enhance our comprehension of tumor growth dynamics and improve our ability to predict and achieve tumor eradication in cancer patients. These approaches provide valuable tools for refining mathematical models of cancer progression and guiding the development of more targeted and personalized treatment approaches.

The rest of this research paper is delineated in the following manner. In Sect. 2, we introduce a deterministic system of four nonlinear coupled ordinary differential equations (ODEs) and conduct a stability analysis around singular points. In Sect. 3, we convert our deterministic system into a stochastic system by introducing a random fluctuating term. Some basic properties, that is, existence, uniqueness, stochastically ultimate bounded, stochastically permanence, and extinction of our stochastic model for the initial density are studied in Sect. 4. Section 5 investigates the asymptotically mean square stable of our stochastic system. In Sect. 6, we have estimated the values of some parameters. Sect. 7 deals with numerical analysis of both the deterministic and stochastic system. Finally, our research paper concludes with a summary in Sect. 8.

2 Deterministic model

In this section, we introduced a mathematical model using a system of nine coupled ordinary differential equations (ODEs), namely tumor cells (T), cytotoxic T-lymphocytes or CD8+ T cells (T_8), macrophages (M), dendritic cells (D), Tregs or regulatory T-cells (T_g), interleukin-10 or IL-10 (I_{10}), transforming growth factor-β or TGF-β (T_β), interleukin-12 or IL-12 (I_{12}) and interferon-γ or IFN-γ (I_γ). Then, our deterministic model is stated as follows

$$
\begin{aligned}
\frac{dT}{dt} &= r_T T(1-b_T T) - \frac{(\alpha_T^{'} M + \gamma_T^{'} T_8)T}{g_T^{'} + I_{10}},\\
\frac{dT_8}{dt} &= \frac{\alpha_8^{'} I_{12}}{g_8^{'} + T_g} - \delta_8 T_8,\\
\frac{dM}{dt} &= s_m + \frac{\alpha_m^{'} I_\gamma}{(g_m^{'} + I_\gamma)} \cdot \frac{1}{(g_{m1}^{'} + T_\beta)}\\
&\quad -\gamma_m M T - \delta_m M,\\
\frac{dD}{dt} &= s_d + \frac{\alpha_d T}{g_d + T} - \delta_d D,\\
\frac{dT_g}{dt} &= \alpha_g T_8 - \delta_g T_g,\\
\frac{dI_{10}}{dt} &= \alpha_{10} M - \delta_{10} I_{10},\\
\frac{dT_\beta}{dt} &= s_\beta + \alpha_\beta T - \delta_\beta T_\beta,\\
\frac{dI_{12}}{dt} &= \alpha_{12} D - \delta_{12} I_{12},\\
\frac{dI_\gamma}{dt} &= \alpha_\gamma T_8 - \delta_\gamma I_\gamma.
\end{aligned}
\tag{1}
$$

- The first equation in (1) represents the tumor cell density at any given time t. Initial term $r_T T(1 - b_T T)$ describes the logistic growth of tumor cells in the absence of any immune response [12]. Here, r_T stands for the intrinsic growth rate, and $\frac{1}{b_T}$ denotes the maximum carrying capacity of tumor cells. The next component describes the elimination of tumor cells through interactions with macrophages [2] and CD8+ T cells [5], each with elimination rates denoted by $\alpha_T^{'}$ and $\gamma_T^{'}$, respectively. The term $g_T^{'}$ represents the half-saturation constant, where $\frac{1}{g_T^{'}+I_{10}}$ serves as a immunosuppressive factor affecting both macrophages and CD8+ T cells.
- The second equation in (1) refers the density of CD8+ T cells. The first term represents the activation of CD8+ T cells at a rate $\alpha_8^{'}$. This activation relies on the presence of CD4+T cells, which are boosted by the cytokine IL-12 [31]. However, the activation of CD8+ T cells is countered by regulatory T-cells [32] at a suppressive rate $g_8^{'}$. The decay rate of CD8+ T cells is denoted by δ_8.
- The third equation in (1) describes to the density of macrophages, where s_m denotes the constant influx rate of macrophages [33]. The recruitment of macrophages ($\alpha_m^{'}$) is directly affected by the presence of IFN-γ [2,33], with $g_m^{'}$ indicat-

ing the half-saturation constant. Additionally, the term $\frac{1}{g_{m1}^{'}+T_\beta}$ serves as an immunosuppressive factor for macrophages, where $g_{m1}^{'}$ represents the half-saturation constant. The third component highlights the deactivation of macrophages resulting from their interactions with tumor cells at a rate denoted by γ_m [2]. Additionally, δ_m represents the decay rate of macrophages.

- The fourth equation in (1) elaborates on the density of antigen-presenting dendritic cells. The term s_d denotes the constant source rate of dendritic cells [34]. The coefficient α_d signifies the activation rate of dendritic cells induced by the direct presence of tumor cells, with g_d acting as the half-saturation constant following Michaelis-Menten kinetics [35]. The death rate of dendritic cells is represented by δ_d.
- The fifth equation in (1) clarifies the behavior of regulatory T-cells (Tregs). Tregs are produced from activated CD8+ T cells [36] with an activation term α_g, while their natural degradation rate is denoted by δ_g.
- The sixth equation in the model (1) illustrates the density of the anti-inflammatory cytokine IL-10. IL-10 is activated by macrophages [33] with a rate denoted by α_{10}, while decay rate is represented by δ_{10}.
- The seventh equation in the model (1) depicts the level of TGF-β. The term s_β signifies the constant production rate of TGF-β [2]. The second term represents the contribution from tumor cells, which is directly proportional to their size, with α_β denoting the release rate per tumor cell [37]. The final term represents the degradation of the immunosuppressive cytokine TGF-β at a constant rate of δ_β.
- The eighth equation in the model (1) describes the concentration of IL-12. IL-12 is produced by dendritic cells, with α_{12} indicating the release rate per antigen-specific dendritic cell [31]. The degradation rate of IL-12 is denoted by δ_{12}.
- The ninth equation in the system (1) outlines the behavior of IFN-γ. We hypothesize that IFN-γ is produced by CD8+ T cells [2,37] with a production rate α_γ. The final term represents the degradation of IFN-γ at a constant rate of δ_γ.

Tumor growth encompasses multiple time scales. The expansion of the tumor cell population spanning over periods ranging from months to years, as well as weeks to months depends on their characteristics. According to the clinical observations, the activation of CD8+ T cells, macrophages, and dendritic cells (antigen-presenting) occurs in shorter time frames, like days to weeks. On the other hand, the degradation and secretion of both immuno-suppressive and immuno-stimulatory cytokines occur on shorter time scales (for example, seconds to hours). To enhance our comprehension of the intricate dynamics involved in the interaction between tumors and the immune system, we apply the quasi-steady-state approximations [38] in our mathematical model for the cytokines concentration. Then, from the cytokine equations of (1), we have

$$
\begin{aligned}
&T_g = \frac{\alpha_g}{\delta_g} T_8, \;\; I_{10} = \frac{\alpha_{10}}{\delta_{10}} M,\\
&T_\beta = \frac{s_\beta}{\delta_\beta} + \frac{\alpha_\beta}{\delta_\beta} T,\\
&I_{12} = \frac{\alpha_{12}}{\delta_{12}} D, \;\; I_\gamma = \frac{\alpha_\gamma}{\delta_\gamma} T_8.
\end{aligned}
$$

After substituting these cytokine expressions into the first to fourth equations of the deterministic system (1), we get the following four nonlinear ODEs of tumor-immune interaction system

$$
\begin{aligned}
\frac{dT}{dt} &= r_T T(1 - b_T T) - \frac{(\alpha_T M + \gamma_T T_8)T}{g_T + M},\\
\frac{dT_8}{dt} &= \frac{\alpha_8 D}{g_8 + T_8} - \delta_8 T_8,\\
\frac{dM}{dt} &= s_m + \frac{\alpha_m T_8}{(g_m + T_8)} \cdot \frac{1}{(g_{m1} + T)} - \gamma_m M T - \delta_m M,\\
\frac{dD}{dt} &= s_d + \frac{\alpha_d T}{g_d + T} - \delta_d D,
\end{aligned}
\tag{2}
$$

with the given following initial densities:

$$
\begin{aligned}
&T(0) = T_0 > 0, \quad T_8(0) = T_{80} > 0,\\
&M(0) = M_0 > 0, \quad D(0) = D_0 > 0,
\end{aligned}
$$

where

$$
\begin{aligned}
&\alpha_T = \frac{\delta_{10}}{\alpha_{10}} \alpha_T^{'}, \quad \gamma_T = \frac{\delta_{10}}{\alpha_{10}} \gamma_T^{'},\\
&g_T = \frac{\delta_{10}}{\alpha_{10}} g_T^{'}, \quad \alpha_8 = \frac{\delta_g}{\alpha_g} \frac{\alpha_{12}}{\delta_{12}} \alpha_8^{'},\\
&g_8 = \frac{\delta_g}{\alpha_g} g_8^{'}, \quad \alpha_m = \frac{\delta_\beta}{\alpha_\beta} \alpha_m^{'},\\
&g_m = \frac{\delta_\gamma}{\alpha_\gamma} g_m^{'}, \quad g_{m1} = \frac{\delta_\beta}{\alpha_\beta} g_{m1}^{'} + \frac{s_\beta}{\alpha_\beta}.
\end{aligned}
$$

Here,

- The first term of the first equation of (2) represents the logistic growth of tumor cell population with no immune response, where r_T is the intrinsic growth rate of tumor cells and $\frac{1}{b_T}$ is the maximum population size of tumor cells.
- The function $\frac{(\alpha_T M+\gamma_T T_8)T}{g_T+M}$ represents the deactivation term of tumor cells due to interaction with macrophages and cytotoxic T-lymphocytes with the deactivation rate α_T and γ_T, respectively. $\frac{1}{g_T+M}$ represents the major immuno-suppressive factor for both macrophages and CD8+ T cells, where g_T is the half-saturation constant.

$$(T_8^1)^2 + g_8 T_8^1 - \frac{\alpha_8 s_d}{\delta_8 \delta_d} = 0. \tag{3}$$

From the above equation, we have the following positive root

$$T_8^1 = \frac{-g_8 + \sqrt{\left(g_8^2 + 4\frac{\alpha_8 s_d}{\delta_8 \delta_d}\right)}}{2}.$$

To study the stability analysis of (2), we evaluate the variational matrix around the singular point $E(T, T_8, M, D)$ is

$$J(E) = \begin{bmatrix} r_T - 2r_T b_T T - \frac{(\alpha_T M+\gamma_T T_8)}{g_T+M} & -\frac{\gamma_T T}{g_T+M} & -\frac{(g_T\alpha_T-\gamma_T T_8)T}{(g_T+M)^2} & 0 \\ 0 & -\frac{\alpha_8 D}{(g_8+T_8)^2} - \delta_8 & 0 & \frac{\alpha_8}{g_8+T_8} \\ -\frac{\alpha_m T_8}{(g_m+T_8)(g_{m1}+T)^2} - \gamma_m M & \frac{\alpha_m g_m}{(g_m+T_8)^2(g_{m1}+T)} & -\gamma_m T - \delta_m & 0 \\ \frac{g_d \alpha_d}{(g_d+T)^2} & 0 & 0 & -\delta_d \end{bmatrix}.$$

- α_8 designates the activation rate of CD8+ T cells due to the direct presence of dendritic cells and the half-saturation constant of CD8+ T cells is g_8.
- The natural death rate of CD8+ T cells is δ_8.
- s_m signifies the constant influx rate of macrophages.
- The function $\frac{\alpha_m T_8}{(g_m+T_8)} \cdot \frac{1}{(g_{m1}+T)}$ describes the activation term of macrophages. α_m is the activation rate of macrophages due to the direct presence of CD8+ T cells, where g_m is the half-saturation constant. $\frac{1}{(g_{m1}+T)}$ is the major immuno-suppressive factor of macrophages and g_{m1} is the suppressive parameter.
- γ_m is the decay rate of macrophages due to the interaction with tumor cells.
- δ_m is the natural death rate of macrophages.
- The constant source rate of dendritic cells is s_d.
- The activation rate of dendritic cells due to the direct presence of tumor cells is represented by the coefficient α_d, with g_d being the half-saturation constant.
- δ_d is natural death rate of dendritic cells.

2.1 Equilibria

The deterministic model (2) has two feasible singular points, namely

(i) tumor-free singular point $E^1 \equiv (T^1, T_8^1, M^1, D^1) = \left(0, T_8^1, \frac{s_m g_{m1}(g_m+T_8^1)+\alpha_m T_8^1}{\delta_m g_{m1}(g_m+T_8^1)}, \frac{s_d}{\delta_d}\right)$, where T_8^1 is the unique positive root of the given equation

At the tumor-free singular point E^1, the variational matrix $J(E^1)$ of (2) has the following eigenvalues:

$$\lambda_1^1 = r_T - \frac{\alpha_T M^1 + \gamma_T T_8^1}{g_T + M^1},$$
$$\lambda_2^1 = -\frac{\alpha_8 D^1}{(g_8 + T_8^1)^2} - \delta_8,$$
$$\lambda_3^1 = -\delta_m,$$
$$\lambda_4^1 = -\delta_d.$$

It is observing that when $\lambda_1^1 < 0$, all eigenvalues of J(E^1) are negative.. Therefore, the tumor-free singular point is locally asymptotically stable if $r_T < \frac{\alpha_T M^1+\gamma_T T_8^1}{g_T+M^1}$, otherwise unstable. Then, we have the following theorem.

Theorem 1 *The tumor-free steady state E^1 of the deterministic system (2) will be locally asymptotically stable if $r_T - \frac{\alpha_T M^1+\gamma_T T_8^1}{g_T+M^1} < 0$, otherwise unstable.*

(ii) The interior singular point is $E^*(T^*, T_8^*, M^*, D^*)$, where (T^*, T_8^*, M^*, D^*) is the positive root of the equations $\frac{dT}{dt} = \frac{dT_8}{dt} = \frac{dM}{dt} = \frac{dD}{dt} = 0$. From an analytical perspective, determining the explicit form of the interior singular point E^* proves to be highly challenging. Hence, we investigate its existence and stability by numerical simulation.

3 Stochastic model

So far we have discussed the suggested tumor-immune interaction model in a deterministic setting. We aim to explore the dynamics of the changed system influenced by white noise, offering a more realistic representation compared to its deterministic counterpart. Although the deterministic tumor-immune interaction model provides significant insight into the dynamics of tumor growth, it does not describe the disease's likelihood of extinction. Due to the presence of some environmental fluctuations, our parameters such as the growth rate, death rate, and activation rate of our cell population also fluctuated. In this case, we introduce stochastic perturbations into our deterministic system to study the effect of environmental fluctuation. To study environmental fluctuation, there are mainly two processes to develop a stochastic perturbation of a deterministic model. In the first type, some important parameters are perturbed by the Gaussian white-noise type in the stochastic differential equation [26]. On the other hand, we introduce a randomly fluctuating term directly into the deterministic system without changing any parameter [25]. In the present paper, we consider the randomly fluctuating effects in our system and aim to investigate their impact around the interior fixed point of the deterministic system (2).

In real-life scenarios, biological systems exhibit inherent variability due to factors such as genetic diversity, environmental fluctuations. This variability can show up as stochastic fluctuations in cell populations, cytokine concentrations, and immune responses within tumor microenvironments. Environmental factors can impact tumor growth and immune system function. The environmental perturbations introduce stochasticity into the system, leading to unpredictable fluctuations in tumor progression and immune response dynamics. Clinical studies have highlighted the stochastic nature of cancer progression and treatment response. Despite similar initial conditions and treatments, patients with the same type and stage of cancer may exhibit varying outcomes, including differences in tumor growth rates, immune responses. This variability underscores the importance of considering stochastic fluctuations in cancer modeling. Experimental studies using in the models of cancer have demonstrated the presence of stochastic fluctuations including proliferation, activation, death. These stochastic fluctuations can arise from inherent biological noise, random molecular interactions, and environmental variability. By providing a comprehensive overview of these biological and medical considerations, we justify the application of white noise for stochastic perturbations in the tumor-immune interaction model. This background information helps establish the biological relevance of incorporating stochasticity into the model and underscores the importance of capturing real-life variability in cancer biology.

The motivation behind introducing stochastic equations in the tumor-immune interaction model lies in capturing the inherent randomness and uncertainty observed in biological systems. In real-world scenarios, biological processes are influenced by environmental factors such as fluctuations in temperature, oxygen levels, and nutrient availability can impact both tumor growth and immune cell function. These environmental fluctuations can introduce randomness into the system, affecting the dynamics of tumor-immune interactions. By incorporating stochasticity into the model, we aim to create a more realistic representation that accounts for the unpredictable nature of these processes. Overall, the motivation for using stochastic equations in the tumor-immune interaction model is to develop a more comprehensive understanding of the complex, inherently stochastic nature of biological systems and their responses to environmental fluctuations. This enables us to generate more realistic predictions and insights that can inform the development of effective cancer treatment strategies.

In the system (2), we consider that the stochastic random perturbations of the state variables around interior singular point $E^*(T^*,\ T_8^*,\ M^*,\ D^*)$ are white noise type, which are directly proportional to the distances of singular point, that is, $T^*,\ T_8^*,\ M^*,\ D^*$ from $T(t), T_8(t), M(t), D(t)$. Therefore, our model has stochastic nature with following form

$$\begin{aligned}
dT &= \left[r_T T(1-b_T T) - \frac{(\alpha_T M+\gamma_T T_8)T}{g_T+M}\right]dt \\
&\quad +\rho_1(T-T^*)dB_1(t), \\
dT_8 &= \left[\frac{\alpha_8 D}{g_8+T_8} - \delta_8 T_8\right]dt + \rho_2(T_8-T_8^*)dB_2(t), \\
dM &= \left[s_m + \frac{\alpha_m T_8}{(g_m+T_8)}\cdot\frac{1}{(g_{m1}+T)} - \gamma_m MT - \delta_m M\right]dt \\
&\quad +\rho_3(M-M^*)dB_3(t), \\
dD &= \left[s_d + \frac{\alpha_d T}{g_d+T} - \delta_d D\right]dt + \rho_4(D-D^*)dB_4(t).
\end{aligned} \tag{4}$$

ρ_i $(i = 1, 2, 3, 4)$ are positive real constants, which are known as intensity of white noise. $B_i(t)$ $(i = 1, 2, 3, 4)$ represents a 4-dimensional independent standard Wiener process [20]. We investigate the asymptotic stochastic stability behavior around the singular point E^* for the stochastic system (4) and comparing the results with the deterministic system (2). In our stochastic model (4), we used the Ito stochastic differential process in the following form

$$\begin{aligned} dX_t &= h(t, X_t)dt + n(t, X_t)dB(t), \\ X_{t_0} &= X_0, t \in [t_0, t_f], \end{aligned} \tag{5}$$

where the solution $\{X_t, t \in [t_0, t_f](t > 0)\}$ is an Ito process, h is the slowly varying continuous component or drift coefficient, n represents the rapidly varying continuous random component or diffusion matrix [20]. Also, $B(t)$ denotes a 4-dimensional random process which have scalar Wiener process with increments $\triangle B_i(t) = B_i(t + \triangle t) - B_i(t)$, $(i = 1, 2, 3, 4)$ are independent of Gaussian random variables $N(0, \triangle t)$. After stochastic integration, the equation (5) can be written in the following form

$$\begin{aligned} X_t = X(t) &= X_0 + \int_{t_0}^{t} h(s, X_s)ds \\ &+ \int_{t_0}^{t} n(s, X_s)dB(s), \end{aligned} \tag{6}$$

where second term of the right hand side of (6) is known as Riemann-Stieltjes integral and last term is known as an Itô integral. Comparing (4) and (5), we have

$$\begin{aligned} X_t &= (T, T_8, M, D)^T, \\ B(t) &= (B_1(t), B_2(t), B_3(t), B_4(t))^T, \end{aligned} \tag{7}$$

$$h = \begin{bmatrix} r_T T(1 - b_T T) - \frac{(\alpha_T M + \gamma_T T_8)T}{g_T + M} \\ \frac{\alpha_8 D}{g_8 + T_8} - \delta_8 T_8 \\ s_m + \frac{\alpha_m T_8}{(g_m + T_8)} \cdot \frac{1}{(g_{m1} + T)} - \gamma_m MT - \delta_m M \\ s_d + \frac{\alpha_d T}{g_d + T} - \delta_d D \end{bmatrix} \tag{8}$$

and

$$n = \begin{bmatrix} \rho_1(T - T^*) & 0 & 0 & 0 \\ 0 & \rho_2(T_8 - T_8^*) & 0 & 0 \\ 0 & 0 & \rho_3(M - M^*) & 0 \\ 0 & 0 & 0 & \rho_4(D - D^*) \end{bmatrix}. \tag{9}$$

The system characterized by the stochastic equation (4) is described as having multiplicative noise, given that the diffusion matrix (9) varies based on the solution $X_t = (T, T_8, M, D)^T$. Also, the stochastic system (4) is said to have a diagonal noise, since there is a diagonal form in the diffusion matrix n.

3.1 Preliminaries

We consider a complete probability space $(\Phi, \{F_t\}_{t\geq 0}, \mathbb{P})$ with filtration $\{F_t\}_{t\geq 0}$ satisfies $X(t) = (T(t), T_8(t), M(t), D(t))$, $|X(t)| = (T^2(t) + T_8^2(t) + M^2(t) + D^2(t))^{\frac{1}{2}}$ and $\mathbb{R}_+^c = \{x \in \mathbb{R}^c : \varphi_j > 0, j = 1, 2, 3, ..., c\}$. To study our stochastic system (4), we need some definitions which are very important in our case.

Definition 3.1 [39] Let us assume that $(T(0), T_8(0), M(0), D(0)) \in \mathbb{R}_+^4$ be the initial densities of the cell populations, then the solution $X(t) = (T(t), T_8(t), M(t), D(t))$ of the stochastic system (4) is said to be stochastically ultimate bounded (SUB), if for every $\kappa \in (0, 1)$, there is a constant $\mu = \mu(\kappa) > 0$, such that

$$\limsup_{t\to+\infty} \mathbb{P}\{|X(t)| > \mu\} < \kappa.$$

Definition 3.2 [39] Let us assume that $(T(0), T_8(0), M(0), D(0)) \in \mathbb{R}_+^4$ be the initial densities of cell populations, then the solution $X(t) = (T(t), T_8(t), M(t), D(t))$ of the stochastic system (4) is said to be stochastically permanence (SP), if for every $\kappa \in (0, 1)$, there is a constant $\mu = \mu(\kappa) > 0$, such that

$$\begin{aligned} &\liminf_{t\to+\infty} \mathbb{P}\{|X(t)| \leq \mu\} > 1 - \kappa, \\ &\liminf_{t\to+\infty} \mathbb{P}\{|X(t)| \geq \varphi\} > 1 - \kappa, \end{aligned}$$

where $\varphi = \varphi(\kappa)$.

4 Basic properties of the stochastic model (4)

In this section, we perform some fundamental properties of our stochastic model (4) including existence & uniqueness, stochastically ultimate bounded (SUB) and stochastically permanence (SP) with respect to the initial densities. To show these properties, we have constructed some suitable $\mathbb{C}^2$-function [39].

Theorem 2 *The solution $X_t = X(t) = (T(t), T_8(t), M(t), D(t))$ of stochastic model (4) is unique on $t \geq$*

0 *for any given initial densities* $X_0 = (T(0),\ T_8(0),\ M(0),\ D(0)) \in \mathbb{R}^4_+$ *and the solution will remain in* $\mathbb{R}_+$ *with* $\mathbb{P}\{T(t),\ T_8(t),\ M(t),\ D(t) \in \mathbb{R}_+,\ \forall\, t \geq 0\} = 1$, *that is, probability* 1 *almost surely.*

Proof For given any initial densities $X_0 = (T(0),\ T_8(0),\ M(0),\ D(0))$, coefficients which are to be used in the stochastic system (4) are continuous and satisfy the locally Lipschtiz condition. If t_e be the explosion time [39], then there must exists a unique solution $X_t = X(t) = (T(t),\ T_8(t),\ M(t),\ D(t)) \in \mathbb{R}^4_+$ of the stochastic system (4) for $t \in [0, t_e)$. To prove the nature of the solution is globally, we will must show that $t_e = \infty$ almost surely. We assume that all of the initial densities $(T(0),\ T_8(0),\ M(0),\ D(0))$ lies between the interval $\left[\frac{1}{p_0}, p_0\right]$, where $p_0 > 0$ be a sufficiently large constant. We consider final time t_p as

$$t_p = \left\{ \begin{array}{r} t \in [0, t_e) \ :\ \min\{T(t),\ T_8(t),\ M(t),\ D(t)\} \leq \frac{1}{p} \\ or\ \max\{T(t),\ T_8(t),\ M(t),\ D(t)\} \geq p \end{array} \right\},$$

and $\inf \phi = \infty$, where ϕ is the void set. It is clear that, if p tends to ∞, then the function t_p is increased. We have $t_\infty = \lim\limits_{p \to +\infty} t_p$ implies that $t_\infty \leq t_e$ almost surely.

Therefore, in order to show that $t_e = \infty$, we have must to prove that $t_\infty = \infty$ almost surely. If possible, let us assume that $t_\infty < \infty$ almost surely. Then, there exists two constants $t_T > 0$ and $\epsilon \in (0, 1)$ in such a way that $\mathbb{P}\{t_\infty \leq t_T\} > \epsilon$. Hence, there exists an integer $p_1 \geq p_0$ such that

$$\mathbb{P}\{t_p \leq t_T\} \geq \epsilon\ \forall\ p \geq p_1. \tag{10}$$

We define a $\mathbb{C}^2$-function $V : \mathbb{R}^4_+ \to \mathbb{R}_+$ such that $V(T,\ T_8,\ M,\ D) = (T + 1 - \ln T) + (T_8 + 1 - \ln T_8) + (M + 1 - \ln M) + (D + 1 - \ln D)$. Using Itô's formula, we get

$$\begin{aligned} &dV(T,\ T_8,\ M,\ D) \\ &= LV(T,\ T_8,\ M,\ D)dt + \rho_1(T - T^*)\Big(1 - \frac{1}{T}\Big)dB_1 \\ &\quad + \rho_2(T_8 - T_8^*)\Big(1 - \frac{1}{T_8}\Big)dB_2 \\ &\quad + \rho_3(M - M^*)\Big(1 - \frac{1}{M}\Big)dB_3 \\ &\quad + \rho_4(D - D^*)\Big(1 - \frac{1}{D}\Big)dB_4, \end{aligned}$$

where

$$\begin{aligned} &LV(T,\ T_8,\ M,\ D) \\ &= \left(1 - \frac{1}{T}\right)\left[r_T T(1 - b_T T) - \frac{(\alpha_T M + \gamma_T T_8)T}{g_T + M}\right] \\ &\quad + \frac{\rho_1^2}{2}\left(1 - \frac{T^*}{T}\right)^2 \\ &\quad + \left(1 - \frac{1}{T_8}\right)\left[\frac{\alpha_8 D}{g_8 + T_8} - \delta_8 T_8\right] + \frac{\rho_2^2}{2}\left(1 - \frac{T_8^*}{T_8}\right)^2 \\ &\quad + \left(1 - \frac{1}{M}\right)\left[s_m + \frac{\alpha_m T_8}{(g_m + T_8)} \cdot \frac{1}{(g_{m1} + T)}\right. \\ &\quad \left. - \gamma_m M T - \delta_m M\right] + \frac{\rho_3^2}{2}\left(1 - \frac{M^*}{M}\right)^2 \\ &\quad + \left(1 - \frac{1}{D}\right)\left[s_d + \frac{\alpha_d T}{g_d + T} - \delta_d D\right] + \frac{\rho_4^2}{2}\left(1 - \frac{D^*}{D}\right)^2. \end{aligned}$$

Positiveness of $T,\ T_8,\ M,\ D$ implies that

$$\begin{aligned} &LV(T,\ T_8,\ M,\ D) \\ &\leq \delta_8 + s_m + \delta_m + s_d + \delta_d \\ &\quad + \frac{\rho_1^2}{2}\left(1 + \left(\frac{T^*}{T}\right)^2\right) + \frac{\rho_2^2}{2}\left(1 + \left(\frac{T_8^*}{T_8}\right)^2\right) \\ &\quad + \frac{\rho_3^2}{2}\left(1 + \left(\frac{M^*}{M}\right)^2\right) + \frac{\rho_4^2}{2}\left(1 + \left(\frac{D^*}{D}\right)^2\right) \\ &\quad + T(r_T + r_T b_T + \gamma_m) \\ &\quad + \frac{(\alpha_T M + \gamma_T T_8)}{g_T + M} + \frac{\alpha_8 D}{g_8 + T_8} \\ &\quad + \frac{\alpha_m T_8}{(g_m + T_8)} \cdot \frac{1}{(g_{m1} + T)} + \frac{\alpha_d T}{g_d + T}. \end{aligned}$$

We define positive constants are as follows

$$\begin{aligned} k_1 &= \delta_8 + s_m + \delta_m + s_d + \delta_d \\ &\quad + \frac{\rho_1^2}{2}\left(1 + \left(\frac{T^*}{T}\right)^2\right) + \frac{\rho_2^2}{2}\left(1 + \left(\frac{T_8^*}{T_8}\right)^2\right) \\ &\quad + \frac{\rho_3^2}{2}\left(1 + \left(\frac{M^*}{M}\right)^2\right) \\ &\quad + \frac{\rho_4^2}{2}\left(1 + \left(\frac{D^*}{D}\right)^2\right), \\ k_2 &= r_T + r_T b_T + \gamma_m. \end{aligned}$$

After some algebraic manipulation, we have

$$\begin{aligned} LV(T,\ T_8,\ M,\ D) \leq k_1 + k_2 T + \frac{(\alpha_T M + \gamma_T T_8)}{g_T + M} \\ + \frac{\alpha_8 D}{g_8 + T_8} + \frac{\alpha_m T_8}{(g_m + T_8)} \\ \cdot \frac{1}{(g_{m1} + T)} + \frac{\alpha_d T}{g_d + T}. \end{aligned}$$

If we take superior of the coefficients of the above inequality, then there exists a positive constant G such that

$$LV \leq G.$$

LV is a diffusion operator of Itô's process with $\mathbb{C}^2$-function V and if x be Itô's process with

$$dx = f dt + \rho dB,$$

then we get

$$\begin{aligned}
&dV(T,\ T_8,\ M,\ D)\\
&\leq G dt + \rho_1(T - T^*)\Big(1 - \frac{1}{T}\Big)dB_1\\
&\quad +\rho_2(T_8 - T_8^*)\Big(1 - \frac{1}{T_8}\Big)dB_2\\
&\quad +\rho_3(M - M^*)\Big(1 - \frac{1}{M}\Big)dB_3\\
&\quad +\rho_4(D - D^*)\Big(1 - \frac{1}{D}\Big)dB_4.
\end{aligned}$$

By taking $t_1 \leq t_T$, we obtain

$$\begin{aligned}
&\int_0^{t_p \wedge t_1} dV(T,\ T_8,\ M,\ D)\\
&\leq \int_0^{t_p \wedge t_1} G dt + \int_0^{t_p \wedge t_1} \rho_1(T - T^*)\Big(1 - \frac{1}{T}\Big)dB_1\\
&\quad + \int_0^{t_p \wedge t_1} \rho_2(T_8 - T_8^*)\Big(1 - \frac{1}{T_8}\Big)dB_2\\
&\quad + \int_0^{t_p \wedge t_1} \rho_3(M - M^*)\Big(1 - \frac{1}{M}\Big)dB_3\\
&\quad + \int_0^{t_p \wedge t_1} \rho_4(D - D^*)\Big(1 - \frac{1}{D}\Big)dB_4,
\end{aligned}$$

where $t_p \wedge t_1 = \min(t_p, t_1)$. This leads to

$$\begin{aligned}
&V(T(t_p \wedge t_1),\ T_8(t_p \wedge t_1),\ M(t_p \wedge t_1),\ D(t_p \wedge t_1))\\
&\leq V(T_0,\ T_{8_0},\ M_0,\ D_0) + \int_0^{t_p \wedge t_1} G dt\\
&\quad + \int_0^{t_p \wedge t_1} \rho_1(T - T^*)\Big(1 - \frac{1}{T}\Big)dB_1\\
&\quad + \int_0^{t_p \wedge t_1} \rho_2(T_8 - T_8^*)\Big(1 - \frac{1}{T_8}\Big)dB_2\\
&\quad + \int_0^{t_p \wedge t_1} \rho_3(M - M^*)\Big(1 - \frac{1}{M}\Big)dB_3\\
&\quad + \int_0^{t_p \wedge t_1} \rho_4(D - D^*)\Big(1 - \frac{1}{D}\Big)dB_4.
\end{aligned}$$

At first, we take the expectation on both sides, followed by the application of Fubini's theorem [40] and the properties of Itô's integral, we have

$$\begin{aligned}
&\mathbb{E}V(T(t_p \wedge t_1),\ T_8(t_p \wedge t_1),\ M(t_p \wedge t_1),\ D(t_p \wedge t_1))\\
&\leq V(T_0,\ T_{8_0},\ M_0,\ D_0) + G\mathbb{E}(t_p \wedge t_1).
\end{aligned}$$

Let us assume that $\Phi_p = \{t_p \leq t_T\}$, for $p \geq p_1$. Then, from equation (10), we have $\mathbb{P}(\Phi_p) \geq \epsilon$.

Now, for every $\omega \in \Phi_p$, there is at least one of $(T(t_p, \omega),\ T_8(t_p, \omega),\ M(t_p, \omega),\ D(t_p, \omega))$ is equal to either p or $\frac{1}{p}$ and $V(T(t_p),\ T_8(t_p),\ M(t_p),\ D(t_p))$ is also not less than the smallest of $\min\{(p + 1 - \log p), \Big(\frac{1}{p} + 1 + \log p\Big)\}$. Consequently,

$$\begin{aligned}
&V(T_0,\ T_{8_0},\ M_0,\ D_0)\\
&\quad \geq \epsilon \max[(p + 1 - \log p) \wedge \Big(\frac{1}{p} + 1 + \log p\Big) \max].
\end{aligned}$$

Indicator function of Φ_p is $1_{\Phi_p}(\omega)$ defined as

$$1_{\Phi_p}(\omega) = \begin{cases} 1\ , if\ \omega \in \Phi_p, \\ 0\ , if\ \omega \notin \Phi_p. \end{cases}$$

If $p \to \infty$, we have $\infty > V(T_0,\ T_{8_0},\ M_0,\ D_0) + Gt_T = \infty$, which resulting in a contradiction. So, we have $t_\infty = \infty$. Hence, the proof of the theorem. □

Theorem 3 *The solution of the stochastic system (4) is stochastically ultimate bounded for initial densities* $(T(0),\ T_8(0),\ M(0),\ D(0)) \in \mathbb{R}_+^4$.

Proof In the previous theorem, we prove that there is a unique solution in $\mathbb{R}_+^4$ for all $t \geq 0$ almost surely. Now, we define a $\mathbb{C}^2$-function $V : \mathbb{R}_+^4 \to \mathbb{R}_+$ such that

$$V(T,\ T_8,\ M,\ D) = e^t(T^\theta + T_8^\theta + M^\theta + D^\theta), \quad (11)$$

where $(T,\ T_8,\ M,\ D) \in \mathbb{R}_+^4$ and $\theta \in (0, 1)$. Differentiating equation (11) by Itô's formula, we get

$$\begin{aligned}
dV(T,\ T_8,\ M,\ D) &= e^t\Bigg[(T^\theta + T_8^\theta + M^\theta + D^\theta)\\
&+\theta T^{\theta-1}\Big(r_T T(1 - b_T T) - \frac{(\alpha_T M + \gamma_T T_8)T}{g_T + M}\Big)\\
&+\theta T_8^{\theta-1}\Big(\frac{\alpha_8 D}{g_8 + T_8} - \delta_8 T_8\Big)\\
&+\theta M^{\theta-1}\\
&\Big(s_m + \frac{\alpha_m T_8}{(g_m + T_8)} \cdot \frac{1}{(g_{m1} + T)} - \gamma_m M T - \delta_m M\Big)\\
&+\theta D^{\theta-1}\Big(s_d + \frac{\alpha_d T}{g_d + T} - \delta_d D\Big)\\
&+\frac{\theta(\theta - 1)}{2}\Big\{\rho_1^2 T^\theta\Big(1 - \frac{T^*}{T}\Big)^2 + \rho_2^2 T_8^\theta\Big(1 - \frac{T_8^*}{T_8}\Big)^2\\
&+\rho_3^2 M^\theta\Big(1 - \frac{M^*}{M}\Big)^2 + \rho_4^2 D^\theta\Big(1 - \frac{D^*}{D}\Big)^2\Big\}\Bigg]dt
\end{aligned}$$

$$
\begin{aligned}
&+e^t\theta\Bigg[\rho_1 T^\theta\left(1-\frac{T^*}{T}\right)dB_1\\
&+\rho_2 T_8^\theta\left(1-\frac{T_8^*}{T_8}\right)dB_2\\
&+\rho_3 M^\theta\left(1-\frac{M^*}{M}\right)dB_3\\
&+\rho_4 D^\theta\left(1-\frac{D^*}{D}\right)dB_4\Bigg]\\
&\le e^t\Bigg[G+\frac{\theta(\theta-1)}{2}\Bigg\{\rho_1^2 T^\theta\left(1-\frac{T^*}{T}\right)^2\\
&+\rho_2^2 T_8^\theta\left(1-\frac{T_8^*}{T_8}\right)^2\\
&+\rho_3^2 M^\theta\left(1-\frac{M^*}{M}\right)^2\\
&+\rho_4^2 D^\theta\left(1-\frac{D^*}{D}\right)^2\Bigg\}\Bigg]dt\\
&+e^t\theta\Bigg[\rho_1 T^\theta\left(1-\frac{T^*}{T}\right)dB_1+\rho_2 T_8^\theta\left(1-\frac{T_8^*}{T_8}\right)dB_2\\
&+\rho_3 M^\theta\left(1-\frac{M^*}{M}\right)dB_3+\rho_4 D^\theta\left(1-\frac{D^*}{D}\right)dB_4\Bigg],\\
&\text{(taking superior of the coefficient of the inequality)}\\
&\le Ge^t dt+e^t\theta\Bigg[\rho_1 T^\theta\left(1-\frac{T^*}{T}\right)dB_1\\
&+\rho_2 T_8^\theta\left(1-\frac{T_8^*}{T_8}\right)dB_2\\
&+\rho_3 M^\theta\left(1-\frac{M^*}{M}\right)dB_3\\
&+\rho_4 D^\theta\left(1-\frac{D^*}{D}\right)dB_4\Bigg],\qquad [\text{since}, (\theta-1)<0].
\end{aligned}
$$

Integrating both sides of the above inequality from 0 to $t_p \wedge t$ and taking expectation leads to the following inequality

$$
\begin{aligned}
&\mathbb{E}V(T(t_p\wedge t),\ T_8(t_p\wedge t),\ M(t_p\wedge t),\ D(t_p\wedge t))\\
&\le V(T(0),\ T_8(0),\ M(0),\ D(0))\\
&\quad+G\mathbb{E}\int_0^{t_p\wedge t}e^p dp.
\end{aligned}
$$

If we take $p\to+\infty$, then we have

$$
\begin{aligned}
&\mathbb{E}V(T(t),\ T_8(t),\ M(t),\ D(t))\\
&\le V(T(0),\ T_8(0),\ M(0),\ D(0))+G(e^t-1),
\end{aligned}
$$

which implies that

$$
\begin{aligned}
&e^{-t}\mathbb{E}V(T(t),\ T_8(t),\ M(t),\ D(t))\\
&\le e^{-t}V(T(0),\ T_8(0),\ M(0),\ D(0))+G.
\end{aligned}
$$

Now, we can express that

$$
\begin{aligned}
|X(t)|^\theta &= (T^2(t)+T_8^2(t)+M^2(t)+D^2(t))^{\frac{\theta}{2}}\\
&\le 4^{\frac{\theta}{2}}\max\{T^\theta(t),\ T_8^\theta(t),\ M^\theta(t),\ D^\theta(t)\}\\
&\le 2^\theta\{T^\theta(t)+T_8^\theta(t)+M^\theta(t)+D^\theta(t)\}.
\end{aligned}
$$

Now, the equation (11) leads to the following form

$$
\begin{aligned}
&T^\theta+T_8^\theta+M^\theta+D^\theta=e^{-t}V(T,\ T_8,\ M,\ D)\\
&\Rightarrow |X(t)|^\theta\le 2^\theta(e^{-t}V(T,\ T_8,\ M,\ D))\\
&\Rightarrow \mathbb{E}|X(t)|^\theta\\
&\le \mathbb{E}[2^\theta(e^{-t}V(T,\ T_8,\ M,\ D))]\\
&\Rightarrow \mathbb{E}|X(t)|^\theta\\
&\le 2^\theta(e^{-t}V(T(0),\ T_8(0),\ M(0),\ D(0))+G),
\end{aligned}
$$

which gives

$$
\lim_{t\to+\infty}\mathbb{E}|X(t)|^\theta\le 2^\theta G<+\infty.
$$

We choose $\theta=\frac{1}{2}$, then there exists a constant $\mu_1>0$, such that

$$
\limsup_{t\to+\infty}\mathbb{E}|X(t)|^{\frac{1}{2}}\le\mu_1.
$$

Using Chebyshev's inequality and taking $\mu=\frac{\mu_1^2}{\kappa^2}$, we get

$$
\begin{aligned}
&\mathbb{P}\{|X(t)|>\mu\}\le\frac{\mathbb{E}|X(t)|^{\frac{1}{2}}}{\mu^{\frac{1}{2}}}\\
&\Rightarrow\limsup_{t\to+\infty}\mathbb{P}\{|X(t)|>\mu\}\\
&\le\frac{\mu_1}{\mu^{\frac{1}{2}}}=\kappa.
\end{aligned}
$$

Therefore, the solution of stochastic model (4) is stochastically ultimate bounded with the given initial densities. □

Theorem 4 *For any initial densities* $(T(0),\ T_8(0),\ M(0),\ D(0))\in\mathbb{R}_+^4$, *the solution of the stochastic model (4) is stochastically permanence.*

Proof Let us assume that a $\mathbb{C}^2$-function $V:\mathbb{R}_+^4\to\mathbb{R}_+$ such that

$$
V(T,\ T_8,\ M,\ D)=\frac{1}{T+T_8+M+D}. \tag{12}
$$

Using by Itô's formula, we have

$$
\begin{aligned}
dV &= LVdt-V^2[\rho_1(T-T^*)dB_1+\rho_2(T_8-T_8^*)dB_2\\
&\quad+\rho_3(M-M^*)dB_3+\rho_4(D-D^*)dB_4],
\end{aligned}
$$

where

$$\begin{aligned}LV = &-V^2\Bigg[r_T T(1-b_T T) - \frac{(\alpha_T M + \gamma_T T_8)T}{g_T + M}\\ &+\frac{\alpha_8 D}{g_8 + T_8} - \delta_8 T_8 + s_m\\ &+\frac{\alpha_m T_8}{(g_m + T_8)} \cdot \frac{1}{(g_{m1} + T)} - \gamma_m MT\\ &-\delta_m M + s_d + \frac{\alpha_d T}{g_d + T} - \delta_d D\Bigg]\\ &+V^3[\rho_1^2(T - T^*)^2 + \rho_2^2(T_8 - T_8^*)^2\\ &+\rho_3^2(M - M^*)^2 + \rho_4^2(D - D^*)^2].\end{aligned}$$

We take a positive constant ψ, such that $\psi < 1$ and define

$$U(T,\ T_8,\ M,\ D) = (1 + V(T,\ T_8,\ M,\ D))^{\psi}.$$

Applying Itô's formula, we get

$$\begin{aligned}LU = &\psi(1+V)^{\psi-1}\Bigg[-V^2\Bigg\{r_T T(1-b_T T)\\ &-\frac{(\alpha_T M + \gamma_T T_8)T}{g_T + M} + \frac{\alpha_8 D}{g_8 + T_8} - \delta_8 T_8\\ &+s_m + \frac{\alpha_m T_8}{(g_m + T_8)} \cdot \frac{1}{(g_{m1} + T)}\\ &-\gamma_m MT - \delta_m M + s_d + \frac{\alpha_d T}{g_d + T} - \delta_d D\Bigg\}\\ &+V^3[\rho_1^2(T - T^*)^2 + \rho_2^2(T_8 - T_8^*)^2\\ &+\rho_3^2(M - M^*)^2 + \rho_4^2(D - D^*)^2]\Bigg]\\ &+\frac{1}{2}\psi(\psi-1)(1+V)^{\psi-2}V^4[\rho_1^2(T - T^*)^2\\ &+\rho_2^2(T_8 - T_8^*)^2 + \rho_3^2(M - M^*)^2\\ &+\rho_4^2(D - D^*)^2]\\ = &\psi(1+V)^{\psi-1}LV\\ &+\frac{1}{2}\psi(\psi-1)(1+V)^{\psi-2}V^4[\rho_1^2(T - T^*)^2\\ &+\rho_2^2(T_8 - T_8^*)^2 + \rho_3^2(M - M^*)^2\\ &+\rho_4^2(D - D^*)^2].\end{aligned}$$

Again, we choose very small positive constant, denoted as n, such that

$$W(T,\ T_8,\ M,\ D) = e^{nt}(1 + V(T,\ T_8,\ M,\ D))^{\psi}.$$

Using Itô's formula, we get

$$\begin{aligned}LW &= ne^{nt}(1+V)^{\psi} + e^{nt}L(1+V)^{\psi}\\ &= e^{nt}(1+V)^{\psi-2}\\ &\Bigg[n(1+V)^2 - \psi(1+V)V^2\Bigg\{r_T T(1-b_T T)\\ &-\frac{(\alpha_T M + \gamma_T T_8)T}{g_T + M} + \frac{\alpha_8 D}{g_8 + T_8} - \delta_8 T_8\\ &+s_m + \frac{\alpha_m T_8}{(g_m + T_8)} \cdot \frac{1}{(g_{m1} + T)} - \gamma_m MT - \delta_m M\\ &+s_d + \frac{\alpha_d T}{g_d + T} - \delta_d D\Bigg\} + \psi(1+V)V^3[\rho_1^2(T - T^*)^2\\ &+\rho_2^2(T_8 - T_8^*)^2 + \rho_3^3(M - M^*)^2 + \rho_4^2(D - D^*)^2]\\ &+\frac{1}{2}\psi(\psi-1)V^4[\rho_1^2(T - T^*)^2 + \rho_2^2(T_8 - T_8^*)^2\\ &+\rho_3^2(M - M^*)^2 + \rho_4^2(D - D^*)^2]\Bigg]\\ &\le e^{nt}(1+V)^{\psi-2}\Bigg[n(1+V)^2 + \psi(1+V)V^2\Bigg\{r_T b_T T^2\\ &+\frac{(\alpha_T M + \gamma_T T8)T}{g_T + M} + \delta_8 T_8 + \gamma_m MT\\ &+\delta_m M + \delta_d D\Bigg\} + \psi(1+V)V^3\Bigg\{\rho_1^2(T - T^*)^2\\ &+\rho_2^2(T_8 - T_8^*)^2 + \rho_3^2(M - M^*)^2 + \rho_4^2(D - D^*)^2\Bigg\}\\ &+\frac{1}{2}\psi(\psi-1)V^4[\rho_1^2(T - T^*)^2 + \rho_2^2(T_8 - T_8^*)^2\\ &+\rho_3^2(M - M^*)^2 + \rho_4^2(D - D^*)^2]\Bigg]\\ &\le e^{nt}(1+V)^{\psi-2}\Bigg[n(1+V)^2 + \psi(1+V)V^2\Bigg\{r_T b_T T^2\\ &+\frac{(\alpha_T M + \gamma_T T8)T}{g_T + M} + \delta_8 T_8 + \gamma_m MT\\ &+\delta_m M + \delta_d D\Bigg\} + \psi(1+V)V^3\Bigg\{\rho_1^2(T - T^*)^2\\ &+\rho_2^2(T_8 - T_8^*)^2 + \rho_3^2(M - M^*)^2 + \rho_4^2(D - D^*)^2\Bigg\}\Bigg],\\ &\text{(since } (\psi - 1) < 0).\end{aligned}$$

We take G is the superior of the coefficient and we have an expression as

$$\begin{aligned}&\psi(1+V)V^3[\rho_1^2(T - T^*)^2 + \rho_2^2(T_8 - T_8^*)^2\\ &+\rho_3^2(M - M^*)^2 + \rho_4^2(D - D^*)^2]\\ &\le \psi(1+V)V(2\max_{i=1,2,3,4}\{\rho_i^2\}).\end{aligned}$$

Therefore,

$$LW \le me^{nt},$$

where

$$m = (1+V)^{\psi-2}[n + V\{2n + \psi(2\max_{i=1,2,3,4}\{\rho_i^2\})\}$$

$$+V^2(n+G\psi+\psi(2\max_{i=1,2,3,4}\{\rho_i^2\}))+V^3G\psi].$$

Thus, we have

$$\begin{aligned}&L[e^{nt}(1+V)^{\psi}]\le me^{nt}\\&\Rightarrow\mathbb{E}[e^{nt}(1+V)^{\psi}]\\&\le(1+V(0))^{\psi}+\frac{m}{n}(e^{nt}-1).\end{aligned}$$

Therefore, we get

$$\begin{aligned}&\limsup_{t\to\infty}\mathbb{E}(V(t)^{\psi})\\&\le\limsup_{t\to\infty}\mathbb{E}((1+V(t))^{\psi})\\&\le\frac{m}{n}.\end{aligned}$$

Since

$$\begin{aligned}(T+T_8+M+D)^{\psi}&\le 4^{\psi}(T^2+T_8^2+M^2+D^2)^{\frac{\psi}{2}}\\&=4^{\psi}|X(t)|^{\psi},\end{aligned}$$

then

$$\begin{aligned}&\limsup_{t\to\infty}\mathbb{E}|X(t)|^{-\psi}\\&\le 4^{\psi}\limsup_{t\to\infty}\mathbb{E}(V(t)^{\psi})\\&\le\frac{4^{\psi}m}{n}=K(\text{constant}).\end{aligned}$$

By previous theorem, we have

$$\begin{aligned}&\limsup_{t\to+\infty}\mathbb{P}\{|X(t)|>\mu\}\le\kappa\\&\Rightarrow\limsup_{t\to+\infty}\mathbb{P}\{|X(t)|\le\mu\}\ge 1-\kappa.\end{aligned}$$

Also, we have

$$\limsup_{t\to+\infty}\mathbb{E}|X(t)|^{-\psi}\le K.$$

For any $\kappa>0$ and $\varphi=\left(\frac{\kappa}{K}\right)^{\frac{1}{\psi}}$, we get

$$\begin{aligned}\mathbb{P}\{|X(t)|<\mu\}&=\mathbb{P}\left\{\frac{1}{|X(t)|}>\frac{1}{\varphi}\right\}\\&\le\varphi^{\psi}\mathbb{E}|X(t)|^{-\psi}=\kappa,\end{aligned}$$

which means that

$$\liminf_{t\to+\infty}\mathbb{P}\{|X(t)|\ge\varphi\}\ge 1-\kappa.$$

Therefore, solution of the stochastic model (4) is stochastically permanence. □

Theorem 5 *Let* $(T(t),\ T_8(t),\ M(t),\ D(t))$ *be the solution of the stochastic system (4) initiating for any value* $(T(0),\ T_8(0),\ M(0),\ D(0))\in\mathbb{R}_+^4$. *Then, the tumor cells extinct exponentially with probability one, that is,* $\lim_{t\to\infty}T(t)=0$ *almost surely if* $r_T\le\rho_1^2(\frac{1}{2}-T^*)$.

Proof Let us assume that $u=\ln T$. Applying Itô's formula, we get

$$\begin{aligned}du=&\left[r_T(1-b_TT)-\frac{(\alpha_TM+\gamma_TT_8)}{g_T+M}\right.\\&\left.-\frac{1}{2}\rho_1^2\left(1-\frac{T^*}{T}\right)^2\right]dt\\&+\rho_1\left(1-\frac{T^*}{T}\right)dB_1.\end{aligned}$$

After some algebraic calculations, above equation leads to

$$\begin{aligned}d(\ln T)\le&[r_T(1-b_TT)-\frac{1}{2}\rho_1^2+\rho_1^2T^*]dt\\&+\rho_1\left(1-\frac{T^*}{T}\right)dB_1.\end{aligned}\tag{13}$$

Now, we take $P(T)=r_T(1-b_TT)-\frac{1}{2}\rho_1^2+\rho_1^2T^*$. Here, we intend to get the supremum value of $P(T)$, we get $P^{'}(T)=-r_Tb_T<0$. Therefore, $P(T)$ is a decreasing function of $T(t)$ on the interval $[0,\ \infty)$ and hence, supremum value of $P(T)$ is

$$P(T)_{\sup t\ge0}=P(0)=r_T-\frac{1}{2}\rho_1^2+\rho_1^2T^*.$$

From equation (13), we get

$$\begin{aligned}d(\ln T)\le&[r_T-\frac{1}{2}\rho_1^2+\rho_1^2T^*]dt\\&+\rho_1\left(1-\frac{T^*}{T}\right)dB_1\\\Rightarrow\ln T\le&\ln T_0+[r_T-\frac{1}{2}\rho_1^2+\rho_1^2T^*]t\\&+\rho_1\left(1-\frac{T^*}{T}\right)B_1.\end{aligned}$$

From strong law of large numbers for local martingles, it follows that

$$\begin{aligned}&\lim_{t\to\infty}\sup\frac{\ln T(t)}{t}\\&\le\lim_{t\to\infty}\sup\left[\frac{\ln T_0}{t}+(r_T-\frac{1}{2}\rho_1^2+\rho_1^2T^*)\right.\\&\left.+\frac{\rho_1}{t}\left(1-\frac{T^*}{T}\right)B_1\right]\\&=r_T-\frac{1}{2}\rho_1^2+\rho_1^2T^*.\end{aligned}$$

Now, using the condition $r_T\le\rho_1^2(\frac{1}{2}-T^*)$, we get

$$\begin{aligned}&\lim_{t\to\infty}\sup\frac{\ln T(t)}{t}\le 0\\&\Rightarrow\lim_{t\to\infty}T(t)=0,\quad\text{almost surely.}\end{aligned}$$

Therefore, tumor cells become extinct. □

5 Stochastic stability of the singular point

By introducing new variables $v_1 = T - T^*,\ v_2 = T_8 - T_8^*,\ v_3 = M - M^*,\ v_4 = D - D^*$, the stochastic differential system (4) can be centered around its interior singular point $E^* = (T^*,\ T_8^*,\ M^*,\ D^*)$. As the system (4) consists of nonlinear equations, then it is very difficult to derive asymptotically stability in mean square sense (with probability 1) by constructing Lyapunov function method. We find out a set of stochastic differential equation by linearizing the drift coefficient h around the singular point $E^* = (T^*,\ T_8^*,\ M^*,\ D^*)$. Then, the linearized system leads to

$$dv(t) = h(v(t))dt + n(v(t))dB, \tag{14}$$

where

$$v(t) = col(v_1(t),\ v_2(t),\ v_3(t),\ v_4(t)),$$

and

$$h(v(t)) = \begin{bmatrix} h_{11}v_1 & h_{12}v_2 & h_{13}v_3 & h_{14}v_4 \\ h_{21}v_1 & h_{22}v_2 & h_{23}v_3 & h_{24}v_4 \\ h_{31}v_1 & h_{32}v_2 & h_{33}v_3 & h_{34}v_4 \\ h_{41}v_1 & h_{42}v_2 & h_{43}v_3 & h_{44}v_4 \end{bmatrix},$$

$$n(v(t)) = \begin{bmatrix} \rho_1 v_1 & 0 & 0 & 0 \\ 0 & \rho_2 v_2 & 0 & 0 \\ 0 & 0 & \rho_3 v_3 & 0 \\ 0 & 0 & 0 & \rho_4 v_4 \end{bmatrix},$$

with

$$h_{11} = r_T - 2r_T b_T T^* - \frac{(\alpha_T M^* + \gamma_T T_8^*)}{g_T + M^*},$$
$$h_{12} = -\frac{\gamma_T T^*}{g_T + M^*},$$
$$h_{13} = -\frac{(g_T \alpha_T - \gamma_T T_8^*)T^*}{(g_T + M^*)^2},$$
$$h_{14} = 0,$$
$$h_{21} = 0,$$
$$h_{22} = -\frac{\alpha_8 D^*}{(g_8 + T_8^*)^2} - \delta_8,$$
$$h_{23} = 0,$$
$$h_{24} = \frac{\alpha_8}{g_8 + T_8^*},$$
$$h_{31} = -\frac{\alpha_m T_8^*}{(g_m + T_8^*)(g_{m1} + T^*)^2} - \gamma_m M^*,$$
$$h_{32} = \frac{\alpha_m g_m}{(g_m + T_8^*)^2 (g_{m1} + T^*)},$$
$$h_{33} = -\gamma_m T^* - \delta_m,$$
$$h_{34} = 0,$$
$$h_{41} = \frac{g_d \alpha_d}{(g_d + T^*)^2},$$
$$h_{42} = 0,$$
$$h_{43} = 0,$$
$$h_{44} = -\delta_d.$$

It is to be observed that, in equation (14) the interior singular point $E^* = (T^*,\ T_8^*,\ M^*,\ D^*)$ corresponds to the trivial solution $(v_1,\ v_2,\ v_3,\ v_4) = (0,\ 0,\ 0,\ 0)$. Let us consider that the set $\sum = \{\mathbb{R}^4 \times (t \geq t_0),\ t_0 \in \mathbb{R}^+\}$. If $W \in \mathbb{C}^2(\sum)$ is a continuous function with respect to t and a twice continuously differentiable function with respect to v, then we can assert the following lemma as presented by Gard T.C. [40].

Lemma 1 *Consider a function $W(v,t) \in \mathbb{C}^2(\sum)$ satisfying the inequalities*

$$c_1|v|^\pi \leq W(v,\ t) \leq c_2|v|^\pi, \tag{15}$$

and

$$LW(v,\ t) \leq -c_3|v|^\pi,\ c_i > 0,\ \pi > 0\ (i = 1,\ 2,\ 3). \tag{16}$$

Then, the trivial solution of (14) is exponentially π-stable, for all $t \geq 0$.

The trivial solution of (14) is said to be exponentially mean square stability if $\pi = 2$. Furthermore, this trivial solution exhibits globally asymptotically stable in the sense of probability. With reference to (14), $LW(v,\ t)$ is given by the following expression:

$$LW(v,\ t) = \frac{\partial W(v,\ t)}{\partial t} + h^T(v(t))\frac{\partial W(v,\ t)}{\partial v} + \frac{1}{2}Tr\left[n^T(v(t))\frac{\partial^2 W(v,\ t)}{\partial v^2}n(v(t))\right], \tag{17}$$

where

$$\frac{\partial W}{\partial v} = col\left(\frac{\partial W}{\partial v_1},\ \frac{\partial W}{\partial v_2},\ \frac{\partial W}{\partial v_3},\ \frac{\partial W}{\partial v_4}\right),$$
$$\frac{\partial^2 W(v,\ t)}{\partial v^2} = \left(\frac{\partial^2 W}{\partial v_i \partial v_j}\right)_{i,j=1,2,3,4}.$$

Now, we shall investigate our main result in the following theorem.

Theorem 6 *If the following conditions*

$$
\begin{aligned}
&(i)\ \rho_1^2 \quad < 2\\
&\quad\Big(-r_T + 2r_T b_T T^* + \tfrac{(\alpha_T M^* + \gamma_T T_8^*)}{g_T + M^*} - \tfrac{1}{4(\eta_1^* + \eta_2^*)}\Big),\\
&(ii)\ \rho_2^2 \quad < 2\Big(\tfrac{\gamma_T T^*}{g_T + M^*} + \tfrac{\alpha_8 D^*}{(g_8 + T_8^*)^2} + \delta_8 - \tfrac{1}{4\eta_2^*}\Big),\\
&(iii)\ \rho_3^2 < 2(\gamma_m T^* + \delta_m),\\
&(iv)\ \rho_4^2 \quad < 2(\delta_d - A^2 - B^2),\quad with\\
&A \qquad = \eta_2^* \tfrac{\alpha_8}{g_8 + T_8^*} + \tfrac{g_d \alpha_d}{(g_d + T^*)^2},\ B = \eta_2^* \tfrac{\alpha_8}{g_8 + T_8^*},
\end{aligned}
$$

hold, then the zero solution of stochastic differential system (4) is asymptotically mean square stable.

Proof To prove the theorem, we consider the positive definite Lyapunov function

$$W(v(t), t) = \frac{1}{2}[\eta_1 v_1^2 + \eta_2 (v_1 + v_2)^2 + \eta_3 v_3^2 + v_4^2], \tag{18}$$

where η_i $(i = 1, 2, 3)$ are real positive constants to be selected later. It is easy to prove that the equations (15) and (16) hold for $\pi = 2$. Using equation (17) to the stochastic system (4), we have

$$
\begin{aligned}
LW(v,t) &= (h_{11}v_1 + h_{12}v_2 + h_{13}v_3 + h_{14}v_4)\eta_1 v_1\\
&+\big((h_{11} + h_{21})v_1 + (h_{12} + h_{22})v_2\\
&+(h_{13} + h_{23})v_3 + (h_{14} + h_{24})v_4\big)\eta_2 (v_1 + v_2)\\
&+(h_{31}v_1 + h_{32}v_2 + h_{33}v_3 + h_{34}v_4)\eta_3 v_3\\
&+(h_{41}v_1 + h_{42}v_2 + h_{43}v_3 + h_{44}v_4)v_4\\
&+\tfrac{1}{2}Tr\Big[n^T(v(t))\tfrac{\partial^2 W(v,\ t)}{\partial v^2} n(v(t))\Big].
\end{aligned}
$$

After some algebraic calculations, we have

$$
\begin{aligned}
LW(v,t) &= \eta_1 v_1\Big[\Big(r_T - 2r_T b_T T^* - \tfrac{(\alpha_T M^* + \gamma_T T_8^*)}{g_T + M^*}\Big)v_1\\
&-\tfrac{\gamma_T T^*}{g_T + M^*}v_2 - \tfrac{(g_T\alpha_T - \gamma_T T_8^*)T^*}{(g_T + M^*)^2}v_3\Big]\\
&+\eta_2 (v_1 + v_2)\Big[\Big(r_T - 2r_T b_T T^* - \tfrac{(\alpha_T M^* + \gamma_T T_8^*)}{g_T + M^*}\Big)v_1\\
&-\Big(\tfrac{\gamma_T T^*}{g_T + M^*} + \tfrac{\alpha_8 D^*}{(g_8 + T_8^*)^2} + \delta_8\Big)v_2\\
&-\tfrac{(g_T\alpha_T - \gamma_T T_8^*)T^*}{(g_T + M^*)^2}v_3 + \tfrac{\alpha_8}{g_8 + T_8^*}v_4\Big]\\
&+\eta_3 v_3\Big[-\Big(\tfrac{\alpha_m T_8^*}{(g_m + T_8^*)(g_{m1} + T^*)^2} + \gamma_m M^*\Big)v_1\\
&+\tfrac{\alpha_m g_m}{(g_m + T_8^*)^2(g_{m1} + T^*)}v_2 - (\gamma_m T^* + \delta_m)v_3\Big]\\
&+v_4\Big[\tfrac{g_d\alpha_d}{(g_d + T^*)^2}v_1 - \delta_d v_4\Big]\\
&+\tfrac{1}{2}Tr\Big[n^T(v(t))\tfrac{\partial^2 W(v,\ t)}{\partial v^2} n(v(t))\Big].
\end{aligned} \tag{19}
$$

Also, we can write

$$\frac{\partial^2 W}{\partial v^2} = \begin{bmatrix} \eta_1 + \eta_2 & \eta_2 & 0 & 0\\ \eta_2 & \eta_2 & 0 & 0\\ 0 & 0 & \eta_3 & 0\\ 0 & 0 & 0 & 1 \end{bmatrix},$$

which implies

$$
\begin{aligned}
&n^T(v(t))\frac{\partial^2 W(v,\ t)}{\partial v^2} n(v(t))\\
&= \begin{bmatrix} (\eta_1 + \eta_2)\rho_1^2 v_1^2 & \eta_2\rho_1\rho_2 v_1 v_2 & 0 & 0\\ \eta_2\rho_1\rho_2 v_1 v_2 & \eta_2\rho_2^2 v_2^2 & 0 & 0\\ 0 & 0 & \eta_3\rho_3^2 v_3^2 & 0\\ 0 & 0 & 0 & \rho_4^2 v_4^2 \end{bmatrix}.
\end{aligned}
$$

Then, we have

$$
\begin{aligned}
&\frac{1}{2}Tr\Big[n^T(v(t))\frac{\partial^2 W(v,\ t)}{\partial v^2} n(v(t))\Big]\\
&= \frac{1}{2}[(\eta_1 + \eta_2)\rho_1^2 v_1^2 + \eta_2\rho_2^2 v_2^2\\
&\quad +\eta_3\rho_3^2 v_3^2 + \rho_4^2 v_4^2].
\end{aligned} \tag{20}
$$

Therefore, the expression (19) leads to

$$
\begin{aligned}
&LW(v,t) = -(\eta_1 + \eta_2)\\
&\Big[-r_T + 2r_T b_T T^* + \frac{(\alpha_T M^* + \gamma_T T_8^*)}{g_T + M^*} - \frac{\rho_1^2}{2}\Big]v_1^2\\
&+\Big[\Big(r_T - 2r_T b_T T^* - \frac{\alpha_T M^* + \gamma_T T_8^*}{g_T + M^*}\\
&-\Big(\frac{\gamma_T T^*}{g_T + M^*} + \frac{\alpha_8 D^*}{(g_8 + T_8^*)^2} + \delta_8\Big)\Big)\eta_2\\
&-\frac{\gamma_T T^*}{g_T + M^*}\eta_1\Big]v_1 v_2\\
&+\Big[\frac{(\gamma_T T_8^* - g_T\alpha_T)T^*}{(g_T + M^*)^2}(\eta_1 + \eta_2)\\
&-\Big(\frac{\alpha_m T_8^*}{(g_m + T_8^*)(g_{m1} + T^*)^2} + \gamma_m M^*\Big)\eta_3\Big]v_1 v_3\\
&+\Big[\eta_2\frac{\alpha_8}{g_8 + T_8^*} + \frac{g_d\alpha_d}{(g_d + T^*)^2}\Big]v_1 v_4\\
&-\eta_2\Big[\frac{\gamma_T T^*}{g_T + M^*} + \frac{\alpha_8 D^*}{(g_8 + T_8^*)^2} + \delta_8 - \frac{\rho_2^2}{2}\Big]v_2^2\\
&+\Big[\eta_3\frac{\alpha_m g_m}{(g_m + T_8^*)^2(g_{m1} + T^*)} - \eta_2\\
&\frac{(g_T\alpha_T - \gamma_T T_8^*)T^*}{(g_T + M^*)^2}\Big]v_2 v_3\\
&+\Big[\eta_2\frac{\alpha_8}{g_8 + T_8^*}\Big]v_2 v_4\\
&-\eta_3\Big[\gamma_m T^* + \delta_m - \frac{\rho_3^2}{2}\Big]v_3^2 - \Big[\delta_d - \frac{\rho_4^2}{2}\Big]v_4^2.
\end{aligned} \tag{21}
$$

If we choose η_1^*, η_2^* and η_3^* in such way that

$$\begin{aligned}
&\left(r_T - 2r_T b_T T^* - \frac{\alpha_T M^* + \gamma_T T_8^*}{g_T + M^*}\right.\\
&\left.-\left(\frac{\gamma_T T^*}{g_T + M^*} + \frac{\alpha_8 D^*}{(g_8 + T_8^*)^2} + \delta_8\right)\right)\eta_2^*\\
&-\frac{\gamma_T T^*}{g_T + M^*}\eta_1^* = 0,\\
&\frac{(\gamma_T T_8^* - g_T\alpha_T)T^*}{(g_T + M^*)^2}(\eta_1^* + \eta_2^*)\\
&-\left(\frac{\alpha_m T_8^*}{(g_m + T_8^*)(g_{m1} + T^*)^2} + \gamma_m M^*\right)\eta_3^* = 0,
\end{aligned}$$

and

$$\begin{aligned}
&\eta_3^*\frac{\alpha_m g_m}{(g_m + T_8^*)^2(g_{m1} + T^*)} - \eta_2^*\frac{(g_T\alpha_T - \gamma_T T_8^*)T^*}{(g_T + M^*)^2}\\
&= 0.
\end{aligned}$$

Then, the expression (21) becomes

$$\begin{aligned}
LW(v,t) &= -(\eta_1^* + \eta_2^*)\\
&\left[-r_T + 2r_T b_T T^* + \frac{(\alpha_T M^* + \gamma_T T_8^*)}{g_T + M^*} - \frac{\rho_1^2}{2}\right]v_1^2\\
&+ Av_1v_4 - \eta_2^*\left[\frac{\gamma_T T^*}{g_T + M^*} + \frac{\alpha_8 D^*}{(g_8 + T_8^*)^2}\right.\\
&\left.+ \delta_8 - \frac{\rho_2^2}{2}\right]v_2^2 + Bv_2v_4\\
&- \eta_3^*\left[\gamma_m T^* + \delta_m - \frac{\rho_3^2}{2}\right]v_3^2 - \left[\delta_d - \frac{\rho_4^2}{2}\right]v_4^2,
\end{aligned} \tag{22}$$

where

$$\begin{aligned}
A &= \eta_2^*\tfrac{\alpha_8}{g_8 + T_8^*} + \tfrac{g_d\alpha_d}{(g_d + T^*)^2},\\
B &= \eta_2^*\tfrac{\alpha_8}{g_8 + T_8^*}.
\end{aligned}$$

Using standard inequality, we have

$$\begin{aligned}
Av_1v_4 &\le \tfrac{1}{4}v_1^2 + A^2v_4^2,\\
Bv_2v_4 &\le \tfrac{1}{4}v_2^2 + B^2v_4^2.
\end{aligned}$$

Thus, the expression (22) leads to

$$\begin{aligned}
LW(v,t) &\le -\left[(\eta_1^* + \eta_2^*)\left(-r_T + 2r_T b_T T^*\right.\right.\\
&\left.\left.+ \frac{(\alpha_T M^* + \gamma_T T_8^*)}{g_T + M^*} - \frac{\rho_1^2}{2}\right) - \frac{1}{4}\right]v_1^2\\
&- \left[\eta_2^*\left(\frac{\gamma_T T^*}{g_T + M^*} + \frac{\alpha_8 D^*}{(g_8 + T_8^*)^2} + \delta_8 - \frac{\rho_2^2}{2}\right) - \frac{1}{4}\right]v_2^2\\
&- \eta_3^*\left[\gamma_m T^* + \delta_m - \frac{\rho_3^2}{2}\right]v_3^2\\
&- \left[\delta_d - \frac{\rho_4^2}{2} - A^2 - B^2\right]v_4^2.
\end{aligned} \tag{23}$$

Then, it can be expressed as

$$LW(v,t) \le -v^T Qv, \tag{24}$$

where

$$Q = \begin{bmatrix} q_{11} & q_{12} & q_{13} & q_{14}\\ q_{21} & q_{22} & q_{23} & q_{24}\\ q_{31} & q_{32} & q_{33} & q_{34}\\ q_{41} & q_{42} & q_{43} & q_{44} \end{bmatrix},$$

with

$$\begin{aligned}
q_{11} &= (\eta_1^* + \eta_2^*)\left(-r_T + 2r_T b_T T^*\right.\\
&\left.+ \frac{(\alpha_T M^* + \gamma_T T_8^*)}{g_T + M^*} - \frac{\rho_1^2}{2}\right) - \frac{1}{4},\\
q_{12} &= q_{21} = 0,\\
q_{13} &= q_{31} = 0,\\
q_{14} &= q_{41} = 0,\\
q_{22} &= \eta_2^*\left(\frac{\gamma_T T^*}{g_T + M^*} + \frac{\alpha_8 D^*}{(g_8 + T_8^*)^2} + \delta_8 - \frac{\rho_2^2}{2}\right) - \frac{1}{4},\\
q_{23} &= q_{32} = 0,\\
q_{24} &= q_{42} = 0,\\
q_{33} &= \eta_3^*\left[\gamma_m T^* + \delta_m - \frac{\rho_3^2}{2}\right],\\
q_{34} &= q_{43} = 0,\\
q_{44} &= \delta_d - \frac{\rho_4^2}{2} - A^2 - B^2.
\end{aligned}$$

Therefore, we have all $q_{ij} \ge 0$; $(i,\ j = 1,\ 2,\ 3,\ 4)$ for $q_{11} > 0$, $q_{22} > 0$, $q_{33} > 0$ and $q_{44} > 0$. Thus, from the previous inequalities, we get

$$\begin{aligned}
\rho_1^2 &< 2\left(-r_T + 2r_T b_T T^* + \frac{(\alpha_T M^* + \gamma_T T_8^*)}{g_T + M^*}\right.\\
&\left.- \frac{1}{4(\eta_1^* + \eta_2^*)}\right),
\end{aligned} \tag{25}$$

$$\rho_2^2 < 2\left(\frac{\gamma_T T^*}{g_T + M^*} + \frac{\alpha_8 D^*}{(g_8 + T_8^*)^2} + \delta_8 - \frac{1}{4\eta_2^*}\right), \tag{26}$$

$$\rho_3^2 < 2(\gamma_m T^* + \delta_m), \tag{27}$$

$$\rho_4^2 < 2(\delta_d - A^2 - B^2). \tag{28}$$

Therefore, Q is real symmetric and positive definite matrix and hence, its eigenvalues λ_1, λ_2, λ_3 and λ_4 will be positive real quantities if the conditions (25), (26), (27) and (28) hold. If λ_m is the $\min\{\lambda_1, \lambda_2, \lambda_3, \lambda_4\}$, then we have $LW(v,t) \le -\lambda_m|v(t)|^2$ and we calculate that the zero solution of stochastic differential system (4) is an asymptotic mean square stable. □

6 Parameter estimation

The system parameters play a crucial role in determining the behavior and analysis of the mathematical model. In this section, we will elaborate on how we estimated specific parameters of our system (1) using information available from existing literature. Our methodology for parameter estimation is delineated as follows.

Decay rate of CD8+ T cells, symbolized as δ_8: The calculated half-life of CD8+ T cells, represented as δ_8, is around 3.9 days as per the research in [41,42]. We can derive the death rate δ_8 of CD8+ T cells using the equation

$$\frac{1}{2}T_8(0) = T_8(0)e^{(-\delta_8 t_{1/2}^{T_8})}.$$

This equation yields the value of δ_8 as

$$\begin{aligned}\delta_8 &= \frac{\ln 2}{3.9}\ \text{day}^{-1}\\ &\approx 0.178\ \text{day}^{-1}.\end{aligned}$$

Decay rate of macrophages, symbolized as δ_m: The parameter δ_m can be computed utilizing the information presented by Wacker et al. [43] & Khajanchi S. [44], who reported a half-life of 12.4 days for macrophages. This can be formulated as

$$\begin{aligned}\delta_m &= \frac{\ln 2}{12.4\ \text{day}}\\ &\approx 0.056\ \text{day}^{-1}.\end{aligned}$$

Decay rate of dendritic cells, labeled as δ_d: Holt et al. [45] suggest that the half-life of dendritic cells is 3 to 4 days. We take a median half-life of 4 days for our computations. Consequently, the decay rate δ_d can be determined as follows

$$\begin{aligned}\delta_d &= \frac{\ln 2}{4\ \text{day}}\\ &\approx 0.17\ \text{day}^{-1}.\end{aligned}$$

Activation rate of dendritic cells, denoted as α_d: The parameter denoting the half-saturation constant for tumor cells is denoted as g_d. This can be mathematically represented as

$$\frac{T}{g_d + T} = \frac{1}{2}.$$

From the research paper conducted by Coventry et al. [46], which observed the density of dendritic cells in breast cancer patients as $D = 4 \times 10^{-4}$ cells, and by incorporating the equilibrium state of the fourth equation in (1), we can deduce the equation

$$\alpha_d \frac{T}{g_d + T} = \delta_d D,$$

which implies

$$\alpha_d = 1.36 \times 10^{-4}\ \text{cell/day}.$$

Constant source rate of dendritic cells, denoted as s_d: The constant source rate s_d is influenced by the presence of tumor cells. In a healthy individual, the presence of tumor cells results in the absence of dendritic cell production. Therefore, at a steady state, we can express this relation as

$$\begin{aligned}s_d &= \delta_d D\\ &= 0.68 \times 10^{-4}\ \text{cell/day}.\end{aligned}$$

Natural degradation rate of Tregs, denoted as δ_g: According to Q. Tang [47], the half-life of regulatory T-cells is 32 h, approximately equivalent to 1.3 days. Therefore, we can calculate the death rate δ_g as follows

$$\begin{aligned}\delta_g &= \frac{\ln 2}{1.3}\ \text{day}^{-1}\\ &\approx 0.53\ \text{day}^{-1}.\end{aligned}$$

Activation rate of Tregs, denoted as α_g: As reported by Q. Tang [47], the estimated average count of circulating regulatory T-cells in an adult human is approximately $0.25 \times 10^9\ pg \cdot ml^{-1}$. Additionally, assuming a density of 2×10^7 CD8+ T cells/ml, we derive the following equation by considering the steady state of the fifth equation in (1)

$$\alpha_g T_8 - \delta_g T_g = 0,$$

which implies

$$\alpha_g = \frac{\delta_g T_g}{T_8}.$$

Substituting the values, we get

$$\alpha_g = \frac{0.53 \times 0.25 \times 10^9 (\text{day}^{-1}.\text{pg.ml}^{-1})}{2 \times 10^7 (\text{cell.ml}^{-1})}.$$

This simplifies to

$$\alpha_g = 6.62\ \text{pg.day}^{-1}.\text{cell}^{-1}.$$

Degradation rate of interleukin-10, denoted as δ_{10}: Huhn et al. [48] reported the half-life of interleukin-10 (IL-10) as 4.5 h, approximately equivalent to 0.1875 days. Hence, we can calculate the degradation rate δ_{10} as follows

$$\delta_{10} = \frac{\ln 2}{0.1875}\ \text{day}^{-1} \approx 3.696\ \text{day}^{-1}.$$

Activation rate of interleukin-10, denoted as α_{10}: Toossi et al. [49] observed that 10^6 alveolar macrophages produced 3,200 pg/mL of interleukin-10 (I_{10}). By utilizing the steady-state equation from the sixth equation in (1), we can express this as

$$\alpha_{10} M - \delta_{10} I_{10} = 0,$$

which implies

$$\alpha_{10} = \frac{3.696 \times 3200}{10^6} \text{ (day}^{-1}\text{.pg.ml}^{-1}\text{)/(cell.ml}^{-1}\text{)}.$$

Simplifying the above expression, we get

$$\alpha_{10} = 0.01182 \text{ pg.day}^{-1}\text{.cell}^{-1}.$$

Death rate of TGF-β, denoted as δ_β: Assuming the estimated median half-life of TGF-β is approximately 20 h, equivalent to 0.83 days, we can calculate the death rate of TGF-β as follows

$$\delta_\beta = \frac{\ln 2}{0.83} \text{ day}^{-1} \approx 0.832 \text{ day}^{-1}.$$

Source rate of TGF-β, denoted as s_β: Peterson et al. [50] reported a TGF-β (T_β) density of 609 pg/ml. It is observed that in a healthy person the concentration of TGF-β is 10 times less than a cancer patient. Assuming a cerebral spinal fluid volume of 150 ml, in the absence of cancer-induced TGF-β production, we can observe at steady state that

$$\begin{aligned} s_\beta &= \delta_\beta T_\beta \\ &= 0.832 \text{ day}^{-1} \times 150 \text{ ml} \times 60.9 \text{ pg} \cdot \text{ml}^{-1} \\ &= 7.6 \times 10^3 \text{ pg} \cdot \text{day}^{-1}. \end{aligned}$$

Release rate of TGF-β by tumor cells, denoted as α_β: The average concentration of the immunosuppressive cytokine TGF-β (T_β) is determined to be 609 pg/ml $\times$ 150 ml = 91350 pg based on the findings by Peterson et al. [50], which pertains to high-grade glioblastoma patients. By applying the seventh equation from the system (1) at an equilibrium state, we can derive that

$$\begin{aligned} \alpha_\beta &= \frac{\delta_\beta T_\beta - s_\beta}{T} \\ &= \frac{91350 \text{ pg} \times 0.832 \text{ day}^{-1} - 7.6 \times 10^3 \text{ pg} \cdot \text{day}^{-1}}{10^6 \text{ cell}} \\ &= 0.0684 \text{ pg.day}^{-1}\text{.cell}^{-1}. \end{aligned}$$

Decay rate of interleukin-12, denoted as δ_{12}: The half-life of interleukin-12 (I_{12}) is 30 h, equivalent to 1.25 days, which is reported by Carreno et al. [51]. Therefore, the decay rate of interleukin-12 (I_{12}) is

$$\delta_{12} = \frac{0.693}{1.25 \text{ day}} \approx 0.55 \text{ day}^{-1}.$$

Release rate of IL-12 by dendritic cells, denoted as α_{12}: In a breast cancer patient, the concentration of interleukin-12 in the blood serum is about 1.5×10^{-10} pg/ml [52]. Meanwhile, the concentration of dendritic cells is 4×10^{-4} cell/ml [46]. Thus, at the steady state of the eighth equation of (1), we can derive that

$$\begin{aligned} \alpha_{12} &= \frac{\delta_{12} I_{12}}{D} \\ &= \frac{1.5 \times 10^{-10} \text{ pg} \cdot \text{ml}^{-1} \times 0.55 \text{ day}^{-1}}{4 \times 10^{-4} \text{ cell} \cdot \text{ml}^{-1}} \\ &= 2.06 \times 10^{-7} \text{pg.day}^{-1}\text{.cell}^{-1}. \end{aligned}$$

Decay rate of IFN-γ, denoted as δ_γ: The median half-life of IFN-γ is calculated to be 6.8 h $\approx$ 0.283 days [53]. Therefore, the decay rate of IFN-γ is

$$\delta_\gamma = \frac{\ln 2}{0.283} \text{ day}^{-1} \approx 2.45 \text{ day}^{-1}.$$

Activation rate of IFN-γ by CD8+ T cells, denoted as α_γ: Kim et al. [54] reported that CD8+ T cells produce 200 pg/ml of IFN-γ. Based on this data, we assume that the concentration of CD8+ T cells is 2×10^7 cell/ml. Therefore, by using the steady state of the ninth equation in (1), we can calculate

$$\begin{aligned} \alpha_\gamma &= \frac{\delta_\gamma I_\gamma}{T_8} \\ &= \frac{200 \text{ pg} \cdot \text{ml}^{-1} \times 2.45 \text{ day}^{-1}}{2 \times 10^7 \text{cell} \cdot \text{ml}^{-1}} \\ &= 2.45 \times 10^{-5} \text{ pg.day}^{-1}\text{.cell}^{-1}. \end{aligned}$$

Table 1 presents a summary of all the model parameters.

7 Numerical results

This section provides extensive numerical illustrations of the theoretical analysis obtained from both deterministic and stochastic tumor-immune interaction models under various situations. We illustrate our tumor-immune interaction model numerically using MATLAB by selecting appropriate parameter values, which are given in Table 1.

7.1 Numerical results for deterministic model

To perform local stability analysis of the deterministic model (2), we run our simulation for 150 days and

Table 1 The parameter values employed for simulating the tumor-immune interaction model are as follows

Par.	Description	Value	Units	Source
r_T	Intrinsic growth rate of tumor cells	0.5822	day^{-1}	[56]
b_T	$1/b_T$ is carrying capacity of tumor cells	1.25×10^{-6}	cell^{-1}	Fit to data
$\alpha_T^{'}$	Tumor cells elimination rate by macrophages	1.5	$\text{pg day}^{-1}\,\text{cell}^{-1}$	[2]
$\gamma_T^{'}$	Tumor cells elimination rate by CD8+ T cells	2.4	$\text{pg day}^{-1}\,\text{cell}^{-1}$	[57]
$g_T^{'}$	Half-saturation constant	10^4	pg	[58]
$\alpha_l^{'}$	CD8+ T cells activation due IL-12	3.5	cell day^{-1}	[59]
$g_l^{'}$	Tregs reduce parameter for CD8+ T cell production	10^2	pg	[60]
δ_l	CD8+ T cells death rate	0.178	day^{-1}	Est.
s_m	Constant source rate of macrophages	5.42×10^2	cell day^{-1}	[61]
$\alpha_m^{'}$	Recruitment rate of macrophage by IFN-γ	0.69	pg cell day^{-1}	[62]
$g_m^{'}$	Half-saturation constant of IFN-γ	1.05×10^4	pg	[2]
$g_{m1}^{'}$	TGF-β reduce parameter for macrophages	10^4	pg	[2,50]
γ_m	Macrophages inactivation rate due to tumor cells	0.4656	$\text{cell}^{-1}\,\text{day}^{-1}$	[2]
δ_m	Natural death rate of macrophages	0.056	day^{-1}	Est.
s_d	Constant source rate of dendritic cells	0.68×10^{-4}	cell day^{-1}	Est.
α_d	Dendritic cells activation rate	1.36×10^{-4}	cell day^{-1}	Est.
g_d	Half-saturation constant	10^6	cell	[4,5]
δ_d	Dendritic cells death rate	0.17	day^{-1}	Est.
α_g	Activation rate of Tregs due to CD8+ T cells	6.62	$\text{pg day}^{-1}\,\text{cell}^{-1}$	Est.
δ_g	Tregs degradation rate	0.53	day^{-1}	Est.
α_{10}	Activation rate of IL-10 due to macrophages	0.01182	$\text{pg day}^{-1}\,\text{cell}^{-1}$	Est.
δ_{10}	IL-10 degradation rate	3.696	day^{-1}	Est.
s_β	Constant source rate of TGF-β	7.6×10^3	pg day^{-1}	Est.
α_β	Release rate of TGF-β by tumor cells	0.0684	$\text{pg day}^{-1}\,\text{cell}^{-1}$	Est.
δ_β	TGF-β decay rate	0.832	day^{-1}	Est.
α_{12}	Release rate of IL-12 by dendritic cells	2.06×10^{-7}	$\text{pg day}^{-1}\,\text{cell}^{-1}$	Est.
δ_{12}	IL-12 degradation rate	0.55	day^{-1}	Est.
α_γ	Activation rate of IFN-γ due to CD8+ T cells	2.45×10^{-5}	$\text{pg day}^{-1}\,\text{cell}^{-1}$	Est.
δ_γ	IFN-γ decay rate	2.45	day^{-1}	Est.

take different initial values. Using parameters value from Table 1, we obtained the tumor-free singular point E^1 $(0,\ 2.94586 \times 10^{-11},\ 9678.57,\ 0.0004)$ and the corresponding eigenvalues are $-0.865106,\ -0.178,\ -0.17,\ -0.056$. We observe that all the eigenvalues are real and have negative real part. Thus, our deterministic system (2) is stable around the tumor-free singular point E^1 (see the Fig. 1). Numerically, we have also checked the condition(s) for the Theorem 1 and calculated that $r_T - \frac{\alpha_T M^1 + \gamma_T T_8^1}{g_T + M^1} = -0.865108 < 0$, which assured the local asymptotic stability of the tumor-free steady state E^1. Theorem 2.1 has significant implications for understanding the dynamics of tumor growth and immune response in biological systems. If the conditions outlined in the theorem are satisfied, indicating that the tumor-free steady state is locally asymptotically stable, it suggests that in the absence of tumors, the biological system tends to remain in a stable equilibrium state. This stability implies that the immune response is effective in controlling of tumor growth. We obtained two interior steady states, namely low tumor-presence singular point $E^2(0.179273,\ 2.94586 \times 10^{-11},\ 3886.16,\ 0.0004)$ and high tumor-presence sin-

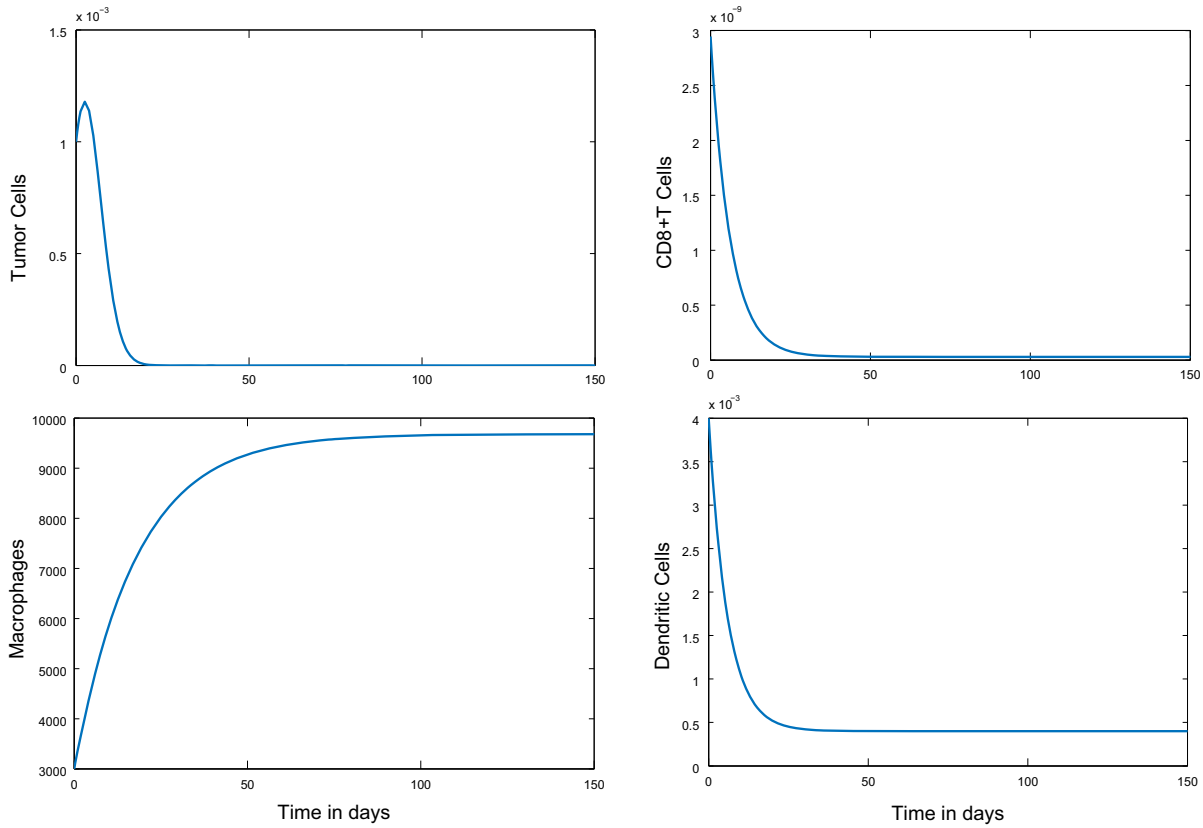

Fig. 1 Time series evolution for tumor-free singular point E^1 of deterministic system (2) shows stable behavior with respect to the initial value $(0.0001,\ 2.94 \times 10^{-9},\ 3000.57,\ 0.00038)$ and parameters value are taken from Table 1

gular point $E^3(800000,\ 5.56441 \times 10^{-11},\ 0.00145511,\ 0.00075)$. The eigenvalues around the low tumor-presence singular point E^2 are $-0.300816,\ -0.178,\ -0.17,\ 0.161346$, which depicts that the our deterministic system (2) is unstable around E^2 (see the Fig. 2). Also, $-372480,\ -0.5822,\ -0.178,\ -0.17$ are the eigenvalues around the high tumor-presence singular point E^3. It can be noticed that all of the eigenvalues are real and have negative real part. Therefore, our deterministic system (2) is stable around the high tumor-presence singular point E^3 (see the Fig. 3).

7.2 Numerical results for stochastic model

Now, we investigate extensive numerical results obtained from the stochastic tumor-immune interaction system (4). We employ Milstein's scheme [55] to evaluate the strong approximation solution of (4) with an initial condition based on the Itô process. This scheme is derived from the Euler-Maruyama technique and involves incorporating a corrective component into the stochastic increment. For numerical illustrations, we only change the values of ρ_1, ρ_2, ρ_3 and ρ_4 to investigate their influence on the dynamics of the tumor-immune interaction model system (4). Now, we discretized the time interval $[t_0,\ t_f]$ as follows:

$$t_0 = 0 < t_1 = t_2 < \ldots\ldots < t_N < t_{N+1} = t_f.$$

We apply the Milstein's scheme in our stochastic system (4) as follows

$$\begin{aligned} T(j+1) = T(j) + \Bigg[& r_T T(j)(1 - b_T T(j)) \\ & - \frac{\alpha_T M(j) + \gamma_T T_8(j))T(j)}{g_T + M(j)} \Bigg] \Delta t \\ & + \rho_1 (T(j) - T^*) I_{1,j} \sqrt{\Delta t} \\ & + \frac{1}{2} \rho_1^2 (T(j) - T^*)(I_{1,j}^2 - 1) \Delta t, \end{aligned}$$

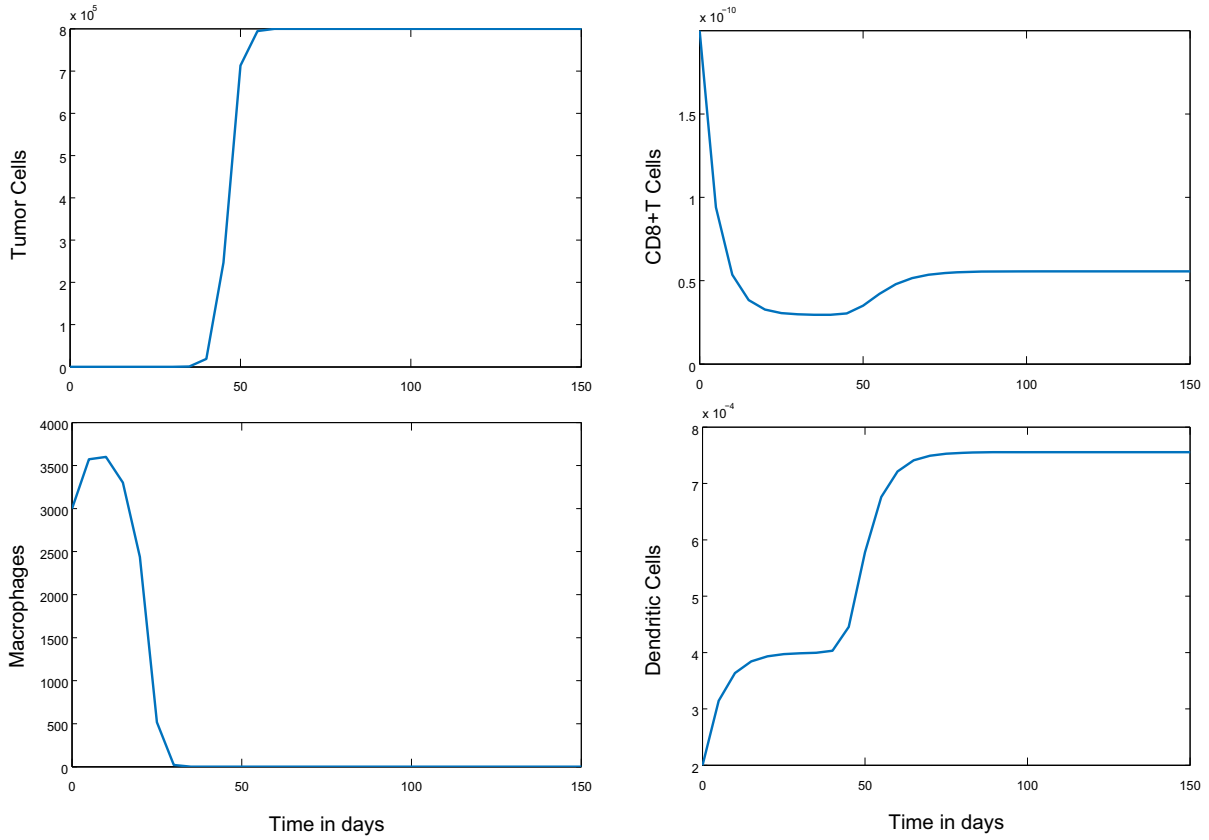

Fig. 2 Time series evolution for low tumor-presence singular point E^2 of deterministic system (2) shows unstable behavior with respect to the initial value $(0.12,\ 2\times10^{-10},\ 3000,\ 0.0002)$ and parameters value are taken from table 1

$$
\begin{aligned}
T_8(j+1) &= T_8(j) + \left[\frac{\alpha_8 D(j)}{g_8 + T_8(j)} \right.\\
&\quad \left. -\delta_8 T_8(j)\right]\Delta t + \rho_2 (T_8(j) - T_8^*) I_{2,j}\sqrt{\Delta t}\\
&\quad + \frac{1}{2}\rho_2^2 (T_8(j) - T_8^*)(I_{2,j}^2 - 1)\Delta t,\\
M(j+1) &= M(j)\\
&\quad + \left[s_m + \frac{\alpha_m T_8(j)}{(g_m + T_8(j))(g_{m1} + T(j))}\right.\\
&\quad \left. -\gamma_m M(j) T(j) - \delta_m(j)\right]\Delta t\\
&\quad + \rho_3 (M(j) - M^*) I_{3,j}\sqrt{\Delta t}\\
&\quad + \frac{1}{2}\rho_3^2 (M(j) - M^*)(I_{3,j}^2 - 1)\Delta t,\\
D(j+1) &= D(j) + \left[s_d + \frac{\alpha_d T(j)}{g_d + T(j)} - \delta_d D(j)\right]\Delta t\\
&\quad + \rho_4 (D(j) - D^*) I_{4,j}\sqrt{\Delta t}\\
&\quad + \frac{1}{2}\rho_4^2 (D(j) - D^*)(I_{4,j}^2 - 1)\Delta t,
\end{aligned}
$$

where $I_{i,\ j}$ (i, j=1, 2, 3, 4) is the j-th realization of I_i and I_i is Gaussian random variable $N(0, 1)$.

A suitable Lyapunov function is considered to demonstrate that the tumor-presence singular point is asymptotically mean square stable. Positive fluctuations $\rho_1, \rho_2,\ \rho_3$ and ρ_4 are depended upon in our stochastic system. For this, $\rho_1 = \rho_2 = \rho_3 = \rho_4 = 0.1$ are chosen and the real positive constants $\eta_1 = \eta_2 = \eta_3 = 0.5$ are set. Now, we have calculated $2\Big(- r_T + 2r_T b_T T^* + \frac{(\alpha_T M^* + \gamma_T T_8^*)}{g_T + M^*} - \frac{1}{4(\eta_1^* + \eta_2^*)}\Big) = 0.6644 > \rho_1^2$, $2\left(\frac{\gamma_T T^*}{g_T + M^*} + \frac{\alpha_8 D^*}{(g_8 + T_8^*)^2} + \delta_8 - \frac{1}{4\eta_2^*}\right) = 383.357 > \rho_2^2$, $2(\gamma_m T^* + \delta_m) = 744.960 > \rho_3^2$ and $2(\delta_d - A^2 - B^2) = 0.34 > \rho_4^2$. Therefore, all conditions of Theorem 6 have been numerically verified. In Fig. 4, we present a time series evolution of our stochastic system (4) with fluc-

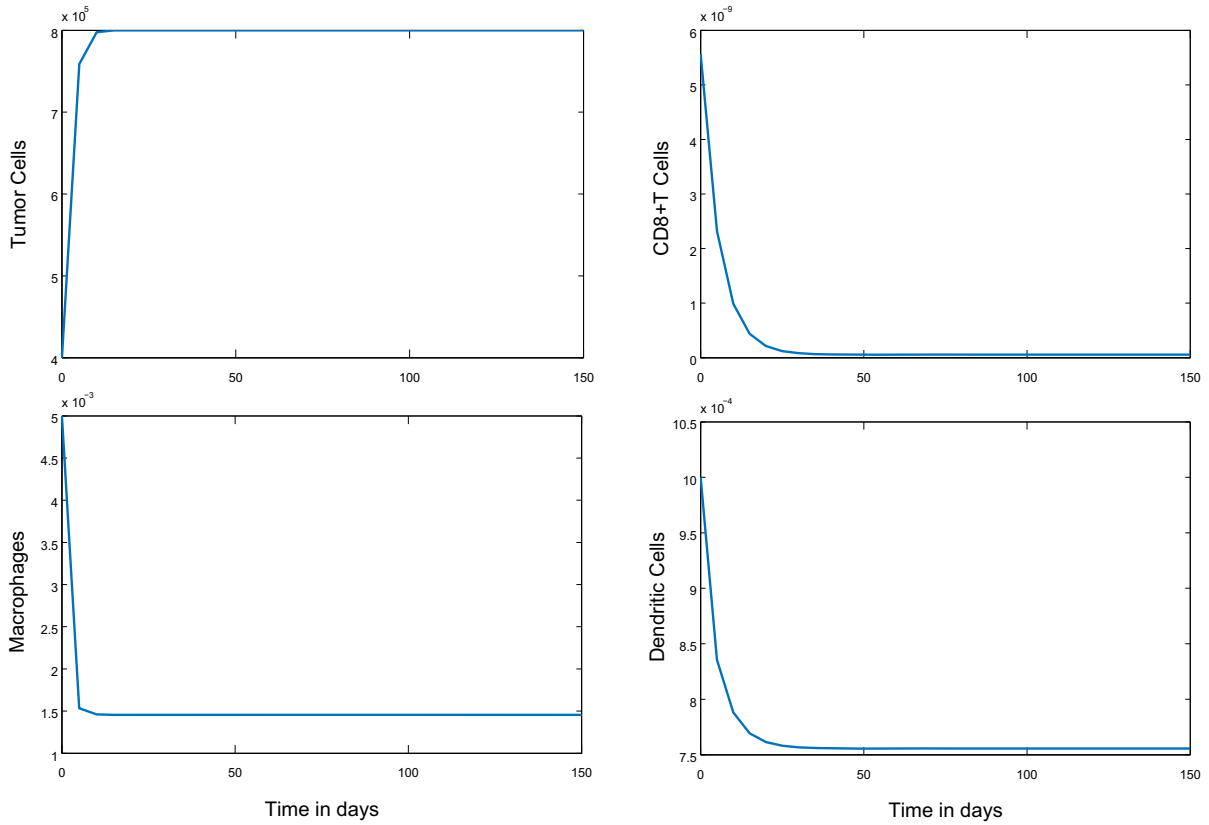

Fig. 3 Time series evolution for high tumor-presence singular point E^3 of deterministic system (2) shows stable behavior with respect to the initial value $(400000,\ 5.56441 \times 10^{-9},\ 0.005,\ 0.001)$ and parameters value are taken from table 1

tuation density $\rho_1 = \rho_2 = \rho_3 = \rho_4 = 0.1$ and the other parameters value are obtained from Table 1. It is observed that the tumor population reaches zero after 20 days. Again, it is observed that the tumor cell population becomes extinct after 30 days due to the high intensity of fluctuation (see Fig. 5). It is to be noted that the extinction criterion, as stated in Theorem 5, is satisfied as $r_T = 0.5822 < 0.601425 = \rho_1^2\left(\frac{1}{2} - T^*\right)$, which provides numerical verification for our analytical results. For this, we consider $\rho_1 = 1.4$, $\rho_2 = \rho_3 = \rho_4 = 0.5$ and $T^* = 0.179273$ (low tumor density), while other parameters value are taken from Table 1. After carefully analyzing the results and observations, we conclude that when the intensity of fluctuation density is small, the tumor cells become extinct, reaching zero in a relatively short time. This deduction is based on the findings obtained from our analysis and serves to highlight the significant impact of fluctuation intensity on the dynamics of tumor cells. In Fig. 6, we present a comparison of our stochastic differential equation (4) under different values of fluctuation intensity. The red curve corresponds to the fluctuation value $\rho_1 = \rho_2 = \rho_3 = \rho_4 = 0.001$, the blue curve represents $\rho_1 = \rho_2 = \rho_3 = \rho_4 = 0.03$, the green curve depicts $\rho_1 = \rho_2 = \rho_3 = \rho_4 = 0.07$ and the black curve indicates $\rho_1 = \rho_2 = \rho_3 = \rho_4 = 0.15$. We observe that increasing the intensity value of population fluctuation leads to greater fluctuations in our cell population. Therefore, the behavior of our stochastic system (4) depends on the intensity value of cell population fluctuations. By adjusting the intensity of fluctuations, we can modulate the level of variability and randomness exhibited by the cell populations, thereby influencing the overall behavior of the system. The dependence of our stochastic system on fluctuation intensity underscores the importance of considering this parameter in the study of tumor growth dynamics and other stochastic processes. Furthermore, we have constructed a three-dimensional phase portrait diagram of the stochastic

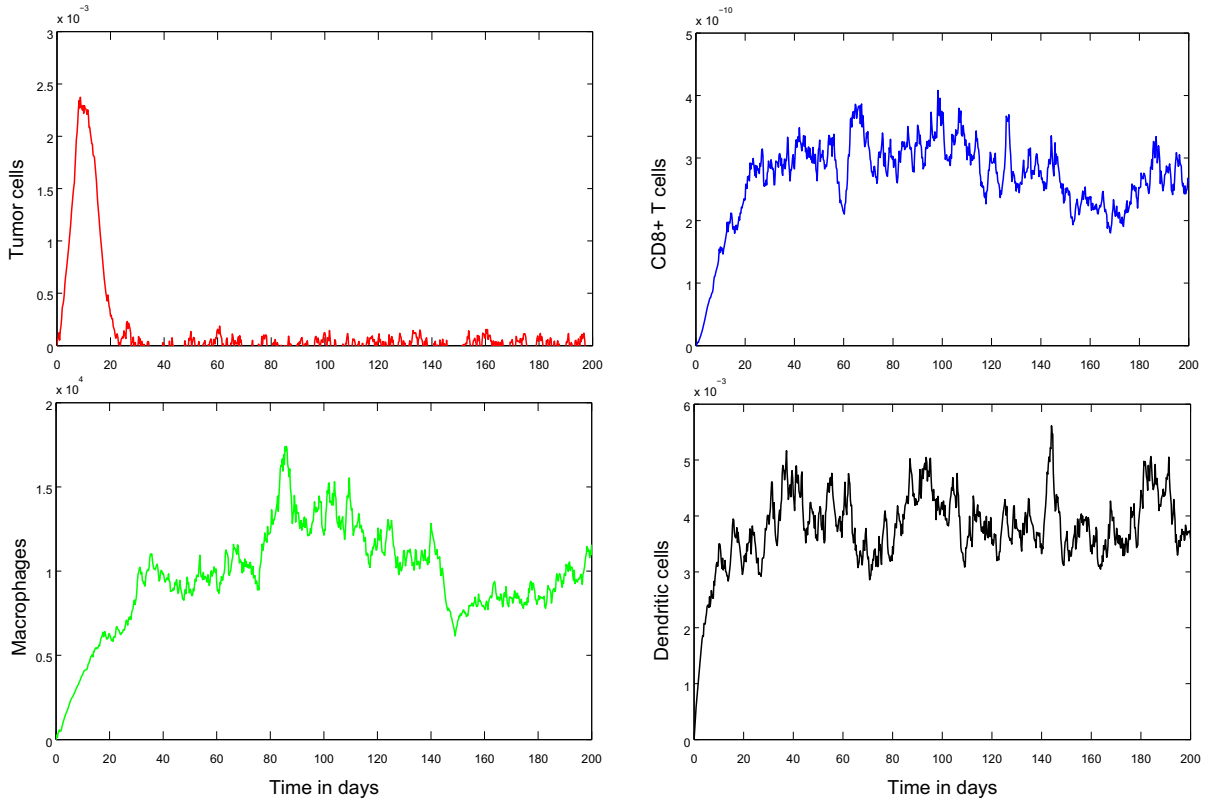

Fig. 4 Time series evolution of the stochastic system (4) for $\rho_1 = \rho_2 = \rho_3 = \rho_4 = 0.1$ with initial density $T(0) = 0.001$, $T_8(0) = 2.94 \times 10^{-12}$, $M(0) = 3000$, $D(0) = 0.0003$ and other parameters value are taken from table 1

system (4) (see Fig. 7) for $\rho_1 = \rho_2 = \rho_3 = \rho_4 = 0.1$, considering initial densities $T(0) = 0.001$, $T_8(0) = 2.94 \times 10^{-12}$, $M(0) = 3000$, $D(0) = 0.0003$ and utilizing other parameters value from Table 1. By analyzing this phase portrait, we can better understand the underlying dynamics and make informed interpretations about tumor growth and its response to varying environmental conditions.

Over the course of 200 days and through approximately 5000 simulations, the mean (μ_{X_i}) and the standard deviation (σ_{X_i}) of the cell populations are

$$\mu_T = 0.000144587, \quad \mu_{T_8} = 2.657 \times 10^{-10},$$
$$\mu_M = 9575.98, \quad \mu_D = 0.00398225$$

and

$$\sigma_T = 0.00101432, \quad \sigma_{T_8} = 7.17345 \times 10^{-11},$$
$$\sigma_M = 1954.66, \quad \sigma_D = 0.000893139.$$

We observe that the stochastic mean closely aligns with its deterministic low tumor-presence singular point E^2. This observation indicates that the dynamics of cell populations are notably influenced by stochastic fluctuations. To further investigate the behavior of our stochastic system (4), we conduct relative frequency density and normal distribution analysis, as illustrated in Fig. 8. The study of relative frequency density and normal distribution provides valuable insights into the probabilistic nature of the stochastic system. These analyses allow us to better comprehend the probability distribution of cell population values and assess how stochastic fluctuations contribute to the overall variability observed in the dynamics of the system.

8 Conclusion

This section provides a concise overview of the research and emphasizes its significant contributions to the field of tumor-immune interaction models using a stochastic system. In this study, a mathematical model based on biology is introduced to elucidate the dynamics of the tumor-immune interaction system. The model

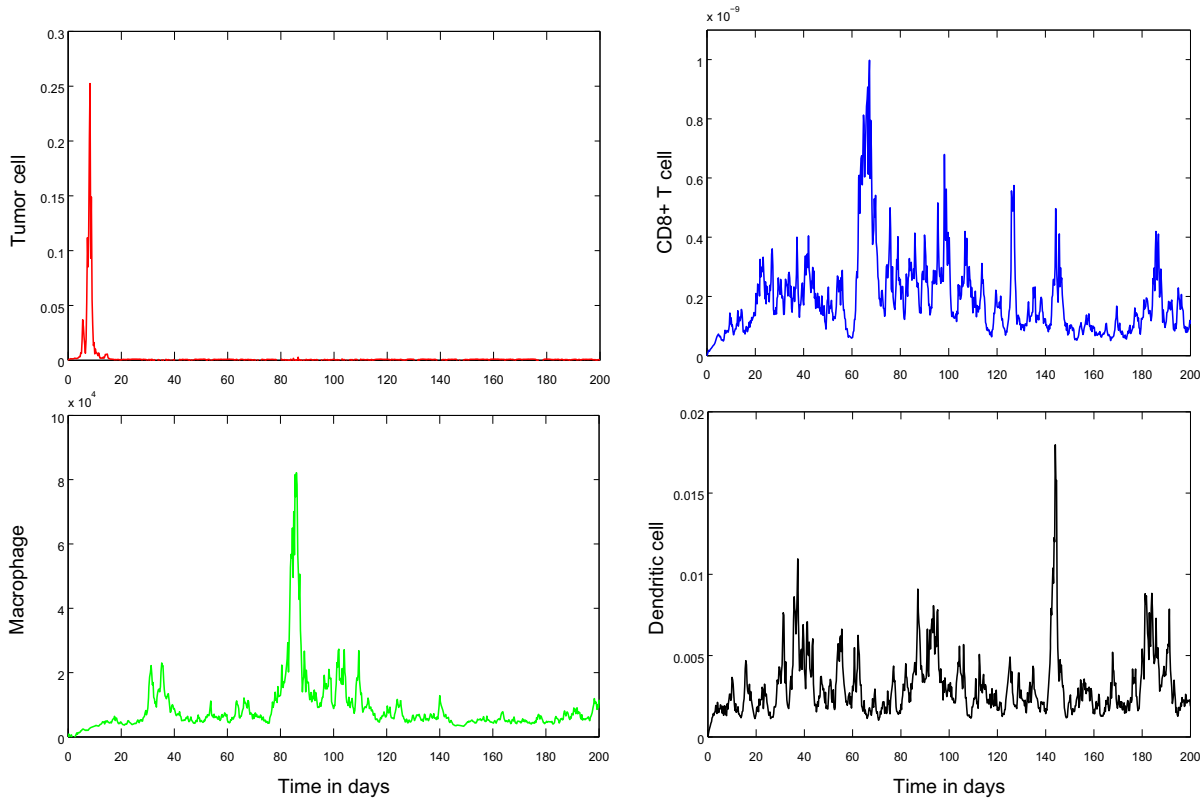

Fig. 5 Time series evolution of the stochastic system (4) for $\rho_1 = 1.4$, $\rho_2 = \rho_3 = \rho_4 = 0.5$ with initial density $T(0) = 0.001$, $T_8(0) = 2.94 \times 10^{-12}$, $M(0) = 3000$, $D(0) = 0.0003$ and other parameters value are taken from Table 1

incorporates various cell types including tumor cells, CD8+ T cells, macrophages, dendritic cells, and several cytokines such as Tregs or regulatory T-cells, TGF-β, IL-10, IL-12, and IFN-γ. To develop the model, we utilized a system of coupled ordinary differential equations. To get a better understanding of the tumor-immune interaction system, we simplified the model using quasi-steady-state approximations for the concentration of cytokines. This reduced model effectively captures the detailed interactions between tumor cells, CD8+ T cells, macrophages, and dendritic cells.

Deterministic models often lead to inaccurate predictions of biological systems due to the influence of environmental fluctuations. Consequently, to study the effects of these fluctuations, we expanded our deterministic system into a stochastic system. In this study, we introduced randomly fluctuating terms without altering any parameters in the original deterministic model. These stochastic random perturbations follow a white noise type which is directly proportional to the distances of the interior singular point from the cell population. In this study, we demonstrate the existence and uniqueness of the solution for our stochastic system (4). Through this analysis, we establish the foundation for exploring the dynamic behavior of the system under stochastic conditions. To further characterize the behavior of the system, we construct the appropriate Lyapunov function. By Itô's lemma, we establish both the stochastically ultimate bounded and stochastically permanence of our stochastic system (4). This key finding highlights the system's ability to remain within certain bounded regions over time and persist in the presence of environmental fluctuations. Moreover, our investigation leads to the identification of an extinction criterion for the tumor cell population. We derive some conditions, as stated in Theorem 6, to ensure the asymptotic mean-square stability of the zero solution in the stochastic system (4). Also, we present several figures of the stochastic system (4) for different values of the intensity of population fluctuation. Through

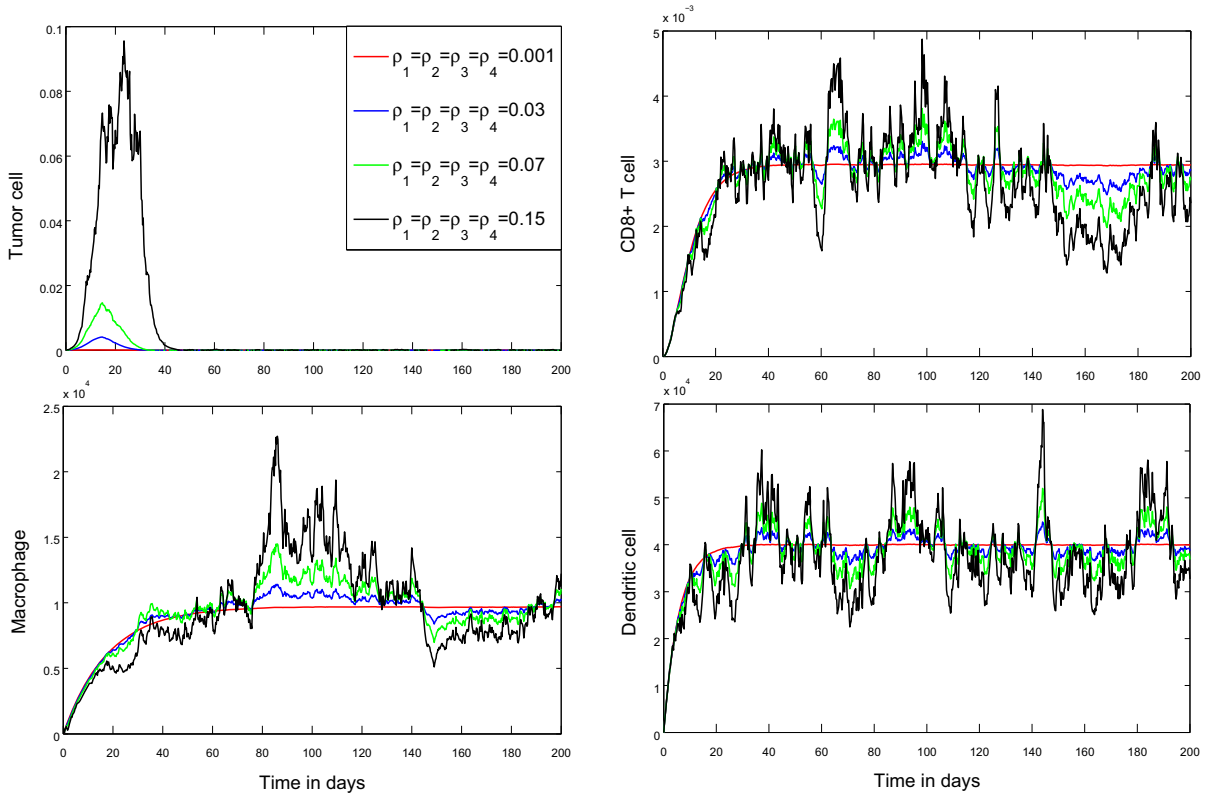

Fig. 6 Time series evolution of the stochastic system (4) for different values of intensity of population fluctuation with initial density $T(0) = 0.001,\ T_8(0) = 2.94 \times 10^{-12},\ M(0) = 3000,\ D(0) = 0.0003$ and other parameters value taken from Table 1

our observations, we have noticed that when the intensity fluctuation parameters in the stochastic system (4) are set to sufficiently small values, the tumor cell population ultimately reaches zero. The observed behavior emphasizes the sensitivity of tumor cell population dynamics to stochastic influences. Even small random fluctuations in the environment can significantly impact the trajectory of the tumor cell population, driving it toward extinction. Furthermore, as we increase the values of population fluctuations, we notice that the nature of the cell population becomes more fluctuated. Comparing the stochastic mean solution to its deterministic solution, we find that it closely aligns with the deterministic low tumor-presence singular point E^2. This observation indicates that stochastic noise has a significant impact on the behavior of the cell populations.

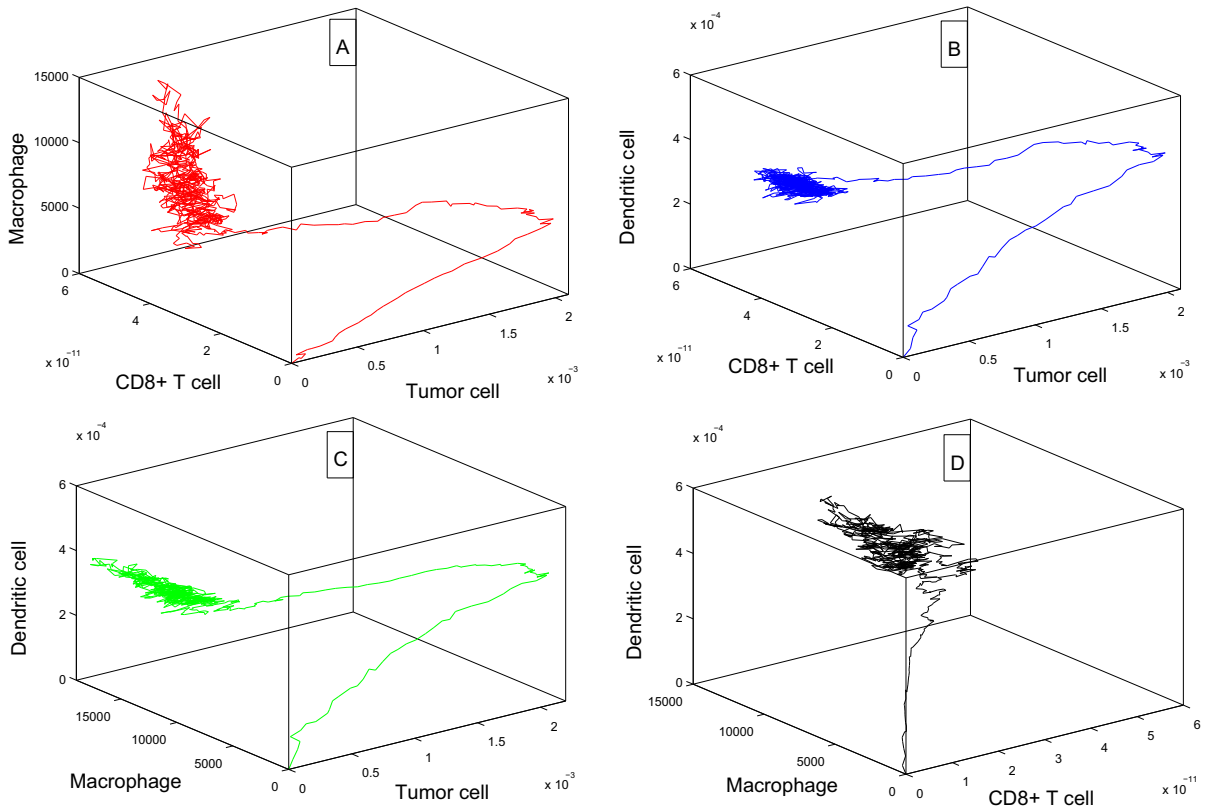

Fig. 7 Three dimensional phase portrait diagram of the stochastic system (4) with initial density $T(0) = 0.001$, $T_8(0) = 2.94 \times 10^{-12}$, $M(0) = 3000$, $D(0) = 0.0003$ and other parameters value taken from Table 1

Overall, this research contributes to a deeper understanding of tumor-immune interaction dynamics and the intricate interplay between deterministic and stochastic components in biological system. The stochastic model allowed us to capture the inherent randomness and uncertainty present in these interactions, leading to a more accurate representation of real-world scenarios. We demonstrated that stochasticity plays a crucial role in shaping the outcome of these interactions, affecting both tumor progression and the effectiveness of immune responses. Our findings have significant implications for cancer research, where environmental fluctuation plays a crucial role. We are hopeful that our mathematical findings will prove beneficial for future researchers working in this field. The insights gained from our study can serve as a valuable contribution to the advancement of knowledge in this area of research. In the future, researchers can integrate stochastic fluctuations into their deterministic models without altering any parameters or introduce stochastic perturbations to key parameters identified in this research paper. Additionally, they can utilize parameter values derived from the findings of this study to ensure consistency and comparability across different investigations. This approach allows for a more comprehensive exploration of the impact of stochasticity on tumor-immune interaction dynamics, facilitating a deeper understanding of the underlying mechanisms and improving the predictive accuracy of mathematical models in this field.

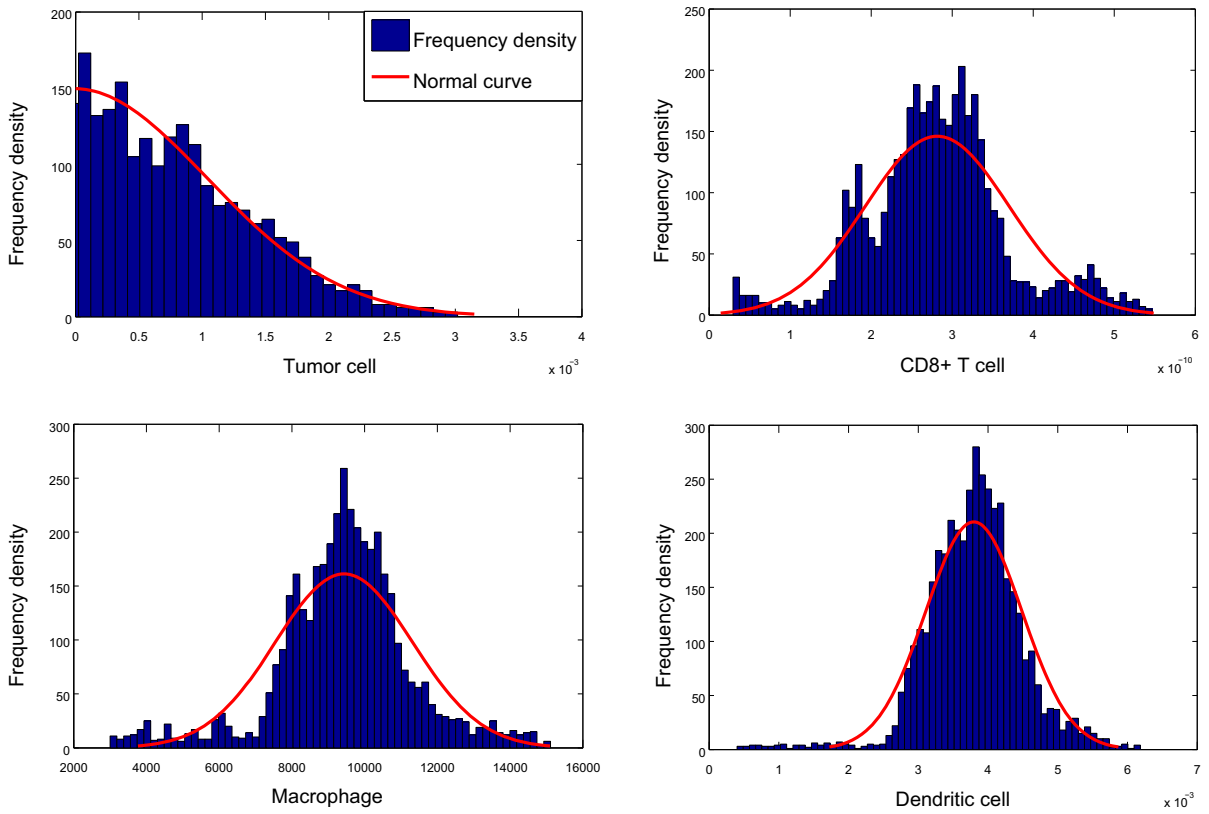

Fig. 8 Relative frequency density of tumor cells, CD8+ T cells, macrophages and dendritic cells of stochastic system (4) for $\rho_1 = \rho_2 = \rho_3 = \rho_4 = 0.1$ and other parameters value taken from Table 1

Acknowledgements Subhas Khajanchi acknowledges the financial support from the Department of Science and Technology (DST), Govt. of India, under the Scheme "Fund for Improvement of S&T Infrastructure (FIST)" [File No. SR/FST/MS-I/2019/41].

Author contributions All the authors equally contributed to this work.

Data availibility Statement All the used data are included in the manuscript.

Declarations

Conflict of interest The authors declares that they have no Conflict of interest.

Informed consent Not Applicable.

References

1. World Cancer Research Fund. https://www.wcrf.org
2. Banerjee, S., Khajanchi, S., Chaudhury, S.: A mathematical model to elucidate brain tumor abrogration by immunotherapy with T11 target struncture. PLoS ONE **10**(5), e0123611 (2015)
3. Pillis, L.G., Radunskaya, A.E., Wiseman, C.L.: A valiadated mathematical model of cell-mediated immune response to tumor growth. Cancer Res. **65**, 7950–7958 (2005)
4. Kirschner, D., Panetta, J.C.: Modeling immunotherapy of the tumor-immune interaction. J. Math. Biol. **37**, 235–252 (1998)
5. Kuznestov, V., Makalkin, I., Taylor, M., Perelson, A.: Nonlinear dynamics of immunogenic tumors: parameter estimation and global bifurcation analysis. Bull. Math. Biol. **56**(2), 295–321 (1994)
6. Khajanchi, S., Ghosh, D.: The combined effects of optimal control in cancer remission. Appl. Math. Comput. **271**, 375–388 (2015)
7. Sardar, M., Biswas, S., Khajanchi, S.: The impact of distributed time delay in a tumor-immune interaction system. Chaos Solitons Fractal **142**, 110483 (2021)
8. de Pillis, L.G., Gu, W., Radunskaya, A.E.: Mixed immunotherapy and chemotherapy of tumors: modeling, applications and biological interpretations. J. Theor. Biol. **238**, 841–862 (2006)
9. Khajanchi, S., Banrjee, S.: A strategy of optimal efficacy of T11 target structure in the treatment of brain tumor. J. Biol. Syst. **27**(2), 225–255 (2019)

10. Khajanchi, S., Sardar, M., Nieto, J.J.: Application of non-singular kernel in a tumor model with strong Allee effect. Differ. Equ. Dyn. Syst. **31**, 687–692 (2022)
11. Sardar, M., Khajanchi, S., Biswas, S., Abdelwahab, S.F., Nisar, K.S.: Exploring the dynamics of a tumor-immune interplay with time delay. Alex. Eng. J. **60**, 4875–4888 (2021)
12. Adam, J.A.: A Survey of Models for Trumor Immune System Dynamics. Springer Science and Business Media, New York (1997)
13. Sardar, M., Khajanchi, S., Ahmad, B.: A tumor-immune interaction model with the effect of impulsive therapy. Commun. Nonlinear Sci. Numer. Simul. **126**, 107430 (2023)
14. Sardar, M., Khajanchi, S., Biswas, S., Ghosh, S.: A mathematical model for tumor-immune competitive system with multiple time delays. Chaos Solitons Fractals **179**, 114397 (2024)
15. Dehingia, K., Yao, S.W., Sadri, K., Das, A., Sarmah, H.K., Zeb, A., Inc, M.: A study on cancer-obesity-treatment model with quadratic optimal control approach for better outcomes. Results Phys. **42**, 105963 (2022)
16. Alharbi, S.A., Dehingia, K., Alqarni, A.J., Alsulami, M., Quarni, A.A., Das, A., Hincal, E.: A study on ODE-based model of risk breast cancer with body mass. Appl. Math. Sci. Eng. **31**(1), 2259059 (2023)
17. Khajanchi, S.: Uniform persistence and global stability for a brain tumor and immune system interaction. Biophys. Rev. Lett. **12**(04), 187–208 (2017)
18. Dehingia, K., Alharbi, Y., Pandey, V.: A mathematical tumor growth model for exploring saturated response of M2 macrophages. Healthc. Anal. **5**, 100306 (2024)
19. Khajanchi, S.: Stability analysis of a mathematical model for glioma-immune interaction under optimal therapy. Int. J. Nonlinear Sci. Numer. Simul. **20**(3–4), 269–285 (2019)
20. Kloeden, P.E., Platen, E.: Numerical Solution of Stochastic Diffrential Equations. Springer, Berlin (1995)
21. Li, D., Cheng, F.: Threshold for extinction and survival in stochastic tumor immune system. Commun. Nonlinear Sci. Numer. Simul. **51**, 1–12 (2017)
22. Lefever, R., Horsthemke, W.: Bistability in fluctuating environments, implications in tumor immunology. Bull. Math. Biol. **41**(4), 469–490 (1979)
23. Li, D., Xu, W., Sun, C., Wang, L.: Stochastic fluctuation induced the competitive between extinction and recurrence in a model of tumor growth. Phys. Lett. A. **376**(22), 1771–1776 (2012)
24. Oroji, A., Omar, M., Yarahmadian, S.: An Itô stochastic differential equations model for the dynamics of the MCF-7 breast cancer cell line treated by radiotherapy. J. Theor. Biol. **407**, 128–137 (2016)
25. Sarkar, R.R., Banerjee, S.: Cancer self remission and tumor stability-a stochastic approach. Math. Bio. **196**, 65–81 (2005)
26. Sardar, M., Khajanchi, S.: Is the Allee effect relevant to stochastic cancer model? J. Appl. Math. Comput. **68**, 2293–2315 (2021)
27. Kim, K.S., Kim, S., Jung, I.H.: Dynamics of tumor virotherapy: a deterministic and stochastic model approach. Stoch. Anal. Appl. **34**(3), 483–495 (2016)
28. Caravagna, G., d'Onofrio, A., Milazzo, P., Barbuti, R.: A Tumor suppression by immune system through stochastic oscillations. J. Theor. Biol. **265**(3), 336–345 (2010)
29. Khajanchi, S.: The impact of immunotherapy on a glioma immune interaction model. Chaos Solitons Fractals **152**, 111346 (2021)
30. Khajanchi, S., Banerjee, S.: Quantifying the role of immunotherapeutic drug T11 target structure in progression of malignant gliomas: Mathematical modeling and dynamical perspective. Math. Biosci. **289**, 69–77 (2017)
31. Lai, X., Friedman, A.: Combination therapy of cancer with cancer vaccine and immune checkpoint inhibitors: a mathematical model. PLoS ONE **12**(5), e0178479 (2017)
32. Thomas, D., Massague, J.: TGF-β directly targets cytotoxic T-cell functions during tumor evasion of immune surveillance. Cancer Cell **8**, 369–380 (2005)
33. Louzoun, Y., Xue, C., Lesinski, G.B., Friedman, A.: A mathematical growth for pancreatic cancer growth and treatments. J. Theor. Biol. **351**, 74–82 (2014)
34. Khajanchi, S., Mondal, J., Tiwari, P.K.: Optimal treatment strategies using dendritic cell vaccination for a tumor model with parameter identifiability. J. Biol. Syst. **31**(2), 487–516 (2023)
35. Tsur, N., Kogan, Y., Rehm, M., Agur, Z.: Response of patients with melanoma to immune checkpoint blockade—insights gleaned from analysis of a new mathematical mechanistic model. J. Theor. Biol. **485**, 110033 (2020)
36. Wilson, S., Levy, D.: A mathematical model of the enhancement of tumor vaccine efficacy by immunotherapy. Bull. Math. Biol. **74**, 1485–1500 (2012)
37. Kronik, N., Kogan, Y., Vainstein, V., Agur, Z.: Improving alloreactive CTL immunotherapy for malignant gliomas using a simulation model of their interactive dynamics. Cancer Immunol. Immunother. **57**(3), 425–439 (2008)
38. Segel, L.A., Slemrod, M.: The quasi-steady-state assumption: a case study in peturbation. SIAM Rev. **31**, 446–477 (1989)
39. Mao, X.R.: Stochastic Differential Equations and Applications. Horwood, New York (1997)
40. Gard, T.C.: Introduction to Stochastic Differential Equations. Marcel Decker, New York (1988)
41. Taylor, G.P., Hall, S.E., Navarrete, S., Michie, C.A., Davis, R., Witkover, A.D., Rossor, M., Nowak, M.A., Rudge, P., Matutes, E., Bangham, C.R., Weber, J.N.: Effect of lamivudine on human T-cell leukemia virus type 1(HTLV-1)bDNA copy number, T-cell phenotype, and anti-tax cytotoxic T-cell frequency in patients with HTLV-1-associated myelopathy. J. Virol. **73**(12), 10289–10295 (1999)
42. Khajanchi, S., Banerjee, S.: Stability and bifurcation analysis of delay induced tumor immune interaction model. Appl. Math. Comput. **248**, 652–671 (2014)
43. Wacker, H.H., Radzun, R.J., Parwaresch, M.R.: Kinetics of Kupffer cells as shown by parabiosis and combined autoradiographic/immunohistochemical analysis. Virchows. Arch. B. Cell Pathol. Incl. Mol. Pathol. **51**(2), 71–78 (1986)
44. Khajanchi, S.: Modeling the dynamics of glioma-immune surveillance. Chaos Solitons Fractals **114**, 108–118 (2018)
45. Holt, P.G., Haining, S., Nelson, D.J., Sedgwick, J.D.: Origin and steady-state turnover of class II MHC-bearing den-

dritic cells in the epithelium of the conducting airways. J. Immunol. **153**(1), 256–61 (1994)
46. Coventry, B.J., Lee, P.L., Gibbs, D., Hart, D.N.: Dendritic cell density and activation status in human breast cancer: CD1a, CMRF-44, CMRF-56 and CD-83 expression. Br. J. Cancer **86**(4), 546–551 (2002)
47. Tang, Q.: Pharmacokinetics of therapeutic Tregs. Am. J. Transpl. **14**(12), 2679–2680 (2014)
48. Huhn, R.D., Radwanski, E., Gallo, J., Affrime, M.B., Sabo, R., Gonyo, G., Monge, A., Cutler, D.L.: Pharmacodynamics of subcutaneous recombinant human interleukin-10 in healthy volunteers. Clin. Pharmacol. Ther. **62**, 171–180 (1997)
49. Toossi, Z., Hirsch, C.S., Hamilton, B.D., Knuth, C.K., Friedlander, M.A., Rich, E.A., Toossi, Z.: Decreased production of TGF-beta 1 by human alveolar macrophages compared with blood monocytes. J. Immunol. **156**(9), 3461–3468 (1996)
50. Peterson, P.K., Chao, C.C., Hu, S., Thielen, K., Shaskan, E.: Glioblastoma, transforming growth factor-beta, and candida meningitis: a potential link. Am. J. Med. **92**, 262–264 (1992)
51. Carreno, V., Zeuzem, S., Hopf, U., Marcellin, P., Cooksley, W.G., Fevery, J., Diago, M., Reddy, R., Peters, M., Rittweger, K., Rakhit, A., Pardo, M.: A phase I/II study of recombinant human interleukin-12 patients with chronic hepatitis B. J. Hepatol. **32**(2), 317–324 (2000)
52. Derin, D., Soydinc, H.O., Guney, N., Tas, F., Camlica, H., Duranyildiz, D., Yasasever, V., Topuz, E.: Serum IL-8 and IL-12 levels in breast cancer. Med. Oncol. **24**(2), 163–168 (2007)
53. Turner, P.K., Houghton, J.A., Petak, I., Tillman, D.M., Douglas, L., Schwartzberg, L., Billups, C.A., Panetta, J.C., Stewart, C.F.: Interferon-gamma pharmacokinetics and pharmacodynamics in patients with colorectal cancer. Cancer Chemother. Pharmacol. **53**, 253–260 (2004)
54. Kim, J.J., Nottingham, L.K., Sin, J.I., Tsai, A., Morrison, L., Oh, J., Dang, K., Hu, Y., Kazahaya, K., Bennett, M., Dentchev, T., Wilson, D.M., Chalian, A.A., Boyer, J.D., Agadjanyan, M.G., Weiner, D.B.: CD8 positive T cells influence antigen-specific immune responses through the expression of chemokines. J. Clin. Invest. **102**, 1112–1124 (1998)
55. Higham, D.J.: An algorithm introduction to numerical simulation of stochastic differential equations. SIAM Rev. **43**(3), 525–546 (2001)
56. Mahasa, K.J., Ouifki, R., Eladdadi, A., de Pillis, L.G.: Mathematical model of tumor-immune surveilance. J. Theor. Biol. **404**, 312–330 (2016)
57. Castiglione, F., Piccoli, B.: Optimal control in a model of dendritic cell transfection cancer immunotherapy. Bull. Math. Biol. **68**, 255–274 (2006)
58. Qomlaqi, M., Bahrami, F., Ajami, M., Hajati, J.: An extended mathematical model of tumor growth and its interaction with the immune system, to be used for developing an optimized immunotherapy treatment protocol. Math. Biosci. **292**, 1–9 (2017)
59. Friedman, A., Hao, W.: The role of exosomes in pancreatic cancer microenvironment. Bull. Math. Biol. **80**, 1111–1133 (2018)
60. Radunskaya, A., Hook, S.: Modelling the kinetics of the immune response. Biomedicine **267**, 282 (2012)
61. Sherratt, J.A., Bianchin, A., Painter, K.J.: A mathematical model for lymphangiogenesis in normal and diabetic wounds. J. Theor. Biol. **383**, 61–86 (2014)
62. Siewe, N., Yakubu, A., Satoskar, A.R., Friedman, A.: Immune response to infection by Leishmania: a mathematical model. Math. Biosci. **276**, 28–43 (2016)