Filomat 38:25 (2024), 8773–8787
https://doi.org/10.2298/FIL2425773K

Published by Faculty of Sciences and Mathematics,
University of Niš, Serbia
Available at: http://www.pmf.ni.ac.rs/filomat

Dynamical behaviour of the stochastic tumor-immune interaction model

Marija Krstić[a], Vuk Vujović[a]

[a]*University of Niš, Faculty of Sciences and Mathematics, Department of Mathematics, Niš, Serbia*

Abstract. Cancer is one of the major causes of death worldwide, despite there are many cancer treatments, such as surgery, radiation, chemotherapy, etc. This is the reason why immunotherapy has gained more attention and become approved for the treatment of many types of cancers. The development of the tumor itself is very complex and multifactorial process, which may differ from one person to the other due to his/hers state of immune system and environmental conditions. Motivated by this fact, in this paper we consider the stochastic tumor-immune interaction model, which dynamics is described by the three-dimensional system of stochastic differential equations. The model is obtained by incorporating white noise into deterministic tumor-immune interaction model, which is of predator-prey type. For our stochastic model, we verify that the environmental noise provides a solution that is positive, global and bounded. Also, we obtain conditions under which our model has an ergodic stationary distribution, which is important due to the fact that under these conditions tumor cells and immune cells are weakly persistent in mean, as well as, the conditions which lead to non-persistence in mean. We close the paper by presenting numerical simulations to verify our theoretical results. For that purpose we use reliable data for growth of the highly malignant *B Lymphoma/Leukemic cells (BCL1)* in the spleen of chimeric mice. Both theoretical and numerical results indicate that the random perturbations may make the model more realistic than its deterministic analogue.

1. Introduction

According to the World Health Organization (WHO) data, cancer is still one of the leading causes of death worldwide. Namely, nearly 10 million deaths in 2020 occur mainly due to breast, lung, colon and rectum, prostate, skin and stomach cancer, and prediction models indicate that by 2030, there will be nearly 21.4 million cases of cancer and number of deaths will rise to 13.5 millions. These numbers indicate that all strategies of cancer treatment (surgery, radiation, hormonal therapy, virotherapy, chemotherapy, and recently immunotherapy) have their lacks. Immunotherapy has been recently approved for the treatment of many types of cancers. The idea of immunotherapy is to increase the efficiency of the immune system in finding and fighting tumor cells. This goal may be achieved in two ways. The first one includes antibody-targeted therapy in order to make effector components of the immune system to attack tumor cells directly.

2020 *Mathematics Subject Classification*. Primary 60H10; Secondary 92D25, 93E15.
Keywords. Ergodic stationary distribution, Existence and Uniqueness, Hunting cells, Interaction, Non-persistence in mean, Resting cells, Tumor cells.
Received: 30 November 2023; Revised: 29 February 2024; Accepted: 16 May 2024
Communicated by Jelena Manojlović
The first author is supported by Ministry of Science, Technological Development and Innovation of the Republic of Serbia, Contract Number: 451-03-65/2024-03/200124.
Email addresses: marija.krstic@pmf.edu.rs (Marija Krstić), vukpharm@gmail.com (Vuk Vujović)

The second one is to enhance the activity of the immune system by using cancer vaccines, cytokines, and adoptive cell therapy. For more details about immunotherapy we refer the reader to [19] and references cited therein.

In the medical literature there is an inexplicable but real phenomenon. Namely, it happens that patients with advanced stage of the tumor, which is considered incurable, are discharged from the hospital. Some of them, after five to seven years, appear without illness. It is considered that a spontaneous remission has occurred, that is, the patients are in the stage of illness where tumor symptoms are almost or completely absent. This type of behaviour of tumor suggests that this disease is not always fatal, and therefore, the interaction between the tumor cells and immune system is very important.

Mathematical models of the interaction of tumor and immune cells are a widely represented topic in mathematical literature (see, [1, 2, 6, 18, 24], for instance). Sarkar et all. [24] developed a deterministic model for spontaneous tumor regression and progression based on the interaction between immunological (CTL and macrophages) and tumor cells, which is described by predator-prey model. The role of predators is played by the cells of the immune system. They occur in two forms: hunting cells and resting cells. Hunting cells absorb tumor cells, eat them and release substances that activate resting T-lymphocytes (resting cells) that coordinate the counter attack. Resting cells cannot kill tumor cells, but they are converted into macrophages, begin to multiply and release substances that further stimulate resting cells.

The deterministic model, presented in [24], is constructed on the basis of the following assumptions. Tumor cells are destroyed at a rate that is proportional to the number of tumor cells and hunting cells. Resting cells are converted into hunting cells either by direct contact with them or by contact with cytokines that produce hunting cells. It is also believed that once a cell is converted from a resting cell to a hunting cell, it never returns to the resting stage. Hunting cells die at a constant rate per unit of time. All resting cells and tumor cells are rich in nutrients and they are in the mitosis phase, too. Tumor cells and resting cells have logistical growth.

Considering the above mentioned assumptions, the deterministic model for interaction between tumor and immune cells is formulated

$$\begin{aligned}
\frac{dM(t)}{dt} &= q + rM(t)\left(1 - \frac{M(t)}{k_1}\right) - \alpha M(t)N(t) \\
\frac{dN(t)}{dt} &= \beta N(t)Z(t) - d_1 N(t) \\
\frac{dZ(t)}{dt} &= sZ(t)\left(1 - \frac{Z(t)}{k_2}\right) - \beta N(t)Z(t) - d_2 Z(t), \ t \geq 0,
\end{aligned} \tag{1}$$

with initial condition:

$$M(0) = M^0, N(0) = N^0, Z(0) = Z^0, \tag{2}$$

where $M(t)$, $N(t)$ i $Z(t)$ denote the number of tummor cells, hunting cells and resting cells at time t, respectively. The parameters of the model are positive constants which are described as follows:

q - the conversion factor of normal cells to malignant ones,

r and s - the growth rates of tumor cells and resting cells, respectively,

k_1 and k_2 - the carrying capacities of tumor cells and resting cells, respectively,

d_1 and d_2 - the death rate of hunting cells and resting cells, respectively,

α - the rate of annihilation of tumor cells in interaction with hunting cells,

β - the conversion rate of resting cells into hunting cells.

2. Motivation and Construction of Stochastic Model

All populations in nature are inevitably exposed to environmental interference from factors, such as temperature, radiation, oxygen supply, nutrients, migrations, etc. Hence, by adding randomness to

deterministic models, we bring population and epidemiological models closer to reality. Environmental randomness can be introduced to mathematical models by supposing that one of the parameters of the model is a linear function of the white noise, as it was done in [5, 10, 11, 14, 15, 17, 21, 23, 25, 27, 29], for instance, or by assuming that random noise is introduced into the deterministic systems in proportion to the distances of the compartments from their steady states (see [12, 13, 16, 24, 26], among others). Another approach, which is represented in the literature lately, is to assume that the model parameters satisfy some mean-reverting stochastic processes, and it was done in [4, 7, 30] with one or more Ornstein-Ulembeck processes, for example.

Almost every person exhibits the malignant transformation of healthy cells into the tumor ones. However, due to the activation of immune system, not all of them develop tumors. The outcome of interaction between tumor and immune cells depends on a several factors such as: characteristics the tumor itself (type of tumor, type of tissue affected by the tumor, position of the tumor, degree of blood circulation of tumor tissue), availability and quantity of nutrients, the creation of certain enzymes and cytokines that promote the spread and growth of tumors. Also, general condition of the host organism has a significant impact on the interaction (age, morbidity, nutrition and genetic predisposition), as well as the state of the immune system (congenital and acquired immunodeficiencies) and environmental conditions. The development of the tumor is very complex and a multifactorial process based on the principle of randomness due to the individual differences of these factors. Given that the immune system response to a tumor is predicated on the hunting cells response, which arise from previously resting cells, it is reasonable to assume that the rate at which these cells become activated is random. Therefore, in the model (1), we perturb the activation rate β with Gaussian white noise, and obtain stochastic system

$$\begin{aligned} dM(t) &= \left[q + rM(t)\left(1 - \frac{M(t)}{k_1}\right) - \alpha M(t)N(t)\right]dt \\ dN(t) &= \left[\beta N(t)Z(t) - d_1 N(t)\right]dt + \sigma N(t)Z(t)dw(t) \\ dZ(t) &= \left[sZ(t)\left(1 - \frac{Z(t)}{k_2}\right) - \beta N(t)Z(t) - d_2 Z(t)\right]dt - \sigma N(t)Z(t)dw(t), \ t \geq 0, \end{aligned} \tag{3}$$

with initial condition

$$M(0) = M_0, N(0) = N_0, Z(0) = Z_0. \tag{4}$$

In system (3) σ is a positive constant that represents the intensity of the Gaussian white noise and $w = \{w(t), t \geq 0\}$ is a standard Brownian motion defined on a complete probability space $\{\Omega, \mathcal{F}, \mathbb{P}\}$ with a filtration $\{\mathcal{F}_t\}_{t\geq 0}$, satisfying the usual conditions (it is right continuous and increasing, while $\mathcal{F}_0$ contains all $\mathbb{P}$-null sets).

The rest of the paper is arranged as follows. In the following section we state existence and uniqueness theorem for global and positive solution of model (3). In addition, we obtain upper bounds for number of tumor and immune cells, as well as the lower bound for resting cells which is reliable result, bearing in mind their permanent presence in organism. In Section 4 we investigate conditions under which the solution of model (3) admits a unique ergodic stationary distribution. Existence of a unique ergodic stationary distribution implies a weak persistence of tumor and immune cells. Furthermore, in Section 5 we obtain the conditions under which we can claim that the tumor cells, as well as the hunting cells of model (3) are non-persistent in mean. In Section 6 we carry out the numerical simulations in order to confirm our theoretical findings. For that purpose we use reliable data for growth of the highly malignant *B Lymphoma/Leukemic cells (BCL1)* in the spleen of chimeric mice. The reason why we use experimental data, and not the cllinically relevant ones lies in the fact that collecting clinical information for the purposes of mathematical modelling, especially when it comes to models of oncoimmunology and oncoimmunotherapy, is very challenging due to limited access to clinically relevant data. We close the paper with Section 7 where we give some concluding remarks about the contributions and advantages of the proposed framework. We also provide possible ways for future investigation of this topic.

3. Existence and Uniqueness of Global Solution

For some applications of stochastic differential equations it is important to determine whether the stochastic model described by them has a unique and global solution. Due to the fact that the coefficients of the system of stochastic differential equations very often do not satisfy conditions of existence and uniqueness theorem of stochastic differential equations (see [20], for example), we present the additional theoretical results which may be used for proving positivity and global character of the solution of stochastic differential equations.

Let us consider the d-dimensional stochastic differential equation

$$dx(t) = f(x(t))dt + \sum_{r=1}^{d} g_r(x(t))dw_r(t), \tag{5}$$

with initial value $x(0) = x_0 \in \mathbb{R}^d$, while $w(t)$ represents m-dimensional standard Brownian motion defined on complete probability space $\{\Omega, \mathcal{F}, \mathbb{P}\}$. Define the differential operator L associated to equation (5) by

$$L = \frac{\partial}{\partial t} + \sum_{i=1}^{d} f_i(t,x)\frac{\partial}{\partial x_i} + \frac{1}{2}\sum_{i,j=1}^{d}\left[g^{\mathrm{T}}(t,x)g(t,x)\right]_{ij}\frac{\partial^2}{\partial x_i \partial x_i}. \tag{6}$$

Theorem 3.1 ($\mathbb{D}$ - invariance [8]). *Let $\mathbb{D}$ and $\mathbb{D}_n$ be open sets in $\mathbb{R}^n$ with*

$$\mathbb{D}_n \subseteq \mathbb{D}_{n+1},\ \mathbb{D} = \bigcup_n \mathbb{D}_n \ \text{ and } \ \overline{\mathbb{D}}_n \subseteq \mathbb{D}$$

and suppose functions a and b satisfy the existence and uniqueness conditions for solution of equation (5) on each set $\{(t,x): t>0, x\in\mathbb{D}_n\}$. Assume there is a nonnegative continuous function $V : [0,T]\times\mathbb{D} \to \mathbb{R}_+$ with continuous partial derivatives of first order with respect to t and first and second order with respect to x and satisfying $LV \le cV$ for some positive constant c and $t > 0$, $x \in \mathbb{D}$. If also

$$\inf_{t>0, x\in\mathbb{D}\setminus\mathbb{D}_n} V(t,x) \to \infty \text{ when } n \to \infty,$$

then, for any $x_0 \in \mathbb{D}$, there is a unique Markovian continuous time solution $x(t)$ of (5) with $x(0) = x_0$ and $x(t) \in \mathbb{D}$, for all $t > 0$, a.s.

Bearing in mind that $M(t)$ represents the number of tumor cells at time t, while $N(t)$ and $Z(t)$ represent the number of hunting and resting cells, respectively, we need to prove that the solution of system (3) is global and positive.

As it was mentioned in the previous section, it is important to point out that the resting cells can remain in a resting state for long periods until they find their specific antigen. Therefore, it is reasonable to consider that there is a lower bound for this kind of cells, for example Z^*. The number of tumor cells tends to zero when the disease disappears. On the other hand when the tumor is in progress (the immune system is weakened) the hunting cells lose the energy needed to fight the cancer and their number can also tends to zero. In the absence of the disease there are no tumor and hunting cells, but the resting cells are still present. In order to take into consideration those real facts, we introduce change of variables $\bar{Z}(t) = Z(t) - Z^*$, $t \ge 0$, where Z^* is a minimal number of resting cells present in organism, and obtain the following system:

$$\begin{aligned}
dM(t) &= \left[q + rM(t)\left(1 - \frac{M(t)}{k_1}\right) - \alpha M(t)N(t)\right]dt \\
dN(t) &= \left[\beta N(t)\left(\bar{Z}(t) + Z^*\right) - d_1 N(t)\right]dt + \sigma N(t)\left(\bar{Z}(t) + Z^*\right)dw(t) \\
d\bar{Z}(t) &= \left[s\left(\bar{Z}(t) + Z^*\right)\left(1 - \frac{\bar{Z}(t) + Z^*}{k_2}\right) - \beta N(t)\left(\bar{Z}(t) + Z^*\right) - d_2\left(\bar{Z}(t) + Z^*\right)\right]dt - \sigma N(t)\left(\bar{Z}(t) + Z^*\right)dw(t), \ t \ge 0,
\end{aligned} \tag{7}$$

with initial condition

$$M(0) = M_0, N(0) = N_0, \bar{Z}(0) = \bar{Z}_0 = Z_0 - Z^*. \tag{8}$$

If we prove that the system (7) has global and positive solution, then, the resting cells $Z(t)$ has the lower bound, i.e. $Z(t) \geq Z^*, t \geq 0$. Thus, let

$$\mathbb{D} = \{(M, N, \bar{Z}) \colon (M, N, \bar{Z}) \in \mathbb{R}^3_+\}, \tag{9}$$

where $\mathbb{R}^d_+ = \{x = (x_1, x_2, \ldots, x_d) \in \mathbb{R}^d : x_i > 0, 1 \leq i \leq d\}$.

Theorem 3.2. *There is a unique continuous time, Markovian global solution* $(M(t), N(t), \bar{Z}(t))$*, of system (7) on* $t \geq 0$*, for any initial condition (8). The solution is invariant with respect to set* $\mathbb{D}$ *with probability 1.*

Proof. Coefficients of system (7) are locally Lipschitz continuous, for any initial condition (8). Consequently, there exists a unique local solution $(M(t), N(t), \bar{Z}(t))$ of system (7) for $t \in [0, \tau(\mathbb{D}))$, where $\tau(\mathbb{D})$ represents the moment of explosion (see [20]). In order to show that this solution is global, we have to prove that $\tau(\mathbb{D}) = \infty$ almost surely. For $n \in \mathbb{N}$ we define sets $\mathbb{D}_n$ as follows

$$\mathbb{D}_n = \left\{(M, N, \bar{Z}) : e^{-n} < M < e^n, e^{-n} < N < e^n, e^{-n} < \bar{Z} < e^n\right\}.$$

The system (7) has a unique local solution up to stopping time $\tau(\mathbb{D}_n)$.

Let $(M_0, N_0, \bar{Z}_0) \in \mathbb{D}$. The first equation of system (7) is differential equation for which holds

$$dM(t) \leq \left(q + rM(t)\left(1 - \frac{M(t)}{k_1}\right)\right)dt, \ t \in [0, \tau(\mathbb{D})),$$

with initial condition $M(0) = M_0$. Equation

$$dX(t) = \left(q + rX(t)\left(1 - \frac{X(t)}{k_1}\right)\right)dt, \ t \geq 0,$$

with initial condition $X(0) = M_0$ is Riccati differential equation that has particular solution

$$X(t) = \frac{k_1}{2} + \frac{\sqrt{k_1(k_1 r + 4q)}\tanh\left[\tanh^{-1}\left[\frac{2M_0\sqrt{rk_1(k_1r+4q)} - \sqrt{k_1^3 r(k_1 r+4q)}}{k_1(k_1 r+4q)}\right] + \frac{\sqrt{r(k_1 r+4q)}}{2\sqrt{k_1}}t\right]}{2\sqrt{r}}.$$

Since

$$\lim_{t\to\infty} X(t) = B,$$

where

$$B = \frac{1}{2}\left(k_1 + \frac{\sqrt{k_1}\sqrt{k_1 r + 4q}}{\sqrt{r}}\right), \tag{10}$$

there exists some t_0 such that for every $t \geq t_0$, according to Comparison theorem for differential equations [22], we conclude that $X(t) \leq B$. Since the function $X(t), t \geq 0$, is monotonically increasing, then

$$M(t) \leq B \text{ for } t \geq 0.$$

On the other hand, for $W(t) = N(t) + \bar{Z}(t), t \in [0, \tau(\mathbb{D}))$, it holds

$$dW(t) \leq \left(-\min\{d_1, d_2\}W(t) + s(\bar{Z} + Z^*) - \frac{s}{k_2}(\bar{Z} + Z^*)^2\right)dt \leq \left(-\min\{d_1, d_2\}W(t) + \frac{sk_2}{4}\right)dt,$$

due to the fact that the maximum value of function $f(x) = -\frac{s}{k_2}x^2 + sx$ is $\frac{sk_2}{4}$.

In addition, we consider linear differential equation

$$dY(t) = \left(-\min\{d_1, d_2\}Y(t) + \frac{sk_2}{4}\right)dt, \ t \geq 0,$$

with initial condition $Y(0) = N_0 + \bar{Z}_0$, that has a particular solution

$$Y(t) = \left(N_0 + \bar{Z}_0 - \frac{sk_2}{4\min\{d_1, d_2\}}\right)e^{-\min\{d_1,d_2\}t} + \frac{sk_2}{4\min\{d_1, d_2\}}.$$

For $t \geq 0$, and $n \in \mathbb{N}$, under assumption $(M_0, N_0, \bar{Z}_0) \in \mathbb{D}$, we obtain $Y(t) \leq \frac{sk_2}{4\min\{d_1,d_2\}}$. By means of the Comparison theorem for differential equations [22], we can conclude that

$$W(t) \leq \frac{sk_2}{4\min\{d_1, d_2\}}, \ t \geq 0,$$

i.e. $N(t) + \bar{Z}(t) \leq \bar{B}$, for $t \geq 0$, where

$$\bar{B} = \frac{sk_2}{4\min\{d_1, d_2\}}. \tag{11}$$

Let us define a function $V \in C^2(\mathbb{D}, \mathbb{R}_+)$

$$V(M, N, \bar{Z}) = M - \ln M + N + \bar{Z}.$$

Nonegativity of this function can be seen from inequality $u - 1 - \ln u \geq 0$ for any $u > 0$. Thus, we can conclude that $V(M, N, \bar{Z}) \geq 1$ for $(M, N, \bar{Z}) \in \mathbb{D}$.

Application of differental operator L on $V(M, N, \bar{Z})$ yields

$$LV(M, N, \bar{Z}) = \left(1 - \frac{1}{M}\right)\left(q + rM\left(1 - \frac{M}{k_1}\right) - \alpha MN\right) - d_1N(t) + s\left(\bar{Z}(t) + Z^*\right)\left(1 - \frac{\bar{Z}(t) + Z^*}{k_2}\right) - d_2\left(\bar{Z}(t) + Z^*\right).$$

Removing some nonpositive terms we obtain

$$LV(M, N, \bar{Z}) \leq c,$$

where $c = q + \frac{rk_1}{4}\left(1 + \frac{1}{k_1}\right)^2 + \alpha\bar{B} + \frac{sk_2}{4}$.

Since $V(M, N, \bar{Z}) \geq 1$ for $(M, N, \bar{Z}) \in \mathbb{D}$, then $LV(M, N, \bar{Z}) \leq cV(M, N, \bar{Z})$ and $\inf_{(M,N,\bar{Z})\in\mathbb{D}\setminus\mathbb{D}_n} V(M, N, \bar{Z}) > \frac{5}{2}e^n$, za $n \in \mathbb{N}$.

Now, we define function $W(t, M, N, \bar{Z}) = e^{-ct}V(M, N, \bar{Z})$ on $[0, \infty) \times \mathbb{D}$. Then

$$LW(t, M, N, \bar{Z}) = e^{-ct}(-cV(M, N, \bar{Z})) + LV(M, N, \bar{Z})) \leq 0.$$

Let $\tau_n = \min\{t, \tau(\mathbb{D}_n)\}$, $n \in \mathbb{N}$, be the array of stopping times for fixed $t \in [0, \infty)$. Application of Dynkin's formula yields

$$\begin{aligned}\mathbb{E}W(\tau_n, M(\tau_n), N(\tau_n), \bar{Z}(\tau_n)) &= \mathbb{E}W(0, M(0), N(0), \bar{Z}(0)) + \mathbb{E}\left[\int_0^{\tau_n} LW(u, M(u), N(u), \bar{Z}(u))du\right] \\ &\leq \mathbb{E}W(0, M(0), N(0), \bar{Z}(0)) \\ &= \mathbb{E}V(M(0), N(0), \bar{Z}(0)) = V(M_0, N_0, \bar{Z}_0).\end{aligned}$$

Next to show $\mathbb{P}(\tau(\mathbb{D}) < t) = 0$, we take the expected value

$$\begin{aligned}\mathbb{E}\left[e^{c(t-\tau_n)}V(M(\tau_n), N(\tau_n), \bar{Z}(\tau_n))\right] &= \mathbb{E}\left[e^{ct}W(\tau_n, M(\tau_n), N(\tau_n), \bar{Z}(\tau_n))\right] \\ &\leq e^{ct}V(M(0), N(0), \bar{Z}(0)).\end{aligned} \tag{12}$$

Bearing in mind that $\mathbb{D}_n \subset \mathbb{D}$, we obtain

$$\begin{aligned}
0 &\le \mathbb{P}(\tau(\mathbb{D}) < t) \le \mathbb{P}(\tau(\mathbb{D}_n) < t) = \mathbb{P}(\tau_n < t) \\
&= \mathbb{E}(\mathbf{1}_{\{\tau_n<t\}}) \\
&\le \mathbb{E}\left[e^{c(t-\tau(\mathbb{D}_n))}\frac{V(M(\tau(\mathbb{D}_n)), N(\tau(\mathbb{D}_n)), \bar{Z}(\tau(\mathbb{D}_n)))}{\inf_{(M,N,\bar{Z})\in\mathbb{D}\setminus\mathbb{D}_n} V(M(t), N(t), \bar{Z}(t))}\mathbf{1}_{\{\tau_n<t\}}\right] \\
&\le e^{ct}\frac{V(M_0, N_0, \bar{Z}_0)}{\inf_{(M,N,\bar{Z})\in\mathbb{D}\setminus\mathbb{D}_n} V(M(t), N(t), \bar{Z}(t))} \\
&\le e^{ct}\frac{V(M_0, N_0, \bar{Z}_0,)}{\frac{5}{2}e^n} \to 0, \quad n \to \infty,
\end{aligned}$$

for arbitrary $(M_0, N_0, \bar{Z}_0) \in \mathbb{D}$ and for all fixed $t \ge 0$. Thus, $\mathbb{P}(\tau(\mathbb{D}) < t) = 0$ for $(M_0, N_0, \bar{Z}_0) \in \mathbb{D}$, $t \ge 0$, that is $\mathbb{P}(\tau(\mathbb{D}) = \infty) = 1$. This proves the invariance property and the global existence of the solution $(M(t), N(t), \bar{Z}(t))$, $t \ge 0$. □

Now, let us denote the set

$$\Gamma = \{(M, N, Z) \in \mathbb{R}^3_+ : M \le B, N + Z \le \bar{B} + Z^*, Z \ge Z^*\}, \tag{13}$$

where B and $\bar{B}$ are the positive constants defined in (10) and (11). Then, the following theorem is a direct corollary of Theorem 3.2.

Theorem 3.3. *The set Γ defined in (13) is almost surely positively invariant set of system (3), i.e. if $(M_0, N_0, Z_0) \in \Gamma$, then, for any $t \ge 0$,*

$$\mathbb{P}((M(t), N(t), Z(t)) \in \Gamma) = 1.$$

4. Existence of Stationary Distribution

In this section, we will establish sufficient conditions for the positive recurrence and the existence of a stationary distribution for system (3). The existence of a stationary distribution indicates the persistence of the disease in the future under some conditions related to the intensity of the white noise. This means that the stochastic model fluctuates around the endemic equilibrium of the corresponding deterministic model, as it was highlighted in [28].

Assume that $x(t)$ is a regular time-homogeneous Markov process in E_d, where E_d denotes the d-dimensional Euclidean space, and satisfies stochastic differential equation (5). The diffusion matrix of the process $x(t)$ is defined as follows

$$A(x) = (a_{ij}(x)), i, j = 1, \ldots, d, \qquad a_{ij}(x) = \sum_{k=1}^{d} g^i_k(x) g^j_k(x).$$

Now, we present lemma which will be used to prove the main result of this section.

Lemma 4.1. *[28] The Markov process $X(t)$ has a unique ergodic stationary distribution $\pi(\cdot)$ if there exists a bounded domain $D \in \mathbb{R}^d$ with smooth boundary ∂D and*

(A.1) There is a positive number $\mathcal{M}$ such that $\sum_{i,j=1}^{d} a_{ij}(x)\xi_i\xi_j \ge \mathcal{M}|\xi|$, $x \in D$, $\xi \in \mathbb{R}^d$.

(A.2) There exists nonnegative C^2 functional V such that LV is negative for any $x \in \mathbb{R}^d \setminus D$.

Remark 4.2. Conditions (A.1) and (A.2) from the previous lemma represent different variants of equivalent sufficient conditions for existence of the unique ergodic stationary distribution which mainly originated from conditions presented in [8]. Related to that, in [31], Remark 3.2, the authors show that condition (A.1)

from Lemma 4.1 can be replaced by a following condition: *There exist some* $i = 1, 2, \dots, d$ *and positive constant* κ *such that*

$$a_{ii}(x) \geq \kappa \quad \text{for any} \quad x \in D.$$

The stated condition is the one which will be proven for system (3).

Theorem 4.3. *Let the following conditions hold*

$$q > B\left(\frac{r}{k_1}B + \alpha(\bar{B} + Z^*) - r\right), \tag{14}$$

$$s > d_1 + d_2, \tag{15}$$

$$\sigma^2 < 2d_1. \tag{16}$$

Then, the solution $(M(t), N(t), Z(t))$, $t \geq 0$, *of system (3) is positive recurrent and admits a unique ergodic stationary distribution in* Γ *for any initial value* $(M_0, N_0, Z_0) \in \Gamma$.

Proof. The diffusion matrix of system (3) is of the form

$$A = \begin{pmatrix} 0 & 0 & 0 \\ 0 & \sigma^2 N(t)^2 Z^2(t) & -\sigma^2 N(t)^2 Z^2(t) \\ 0 & -\sigma^2 N(t)^2 Z^2(t) & \sigma^2 N(t)^2 Z^2(t) \end{pmatrix}.$$

Let us denote bounded open subset of Γ by

$$D_\varepsilon = \{(M, N, Z) \in \Gamma \ : \varepsilon < M < B - \varepsilon,\ \varepsilon < N < \bar{B} + Z^* - \varepsilon,\ Z^* - \varepsilon < Z < \bar{B} + Z^* - \varepsilon\},$$

where $\varepsilon \in (0, 1)$. For any $(M, N, Z) \in D_\varepsilon$, and, for example $i = 3$, we have

$$a_{33}(M, N, Z) = \sigma^2 N^2(t) Z^2(t) > \sigma^2 \varepsilon^2 (Z^* - \varepsilon)^2,$$

which proves the condition $(A.1)$ of Lemma 4.1, according to the Remark 4.2. Thus, to prove the theorem, in view of Remark 4.2, we only need to verify the condition (ii) in Lemma 4.1, i.e. to construct a nonnegative C^2-function $V \in C^2(\Gamma, [0, \infty))$, such that $LV(M, N, Z) < 0$ for any $(M, N, Z) \in \Gamma \setminus D_\varepsilon$. For that purpose let us denote by

$$p(M) = q + rM - \frac{r}{k_1}M^2$$

a quadratic function with respect to M. Motivated by the discussion in [27], we conclude that this quadratic function has two real roots, $M_0 = B$, where B is defined in (10) and $-M_1 = \frac{1}{2}\left(k_1 - \frac{\sqrt{k_1}\sqrt{k_1 r + 4q}}{\sqrt{r}}\right)$. Thus,

$$p(M) = -\frac{r}{k_1}(M - B)(M + M_1).$$

Bearing in mind that $-(M-B)^2 = -(M-B)(M+M_1) + (M-B)(B+M_1) \leq 0$, we obtain that $(M-B)(M+M_1) \geq (M-B)(B+M_1)$, and, therefore,

$$p(M) = -\frac{r}{k_1}(M - B)(M + M_1) \leq -\frac{r}{k_1}(M - B)(B + M_1).$$

Now, we define functions

$$W_1 = \frac{M}{B + M_1} \quad W_2 = -\frac{1}{B + M_1}\ln M.$$

By applying the Itô formula, we obtain

$$LW_1 \leq \frac{p(M)}{B + M_1} \leq -\frac{r}{k_1}(M - B),$$

$$LW_2 = \frac{1}{B + M_1}\left(-\frac{q}{M} - r + \frac{r}{k_1}M + \alpha N\right) \leq \frac{1}{B + M_1}\left(-\frac{q}{M} - r + \frac{r}{k_1}B + \alpha\left(\bar{B} + Z^*\right)\right).$$

In the sequel we construct the function $U_1 = c_1W_1 + c_2W_2$. Using the results which we have already obtained, as well as $AM - GM$ inequality, we conclude that

$$\begin{aligned} LU_1 &\le -c_1\frac{r}{k_1}M + c_1\frac{r}{k_1}B - \frac{c_2}{B+M_1}\frac{q}{M} + \frac{c_2}{B+M_1}\left(\frac{r}{k_1}B + \alpha\left(\bar{B}+Z^*\right) - r\right) \\ &\le -2\sqrt{\frac{c_1c_2rq}{k_1(B+M_1)}} + c_1\frac{r}{k_1}B + \frac{c_2}{B+M_1}\left(\frac{r}{k_1}B + \alpha\left(\bar{B}+Z^*\right) - r\right). \end{aligned}$$

Let

$$c_1 = \frac{q}{B(B+M_1)}, \qquad c_2 = \frac{rq}{k_1\left(\frac{r}{k_1}B + \alpha\left(\bar{B}+Z^*\right) - r\right)}.$$

Then, the function U_1 is positive, and

$$\begin{aligned} LU_1 &\le -2\frac{rq}{k_1(B+M_1)}\left(\sqrt{\frac{q}{B\left(\frac{r}{k_1}B + \alpha\left(\bar{B}+Z^*\right) - r\right)}} - 1\right) \\ &\le -2\frac{rq}{k_1(B+M_1)}Q, \end{aligned}$$

where $Q = \sqrt{\frac{q}{B\left(\frac{r}{k_1}B+\alpha\left(\bar{B}+Z^*\right)-r\right)}} - 1$ is a positive constant, due to condition (14).

The next step in this proof is to define functions

$$V_1 = N + Z, \quad V_2 = -\ln N, \quad V_3 = -\ln Z, \quad V_4 = (M - \ln M), \quad V_5 = \frac{(N+Z)^2}{2}, \quad V_6 = CZ,$$

where C represents positive constant which will be determined in the sequel. By applying the Itô formula, we obtain

$$\begin{aligned} LV_1 &= -d_1N + sZ - \frac{s}{k_2}Z^2 - d_2Z, \\ LV_2 &= -\beta Z + d_1 + \frac{\sigma^2}{2}Z^2, \\ LV_3 &= -s + \frac{s}{k_2}Z + \beta N + d_2 + \frac{\sigma^2}{2}N^2, \\ LV_4 &= q + rM - \frac{r}{k_1}M^2 - \alpha MN - \frac{q}{M} - r + \frac{r}{k_1}M + \alpha N \le q + rM - \frac{r}{k_1}M^2 - r + \frac{r}{k_1}M + \alpha N, \\ LV_5 &= -d_1N^2 + (s - d_1 - d_2)NZ - \frac{s}{k_2}NZ^2 + (s-d_2)Z^2 - \frac{s}{k_2}Z^3 \le -d_1N^2 + (s - d1 - d_2)NZ + (s-d_2)Z^2 - \frac{s}{k_2}Z^3 \\ LV_6 &= -C\beta NZ + C(s-d_2)Z - \frac{s}{k_2}Z^2. \end{aligned}$$

Having in mind that $(M, N, Z) \in \Gamma \setminus D_\varepsilon$, for

$$U_2(M, N, Z) = V_1 + V_2 + V_3 + V_4 + V_5 + V_6,$$

we obtain

$$\begin{aligned} LU_2 \le{}& (d_1 + d_2 - s + q - r) - \frac{r}{k_1}M^2 + r\left(1 + \frac{1}{k_1}\right)M - \left(d_1 - \frac{\sigma^2}{2}\right)N^2 + (\alpha + \beta - d_1)N \\ &- \frac{s}{k_2}Z^3 + \left(s - d_2 - 2\frac{s}{k_2} + \frac{\sigma^2}{2}\right)Z^2 + \left(s\left(1 + \frac{1}{k_2}\right) - d_2 - \beta + C(s-d_2)\right)Z + (s - d_1 - d_2 - C\beta)NZ. \end{aligned}$$

Now, we choose constant C to annul the quantity in the brackets multiplying NZ, i.e.

$$C = \frac{s - (d_1 + d_2)}{\beta},$$

which is positive constant, due to condition (15). Note that, under condition (16), LU_2 is bounded by some positive constant, for example D, for all $(M, N, Z) \in \Gamma$.

Therefore, if we define nonnegative function $V \in C^2(\Gamma, \mathbb{R}_+)$ as follows

$$V(M, N, Z) = \bar{K}U_1 + U_2,$$

where $\bar{K}$ is a positive constant such that

$$\bar{K} > \frac{D + 1}{2\sqrt{\frac{rq}{k_1(B+M_1)}}Q},$$

we have

$$LV \leq -2\bar{K}\sqrt{\frac{rq}{k_1(B + M_1)}}Q + D \leq -1,$$

which means that the condition $(A.2)$ of Lemma 4.1 is satisfied. This proves the theorem. □

Remark 4.4. From the previous theorem, we conclude that our results align with expected tumor-immune interaction trends. Namely, condition (14) indicates that if $k_1 \sim B$ and an annihilation rate α is small enough, while the growth rate of resting cells s is greater then the sum of death rates for immune cells $d_1 + d_2$ (condition (15)), the tumor cells, as well as the immune cells will be persistent in organism.

5. Non-Persistence in Mean

If the number of tumor cells and hunting cells tends to zero, then the organism is in a state of remission, that is, the stage of absence of the disease. A decrease in the number of tumor cells and hunting cells indicates decreased activity of tumor, which leads to curing. In this case, it is said that the tumor cells and hunting cells of the system (3) are non-persistent in mean. Thus, in the sequel we state the theorem to obtain conditions under which $M(t)$ and $N(t)$, $t \geq 0$, of system (3) are non-persistent in mean

Theorem 5.1. *Let the parameters of model (3) satisfy conditions*

$$s < d_2, \tag{17}$$

$$\beta\frac{q + d_1 + \frac{rk_1}{2} + \frac{r}{2k_1}}{d_2 - s} \leq \alpha, \tag{18}$$

$$\sigma^2 \leq 2\left(d_2 - s\left(1 - \frac{1}{k_2}\right)\right), \tag{19}$$

for any given initial data (4). Then, the tummor cells $M(t)$ and hunting cells $N(t)$, $t \geq 0$, of system (3) are non-persistent in mean, i.e.

$$\limsup_{t\to\infty} \frac{1}{t}\left[\frac{r}{k_1}\int_0^t M^2(s)ds + \left(d_1 + \frac{\sigma^2}{2}\right)\int_0^t N^2(s)ds\right] = 0, \quad \text{a.s.}$$

Proof. Define the functions $V_i \in C^2(\Gamma, \mathbb{R})$, $i = 1, 2, 3, 4$, as follows

$$V_1(M) = M - \ln M, \quad V_2(N, Z) = \frac{1}{2}(N + Z)^2, \quad V_3(Z) = \ln Z, \quad V_4(N) = -\ln N.$$

Since $(M(t), N(t), Z(t)) \in \Gamma$, $t \geq 0$, application of the Itô formula yields

$$LV_1 = q + rM - \frac{r}{k_1}M^2 - \alpha MN - \frac{q}{M} - r + \frac{r}{k_1}M + \alpha N \leq q + rM - \frac{r}{k_1}M^2 - r + \frac{r}{k_1}M + \alpha N \leq q - r + \frac{rk_1}{2}\left(1 + \frac{1}{k_1}\right)^2 - \frac{r}{2k_1}M^2 + \alpha N,$$

The last estimation follows from the fact that the quadratic function $f(M) = -\frac{r}{2k_1}M^2 + r\left(1+\frac{1}{k_1}\right)M$ has maximum value $\frac{rk_1}{2}\left(1+\frac{1}{k_1}\right)^2$ for $M = k_1\left(1+\frac{1}{k_1}\right)$. Similarly,

$$LV_2 = -d_1N^2 + (s-d_1-d_2)NZ - \left(\frac{s}{k_2}+d_2-s\right)Z^2 - \frac{s}{k_2}Z^3.$$

Condition (17) guaranties that the expression in the brackets that multiplies NZ is negative. Thus, we have

$$LV_2 \leq -d_1N^2 - \left(\frac{s}{k_2}+d_2-s\right)Z^2.$$

Moreover,

$$LV_3 = s - \frac{s}{k_2}Z - \beta N - d_2 - \frac{\sigma^2}{2}N^2.$$

By applying the Itô formula on V_4, we get

$$LV_4 = -\beta Z + d_1 + \frac{\sigma^2}{2}Z^2.$$

We consider the function $U(\mathbf{X})$, $\mathbf{X} = (M, N, Z)$, determined by

$$U(\mathbf{X}) = V_1 + V_2 + aV_3 + V_4,$$

where a is nonnegative constant which will be determined in the sequel . According to the previously obtained inequalities, we get

$$LU \leq \left(q - r + \frac{rk_1}{2}\left(1+\frac{1}{k_1}\right)^2 + d_1 - a(d_2-s)\right) - \frac{r}{2k_1}M^2 - \left(d_1+\frac{\sigma^2}{2}\right)N^2 - \left(d_2+\frac{s}{k_2}-s-\frac{\sigma^2}{2}\right)Z^2 - (a\beta-\alpha)N.$$

We can choose a positive constant $a = \frac{\alpha}{\beta}$ to eliminate the term in the brackets multiplying N. On the other hand, conditions (17) and (19) guarantee the positivity of the therm in brackets by Z^2. Hence, we get

$$LU \leq -\frac{r}{2k_1}M^2 - \left(d_1+\frac{\sigma^2}{2}\right)N^2 - \left(\frac{\alpha}{\beta}(d_2-s) - \left(q+\frac{rk_1}{2}+\frac{r}{2k_1}\right)\right).$$

The constant $W = \frac{\alpha}{\beta}(d_2-s) - \left(q+\frac{rk_1}{2}+\frac{r}{2k_1}\right)$ is positive, due to condition (18). Finally,

$$dU(t) \leq \left[-\frac{r}{k_1}M^2(t) - \left(d_1+\frac{\sigma^2}{2}\right)N^2(t)\right]dt - \sigma\left(N(t)+Z(t)\right)dw(t).$$

Integrating the last inequality from 0 to t and dividing both sides by t we obtain

$$\frac{U(t)-U(0)}{t} \leq \frac{1}{t}\int_0^t \left[-\frac{r}{k_1}M^2(s) - \left(d_1+\frac{\sigma^2}{2}\right)N^2(s)\right]ds + \frac{\bar{H}(t)}{t}, \tag{20}$$

where $\bar{H}(t) = -\int_0^t \sigma(N(s)+Z(s))dw(s)$ is a local continuous martingale with $\bar{H}(0) = 0$ and $\limsup_{t\to\infty}\frac{\langle \bar{H},\bar{H}\rangle_t}{t} \leq \sigma^2\bar{B}^2(\bar{B}+Z^*)^2 < \infty$ a.s. By using Strong law of large numbers for martingales, we conclude that $\lim_{t\to\infty}\frac{\bar{H}(t)}{t} = 0$. Letting $t \to \infty$ in (20) yields

$$\limsup_{t\to\infty}\frac{1}{t}\left[\frac{r}{k_1}\int_0^t M^2(s)ds + \left(d_1+\frac{\sigma^2}{2}\right)\int_0^t N^2(s)ds\right] = 0, \quad a.s.$$

which completes the proof. □

Remark 5.2. Let us highlight that, opposite to conditions of Theorem 4.3 and discussion in Remark 4.4, from the conditions of Theorem 5.1 it follows that greater α and small β (condition (18)) and the growth rate of resting cells s greater then its death rate d_2 (condition (17)), leads the tumor cells, as well as the hunting immune cells to extinction.

6. Numerical Simulations

In order to verify our theoretical results and become aware of their biological significance, we consider dynamics of growth of highly malignant *B Lymphoma/Leukemic cells (BCL1)* in the spleen of chimeric mice.

Using the Milstein higher order method mentioned in [3, 9, 29], we get the discretization equation of system

$$\begin{aligned} M_{k+1} &= M_k + \left[q + rM_k\left(1 - \frac{M_k}{k_1}\right) - \alpha M_k N_k\right]\Delta t \\ N_{k+1} &= N_k + \left[\beta N_k Z_k - d_1 N_k\right]\Delta t + \sigma N_k Z_k \sqrt{\Delta t}\xi_k + \frac{\sigma^2}{2} N_k Z_k^2 \sqrt{\Delta t}\left(\xi_k^2 - 1\right) \\ Z_{k+1} &= Z_k + \left[sZ_k\left(1 - \frac{Z_k}{k_2}\right) - \beta N_k Z_k - d_2 Z_k\right]\Delta t - \sigma N_k Z_k \sqrt{\Delta t}\xi_k + \frac{\sigma^2}{2} N_k^2 Z_k \sqrt{\Delta t}\left(\xi_k^2 - 1\right), \ t \geq 0, \end{aligned} \tag{21}$$

where ξ_k, $k = 1, \ldots, n$ are the independent Gaussian random variables $N(0,1)$ and $\Delta t > 0$ is the time increment. The reason why we used the Milstein method is because it is more effective than the Euler-Maruyama method, due to its higher order of convergence (1) compared to order of convergence for the Euler-Maruyama method (0.5).

It should be pointed out once again that collecting clinical information for the purposes of mathematical modelling is a major challenge, especially when it comes to models of oncoimmunology and oncoimmunotherapy, due to limited access to clinically relevant data. Also, the complexity of information involving tumor, immune and organic systems on molecular, cellular and tissue level is also an obstacle. Even assuming that such information is available, it is difficult to give satisfying interpretation in terms of the meaning of the parameter values. Thus, models should be constructed on the basis on the availability of informations about their parameters and meaningful interpretation, which is not a trivial task.

All the parameters used in this example are reliable data which can be found in [2] and references cited therein, and they are all joined in the following table.

Parameter	Unit	Value
k_1	cells	$3.3 \cdot 10^2$
k_2	cells	$5 \cdot 10^4$
q	cells/day	10
r	cells/day	0.0185
s	cells/day	0.0245
β	cells/day	$6.2 \cdot 10^{-7}$
α	cells/day	0.0422
d_1	cells/day	0.0412
d_2	cells/day	0.03
σ^2	/	0.01

Table 1: The values of the model parameters

Parameters from Table 1 satisfy conditions (17), (18) and (19) of Theorem 5.1. For the initial value

$$M_0 = 1.5 \cdot 10^2, \ N_0 = 2.04 \cdot 10^2, \ Z_0 = 5.33 \cdot 10^3, \tag{22}$$

we obtain numerical simulations of tumor and immune cells. Namely, the trajectories of number of tumor cells $M(t), t \geq 0$, of system (3) are presented on Figure 1. On Figure 2 we plot the trajectories that simulate the number of hunting cells $N(t), t \geq 0$, and resting cells $Z(t), t \geq 0$, of system (3).

Based on the presented numerical simulations, we can conclude that immunotherapy is very effective. Namely, after about one month of treatment, the number of tumor cells in chimeric mice is significantly reduced (Figure 1). Along with that, the hunting immune cells also reduce their activity, which results in a decrease of their number in about 100 days after the beginning of treatment. As it was expected, and proved by Theorems 3.2 and 3.3, number of resting cells is reduced, but resting cells do not tend to zero, as it is shown in Figure 2.

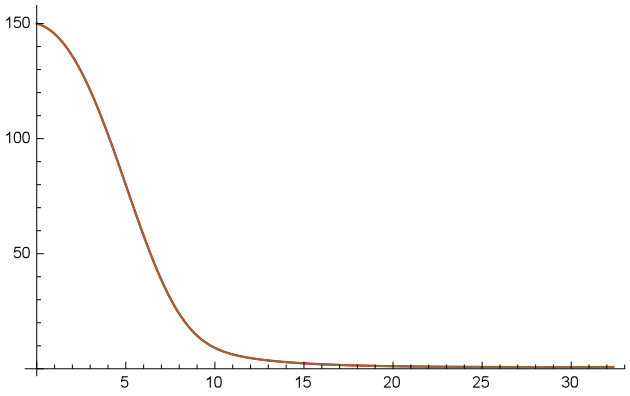

Figure 1: Deterministic and stochastic trajectories for tumor cells $M(t)$ of model (3) with model parameters from Table 1, initial value (22), and unit of time $\triangle t = \frac{1}{24 \cdot 60}$ day.

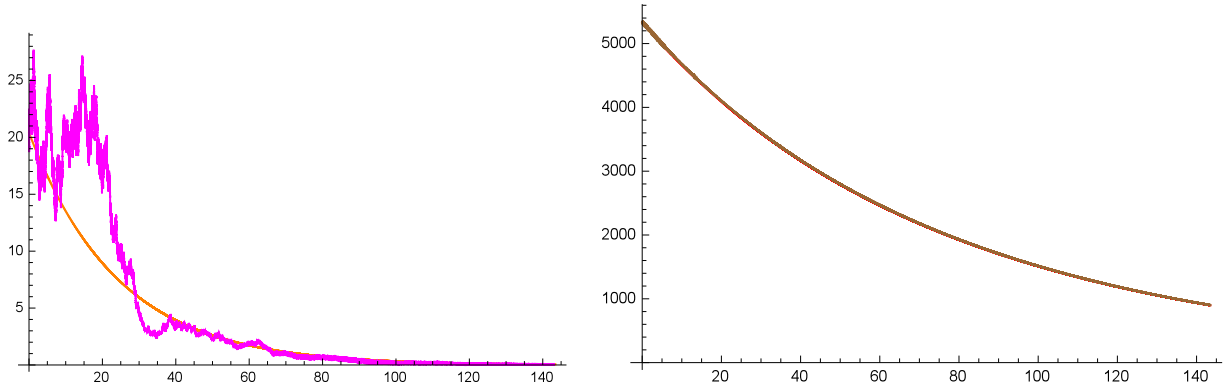

Figure 2: Deterministic and stochastic trajectories for immune cells: hunting cells $N(t)$ (left) and resting cells $Z(t)$ (right) of model (3) with model parameters from Table 1, initial value (22), and unit of time $\triangle t = \frac{1}{24 \cdot 60}$ day.

7. Concluding Remarks

Before closing the paper, let us highlight one more time that cancer is one of the greatest causes of death worldwide, it is ubiquitous, unlike some epidemics that appear and vanish, and that is the main reason why the control of tumor growth requires special attention.

In this paper, we developed a stochastic predator–prey like model of interaction between malignant (tumor) and immune cells. We constructed our model by assuming that environmental fluctuations will manifest themselves through the conversion rate of resting cells into hunting ones. Namely, given that the immune system response to a tumor is caused by the hunting cells response, and they arise from previously resting cells, it is reasonable to assume that the rate at which these cells become activated is random. Also, we prove that resting cells are bounded from below, due to the fact that resting cells are part of the immune system and develop from stem cells in the bone marrow, and, hence, they are always present in the organism, waiting for infected or cancerous cells to activate. To the best of our knowledge, in the existing mathematical literature, there are no papers that include this property in the model of interaction between tumor and immune cells.

In addition, we obtained the conditions under which the solution of model (3) fluctuates around the interior endemic equilibrium point of model (1), which stability is discussed in [24] in terms of the rate of predation of tumor cells by hunting cells (α) and the conversion rate (β). Our results, presented in Theorem 4.3, are also related to the rate α, and they completely agree with the results obtained for the deterministic model, when the intensity of the noise is small enough. On the other hand, in comparison with the results obtained for the stochastic model, our results are much simpler and, therefore, more applicable for the

medical practitioners, experimental scientists, and others who may use them to control the disease. Also, in our analysis, the important factor is relation between the growth rate of resting cells s and death rates of immune cells d_1 and d_2. More precisely, if $s > d_1 + d_2$ and α and σ^2 are small enough, the density of the malignant tumor cells decreases to an equilibrium value and fluctuates around it, that is, there occurs the regression of malignancy. On the other hand, if $s < d_2$, β and σ^2 are small enough, while α is large enough, we expect the disease to become non-persistent in mean, which is proved in Theorem 5.1.

Since the reasons for spontaneous regression and progression of a malignant tumor system and its possible control mechanism is still in infancy, we hope that there will be more mathematical models which will require special attention to this topic. Possible future models may become more realistic than our model by adding telegraph or coloured noise to describe the switching from one environmental regime to another, or Lévy noise to represent certain sudden environmental catastrophes which can affect the human body, and, therefore, human immune system. Also, it is important to consider time delay, since activation process and conversion from resting into hunting cells are not instantaneous but followed by some time lag. All these challenges would improve applicability of our model in validating the future course of the cancers that can be cured by immunotherapy.

Acknowledgment

The authors extend their appreciations to the editor and anonymous referee for their very constructive and helpful comments and suggestions which greatly improve the quality of the paper into its present form.

References

[1] S. Banerjee, *Immunotherapy with interleukin-2: a study based on mathematical modeling*, International Jornal of Applied Mathematics and Computer Science, 18 (3) (2008) 389–398.
[2] S. Banerjee and R. R. Sarkar, *Delay-induced model for tumor-immune interaction and control of malignant tumor growth*, Biosystems, 91 (1) (2008) 268–288.
[3] M. Bayram, T. Partal, G. Orucova Buyukoz, *Numerical methods for simulation of stochastic differential equations*, Advances in Difference Equations (2018) 2018:17 https://doi.org/10.1186/s13662-018-1466-5.
[4] J. Đorđević, B. Jovanović, *Dynamical analysis of a stochastic delayed epidemic model with lévy jumps and regime switching*, Journal of the Franklin Institute 360 (2023), 1252-1283.
[5] J. Đorđević, I. Papić, N. Šuvak, *A two diffusion stochastic model for the spread of the new corona virus SARS-CoV-2*, Chaos, Solitons and Fractals 148 (2021) 110991.
[6] M. Galach, *Dynamics of the tumor-immune system competition-the effect of time delay*, International Journal of Applied Mathematics and Computer Science, 13 (3) (2003) 395–406.
[7] C. Han, Y. Wang, D. Jiang, *Dynamics analysis of a stochastic HIV model with non-cytolytic cure and Ornstein–Uhlenbeck process*, Chaos, Solitons & Fractals 175(1) (2023), 113930.
[8] R.Z. Has'minskij, *Stochastic Stability of Differential Equations*, Sijthoof & Noordhoof, Aplohen aan der Rijn, The Nederlands, 1980.
[9] D.J. Higham, *An algorithmic introduction to numerical simulation of stochastic differential equations*, SIAM review 43 (3) (2001) 525–546.
[10] B. Jovanović, J. Đorđević, J. Manojlović, Nenad Šuvak, *Analysis of Stability and Sensitivity of Deterministic and Stochastic Models for the Spread of the New Corona Virus SARS-CoV-2*, Filomat 35:3 (2021), 10451063.
[11] M. Jovanović, M. Krstić, *Extinction in stochastic predator-prey population model with Allee effect on prey*, Discrete Contin. Dyn. Syst., Ser. B 22(7) (2017), 2651-2667.
[12] M. Jovanović, M. Krstić, *Stochastically perturbed vector-borne disease models with direct transmission*, Applied Mathematical Modelling 36 (2012), 5214-5228.
[13] M. Jovanović, M. Krstić, *The influence of time-dependent delay on behavior of stochastic population model with the Allee effect*, Applied Mathematical Modelling 39(2) (2015), 733-746.
[14] M. Jovanović, V. Vujović, *Stability of stochastic heroin model with two distributed delays*, Discrete Contin. Dyn. Syst., Ser. B 25(7) (2020), 2407-2432.
[15] M. Krstić, *On Stability of Stochastic Delay Model for Tumor-Immune Interaction*, Filomat 32:4 (2018), 1273-1283.
[16] M. Krstić, *The effect of stochastic perturbation on a nonlinear delay malaria epidemic model*, Mathematics and Computers in Simulation 82 (2011), 558-569.
[17] M. Krstić, M. Jovanović, *On stochastic population model with the Allee effect*, Mathematical and Computer Modelling 52 (1–2) (2010), 370-379.
[18] V. A. Kuznetsov, I. A. Makalkin, M. A. Taylor, *Nonlinear dynamics of immunogenic tumors: parameter estimation and global bifurcation analysis*, Bulletin of Mathematical Biology, 56 (2) (1994) 295–321.
[19] A. M. Makhlouf, L. El-Shennawy, H. A. Elkaranshawy, *Mathematical Modelling for the Role of $CD4^+T$ Cells in Tumor-Immune Interactions*, Hindawi Computational and Mathematical Methods in Medicine, 2020, Article ID 7187602, 16 pages, https://doi.org/10.1155/2020/7187602.

[20] X. Mao, *Stochastic Differential Equations and Applications*, Horvood, Chichester, UK, 2007(Second edition).
[21] M. Marković, M. Krstić, *On a stochastic generalized delayed SIR model with vaccination and treatment*, Nonlinearity, 36(12) (2023), 7007.
[22] A. McNabb, *Comparison theorems for differential equations*, Journal of mathematical analysis and applications, 119 (1-2) (1986) 417–428.
[23] M. Milunović, M. Krstić, *Long Time Behavior of an Two Diffusion Stochastic SIR Epidemic Model with Nonlinear Incidence and Treatment*, Filomat 36:8 (2022), 2829-2846.
[24] R.R.Sarkar, S.Banerjee, *Cancer self remission and tumor stability a stochastic approach*, Mathematical Biosciences, 196 (1) (2005) 65–81.
[25] V. Vujović, *Influence of environmental fluctuations on Hepatitis C transmission*, Mathematics and Computers in Simulation 191 (2022), 203-218.
[26] V. Vujović, M. Krstić, *Stability of Stochastic Model for Hepatitis C Transmission with an Isolation Stage*, Filomat 34:14 (2020), 4795-4809.
[27] Y. Wang, M. Lu, D. Jiang, *Dynamic Behavior of a General Stochastic HIV MOdel withVirus–to–Cell Infection, Cell–to–Cell transmission, Immune Response and Distributed delays*, Journal of Nonlinear Science 33:97 (2023), https://doi.org/10.1007/s00332-023-09955-5.
[28] X. Zhang, R. Yuan, *The existence of stationary distribution of a stochastic delayed chemostat model*, Applied Mathematics Letters (2019) 93, 15-21.
[29] X. Zhou, *Dynamical Analysis of a Stochastic Cholera Epidemic Model*, Mathematics 2022, 10, 2830. https://doi.org/10.3390/math10162830.
[30] B. Zhou, D. Jiang, T. Hayat, *Analysis of a stochastic population model with mean-reverting Ornstein–Uhlenbeck process and Allee effects*, Communications in Nonlinear Science and Numerical Simulation 111 (2022), 106450.
[31] C. Zhu, G. Yin, *Asymptotic prorerties of hybrid diffusion systems*, SIAM Journal on Control and Optimization 46 (2007),1155–1179.