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On Stability of Stochastic Delay Model for Tumor-Immune Interaction

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Abstract. In this paper we study a stochastic model for tumor-immune interaction with delay. More precisely, we extend the deterministic delay tumor-immune interaction model by introducing random perturbations and obtain stochastic model. For this model, we first prove existence and uniqueness of the global positive solution, and then, by using suitable Lyapunov functionals, we obtain stability conditions for the equilibrium state when tumor cells and resting cells approach their carrying capacities. We also carry numerical simulation with reliable data to illustrate our theoretical findings.

1. Introduction

Cancer is one of the greatest killer diseases in human population. It is well known that millions of people die from cancer every year, and although the great progress has been achieved in fields of cancer prevention and surgery and many novel drugs are available for medical therapies, the worldwide trends indicate that millions more will die from this disease in the future. Cancer is a group of diseases that manifests itself through rapid growth with the potential to expand and involve other organs in the body. It is important to highlight that not all tumors are cancerous. There exists benign tumors that do not spread to other parts of the body. Nowadays, over 100 types of cancers that affect humans are known.

In most cases of cancers (90-95%), genetic mutations from environmental factors are responsible for the disease, and the remaining 5-10% are due to inherited genetics [1]. Environmental factors does not include just pollution, but all causes that are not inherited genetically, such as lifestyle, economic and behavioral factors, tobacco (25-30%), diet and obesity (30-35%), infections (15-20%), radiation (up to 10%), stress, lack of physical activity etc.

Due to the fact that this is a very widespread and dangerous disease, many methods of cancer treatment have developed over time. The primary ones include surgery, chemotherapy, radiation therapy, hormonal therapy, targeted therapy and palliative care. Which treatments are used depends on the type, location and grade of the cancer as well as the patient's health and preferences. Surgery and chemotherapy play an important role in treating cancer, but they do not represent a cure. In order to control spread of the disease, we need a successful treatment strategies. One of these strategies is investigated through immunotherapy which represents the interaction between effector cells and tumor cells, and it is used since 1997. This idea

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of immunotherapy is promising, but controversial from the point of view of the results obtained in medical investigations.

Immunotherapies can be categorized as active, passive or hybrid (active and passive). These approaches exploit the fact that cancer cells often have molecules on their surface that can be detected by the immune system, known as tumor-associated antigens (TAAs). Active immunotherapy directs the immune system to attack tumor cells by targeting TAAs. Passive immunotherapies enhance existing anti-tumor responses and include the use of monoclonal antibodies, lymphocytes and cytokines.

One form of passive immunization is by the transfusion of T-cells (adoptive T-cell therapy). These cells are found in blood and tissue and usually activate when they find foreign pathogens. Specifically they activate when the T-cell's surface receptors encounter cells that display parts of foreign proteins on their surface antigens. These can be either infected cells, or antigen presenting cells (APCs). They are found in normal tissue and in tumor tissue, where they are known as tumor infiltrating lymphocytes (TILs). They are activated by the presence of APCs such as dendritic cells that present tumor antigens.

Multiple ways of producing and obtaining tumor targeted T-cells have been developed. T-cells specific to a tumor antigen can be removed from a tumor sample (TILs) or filtered from blood. Subsequent activation and culturing is performed ex vivo, with the results reinfused. Activation can take place through gene therapy, or by exposing the T-cells to tumor antigens.

The theoretical study of tumor–immune interaction has a long history. There are many papers in the literature in which this interaction is regarded as competitive model between tumor cells and immune system, or as a predator–prey like relationship (see [2, 5, 14] and references cited therein). In all this papers tumor–immune interaction is described by defining a model of differential equations that represents the interaction between effector cells and tumor cells.

As we have already mentioned, environmental factors affect spread of cancer, and that is why it is important to consider stochastic models. There are so many methods to introduce stochastic perturbations in the system. From biological perspective, random effects can be expressed in Itô or Stratonovich stochastic integrals. The Stratonovich integral lacks the important property of the Itô integral, which does not "look into the future". In many real-world applications, one only has information about past events, and hence the Itô interpretation is more natural. In [14] the authors consider stochastic model for tumor–immune interaction. However, since activation process and conversion from resting T-cells into hunting T-cells are not instantaneous, but followed by some time lag, in this paper we consider delay stochastic model of tumor-immune interaction. We construct our model on the basis of models considered in [2] and [14] by assuming that environmental changes affect conversion rate of resting into hunting T-cells. For our model, we investigate stability properties of the equilibrium states by using well known method based on construction of appropriate Lyapunov functionals. The general method of Lyapunov functionals construction was proposed and developed by Kolmanovskii and Shaikhet [8] and Shaikhet (see [15–18], for instance) for different types of stochastic differential equations. This method is used in many papers for stability investigation of the equilibrium states of stochastic population and epidemiological delay models (see [3, 4, 9, 12], among the others).

The paper is organized in the following way: In Section 2, we outline the deterministic models presented in [2] and [14] on the basis of which we construct the stochastic model. In Section 3 we verify that there exists a unique nonnegative solution for our model. In Section 4 by using Lyapunov functionals, we investigate stochastic asymptotic stability of the equilibrium state when tumor and resting cells approach their carrying capacities, and establish some sufficient stability conditions regardless of incubation period. Section 5 is devoted to the numerical simulation of the results obtained through the paper in order to show that the stochastic model for dynamics of growth of highly malignant *B Lymphoma/Leukemic cells (BCL_1)* in the spleen of chimeric mice, with quantities which are reliable data, is compatible with our mathematical findings. We close the paper with Section 6, where we combine the results obtained through the paper and give some possible directions for the future research.

2. The model

In this section, we briefly present the result by Banerjee et al. [2], who modify results from [14] by introducing time delay into deterministic tumor-immune model. In order to model tumor-immune interaction, the authors consider two cellular species, T-cells, which they classify into hunting and resting cells, and the malignant tumor cells. Hunting cells attack tumor cells and destroy them, and resting cells can not kill the tumor cells, but they release various cytokines which stimulate hunting cells so they can hunt and destroy even more tumor cells. The authors regard the growth of tumor and resting cells as the logistic growth. They denote $M(t)$, $N(t)$ and $Z(t)$ to be number of tumor, hunting and resting cells at time t, respectively. The assumptions of the model are the following: the tumor cells are destroyed at a rate which is proportional to the densities of tumor and hunting cells according to the low of mass action, the resting cells are converted to the hunting cells either by direct contact with them, or by contact of hunting cells with cytokines which is produced by resting cells, conversion of resting cells into hunting ones is not instantaneous but followed by some time lag and once a cell has been converted it will never return to resting state.

Thus, the dynamics of T-cells and tumor cells is given by the system of ordinary differential equations:

$$\begin{aligned}
\frac{dM(t)}{dt} &= r_1 M(t)\left(1-\frac{M(t)}{k_1}\right)-\alpha_1 M(t)N(t),\\
\frac{dN(t)}{dt} &= \beta N(t)Z(t-\tau)-d_1 N(t)-\alpha_2 M(t)N(t),\\
\frac{dZ(t)}{dt} &= r_2 Z(t)\left(1-\frac{Z(t)}{k_2}\right)-\beta N(t)Z(t-\tau),
\end{aligned} \tag{1}$$

with initial conditions $M(\theta)=M_0$, $N(\theta)=N_0$, $Z(\theta)=Z_0$, $\theta\in[-\tau,0]$. The parameters in model (1) are positive constants which are described as follows:

r_1 and r_2 - the growth rate of tumor cells and resting cells, respectively,
k_1 and k_2 - the carrying capacity of tumor cells and resting cells, respectively,
d_1 - the death rate of hunting cells,
α_1 - the rate of annihilation of tumor cells in interaction with hunting cells,
α_2 - the rate of annihilation of hunting cells in interaction with tumor cells,
β - the conversion rate of resting cells into hunting cells,
τ - time delay.

In [2], the authors consider model (1) in the set

$$\Gamma=\left\{(M,N,Z)\in\mathbb{R}^3_+ : N+Z\le k_2, M\le B\right\}, \tag{2}$$

where B is a positive constant defined by $B=\left(\frac{k_1}{4r_1}(r_1+d_1)^2+\frac{k_2}{4r_2}(r_2+d_1)^2\right)/d_1$.

On the basis of model (1) we construct the stochastic delay model by perturbing the conversion rate β with $\beta\to\beta+\sigma\dot{w}(t)$, where $\dot{w}(t)$ is a white noise with the intensity σ^2. Hence, we obtain system

$$\begin{aligned}
dM(t) &= \left[r_1 M(t)\left(1-\frac{M(t)}{k_1}\right)-\alpha_1 M(t)N(t)\right]dt,\\
dN(t) &= [\beta N(t)Z(t-\tau)-d_1 N(t)-\alpha_2 M(t)N(t)]dt+\sigma N(t)Z(t-\tau)dw(t),\\
dZ(t) &= \left[r_2 Z(t)\left(1-\frac{Z(t)}{k_2}\right)-\beta N(t)Z(t-\tau)\right]dt-\sigma N(t)Z(t-\tau)dw(t),
\end{aligned} \tag{3}$$

with initial value

$$M(\theta)=M_0,\ N(\theta)=N_0,\ Z(\theta)=Z_0,\ \theta\in[-\tau,0], \tag{4}$$

where $w(t)$ represents a standard Brownian motion defined on a complete probability space $\{\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t\geq 0}, P\}$ 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 P-null sets) and σ is a real constant.

Let us note here that stochastic model (3) has four equilibrium states: trivial equilibrium state $E_0(0,0,0)$, $E_M(k_1,0,0)$, $E_Z(0,0,k_2)$, $E_{M,Z}(k_1,0,k_2)$. In comparison with system (1), it has two equilibrium states less than deterministic system. Our goal is to investigate stability properties of equilibrium state $E_{M,Z}$.

Through the paper, unless otherwise specified, we will consider model (3) with initial data (4) in the set Γ defined in (2).

3. Positive and global solution

As $M(t)$, $N(t)$ and $Z(t)$ in system (3) represent cell numbers at the moment t, we are only interested in the positive solutions. Moreover, in order for a stochastic differential equation to have a unique global solution (i.e. solution that does not explode in finite time) for any given initial data, the coefficients of stochastic differential equation are generally required to satisfy the linear growth condition and local Lipschitz condition [13]. By the following theorem we establish some conditions under which the solution of system (3) is positive and global.

Theorem 3.1. *For any initial value (4), there exists a unique positive global solution* $(M(t), N(t), Z(t))$ *to system (3) on* $t \geq -\tau$.

Proof. Since the coefficients of system (3) are locally Lipschitz continuous, then, for any initial value there exists a unique local solution $(M(t), N(t), Z(t))$ on $t \in [-\tau, \tau_e)$, where τ_e represents explosion time. To show that this solution is global, we need to prove that $\tau_e = \infty$ a.s. Let $k_0 > 0$ be sufficiently large such that $M(\theta)$, $N(\theta)$ and $Z(\theta)$ all lie within the interval $\left[\frac{1}{k_0}, k_0\right]$ for $\theta \in [-\tau, 0]$. For each integer $k \geq k_0$ define the stopping time

$$\tau_k = \inf\left\{t \in [-\tau, \tau_e) : M(t) \notin \left(\frac{1}{k}, k\right) \vee N(t) \notin \left(\frac{1}{k}, k\right) \vee Z(t) \notin \left(\frac{1}{k}, k\right)\right\},$$

where throughout this paper we set $\inf \emptyset = \infty$ (as usual $\emptyset$ represents the empty set). Clearly, τ_k is increasing as $k \to \infty$. Set $\tau_\infty = \lim_{k\to\infty} \tau_k$. If we can show that $\tau_\infty = \infty$ a.s., then $\tau_e = \infty$ a.s. and $(M(t), N(t), Z(t))$ is a positive global solution of system (3). Thus, we only need to show that $\tau_\infty = \infty$ a.s. If this is not true, then there exists a constant $T > 0$ such that $P\{\tau_k \leq T\} \to \infty$ when $k \to \infty$.

Let us define a C^2 functional $V_1 : \mathbb{R}^3_+ \to \mathbb{R}_+$ by

$$V_1(M, N, Z) = M - \ln M + N^2 - 2\ln N + Z - \ln Z.$$

Nonnegativity of this functional can be seen from inequality $u - \ln u \geq 0$ far any $u > 0$. Let $k \geq k_0$ and $T > 0$ be arbitrary. For $0 \leq t \leq \tau_k \wedge T$ we apply the Itô formula to $V_1(M, N, Z)$ and obtain

$$dV_1(M(t), N(t), Z(t)) = LV_1(M(t), N(t), Z(t), Z(t-\tau))dt + \sigma Z(t-\tau)\left(2(N^2(t) - 1) - \frac{Z(t) - 1}{Z(t)}\right)dw(t),$$

where

$$\begin{aligned} LV_1(M, N, Z, Z_1) = {} & (M-1)\left(r_1\left(1 - \frac{M}{k_1}\right) - \alpha_1 N\right) + 2(N^2 - 1)(\beta Z_1 - d_1 - \alpha_2 M) + \sigma^2 Z_1^2 \\ & + (Z-1)\left(r_2\left(1 - \frac{Z}{k_2}\right) - \beta\frac{NZ_1}{Z}\right) + \frac{\sigma^2}{2}\frac{(NZ_1)^2}{Z^2}. \end{aligned}$$

Bearing in mind that we are working on the set Γ defined by (2), we calculate

$$\begin{aligned} LV_1(M, N, Z, Z_1) \leq {} & -\frac{r_1}{k_1}M^2 + \left(r_1\left(1 + \frac{1}{k_1}\right) + 2\alpha_2\right)M - r_1 + 2d_1 - r_2 \\ & - 2d_1 N^2 + \alpha_1 N - \frac{r_2}{k_2}Z^2 + r_2\left(1 + \frac{1}{k_2}\right)Z + 2\beta k_2^2 Z_1 + \sigma^2 k_2^2 + \sigma^2\frac{k_2^4}{2Z^2}. \end{aligned}$$

In order to eliminate the terms with delay, we introduce the nonnegative functional

$$V_2(Z(t)) = 2\beta k_2^2 \int_{t-\tau}^{t} Z(s)ds.$$

Thus, for $V = V_1 + V_2$, we obtain that $LV \leq K$, where K is a positive constant. Therefore,

$$dV(M,N,Z) \leq Kdt + \sigma Z(t-\tau)\left(2(N^2(t)-1) - \frac{Z(t)-1}{Z(t)}\right)dw(t).$$

The rest of the proof is rather standard for this type of theorems, and, hence, is omitted. □

4. Stability analysis

As we have already mentioned, our main goal is to investigate the stability conditions of the equilibrium state $E_{M,Z}(k_1, 0, k_2)$ of system (3). For that purpose, we use the well known general method of Lyapunov functionals construction. Let us first center system (3) around the mentioned equilibrium state. Hence, we make change of variables $x(t) = M(t) - k_1$, $y(t) = Z(t) - k_2$ and obtain

$$\begin{aligned}
dx(t) &= -\left[r_1(x(t)+k_1)\frac{x(t)}{k_1} + \alpha_1(x(t)+k_1)N(t)\right]dt,\\
dN(t) &= [\beta N(t)(y(t-\tau)+k_2) - d_1 N(t) - \alpha_2(x(t)+k_1)N(t)]dt + \sigma N(t)(y(t-\tau)+k_2)dw(t),\\
dy(t) &= -\left[r_2(y(t)+k_2)\frac{y(t)}{k_2} + \beta N(t)(y(t-\tau)+k_2)\right]dt - \sigma N(t)(y(t-\tau)+k_2)dw(t),
\end{aligned} \tag{5}$$

It is obvious that stability in probability of equilibrium state $E_{M,Z}$ of system (3) is equivalent to stability in probability of the trivial equilibrium state of system (5).

Before we proceed, we establish some definitions and statements for the stability of stochastic functional differential equations (see [7], for instance).

Let $(\Omega, \mathcal{F}, \{\mathcal{F}_t\}_{t\geq 0}, P)$ be a given complete probability space with the filtration $\{\mathcal{F}_t\}_{t\geq 0}$ satisfying the usual conditions, and let $w(t)$ be an m-dimensional Brownian motion defined on the space. Denote that $\mathcal{C} = C([-\tau, 0]; \mathbb{R}^d)$ is the family of continuous functions $\varphi : [-\tau, 0] \to \mathbb{R}^d$ with the norm $\|\varphi\| = \sup_{-\tau\leq\theta\leq 0} |\varphi(\theta)|$ and $\mathcal{D}$ the space of $\mathcal{F}_0$-adapted function $\varphi \in \mathcal{C}$.

Consider the d-dimensional stochastic functional differential equation

$$\begin{aligned}
&dy(t) = f(t, y_t)dt + g(t, y_t)dw(t), \geq 0,\\
&y_0 = \varphi = \{\varphi(\theta) : -\tau \leq \theta \leq 0\},
\end{aligned} \tag{6}$$

where $y_t = \{y(t+\theta) : -\tau \leq \theta \leq 0\}$ is a $\mathcal{C}$-valuated stochastic process and $y_0 \in \mathcal{D}$, such that $E\|\varphi\|^2 < \infty$, while $f(t, \varphi)$ is d-dimensional vector and $g(t, \varphi)$ is $d \times m$-dimensional matrix, both defined for $t \geq 0$. We assume that Eq. (6) has a unique global solution $y(t; \varphi)$, as well as that $f(t, 0) = g(t, 0) \equiv 0$. So, Eq. (6) has the trivial solution $y(t) \equiv 0$ corresponding to the initial condition $y_0 = 0$.

Definition 4.1. *The trivial solution of Eq. (6) is said to be stochastically stable if for every $\varepsilon \in (0, 1)$ and $r > 0$, there exists a $\delta = \delta(\varepsilon, r, 0) > 0$ such that*

$$P\{|y(t; \varphi)| > r, t \geq 0\} \leq \varepsilon,$$

for any initial condition $\varphi \in \mathcal{D}$ satisfying $P\{\|\varphi\| \leq \delta\} = 1$.

Definition 4.2. *The trivial solution of Eq. (6) is said to be mean square stable if for every $\varepsilon > 0$, there exists a $\delta > 0$ such that $E|y(t; \varphi)|^2 < \varepsilon$ for any $t \geq 0$ provided that $\sup_{-\tau\leq\theta\leq 0} E|\varphi(\theta)|^2 < \delta$.*

Definition 4.3. *The trivial solution of Eq. (6) is said to be asymptotically mean square stable if it is mean square stable and $\lim_{t\to\infty} E|y(t; \varphi)|^2 = 0$.*

The differential operator associated to Eq. (6) is defined by the formula

$$LV(t,\varphi) = \limsup_{\Delta\to 0} \frac{\mathbf{E}_{t,\varphi} V(t+\Delta, y_{t+\Delta}) - V(t,\varphi)}{\Delta},$$

where $y(s), s \geq t$ is the solution of Eq. (6) satisfying the initial condition $y_t = \varphi$, and $V(t,\varphi)$ is a functional defined for $t \geq 0$ and for functions $\varphi \in \mathcal{D}$.

Let us reduce a class of functionals $V(t,\varphi)$ so that the operator L can be calculated. First, for $t \geq 0$ and function $\varphi \in \mathcal{D}$, let $V(t,\varphi) = V(t,\varphi(0),\varphi(\theta))$, $-\tau \leq \theta \leq 0$. Then, we define the function

$$V_\varphi(t,y) = V(t,\varphi) = V(t,y_t) = V(t,y,y(t+\theta)),\ -\tau \leq \theta \leq 0,$$

where $\varphi = y_t,\ y = \varphi(0) = y(t)$.

Let us denote that $C_{1,2}$ is a class of functionals $V(t,\varphi)$ so that, for almost all $t \geq 0$, the first and second derivatives with respect to y of $V_\varphi(t,y)$ are continuous, and the first derivative with respect to t is continuous and bounded. Then, the application of the generating operator L of Eq. (6) yields

$$LV(t,y_t) = \frac{\partial V_\varphi(t,y)}{\partial t} + f^T(t,y_t)\frac{\partial V_\varphi(t,y)}{\partial y} + \frac{1}{2} trace\left[g^T(t,y_t)\frac{\partial^2 V_\varphi(t,y)}{\partial y^2} g(t,y_t)\right].$$

The following theorems [7] contain conditions under which the trivial solution of Eq. (6) is asymptotically mean square stable and stochastically stable.

Theorem 4.4. *Let there exist a functional $V(t,\varphi) \in C_{1,2}$ such that*

$$c_1 E|y(t)|^2 \leq EV(t,y_t) \leq c_2 \sup_{-\tau\leq\theta\leq 0} E|y(t+\theta)|^2,$$
$$ELV(t,y_t) \leq -c_3 E|y(t)|^2,$$

for $c_i > 0$, $i = 1,2,3$. Then, the trivial solution of Eq. (6) is asymptotically mean square stable.

Theorem 4.5. *Let there exist a functional $V(t,\varphi) \in C_{1,2}$ such that*

$$c_1|y(t)|^2 \leq V(t,y_t) \leq c_2 \sup_{-\tau\leq\theta\leq 0} |y(t+\theta)|^2 \quad and \quad LV(t,y_t) \leq 0,$$

for $c_i > 0$, $i = 1,2$ and for any $\varphi \in \mathcal{D}$ such that $P\{\|\varphi\| \leq \delta\} = 1$, where $\delta > 0$ is sufficiently small. Then, the trivial solution of Eq. (6) is stochastically stable.

Now, we can proceed with our results.

The corresponding linearized system of system (5) is

$$\begin{aligned} d\tilde{x}(t) &= -\left[r_1\tilde{x}(t) + \alpha_1 k_1 \tilde{N}(t)\right]dt, \\ d\tilde{N}(t) &= -\left[d_1 + \alpha_2 k_1 - \beta k_2\right]\tilde{N}(t)dt + \sigma k_2 \tilde{N}(t)dw_t, \\ d\tilde{y}(t) &= -\left[r_2\tilde{y}(t) + \beta k_2 \tilde{N}(t)\right]dt - \sigma k_2 \tilde{N}(t)dw_t. \end{aligned} \tag{7}$$

Theorem 4.6. *Let, for an arbitrary numbers $\tilde{a}$, $\tilde{b}$ and $\tilde{c}$ such that*

$$\tilde{b} > \frac{\tilde{a}\alpha_1 k_1 + \tilde{c}\beta k_2}{2(d_1 + \alpha_2 k_1 - \beta k_2)}, \tag{8}$$

the model parameters of system (5) satisfy the conditions

$$\alpha_1 k_1 < 2r_1, \tag{9}$$
$$\beta k_2 < \min\{d_1 + \alpha_2 k_1, 2r_2\} \tag{10}$$
$$0 \leq \sigma^2 < \frac{2\tilde{b}(d_1 + \alpha_2 k_1 - \beta k_2) - \tilde{a}\alpha_1 k_1 - \tilde{c}\beta k_2}{(\tilde{b} + \tilde{c})k_2^2}. \tag{11}$$

Then the trivial solution of system (7) is asymptotically mean square stable.

Proof. Let us construct Lyapunov functional V

$$V = a\tilde{x}^2(t) + b\tilde{N}^2(t) + c\tilde{y}^2(t),$$

where a, b and c are non-negative constants to be selected in the sequel. Application of the generating operator L on system (7) and some basic calculations yield

$$LV = -2ar_1\tilde{x}^2(t) - 2a\alpha_1 k_1 \tilde{x}(t)\tilde{N}(t) - 2b\left(d_1 + \alpha_2 k_1 - \beta k_2\right)\tilde{N}^2(t) - 2cr_2\tilde{y}^2(t) - 2c\beta k_2 \tilde{N}(t)\tilde{y}(t) + (b+c)k_2^2\sigma^2\tilde{N}^2(t).$$

By using the elementary inequality $\pm 2uv \leq u^2 + v^2$, we deduce

$$\begin{aligned} LV \leq & -a\left[2r_1 - \alpha_1 k_1\right]\tilde{x}^2(t) \\ & -\left[2b\left(d_1 + \alpha_2 k_1 - \beta k_2\right) - a\alpha_1 k_1 - c\beta k_2 - (b+c)k_2^2\sigma^2\right]\tilde{N}^2(t) \\ & -c\left[2r_2 - \beta k_2\right]\tilde{y}^2(s)ds. \end{aligned} \tag{12}$$

For an arbitrary positive constants $\tilde{a}$ and $\tilde{c}$ we can choose constant $\tilde{b}$ as defined in (8). Such a choice of constants in addition to conditions (9)-(11), guaranties positivity of the quantities in the brackets of the last inequality, which completes the proof. □

Let us note that system (5) has the order of nonlinearity more than one. From [16, 17] it follows that if the order of nonlinearity of the system under consideration is more than one then the conditions, which are sufficient for asymptotic mean square stability of the trivial solution of the linear part of this system, are sufficient for stochastic stability of the trivial solution of the whole system. Thus, if conditions (9)-(11) hold then the trivial solution of the system (5) is stochastically stable, which is formulated in the next statement.

Corollary 4.7. *Let all conditions of Theorem 4.6 hold. Then, the trivial solution of system (5) is stochastically stable.*

From Corollary 4.7 it is obvious that tumor cells and hunting cells will reach their maximum value $M(t) = k_1$ and $Z(t) = k_2$ if annihilation rate of tumor cells multiplied by their carrying capacity is smaller than their growth rate, and conversion rate of resting cells into the hunting ones multiplied by their carrying capacity is smaller than their growth rate. In other words, if growth rates of tumor and resting cells are large enough, than their number reach carrying capacities, in the absence of hunting cells. From the biological point of view, from condition (10) we can conclude that if the conversion rate from resting to hunting stage of T-cells (β) does not exceed certain value, the malignant cell density tends to the maximum level and we obtain stability of hunting cell-free equilibrium state. However, for applications, it is important to control malignant cell density. Thus, if we enhance the conversion rate, we can reduce number of malignant tumor cells, which will be shown in Figures 3 and 5 in Section 5.

At the end of this section, let us highlight that in Theorem 4.6 and Corollary 4.7 we obtained stability conditions for equilibrium state $E_{M,Z}$ regardless of the length of time delay, i.e. this conditions is valid for every τ.

5. Numerical simulation

In order to get some conclusions about biological significance of the stability of equilibrium state $E_{M,Z}$ of model (3), let us consider dynamics of growth of highly malignant *B Lymphoma/Leukemic cells (BCL_1)* in the spleen of chimeric mice. All the parameters used in order to carry numerical simulation are reliable data which can be found in [2] and references cited therein. For numerical simulation, we use the Euler-Maruyama approximate method (see [6]) to simulate the solutions of the considered equations[1)].

[1)] All simulations are made by using *MATHEMATICA* programme.

From [2, 14] we can take model parameters in the following form

$$\begin{aligned} &k_1 = 3.3 \cdot 10^6 \text{ cells}, \ k_2 = 6.5 \cdot 10^6 \text{ cells}, \\ &\alpha_1 = 1.101 \cdot 10^{-7} \text{ cells/day}, \ \alpha_2 = 6.422 \cdot 10^{-10} \text{ cells/day}, \ d_1 = 0.0412 \text{ cells/day}, \\ &r_1 = 0.185 \text{ cells/day}, \ r_2 = 0.0245 \text{ cells/day}, \ \beta = 6.2 \cdot 10^{-9} \text{ cells/day}. \end{aligned} \tag{13}$$

With such choice of parameters, and, for $\tilde{a} = 10^{-20}$ and $\tilde{c} = 10^{-10}$ we can choose $\tilde{b} = 10^6$. We can easily verify that these constants with parameters (13) satisfy condition (8), as well as (9) and (10). From the condition (11) we can calculate σ^2. For this model we choose small intensity of noise $\sigma^2 = 1.429 \cdot 10^{-16}$ which is reasonable for our model (3), because of the fact that σ^2 represents intensity of noise which affects parameter β, and from (13) we can see that it is very small. Now, let us highlight once more that Theorem 4.6 gives us stability conditions which are independent of the length of time delay. Thus, we choose $\tau = 40$ days. This is realistic choice because of the fact that for acute lymphobastic leukaemia, the cancer in which too many white cells form and it develops in the chest, procedure is to start with aggressive chemotherapy, and after that the blood stem cells from donor's bone marrow are injected. The recommended time frame for doing that is up to two months after achievement of remission. Since time delay affects resting cells, we suppose that initial values for tumor cells and hunting T-cells are constant, and initial data for resting T-cells is decreasing function of θ. Thus, we have initial data

$$M(\theta) = 2.7 \cdot 10^6, \ N(\theta) = 2.04 \cdot 10^5, \ Z(\theta) = 5.33 \cdot 10^6 e^{-\frac{\theta}{10640}}, \ -40 \le \theta \le 0. \tag{14}$$

For model parameters (13), $\sigma^2 = 1.429 \cdot 10^{-16}$, $\tau = 40$ days and initial data (14), we can observe stability of equilibrium state $E_{M,Z}$ of system (3) in Figures 1 (for $M(t)$) and 2 (for $N(t)$ and $Z(t)$).

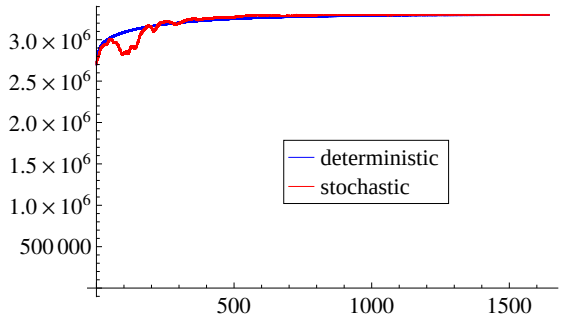

Figure 1: Deterministic and stochastic trajectories for tumor cells $M(t)$ of models (1) and (3) for $\beta = 6.2 \cdot 10^{-9}$.

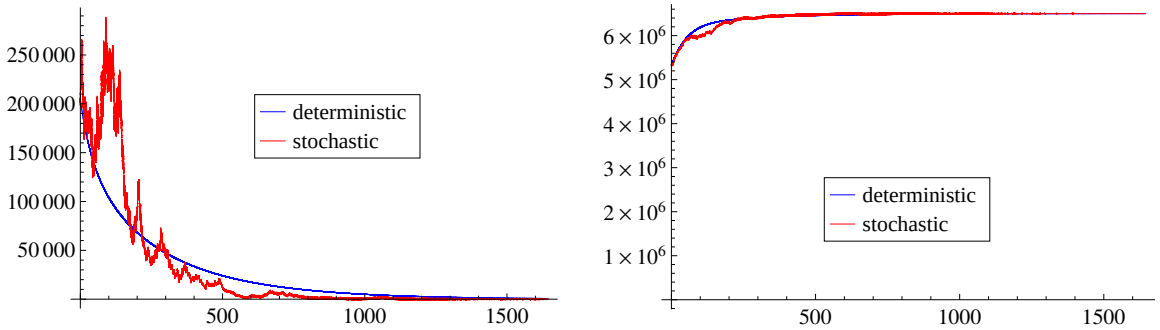

Figure 2: Deterministic and stochastic trajectories for T-cells: hunting cells $N(t)$ (left) and resting cells $Z(t)$ (right) of models (1) and (3) for $\beta = 6.2 \cdot 10^{-9}$.

As we have already mentioned, if we enhance the conversion rate, we can reduce number of malignant tumor cells. Thus, let us set $\beta = 8 \cdot 10^{-9}$, and the other model parameters be the same as in previous simulation. For such a choice of model parameters, condition (10) does not hold, and we can observe in Figures 3 and 4 that equilibrium state $E_{M,Z}$ of system (3) is not stable.

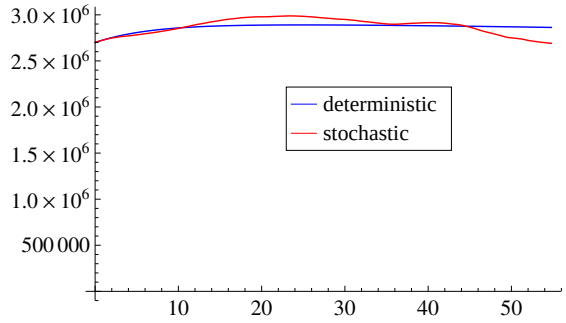

Figure 3: Deterministic and stochastic trajectories for tumor cells $M(t)$ of models (1) and (3) for $\beta = 8 \cdot 10^{-9}$.

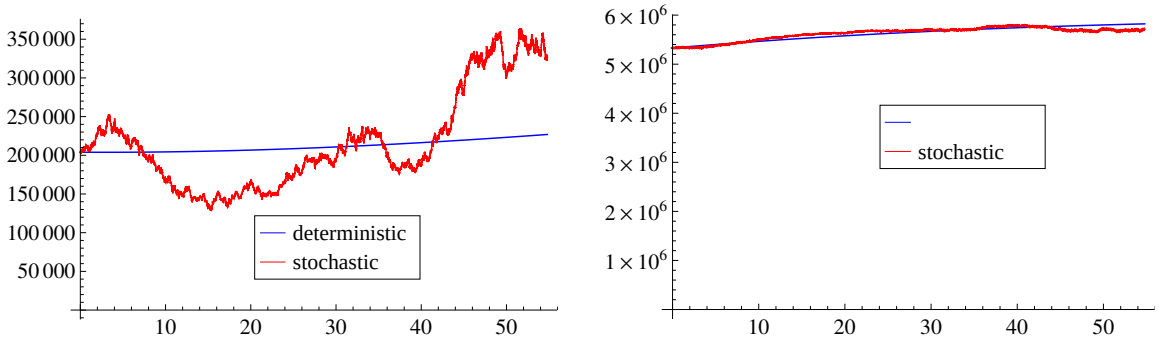

Figure 4: Deterministic and stochastic trajectories for T-cells: hunting cells $N(t)$ (left) and resting cells $Z(t)$ (right) of models (1) and (3) for $\beta = 8 \cdot 10^{-9}$.

Since deterministic model (1) has two more equilibrium states than stochastic model (3), which is already mentioned in Section 2, from Figures 3 and 4, we may conclude that stochastic model may approach the interior equilibrium state $E^*(M^*, N^*, Z^*)$ in some sense, where $M^* = \frac{k_1[r_1 k_2 \beta^2 - \alpha_1 r_2(\beta k_2 - d_1)]}{\beta^2 k_2 r_1 - \alpha_1 \alpha_2 k_1 r_2}$, $N^* = \frac{r_1}{\alpha_1}\left(1 - \frac{M^*}{k_1}\right)$, $Z^* = \frac{\alpha_2 M^* + d_1}{\beta}$.

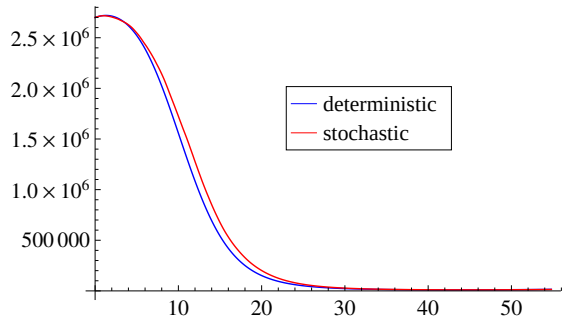

Figure 5: Deterministic and stochastic trajectories for tumor cells $M(t)$ of models (1) and (3) for $\beta = 6.2 \cdot 10^{-8}$.

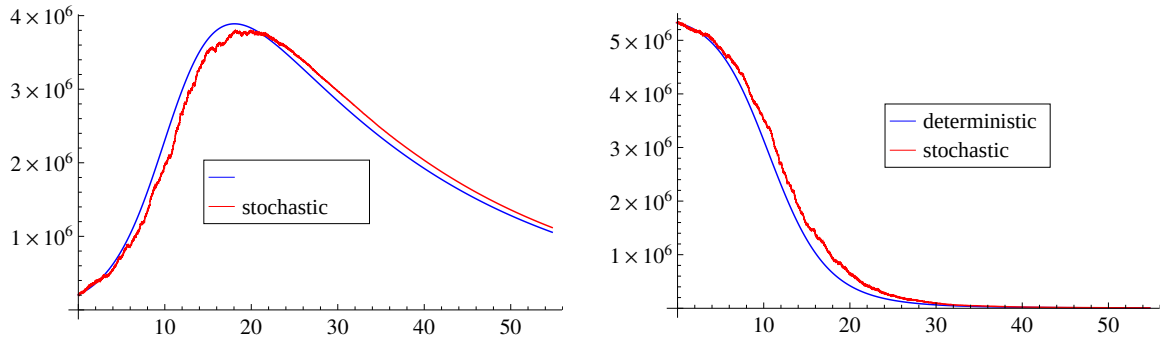

Figure 6: Deterministic and stochastic trajectories for T-cells: hunting cells $N(t)$ (left) and resting cells $Z(t)$ (right) of models (1) and (3) for $\beta = 6.2 \cdot 10^{-8}$.

If we keep with enhancing the conversion rate, and set $\beta = 6.2 \cdot 10^{-8}$, malignant tumor cells will become extinct, as well as resting T-cells, in approximately 35 days, and this is presented in Figures 5 and 6.

In the end let us underline that conditions obtained from the Theorem 4.6 and Corollary 4.7 give sufficient but not necessary conditions for equilibrium state $E_{M,Z}$ of system (3) to be stable in some sense.

6. Conclusion

This paper considers the effects and interactions of tumor cells and immune cells. More precisely, system of nonlinear delay differential equations considered in [2] is used as a basis in order to obtain the stochastic model for tumor-immune interaction with delay. For this model, we first prove existence and uniqueness of the global positive solution for any initial conditions. In the tumor-immune dynamics we consider, key role is played by by the activation rate β from the resting to hunting stage of immune cells. Namely, our results reveal that there is a certain threshold for the activation rate, and when the value of β is below it, and intensity of noise is small enough, the malignant cell density tends to the maximum level and we obtain stability of hunting cell-free equilibrium state. Thus, if we want to control tumor cell density, we may enhance the conversion (activation) rate.

In order to illustrate our theoretical results, we carry numerical simulation with reliable data which refer to the dynamics of growth of highly malignant *B Lymphoma/Leukemic cells (BCL_1)* in the spleen of chimeric mice.

At the end, let us point out that in this paper we only considered the white noises. However, there are some random perturbations which involve other types of environmental noise, especially, the telephone noise. Recently, stochastic models with the telephone noise have been studied by many authors (for example, see [10, 11]) and this can be interesting topics for some further investigations.

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