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MATHEMATICAL MODELING OF B-CELL CHRONIC LYMPHOCYTIC LEUKEMIA AND IMMUNE SYSTEMS WITH THERAPY

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Abstract. A quantitative understanding of the dynamics of the immune system to treatment is important in planning treatment strategies, such as timing, dosing, and predicting the response to a certain treatment. In this context, mathematical modeling of the relationship between disease-causing cells and the immune system, along with treatment, is one of the effective methods. In this study, we establish a nonlinear dynamical system that models the interaction between B-cell chronic lymphocytic leukemia and the immune system with a chemo-drug. We examined behaviour of the solution of the system around equilibrium points via phase-space analysis. Local stability analysis is performed on the nonlinear system, and stability conditions are also derived in the Lyapunov sense. Finally, numerical results are obtained with respect to the cases, tumor size, parameter change, and drug addition.

Keywords: mathematical modeling; chronic lymphocytic leukemia of B cells; immune system; chemodrug; stability of dynamical systems.

2020 AMS Subject Classification: 34D20, 34D23.

1. Introduction

In modern mathematical biology, the analysis of non-spatial dynamical models of cancer growth processes in the broad perspective of immune-tumor interactions is one of the most rapidly improving areas [1, 2, 3, 4, 5]. This investigation provides a powerful strategy for describing interactions between the cancer cells and the immune system via a system of ordinary

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differential equations. It enables us to make some operations on the biological processes more clear, such as for simulations and predictions, see works [6, 7, 8, 9, 10]. There is a sequence of mathematical models, including a piecewise constant argument for tumor-immune interactions under drug therapy, a delay-induced mathematical model of cancer, and a fractional-order mathematical model of tumor-immune system interactions [11, 12, 13, 14, 15]. In 2000, following the "Jeff's phenome-non" based on clinically observed asynchronous tumor-drug interactions, Pillis and Radunskaya developed a four-population model comprising tumor cells, host cells, and immune cells with drug effects and first investigated the system without any drug addition to understand the dynamics of the target basin of attraction via optimal control theory [16]. Later, they developed an extension of the earlier model by including a representative variable for the intensity of a cytotoxic factor in the tumor area and deduced that a more flexible set of objective functions should be explored to define more efficient treatment protocols [17]. Alade et al. studied two higher-dimensional models focusing on the within-host Chikungunya virus and using the method of Lyapunov function, derived stability conditions on a biological threshold that determines clearance of the virus in the body [18]. Similarly, Guido and Flippo investigated qualitative features of a mathematical model formulating prey-predator interactions between immune cells and muscle cells in Duchenne muscular dystrophy disease [19]. In 2020, Liu et al. presented an ODE system of tumor-immune interactions with chemotherapeutic drug effects and they determined the existence of chaos by computing the Lyapunov exponents and dimensions of the model [20]. In later studies, Jung and Wei performed numerical bifurcation analysis to investigate the outcomes of oncologic virus therapy [21]. Considering the mathematical model of Radunskaya and Pillis on chronic lymphocytic leukemia of B-cell disease which is characterized by a clonal semination and uncontrolled accumulation of neoplastic B-lymphocytes in the blood, Belgaid et al. reported the coexistence equilibrium of all populations in the model explicitly and completed a part of an earlier study [22, 23, 24, 25, 26]. When we regard the treatment protocols for such type of diseases in the literature, as one of the most effective scenarios, a mathematical model of the combination of chemo immune and vaccine therapies is presented to clear the entire tumor, and numerical analysis is performed to develop the protocols by qualitative characterization of system dynamics [27, 28, 29, 30, 31, 32, 33, 34].

To elaborate mathematically, the equilibrium points are located, the stability properties are determined, bifurcation analysis is performed, and the basins of attraction are identified [35, 36]. Shakmurov et al. perused the range of attraction sets of a theoretical dynamical model with Lyapunov stability analysis [37]. Next, Bellomo and Preziosi critically reviewed the literature on mathematical models and described the mathematical structure of macroscopic and kinetic modeling [38]. Pillis et al. focused on the creation of biological factors from experimental data when constructing the model, and they stated particular values for these parameters [39].

In the recent studies, Bodrar et al. generalized the formulation of brain tumor glioblastoma and obtained sufficient conditions for local and global equilibrium stability under constant and periodic treatments [40]. Wang and Zou introduced generic measures and quantitative indicators to scale the rate of competition between drug-sensitive and drug-resistant cells [41]. Yang et al. investigated the dynamics of the conjugate compartment and considered the effects of a conjugate compartment on the long-term steady-state, time to achieve equilibrium and possibility of tumor rupture [42]. Additionally, individuals have been subjected to uncertainty and sensitivity analyses to evaluate the effects of optimal control strategies in some combination therapy models [43, 44, 45, 46, 47, 48].

In our current work, we focus on a mathematical model of B-cell chronic lymphocytic leukemia and immunotherapy dynamics. Following the ideas of de Pillis and Radunskaya, we present a model with a simplistic ODE-based strategy that was inspired by concepts from the literature.

We consider the following mathematical four-state nonlinear model

$$\begin{aligned} \acute{B} &= b_1 + (r-\beta_1)B - d_1BN - d_2BT - k_1(1-e^{-u}), \\ \acute{N} &= b_2 - \beta_2 N - d_3 NB - k_2(1-e^{-u}), \\ \acute{T} &= b_3 - \beta_3 T - d_4 TB - k_3(1-e^{-u}), \\ \acute{u} &= v(t) - du, \end{aligned} \tag{1.1}$$

subject to the initial values

$$B(t_0) = B_0, N(t_0) = N_0, T(t_0) = T_0, \tag{1.2}$$

$$u(t_0) = u_0, t \in [0, t_0],$$

where $B = B(t)$, $N = N(t)$, $T = T(t)$ and $u = u(t)$ are denoted. The concentration of B cell chronic lymphocytic leukemia is known to have major clinical heterogeneity. We indicate natural killer cells with NKs and cytotoxic T cells (such as CD8+T cells) with T cells in the model. Parameter u represents the concentration of chemotherapy. $v(t)$ describes the rate of drug delivery, where $b_i (i = 1, 2, 3)$ and $\beta_i (i = 1, 2, 3)$ are the birth and death rates, respectively. $d_i (i = 1, 2, 3, 4)$ are the loss rates resulting from the struggle of cells with each other. The rate of damage is k_i for each cell population $i = 1, 2, 3$.

2. BOUNDEDNESS AND DISSIPATIVITY

We put

$$B(t) = x_1(t), N(t) = x_2(t), T(t) = x_3(t), u(t) = x_4(t).$$

Then the problem $(1.1) - (1.2)$ is reduced to the following form:

$$\dot{x}_1(t) = f_1(x), \dot{x}_2(t) = f_2(x), \dot{x}_3(t) = f_3(x), \dot{x}_4(t) = f_4(x), \tag{2.1}$$

where

$$x = x(t) = (x_1, x_2, x_3, x_4), x_k = x_k(t), k = 1, 2, 3, 4.$$

and let $b_1 = 3c_1$, $b_2 = 3c_2$, $b_3 = 3c_3$ to be convenient, then we have

$$f_1(t) = 3c_1 + (r - \beta_1)x_1 - d_1x_1x_2 - d_2x_1x_3 - k_1(1 - e^{-x_4}),$$

$$f_2(t) = 3c_2 - \beta_2x_2 - d_3x_2x_1 - k_2(1 - e^{-x_4}), \tag{2.2}$$

$$f_3(t) = 3c_3 - \beta_3x_3 - d_4x_3x_1 - k_3(1 - e^{-x_4}),$$

$$f_4(t) = v(t) - dx_4(t)$$

Let

$$\mathbb{R}^4_+ = \left\{x = (x_1, x_2, x_3, x_4) \in \mathbb{R}^4, x_k > 0\right\}$$

and

$$\Omega = \{x \in \mathbb{R}^4 : (d_4 - d_3)x_1 + d_2x_2 + d_1x_3 \geq r - (\beta_1 + \beta_2 + \beta_3) - d\}$$

Then we have the following theorem.

Condition 2.1. The following set of inequalities is assumed to be satisfied.

$$\beta_1, \beta_2, \beta_3, d_1, d_2, d_3, d_4, d < 0 \textit{ and } r > 0$$

Theorem 2.1. Let the above inequalities hold. The system (2.2) has negative divergence and dissipative on the domain $\Omega \subset \mathbb{R}^4_+$.

Proof. Indeed, from (2.2) we have

$$\frac{\partial f_1}{\partial x_1} + \frac{\partial f_2}{\partial x_2} + \frac{\partial f_3}{\partial x_3} + \frac{\partial f_4}{\partial x_4} = r - (\sum_{i=1}^{3} \beta_i) - d - d_1 x_3 - d_2 x_2 - d_3 x_1 - d_4 x_1$$

$$= r - (\sum_{i=1}^{3} \beta_i) - d - (d_3 - d_4) x_1 - d_2 x_2 - d_1 x_3 < 0$$

This proves the theorem.

3. The local stability of equilibrium points

In this section, we obtain the stability conditions of the equilibrium points of the system (2.1). Let

$$B_r(\bar{x}) = \left\{ x \in \mathbb{R}^4, \ \|x - \bar{x}\|_{\mathbb{R}^3} < r \right\}.$$

Condition 3.1. Let the following assumption hold

$$\Delta_1 = q^2 + \frac{4p^3}{27} \geq 0 \tag{3.1}$$

$$\Delta_2 = (b + a x_1^*)^2 - 4a(c + (b + a x_1^*) x_1^*) \geq 0 \tag{3.2}$$

where

$$q = \frac{3ac - b^2}{3a^2},$$

$$p = \frac{2b^3 - 9abc + 27a^2 d}{27a^3}$$

$$x_1^* = \sqrt[3]{\frac{-q - \sqrt{\Delta_1}}{2}} + \sqrt[3]{\frac{-q + \sqrt{\Delta_1}}{2}} - \frac{b}{3a}$$

$$a = [(r - \beta_1) d_3 d_4],$$

$$b = [(r-\beta_1)(\beta_2 d_4 + d_3\beta_3) + v_1(d_1 d_4 + d_3 d_4) + v_3 d_3 d_2],$$

$$c = [(r-\beta_1)\beta_2\beta_3 + v_1(d_1\beta_3 + \beta_2 d_4 + d_3\beta_3) + v_3 d_2 \beta 2],$$

$$d = v_1\beta_2\beta_3,\ b_1 = 3c_1,\ b_2 = 3c_2,\ b_3 = 3c_3$$

$$v_1 = 3c_1 - k_1(1 - e^{-\frac{v}{d}})$$

$$v_2 = 3c_2 - k_2(1 - e^{-\frac{v}{d}})$$

$$v_3 = 3c_3 - k_3(1 - e^{-\frac{v}{d}})$$

$$x_1^2 = \frac{-b - ax_1^* - \sqrt{\Delta_2}}{2a}$$
$$x_1^3 = \frac{-b - ax_1^* + \sqrt{\Delta_2}}{2a}$$

Theorem 3.1. Assume that the conditions (3.1) and (3.2) are satisfied.Then, there are three real equilibrium points of the system (2.1) in Ω.

$$p_1 = (x_1^*, \frac{v_1}{\beta_2 + x_1^* d_3}, \frac{v_2}{\beta_3 + x_1^* d_4}, \frac{v}{d})$$
$$p_2 = (x_1^2, \frac{v_1}{\beta_2 + x_1^2 d_3}, \frac{v_2}{\beta_3 + x_1^2 d_4}, \frac{v}{d})$$
$$p_3 = (x_1^3, \frac{v_1}{\beta_2 + x_1^3 d_3}, \frac{v_2}{\beta_3 + x_1^3 d_4}, \frac{v}{d})$$

Remark 3.1. If only the condition (3.1) is verified, then the system (2.1) admits a single real equilibrium point P_1.

Proof: According to the definition of equilibrium points, we have

$$x_4 = \frac{v}{d}.$$

Now, substituting in the other three equations, we find

$$3c_1+(r-\beta_1)x_1-d_1x_1x_2-d_2x_1x_3-k_1(1-e^{-\frac{v}{d}})=0$$
$$3c_2+\beta_2x_2-d_3x_2x_1-k_2(1-e^{-\frac{v}{d}})=0$$
$$3c_3+\beta_3x_3-d_4x_3x_1-k_3(1-e^{-\frac{v}{d}})=0$$

From the last two equations, we obtain

$$x_2=\frac{v_2}{\beta_2+d_3x_1}$$
$$x_3=\frac{v_3}{\beta_3+d_4x_1}$$

Substituting into the first equation, we have

$$[(r-\beta_1)d_3d_4]x_1^3+[(r-\beta_1)(\beta_2d_4+d_3\beta_3)+v_1(d_1d_4+d_3d_4)+v_3d_3d_2]x_1^2+$$
$$[(r-\beta_1)\beta_2\beta_3+v_1(d_1\beta_3+\beta_2d_4+d_3\beta_3)+v_3d_2\beta 2]x_1+v_1\beta_2\beta_3=0.$$

This last equation can be rewritten as:

$$ax^3+bx^2+cx+d=0.$$

Now, we use the Tschirnhaus method and the Cardan method to find the real roots of this third-degree equation. To do this, when

$$\Delta_1=q^2+\frac{4p^3}{27}\geq 0,$$

where

$$q=\frac{3ac-b^2}{3a^2},p=\frac{2b^3-9abc+27a^2d}{27a^3}.$$

There is a real root x_1^* such that

$$x_1^*=\sqrt[3]{\frac{-q-\sqrt{\Delta_1}}{2}}+\sqrt[3]{\frac{-q+\sqrt{\Delta_1}}{2}}-\frac{b}{3a}.$$

Hence, a single real equilibrium point exists. Thus, if $\Delta_2\geq 0$, then there are two real roots,

$$x_1^2=\frac{-b-ax_1^*-\sqrt{\Delta_2}}{2a}$$
$$x_1^3=\frac{-b-ax_1^*+\sqrt{\Delta_2}}{2a}$$

This completes the demonstration.

Recall that the equilibrium points of (2.1) are the roots of the system (2.2). Now, consider the linearized matrix of (2.1), i.e. the Jacobian matrix according to system (2.1)

$$\frac{Df}{Dx} = \begin{bmatrix} \frac{\partial f_1}{\partial x_1} & \frac{\partial f_1}{\partial x_2} & \frac{\partial f_1}{\partial x_3} & \frac{\partial f_1}{\partial x_4} \\ \frac{\partial f_2}{\partial x_1} & \frac{\partial f_2}{\partial x_2} & \frac{\partial f_2}{\partial x_3} & \frac{\partial f_2}{\partial x_4} \\ \frac{\partial f_3}{\partial x_1} & \frac{\partial f_3}{\partial x_2} & \frac{\partial f_3}{\partial x_3} & \frac{\partial f_3}{\partial x_4} \\ \frac{\partial f_4}{\partial x_1} & \frac{\partial f_4}{\partial x_2} & \frac{\partial f_4}{\partial x_2} & \frac{\partial f_4}{\partial x_3} \end{bmatrix} = $$

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

where

$$a_{11}(t) = r - \beta_1 - d_1x_2 - d_2x_3, a_{12}(t) = -d_1x_2, \; a_{13}(t) = -d_2x_3, \; a_{14}(t) = -k_1e^{-x_4}$$

$$a_{21}(t) = -d_3x_2, \; a_{22}(t) = -\beta_2 - d_3x_1, \; a_{23}(t) = 0, \; a_{24}(t) = -k_2e^{-x_4} \tag{3.3}$$

$$a_{31}(t) = -d_4x_3, \; a_{32}(t) = 0, \; a_{33}(t) = -\beta_3 - d_3x_1, \; a_{34}(t) = -k_3e^{-x_4}$$

$$a_{41}(t) = a_{42}(t) = a_{43}(t) = 0, \; a_{44}(t) = -d.$$

Then, the matrix of partial derivatives (2.1) at the point $P_0 = (0,0,0,0)$ is

$$A_0 = \frac{Df}{Dt}(0) = \begin{bmatrix} r-\beta_1 & 0 & 0 & -k_1 \\ 0 & -\beta_2 & 0 & -k_2 \\ 0 & 0 & -\beta_3 & -k_3 \\ 0 & 0 & 0 & -d \end{bmatrix} \tag{3.4}$$

Note that the Jacobian matrices of (2.1) with respect to other equilibrium points P_i are assumed to satisfy the next condition.

Condition 3.2. Assume that the following restrictions are satisfied.

Let $A_i = \frac{Df}{Dt}(P_i) = (a_{kj})$ and $a_{kj} = a_{jk}$. Then, we have the following results.

Theorem 3.1. The point P_0 is a saddle point for the linearized system of (2.1).

Proof. In fact, we observe that $\lambda_1 = r - \beta_1$, $\lambda_2 = -\beta_2$, $\lambda_3 = -\beta_3$ and $\lambda_4 = -d$ are the eigenvalues of the matrix A_0. Since λ_1 is positive and λ_2,λ_3,λ_4 are negative, P_0 is a saddle point of the linearized system for (2.1).

Theorem 3.2. Let the condition (3.1) hold and $d_1 - d_2 < 0$. Then the points P_i are locally stable for the linearized system of (2.1).

Proof. The eigenvalues of A_i can be derived as roots of the following characteristic equations

$$det(A_i - \lambda I) = det \begin{bmatrix} a_{11}-\lambda & a_{12} & a_{13} & a_{14} \\ a_{21} & a_{22}-\lambda & 0 & a_{24} \\ a_{31} & 0 & a_{33}-\lambda & a_{34} \\ 0 & 0 & 0 & a_{44}-\lambda \end{bmatrix} =$$

$$(a_{44}-\lambda)\, det \begin{bmatrix} a_{11}-\lambda & a_{12} & a_{13} \\ a_{21} & a_{22}-\lambda & 0 \\ a_{31} & 0 & a_{33}-\lambda \end{bmatrix} =$$

$$(a_{44}-\lambda)\left[\prod_{k=1}^{3}(a_{kk}-\lambda) + a_{12}a_{21}(a_{33}-\lambda) - a_{13}a_{31}(a_{22}-\lambda)\right] = 0$$

Let $(a_{33}-\lambda)(a_{22}-\lambda)(a_{11}-\lambda) = 0$, i.e, $\lambda_1 = a_{33}$, $\lambda_2 = a_{22}$ and $\lambda_3 = a_{11}$ are the eigenvalues of A. Another eigenvalue can be derived by solving the equation

$$a_{12}a_{21}(a_{33}-\lambda) - a_{13}a_{31}(a_{22}-\lambda) = 0$$

This implies that $a_{33}a_{12}a_{21} - \lambda a_{12}a_{21} - a_{13}a_{31}a_{22} + \lambda a_{13}a_{31} = 0$. Here, we obtain the fourth eigenvalue of the matrix A_i as

$$\lambda_4 = \frac{a_{33}a_{12}a_{21} - a_{13}a_{31}a_{22}}{a_{21}a_{12} - a_{13}a_{31}}$$

For the system (1.1) to be locally stable, we need to show that all the eigenvalues of matrix A_i are negative.

Recall that $a_{11} = r - \beta_1 - d_1x_2 - d_2x_3$, $a_{22} = -\beta_2 - d_3x_1$ and $a_{33} = -\beta_3 - d_3x_1$. Since $r - \beta_1 < d_1x_2 - d_2x_3$, $-(\beta_2 + d_3x_1) < 0$ and $-(\beta_3 + d_3x_1) < 0$ and if

$$\frac{a_{33}a_{12}a_{21} - a_{13}a_{31}a_{22}}{a_{21}a_{12} - a_{13}a_{31}} < 0$$

for all equilibrium points then the points P_i are locally stable.

Owing to symmetry, λ_4 is equal to $\dfrac{a_{33}(a_{12})^2 - a_{22}(a_{13})^2}{(a_{12})^2 - (a_{13})^2}$ and this quantity is negative if $(a_{12})^2 - (a_{13})^2$ is negative. This implies that $d_1 - d_2$ is negative, and as a result, this proves the theorem.

4. Lyapunov Stability of Equilibrium Points

In this section, we obtain the following results.

Theorem 4.1. The system (2.1) is unstable at the equilibrium point P_0 in the Lyapunov sense.

Proof. Since one of the eigenvalues of the Jacobian matrix A_0 is positive, then the system (2.1) is not stable at the point P_0 .

Now, we consider other equilibrium points P_i and prove the next result.

Theorem 4.2. Assume that the condition (3.1) is satisfied. The system (2.1) is then asymptotically stable at the points P_i in the Lyapunov sense.

Proof. Let the following Jacobian matrix A_i at the point P_i be given as defined in condition (3.2), i.e.

From equation (1.1), we find that $u = g(t)$. The solution of the remaining system of 3 variables is calculated as follows

$$A_i = \begin{bmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & 0 \\ a_{31} & 0 & a_{33} \end{bmatrix},$$

where $a_{kj} = a_{kj}(P_i)$ are defined by condition (3.2).

Now, consider the Lyapunov equation

$$B_i A_i + A_i^T B_i = -I, \tag{4.1}$$

where

$$B_i = \begin{bmatrix} b_{11} & b_{12} & b_{13} \\ b_{21} & b_{22} & b_{23} \\ b_{31} & b_{32} & b_{33} \end{bmatrix}, b_{kj} = b_{kj}(i), b_{kj} = b_{jk}.$$

It is clear that

$$B_iA_i = \begin{bmatrix} b_{11} & b_{12} & b_{13} \\ b_{21} & b_{22} & b_{23} \\ b_{31} & b_{32} & b_{33} \end{bmatrix} \begin{bmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & 0 \\ a_{31} & 0 & a_{33} \end{bmatrix} = \left[c_{kj}\right],$$

$$A_i^T B_i = \begin{bmatrix} a_{11} & a_{21} & a_{31} \\ a_{12} & a_{22} & 0 \\ a_{13} & 0 & a_{33} \end{bmatrix} \begin{bmatrix} b_{11} & b_{12} & b_{13} \\ b_{21} & b_{22} & b_{23} \\ b_{31} & b_{32} & b_{33} \end{bmatrix} = \left[l_{kj}\right],$$

from equation (4.1), we have

$$2.a_{11}.b_{11}+a_{21}.b_{12}+a_{21}.b_{21}+a_{31}.b_{13}+a_{31}.b_{31} = -1,$$

$$a_{11}.b_{12}+a_{12}.b_{11}+a_{22}.b_{12}+a_{21}.b_{22}+a_{31}.b_{32} = 0,$$

$$a_{11}.b_{13}+a_{13}.b_{11}+a_{21}.b_{23}+a_{33}.b_{13}+a_{31}.b_{33} = 0,$$

$$a_{12}.b_{11}+a_{11}.b_{21}+a_{21}.b_{22}+a_{22}.b_{21}+a_{31}.b_{23} = 0,$$

$$a_{12}.b_{12}+a_{12}.b_{21}+2.a_{22}.b_{22} = -1,$$

$$a_{12}.b_{13}+a_{13}.b_{21}+a_{22}.b_{23}+a_{33}.b_{23} = 0,$$

$$a_{12}.b_{11}+a_{11}.b_{31}+a_{21}.b_{32}+a_{31}.b_{33}+a_{33}.b_{31} = 0,$$

$$a_{13}.b_{12}+a_{12}.b_{31}+a_{22}.b_{32}+a_{33}.b_{32} = 0,$$

$$a_{13}.b_{13}+a_{13}.b_{31}+2.a_{33}.b_{33} = -1.$$

from the above equations b_{11}, b_{12} and b_{13} are respectively found as below. Similarly, one can find the unknowns b_{22}, b_{23} and b_{33}.

$b_{11} = (a_{11}^2.a_{22}^2.a_{33} + a_{11}^2.a_{22}.a_{33}^2 - 2.a_{11}.a_{12}.a_{21}.a_{22}.a_{33} - a_{11}.a_{12}.a_{21}.a_{33}^2 - a_{11}.a_{13}.a_{22}^2.a_{31} - 2.a_{11}.a_{13}.a_{22}.a_{31}.a_{33} + a_{11}.a_{21}^2.a_{22}.a_{33} + a_{11}.a_{21}^2.a_{33}^2 + a_{11}.a_{22}^3.a_{33} + a_{11}.a_{22}^2.a_{31}^2 + 2.a_{11}.a_{22}^2.a_{33}^2 + a_{11}.a_{22}.a_{31}^2.a_{33} + a_{11}.a_{22}.a_{33}^3 + a_{12}^2.a_{21}^2.a_{33} + a_{12}.a_{13}.a_{21}.a_{22}.a_{31} + a_{12}.a_{13}.a_{21}.a_{31}.a_{33} - a_{12}.a_{21}^3.a_{33} - a_{12}.a_{21}.a_{22}^2.a_{33} - a_{12}.a_{21}.a_{22}.a_{33}^2 - a_{12}.a_{21}.a_{31}^2.a_{33} - a_{12}.a_{21}.a_{33}^3 + a_{13}^2.a_{22}.a_{31}^2 - a_{13}.a_{21}^2.a_{22}.a_{31} - a_{13}.a_{22}^3.a_{31} - a_{13}.a_{22}.a_{31}^3 - a_{13}.a_{22}.a_{31}.a_{33}^2 + a_{21}^2.a_{33}^3 + a_{22}^3.a_{31}^2 + a_{22}^3.a_{33}^2 +$

$a_{22}^2.a_{31}^2.a_{33}+a_{22}^2.a_{33}^3)/(2.(a_{12}.a_{21}.a_{33}-a_{11}.a_{22}.a_{33}+a_{13}.a_{22}.a_{31}).$
$(a_{11}.a_{22}^2 + a_{11}^2.a_{22} + a_{11}.a_{33}^2 + a_{11}^2.a_{33} + a_{22}.a_{33}^2 + a_{22}^2.a_{33} - a_{11}.a_{12}.a_{21}- a_{11}.a_{13}.a_{31} -$
$a_{12}.a_{21}.a_{22}+2.a_{11}.a_{22}.a_{33}-a_{13}.a_{13}.a_{33}))$

$b_{12}=-(a_{11}^2.a_{21}.a_{22}.a_{33}+a_{11}^2.a_{21}.a_{33}^2-a_{11}a_{12}.a_{21}^2.a_{33}+a_{11}.a_{12}.a_{22}^2.a_{33}+a_{11}.a_{12}.a_{22}.a_{31}^2+$
$a_{11}.a_{12}.a_{22}.a_{33}^2-a_{13}.a_{11}.a_{21}.a_{22}.a_{31}+a_{11}.a_{21}.a_{22}.a_{33}^2-a_{13}.a_{11}.a_{21}.a_{31}.a_{33}+a_{11}.a_{21}.a_{33}^3-$
$a_{12}^2.a_{21}.a_{22}.a_{33}+a_{12}.a_{22}^2.a_{31}^2-a_{13}.a_{12}.a_{22}^2.a_{31}+a_{12}.a_{22}^2.a_{33}^2+a_{12}.a_{22}.a_{31}^2.a_{33}+a_{12}.a_{22}.a_{33}^3-$
$a_{13}.a_{21}.a_{22}.a_{31}.a_{33}-a_{13}.a_{21}.a_{31}.a_{33}^2)/(2.(a_{12}.a_{21}.a_{33}-a_{11}.a_{22}.a_{33}+a_{13}.a_{12}.a_{31}).$
$(a_{11}.a_{22}^2 + a_{11}^2.a_{22} + a_{11}.a_{33}^2 + a_{11}^2.a_{33} + a_{22}.a_{33}^2 + a_{22}^2.a_{33} - a_{11}.a_{12}.a_{21} - a_{11}.a_{13}.a_{31} -$
$a_{12}.a_{21}.a_{22}+2.a_{11}.a_{22}.a_{33}-a_{13}.a_{31}.a_{33}))$

$b_{13}=-(a_{11}^2.a_{22}^2.a_{31}+a_{11}^2.a_{22}.a_{31}.a_{33}+a_{11}.a_{13}.a_{21}^2.a_{33}+a_{11}.a_{13}.a_{22}^2.a_{33}-a_{11}.a_{13}.a_{22}.a_{31}^2+$
$a_{11}.a_{13}.a_{22}.a_{33}^2-a_{12}.a_{11}.a_{21}.a_{22}.a_{31}-a_{12}.a_{11}.a_{21}.a_{31}.a_{33}+a_{11}.a_{22}^3.a_{31}+a_{11}.a_{22}^2.a_{31}.a_{33}-$
$a_{13}^2.a_{22}.a_{31}.a_{33}+a_{13}.a_{21}^2.a_{22}.a_{33}+a_{13}.a_{21}^2.a_{33}^2-a_{12}.a_{13}.a_{21}.a_{33}^2+a_{13}.a_{22}^3.a_{33}+a_{13}.a_{22}^2.a_{33}^2-$
$a_{12}.a_{21}.a_{22}^2.a_{31}-a_{12}.a_{21}.a_{22}.a_{31}.a_{33})/(2.(a_{12}.a_{21}.a_{33}-a_{11}.a_{22}.a_{33}+a_{13}.a_{22}.a_{31}).(a_{11}.a_{22}^2+$
$a_{11}^2.a_{22}+a_{11}.a_{33}^2+a_{11}^2.a_{33}+ a_{22}.a_{33}^2+a_{22}^2.a_{33}-a_{11}.a_{12}.a_{21}-a_{11}.a_{13}.a_{31}-a_{12}.a_{21}.a_{22}+$
$2.a_{11}.a_{22}.a_{33}-a_{13}.a_{31}.a_{33}))$

Note that $b_{kj}=b_{jk}$. Now, we clarify Lyapunov function and assume that

$$b_{kk}>0,\ k=1,2,3,4. \tag{4.2}$$

Consider the quadratic function

$$V_i(x)=X^TB_iX=b_{11}x_1^2+b_{22}x_2^2+2b_{12}x_1x_2+2b_{13}x_1x_3+$$

$$b_{33}x_3^2+2b_{23}x_2x_3+2b_{24}x_2x_4+b_{44}x_4^2+2b_{14}x_1x_4+2b_{34}x_3x_4=$$

$$\frac{1}{4}b_{11}\left(x_1+\frac{4b_{12}}{b_{11}}x_2\right)^2+\left(\frac{1}{3}b_{22}-\frac{4b_{12}^2}{b_{11}}\right)x_2^2+ \tag{4.3}$$

$$\frac{1}{4}b_{11}\left(x_1+\frac{b_{13}}{b_{11}}x_3\right)^2+\left(\frac{1}{3}b_{33}-\frac{4b_{13}^2}{b_{11}}\right)x_3^2+$$
$$b_{11}\left(x_1+\frac{b_{14}}{b_{11}}x_4\right)^2+\left(\frac{1}{3}b_{44}-\frac{4b_{14}^2}{b_{11}}\right)x_4^2+$$

$$\frac{1}{3}b_{22}\left(x_2+\frac{3b_{23}}{b_{22}}x_3\right)^2+\left(\frac{1}{3}b_{33}-\frac{9b_{23}^2}{b_{22}}\right)x_4^2+$$

$$\frac{1}{3}b_{22}\left(x_2+\frac{3b_{24}}{b_{22}}x_4\right)^2+\left(\frac{1}{3}b_{44}-\frac{9b_{24}^2}{b_{22}}\right)x_4^2.$$

$$\frac{1}{3}b_{33}\left(x_3+\frac{3b_{34}}{b_{33}}x_4\right)^2+\left(\frac{1}{3}b_{44}-\frac{9b_{34}^2}{b_{22}}\right)x_4^2+\frac{b_{11}}{2}x_1^2.$$

From (4.3) we deduce that $V_i(x)\geq 0$ when the following inequalities hold

$$\begin{aligned}&\frac{1}{3}b_{22}\geq\frac{4b_{12}^2}{b_{11}},\ \frac{1}{3}b_{33}\geq\frac{4b_{13}^2}{b_{11}},\ \frac{1}{3}b_{44}\geq\frac{4b_{14}^2}{b_{11}},\ \frac{1}{3}b_{33}\geq\frac{9b_{23}^2}{b_{22}}\\&\frac{1}{3}b_{44}\geq\frac{9b_{24}^2}{b_{22}},\ \frac{1}{3}b_{33}\geq\frac{9b_{34}^2}{b_{22}}\ \textit{and}\ \frac{b_{11}}{2}\geq 0\end{aligned}\tag{4.4}$$

Thus, $V_i(x)$ are positive definite Lyapunov functions. Now, we need to determine the domains Ω_i on which $\dot{V}_i(x)$ is negatively defined, see corollary 8.2 in [49]. Here, we assume that $x_k\geq 0$, $k=1,2,3,4$, and we will obtain conditions that construct the domain of the following inequality

$$\dot{V}_i(x)=\sum_{j=1}^{4}\frac{\partial V_i}{\partial x_j}f_j(x)=\tag{4.5}$$

$$2B_1(x)\left[b_1+(r-\beta_1)x_1-d_1x_1x_2-d_2x_1x_3-k_1(1-e^{-x_4})\right]+$$

$$2B_2(x)\left[b_2-\beta_2x_2-d_3x_2x_1-k_2(1-e^{-x_4})\right]+$$

$$2B_3(x)\left[b_3-\beta_3x_3-d_4x_3x_1-k_3(1-e^{-x_4})\right]+2B_3(x)(v(t)-dx_4(t))\leq 0,$$

where

$$B_j(x)=\sum_{k=1}^{4}b_{jk}x_k\ j=1,2,3,4.$$

Since by assumption $x_k\geq 0$ and $b_k>0$, equation (4.5) clearly holds, when

$$\left[b_1+(r-\beta_1)x_1-d_1x_1x_2-d_2x_1x_3-k_1(1-e^{-x_4})\right]\leq 0$$

$$\left[b_2-\beta_2x_2-d_3x_2x_1-k_2(1-e^{-x_4})\right]\leq 0,$$

$$\left[b_3-\beta_3x_3-d_4x_3x_1-k_3(1-e^{-x_4})\right]\leq 0,$$

$$\left[v(t)-dx_4(t)\right]\leq 0$$

that is, we find the following domain such that $\dot{V}_i(x)\leq 0$

$$\Omega_1=\{x\in\mathbb{R}_+^4\colon (r-\beta_1)x_1-d_1x_1x_2-d_2x_1x_3-k_1(1-e^{-x_4})\leq b_1,$$

$$\beta_2 x_2 + d_3 x_2 x_1 + k_2(1 - e^{-x_4}) \leq -b_2,\ \beta_3 x_3 + d_4 x_3 x_1 + k_3(1 - e^{-x_4}) \leq -b_3,$$
$$x_4 \geq \frac{v(t)}{d}\}$$

As a result, the system (2.1) is asymptotically stable at P_i for all $i = 1,2,3$ on the domain Ω_1

5. NUMERICAL STUDY

This section is devoted to numerical results and simulations of the model. In this section, we obtained several graphs that concretely demonstrate the relationships between tumors and immune cells with the addition of drugs. Therefore, we created a nonlinear model file to solve a four-state system of ODEs (1.1) in the COMSOL Multiphysics 6.2a version, which is a commercial numerical solver based on the finite element method (see http://www.comsol.com/). In the Model Wizard, we selected the global ODE and DAE interface for a time-dependent study. We describe parameters with the values and define the model variables B, N, T, and u and related equations with initial values in accordance with $f(u, u_t, u_{tt}, t)$, which accepts nonlinear ODEs in implicit form. Next, in the time-dependent setting window, we arrange the output times to $[0,3]$, $[0,2]$, $[0,1]$ with a step size of 0.1. The parameter values of the system are given in Table 1. As the final step, the computation yields the following figures.

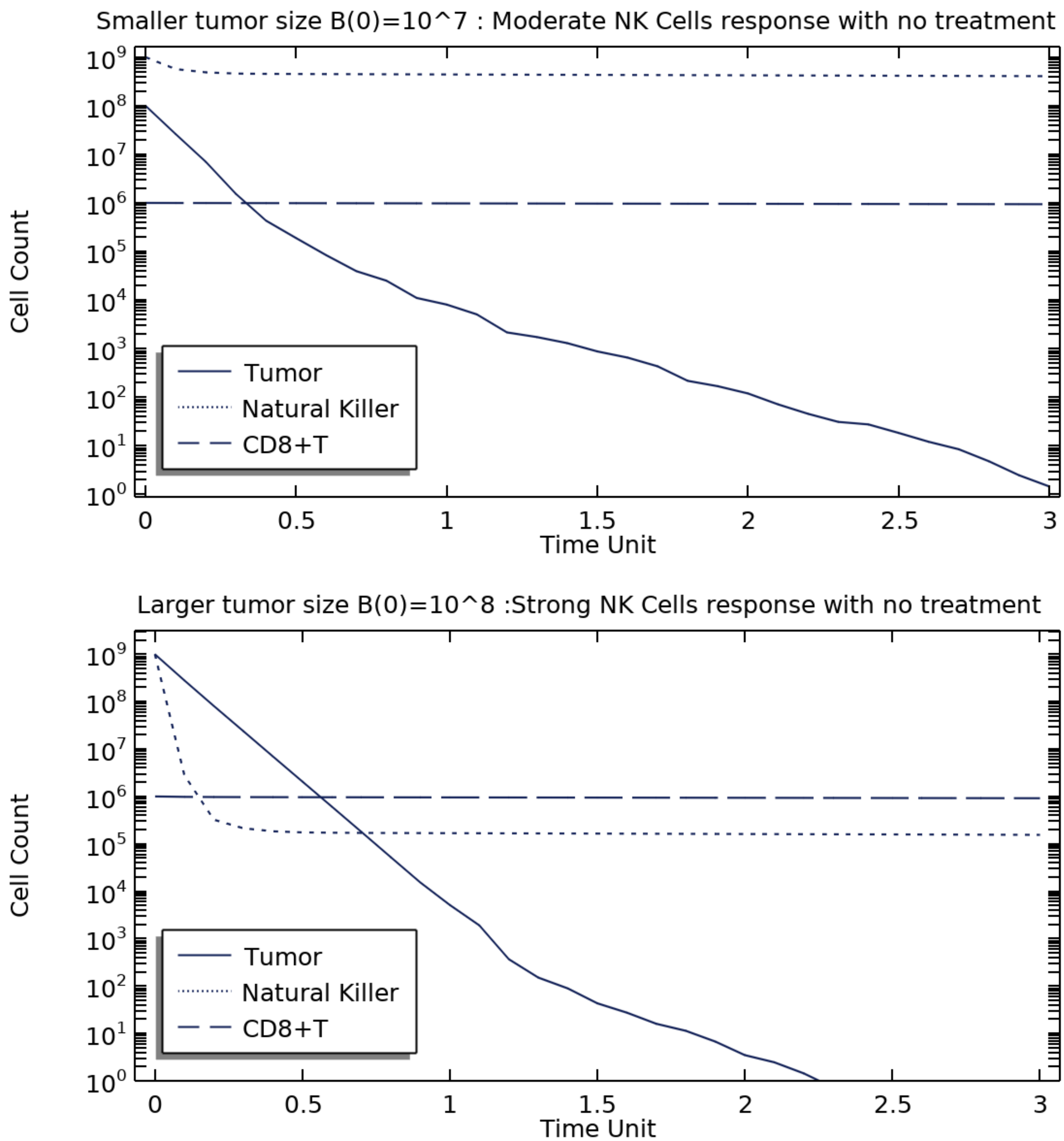

FIGURE 1. Comparison of two different tumor sizes

In Figure (1), we compare tumor cells $B(t)$ and NK immune cells $N(t)$ under no drug addition or no treatment. The first graphic demonstrates a moderate response of NK cells to the smaller initial tumor with $B(0) = 10^7$, but the second graphic shows a stronger response to a larger initial tumor with $B(0) = 10^8$. In both cases, the initial values are $N(0) = 10^8$ and $T(0) = 10^5$.

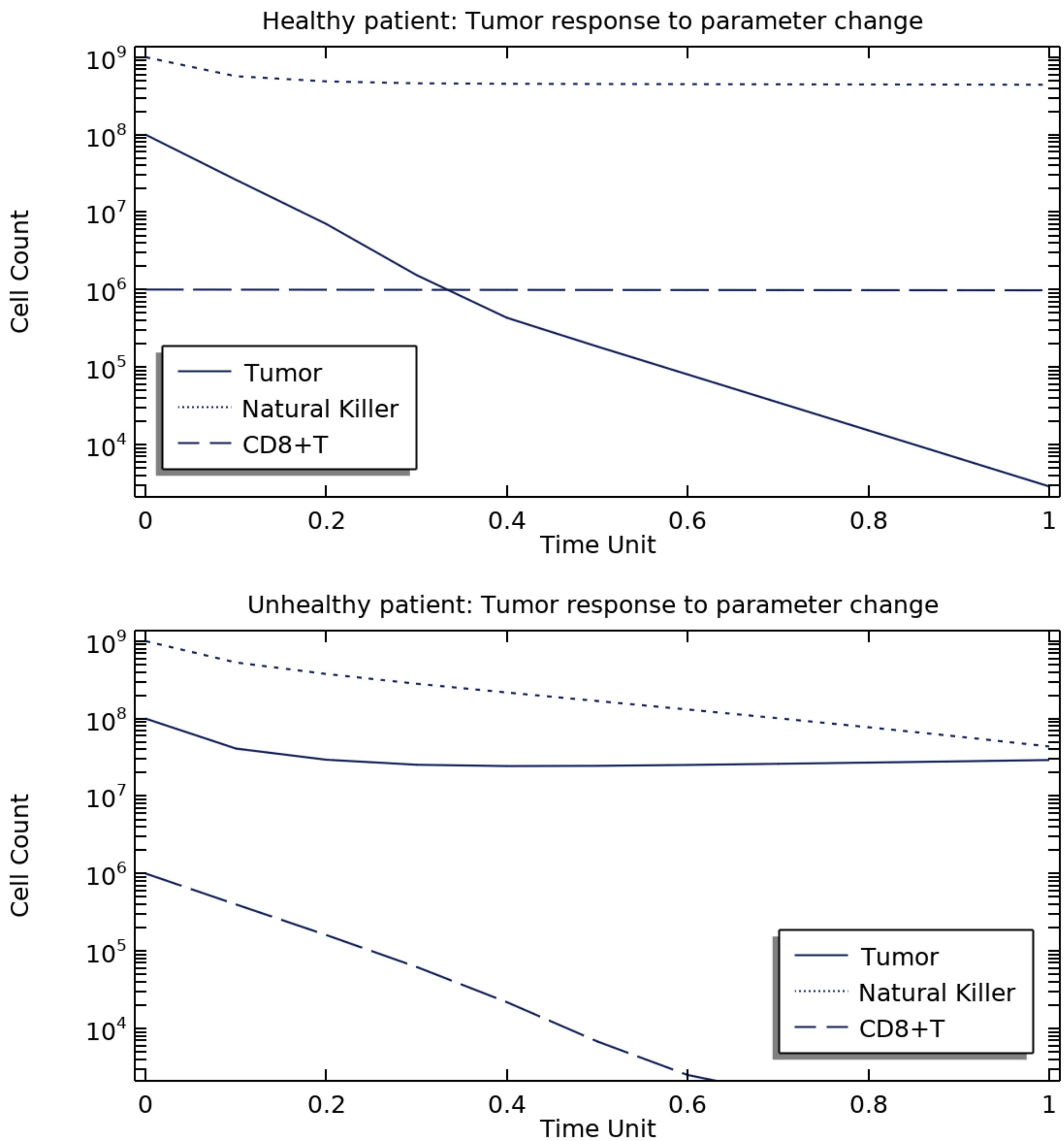

FIGURE 2. Comparison of two different immune systems

In figure (2), we match the tumor responses to the parameter β_3 change. In the first graph, the tumor is killed by a healthy immune system with $\beta_3 = 0.02$. In the second, we set $\beta_3 = 9.12$ and the unhealthy immune system does not survive. The initial values in both pictures are $B(0) = 10^7$, $N(0) = 10^8$ and $T(0) = 10^5$.

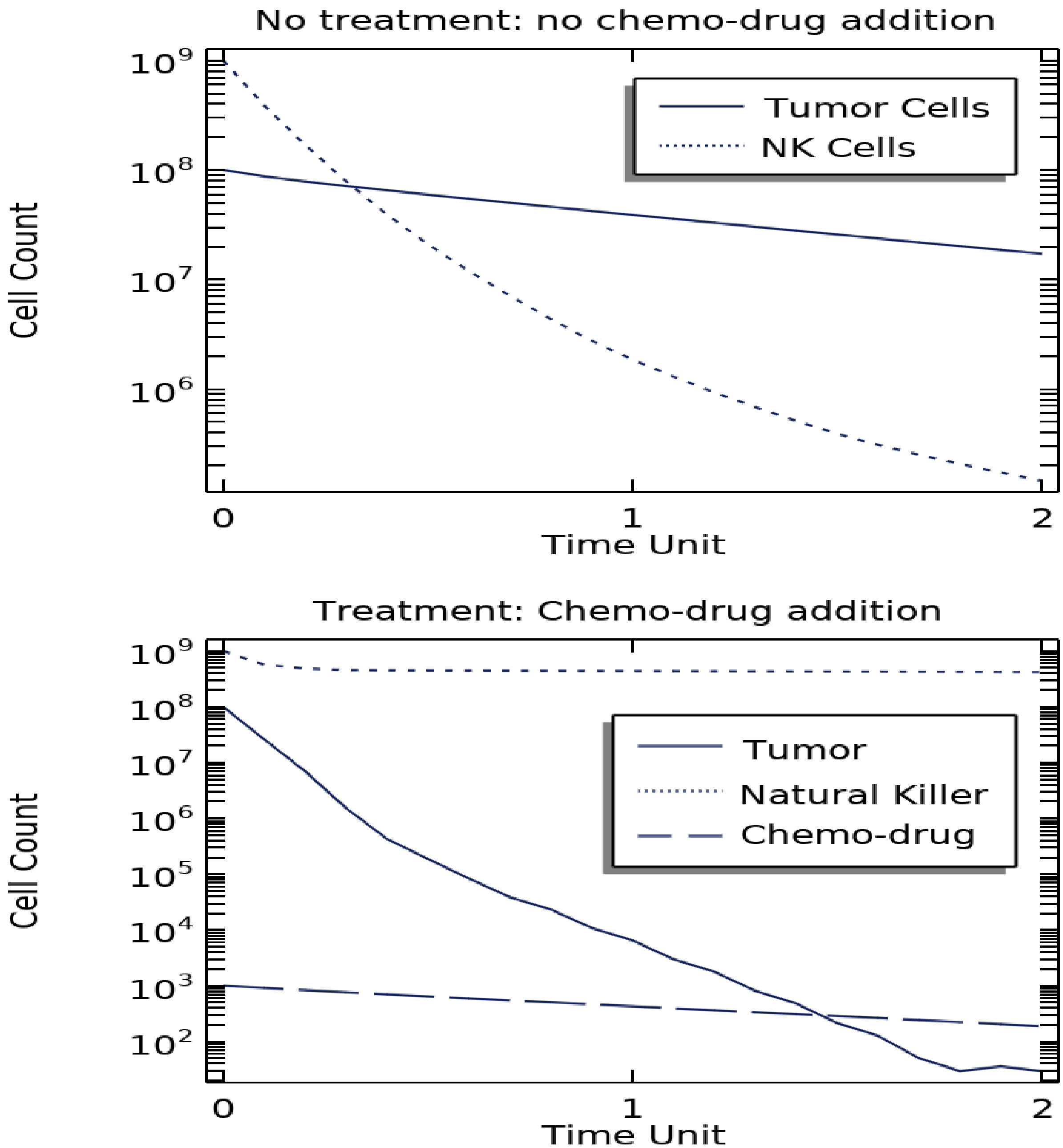

FIGURE 3. Comparison of tumor responses with drug addition and without drug addition

In figure (3), the first graphic illustrates tumor cells and NK Cells response without chemo-drug addition, i.e, initial drug concentration $u(0) = 0$ and chemo-dose $v(t) = 0$. In the second graph, we arrange $u(0) = 10^3$, $v(t) = 10$, and the tumor decays to 0 in time.

Parameter	**Value**
$r-\beta_1$	0.431
b_1	0.05
b_2	0.05
b_3	0.1
β_2	0.0412
β_3	0.02
d_1	7.13E-10
d_2	1.3218E-5
d_3	1E-7
d_4	3.42E-10
k_1	0.9
k_2	0.6
k_3	0.6
d	0.9
$v(t)$	10

TABLE 1. Values of model parameters from the source [29]

6. DISCUSSION AND CONCLUSION

In this work, we develop a new nonlinear mathematical ODE model that formulates the interaction between chronic lymphocytic leukemia disease involving B cells and the immune system under drug addition. We first prove that the system is dissipative and hence the model is biologically durable. To determine the stability properties and find equilibrium points, we linearize the nonlinear ODE system and obtain stability and instability conditions of the solution, which are also in the Lyapunov sense. In the numerical study section, we analyze six different situations and compare them pair by pair on the basis of tumor size, a parameter change, and drug addition. The response of NK cells to different tumor cell counts was investigated, and the results are shown was in Figure (1). In Figure (2), we play with a parameter to match the healthy and unhealthy patients. In Figure (3), a chemical drug is added to the system, and we analyze the tumor response to the drug under initial conditions.

In future studies, we plan to focus on the validity and practicality of the constructed model through empricial observations.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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