

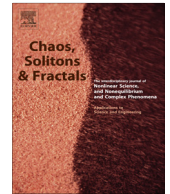


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## Stability and bifurcation analysis of a mathematical model for tumor–immune interaction with piecewise constant arguments of delay

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### ABSTRACT

In this paper, we propose and analyze a Lotka–Volterra competition like model which consists of system of differential equations with piecewise constant arguments of delay to study of interaction between tumor cells and Cytotoxic T lymphocytes (CTLs). In order to get local and global behaviors of the system, we use Schur–Cohn criterion and constructed a Lyapunov function. Some algebraic conditions which satisfy local and global stability of the system are obtained. In addition, we investigate the possible bifurcation types for the system and observe that the system may undergo Neimark–Sacker bifurcation. Moreover, it is predicted a threshold value above which there is uncontrollable tumor growth, and below periodic solutions that leading to tumor dormant state occur.

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### 1. Introduction

The theoretical studies of cancer growth under immunological activities have a long history. These studies are concerned with the behavior of cancer growth under the effect of immunity as well as the effect of therapy. An interesting therapeutic approach is immunotherapy which consists in strengthening inherent ability of the immune system to fight cancer [1]. The immune system consists of effector cells which perform the immune response against tumor, such as T lymphocyte, macrophages and natural killer cells. T lymphocyte can be categorized into two subclasses, namely, Cytotoxic T lymphocytes (CTLs) and T-Helper cells (resting cells) [2]. CTLs are important effector cells of the immune system which can remove

infected cells and tumor cells. The resting cells do not directly kill tumor cells, as CTLs do. Instead they help the activity of native CTLs by releasing cytokines.

Keeping in mind the above biological scenario, many authors have used Lotka–Volterra like models for describing the interactions between the immune system and growing tumors [1–11]. Through this mathematical modeling, Costa et al. [3] have proposed the predator–prey like model including new terms taking into account tumor aggressiveness, the diffusion of lymphocyte and the effect caused by cytokines on the tumor. Based on the Costa model, a family of models has been investigated by Onofrio [4]. On the other hand, Kuznetsov and Taylor [5] have proposed a mathematical model of the CTLs response to the growth of an immunogenic tumor. Their model exhibits a number of phenomena that are seen in vivo. Kirschner and Panetta [6] have generalized Kuznetsov model and they have studied the role of IL-2 in tumor dynamics. Their model expresses short tumor oscillations in tumor sizes as well as long-term tumor relapse. Sarkar and Banerjee [7]

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have constructed very interesting predator–prey like model which includes tumor cells, hunting predator cells and resting predator cells. Spontaneous regression and progression of a malignant tumor system have been explained in this model. Another interesting Lotka–Volterra model for describing the interactions between tumor and normal cells has been studied by Gatenby [8]. In study of Gatenby, tumor cells compete with normal cells for space and other resources in an arbitrarily small volume of tissue within an organ.

Now, it is interesting to note that some researchers have realized that some sets of experimental data exhibit the existence of a time-lag (or delay) in the tumor cell division phase ([12–17]). Baker et al. [12] have explained this situation well. They have showed that a mathematical model of cell growth that takes into account a time lag in the cell division phase is more suitable for experimental data than the growth model of classical exponential ordinary differential equations. Using the time delay factor, Sarkar and Banerjee [13] have extended their system in [7] and have analyzed the solutions of the system. In their model, growth of malignant tumor cell densities has been controlled by different threshold values of the parameters. Also, Villasana and Radunskaya [14] have studied Hopf bifurcations and periodic solutions in a competition model which incorporated a time-lag in the phases of the cell cycle which regulate proliferation of the tumor cells.

Proliferation and activation of tumor cells together with their competition with immune system are referred in microscopic (cellular) level while macroscopic level refers to cancer invasion and metastases [18]. For the microscopic level, many authors have used a discrete model or discrete value variable to describe the tumor immune interaction because microscopic biological state is discrete rather than continuous [18–22].

On the other hand, for a better understanding of the process occurring in the growth of tumors, mathematical models which can look at the interactions from the microscopic level and from the macroscopic level at the same time should be composed [19]. When the microscopic level and the macroscopic level are considered at the same time, there are two events to see in a population: a continuity and the resting time of the tumor. For both time situations; continuous and discrete, there are some population dynamics in ecosystem which combine the properties of both differential and difference equations. For such biological events, Gopalsamy and Liu [23], Liu and Gopalsamy [24], So and Yu [25], Muroya [26], Ozturk et al. [27], Bozkurt [28], Gurcan and Bozkurt [29] have constructed a model with piecewise constant arguments.

By using piecewise constant arguments to investigate population density of a single species, Gopalsamy and Liu [23] have considered the differential equation

$$\frac{dN(t)}{dt} = rN(t)\{1 - aN(t) - bN(\llbracket t \rrbracket)\}, \quad (1)$$

where  $N(t)$  represents the population density,  $r$ ,  $a$ ,  $b$  are positive numbers and  $\llbracket t \rrbracket$  is the integer part of  $t \in (0, \infty)$ . The right hand side includes both regular and piecewise constant arguments, the second one estimates of the population growth performed at equally spaced time intervals.

Following these studies ([23–26]), Ozturk et al. [27] have modeled a population density of a bacteria species in a microcosm as

$$\frac{dx(t)}{dt} = rx(t)\{1 - \alpha x(t) - \beta_0 x(\llbracket t \rrbracket) - \beta_1 x(\llbracket t - 1 \rrbracket)\}, \quad (2)$$

which includes both continuous and discrete time for a bacteria population. Bozkurt [28] has modeled an early brain tumor growth by using differential equations with piecewise constant arguments

$$\begin{aligned} \frac{dx(t)}{dt} = x(t)\{r(1 - \alpha x(t) - \beta_0 x(\llbracket t \rrbracket) - \beta_1 x(\llbracket t - 1 \rrbracket)) \\ + \gamma_1 x(\llbracket t \rrbracket) + \gamma_2 x(\llbracket t - 1 \rrbracket)\}. \end{aligned}$$

In the present study, we construct a model with piecewise constant arguments to describe tumor immune system competition.

## 2. Model formulation

To construct our model, we first consider the following model proposed by Gatenby [8].

$$\begin{cases} \frac{dN_1}{dt} = r_1 N_1 \left(1 - \frac{N_1}{k_1}\right) - \frac{r_1 \alpha_{12t}}{k_1} N_1 N_2 + \frac{r_1 \alpha_{12s}}{k_1} N_1 N_2, \\ \frac{dN_2}{dt} = r_2 N_2 \left(1 - \frac{N_2}{k_2}\right) - \frac{r_2 \alpha_{21}}{k_2} N_1 N_2, \end{cases}$$

where  $N_1$  is the tumor population,  $N_2$  is the population of normal cells from which the tumor arises.

The study of Gatenby relates to only continuous time situations. We have extended his model including discrete and continuous time situations with some extra terms and have obtained the following Lotka–Volterra competition like model with piecewise constant arguments of delay which provides a description of tumor cells in competition with the immune system:

$$\begin{cases} \frac{dx}{dt} = r_1 x(t) \left(1 - \frac{x(t)}{k_1}\right) - \alpha_1 x(t)y(\llbracket t \rrbracket) + \alpha_2 x(t)y(\llbracket t - 1 \rrbracket), \\ \frac{dy}{dt} = r_2 y(t) \left(1 - \frac{y(t)}{k_2}\right) + \alpha_1 y(t)x(\llbracket t \rrbracket) - \alpha_2 y(t)x(\llbracket t - 1 \rrbracket) - d_1 y(t), \end{cases} \quad (3)$$

where  $\llbracket t \rrbracket$  denotes the integer part of  $t \in [0, \infty)$  and all these parameters are positive. Here  $x(t)$  is the population density,  $r_1$  the growth rate and  $k_1$  the carrying capacity of tumor cells.  $y(t)$  is the population density,  $r_2$  the growth rate,  $k_2$  the carrying capacity and  $d_1$  death rate of CTLs.

The model includes both discrete and continuous time for each populations because tumor population has different dynamics properties that can be described using both differential and difference equations. In the first and second equation, the first terms (logistic terms) include a time-continuity for the growth of tumor cells and CTLs and the term  $-d_1 y(t)$  includes a time-continuity for the death of CTLs.

Since the competition between tumor cells and CTLs is referred microscopic (cellular) level [18], we add discrete time  $\llbracket t \rrbracket$  in competition term  $x(t)y(t)$ . These results arise following situation. T lymphocyte can be categorized into two subclasses, namely, resting cells and Cytotoxic T lymphocytes (CTLs) which can remove tumor cells. On the

other hand, the resting cells do not directly kill tumor cells, as CTLs do. They are converted to the CTLs to kill tumor cells. We assume that this conversion is not instantaneous but followed by a discrete time. Therefore, the population of CTLs may increase at discrete time interval during the competition of tumor cells which is represented  $y(\lfloor t \rfloor)$ . Thus, the term  $-\alpha_1 x(t)y(\lfloor t \rfloor)$  is the loss of tumor cells due to the competition between the CTLs and tumor cells.

On the other hand, proliferation of the tumor cells is arranged mitosis and needs a discrete time delay where tumor cells have resting time and then again begin to proliferate which is represented  $x(\lfloor t - 1 \rfloor)$ . In addition, the immune system also needs some time delay to develop a suitable response after the recognition of tumor cells which is represented  $y(\lfloor t - 1 \rfloor)$  ([15,16]). Therefore, we have some discrete time delay during the competing populations which are represented  $y(t)x(\lfloor t - 1 \rfloor)$  and  $x(t)y(\lfloor t - 1 \rfloor)$ . Thus the term  $-\alpha_2 y(t)x(\lfloor t - 1 \rfloor)$  is the loss of CTLs due to the competition between the tumor cells and CTLs.

Because the competition phenomenon is complex and variable, it also includes growth stimulator factors which lead to positive effect on each population [8]. Thus, the term  $\alpha_1 y(t)x(\lfloor t \rfloor)$  is the positive effect on CTLs due to interaction tumor cells which stimulate CTLs growth and  $\alpha_2 x(t)y(\lfloor t - 1 \rfloor)$  denotes positive effect on tumor cells due to interaction with CTLs which stimulate tumor cell growth. After a tumor cell is recognized by immune cells, a competition may end up either with destruction of tumor cells or with the inhibition and depression of the immune system.

In our model, we assume that the growths of both tumor cells and CTLs have a logistic growth and the carrying capacity of tumor cells is greater than CTLs [2]. In addition, most of the parameter values are taken in [2] in terms of consistency with the biological facts and these parameter values are given in Table 1.

### 3. Local and global stability analysis

An integration of each equation in system (3) on an interval of the form  $t \in [n, n + 1)$  leads to

$$\begin{cases} x(t) = x(n)e^{\int_n^t x(s)(r_1(1-x(s)K_1) - \alpha_1 y(n) + \alpha_2 y(n-1)) ds}, \\ y(t) = y(n)e^{\int_n^t y(s)(r_2(1-y(s)K_2) + \alpha_1 x(n) - \alpha_2 x(n-1) - d_1) ds}, \end{cases}$$

where  $\frac{1}{k_1} = K_1, \frac{1}{k_2} = K_2$ . It is easy to see that if  $x(n), y(n) > 0$ , then  $x(t), y(t) > 0$ . Furthermore, if we let

**Table 1**  
Parameters values used for numerical analysis.

Parameters	Values
$r_1$ (growth rate of tumor cells)	0.18 day <sup>-1a</sup>
$r_2$ (growth rate of CTLs)	0.1045 day <sup>-1a</sup>
$k_1$ (carrying capacity of tumor cells)	$5.0 \times 10^6$ cells <sup>a</sup>
$k_2$ (carrying capacity of CTLs)	$3.0 \times 10^6$ cells <sup>a</sup>
$\alpha_1$ (decay rate of tumor cells by CTLs)	$4.401 \times 10^{-8}$ cells <sup>-1</sup> day <sup>-1b</sup>
$\alpha_2$ (decay rate of CTLs by tumor cells)	$3.422 \times 10^{-9}$ cells <sup>-1</sup> day <sup>-1a</sup>
$d_1$ (death rate of CTLs)	0.0412 day <sup>-1a</sup>

<sup>a</sup> Sarkar and Banerjee [2].

<sup>b</sup> Parameter values within a biologically meaningful range.

$t \rightarrow n + 1$ , we obtain  $x(n + 1), y(n + 1) > 0$ . This implies that by using positive initial conditions we will have positive solutions of system (3).

On the other hand, on an interval of the form  $t \in [n, n + 1)$ , we can write system (3) as

$$\begin{cases} \frac{dx}{dt} - \{r_1 - \alpha_1 y(n) + \alpha_2 y(n-1)\}x(t) = -r_1 K_1 (x(t))^2, \\ \frac{dy}{dt} - \{r_2 + \alpha_1 x(n) - \alpha_2 x(n-1) - d_1\}y(t) = -r_2 K_2 (y(t))^2. \end{cases} \tag{4}$$

It can be easily seen that each equation in system (4) is a Bernoulli differential equation and so we obtain

$$\begin{cases} \frac{d}{dt} \left[ \frac{1}{x(t)} e^{\int_n^t [r_1 - \alpha_1 y(n) + \alpha_2 y(n-1)] ds} \right] = r_1 K_1 e^{\int_n^t [r_1 - \alpha_1 y(n) + \alpha_2 y(n-1)] ds}, \\ \frac{d}{dt} \left[ \frac{1}{y(t)} e^{\int_n^t [r_2 + \alpha_1 x(n) - \alpha_2 x(n-1) - d_1] ds} \right] = r_2 K_2 e^{\int_n^t [r_2 + \alpha_1 x(n) - \alpha_2 x(n-1) - d_1] ds}, \end{cases} \tag{5}$$

where  $n \leq t < n + 1$ . Integrating both sides of each equations of (5) with respect to  $t$  on  $[n, t)$  and letting  $t \rightarrow n + 1$ , we get

$$\begin{cases} x(n+1) = \frac{x(n) e^{\int_n^{n+1} [r_1 - \alpha_1 y(n) + \alpha_2 y(n-1)] ds}}{[r_1 - \alpha_1 y(n) + \alpha_2 y(n-1) - r_1 K_1 x(n)] e^{-\int_n^{n+1} [r_1 - \alpha_1 y(n) + \alpha_2 y(n-1)] ds} + r_1 K_1 x(n)}, \\ y(n+1) = \frac{y(n) e^{\int_n^{n+1} [r_2 + \alpha_1 x(n) - \alpha_2 x(n-1) - d_1] ds}}{[r_2 + \alpha_1 x(n) - \alpha_2 x(n-1) - d_1 - r_2 K_2 y(n)] e^{\int_n^{n+1} [r_2 + \alpha_1 x(n) - \alpha_2 x(n-1) - d_1] ds} + r_2 K_2 y(n)}. \end{cases} \tag{6}$$

Now, we have a two dimensional system of difference equations. To investigate more about the system we need to determine an equilibrium point of the system. Under the conditions

$$\alpha_1 > \alpha_2, r_2 > d_1 \text{ and } r_1 > \frac{(\alpha_1 - \alpha_2)(r_2 - d_1)}{K_2 r_2}, \tag{7}$$

we have a positive equilibrium point of system (6) as;

$$(\bar{x}, \bar{y}) = \left( \frac{K_2 r_1 r_2 + (\alpha_2 - \alpha_1)(r_2 - d_1)}{K_1 K_2 r_1 r_2 + (\alpha_1 - \alpha_2)^2}, \frac{K_1 r_1 (r_2 - d_1) + r_1 (\alpha_1 - \alpha_2)}{K_1 K_2 r_1 r_2 + (\alpha_1 - \alpha_2)^2} \right). \tag{8}$$

The linearized system of (6) about  $(\bar{x}, \bar{y})$  is  $w(n + 1) = Bw(n)$ , where  $B$  is a matrix as

$$B = \begin{pmatrix} e^{-K_1 r_1 \bar{x}} & 0 & -\frac{(1 - e^{-K_1 r_1 \bar{x}}) \alpha_1}{K_1 r_1} & \frac{(1 - e^{-K_1 r_1 \bar{x}}) \alpha_2}{K_1 r_1} \\ 1 & 0 & 0 & 0 \\ \frac{(1 - e^{-K_2 r_2 \bar{y}}) \alpha_1}{K_2 r_2} & -\frac{(1 - e^{-K_2 r_2 \bar{y}}) \alpha_2}{K_2 r_2} & e^{-K_2 r_2 \bar{y}} & 0 \\ 0 & 0 & 1 & 0 \end{pmatrix}.$$

The characteristic equation of the matrix  $B$  can be given as follows;

$$\begin{aligned} A(\lambda) = & \lambda^4 + \lambda^3 (-e^{-K_1 r_1 \bar{x}} - e^{-K_2 r_2 \bar{y}}) \\ & + \lambda^2 \left\{ e^{-K_2 r_2 \bar{y}} - K_1 r_1 \bar{x} + \frac{\alpha_1^2}{K_1 r_1 K_2 r_2} (1 - e^{-K_1 r_1 \bar{x}}) (1 - e^{-K_2 r_2 \bar{y}}) \right\} \\ & + \lambda \left\{ \frac{-2\alpha_1 \alpha_2}{K_1 r_1 K_2 r_2} (1 - e^{-K_1 r_1 \bar{x}}) (1 - e^{-K_2 r_2 \bar{y}}) \right\} \\ & + \frac{\alpha_2^2}{K_1 r_1 K_2 r_2} (1 - e^{-K_1 r_1 \bar{x}}) (1 - e^{-K_2 r_2 \bar{y}}). \end{aligned} \tag{9}$$

Since we have a fourth order characteristic equation, we can apply Schur–Cohn criterion to determine stability conditions of discrete systems.

**Theorem A [30].** The characteristic polynomial

$$A(\lambda) = \lambda^4 + a_3\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0,$$

has all its roots inside the unit open disk ( $|\lambda| < 1$ ) if and only if

- (a)  $A(1) > 0$  and  $A(-1) > 0$ ,
- (b)  $D_1^+ = 1 + a_0 > 0$  and  $D_1^- = 1 - a_0 > 0$ ,
- (c)  $D_3^+ = (1 - a_0)(1 + a_0)(a_2 + 1 + a_0) + (a_0a_3 - a_1)(a_3 + a_1) > 0$ ,
- (d)  $D_3^- = (1 - a_0)^2(1 + a_0 - a_2) + (a_0a_3 - a_1)(a_1 - a_3) > 0$ .

By using **Theorem A**, we can analyze the local behavior of system (6) in the following theorem.

**Theorem 3.1.** Let  $(\bar{x}, \bar{y})$  the positive equilibrium point of system (6) and

$$\alpha_1 > 2\alpha_2 + \sqrt{5}\alpha_2 \quad r_2 > d_1, \quad K_2 > \frac{(\alpha_1 - \alpha_2)(r_2 - d_1)}{r_2 \ln\left(\frac{\alpha_1^2 - \alpha_2^2}{\alpha_1^2 - 2\alpha_2^2 - 2\alpha_1\alpha_2}\right)}.$$

The positive equilibrium point of the system is local asymptotically stable if

$$\frac{(\alpha_1^2 - \alpha_2^2)(e^{r_1} - 1)}{r_1K_2r_2e^{r_1}} < K_1 < \frac{\alpha_1^2 - \alpha_2^2 - 2\alpha_1\alpha_2}{r_1K_2r_2},$$

and

$$\ln\left(\frac{\alpha_1^2 - \alpha_2^2}{\alpha_1^2 - 2\alpha_2^2 - 2\alpha_1\alpha_2}\right) < r_1 < \ln\left(\frac{\alpha_1^2 - \alpha_2^2}{2\alpha_1\alpha_2}\right).$$

**Proof.** From (9), we have

$$\begin{aligned} a_3 &= -e^{-K_1r_1\bar{x}} - e^{-K_2r_2\bar{y}}, \\ a_2 &= e^{-K_2r_2\bar{y}-K_1r_1\bar{x}} + \frac{\alpha_1^2}{K_1r_1K_2r_2}(1 - e^{-K_1r_1\bar{x}})(1 - e^{-K_2r_2\bar{y}}), \\ a_1 &= \frac{-2\alpha_1\alpha_2}{K_1r_1K_2r_2}(1 - e^{-K_1r_1\bar{x}})(1 - e^{-K_2r_2\bar{y}}), \\ a_0 &= \frac{\alpha_2^2}{K_1r_1K_2r_2}(1 - e^{-K_1r_1\bar{x}})(1 - e^{-K_2r_2\bar{y}}). \end{aligned}$$

By analyzing the condition (a) of **Theorem A**, we get

$$A(1) = \left(\frac{(\alpha_1 - \alpha_2)^2}{K_1r_1K_2r_2} + 1\right)(1 - e^{-K_1r_1\bar{x}})(1 - e^{-K_2r_2\bar{y}}) > 0, \quad (10)$$

$$A(-1) = \left(\frac{(\alpha_1 + \alpha_2)^2}{K_1r_1K_2r_2} + 1\right)(1 + e^{-K_1r_1\bar{x}})(1 + e^{-K_2r_2\bar{y}}) > 0. \quad (11)$$

These inequalities show that (a) always holds. Through the analyzes of (b), we get

$$D_1^+ = 1 + (1 - e^{-K_1r_1\bar{x}})(1 - e^{-K_2r_2\bar{y}}) \frac{\alpha_2^2}{K_1r_1K_2r_2} > 0, \quad (12)$$

$$D_1^- = 1 - (1 - e^{-K_1r_1\bar{x}})(1 - e^{-K_2r_2\bar{y}}) \frac{\alpha_2^2}{K_1r_1K_2r_2} > 0. \quad (13)$$

It is clear that condition (12) is always available. If

$$K_1 > \frac{\alpha_2^2}{r_1K_2r_2}, \quad (14)$$

then (13) holds.

Considering (c) of **Theorem A**, we have

$$\begin{aligned} D_3^+ &= \left\{1 + (1 - e^{-K_1r_1\bar{x}})(1 - e^{-K_2r_2\bar{y}}) \frac{\alpha_2^2}{K_1r_1K_2r_2}\right\} \\ &\times \left\{1 - (1 - e^{-K_1r_1\bar{x}})(1 - e^{-K_2r_2\bar{y}}) \frac{\alpha_2^2}{K_1r_1K_2r_2}\right\} \\ &\times \left\{1 + e^{-K_2r_2\bar{y}-K_1r_1\bar{x}} + (1 - e^{-K_1r_1\bar{x}})(1 - e^{-K_2r_2\bar{y}}) \left(\frac{\alpha_1^2 + \alpha_2^2}{K_1r_1K_2r_2}\right)\right\} \\ &- \left\{(1 - e^{-K_1r_1\bar{x}})(1 - e^{-K_2r_2\bar{y}}) \left(\frac{2\alpha_1\alpha_2 - \alpha_2^2(e^{-K_1r_1\bar{x}} + e^{-K_2r_2\bar{y}})}{K_1r_1K_2r_2}\right)\right\} \\ &\times \left\{e^{-K_1r_1\bar{x}} + e^{-K_2r_2\bar{y}} + (1 - e^{-K_1r_1\bar{x}})(1 - e^{-K_2r_2\bar{y}}) \frac{2\alpha_1\alpha_2}{K_1r_1K_2r_2}\right\} > 0. \quad (15) \end{aligned}$$

Analyzing (15) we hold

$$K_1 > \frac{\alpha_2^2 + 2\alpha_1\alpha_2}{r_1K_2r_2}.$$

Regarding (d), we will get

$$\begin{aligned} D_3^- &= \left\{1 - (1 - e^{-K_1r_1\bar{x}})(1 - e^{-K_2r_2\bar{y}}) \frac{\alpha_2^2}{K_1r_1K_2r_2}\right\}^2 \\ &\times \left\{1 - e^{-K_2r_2\bar{y}-K_1r_1\bar{x}} - (1 - e^{-K_1r_1\bar{x}})(1 - e^{-K_2r_2\bar{y}}) \left(\frac{\alpha_1^2 - \alpha_2^2}{K_1r_1K_2r_2}\right)\right\} \\ &+ \left\{(1 - e^{-K_1r_1\bar{x}})(1 - e^{-K_2r_2\bar{y}}) \frac{2\alpha_1\alpha_2 - \alpha_2^2(e^{-K_1r_1\bar{x}} + e^{-K_2r_2\bar{y}})}{K_1r_1K_2r_2}\right\} \\ &\times \left\{e^{-K_1r_1\bar{x}} + e^{-K_2r_2\bar{y}} - (1 - e^{-K_1r_1\bar{x}})(1 - e^{-K_2r_2\bar{y}}) \frac{2\alpha_1\alpha_2}{K_1r_1K_2r_2}\right\} > 0. \quad (16) \end{aligned}$$

If

$$K_1 < \frac{\alpha_1^2 - \alpha_2^2 - 2\alpha_1\alpha_2}{r_1K_2r_2} \quad \text{and} \quad K_1 > \frac{(\alpha_1^2 - \alpha_2^2)(e^{r_1} - 1)}{r_1K_2r_2e^{r_1}},$$

then (16) holds. Under the following conditions

$$\frac{(\alpha_1 - \alpha_2)(r_2 - d_1)}{K_2r_2} < \ln\left(\frac{\alpha_1^2 - \alpha_2^2}{\alpha_1^2 - 2\alpha_2^2 - 2\alpha_1\alpha_2}\right) < r_1 < \ln\left(\frac{\alpha_1^2 - \alpha_2^2}{2\alpha_1\alpha_2}\right),$$

we can write

$$\frac{\alpha_2^2}{r_1K_2r_2} < \frac{\alpha_2^2 + 2\alpha_1\alpha_2}{r_1K_2r_2} < \frac{(\alpha_1^2 - \alpha_2^2)(e^{r_1} - 1)}{r_1K_2r_2e^{r_1}} < K_1 < \frac{\alpha_1^2 - \alpha_2^2 - 2\alpha_1\alpha_2}{r_1K_2r_2},$$

where

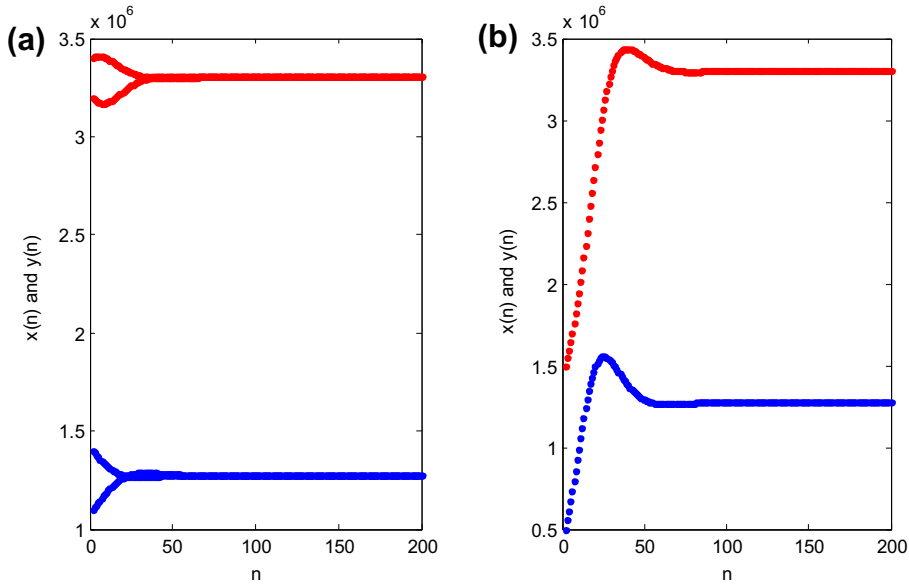
$$\alpha_1 > 2\alpha_2 + \sqrt{5}\alpha_2 \quad \text{and} \quad K_2 > \frac{(\alpha_1 - \alpha_2)(r_2 - d_1)}{r_2 \ln\left(\frac{\alpha_1^2 - \alpha_2^2}{\alpha_1^2 - 2\alpha_2^2 - 2\alpha_1\alpha_2}\right)}.$$

This completes the proof.  $\square$

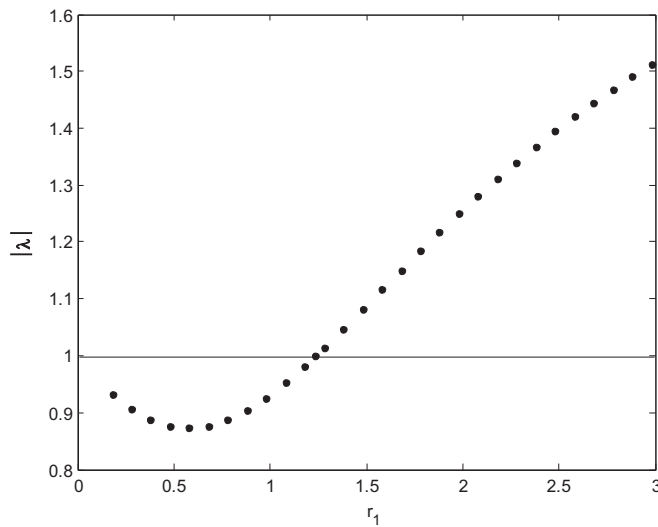
**Example 3.1.** Using parameter values in **Table 1** and initial conditions  $x(1) = 1.1 \times 10^6$ ,  $x(2) = 1.4 \times 10^6$ ,  $y(1) = 3.2 \times 10^6$ ,  $y(2) = 3.4 \times 10^6$ , the graph of the first 200 iterations of system (6) is obtained as in **Fig. 1a**. It can be shown that under the conditions given in **Theorem 3.1**, the equilibrium point  $(\bar{x}, \bar{y}) = (1.27552 \times 10^6, 3.30347 \times 10^6)$  is local asymptotically stable. Here, blue and red graphs represent population density of tumor cells and CTLs respectively.

**Theorem 3.2.** Suppose that the conditions in **Theorem 3.1** hold and assume that

$$\begin{aligned} r_1 - \alpha_1y(n) + \alpha_2y(n - 1) &> 0 \quad \text{and} \\ r_2 + \alpha_1x(n) - \alpha_2x(n - 1) - d_1 &> 0. \end{aligned}$$



**Fig. 1.** Graph of the iteration solution of  $x(n)$  and  $y(n)$  for different initial conditions. The parameter set is taken from Table 1. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



**Fig. 2.** Graph of the  $(r_1, |\lambda|)$ , where  $k_1 = 5 \times 10^8$  and other parameter set is taken from Table 1.

If

$$r_1 K_1 x(n) < r_1 - \alpha_1 y(n) + \alpha_2 y(n-1) < \ln \left( \frac{2\bar{x} - x(n)}{x(n)} \right), \quad (17)$$

$$r_2 K_2 y(n) < r_2 + \alpha_1 x(n) - \alpha_2 x(n-1) - d_1 < \ln \left( \frac{2\bar{y} - y(n)}{y(n)} \right) \quad (18)$$

and

$$x(n) < \bar{x}, \quad y(n) < \bar{y},$$

then the positive equilibrium point of system (6) is global asymptotically stable.

**Proof.** Suppose that  $\bar{z} = (\bar{x}, \bar{y})$  is a positive equilibrium point of system (6). We consider a Lyapunov function  $V(n)$  defined as

$$V(n) = [Z(n) - \bar{z}]^2, \quad n = 0, 1, 2 \dots$$

The change along the solutions of the system is

$$\begin{aligned} \Delta V(n) &= V(n+1) - V(n) \\ &= \{Z(n+1) - \bar{z}\} \{Z(n+1) + Z(n) - 2\bar{z}\}. \end{aligned}$$

From the first equation in (6), we obtain

$$\Delta V_1(n) = [x(n+1) - x(n)][x(n+1) + x(n) - 2\bar{x}].$$

Since  $r_1 K_1 x(n) < r_1 - \alpha_1 y(n) + \alpha_2 y(n-1)$ , we get  $x(n+1) - x(n) > 0$ . If we add  $x(n) < 2\bar{x}$  to (17), we have  $x(n+1) + x(n) - 2\bar{x} < 0$ . From  $\ln\left(\frac{2\bar{x}-x(n)}{x(n)}\right) > 0$ , we have  $x(n) < \bar{x}$ . Thus, it is obtained that  $\Delta V_1(n) < 0$ . Similarly, It can be shown that  $\Delta V_2(n) < 0$ . Consequently, we obtain  $\Delta V(n) = (\Delta V_1(n), \Delta V_2(n)) < 0$ . This completes the proof.  $\square$

**Example 3.2.** Considering the conditions of Theorem 3.2, we can use initial conditions  $x(1) = 0.5 \times 10^6$ ,  $x(2) = 2.5 \times 10^6$ ,  $y(1) = 1.5 \times 10^6$ ,  $y(2) = 4.5 \times 10^6$ . The graph of the first 200 iterations of system (6) is given in Fig. 1b where blue and red graphs represent population density of tumor cells and CTLs respectively.

In our study, a pivotal role has been played by two parameters;  $k_1$  (carrying capacity of tumor cells) and  $r_1$  (growth rate of tumor cells). To get some information about stability of the system according to changing of these parameters, the value of  $k_1$  is increased to  $5 \times 10^8$  and norms of dominant eigenvalues of the system are examined against to  $r_1$  (Fig. 2). Until  $r_1$  reaches a certain threshold value, the norms are less than 1 and the system is stable. If  $r_1$  is increased beyond this threshold value, the norms will be greater than 1 and stability of the system switches to unstable situation. In bifurcation analysis, we can also determine this threshold value of  $r_1$  by using the Schur–Cohn criterion.

#### 4. Bifurcation analysis

In this section, we investigate the possible bifurcation types for the system by using Schur–Cohn criterion. It is well known that replacing condition (a) in Theorem A by  $A(1) = 0$  and  $A(-1) > 0$ , the algebraic conditions under which the system may undergo stationary bifurcation are

obtained. Replacing condition (a) in Theorem A by  $A(1) > 0$  and  $A(-1) = 0$ , conditions of period doubling bifurcation are obtained. But these conditions are not hold for the system because of the inequalities (10) and (11). Hence stationary bifurcation and period doubling bifurcation do not exist for the system.

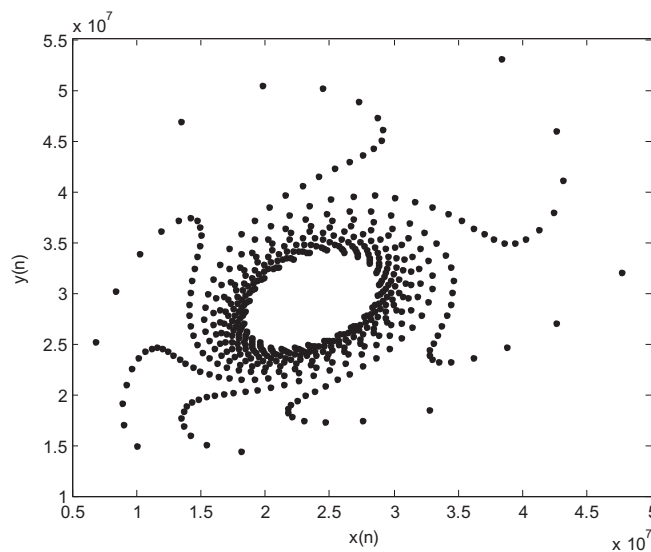
Now, we can investigate the Neimark–Sacker bifurcation in our system. The Neimark–Sacker bifurcation is the discrete-time version of the Hopf bifurcation in the continuous case where periodic solutions arise as a consequence of this bifurcation. The existence of periodic solutions is relevant cancer models. It implies that the tumor levels may oscillate around an equilibrium point even in absence of any treatment. Such a phenomenon, which is known as Jeff’s Phenomenon has been observed clinically [31] and has arisen many cancer models [2,5,6,13–15]. To get algebraic conditions of Neimark–Sacker bifurcation, we need to put the  $D_3^- = 0$  instead of  $D_3^- > 0$  in the Theorem A. Thus, algebraic conditions for Neimark–Sacker bifurcation of the system can be obtained. Using these algebraic conditions, we can determine bifurcation point of the system as in the following example.

**Example 4.1.** For the Neimark–Sacker bifurcation, we must verify conditions  $A(1) > 0$ ,  $A(-1) > 0$ ,  $D_1^+ > 0$ ,  $D_3^+ > 0$  and  $D_3^- = 0$ . We have already seen that conditions  $A(1) > 0$ ,  $A(-1) > 0$  and  $D_1^+ > 0$  are always satisfied in the local stability analysis. For  $k_1 = 5 \times 10^8$ , If we solve  $D_3^- = 0$ , then we have  $\bar{r}_1 = 1.23638$ . Clearly, for this  $\bar{r}_1$  we have also  $D_1^- = 0.995144 > 0$  and  $D_3^+ = 1.98142 > 0$ .

Another way to see Neimark–Sacker bifurcation, we can compute norm of eigenvalues of system (6) as follows;

$$|\lambda_{1,2}| = |0.0595655 \pm 0.0361638i| = 0.0696841 < 1,$$

$$|\lambda_{3,4}| = |0.594205 \pm 0.804314i| = 1.$$



**Fig. 3.** Graph of Neimark–Sacker bifurcation of system 6 for  $\bar{r}_1 = 1.23638$ , where  $k_1 = 5 \times 10^8$ ,  $x(1) = x(2) = 1 \times 10^7$ ,  $y(1) = y(2) = 1.5 \times 10^7$  and other parameters are taken from Table 1.



These norms of eigenvalue show that a pair of complex conjugate eigenvalue is on the unit circle and the other eigenvalues are inside the circle. These results confirm that Neimark–Sacker bifurcation exists for the system (Fig. 3).

Now we simulate the behavior of the model both before ( $r_1 < \bar{r}_1 = 1.23638$ ) and after the bifurcation point ( $r_1 > \bar{r}_1$ ). For  $r_1 < \bar{r}_1$ , the solution of the system has damped oscillations and the positive equilibrium point is local asymptotically stable (Fig. 4a). These damped oscillations persist up to  $\bar{r}_1$ . If  $r_1$  is increased beyond this value, the positive equilibrium point of the system tends to unstable situation (Fig. 4b). In addition, we plot bifurcation diagram of the system with respect to parameter  $r_1$  (Fig. 5) and observe dynamic behavior of the system. The figure shows that the system may exhibit chaotic behavior after the bifurcation point. In the following subsection, we investigate the chaotic dynamics of the system according to Fig. 5 by using Lyapunov characteristic exponents that are a classic analytic tool to measure chaos.

#### 4.1. Determining chaotic behavior of the system

Discrete dynamical systems may exhibit different dynamics behavior such as stable dynamics or unstable dynamics which may lead to chaos. To determine whether or not the system exhibits chaotic motion one can use Lyapunov exponents or Lyapunov characteristic exponents (LCEs) which are a useful tool to examine stability dynamics of both continuous and discrete dynamical system. LCEs measure the separation in time of two orbits starting from arbitrary close initial points. If a Lyapunov exponent is positive, then one can say that the system is chaotic. This implies that two trajectories that start close to each other will diverge as time increases, as seen in Fig. 4b.

In this paper, we use a method presented in [32,33] for estimating Lyapunov exponents of discrete dynamical

system  $x_{k+1} = F(x_k)$ ,  $k = 0, 1, \dots$ . The method based on computing the QR decomposition of the Jacobian matrix  $B$  and can be summarized as follows. Firstly, we consider orthogonal matrix  $Q_0$  such that  $Q_0^T Q_0 = I$ . By solving  $Z_{k+1} = B_k \cdot Q_k$ ,  $k = 0, 1, \dots$ , we can obtain the decomposition  $Z_{k+1} = Q_{k+1} \cdot R_{k+1}$ , where  $Q_{k+1}$  is an orthogonal matrix and  $R_{k+1}$  is upper triangular matrix with positive diagonal elements [32]. Thus, the LCEs can be calculated as

$$\lambda_i = \lim_{k \rightarrow \infty} \frac{1}{k} \ln \left( (R_i)_{jj} \right), \quad j = 1, \dots, m. \tag{19}$$

Now, we can obtain the Lyapunov exponents of the system by using the formula (19). The calculated LCEs of the system according to Fig. 5 are given Table 2 and converge of the LCEs is shown in Fig. 6. It is shown from Table 2 and Fig. 6 that the system exhibits chaotic behavior for  $r_1 > \bar{r}_1$ .

### 5. Results and discussion

In this study, we have proposed and analyzed a mathematical model for the study of interaction between tumor cells and CTLs which is main struggle of immune system. For this, we have used Schur–Cohn criterion and constructed Lyapunov function in order to obtain sufficient conditions that ensure local and global stability of the system. To support theoretical results with numerically, we have used some realistic parameter values that are taken in [2] in terms of consistency with the biological facts.

In our model, the parameter  $k_1$  (carrying capacity of tumor cells) and  $r_1$  (growth rate of tumor cells) have a strong effect on the stability of the system. To see this effect, carrying capacity of tumor cells is increased to  $5 \times 10^8$  and we analyze stability of the system according to changing  $r_1$  parameter and obtain a threshold (bifurcation point) according to this parameter. If  $r_1 < \bar{r}_1 = 1.23638$ , then the

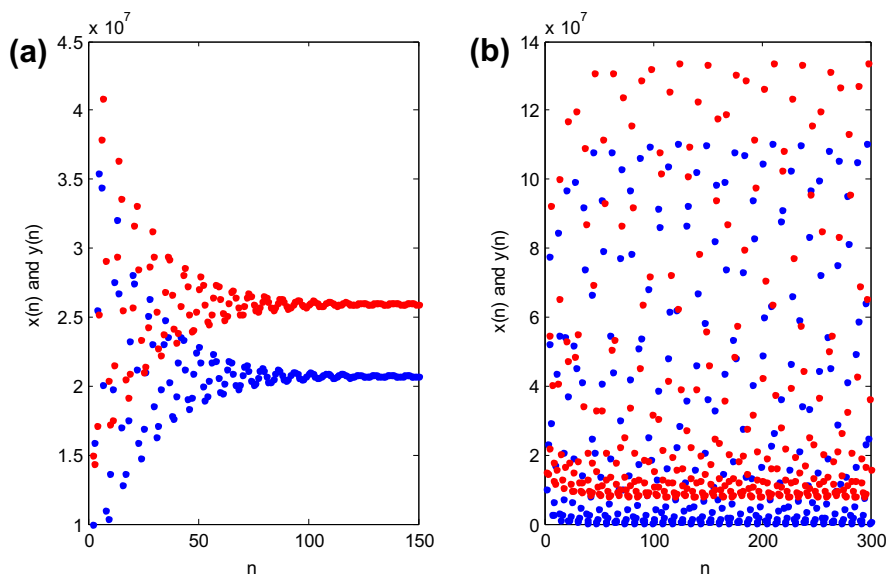
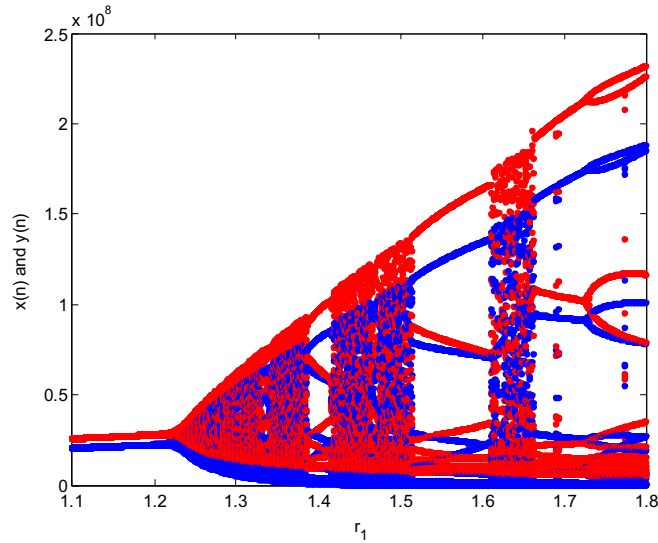


Fig. 4. Graph of the iteration solution of  $x(n)$  and  $y(n)$  for  $r_1 = 1.1$  (a) and  $r_1 = 1.5$  (b) where  $k_1 = 5 \times 10^8$ . Initial conditions and other parameters are the same as Fig. 3. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



**Fig. 5.** Graph of  $(r_1, (x(n), y(n)))$  where  $k_1 = 5 \times 10^8$ . Initial conditions and other parameters are the same as Fig. 3. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

**Table 2**

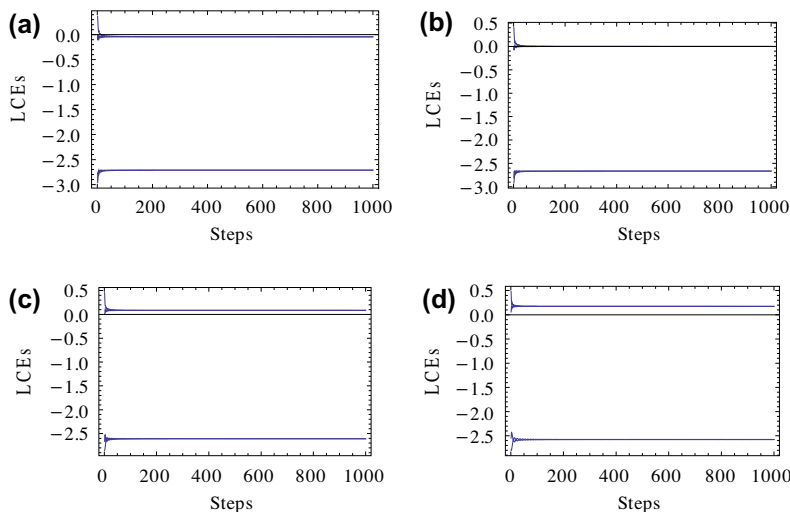
The calculated LCEs of the system according to Fig. 5.

Parameter values	Lyapunov exponents
$r_1 = 1.1$	$\{-0.0420568, -0.0425353, -2.71125, -2.71144\}$
$\bar{r}_1 = 1.23638$	$\{0.000545118, -0.00010682, -2.66393, -2.66407\}$
$r_1 = 1.3$	$\{0.0210309, 0.0203559, -2.64698, -2.64715\}$
$r_1 = 1.4$	$\{0.0532232, 0.0527537, -2.62524, -2.62563\}$
$r_1 = 1.5$	$\{0.0851813, 0.0845747, -2.60827, -2.60895\}$
$r_1 = 1.6$	$\{0.116046, 0.115799, -2.59543, -2.59545\}$
$r_1 = 1.7$	$\{0.145993, 0.145694, -2.58465, -2.58547\}$
$r_1 = 1.8$	$\{0.17468, 0.174265, -2.57628, -2.57742\}$

solution of system (6) has damped oscillation and the positive equilibrium point is local asymptotically stable (Figs. 2, 4a and 5). These oscillations give way to a stable spiral with very quick damping, leading to small and persistent tumor.

This means that the populations of CTLs and tumor cells coexist and their sizes do not vary, namely tumor dormant state [11]. This result can be seen in Figs. 4a and 5 where blue and red graphs represent population density of tumor cells and CTLs respectively. In addition, Fig. 7 helps us to identify stable region of the system with respect to changing the parameter  $r_1$  and  $k_1$ .

On the other hand, we observe that stability switches at  $\bar{r}_1 = 1.23638$  that is bifurcation point (Figs. 3 and 5). If  $r_1$  is increased beyond  $\bar{r}_1$ , the system tends to unstable situation even in absence of any treatment. Moreover, Fig. 5 shows that this unstable situation leads to uncontrolled tumor growth and chaotic behavior occurs for the tumor cells in the interval  $r_1 > \bar{r}_1$  (Table 2 and Fig. 6). Therefore, the system needs external intervention until the growth rate of tumor cells reaches to  $\bar{r}_1$ . Otherwise the patient may be



**Fig. 6.** Converge plot of the Lyapunov spectrum for the system with respect to parameter  $r_1 = 1.1$  (a),  $\bar{r}_1 = 1.23638$  (b),  $r_1 = 1.5$  (c) and  $r_1 = 1.8$  (d).



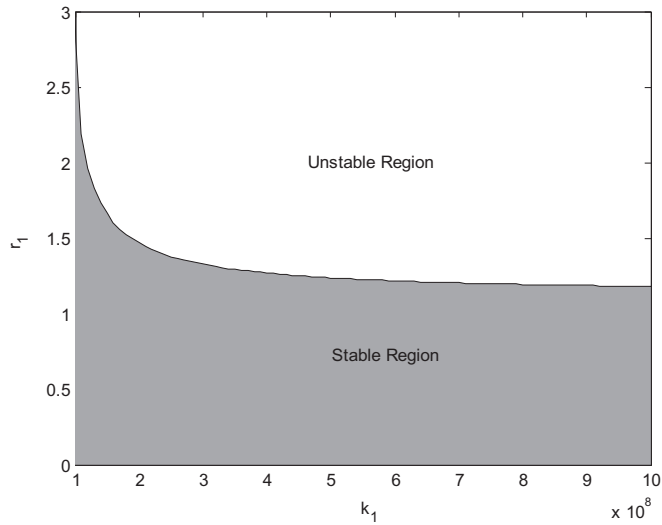


Fig. 7. Bifurcation diagram with respect to parameter  $r_1$  and  $k_1$ .

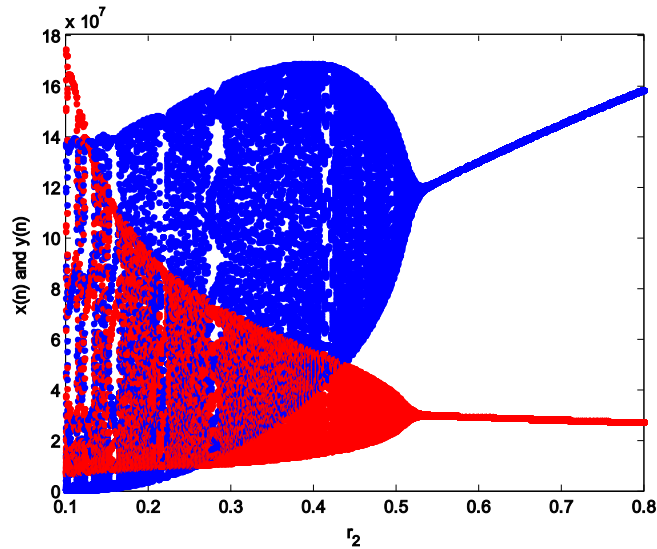


Fig. 8. Bifurcation diagram of the system with respect to parameter  $r_2$  where  $r_1 = 1.6$ . The other parameters and initial conditions are the same as Fig. 3.

died as a result of uncontrolled tumor growth. The external intervention may be increasing the growth rate of CTLs since the growth rate of CTLs ( $r_2$ ) plays an important role in expanding the stable interval of the system. For example, if the growth rate of CTLs ( $r_2$ ) is increased from 0.1045 to 0.1245, the bifurcation point of the system rises from  $\bar{r}_1 = 1.23638$  to  $\bar{r}_{11} = 1.24093$ . In biologically, the growth rate of CTLs may be increased by the treatment *Adaptive Cellular Immunotherapy (ACI)* [13]. As seen above theoretical results, it can be seen that determining bifurcation point is a very important issue for controlling unlimited tumor growth.

We also investigate the dynamic behavior of the system in chaotic region ( $r_1 > \bar{r}_1$ ). In this region, the growth rate of CTLs ( $r_2$ ) plays an important role in controlling tumor cells

growth. The bifurcation plot (Fig. 8) for  $r_2$  helps us to identify the region ( $r_2 > 0.513443$ ) where the chaotic behavior for tumor cells end up. In addition, we observe that the parameter  $\alpha_1$  (decay rate of tumor cells) is another important parameter for the control the tumor cells in chaotic region. As the parameter  $\alpha_1$  is increased in this region, the population size of tumor cells can be constrained to low or null values namely tumor remission (Fig. 9). In this situation, the system tends a new equilibrium point  $(\bar{x}, \bar{y}) = (0, -\frac{d_1 - r_2}{k_2 r_2})$  where the tumor cells eliminate by CTLs. Therefore, it is possible to reach the tumor-free steady state by increasing the parameter  $\alpha_1$ . As a result we can say that the parameters  $r_2$  and  $\alpha_1$  are effective tools to control the tumor growth in chaotic region. Thus, we

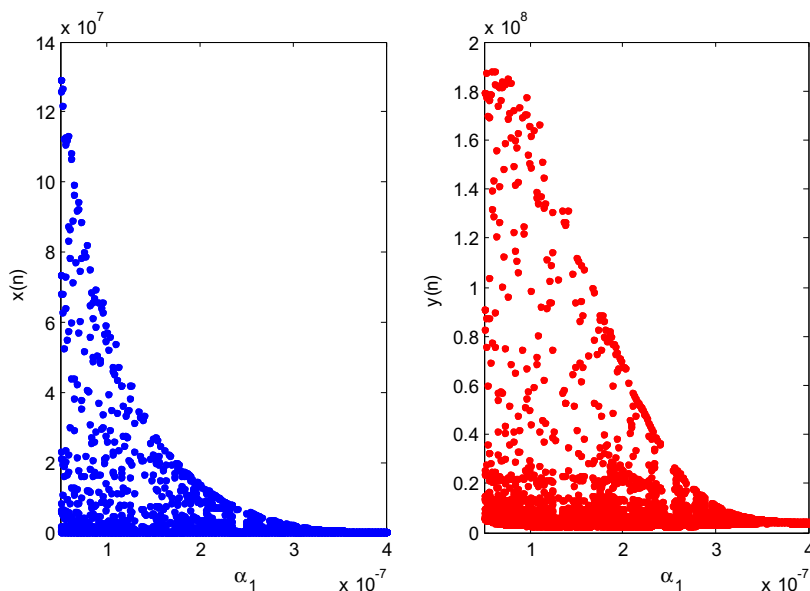


Fig. 9. Bifurcation diagram of the system with respect to parameter  $\alpha_1$  where  $r_1 = 1.6$ . The other parameters and initial conditions are the same as Fig. 3.

explain the different dynamics behavior of tumor cells such as tumor dormant state, tumor remission and uncontrolled tumor growth.

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