Cumhuriyet Sci. J., 44(2) (2023) 345-355
DOI: https://doi.org/10.17776/csj.1239101

Cumhuriyet Science Journal

| csj.cumhuriyet.edu.tr | Founded: 2002 ISSN: 2587-2680 e-ISSN: 2587-246X Publisher: Sivas Cumhuriyet University

Chaos in a Three-Dimensional Cancer Model with Piecewise Constant Arguments

Şenol Kartal [1,a,*]

[1] *Department of Science and Mathematics Education, Faculty of Education, Nevsehir Hacı Bektas Veli University, Nevsehir, Türkiye.*
**Corresponding author*

Research Article

History
Received: 19/01/2023
Accepted: 01/05/2023

ABSTRACT

In this study, we analyze a cancer model which includes the interactions among tumor cells, healthy host cells and effector immune cells. The model with continuous case has been studied in the literature and it has been shown that it exhibits chaotic behavior. In this paper, we aim to build a better understanding of how both discrete and continuous times affect the dynamic behavior of the tumor growth model. So, we reconsider the model as a system of differential equations with piecewise constant argument. To analyze dynamical behavior of the model, we consider the solution of the system in a certain subinterval which leads to the system of difference equations. Some theoretical results are obtained for local behavior of the system. In addition, we study chaotic dynamic of the system through Neimark-Sacker bifurcation by using Lyapunov exponents

Keywords: *Tumor model, Difference equation, Stability, Neimark-Sacker bifurcation, Lyapunov exponents*

[a] senol.kartal@nevsehir.edu.tr https://orcid.org/0000-0003-1205-069X

Introduction

Interaction of tumor cells with other cells of the body, i.e. healthy host cells and immune system cells is very complex phenomenon because tumor cells have different dynamics such as unbounded growth, tumor dormancy, tumor recurrence and tumor remission. In order to understand the dynamic behavior of the disease, a variety of mathematical models have been developed in the literature [1-19]. Using the Lotka-Volterra equations in these models is one of the most common ideas. A very simple model based on the Lotka-Volterra predator-prey model has been presented by Costa and et al. [1]. Their model explains tumor aggressiveness, the diffusion of lymphocytes and the effect caused by cytokines on the tumor. Based on the Costa model, a family of Lotka-Volterra models has been investigated by D'Onofrio [2]. Another familiar tumor growth model has been proposed by Kuznetsov and et al. [3] and they have explained two different stages of the tumor: the dormant tumor and the sneaking-through mechanism. In 1998, Kirschner and Panetta [4] described the dynamics among tumor cells, immune effector cells and Interleukin-2 by using the generalized Kuznetsov model.

Recent studies have shown that some tumor growth models which are based on Lotka-Volterra type systems exhibit chaotic dynamics. Itik and Banks [5] have analyzed the chaotic dynamics of a very simple tumor growth model

$$\begin{cases} \dfrac{dx}{dt} = x(t)\big(1 - x(t)\big) - ax(t)y(t) - bx(t)z(t), \\ \dfrac{dy}{dt} = cy(t)\big(1 - y(t)\big) - dx(t)y(t), \\ \dfrac{dz}{dt} = \dfrac{ex(t)z(t)}{x(t) + f} - gx(t)z(t) - hz(t). \end{cases} \qquad (1)$$

Calculating Lyapunov exponents and Lyapunov dimension show that a chaotic attractor occurs around the positive equilibrium point. Model (1.1) has also been studied by Galindo et al. [6]. They have observed that tumor cells, immune cells and healthy cells coexist through the Hopf bifurcation which causes a stable limit cycle. A more general form of this model with chemotherapy treatment has been studied in study [7].

In the early 1980s, Busenberg and Cooke [20], Cooke and Györi [21], Shah and Wiener [22] developed a new type of differential equation that is called differential equation with piecewise constant arguments [23]. Using the method of reduction to discrete equations, many authors have analyzed the existence and uniqueness of solutions; oscillations, stability and periodic solutions of these equations [23-27]. Besides the theoretical analysis, various types of biological models have been constructed using differential equations with piecewise constant arguments [20, 28-31]. The first biological model has been presented by Buseenberg and Cooke [20] to investigate vertically transmitted diseases. Following this work, Ozturk et al. [28], Bozkurt et al. [29], Gurcan et al. [30], Kartal and Gurcan [31], have constructed a mathematical model with piecewise constant arguments for some biological phenomena such as bacteria population and tumor growth.

In the present paper, our aim is a better understanding of how both discrete and continuous times affect the dynamic behavior of the tumor growth model (1). So we will reconsider the model as a system of differential equations with piecewise constant arguments such as;

$$\begin{cases} \frac{dx}{dt} = x(t)\big(1 - x(t)\big) - ax(t)y([\![t]\!]) - bx(t)z([\![t]\!]), \\ \frac{dy}{dt} = cy(t)\big(1 - y(t)\big) - dx([\![t]\!])y(t), \\ \frac{dz}{dt} = \frac{ex([\![t]\!])z(t)}{x([\![t]\!]) + f} - gx([\![t]\!])z(t) - hz(t). \end{cases} \quad (2)$$

In this model, $x(t)$, $y(t)$ and $z(t)$ represent the tumor cell, healthy host cell and effector immune cell population respectively. $[\![t]\!]$ denotes the integer part of $t \in [0, \infty)$ and all these parameters are positive. In the first equation, the first term is logistic growth of tumor cells, the second and last terms represent the negative effect due to the interaction tumor-host cells and tumor-immune cells respectively. In the second equation, the healthy cells also grow logistically, with growth rate c and have loss of their population due to interaction with tumor cells that are represented in the second term. In the last equation, the first term is the stimulation of the immune system by tumor cells, the second term describes the loss of immune cells due to interaction with tumor cells and last term represents the natural death rate of the effector immune cells [5-6].

Local Stability Analysis

System (2) can be written in the interval $t \in [n, n+1)$ as follows:

$$\begin{cases} \frac{dx}{dt} - x(t)\big(1 - ay(n) - bz(n)\big) = -x^2(t), \\ \frac{dy}{dt} - y(t)(c - dx(n)) = -cy^2(t), \\ \frac{dz}{dt} = z(t)\left[\frac{ex(n)}{x(n) + f} - gx(n) - h\right]. \end{cases} \quad (3)$$

Solving system (3) in the interval $t \in [n, n+1)$ and letting $t \to n+1$ gives system of difference equation

$$\begin{cases} x(n+1) = \frac{x(n)[1 - ay(n) - bz(n)]}{[1 - ay(n) - bz(n) - x(n)]e^{-[1 - ay(n) - bz(n)]} + x(n)}, \\ y(n+1) = \frac{y(n)[c - dx(n)]}{[c - dx(n) - cy(n)]e^{-[c - dx(n)]} + cy(n)}, \\ z(n+1) = z(n)e^{\frac{ex(n)}{x(n)+f} - gx(n) - h}. \end{cases} \quad (4)$$

System (4) reflects the rich dynamical characteristics and the asymptotic behavior of the system of differential equations with piecewise constant argument. Now, we need to obtain the equilibrium points to study the local behavior of the system. The positive equilibrium point of system (4) can be obtained as $E = (\bar{x}, \bar{y}, \bar{z})$ where

$$\bar{x} = \frac{e - fg - h - q}{2g}, \quad \bar{y} = \frac{-de + 2cg + dfg + dh + dq}{2cg}, \bar{z} = \frac{-ad(-e + fg + h + q) + c(-e + 2g - 2ag + fg + h + q)}{2bcg}$$

and

$$q = \sqrt{e^2 + (-fg + h)^2 - 2e(fg + h)}.$$

Let

$$f\big(x(n), y(n), z(n)\big) = \frac{x(n)[1 - ay(n) - bz(n)]}{[1 - ay(n) - bz(n) - x(n)]e^{-[1 - ay(n) - bz(n)]} + x(n)},$$

$$g\big(x(n), y(n), z(n)\big) = \frac{y(n)[c - dx(n)]}{[c - dx(n) - cy(n)]e^{-[c - dx(n)]} + cy(n)}$$

and

$$h\big(x(n), y(n), z(n)\big) = z(n)e^{\frac{ex(n)}{x(n)+f} - gx(n) - h}.$$

Then, the linearized system of (4) about $(\bar{x},\bar{y},\bar{z})$ is $w(n+1)=Aw(n)$ where the Jacobian matrix A can be calculated;

$$A=\begin{pmatrix} a_{11}=\frac{\partial f}{\partial x(n)}(\bar{x},\bar{y},\bar{z}) & a_{12}=\frac{\partial f}{\partial y(n)}(\bar{x},\bar{y},\bar{z}) & a_{13}=\frac{\partial f}{\partial z(n)}(\bar{x},\bar{y},\bar{z}) \\ a_{21}=\frac{\partial g}{\partial x(n)}(\bar{x},\bar{y},\bar{z}) & a_{22}=\frac{\partial g}{\partial y(n)}(\bar{x},\bar{y},\bar{z}) & a_{23}=\frac{\partial g}{\partial z(n)}(\bar{x},\bar{y},\bar{z}) \\ a_{31}=\frac{\partial h}{\partial x(n)}(\bar{x},\bar{y},\bar{z}) & a_{32}=\frac{\partial h}{\partial y(n)}(\bar{x},\bar{y},\bar{z}) & a_{33}=\frac{\partial h}{\partial z(n)}(\bar{x},\bar{y},\bar{z}) \end{pmatrix}. \tag{5}$$

The elements of the A matrix are

$$a_{11}=e^{\frac{-e+fg+h+q}{2g}}=e^{-\bar{x}},\ a_{12}=a\left(-1+e^{\frac{-e+fg+h+q}{2g}}\right)=a(-1+e^{-\bar{x}}),\ a_{13}=b\left(-1+e^{\frac{-e+fg+h+q}{2g}}\right)=b(-1+e^{-\bar{x}}),$$

$$a_{21}=\frac{d\left(-1+e^{-c-\frac{dq}{2g}}\right)}{c}=\frac{d}{c}(-1+e^{-c\bar{y}}),\ a_{22}=e^{-c-\frac{d(-e+fg+h+q)}{2g}}=e^{-c\bar{y}},\ a_{23}=0,$$

$$a_{31}=\bar{z}\frac{2g(-e^2+(fg-h)(-fg+h+q)+e(2fg+2h+q))}{(-e-fg+h+q)^2},\qquad a_{32}=0,\qquad a_{33}=1$$

Now, the characteristic equation of the matrix A can be obtained as

$$\begin{aligned} p(\lambda)&=\lambda^3+\lambda^2(-e^{-\bar{x}}-e^{-c\bar{y}}-1)\\ &+\lambda\left(-\frac{ad}{c}(1-e^{-\bar{x}})(1-e^{-c\bar{y}})+b(1-e^{-\bar{x}})a_{31}+e^{-\bar{x}}+e^{-c\bar{y}}+e^{-\bar{x}}e^{-c\bar{y}}\right)\\ &+\frac{ad}{c}(1-e^{-\bar{x}})(1-e^{-c\bar{y}})-b(1-e^{-\bar{x}})a_{31}e^{-c\bar{y}}-e^{-\bar{x}}e^{-c\bar{y}}=0 \end{aligned} \tag{6}$$

where

$$p_2=-e^{-\bar{x}}-e^{-c\bar{y}}-1,$$

$$p_1=-\frac{ad}{c}(1-e^{-\bar{x}})(1-e^{-c\bar{y}})+b(1-e^{-\bar{x}})a_{31}+e^{-\bar{x}}+e^{-c\bar{y}}+e^{-\bar{x}}e^{-c\bar{y}},$$

and

$$p_0=\frac{ad}{c}(1-e^{-\bar{x}})(1-e^{-c\bar{y}})-a_{31}b(1-e^{-\bar{x}})e^{-c\bar{y}}-e^{-\bar{x}}e^{-c\bar{y}}.$$

Theorem 1. Suppose that $E=(\bar{x},\bar{y},\bar{z})$ is the equilibrium point of the system (4) and the characteristic polynomial of the Jacobian matrix of the linearized system for the model (4) is

$$p(\lambda)=\lambda^3+p_2\lambda^2+p_1\lambda+p_0\,. \tag{7}$$

The equilibrium point of the system (4) is local asymptotically stable if and only if

a) $p(1)=1+p_2+p_1+p_0>0$,

b) $(-1)p(-1)=1-p_2+p_1-p_0>0$,

c) $D_2^+=1+p_1-{p_0}^2-p_0p_2>0$,

d) $D_2^-=1-p_1+p_0p_2-{p_0}^2>0$.

The conditions of Theorem 1 can be easily obtained from the Schur-Cohn criteria [32]. Because analyzing the conditions of Theorem 1 is quite difficult, we will analyze these conditions numerically. For the parameter values $c = 0.6,\ d = 1,$ $e = 3.5,\ f = 1.8,\ g = 0.2, h = 0.5,\ b = 2, a = 0.5$ and initial conditions $x(1) = y(1) = z(1) = 0.5$ which satisfy the conditions of Theorem 1, the positive equilibrium point $(\bar{x}, \bar{y}, \bar{z}) = (0.3502, 0.416333, 0.220817)$ is local asymptotically stable where blue, red and black graphs represent population density of tumor, healthy and immune cells respectively. (Figure 1).

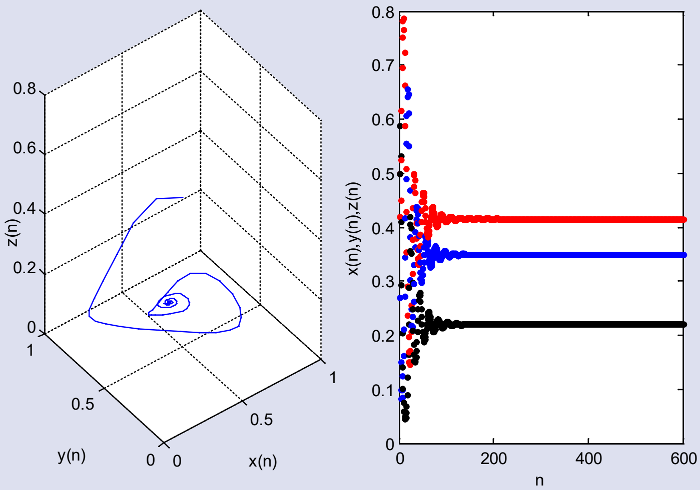

Figure 1. Graph of the iteration solution of x(n),y(n) and z(n) for the parameter values c=0.6,a=0.5,d=1,e=3.5,f=1.8, g=0.2,h=0.5,b=2 and initial conditions x(1)=y(1)=z(1)=0.5.

Neimark Sacker bifurcation and Chaotic Dynamics

In this section, we will prove that the system exhibits chaotic dynamics through Neimark-Sacker bifurcation which is a discrete version of Hopf bifurcation in continuous case. For this reason, we will calculate the Lyapunov exponent for the selected parameter sets.

Neimark Sacker bifurcation analysis

The following theorem gives necessary and sufficient algebraic conditions of Neimark-Sacker bifurcation.

Lemma [33]: Consider the following n-dimensional system:

$$X_{n+1} = f_q(X_n) \tag{8}$$

where $q \in R$ is considered as a bifurcation parameter. Suppose that characteristic polynomial of $J|_X$ about X of n-dimensional discrete dynamical system, which is depicted in system (8), is

$$P(\lambda) = \lambda^n + p_1\lambda^{n-1} + p_2\lambda^{n-2} + \cdots + p_n \tag{9}$$

Now considering the determinants: $\Delta_0^{\pm}(q) = 1, \Delta_1^{\pm}(q), \ldots, \Delta_n^{\pm}(q)$, which can be expressed as

$$\Delta_j^{\pm}(q) = \left| \begin{pmatrix} 1 & p_1 & p_2 & \ldots & p_{j-1} \\ 0 & 1 & p_1 & \ldots & p_{j-2} \\ 0 & 0 & 1 & \ldots & p_{j-3} \\ \ldots & \ldots & \ldots & \ldots. & \ldots \\ 0 & 0 & 0 & \ldots & 1 \end{pmatrix} \mp \begin{pmatrix} p_{n-j+1} & p_{n-j+2} & \ldots & p_{n-1} & p_n \\ p_{n-j+2} & p_{n-j+3} & \ldots & p_n & 0 \\ \ldots & \ldots & \ldots. & \ldots & \ldots \\ p_{n-1} & p_n & \ldots & 0 & 0 \\ p_n & 0 & \ldots & 0 & 0 \end{pmatrix} \right| \tag{10}$$

where j=1,…n. Furthermore, Neimark-sacker bifurcation occurs at critical value $q = q_0$ if following parametric condition hold:

NS1) Eigenvalue assignment: $P_{q_0}(1) > 0$, $(-1)^n P_{q_0}(-1) > 0$, $\Delta^-_{n-1}(q_0) = 0$, $\Delta^+_{n-1}(q_0) > 0$, $\Delta^{\pm}_j(q_0) > 0$ where $j = n-3, n-5, \dots, 1$ (or 2), when n is even (or odd, respectively).

NS2) Transversality condition: $\frac{d}{dq}\Delta^-_{n-1}(q_0) \neq 0$

NS3) Nonresonance condition: $\frac{\cos(2\pi)}{l} \neq 1 - 0.5P_q(1)\frac{\Delta^-_{n-3}(q_0)}{\Delta^-_{n-2}(q_0)}$ or resonance condition $\frac{\cos(2\pi)}{l} = 1 - 0.5P_{q_0}(1)\frac{\Delta^-_{n-3}(q_0)}{\Delta^-_{n-2}(q_0)}$ where $l = 3,4, \dots$

Theorem 2: Suppose that $E = (\bar{x}, \bar{y}, \bar{z})$ is the equilibrium point of the system (4). If

$$1 + p_2 + p_1 + p_0 > 0, \tag{11}$$

$$1 - p_2 + p_1 - p_0 > 0, \tag{12}$$

$$1 - p_1 + p_0 p_2 - {p_0}^2 = 0, \tag{13}$$

$$1 + p_1 - {p_0}^2 - p_0 p_2 > 0, \tag{14}$$

$$\frac{d}{dq}\left(\Delta^-_1(q)\right)|_{q=q_0} = \frac{d}{dq}(1 - p_1 + p_0 p_2 - {p_0}^2)|_{q=q_0} \neq 0 \tag{15}$$

and

$$\frac{\cos(2\pi)}{l} \neq 1 - 0.5P_q(1) = 1 - \frac{1 + p_2 + p_1 + p_0}{2} = \frac{1 - p_2 - p_1 - p_0}{2}. \tag{16}$$

Then the discrete dynamical system undergoes a Neimark-Sacker bifurcation about $E = (\bar{x}, \bar{y}, \bar{z})$

Proof:
The proof of the theorem can be easily seen from the conditions of Lemma for n=3.
Since it is very difficult to prove the conditions of Theorem 2 analytically, we will consider these conditions numerically. For this purpose we choose the parameter a as a bifurcation parameter and fixed all other parameter values such as $c = 0.6$, $d = 1.5$, $e = 3.5$, $f = 1.8$, $g = 0.2, h = 0.5$, $b = 0.2$. For these values we hold

$$p_2 = -2.58749,$$

$$p_1 = 2.20956 + 1.43128\,(0.6\,(0.25992 - 0.4\,a) + 0.21012\,a) - 0.0864656\,a$$

and

$$p_0 = -0.622072 - 1.26373(0.6(0.25992 - 0.4a) + 0.21012a) + 0.086456a.$$

From the solutions of equation (13), the critical Neimark-Sacker bifurcation is obtained as $\bar{a} = 0.877595$. In addition from the equations (11), (12) and (14) we have $1 + p_2 + p_1 + p_0 = 0.0217342 > 0$, $1 - p_2 + p_1 - p_0 = 6.61698 > 0$ and $1 + p_1 - {p_0}^2 - p_0 p_2 = 0.977606 > 0$. In addition from the equations (15) and (16), one can obtain $\frac{d}{dq}\left(\Delta^-_1(q)\right)|_{q=q_0} = -0.0157666 \neq 0$ and $\frac{\cos(2\pi)}{l} \neq 0.989132$. Now all of the Neimark-Sacker bifurcation conditions are satisfied. For the critical value of $\bar{a}$, the eigenvalues are $\lambda_1 = 0.529395$, $\lambda_{2,3} = 0.977054 \pm 0.21299i$. Now, the conditions of Theorem 2 are satisfied and system (4) undergoes Neimark-Sacker bifurcation for the critical value $\bar{a} = 0.877595$ (Figure 2 and Figure 3).

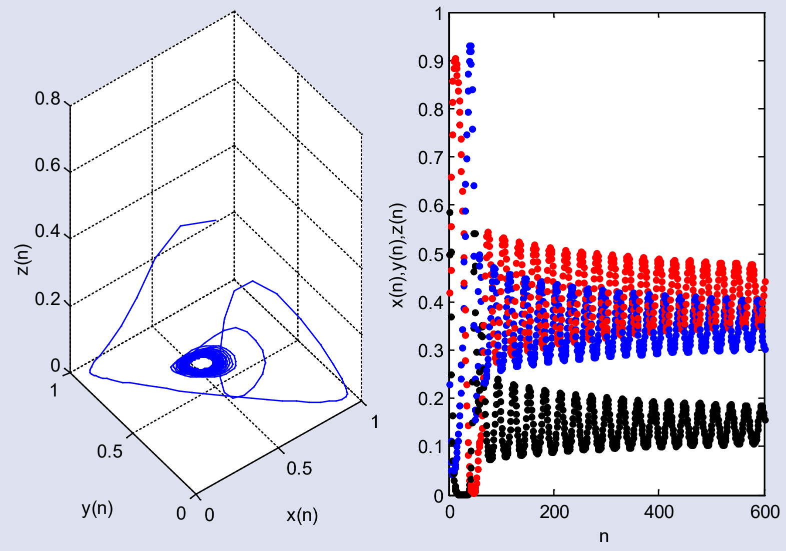

Figure 2. Time series plot and phase diagram of the discrete system (4) for $\bar{a} = 0.877595$. Initial conditions and other parameters are taken from Figure 1.

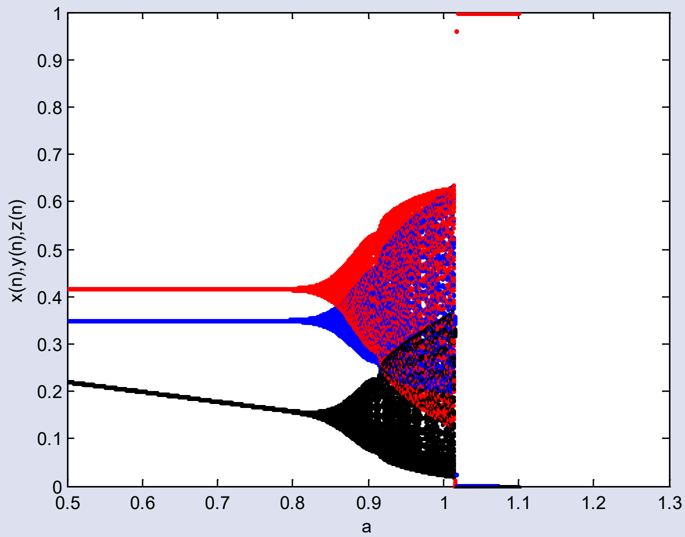

Figure 3. Bifurcation diagram of the discrete system (4) with respect to parameter a. Initial conditions and other parameters are the same as in Figure 1.

In addition, if we determine the bifurcation parameter as e then the critical bifurcation point is $\bar{e} = 4.47863$. In this situation, we have $p(1) = 0.0514048 > 0$, $(-1)p(-1) = 6.25374 > 0$ and $D_2^+ = 1.23655 > 0$ for the parameter value $\bar{e} = 4.47863$ where the eigenvalues of the Jacobian matrix are $\lambda_1 = 0.617838$, $\lambda_{2,3} = 0.932745 \pm 0.360538i$ (Figure 4 and Figure 5).

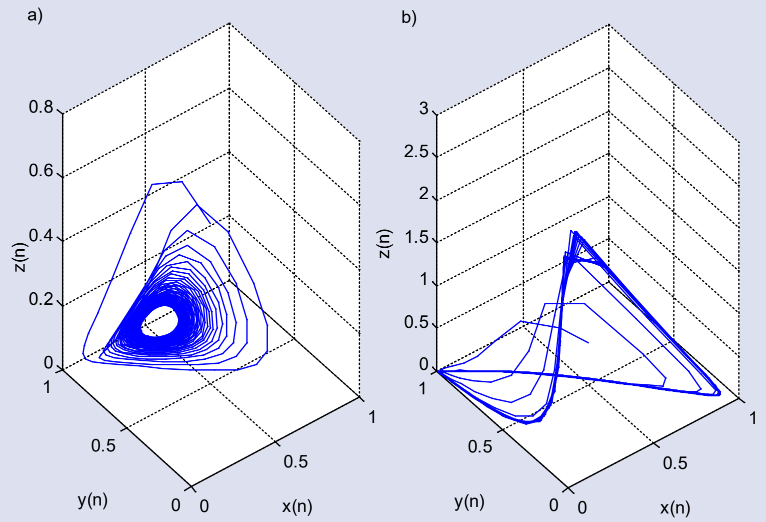

Figure 4. Time series plot and phase diagram of the discrete system (4) $\bar{e} = 4.47863$ (a) and e=6 (b) Initial conditions and other parameters are taken from Figure 1.

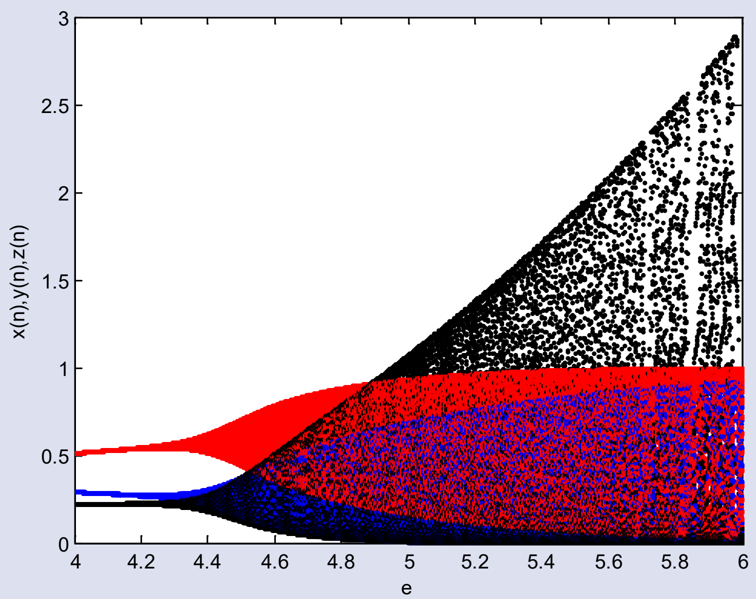

Figure 5. Bifurcation diagram of the system (4) with respect to parameter e. Initial conditions and other parameters are the same as in Figure 1.

The bifurcation point with respect to parameter f can be determined as $\bar{f} = 1.32821$, where $p(1) = 0.0499731 > 0$, $(-1)p(-1) = 6.24281 > 0$ and $D_2^+ = 1.24912 > 0$ and eigenvalues of the Jacobian matrix are $\lambda_1 = 0.61273$, $\lambda_{2,3} = 0.93548 \pm 0.353379i$ (Figure 6 and Figure 7).

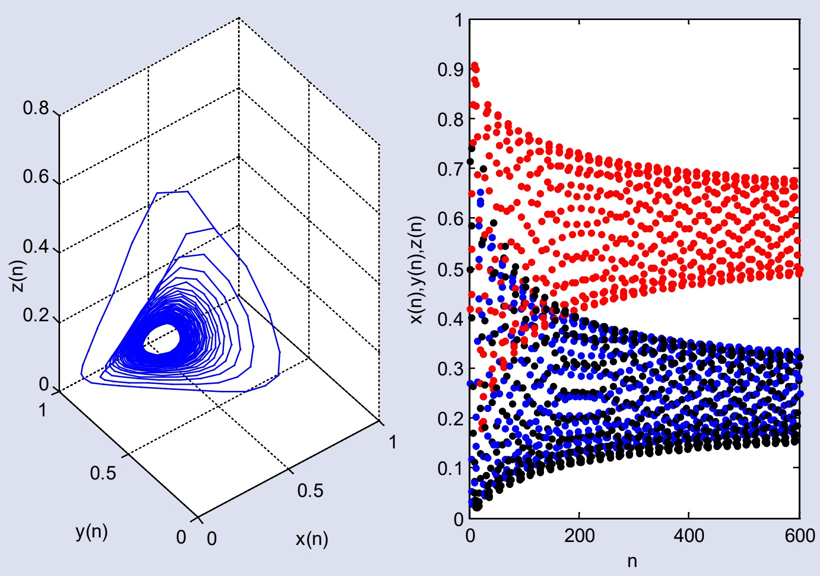

Figure 6. Time series plot and phase diagram of the discrete system (4) $\bar{f} = 1.32821$. Initial conditions and other parameters are taken from Figure 1.

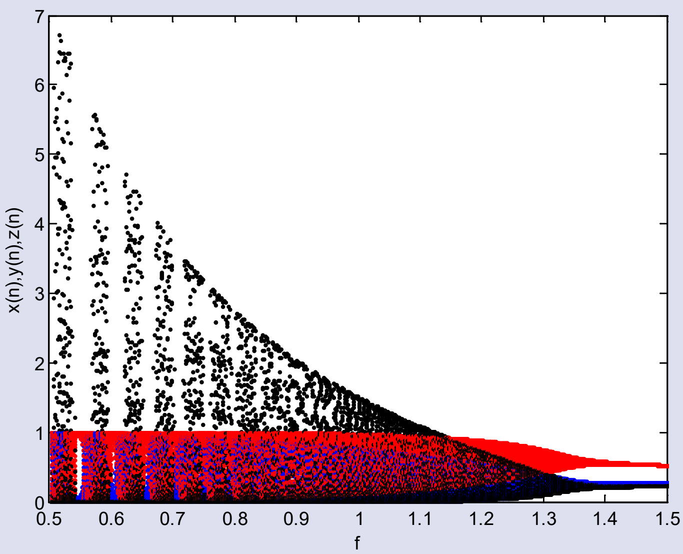

Figure 7. Bifurcation diagram of the discrete system (4) with respect to parameter f. Initial conditions and other parameters are the same as in Figure 1.

Chaotic Dynamics

In continuous and discrete dynamical systems, Lyapunov exponents or Lyapunov characteristic exponents (LCEs) are a useful tools to determine whether or not the system exhibits chaotic motion. If a Lyapunov exponent is positive, one can say that the system is chaotic. For discrete dynamical system $x_{k+1} = F(x_k), k = 0,1, \ldots,$ one can use a method presented in [34-35] to determine Lyapunov exponents. The method is based on computing the QR decomposition of the Jacobian matrix A and can be summarized as follows:

Let Q_0 be an orthogonal matrix such that $Q_0{}^T.Q_0 = I$. Now, it can be obtained the decomposition $Z_{k+1} = Q_{k+1}.R_{k+1}$ by solving $Z_{k+1} = A_k.Q_k, k = 0,1, \ldots,$ where Q_{k+1} is an orthogonal matrix and R_{k+1} is upper triangular matrix with positive diagonal elements [34]. Thus, the LCEs can be calculated as

$$\lambda_i = \lim_{k\to\infty} \frac{1}{k} \ln((R_i)_{jj}), \qquad j = 1, \ldots, m. \tag{17}$$

Now, we can obtain the Lyapunov exponents of the system by using the formula (17). The calculated LCEs of the system according to Figure 3, Figure 5 and Figure 7 are plotted in Figure 8, Figure 9 and Figure 10 respectively. It is understood from these figures that the system exhibits chaotic behavior for $a > \bar{a}$, $e > \bar{e}$ and $f > \bar{f}$.

Result and Discussion

In this paper we analyze a discrete-continuous time model describing the interactions among healthy cells, tumor cells and immune system cells. The idea of the model comes from the paper M. Itik and Banks [5]. Some numerical results are obtained for the local behavior of the model. To test these numerical results, most of the parameters values are taken from the study [5-6] in terms of consistency with the biological facts. Figure 1 shows the stable dynamics at the positive equilibrium point under the condition $a < 0.877595$ where all of the populations are exist.

For the bifurcation analysis, we select the parameters $a, e,$ and f as bifurcation parameters. Neimark-Sacker bifurcation point is obtained as $\bar{a}$ =0.877595 (Figure 2). Increasing values of the parameter a shows that both tumor cells and immune system cells populations are extinct and healthy cells tend to their carrying capacity after the chaotic dynamics (Figure 3). This result is also valid for the study [6]. Another bifurcation points are obtained as $\bar{e}$ =4.47863 and $\bar{f} = 1.32821$ (Figure 4, Figure 5, Figure 6, Figure 7). Moreover, calculating Lyapunov exponents show that chaotic dynamics occur, if the parameter values a, e, f exceed bifurcation points (Figure 8, Figure 9 and Figure 10).

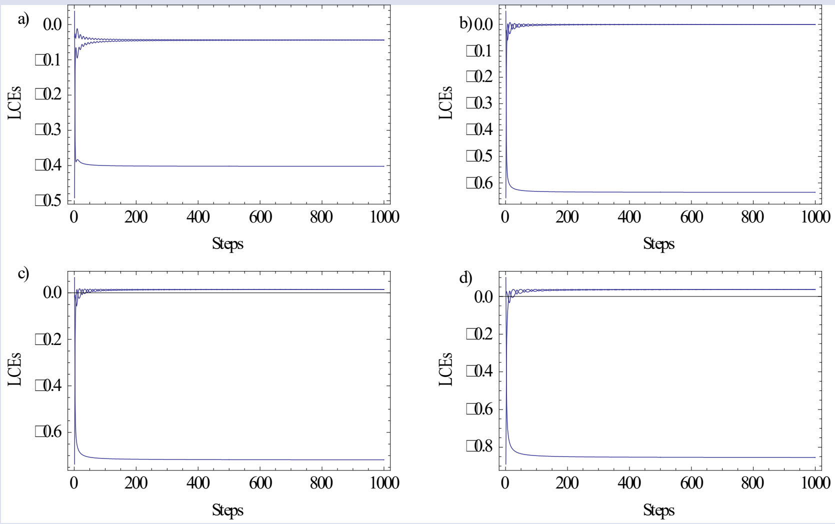

Figure 8. Converge plot of the Lyapunov spectrum for the system with respect to parameter a=1.5 (a), $\bar{a}$=0.87759 (b), a=1 (c) and r_1=1.2 (d).

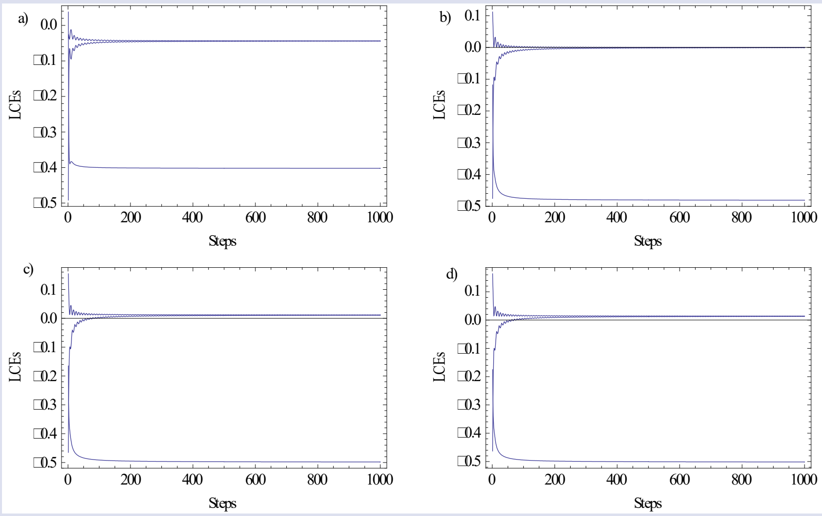

Figure 9. Converge plot of the Lyapunov spectrum for the system with respect to parameter e=3.5 (a), $\bar{e}$=4.47863 (b), e=4.9 (c) and e=5 (d).

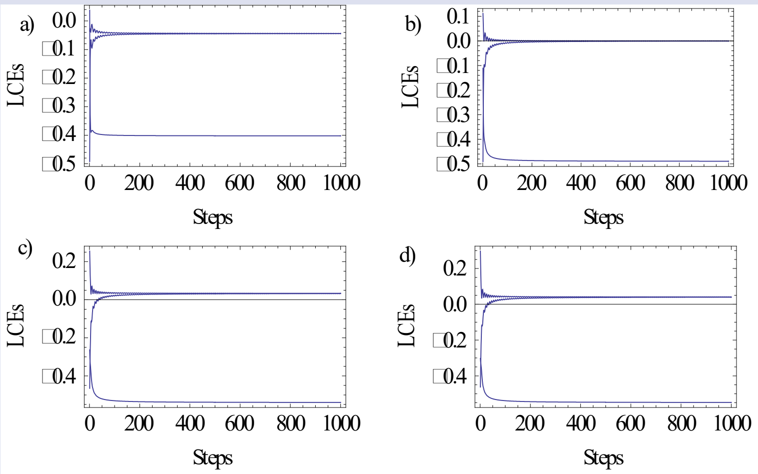

Figure 10. Converge plot of the Lyapunov spectrum for the system with respect to parameter f=1.8 (a), f̄=1.32821 (b), f=0.9 (c) and f=0.8 (d).

Conflicts of interest

There are no conflicts of interest in this work.

References

[1] Costa O.S., Molina L.M., Perez D.R., Antoranz J.C., Reyes M.C., Behavior of tumors under nonstationary therapy, *Physica D.,* 178 (2003) 242-253.

[2] Onofrio A.D., A general framework for modeling tumor-immune system competition and immunotherapy: mathematical analysis and biomedical inferences, *Physica D.,* 208 (2005) 220-235.

[3] Kuznetsov V.A., Makalkin I.A., Taylor M.A., Perelson A.S., Nonlinear dynamics of immunogenic tumors: parameter estimation and global bifurcation analysis, *Bull. Math. Biol.,* 56 (1994) 295-321.

[4] Kirschner D., Panetta J.C., Modeling immunotherapy of the tumor-immune interaction, *J. Math. Biol.*, 37 (1998) 235-252.

[5] Itık M., Banks S.P., Chaos in a three-dimensional cancer model, *Int. J. Bifurcat. Chaos.,* 20 (2010) 71-79.

[6] Galindo M.C., Nespoli C., Messias M., Hopf bifurcation, cascade of period-doubling, chaos, and the possibility of cure in a 3D cancer model, *Abstr. Appl. Anal.,* (2015) Article ID:354918.

[7] De Pillis L.G., Radunskaya A., The dynamics of an optimally controlled tumor model: A case study, *Math. Comput. Model.,* 37 (2003) 1221-1244.

[8] Sarkar R.R., Banerjee S., Cancer self remission and tumor stability- a stochastic approach, *Math. Biosci.,* 196 (2005) 65-81.

[9] Cho H., Lewis A.L, Storey K.M., Byrne H.M., Designing experimental conditions to use the Lotka–Volterra model to infer tumor cell line interaction types, *J. Theor. Biol.,* 559 (2023) 111377.

[10] Pham H., Mathematical Modeling the Time-Delay Interactions between Tumor Viruses and the Immune System with the Effects of Chemotherapy and Autoimmune Diseases, *Mathematics,* 10(5) (2022) 756.

[11] Das A., Dehingia K., Sarmah H.K., Hosseini K., Sadri K., Salahshour S., Analysis of a delay-induced mathematical model of cancer, *Adv. Cont. Discr. Mod.,* 15 (2022).

[12] Abernathy Z., Abernathy K., Stevens J., A mathematical model for tumor growth and treatment using virotherapy, *AIMS Math.,* 5(5) (2020) 4136-4150.

[13] Rihan F.A., Alsakaji H.J., Kundu S., Mohamed O., Dynamics of a time-delay differential model for tumour-immune interactions with random noise, *Alex. Eng. J.,* 61(12) (2022) 11913-11923.

[14] Bekker R.A., Kim S., Thomas S.P., Enderling H., Mathematical modeling of radiotherapy and its impact on tumor interactions with the immune system, *Neoplasia*, 28 (2022) 100796.

[15] Hussain J., Bano Z., Ahmed W., Shahid S., Analysis of stochastic dynamics of tumor with drug interventions, *Chaos Soliton Fract.,* 157 (2022) 111932.

[16] Hu X., Jang S.R.J., Dynamics of tumor–CD4–cytokine–host cells interactions with treatments, *Appl. Math. Comput.,* 321, (2018) 700-720.

[17] Rivaz A., Azizian M., Soltani M., Various Mathematical Models of Tumor Growth with Reference to Cancer Stem Cells: A Review, *Iran J. Sci. Technol. Trans. Sci.,* 4 (2019) 687–700.

[18] Kemwoue F.F., Deli V., Mendimi J.M., Gninzanlong C.L., Tagne J.F., Atangana J., Dynamics of cancerous tumors under the effect of delayed information: mathematical and electronic study, *Int. J. Dynam. Control.,* (2022).

[19] Banerjee S., Sarkar R.R., Delay-induced model for tumor-immune interaction and control of malignant tumor growth, *Biosystems.,* 91 (2008) 268-288.

[20] Busenberg, S., Cooke, K.L., Models of vertically transmitted diseases with sequential continuous dynamics, Nonlinear Phenomena in Mathematical Sciences, Academic Press, New York (1982).

[21] Cooke K.L., Györi I., Numerical approximation of the solutions of delay-differential equations on an infinite interval using piecewise constant argument, *Comput. Math. Appl.,* 28 (1994) 81-92.

[22] Shah S.M., Wiener J., Advanced differential equations with piecewise constant argument deviations*, Int. J. Math. Math. Sci.,* 6 (1983) 671–703.

[23] Akhmet M., Nonlinear hybrid continuous/discrete-time models, Atlantis Press (2011).

[24] Karakoç F., Oscillation of a first order linear impulsive delay differential equation with continuous and piecewise constant arguments, *Hacet. J. Math. Stat.,* 47(3) (2018) 601- 613.

[25] Chiu, K.S. Jeng, J.C. Stability of oscillatory solutions of differential equations with general piecewise constant arguments of mixed type, Math. *Nachrichten.,* 288(10) (2015) 1085-1097.

[26] Oztepe G.S., Existence and qualitative properties of solutions of a second order mixed type impulsive differential equation with piecewise constant arguments, *Hacet. J. Math. Stat.,* 46(6) (2017) 1077 – 1091.

[28] Ozturk, I., Bozkurt, F., Gurcan, F.: Stability analysis of a mathematical model in a microcosm with piecewise constant arguments, *Math. Biosci.*, 240 (2012) 85-91.

[29] Bozkurt F., Yousef A., Bilgil H., Baleanu D., A mathematical model with piecewise constant arguments of colorectal cancer with chemo-immunotherapy, *Chaos Soliton Fract.,* 168 (2023) 113207.

[30] Gurcan, F., Kartal, S., Ozturk, I., Bozkurt, F.: Stability and bifurcation analysis of a mathematical model for tumor-immune interaction with piecewise constant arguments of delay, *Chaos Soliton. Fract.* 68 (2014) 169-179.

[31] Kartal, S., Gurcan, F.: Stability and bifurcations analysis of a competition model with piecewise constant arguments, *Math. Methods. Appl. Sci.* 38 (2015) 1855-1866.

[27] Oztepe G.S., Karakoç F., Bereketoglu H., Oscillation and Periodicity of a Second Order Impulsive Delay Differential Equation with a Piecewise Constant Argument, *Commun. Math.,* 25 (2017) 89–98.

[32] Li, X., Mou, C., Niu, W., Wang, D.: Stability analysis for discrete biological models using algebraic methods, *Math. Comput. Sci.* 5 (2011) 247-262.

[33] Khan, A.Q., Qureshi, S.M., Alotaibi, A.M.: Bifurcation analysis of a three species discrete-time predator-prey model, *Alex. Eng. J.* 61 (2022) 2853-7875.

[34] Sandri, M.: Numerical Calculation of Lyapunov Exponents, *The Mathematica Journal.*, 6 (1996) 78-84.

[35] Benettin, G., Galgani, L., Giorgilli, A., Strelcyn, J.M.: Lyapunov characteristic exponents for smooth dynamical systems and for Hamiltonian systems: A method for computing all of them. Part 2: Numerical application, 15 (1980) 21-30.