A DISCRETE DYNAMICS APPROACH TO TUMOR SYSTEM

T. SAEED[1], KAMEL DJEDDI[2], JUAN L.G. GUIRAO[1,3,4], HAMED H. ALSULAMI[1], MOHAMMED SH. ALHODALY[1]

Abstract. In this paper, we present the cancer system in the continuous state with some numerical results. After, we present some discretization methods a system, for example Euler method, Taylor series expansion method and Runge-Kutta method, and we apply them to the cancer system and we study the stability of the fixed points in the discrete cancer system and we prove that the discrete cancer system is chaotic, using the new version of Marotto's theorem at a fixed point. Finally, we present numerical simulations, for example, Lyapunov exponents and bifurcations diagrams.

1. Introduction

Cancer is a group of diseases involving abnormal cells growth. These cells may form a mass called a tumor. A malignant tumor means it can spread into, or invade, nearby tissues. Therefore, at these tumor grow, some cancer cells can break off and travel to distant places in the body and form new tumors far from the original tumor. A benign tumor means the tumor can grow, but will not spread.

Many authors have used mathematical models to describe The main components of this model are the interactions of three types of cells, cancer cells with healthy host cells and cells of the immune system. These interactions may lead to different outcomes. There are many existing reviews of mathematical systems of tumor see [4, 1, 2, 3].

Actually discrete-time systems described are more reasonable than the continuous-time systems when populations have nonoverlapping generations. Moreover, using discrete-time models is more efficient for computation and numerical simulations. By analysis, it is proved that the discrete-time system has different properties and structures compared with the continuous one and these results reveal far richer dynamical behaviors of the discrete-time system compared to the continuous one see [9, 5, 4, 8].

Chaos can be found in many biological systems. Chaotic systems have an intrinsic property in their dynamics that can result in slight perturbations of the initial conditions leading to behavior, over time, that is unlike the behavior of the trajectory though the original initial condition. Often it is said that a chaotic system exhibits sensitive dependence on initial conditions. Chaotic behaviors are complex, irregular and generally undesirable in biological systems. In many scientific system applications require a methods mathematicals that minimizes complexity and eliminates undesired behaviors in order to improve performance of the system. However, chaotic In the analysis of chaotic system, two representation types confront to us which are continuous time and discrete time modelling. In digital applications, discrete time modelling must be used in order to process the system behavior onto digital processors. For this purpose, there are many discretization methods in literature.

1991 *Mathematics Subject Classification.* 37C80 · 37G15 · 37C30.

Key words and phrases. Cancer system, Discretization methods, Stability, Chaos, Lyapunov exponents, Bifurcation.

When using a discretization method is used to study a system, it is definitely considered by the mathematician whether the method performs in accuracy and resource utilization or not. In this study, Taylor series expansion, Euler and Runge-Kutta discretization methods are used to represent differential equations of tumor chaotic system in discrete time domain. Selection of the optimal discretization method is important to have desired performance. Forward Euler and Runge-Kutta numerical integration methods are used for simulating the chaotic behavior of multi-scroll chaotic oscillator and results are compared.

In this paper, we consider on the model presented by Pillis and Radunskaya see [1]. In the second section after the introduction we present the cancer system in the continuous state with some numerical results. In the third section we present some discretization methods a system, for example Euler method, Taylor series expansion method and Runge-Kutta method, and we apply them to the cancer system. In the fourth section, we study the stability of the fixed points in the discrete cancer system. In the fifth section, we prove that the discrete cancer system is chaotic, using the new version of Marotto's theorem at a fixed point. In sixth section, we present numerical simulations, for example, Lyapunov exponents and bifurcations diagrams. Finally, we present a conclusion.

2. The continuous version of the cancer system

Aims model to describe the competition and the interaction among tumour cells, healthy host cells and effector immune cells. Essentially, cancer models which include interacting cell , we focus on cells near the tumor site, populations are based on the prey– predator models and law terms exponential growth. Although the previous models are simple, they may explain some important aspects of the growth dynamics of cancer according with other cells of the body such as immune system cells and surrounding tissue cells. We will present of this section to describe the biological tumor system which is given in the form of ordinary differential equation as follows

$$\begin{cases} \dot{N} = \rho_2 N\left(1 - b_2 N\right) - c_4 N T, \\ \dot{T} = \rho_1 T\left(1 - b_1 T\right) - c_2 T I - c_3 T N, \\ \dot{I} = \left(\dfrac{\rho I T}{\alpha + T}\right) - c_1 I T - d_1 I + s, \end{cases} \tag{1}$$

where N denotes the healthy host cells, T denotes the number of cancer cells and I denotes effector immune cells, and $\rho_1, \rho_2, \rho, b_1, b_2, \alpha, c_1, c_2, c_3, c_4, d_1$ and s are positive parameters see [1, 2, 4]. Here ρ_1 represents the growth rate of cancer cells in the absence of any effect from other cell populations with maximum carrying capacity $1/b_1$, c_2 and c_3 refers to the cancer cells killing rate by the healthy host cells and effector cells respectively, ρ_2 represents the growth rate of healthy host cells with maximum carrying capacity $1/b_2$, c_4 represents the rate of inactivation of the healthy cells by cancer cells. The rate of recognition of the cancer cells by the immune system depends on the antigenicity of the cancer cells. Since this recognition process is very complex, in order to keep the model simple, assume the stimulation of the immune system depends directly on the number of cancer cells with positive constants ρ and α. The effector cells are inactivated by the cancer cells at the rate c_1 as well as they die naturally at the rate d_1 and s is a constant influx of immune cells.

For simplify the study of this system (1). we reduce the number of parameters by introducing this change of variables:

$$x = b_1 T, y = b_2 N, z = \frac{I}{\alpha} \text{ et } \tau = \rho_1 t,$$

and the new parameters:

$$a_{12} = \frac{c_2}{b_2 \rho_1}, r_2 = \frac{\rho_1}{\rho_2}, a_{21} = \frac{c_4}{b_1 \rho_1}, r_3 = \frac{\rho}{\rho_1},$$

$$k_3 = \alpha b_1, a_{31} = \frac{c_1}{b_1 \rho_1}, a_{13} = \frac{\alpha c_3}{\rho_1} \text{ and } d_3 = \frac{d_1}{\rho_1}.$$

then the system (1) is converted to

$$\begin{cases} \dot{x} = x(1-x) - a_{12}xy - a_{13}xz, \\ \dot{y} = r_2 y(1-y) - a_{21}xy, \\ \dot{z} = r_3 \left(\dfrac{xz}{x + k_3} \right) - a_{31}xz - d_3 z. \end{cases} \quad (2)$$

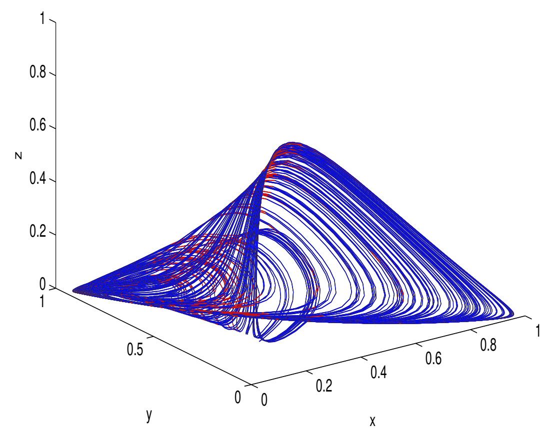


FIGURE 1. Cancer attractor with $x_0 = 0.1, y_0 = 0.1,\ z_0 = 0.1$ and parameter values $r_2 = 0,6, r_3 = 4,5, a_{12} = 1, a_{21} = 1,5, a_{13} = 2,5, a_{31} = 0,2, k_3 = 1, d_3 = 0,5$.

The Lyapunov exponents of system (2) are computed to be $\lambda_1 = 0.021909, \lambda_2 = -0.00085097$ and $\lambda_3 = -0.54025$. The Lyapunov dimension for system (2) is $D_L = 2 + \frac{\lambda_1 + \lambda_2}{\lambda_3} \simeq 2.04$.

3. Discretization Methods

3.1. **Euler Discretization Method.** The simplest method for approximating the solution of (2) is called the Euler Method named after Leonhard Euler see [9, 15]. The expression of Euler method is given in Eq. 3 and discretized model is expressed in Eq. 4.

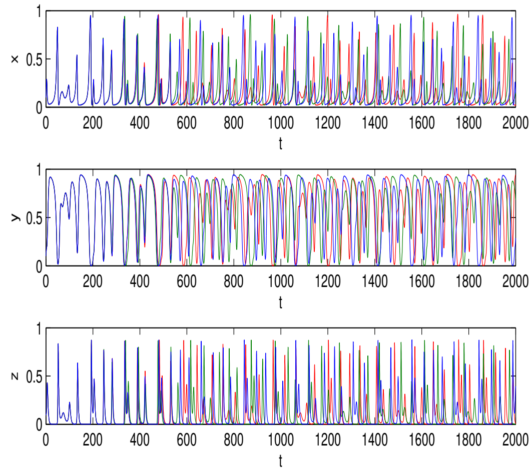
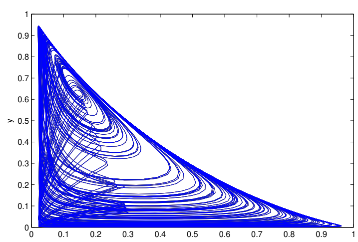
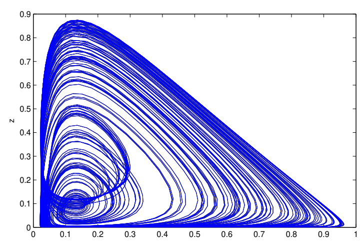


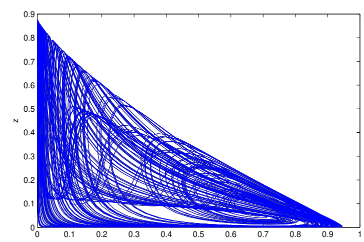
FIGURE 2. The time series for the system (2) with $x_0 = 0.1, y_0 = 0.1$, $z_0 = 0.1$ and parameter values $r_2 = 0,6, r_3 = 4,5, a_{12} = 1, a_{21} = 1,5, a_{13} = 2,5, a_{31} = 0,2, k_3 = 1, d_3 = 0,5$.



(a) Normal cells : $X = x$.



(b) Effector immune cells : $X = y$.



(c) Tumor cells : $X = z$.

FIGURE 3. Two-dimensional projections of the phase portraits onto the $X-Y$ by each of the variables x, y and z.

$$\begin{cases} \dot{x}(t) = \dfrac{x(t+h)-x(t)}{h} \\ \dot{y}(t) = \dfrac{y(t+h)-y(t)}{h} \\ \dot{z}(t) = \dfrac{z(t+h)-z(t)}{h}, \end{cases} \quad (3)$$

$$\begin{cases} x_{k+1} = \left(x_k(1-x_k) - a_{12}x_k y_k - a_{13}x_k z_k\right).h + x_k, \\ y_{k+1} = \left(r_2 y_k(1-y_k) - a_{21}x_k y_k\right).h + y_k, \\ z_{k+1} = \left(r_3\left(\dfrac{x_k z_k}{x_k + k_3}\right) - a_{31}x_k z_k - d_3 z_k\right).h + z_k. \end{cases} \quad (4)$$

3.2. **Taylor Series Expansion Method.** In this section, we give a numerical method to compute numerical solutions of (2) by using a Taylor polynomial see [15, 8] for $x(t+h), y(t+h)$ and $z(t+h)$ as follows:

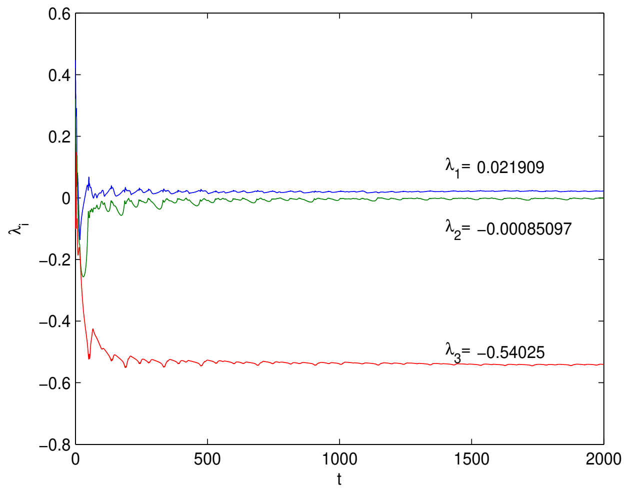


FIGURE 4. The Lyapunov exponents of system (2) with $x_0 = 0.1, y_0 = 0.1$, $z_0 = 0.1$ and parameter values $r_2 = 0,6, r_3 = 4,5, a_{12} = 1, a_{21} = 1,5, a_{13} = 2,5, a_{31} = 0,2, d_3 = 0,5$.

$$\begin{cases} x(t+h) = x(t) + \sum_{m+1}^{\infty} \frac{1}{m!}.h^m.x^{(m)} \\ y(t+h) = y(t) + \sum_{m+1}^{\infty} \frac{1}{m!}.h^m.y^{(m)} \\ z(t+h) = z(t) + \sum_{m+1}^{\infty} \frac{1}{m!}.h^m.z^{(m)} \end{cases} \quad (5)$$

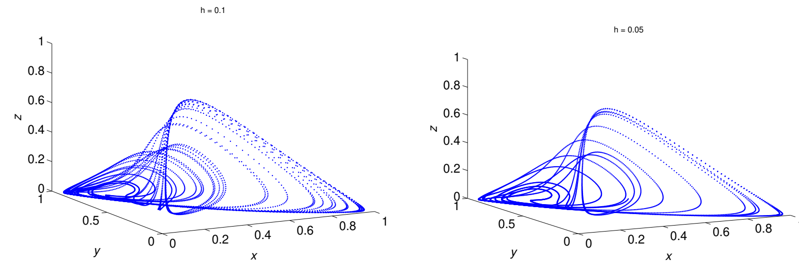
Taylor series expansion method is executed for $m = 2$ and h. In this situation, discrete time state equations of the cancer system with Taylor series expansion method is obtained as follow.

$$\begin{cases} x_{k+1} = x_k + h.\dot{x}_k + \frac{1}{2}.h^2.\ddot{x}_k \\ y_{k+1} = y_k + h.\dot{y}_k + \frac{1}{2}.h^2.\ddot{y}_k \\ z_{k+1} = z_k + h.\dot{z}_k + \frac{1}{2}.h^2.\ddot{z}_k, \end{cases} \quad (6)$$

where

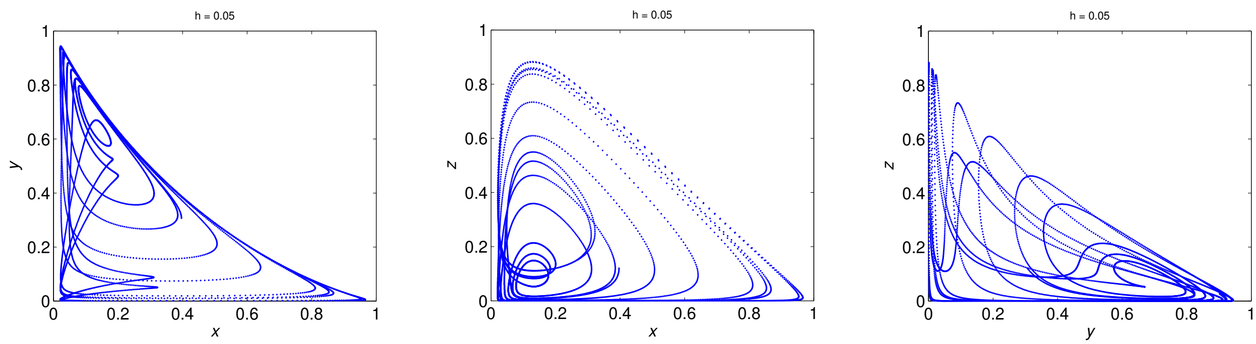
$$\begin{cases} \dot{x}_k = x_k(1-x_k) - a_{12}x_k y_k - a_{13}x_k z_k, \\ \dot{y}_k = r_2 y_k(1-y_k) - a_{21}x_k y_k, \\ \dot{z}_k = r_3\left(\frac{x_k z_k}{x_k + k_3}\right) - a_{31}x_k z_k - d_3 z_k. \end{cases} \quad (7)$$

3.3. **Runge-Kutta Discretization Method.** The Runge-Kutta method of four-order is executed for h. In this situation, the discrete cancer system (4 with the Runge-Kutta method of four-order see [16, 13] are obtained as follows.



(a) $h = 0.1$. (b) $h = 0.05$.

FIGURE 5. Discrete cancer system attractor with methode of euler.



(a) Host cells: $X = x$. (b) Immune effector cells: $X = y$. (c) Tumor cells: $X = z$.

FIGURE 6. Projection of the attractor to system (1) onto the planes by each of the variables x, y and z.

$$
\begin{aligned}
\alpha_1 &= h.f(x_k, y_k, z_k) = h.x_{k+1},\\
l_1 &= h.g(x_k, y_k, z_k) = h.y_{k+1},\\
m_1 &= h.p(x_k, y_k, z_k) = h.z_{k+1},\\
\alpha_2 &= h.f((x_k + \tfrac{1}{2}\alpha_1, (y_k + \tfrac{1}{2}l_1), (z_k + \tfrac{1}{2}m_1)),\\
l_2 &= h.g((x_k + \tfrac{1}{2}\alpha_1, (y_k + \tfrac{1}{2}l_1), (z_k + \tfrac{1}{2}m_1)),\\
m_2 &= h.p((x_k + \tfrac{1}{2}\alpha_1, (y_k + \tfrac{1}{2}l_1), (z_k + \tfrac{1}{2}m_1)),\\
\alpha_3 &= h.f((x_k + \tfrac{1}{2}\alpha_2, (y_k + \tfrac{1}{2}l_2), (z_k + \tfrac{1}{2}m_2)),\\
l_3 &= h.g((x_k + \tfrac{1}{2}\alpha_2, (y_k + \tfrac{1}{2}l_2), (z_k + \tfrac{1}{2}m_2)),\\
m_3 &= h.p((x_k + \tfrac{1}{2}\alpha_2, (y_k + \tfrac{1}{2}l_2), (z_k + \tfrac{1}{2}m_2)),\\
\alpha_4 &= h.f((x_k + \alpha_3), (y_k + l_3), (z_k + m_3)),\\
l_4 &= h.g((x_k + \alpha_3), (y_k + l_3), (z_k + m_3)),\\
m_4 &= h.p((x_k + \alpha_3), (y_k + l_3), (z_k + m_3)),\\
x_{k+1} &= x_k + \tfrac{1}{6}(\alpha_1 + 2\alpha_2 + 2\alpha_3 + \alpha_4),\\
y_{k+1} &= y_k + \tfrac{1}{6}(l_1 + 2l_2 + 2l_3 + l_4),\\
z_{k+1} &= z_k + \tfrac{1}{6}(m_1 + 2m_2 + 2m_3 + m_4).
\end{aligned}
\tag{8}
$$

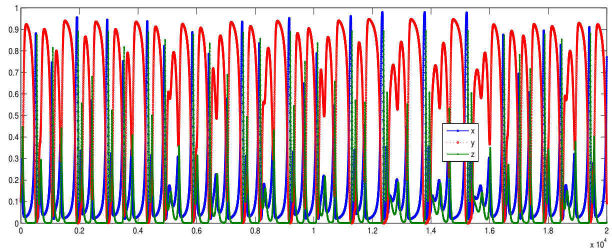


FIGURE 7. Time responses of the system (4) whith the parameters given in (18) and $h = 0.1$.

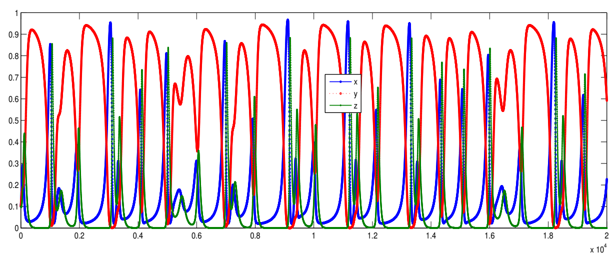


FIGURE 8. Time responses of the system (4) whith the parameters given in (18) and $h = 0.05$.

4. Stability analysis for discrete cancer system

In order to find the fixed points, the three discrete cancer equations are set to x, y, z coordinates of each fixed point that determined by solving the following equations:

$$\begin{cases} x = \left(x(1-x) - a_{12}xy - a_{13}xz\right).h + x, \\ y = \left(r_2 y(1-y) - a_{21}xy\right).h + y, \\ z = \left(r_3\left(\dfrac{xz}{x+k_3}\right) - a_{31}xz - d_3 z\right).h + z. \end{cases}$$

In order to obtain the fixed points of the system (4), we set

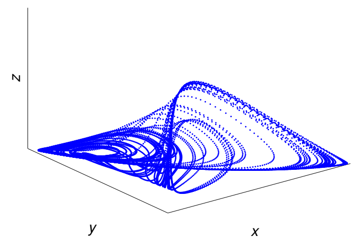
$$\begin{cases} x = 0, \\ x = 1 - a_{12}y - a_{13}z. \end{cases} \tag{9}$$

$$\begin{cases} y = 0, \\ y = \dfrac{1}{r_2} - \dfrac{a_{21}}{r_2}x. \end{cases} \tag{10}$$

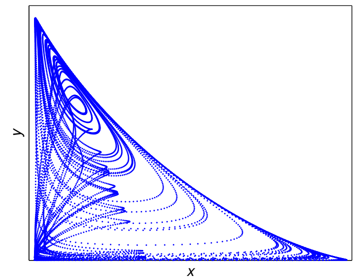
$$\begin{cases} z = 0, \\ x^2 + \left(k_3 + \dfrac{d_3 - r_3}{a_{31}}\right)x + \dfrac{k_3 d_3}{a_{31}} = 0. \end{cases} \tag{11}$$

The solution of Equations (9)-(11) together yields to six fixed points. We discuss their local behavior according to their biological relevance. Now, we study the stability of these fixed points.

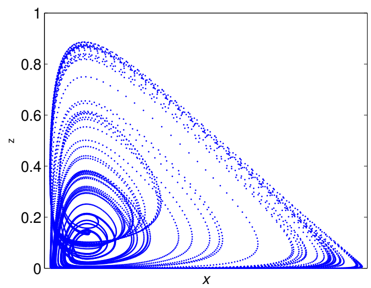
In this paper, we study h in interval $[0.01, 0.1]$



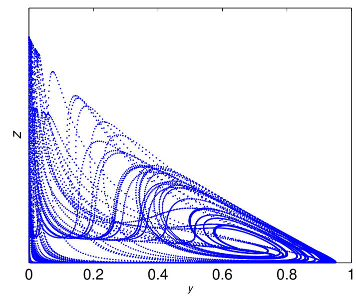
(a) Strange attractor



(b) Host cells: $X = x$.



(c) Immune effector cells: $X = y$.



(d) Tumor cells: $X = z$.

FIGURE 9. (a) Strange attractor of system (6) with Taylor method and $h = 0.1$. (b), (c) and (d) Projection of the attractor to system (6) onto the planes by each of the variables x, y and z.

(1) For the first fixed point is trivial and given as $v_1 = (0, 0, 0)$, the corresponding eigenvalues are $\lambda_1 = h + 1$, $\lambda_2 = hr_2 + 1$ and $\lambda_3 = -hd_3 + 1$. Since h is small positive and all the parameters are positive and $\mid \lambda_i \mid < 1$ $(i = 1, 2)$, therefore,

Proposition 4.1.

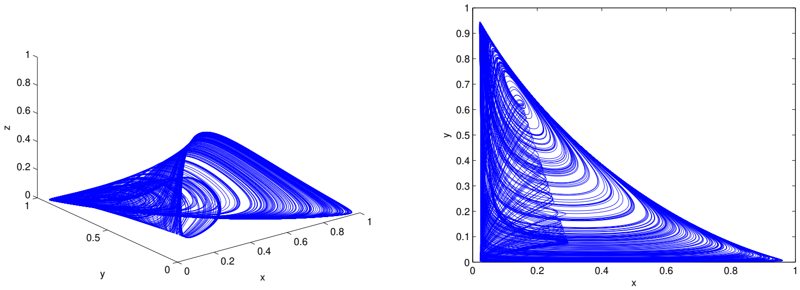
- *If* $hd_3 > 2$ *then* $\mid \lambda_3 \mid > 1$, *we have a saddle at this fixed point.*
- *If* $hd_3 < 2$ *then* $\mid \lambda_3 \mid < 1$, *we have a node stable at this fixed point.*

(2) The second fixed point is obtained as $v_2 = (0, 1, 0)$, the Jacobian matrix evaluated at v_2 is given by

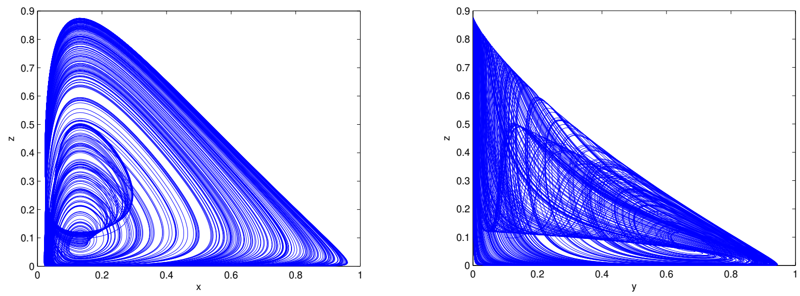
$$J(v_2) = \begin{bmatrix} (-a_{12} + 1)\, h + 1 & 0 & 0 \\ -a_{21} h & -r_2 h + 1 & 0 \\ 0 & 0 & -d_3 h + 1 \end{bmatrix} \tag{12}$$

Clearly, $J(v_2)$ has eigenvalues $\lambda_1 = 1 - r_2 h$, $\lambda_2 = 1 + (-a_{12} + 1)\, h$ and $\lambda_3 = 1 - d_3 h$. where $h \in [0.01, 01]$. In fact, in biology they r_2, d_3 are smaller than h^{-1}. Then $\mid \lambda_1 \mid < 1$ and $\mid \lambda_3 \mid < 1$. Stability of this fixed point depends on the value of parameter a_{12}, if $a_{12} < 1$ then $\lambda_2 > 1$, this fixed point has two stable and one unstable eigenvalue. Therefore, we have a saddle at v_2 and if $a_{12} > 1$ then $\lambda_2 < 1$, this fixed point has three stable eigenvalue. Therefore, we have a node at this fixed point.

and if $a_{12} = 1$ then $\lambda_2 = 1$, as a consequence, study fails to give any information about the stability of v_2. In our numerical simulations, we obtained very different results by altering the value of a_{12} as it also affects some other fixed. Especially we have observed that chaotic



(a) Strange attractor (b) Host cells: $X = x$.



(c) Immune effector cells: $X = y$. (d) Tumor cells: $X = z$.

FIGURE 10. (a) Strange attractor of system (8) with Runge-Kutta 4 method and $h = 0.1$. (b), (c) and (d) Projection of the attractor to system (8) onto the planes by each of the variables x, y and z.

dynamics start close to $a_{12} = 1$. The selection of $a_{12} < 1$ yields different dynamical behavior such as converging to a stable spiral. However, in this study, we shall focus on the parameter a_{12} where we observe the chaotic attractor.

(3) The third fixed point is $v_3 = (1, 0, 0)$ the Jacobian matrix evaluated at v_2 is given by

$$J(v_3) = \begin{bmatrix} -h+1 & -a_{12}h & -a_{13}h \\ 0 & (r_2 - a_{21})\,h + 1 & 0 \\ 0 & 0 & \left(\dfrac{r_3}{1+k_3} - a_{31} - d_3\right) h + 1 \end{bmatrix} \tag{13}$$

The eigenvalues of the Jacobian matrix (13) at this fixed point are obtained as $\lambda_1 = -h+1$, $\lambda_2 = (r_2 - a_{21})\,h + 1$ and $\lambda_3 = \left(\dfrac{r_3}{1+k_3} - a_{31} - d_3\right) h + 1$. Then $\mid \lambda_1 \mid < 1$. We obtain λ_1 is stable, and λ_2, λ_3 are stabe with the selected parameters.

(4) The fourth fixed point is $v_4 = (x^*, 0, z^*)$. The Jacobian matrix evaluated at v_4 is given by

$$J(v_4) = \begin{pmatrix} L_{11} & L_{12} & L_{13} \\ 0 & L_{22} & 0 \\ L_{31} & 0 & L_{33}, \end{pmatrix}$$

where

$$L_{11} = (1 - a_{13}\overline{z} - 2\,\overline{x})\,h + 1,$$

$$L_{12} = -a_{12}\overline{x}h,$$
$$L_{13} = -a_{13}\overline{x}h,$$
$$L_{22} = (r_2 - a_{21}\overline{x})\, h + 1,$$
$$L_{31} = \left(\frac{r_3\overline{z}}{\overline{x}+k_3} - \frac{r_3\overline{x}\overline{z}}{(\overline{x}+k_3)^2} - a_{31}\overline{z}\right) h,$$
$$L_{33} = \left(\frac{r_3\overline{x}}{\overline{x}+k_3} - a_{31}\overline{x} - d_3\right) h + 1.$$

The eigenvalues of the Jacobian matrix at this point are

$$\lambda_1 = L_{22} = (r_2 - a_{21}\overline{x})\, h + 1, \tag{14}$$

$$\lambda_{2,3} = \frac{1}{2}\left[(L_{11}+L_{33}) \mp \sqrt{(L_{11}-L_{33})^2 + 4L_{31}L_{13}}\right]. \tag{15}$$

(i): If $(L_{11}-L_{33})^2 + 4L_{31}L_{13} > 0$ we have three real eigenvalues.

(ii): If $(L_{11}-L_{33})^2 + 4L_{31}L_{13} < 0$ we have at this point has one real and two complex eigenvalues stable with the selected parameter sets.

And the characteristic equation of the Jacobian matrix $J(v_4)$ can be written as

$$P(\lambda) = \lambda^3 + A_2\lambda^2 + A_1\lambda + A_0, \tag{16}$$

where

$$A_0 = -L_{33}L_{22}L_{11} + L_{31}L_{13}L_{22},$$
$$A_1 = L_{11}L_{22} + L_{11}L_{33} - L_{13}L_{31} + L_{33}L_{22},$$
$$A_2 = -L_{33} - L_{22} - L_{11}.$$

According to the Jury conditions [7], in order to find the asymptotically stable region of v_4, we need to find the region that satisfy the following conditions:

$$P(1) > 0, P(-1) < 0, \mid A_0 \mid < A_n, \mid B_0 \mid > \mid B_{n-1} \mid$$

where $B_k = \begin{vmatrix} A_0 & A_{n-k} \\ A_n & A_k \end{vmatrix}$. Then

$$P(1) = 1 + A_2 + A_1 + A_0,$$
$$P(-1) = -1 + A_2 - A_1 + A_0,$$

According the relations $P(1) > 0, P(-1) < 0, \mid A_0 \mid < A_n, \mid B_0 \mid > \mid B_{n-1} \mid$, we have that $\mid A_0 \mid < 1$, $\mid A_0 + 1 \mid > \mid A_1 \mid$ and $\mid A_0 - 1 \mid\mid A_0 + A_1 + 1 \mid > \mid A_0A_1 - A_2 \mid$.

(5) The fifth fixed point is $v_5 = \left(\frac{r_2(a_{12}-1)}{a_{12}a_{21}-r_2}, \frac{a_{12}-r_2}{a_{12}a_{21}-r_2}, 0\right)$ where $a_{12}a_{21} - r_2 \neq 0$. The Jacobian matrix of the system (4) at v_5 is given by

$$J(v_5) = \frac{1}{q}\begin{pmatrix} M_{11} & M_{12} & M_{13} \\ M_{21} & M_{22} & 0 \\ 0 & 0 & M_{33} \end{pmatrix},$$

where $q = a_{12}a_{21} - r_2$ and

$$M_{11} = -h{a_{12}}^2 - r_2ha_{12} + 2\,r_2h + 2\,q$$

$$M_{12} = -a_{12}r_2\left(a_{12}-1\right)h$$
$$M_{13} = -a_{13}r_2\left(a_{12}-1\right)h$$
$$M_{21} = -a_{21}\left(a_{12}-r_2\right)h$$
$$M_{22} = -ha_{12}a_{21}r_2 + hqr_2 - 2\,r_2ha_{12} + r_2ha_{21} + q$$
$$M_{33} = \left(\frac{r_3r_2q\left(a_{12}-1\right)}{r_2\left(a_{12}-1\right)+qk_3} - a_{31}r_2\left(a_{12}-1\right) - d_3q\right)h + q$$

And the characteristic equation of the Jacobian matrix $J(v_6)$ can be written as

$$P^*\left(\lambda\right) = \lambda^3 + B_2\lambda^2 + B_1\lambda + B_0 = 0.$$

where

$$B_0 = -\frac{M_{33}\left(M_{22}M_{11} - M_{21}M_{12}\right)}{q^3},$$
$$B_1 = \frac{M_{22}M_{11} + M_{33}M_{11} - M_{21}M_{12} + M_{33}M_{22}}{q^2},$$
$$B_2 = -\frac{M_{33} + M_{22} + M_{11}}{q}.$$

The eigenvalues of the Jacobian matrix at this fixed point are

$$\lambda_1 = \frac{M_{33}}{q},$$

and

$$\lambda_{2,3} = \frac{1}{2q}\left(M_{22} + M_{11} \mp \sqrt{\Delta}\right),$$

where $\Delta = {M_{11}}^2 - 2\,M_{22}M_{11} + 4\,M_{21}M_{12} + {M_{22}}^2$,

(6) The sixth fixed point is a nontrivial $v_6 = (x^*, y^*, z^*)$. The Jacobian matrix of the system (4) at v_6 is given by

$$J(v_6) = \left(\begin{array}{ccc} S_{11} & S_{12} & S_{13} \\ S_{21} & S_{22} & 0 \\ S_{31} & 0 & S_{33} \end{array}\right), \tag{17}$$

where

$$S_{11} = \left(-a_{12}y^* - a_{13}z^* - 2\,x^* + 1\right)h + 1,$$
$$S_{12} = -a_{12}x^*h,$$
$$S_{13} = -a_{13}x^*h, S_{21} = -a_{21}y^*h,$$
$$S_{22} = -2\,y^*hr_2 - x^*ha_{21} + hr_2 + 1$$
$$S_{31} = z^*\left(a_{31}\left(x^*\right)^2 + 2\,a_{31}x^*k_3 + a_{31}{k_3}^2 - r_3k_3\right)h(x^* + k_3)^2,$$
$$S_{33} = \left(\frac{r_3x^*}{x^* + k_3} - a_{31}x^* - d_3\right)h + 1.$$

And the characteristic equation of the Jacobian matrix $J(v_6)$ can be written as

$$P^*\left(\lambda\right) = \lambda^3 + C_2\lambda^2 + C_1\lambda + C_0 = 0.$$

According to the Jury conditions [7], in order to find the asymptotically stable region of v_6, we need to find the region that satisfy the following conditions:

$$P^*(1) > 0, \quad P^*(-1) < 0, \quad \mid C_0 \mid < C_n, \quad \mid D_0 \mid > \mid D_{n-1} \mid,$$

where $D_k = \begin{vmatrix} C_0 & C_{n-k} \\ C_n & C_k \end{vmatrix}$.

Since

$$P^*(1) = 1 + C_2 + C_1 + C_0,$$
$$P^*(-1) = -1 + C_2 - C_1 + C_0,$$

Proposition 4.2. *The fixed point v_6 is asymptotically stable if the following conditions are satisfied:*
$\mid C_0 \mid < 1$, $\mid C_0 + 1 \mid > \mid C_1 \mid$ *and* $\mid C_0 - 1 \mid \mid C_0 + C_1 + 1 \mid > \mid C_0 C_1 - C_2 \mid$.

5. Chaotic discrete cancer system

Marotto presented result mathematical of discrete chaos to n-dimensional dynamical systems, there exists an error in the condition of the original Marotto theorem, it has been corrected and modified this important theorem by Shi and Chen see [11]. In this section, we shall prove that the system (4) exhibit chaotic dynamics with $h = 0.05$ or $h = 0.1$ the parameters following

$$\begin{gathered} a_{12} = 1, a_{13} = 2.5, a_{21} = 1.5, a_{31} = 0.2, d_3 = 0.5, \\ k_3 = 1, r_2 = 0.6, r_3 = 4.5. \end{gathered} \tag{18}$$

Theorem 5.1. *Marotto theorem given in* [10]*. consider the following n-dimensional discrete system:*

$$v_{n+1} = F(v_n), \quad n = 0, 1, 2, ..., \tag{19}$$

where $v_n \in \mathbb{R}^n$ and $F : \mathbb{R}^n \to \mathbb{R}^n$ is continuous. Let $B_r(v)$ denote the ball in $\mathbb{R}^n$ of radius r centred at point v and $\overline{B}_r(v)$ its interior. Also, let $\| v \|$ be the usual euclidean norm of v in $\mathbb{R}^n$. Then, (1) $\Rightarrow$ (2)

- **(1):** *All eigenvalues of the Jacobian $DF(v)$ of map (11) at the fixed point v are greater than one with euclidean norm.*
- **(2):** *There exist some $s > 1$ and $r > 0$, such that for all $u, v \in B_r(v)$,*

$$\| F(u) - F(v) \| > s \| u - v \| .$$

Shi and Chen (2004b), proved that there exists an error in the condition of the original Marotto theorem which has been corrected and a modified version of this theorem is given as follows:

Theorem 5.2. *(A Modified Version of the Marotto Theorem see* [11]*)*
Consider the n-dimensional discrete dynamical system:

$$v_{n+1} = F(v_n), \quad n = 0, 1, 2, ..., \tag{20}$$

where $v_n \in \mathbb{R}^n$ and $F : \mathbb{R}^n \to \mathbb{R}^n$, suppose that the system (12) has a fixed point v^*. Assume that

(1): *F is continuously differentiable in some neighbourhood of v^* and all the eigenvalues of $DF(v^*)$ have absolute values larger than 1, which implies that there exists a positive constant r and a euclidean norm, such that F is expanding in $B_r(v^*)$ in euclidean norm, and*

(2): *v^* is a snap-back repeller of F with $F^m(v_0) = v^*$ for some $v_0 \in B_r(v^*)$, $v_0 \neq v^*$ and some positive integer m. Furthermore, F is continuously differentiable in some neighbourhoods of $v_0, v_1, ..., v_{m-1}$, respectively, and $\det[DF(v_j)] \neq 0$ for $0 \leq j \leq m-1$, where $v_j = F(v_{j-1})$.*

Then, all the results of the Marotto Theorem hold.

5.1. **A Proof the chaos of the discrete cancer system (4). Step 1.** Let $v_2 = (0, 1, 0)$ the fixed point of the system (4).

$F(v_2)$ given in Theorem 5.2 of system (4), its continuously differentiable in $B_r(v_2)$ for some $r > 0$. The Jacobian matrix evaluated at the fixed point v_2 is given in (12).

And (12) has eigenvalues $\lambda_1 = 0.94$, $\lambda_2 = 1$ and $\lambda_3 = 0.95$.

Step 2. According to, Definition of (Theorem 5.2) snap-back repeller, we need to find one point $u \in B_r(v_2)$, such that $u \neq v_2$, $F^M(u) = v_2$, and $\det\left[DF^M(u)\right] \neq 0$, for some positive integer M.

In fact, we have

$$\begin{cases} (x(1-x) - a_{12}xy - a_{13}xz).h + x = x_1 \\ (r_2y(1-y) - a_{21}xy).h + y = y_1 \\ \left(\frac{r_3xz}{x+k_3} - a_{31}xz - d_3z\right).h + z = z_1 \end{cases} \tag{21}$$

$$\begin{cases} (x_1(1-x_1) - a_{12}x_1y_1 - a_{13}x_1z_1).h + x = 0 \\ (r_2y_1(1-y_1) - a_{21}x_1y_1).h + y = 1 \\ \left(\frac{r_3x_1z_1}{x_1+k_3} - a_{31}x_1z_1 - d_3z_1\right).h + z = 0 \end{cases} \tag{22}$$

Finally, the system (4) is verify the conditions of Theorem 5.2 with the parameters given in (18) and $h = 0.1$, the fixed point v_2 has two stable and one unstable eigenvalue. Therefore, we have a saddle at this fixed point and there exists a point $u = (-1.1903, 0.7563, 2.2828)$ solution of (21) and (22), satisfies that $F^2(u) = v_2$ and $\det(F(u)) = -6.6158 \neq 0$ $\det(F^2(u)) = 27.9025 \neq 0$. Thus, v_2 is a snap-back repeller.

6. Numerical simulations

6.1. **Lyapunov exponents.** In this subsection we calculated the Lyapunov exponents. The Lyapunov exponents for a discrete n-dimensional systems is given in [14] the following definition:

Definition 6.1. Consider the n-dimensional discrete dynamical system:

$$v_{k+1} = F(v_k), v_k \in \mathbb{R}^n, k = 0, 1, 2, ... \tag{23}$$

where $F : \mathbb{R}^n \to \mathbb{R}^n$, is the vector field associated with map (15), let $J(v)$be its Jacobian evaluated at v, also define the matrix: $T_p(v_0) = J(v_{p-1})J(v_{p-2})...J(v_1)J(v_0)$.

Moreover, let $J_i(v_0, l)$ be the modulus of the i^{th} eigenvalue of the l^{th} matrix $T_p(v_0)$ where $i = 1, 2, ..., n$ and $p = 0, 1, 2, ...$.

Now, the Lyapunov exponents of a n-dimensional discrete time models are defined by: $\lambda_i(v_0) = \ln\left(\lim_{p\to+\infty}\left(J_i(v_0,\ p)^{\frac{1}{p}}\right)\right)$.

Therefore, the Lyapunov exponents of system (4) with parameters given in (18) and $h = 0.1$ are computed to be $\lambda_1 = 0.95003, \lambda_2 = -1.0546$ and $\lambda_3 = -5.6174$. The Lyapunov dimension for system (4) equal dimension of space state that is to say equal 3. Because the sum of the Lyapunov exponents is negative $\lambda_1 + \lambda_2 + \lambda_3 < 0$.

And the Lyapunov exponents of system (4) with parameters given in (18) and $h = 0.05$ are computed to be $\lambda_1 = 0.97478, \lambda_2 = -1.0238$ and $\lambda_3 = -5.5697$.

If at least one Lyapunov exponent is positive for some control parameters values (18), then the system (4) is chaotic at that control parameters.

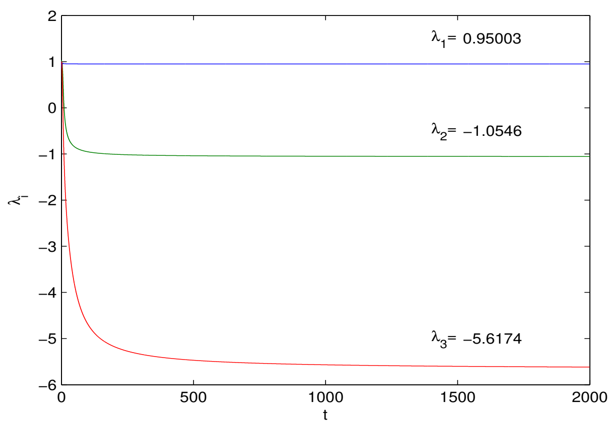


FIGURE 11. Lyapunov exponents of system (4) with parameters given in (18) and $h = 0.1$

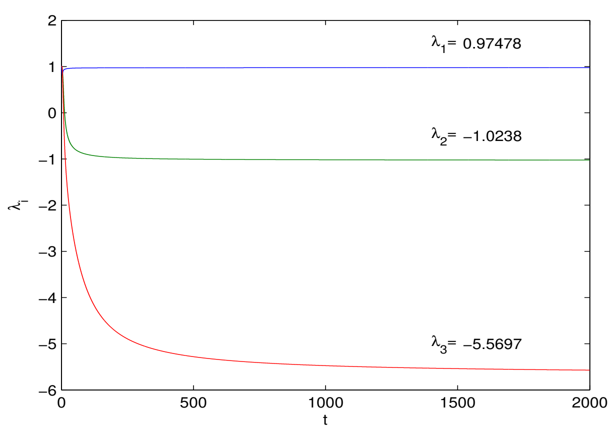
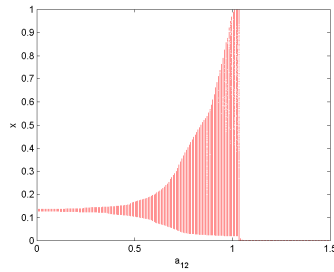
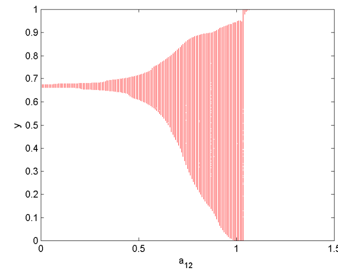


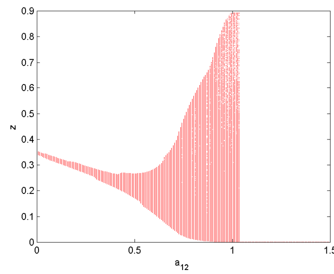
FIGURE 12. Lyapunov exponents of system (4) with parameters given in (18) and $h = 0.05$



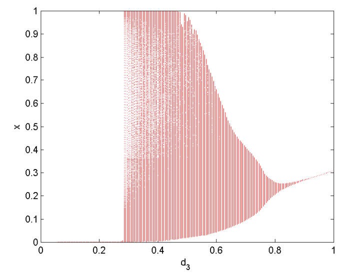
(a) The $a_{12} - x$ plane



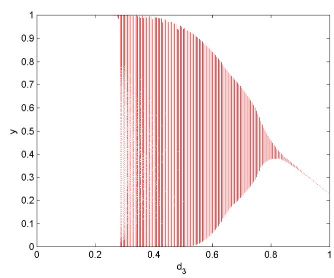
(b) The $a_{12} - y$ plane



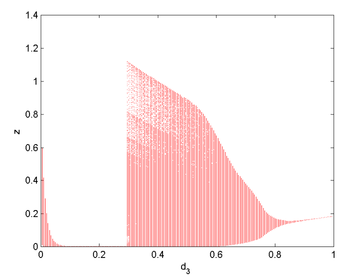
(c) The $a_{12} - z$ plane



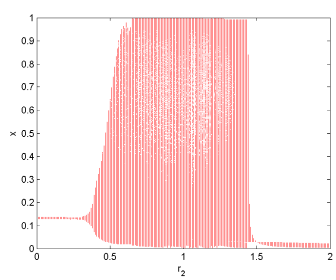
(d) The $d_3 - x$ plane



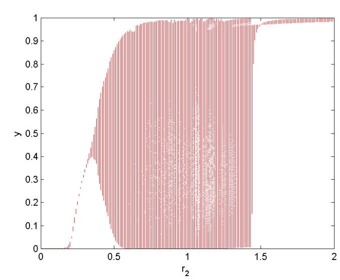
(e) The $d_3 - y$ plane



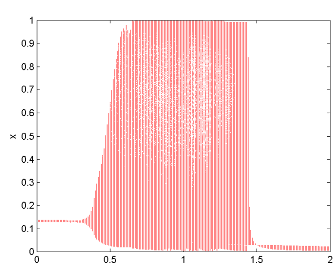
(f) The $d_3 - z$ plane



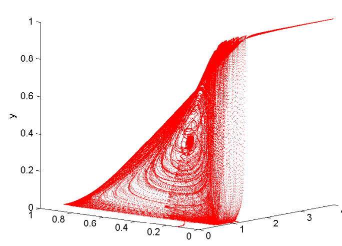
(g) The $r_2 - x$ plane



(h) The $r_2 - y$ plane



(i) The $r_2 - z$ plane



(j) The (r_2, x, y) space

FIGURE 13. Bifurcations diagrams of system (4) with the parameters given in (18) and $h = 0.1$.

7. Conclusion

This paper is contributed to the study of the discrete cancer system with numerical and theoretical methods. As a result of this study, it is clearly understood that Runge-Kutta method has the best method for discretization of the cancer system. And also, Taylor series expansion method It has good accuracy. As for the Euler discretization method, it is less accurate but easy to perform. The simulation plots suggest that a cancer system and simulation study reveals that dynamical pattern of cancer system is dependent on the initial parametric values of the system variables. Hence, for getting a system prediction of a cancer system, accurate quantification of the parametric values of different variables is important. By using this study would help biologists to understand and appreciate the essence of measurement accuracy in different biological experiments and the power of inferences through experiment.
As a future work, we will study the control of chaos in cancer system as well as we will generalize this system in fourth dimension.

Funding

This research work was funded by Institutional Fund Projects under grant no. (IFPHI-228-130-2020). Therefore authors gratefully acknowledge technical and financial support from the Ministry of Education and King Abdulaziz University, DSR, Jeddah, Saudi Arabia.

References

[1] L. G. De Pillis and A. Radunskaya, The dynamics of an optimally controlled tumor model: A case study. Mathematical and computer modelling, 37(11) (2003), 1221 − 1244.
[2] L. G. De Pillis, A. E. Radunskaya and C. L. Wiseman, A validated mathematical model of cell-mediated immune response to tumor growth. Cancer research, 65(17) (2005), 7950 − 7958.
[3] R. Eftimie, et al, Bifurcations and chaotic dynamics in a tumour-immune-virus system. Mathematical Modelling of Natural Phenomena, 11(5) (2016), 65 − 85.
[4] D. Kamel, Dynamics in a Discrete -Time Three Dimensional Cancer System, International Journal of Applied Mathematics, 49(4) (2019), 1 − 7.
[5] B. Karakaya et al, Selection of optimal numerical method for implementation of Lorenz Chaotic system on FPGA, International Advanced Researches and Engineering Journal, 2 (2) (2018), 147 − 152.
[6] L. Kocarev, et al, Discrete chaos-i: Theory. IEEE Transactions on Circuits and Systems I: Regular Papers, 53(6) (2006), 1300 − 1309.
[7] J. D. Murray, Mathematical Biology I: An Introduction, 3rd ed., Interdiscip. Appl. Math. 17, Springer, New York, 2002.
[8] S. Sarif Hassan, Computational Complex Dynamics Of The Discrete Lorenz System. arXiv e-prints, (2016) arXiv-1604.
[9] A. G. Selvam, D. Roslin and J. Rajendran, A discrete model of Rössler system, International Journal of Advanced Technology in Engineering and Science, 02 (2014).
[10] Y. Shi and G. Chen, Chaos of discrete dynamical systems in complete metric spaces. Chaos, Solitons & Fractals, 22(3) (2004), 555 − 571.
[11] Y. Shi and G. Chen, Discrete chaos in Banach spaces. Science in China Series A: Mathematics, 48(2) (2005), 222 − 238.
[12] Y. Shi and G. Chen, Introduction to anti-control of discrete chaos: theory and applications. Philosophical Transactions of the Royal Society A: Mathematical, Physical and Engineering Sciences, 364(1846) (2006), 2433 − 2447.
[13] W. Song and J. Liang, Difference equation of Lorenz system, International Journal of Pure and Applied Mathematics, 83 (1) (2013), 101 − 110.

[14] A. Wolf, et al, Determining Lyapunov exponents from a time series. Physica D: nonlinear phenomena, 16(3) (1985), 285 – 317.

[15] G. Yuksel and O. R. Isik, Numerical analysis of Backward-Euler discretization for simplified magnetohydrodynamic flows, Applied Mathematical Modelling, 39 (7) (2015), 1889 – 1898.

[16] K. Zwarycz-Makles and D. Majorkowska-Mech, Gear and Runge-Kutta Numerical Discretization Methods in Differential Equations of Adsorption in Adsorption Heat Pump, Applied Sciences, 8 (12) (2018), 2437.

[1] Nonlinear Analysis and Applied Mathematics (NAAM)-Research Group, Department of Mathematics, Faculty of Science, King Abdulaziz University, P.O. Box 80203, Jeddah 21589, Saudi Arabia

Email address: tsalmalki@kau.edu.sa, jlgarcia@kau.edu.sa, hhaalsalmi@kau.edu.sa, malhuthali@kau.edu.sa

[2] Department of Mathematics and Computer Science, Laboratory of Dynamical Systems and Control, Larbi Ben MHidi University, 4000 Oum El Bouaghi., Algeria

Email address: djeddi.kamel@gmail.com, kamel.djeddi@univ-oeb.dz

[3] Departamento de Matemáca Aplicada y Estadística. Universidad Politécnica de Cartagena, 30202-Cartagena, Región de Murcia, Spain, Spain

Email address: juan.garcia@upct.es

[4] Lab Theor Cosmology, Int Centre of Gravity and Cosmos , TUSUR, 634050 Tomsk Russia