Chaos in a Discrete Cancer Model

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Abstract

In this paper, we construct and analyse a discrete cancer mathematical model. Essential dynamic properties such as positivity and boundedness of solutions are discussed. Using the Lyapunov stability theorem, we prove that one of the tumor-free equilibria is globally asymptotically stable. Furthermore, the discrete model exhibits chaos for certain parameter values and this is supported by the existence of a positive Lyapunov exponent. Numerical simulations are performed to demonstrate our analytical results.

Keywords

Cancer model
Lyapunov exponents
Lyapunov stability theorem
Nonstandard finite difference method

1 Introduction

Cancer is often regarded as one of the most feared diseases worldwide because of the pain and sorrow associated with some of its treatments and untimely deaths it causes. According to [1], cancer accounted for about 9 million deaths globally in 2016. In the study of mechanisms of carcinogenesis [2–6], this disease is partly understood to be a consequence of some damage to the DNA of an organism, which fails to successfully undergo DNA repair and restoration; see for instance [3, 4, 7–9]. The damaged DNA undergoes mutation which results in genetic changes. Cell division may be affected by these changes in ways that lead to excessive and abnormal growth of cells known as tumor [4, 10–12], which could be classified as either benign or malignant. A benign tumor is regarded as less harmful unless it is situated on a vital organ such as the brain, whereas a malignant tumor is regarded as cancerous because it may progress to invade the nearby tissues and ultimately metastasise to other organs. Pathogenesis, progression and management of cancer are very complicated and this is one of the reasons why interdisciplinary research in this area has become imperative. We acknowledge that clinical trials are very essential for the study of diseases, however, they are often costly [13] and sometimes take a relatively long time to yield reliable results [14].

Probably as either an alternative or a supplement, mathematical modeling has proven to be a useful tool for understanding disease dynamics and less costly. Mathematical models are widely used to study the dynamics of complex systems such as disease transmission [11, 15–18], electric circuits [19, 20], population dynamics [21, 22], and the list is endless. Several cancer mathematical models have been developed; see for instance [23–31] for the continuous setting and [32–37] for the discrete setting. In particular, the discrete model in [33] is without a doubt inspired by the model in [25]; however, it has a pitfall of producing negative discrete solutions. Since human cells, or any other cells for that matter, are non-negative quantities, it is essential that the discrete solutions remain in the biologically feasible domain. In this paper, our main objective is to construct a discrete cancer model by considering the parameters in the continuous model [25]. This research is necessary because statistical data about systems is observed and collected in discrete time [15]. Furthermore, in order to simulate continuous time models, the time interval needs to be discretised first.

Most importantly, our discrete model should preserve the essential dynamic properties of its continuous counterpart and precisely the following: (i) equlibria (ii) positivity and boundedness of solutions (iii) global asymptotic stability (GAS) of tumor-free equilibrium (iv) chaotic attractor.

A lot of work involving the construction of schemes that capture certain dynamic properties has been done, namely: dynamically consistent schemes [16, 38–40], bifurcation preserving [41, 42], and many more which are not mentioned here. However, the works on numerical schemes that preserve the GAS property are relatively few; see for instance [43–45] and their analysis often poses a great challenge [46]. Our discrete model will not only preserve GAS property, but also preserve chaos; and this is an important contribution of this paper. This is critical because chaos is defined as the sensitive dependence of a dynamical system on initial conditions; see for instance [47–50]. Meaning that, in the context of cancer, a small change of some clinical parameters might result to a change from a stable clinical state of the patient to an unstable one. This phenomenon could be one of the major contributors to the causes of unexpected deaths of patients who are in hospices and palliative care units; see for instance [51–53].

The remainder of the paper is organised as follows: In Section 2 we introduce the continuous model [25]. We construct the discrete model and analyse it in Section 3. Section 4 is devoted to numerical simulations. The conclusion is in Section 5.

2 The continuous model

A nondimensionalised cancer mathematical model is studied in [12, 25, 54] and it reads as follows:

$$\frac{dx_1}{dt} = x_1(1-x_1) - a_{12}x_1x_2 - a_{13}x_1x_3, \tag{1}$$

$$\frac{dx_2}{dt} = r_2x_2(1-x_2) - a_{21}x_1x_2, \tag{2}$$

$$\frac{dx_3}{dt} = \frac{r_3x_1}{x_1+k_3}x_3 - a_{31}x_1x_3 - d_3x_3, \tag{3}$$

which is a dynamical system in the nonnegative orthant:

$$\Gamma_C = \left\{(x_1,x_2,x_3) \in \mathbb{R}^3 | 0 \le x_1 \le 1, 0 \le x_2 \le 1, x_3 \ge 0\right\}.$$

The system in (1)-(3) represents the rate of change in tumor cell (x_1), heathy cell (x_2), and effector cell (x_3) populations, respectively. The model parameters a_{12}, a_{13}, a_{21} and a_{31} account for a destructive interaction between the tumor cells and the other cells [9, 55–57], while r_2, r_3 and k_3 reflect the impact of growth stimulation on the healthy cells and the immune cells. Immune cells die naturally at the rate d_3.

Table 1 Nonlocal discretisations of System (1)-(3).

Eq.(1)	$x_1^2 \longrightarrow x_1^{i+1}x_1^i$
	$a_{12}x_1x_2 \longrightarrow a_{12}x_1^{i+1}x_2^i$
	$a_{13}x_1x_3 \longrightarrow a_{13}x_1^{i+1}x_3^i$
Eq.(2)	$r_2x_2^2 \longrightarrow r_2x_2^{i+1}x_2^i$
	$a_{21}x_1x_2 \longrightarrow a_{21}\left(2x_1^{i+1}x_2^{i+1} - x_1^{i+1}x_2^i\right)$
Eq.(3)	$\frac{r_3x_1x_3}{x_1+k_3} \longrightarrow \frac{r_3x_1^{i+1}x_3^i}{x_1^{i+1}+k_3}$
	$a_{31}x_1x_3 \longrightarrow a_{31}\left(2x_1^{i+1}x_3^{i+1} - x_1^{i+1}x_3^i\right)$
	$d_3x_3 \longrightarrow d_3x_3^{i+1}$

3 The discrete model

In this Section we construct a discrete system which preserves nonnegativity and boundedness of solutions, equilibria, global asymptotic stability and chaos of the system in (1)-(3). Let the step size $h=\frac{t_N-t_0}{N}$, where $t_i=ih$ $(i=0,1,2,\cdots,N)$ and $x_k^{i+1}\approx x_k(t_i+h)$ $(k=1,2,3)$.

We introduce the nonlocal discretisations in Table 1; see for instance [39,41,58–61]. If we substitute these nonlocal discretisations into the system in (1)-(3), we then obtain the following system of difference equations:

$$\begin{cases} x_1^{i+1}-x_1^i= x_1^i-x_1^{i+1}x_1^i-a_{12}x_1^{i+1}x_2^i-a_{13}x_1^{i+1}x_3^i, \\ x_2^{i+1}-x_2^i= r_2x_2^i-r_2x_2^{i+1}x_2^i-a_{21}\left(2x_1^{i+1}x_2^{i+1}-x_1^{i+1}x_2^i\right), \\ x_3^{i+1}-x_3^i= \dfrac{r_3x_1^{i+1}x_3^i}{x_1^{i+1}+k_3}-a_{31}\left(2x_1^{i+1}x_3^{i+1}-x_1^{i+1}x_3^i\right)-d_3x_3^{i+1} \end{cases} \tag{4}$$

System (4) can be expressed in explicit form:

$$\begin{cases} x_1^{i+1}= \dfrac{2x_1^i}{1+x_1^i+a_{12}x_2^i+a_{13}x_3^i}, \\ x_2^{i+1}= \dfrac{(1+r_2+a_{21}x_1^{i+1})x_2^i}{1+r_2x_2^i+2a_{21}x_1^{i+1}}, \\ x_3^{i+1}= \dfrac{(1+\frac{r_3x_1^{i+1}}{x_1^{i+1}+k_3}+a_{31}x_1^{i+1})x_3^i}{1+2a_{31}x_1^{i+1}+d_3}. \end{cases} \tag{5}$$

3.1 Positivity and boundedness

Theorem 1. *If $0\le x_k^i\le 1$ $(k=1,2,3)$, then $0\le x_k^{i+1}\le 1$ $(k=1,2)$ and there exists $\delta=\frac{1+r_3}{1+d_3}$ such that $0\le x_3^{i+1}<\delta$ whenever $d_3<1+2r_3$.*

Proof. We consider,

$$x_1^{i+1}=\frac{2x_1^i}{1+x_1^i+a_{12}x_2^i+a_{13}x_3^i}\le\frac{2x^i}{1+x_1^i}\le 1.$$

Then,

$$\begin{aligned} x_2^{i+1} &= \frac{(1+r_2+a_{21}x_1^{i+1})x_2^i}{1+r_2x_2^i+2a_{21}x_1^{i+1}} \\ &\le \frac{1+r_2x_2^i+a_{21}x_1^{i+1}}{1+r_2x_2^i+2a_{21}x_1^{i+1}} \\ &\le 1. \end{aligned}$$

Finally,

$$\begin{aligned} x_3^{i+1} &= \frac{(1+\frac{r_3x_1^{i+1}}{x_1^{i+1}+k_3}+a_{31}x_1^{i+1})x_3^i}{1+2a_{31}x_1^{i+1}+d_3}. \\ &\le \frac{1+r_3+a_{31}x_1^{i+1}}{1+d_3+2a_{31}x_1^{i+1}} \\ &\le \frac{1+r_3}{1+d_3}. \end{aligned}$$

The proof is complete.

Lemma 2. *The discrete System (5) is a dynamical system defined on the region*

$$\Gamma_D = \left\{(x_1^i, x_2^i, x_3^i) \in \mathbb{R}^3 | 0 \le x_1^i \le 1,\ 0 \le x_2^i \le 1,\ 0 \le x_3^i \le \delta,\ d_3 < 1 + 2r_3\right\}. \tag{6}$$

3.2 Equilibria

The steady state of system (5) satisfies the following equations:

$$x_1 = \frac{2x_1}{1 + x_1 + a_{12}x_2 + a_{13}x_3}, \tag{7}$$

$$x_2 = \frac{(1 + r_2 + a_{21}x_1)x_2}{1 + r_2x_2 + 2a_{21}x_1}, \tag{8}$$

$$x_3 = \frac{(1 + \frac{r_3x_1}{x_1 + k_3} + a_{31}x_1)x_3}{1 + 2a_{31}x_1 + d_3}. \tag{9}$$

From the equations in (7)-(9), we obtain the system of equations in (10)-(12), respectively. And these should be solved simultaneously.

$$Eq.(7) \Rightarrow \begin{cases} x_1 = 0, \\ x_1 = 1 - a_{12}x_2 - a_{13}x_3. \end{cases} \tag{10}$$

$$Eq.(8) \Rightarrow \begin{cases} x_2 = 0, \\ x_2 = \dfrac{1 - a_{21}x_1}{r_2}. \end{cases} \tag{11}$$

$$Eq.(9) \Rightarrow \begin{cases} x_3 = 0, \\ x_1^2 + (k_3 + \dfrac{d_3}{a_{31}} - \dfrac{r_3}{a_{31}})x_1 + \dfrac{d_3k_3}{a_{31}} = 0. \end{cases} \tag{12}$$

Remark 1. The equations in (10)-(12) are similar to the equations obtained in [25] for the continuous model.

Table 2 Fixed points of Model (5)

$E_0 = (0,0,0)$
$E_1 = (0,1,0)$
$E_2 = (1,0,0)$
$E_3 = (1-\phi-\psi, 0, \phi+\psi)$
$E_4 = (1+\phi-\psi, 0, \frac{\psi-\phi}{a_{13}})$
$E_5 = (\frac{r_2(a_{12}-1)}{a12a_{21}-r_2}, \frac{a_{21}-r_2}{a_{12}a_{21}-r_2}, 0)$
$E_6 = (1-\phi-\psi, \frac{r_2+a_{21}(\phi+\psi-1)}{r_2}, \frac{r_2(a_{12}-1)+(\phi+\psi-1)(a_{12}a_{21}-r_2)}{r_2a_{13}})$
$E_7 = (1+\psi-\phi, \frac{r_2-a_{21}(1+\phi-\phi)}{r_2}, \frac{r_2(1-a_{12})+(1+\phi-\psi)(a_{12}a_{21}-r_2)}{r_2a_{13}})$

Lemma 3. *Model (5) has 8 fixed points and are given in Table 2, where we assume that*

$$\psi = \frac{a_{31}(k_3+2)+d_3-r_3}{2a_{31}} \text{ and } \phi = \frac{\sqrt{(a_{31}k_3+d_3-r_3)^2 - 4a_{31}d_3k_3}}{2a_{31}} \in \mathbb{R}. \tag{13}$$

Remark 2. The equilibria E_0, E_1 and E_2 are always nonnegative. However, E_j $(j = 3, \cdots, 7)$ might have negative components for certain parameter values. As a result, the study of the stability of these equilibria is a complicated task and may be done numerically.

3.3 Stability analysis

The tumor free equilibria are of great interest because they mean the eradication of cancer. Hence, in this Subsection we study the stability of the fixed point E_1.

Theorem 4. *If $a_{12} > 1$, then the fixed point E_1 is locally asymptotically stable.*

Proof. Let $f_j\left(x_1^i, x_2^i, x_3^i\right)$ $(j = 1,2,3)$ denote the Right Hand Side of System (5) corresponding to x_j^{i+1}, respectively. The corresponding Jacobian matrix J evaluated at E_1 is given by the equation

$$J(E_1) = \begin{pmatrix} \frac{2}{a_{12}+1} & 0 & 0 \\ -\frac{2a_{21}}{(a_{12}+1)(r_2+1)} & 1-\frac{r_2}{r_2+1} & 0 \\ 0 & 0 & \frac{1}{d_3+1} \end{pmatrix}, \tag{14}$$

where

$$J_{kj} = \frac{\partial f_k}{\partial x_j} \ (j = 1,2,3) \text{ and } (k = 1,2,3). \tag{15}$$

The eigenvalues of $J(E_1)$ are $\lambda = diag[J(E_1)]$. Clearly, if $a_{12} > 1$, then all the eigenvalues are nonzero and have magnitudes less than 1. Hence, the fixed point E_1 is locally asymptotically stable [62]. ■

Theorem 5. *Let $\Gamma_L = \left\{(x_1^i, x_2^i, x_3^i) \in \mathbb{R}^3 | 0 < x_1^i \leq 1, x_2^i = 1, 0 < x_3^i \leq 1\right\}$. If $a_{12} > 1$, then the fixed point E_1 is globally asymptotically stable with respect to Γ_L.*

Proof. Let $V_i = V(x_1^i, x_2^i, x_3^i) = x_1^i$ be a Lyapunov function [69, pp. 450–453]. The function V satisfies $V : \Gamma_L \to \mathbb{R}_+$ and also,

$$\Delta V_i = \frac{2x_1^i}{1 + x_1^i + a_{12}x_2^i + a_{13}x_3^i} - x_1^i$$

Table 3 Model parameters used in simulation [25] .

a_{21}	a_{13}	a_{31}	r_2	r_3	k_3	d_3
1.5	2.5	0.2	0.6	4.5	1	0.5

$$= \frac{x_1^i(1 - a_{12}x_2^i) - \left(x_1^i\right)^2 - a_{13}x_1^i x_3^i}{1 + x_1^i + a_{12}x_2^i + a_{13}x_3^i}.$$

Note that $\Delta V_i < 0$ if $a_{12} > 1$ and $x_2^i = 1$. Also, $\Delta V_i(E_1) = 0$. By the Lyapunov stability theorem [69, pp. 453], the proof is complete. ■

3.4 Chaos and Lyapunov exponents

We introduce the method in [63] that will be used to calculate Lyapunov exponents of the discrete system (5). Lyapunov exponents are numerical values that are used to determine chaotic behaviour of attractors; see for instance [25, 63]. Nonchaotic attractors have only nonpositive Lyapunov exponents, whereas chaotic attractors have at least one positive Lyapunov exponent. Let

$$x^i = (x_1^i, x_2^i, x_3^i) \quad \text{and} \quad G = J(x^0)J(x^1)\cdots J(x^M), \tag{16}$$

where J is defined in Eq. (15). If $\lambda_1, \lambda_2, \lambda_3$ are the eigenvalues of the matrix G in Eq. (16), then the Lyapunov exponents (LE) of system (5) are

$$LE_j = \frac{1}{M} \ln |\lambda_j| \ , \ (j = 1,2,3). \tag{17}$$

The Lyapunov dimension [25] is given by

$$d_L = j + \frac{\sum_{n=1}^{j} LE_n}{|LE_{j+1}|} \tag{18}$$

where j satisfies the condition that

$$\sum_{n=1}^{j} LE_n > 0 \quad \text{and} \quad \sum_{n=1}^{j+1} LE_n < 0. \tag{19}$$

4 Simulations

In this Section we use numerical illustrations to confirm theoretical findings. In all our simulations we will use the parameter values in Table 3 with varying a_{12}.

Example 1. To validate Theorem 4, we use $a_{12} = 1.2$ and the initial values $x^0 = (0.1, 0.8, 0.1)$. Specifically, we demonstrate that if system (5) starts close to the equilibrium point E_1, then the solution asymptotically approaches E_1. This is shown in Fig. 1. On the other hand, if we start at a point $x^0 = (0.9, 0.001, 0.001)$ that is a little further than E_1, then the solution approaches E_1 in an oscillatory manner; see Fig. 2. In this scenario, both tumor and immune cells are destroyed.

Example 2. We validate Theorem 5, by using $a_{12} = 1.2$ and four different sets of initial values $x^0 \in \Gamma_L$. Precisely, in Fig. 3 we demonstrate that for all these initial values, the solutions of system (5) will always asymptotically approach E_1.

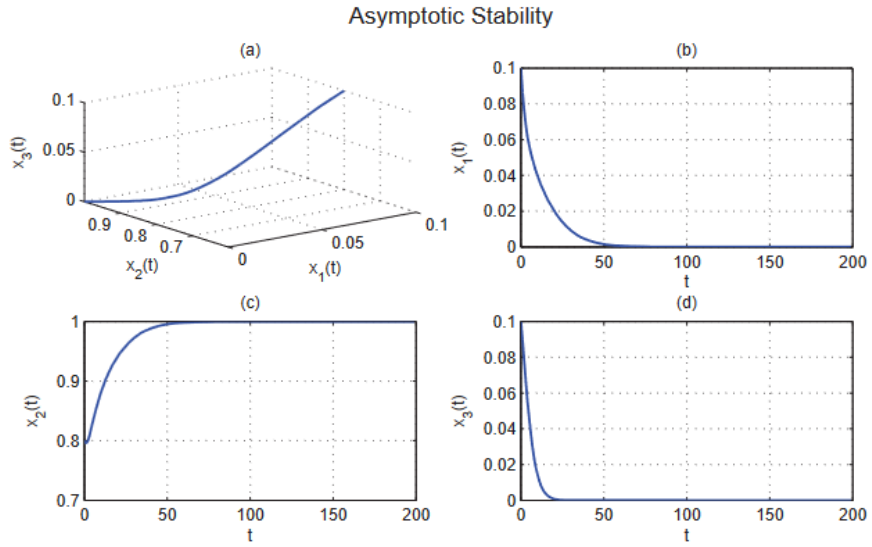

Fig. 1 To illustrate Example 1, the initial point $x^0 = (0.1, 0.8, 0.1)$, $N = 200$ and $a_{12} = 1.2$ are used with parameter values in Table 3. Solution of Model (5) monotonically converges to the equilibrium point $E_1 = (0, 1, 0)$ as seen in (a), (b), (c) and (d).

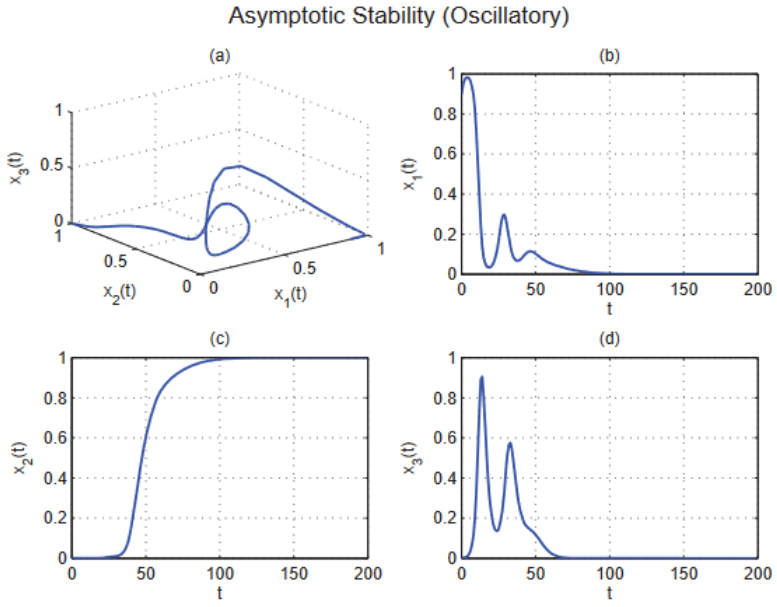

Fig. 2 We further illustrate Example 1 by starting at the initial point $x^0 = (0.9, 0.001, 0.001)$ while keeping $N = 200$ and $a_{12} = 1.2$. In this case x_1 and x_3 converge to E_1 in a slightly oscillatory manner as seen in (b) and (d), while x_2 approaches E_1 monotonically in (c). The phase portrait of $x_1 - x_2 - x_3$ is in (a).

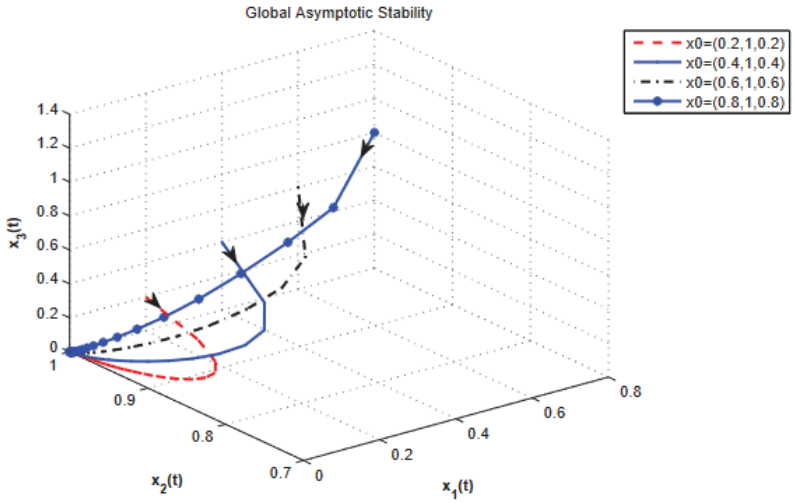

Fig. 3 To illustrate Example 2, we consider four initial points in the region Γ_L: $x^0 = (0.2, 1, 0.2)$, $x^0 = (0.4, 1, 0.4)$, $x^0 = (0.6, 1, 0.6)$ and $x^0 = (0.8, 1, 0.8)$, $N = 200$ and $a_{12} = 1.2$. All trajectories in this phase portrait converge to E_1.

Remark 3. The equilibrium point in Examples 1 and 2, together with the corresponding Figures 1-3, appear to be biologically questionable; however, this scenario makes sense if we consider the theory of super-competitor cells [56,64]; whereby one cell group has over-expression of MYC which might induce apoptosis in its comparatively MYC-deprived neighbours, see for instance [65–68]. We nevertheless, emphasise that research in this direction is ongoing and less definitive.

Example 3. To calculate the Lyapunov exponents, we consider $a_{12} = 1$, the initial values $x^0 = (0.1, 0.1, 0.1)$ and Eq. (16). Taking $M = 78$, we obtain the matrix G. Then, from Eq. (17) we get the following Lyapunov exponents:

$$LE_1 = 0.12969\ ,\ LE_2 = -0.11936\ ,\ LE_1 = -0.34887, \tag{20}$$

and the Lyapunov dimension is

$$d_L = 2 + \frac{LE_1 + LE_2}{|LE_3|} \approx 2.0296. \tag{21}$$

Clearly, $LE_1 > 0$. Hence, the following proposition:

Proposition 6. *If $a_{12} = 1$, then the discrete model (5) is chaotic for the parameter values in Table 3.*

In order to support Proposition 1, the phase portrait of a chaotic attractor, its projections onto phase spaces $x_1 - x_2$, $x_1 - x_3$ and $x_2 - x_3$ are shown in Fig. 4 (a), (b), (c) and (d), respectively. In particular, sub-figure 4(a) depicts a chaotic attractor surrounding the biologically-feasible interior equilibrium point. We can see from sub-figures (b), (c) and (d) that the trajectories of the chaotic attractor come very close to all the equilibria. Surely, getting too close to the equilibria E_0, E_2, E_3 and E_4 could cause deterioration in the clinical state of the patient because the healthy cells are depleted.

5 Conclusion

In this paper, a continuous chaotic cancer model is introduced and then its discrete counterpart is constructed and analysed. It is proven that the discrete model exhibits the following essential dynamic properties: positivity and boundedness of solutions, local and global asymptotic stability of some equilibria and chaos. Numerical simulations support all our analytical results.

These results are important because chaos is capable of changing the patients' stable clinical states to very unstable ones. Thus, more awareness of this phenomenon is recommended to the care-givers in hospices and palliative care units.

It has to be noted that analysis of discrete models is challenging and the literature is not as vast as for the continuous setting. According to the authors' knowledge, very few works exist on discrete models that preserve global asymptotic stability and chaos.

Our immediate plan is to apply the mathematical techniques in this paper to other dynamically challenging models in science and engineering.

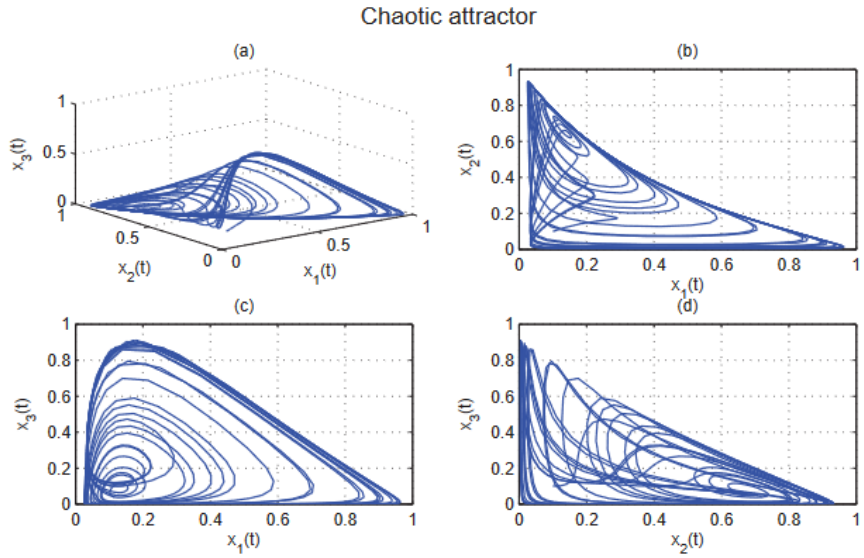

Fig. 4 In this illustration the initial point $x^0 = (0.1, 0.1, 0.1)$, $a_{12} = 1$ and $N = 1500$ are used. We demonstrate Proposition 1 in (a) where a chaotic attractor is depicted in phase space $x_1 - x_2 - x_3$. Its projections onto $x_1 - x_2$, $x_1 - x_3$ and $x_2 - x_3$ phase spaces appear in (b), (c) and (d), respectively.

6 Conflict of Interest

The authors declare that there is no conflict of interest.

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