CHAOS IN A THREE-DIMENSIONAL CANCER MODEL

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In this study, we develop a new dynamical model of cancer growth, which includes the interactions between tumour cells, healthy tissue cells, and activated immune system cells, clearly leading to chaotic behavior. We explain the biological relevance of our model and the ways in which it differs from the existing ones. We perform equilibria analysis, indicate the conditions where chaotic dynamics can be observed, and show rigorously the existence of chaos by calculating the Lyapunov exponents and the Lyapunov dimension of the system. Moreover, we demonstrate that Shilnikov’s theorem is valid in the parameter range of interest.

Keywords: Chaos; chaotic attractor; cancer model; tumour growth.

1. Introduction

Mathematical models for tumour growth have been extensively studied in the literature to understand the mechanism of the disease and to predict its future behavior. Interactions of tumour cells with other cells of the body, i.e. healthy host cells and immune system cells are the main components of these models and these interactions may yield different outcomes. Some important phenomena of the tumour progression such as tumour dormancy, creeping through, and escape from immune surveillance have been investigated by using these models. Kuznetsov et al. [1994] proposed a model of second order, governed by ordinary differential equations (ODEs), which includes the effector immune cell and the tumour cell populations. They demonstrated that even with two cell populations, these models can provide very rich dynamics depending on the system parameters and explained some very important aspects of the stages of cancer progression.

This model has been used in many further studies with some modifications. For instance, de Pillis and Radunskaya [2003] included a normal tissue cell population in this model, performed phase space analysis and investigated the effect of chemotherapy treatment by using optimal control theory. Another interesting model is proposed by Kirschner and Panetta [1998]. They examined the tumour cell growth in the presence of the effector immune cells and the cytokine IL-2 which has an essential role in the activation and stimulation of the immune system. They implied that antigenicity of the tumour cells plays an essential role in the recognition of the tumour cells by the immune system. They observed oscillations in the tumour cell populations which is also demonstrated in the Kuznetsov’s model and in addition, they obtained a stable limit cycle for some parameter range of the antigenicity. One can find many other models of the tumour-immune interactions with their dynamical analysis as well as
investigations of optimal therapy effects. Although all these models include different cell populations, they share basic common characteristics such as existence of tumour-free equilibria which is the main attention of investigating the therapy effects; coexisting equilibria where the tumour and other cells are present in the body and in competition, and finally the tumour escape and uncontrolled growth [d’Onofrio, 2005]. It has been observed that most of the interesting dynamics occur around coexisting equilibria which may yield oscillations in the cell populations, and converge to a stable limit cycle, as we mentioned before.

Deterministic chaos is a common behavior in continuous systems with dimensions three or more. Recent studies show that the models for interacting species which are basically Volterra–Lotka type systems exhibit chaotic dynamics [Vano et al., 2006; Gakkhar & Naji, 2003; Tang & Chen, 2002]. On the other hand, tumour growth models which include interactions between cell populations are mainly based on population dynamics which are also derived from the idea of Volterra–Lotka type prey-predator models. Therefore, they may also exhibit chaos. However, the existence of chaotic dynamics in cancer models has yet to be demonstrated although it has been mentioned that the dynamics of the interactions of the tumour cells with other cells may exhibit chaos [Ahmed, 1993; Mayer et al., 1995; Dalgleish, 1999; Nani & Freedman, 2000].

In this study, we develop and analyze a very simple tumour growth model which exhibits chaos in the parameter range of interest. The model consists of three cell populations which are \( T(t) \): tumour cells, \( H(t) \): healthy host cells, and \( E(t) \): effector immune cells. Although our model shares very common terms with the other cancer models, it represents chaotic dynamics which is a very important phenomenon for nonlinear systems. We show a new chaotic attractor in our model with numerical simulations and then confirm it by calculating the Lyapunov exponents and the Lyapunov dimension. Moreover, we illustrate that the system has Shilnikov-like connections.

This paper is organized as follows: we introduce the model and explain its biological relevance in Sec. 2. In addition, we normalize the system states and reduce the number of the parameters to simplify the analysis. Section 3 is devoted to the study of the equilibria of the system and their stability. We show the chaotic attractor in Sec. 4 for the parameter range of interest and compute the Lyapunov exponents and the Lyapunov dimension of the system. Finally, we draw the conclusion and discuss the possible future work in Sec. 5.

2. Mathematical Cancer Model

Our model contains three cell populations: \( T(t) \) denotes the number of tumour cells at time \( t \), \( H(t) \) is the number of healthy host cells at time \( t \), and \( E(t) \) refers to the number of effector immune cells at time \( t \) in the single-tumor-site compartment. Like some other models in the literature [Kuznetsov et al., 1994; Kirschner & Panetta, 1998; Kuznetsov & Knott, 2001; de Pillis & Radunskaya, 2003; de Pillis et al., 2006; Itik et al., 2009; Bajer et al., 1996], our model is based on similar principles, and aims to describe the competition and the interaction among these cells. Essentially, cancer models which include interacting cell populations are based on the Volterra–Lotka type prey-predator models. Although they are simple models, 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 shall devote this section to describe the biological relevance of our model. The system of ODEs which describes the cancer model is:

\[
\frac{dT}{dt} = r_1 T \left( 1 - \frac{T}{k_1} \right) - a_{12} TH - a_{13} TE, \tag{1}
\]

\[
\frac{dH}{dt} = r_2 H \left( 1 - \frac{H}{k_2} \right) - a_{21} TH, \tag{2}
\]

\[
\frac{dE}{dt} = \frac{r_3 TE}{T + k_3} - a_{11} TE - d_3 E. \tag{3}
\]

Equation (1) gives the rate of change in the population of the tumour cells with time \( t \). The first term of Eq. (1) refers to the logistic growth of the tumour cells in the absence of any effect from other cell populations with the growth rate of \( r_1 \) and maximum carrying capacity \( k_1 \). The competition between the host cells \( H(t) \) and the tumour cells \( T(t) \) which results in the loss of the tumour cell population is given by the term \( a_{12} TH \). \( a_{13} \) refers to the tumour cell killing rate by the effector cells \( E(t) \). In Eq. (2), the healthy tissue cells also grow logistically with the growth rate of \( r_2 \) and maximum carrying capacity \( k_2 \). We assume that the
cancer cells proliferate faster than the healthy cells and thus $r_1 > r_2$. The tumour cells also inactivate the healthy cells at the rate of $a_{21}$. The final equation of the model describes the change in the immune cell population with time $t$. The first term of Eq. (3) illustrates the stimulation of the immune system by the tumour cells with tumour specific antigens. The rate of recognition of the tumour cells by the immune system depends on the antigenicity of the tumour cells. Since this recognition process is very complex, in order to keep the model simple, we assume that the stimulation of the immune system depends directly on the number of tumour cells with positive constants $r_3$ and $k_3$. The Effector cells are inactivated by the tumour cells at the rate of $a_{31}$ as well as they die naturally at the rate $d_3$. We note that all the system parameters are positive.

Although our model looks very similar to the model given in [de Pillis & Radunskaya, 2003], we did not include the constant influx of the effector cells in the third equation of our model. We assume that the effector cells are cytotoxic T-cells (CTLs) and they are produced as naive cells, which cannot show any response to the tumour cells unless they are activated by antigen presenting cells (APCs) via some MHC-I and MHC-II (MHC: Major histocompatibility complex) pathways in the presence of the tumour specific antigens. The activation mechanism of the immune system depends on the antigenicity of the tumours. Therefore, we neglect the constant influx of the activated effector cells which was also proposed in [Kirschner & Panetta, 1998; Kronik et al., 2008]. For the sake of simplicity of analysis, we first nondimensionalise the system (1)–(3), and then perform a steady-state analysis on the scaled system.

### 2.1. Nondimensionalization and parameter reduction

We nondimensionalize our model (1)–(3) by using the following rescaling. We underline that there are many possible different rescalings.

$$\begin{align*}
x_1 &= \frac{T}{k_1}, & x_2 &= \frac{H}{k_2}, & x_3 &= \frac{E}{k_3}, & t &= r_1 t, \\
& \text{where the new parameters:} \\
& \tilde{a}_{12} = \frac{a_{12}k_2}{r_1}, & \tilde{a}_{13} = \frac{a_{13}k_3}{r_1}, \\
& \tilde{r}_2 = \frac{r_2}{r_1}, & \tilde{a}_{21} = \frac{a_{21}k_1}{r_1}, & \tilde{r}_3 = \frac{r_3}{r_1}, \\
& \tilde{k}_3 = \frac{k_3}{k_1}, & \tilde{a}_{31} = \frac{a_{31}k_1}{r_1}, & d_3 = \frac{d_3}{r_1}.
\end{align*}$$

We omit the tilde notation on the parameters.

$$\begin{align*}
& \frac{dx_1}{dt} = x_1(1 - x_1) - a_{12}x_1x_2 - a_{13}x_1x_3, \\
& \frac{dx_2}{dt} = r_2x_2(1 - x_2) - a_{21}x_1x_2, \\
& \frac{dx_3}{dt} = \frac{r_{13}x_1}{x_1 + k_3} - a_{31}x_1x_3 - d_3x_3.
\end{align*}$$

We give the parameters of the system (6)–(8) in Sec. 4. In the next section, we will obtain the stationary points of our system and analyze their local behavior.

### 3. Equilibria of the System

We shall carry out the rest of our analysis and simulations on the rescaled system (6)–(8). As we are interested in the chaotic dynamics of the system, we shall focus on the equilibria and the parameter ranges where we observe chaos.

We start with linearizing the system and obtain the Jacobian matrix to discuss local behavior of its equilibria. The Jacobian matrix of the system is

$$\begin{pmatrix}
1 - 2x_1 - a_{12}x_2 - a_{13}x_3 & -a_{12}x_1 & -a_{13}x_1 \\
-a_{21}x_2 & r_2 - 2r_2x_2 - a_{21}x_1 & 0 \\
r_{13}x_1 & \frac{r_{13}x_1}{x_1 + k_3} - a_{31}x_1 - d_3 & 0
\end{pmatrix}. \tag{9}$$
In order to obtain the fixed points of the system (6)–(8), we set

\[ \dot{x}_1 = 0 \Rightarrow \begin{cases} x_1 = 0, \\ x_1 = 1 - a_{12}x_2 - a_{13}x_3. \end{cases} \tag{10} \]

\[ \dot{x}_2 = 0 \Rightarrow \begin{cases} x_2 = 0, \\ x_2 = \frac{1 - a_{21}x_1}{r_2}. \end{cases} \tag{11} \]

\[ \dot{x}_3 = 0 \Rightarrow \begin{cases} x_3 = 0, \\ x_3 = \left( k_1 + \frac{d_3}{a_{31}} - \frac{r_3}{a_{31}} \right) x_1 + \frac{d_3k_1}{a_{31}} = 0. \end{cases} \tag{12} \]

Solution of Eqs. (10)–(12) together yields eight fixed points. We give these equilibria and discuss their local behavior according to their biological relevance below.

(1) The first equilibrium point is trivial and given as \( E_1 = [0,0,0] \), which means none of the cell populations exists. The eigenvalues of the Jacobian matrix at this point are \( \lambda_1 = 1, \lambda_2 = 0 \), and \( \lambda_3 = -d_2 \). Since all the parameters are positive this equilibrium has two unstable and one stable eigenvalue. Therefore, we have a saddle at this point.

(2) The second equilibrium point is obtained as \( E_2 = [0,1,0] \). This equilibrium point means that system is in healthy stage. The eigenvalues of the Jacobian matrix at the tumour-free equilibrium point are \( \lambda_1 = -r_2, \lambda_2 = -d_2, \) and \( \lambda_3 = 1 - a_{12} \). Stability of this point depends on the value of \( a_{12} \) since two of the eigenvalues are negative but \( \lambda_3 \) can be either negative, positive or zero. \( a_{12} < 1 \) makes \( \lambda_3 \) unstable and system shows a saddle type behavior around this point. \( a_{12} > 1 \) gives a stable equilibrium point and finally \( a_{12} = 1 \) makes \( \lambda_3 = 0 \), as a consequence, linearization fails to give any information about the local stability of this point. In our simulations, we obtained very different results by altering the value of \( a_{12} \) as it also affects some other equilibrium points. Especially we have observed that chaotic dynamics start close to \( a_{12} = 1 \). The selection of \( a_{12} < 1 \) yields different dynamical behavior such as converging to a stable spiral or a limit cycle. However, in this study, we shall focus on the parameter range of \( a_{12} \) where we observe the chaotic attractor.

(3) The third fixed point of the system is \( E_3 = [1,0,0] \). This means that the tumour population is in the maximum limit in that compartment. The eigenvalues of the Jacobian matrix at this point are obtained as \( \lambda_1 = -1, \lambda_2 = r_2 - a_{21}, \) and \( \lambda_3 = \frac{(r_3 - d_3 - a_{31} - a_{13}k_1 - d_3k_1)}{k_1 + 1} \). We obtain \( \lambda_3 \) is stable, and \( \lambda_1 \) is unstable with the selected parameters given in Sec. 4, hence this point is also a saddle.

(4) The fourth equilibrium point is \( E_4 = [\bar{x}_1,0,\bar{x}_3] \) assuming \( \bar{x}_1 \) and \( \bar{x}_3 \) are positive. The eigenvalues of the system are

\[ \lambda_1 = J_{11} \]

\[ \lambda_{2,3} = \frac{1}{2} J_{11} + J_{13} \mp (\sqrt{(J_{11} - J_{13})^2 + 4 J_{13} J_{31}})^{1/2}, \]

where \( J_{ij} \) \((i,j = 1,2,3)\) are the elements of the Jacobian matrix at this point and given by

\[ J_{11} = 1 - 2\bar{x}_1 - a_{13}\bar{x}_3 \]

\[ J_{13} = -a_{13}\bar{x}_1 \]

\[ J_{31} = \frac{r_3\bar{x}_3}{\bar{x}_1 + k_3} \left( 1 - \frac{\bar{x}_1}{\bar{x}_1 + k_3} \right) - a_{31}\bar{x}_3 \]

\[ J_{33} = \frac{r_3\bar{x}_3}{\bar{x}_1 + k_3} - a_{31}\bar{x}_1 - d_3. \]

This point has one unstable real and two complex eigenvalues with stable real parts with the selected parameter sets.

(5) The fifth equilibrium point is \( E_5 = [\bar{x}_1,0,\bar{x}_3] \). However, this equilibrium has a negative value for \( x_3 \). Hence, we neglect this equilibrium point since it is biologically irrelevant.

(6) The sixth fixed point is \( E_6 = (r_2(a_{12} - 1)/(-r_2 + a_{12}a_{21})), (-r_2 + a_{21})/(-r_2 + a_{12}a_{21}), 0 \) provided that \( r_2 \neq a_{12}a_{21} \). In order to obtain a biologically feasible equilibrium point \( a_{12} \geq 1 \) must be satisfied. On the other hand, the case of \( a_{12} = 1 \) results in the coalescence of \( E_6 \) with \( E_2 \). \( a_{12} > 1 \) yields the real eigenvalues with signs (+,−,−). The selection of \( a_{12} < 1 \) results in a stationary point in the negative coordinate plane.

(7) The seventh equilibrium point is a nontrivial one, \( E_7 = [\bar{x}_1,\bar{x}_2,\bar{x}_3] \). When we fix all the parameters except \( a_{12} \), we obtain \( \bar{x}_1 > 0, \bar{x}_2 > 0 \) and \( \bar{x}_3 = \varphi - \psi a_{12} \), where \( \varphi \) and \( \psi \) are positive numbers. So, in order to have a biologically relevant point, \( \varphi - \psi a_{12} \geq 0 \) must be satisfied. With the parameter range given in Sec. 4, this
point has one real unstable eigenvalue and two complex eigenvalues with positive real parts.

(8) The eighth and last equilibrium point for our system is $E_8 = [\bar{x}_1, \bar{x}_2, \bar{x}_3]$. This point has non-positive value for $x_2$. Thus this point is not of interest for our analysis.

As we are interested in biologically relevant solutions of the system, the next two results show that the positive octant is invariant and that all trajectories in this octant are recurrent.

**Lemma 3.1.** With all positive or zero initial conditions $x_1(0), x_2(0), x_3(0)$, the solutions $x_1(t), x_2(t), x_3(t)$ of the system (6)–(8) stay in $\mathbb{R}^3^+$ := \{(x_1, x_2, x_3) \in \mathbb{R}^3 : x_i \in \mathbb{R}^+_0 \} for all $t \geq 0$.

**Proof.** This follows by looking on each coordinate hyperplane, i.e. $x_1 = 0, x_2 = 0, x_3 = 0$. When $x_1 = 0, x_1 = 0$ so clearly the hyperplane $x_1 = 0$ is invariant. Similarly when $x_2 = 0, x_2 = 0$ and when $x_3 = 0, x_3 = 0$. i.e. all coordinate hyperplanes are invariant. \[\blacksquare\]

**Lemma 3.2.** The solutions $x_1(t), x_2(t), x_3(t)$ of the system (6)–(8) with initial values in $\mathbb{R}^3^+$ are bounded in $\mathbb{R}^3^+$ for all $t \geq 0$.

**Proof.** By Lemma 3.1 the positive octant is invariant so we just need to consider solutions in this octant. Note that if $x_1 > 1$ then $(dx_1/dt) < 0$ and if $x_2 > 1$ then $(dx_2/dt) < 0$, so all solutions will eventually reach the region

$$S_1 = \{ (x_1, x_2, x_3) : x_1 < 1, x_2 < 1 \}.$$ 

Now consider $x_3$; if $(dx_3/dt) = 0$

$$x_3 = 0,$$

i.e.

$$- \left( \frac{a_{11} - 4a_{13} \psi}{a_{11}} \right) x_3 + k_1 = 0.$$ 

For the parameters of interest,

$$\frac{\psi}{d_1 + k_1 \alpha_{13}}$$

and so there are either no real solutions or two real positive solutions. In the real case, call the two solutions $\xi_1$ and $\xi_2$. Then $(dx_3/dt) > 0$ in the slab $S_2 = \{ (x_1, x_2, x_3) : x_2 \geq 0, x_3 \geq 0, \xi_1 \leq x_1 \leq \xi_2 \}$ Since, by the above, all solutions enter the region $S_1$, the only way for the solutions to “escape” to $\infty$ (i.e. to be unbounded) is for them to remain in $S_1 \cap S_2$ i.e. in

$$\{ (x_1, x_2, x_3) : 0 \leq x_2 \leq 1, 0 < \xi_1 \leq x_1 \leq \max(1, \xi_2), x_3 \geq 0 \}.$$ 

However, this would mean that $x_3$ would become arbitrarily large in $S_1 \cap S_2$. But if $x_3$ is large enough then $(dx_3/dt) < 0$ for $x_3 > (1 - x_3 - a_{12} \psi)/(a_{13})$ and so the solution would leave $S_1 \cap S_2$. \[\blacksquare\]

4. Chaotic Dynamics

In this section, we shall prove that the system exhibits chaotic dynamics with the selected parameter set. We shall show that the system has Shilnikov-like connections and calculate the Lyapunov exponents and the Lyapunov dimension.

**Theorem 4.1.** The phase space solutions of the system (6)–(8) with parameters: $a_{11} = 1.5$, $d_1 = 0.5$, $r_2 = 0.6$, $a_{12} = 0.2$, $r_3 = 4.5$, $a_{13} = 2.5$, $k_3 = 1$ and $a_{12} = 1$ contain chaotic attractor.

**Proof.** We will prove this result by showing the existence of a Shilnikov-like connection and apply Shilnikov’s theorem which states that a system contains (an infinite number of) Shilnikov-type homoclinic connections if it has a Shilnikov connection (i.e. a homoclinic or near homoclinic connection) consisting of a hyperbolic fixed point with a two-dimensional stable (spiral) and a one-dimensional unstable manifold. This means that the eigenvalues $\lambda_1, \lambda_2, \lambda_3$ of the linearization near the fixed point satisfy

$$\lambda_1 = \lambda_2 = -\lambda^* \pm \omega_i, \quad \lambda_3 = \lambda^*, \quad \text{real, (13)}$$

and

$$\lambda^* > \lambda^* > 0, \ \omega \neq 0. \quad (14)$$

This can be seen to be true from the connection shown in Fig. 1. Although the unstable manifold of the equilibrium point does not return (as a homoclinic orbit), it is clear that there are arbitrarily close trajectories which do return, so there is a Shilnikov-like connection as can be seen in Fig. 1. The result now follows. \[\blacksquare\]

As it can be seen in Fig. 1, solutions of the system come very close to the equilibrium point $E_4$, which is on the $x_2 = 0$ plane. The unstable eigenvector of $E_4$ forces the solutions to diverge from this point. As time increases, the chaotic dynamics become more apparent (Fig. 2). We can also prove chaotic behavior by examining the Lyapunov exponents and the
Lyapunov dimension of the system. Hence, we give a brief summary about how to compute the Lyapunov exponents and the Lyapunov dimension in the following section.

### 4.1. **Lyapunov exponents and dimension**

Lyapunov exponents provide vital information about the chaotic attractor through the exponential divergence or convergence of neighboring points along the trajectory of the dynamical system [Matsumoto et al., 1985; Chua et al., 1986; Ramasubramanian & Sircar, 2000]. We, therefore, find appropriate to study the Lyapunov exponents of the cancer model and calculate the Lyapunov dimension. Consider the nonlinear system in the form

\[ \dot{x} = f(x, t), \]  

where \( x \in \mathbb{R}^n \) and \( n \geq 3 \). Let \( x^*(t) = [x_1(t), x_2(t), x_3(t)] \) be a particular solution for the system which satisfies the initial condition vector \( x^*(0) \). Consider now a solution \( x(t) = x^*(t) + \eta \) in the small perturbation of \( x^*(t) \), where \( \eta = [\eta_1, \eta_2, \eta_3]^T \) is tangent map which satisfies the linear equation

\[ \dot{\eta} = J_\eta. \]  

Here, \( J \) is the \( n \times n \) Jacobian matrix of the nonlinear system. In order to solve Eq. (16), we first choose \( n \) orthogonal tangent vectors as initial conditions. For the sake of simplicity initial orthogonal vectors is usually selected as \( \nu_1(0) = (1, 0, 0, \ldots, 0) \); \( \nu_2(0) = (0, 1, 0, \ldots, 0) \); \( \nu_3(0) = (0, 0, 1, \ldots, 0) \). Equation (16) is solved for each of the initial conditions \( \nu_1(0), \nu_2(0), \ldots, \nu_n(0) \) over \( t_0 \leq t \leq t_1 \). The solution vectors \( \nu(t) = [\nu_1(t), \nu_2(t), \ldots, \nu_n(t)] \) is orthonormalized by using Gram-Schmidt orthonormalization (GSO) method for every time span \( \tau = t_{i+1} - t_i \), \( i = 0, 1, \ldots, m \), where \( m = (t_f - t_0)/\tau \). Here \( t_f \) refers to final computation time. The orthonormalized vectors obtained by GSO procedure

\[ \nu'_1 = \frac{\nu_1}{|\nu_1|}, \]
\[ \nu'_2 = \frac{\nu_2 - \langle \nu_2, \nu'_1 \rangle \nu'_1}{|\nu_2 - \langle \nu_2, \nu'_1 \rangle \nu'_1|}, \]
\[ \nu'_3 = \frac{\nu_3 - \langle \nu_3, \nu'_1 \rangle \nu'_1 - \langle \nu_3, \nu'_2 \rangle \nu'_2}{|\nu_3 - \langle \nu_3, \nu'_1 \rangle \nu'_1 - \langle \nu_3, \nu'_2 \rangle \nu'_2|}. \]

We then call the norms in the denominators of Eq. (17) as \( N_p(t) \) where \( p = 1, \ldots, n; n \) is the dimension of the system and \( i = 0, 1, \ldots, m \). The Lyapunov exponents are

\[ \mu_p = \lim_{m \to \infty} \frac{1}{m} \sum_{i=1}^{m} \ln N_p(t). \]

Furthermore, the Lyapunov dimension can be obtained from the equation [Matsumoto et al., 1985; Banks, 1999].

\[ d_L = j + \frac{\sum_{p=1}^{j+1} \mu_p}{|\sum_{p=1}^{j} \mu_p|}, \]

where \( j \) is defined by the condition that

\[ \sum_{p=1}^{j} \mu_p > 0, \quad \text{and} \quad \sum_{p=1}^{j+1} \mu_p < 0. \]
Lyapunov dimension of our model for the selected parameter sets. The Lyapunov exponents are computed to be $\mu_1 = 0.021468$, $\mu_2 = -0.005424$, $\mu_3 = -0.540526$. The Lyapunov exponents are illustrated in Fig. 3. Since $\mu_1 > 0$, $\mu_2 > 0$ and $\mu_1 + \mu_2 + \mu_3 < 0$, the Lyapunov dimension is

$$d_L = 2 + \frac{\mu_1 + \mu_2}{|\mu_3|} \approx 2.0297. \quad (21)$$

The Lyapunov dimension is obtained to be fractal. However, comparing to the Lyapunov dimension of the Lorenz equation ($d_L = 2.06$ with the parameters $\sigma = 16$, $\beta = 4$ and $\rho = 40$), our attractor is thinner than the Lorenz one.

In our simulations, we use the parameter set: $a_{11} = 1.5$, $d_1 = 0.5$, $r_2 = 0.6$, $a_{11} = 0.2$, $r_3 = 4.5$, $a_{11} = 2.5$, $k_3 = 1$ and $a_{12} = 1$. Using this parameter set we obtain six equilibria in the positive octant, the other two equilibria contain negative points in the coordinate plane, hence they are not of our interest. We give the equilibria and the eigenvalues of the Jacobian matrices at these points in the same order as in Sec. 2. $E_1 = (0, 0, 0)$ and $E_3 = (1, 0, 0)$ and $E_3 = (1, 0, 0)$ and $E_6 = (0, 0, 0)$. $E_6$ has a negative value for $x_3$: $E_6 = (0, 1, 0)$ and it coalesces with $E_2$: 

![Fig. 3. The Lyapunov exponents.](image)

![Fig. 4. Chaotic attractor with different initial conditions; case 1: $x(0) = [0.8, 0.01, 0.9]$, case 2: $x(0) = [0.5, 0.01, 0.01]$ and case 3: $x(0) = [0.9, 0.01, 0.01]$.](image)

![Fig. 5. Time responses of the system states.](image)

![Fig. 6. Projection of the attractor onto the $x_1-x_2$ plane.](image)
Fig. 7. Projection of the attractor onto the $x_1 - x_3$ plane.

$E_7 = (0.1325, 0.6687, 0.0795)$ and $\lambda_1 = -0.61435$, $\lambda_2 = 0.4030 + 0.2351i$, $\lambda_3 = 0.4030 - 0.2351i$ and finally $E_8$ has a negative value for $x_2$.

We performed our simulations with $t = 50000$ time steps. However chaotic behavior is also observed in the earlier time steps. We have illustrated the new chaotic attractor in Fig. 2. Figure 4 illustrates the chaotic attractor with different initial conditions. Time responses of the states $x_1$, $x_2$ and $x_3$ are illustrated in Fig. 5 for the initial conditions $x(0) = [0.1, 0.1, 0.1]$ and the projection of the attractor onto the two-dimensional coordinate planes are shown in Figs. 6–8.

5. Concluding Remarks

In this paper, we have developed and analyzed a new model for the evolution of the cancer cells. The model is inspired by population dynamics and contains terms which refer to the interactions and competitions between tumor cells and other cells of the body i.e. effector immune cells and health tissue cells. We have showed that the model exhibits chaotic dynamics by showing it has Shilnikov-like connections. Moreover, we have confirmed the chaotic dynamics by computing the Lyapunov exponents and the Lyapunov dimension which is obtained to be fractal. We have observed that there exists a chaotic attractor in the neighborhood of the parameter $a_{12} = 1.0$. Although there are some studies in the literature which claim that some similar cancer models may exhibit chaos, they have not shown explicitly the existence of it. Hence this work is encouraging to develop more realistic models which also include chaos. In the next papers we shall study the fine structure of the chaotic attractor. In particular, we will examine the branch manifolds of the attractor and the existence of knotted periodic orbits.

References


