Dynamics of a Three Dimensional Chaotic Cancer Model

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Abstract

Interactions in the immune system of human body with a target population of, e.g., bacteria, viruses, antigens, or tumor cells must be considered as a dynamic process. It is argued that tumor growth, considered as a chaotic dynamical system which is sensitive to the initial conditions. It is evident that chaotic models are proposed which fit the observations well. In this present article, a new chaotic three dimensional model of cancer tumour growth, which includes the interactions between tumour cells, healthy tissue cells, and activated immune system cells, clearly leading to chaotic behavior. The dynamics of the model are explored by performing computationally the local equilibria stability, which indicate the conditions where chaotic dynamics can be observed, and show rigorously the existence of chaos in the proposed model.

Keywords: Cancer Model, Tumour growth, Immune system, Chaos & Fractal.

1   Introduction and Background

One of the major causes of death is the Cancer of which much is still unknown about its functions of establishment and growth. There are few ways of treatment viz. surgery and/or radiotherapies which played an important role. There are new medical techniques such as gene therapy and immunotherapy. In these clinical curative techniques for tackling cancer, the amount of administered therapy (drugs in chemotherapy or radiation in radio therapy) is very important for patient's survival. This is because in these cases, the therapy does not only kill the tumour cells, it also kills some of the healthy tissues or results in their serious damage. Hence the dosage of the therapy must be carefully adjusted in order to cause the minimum damage to healthy tissue whilst killing a maximum number of tumour cells [1]. But it is admissible fact that these techniques are still in their infancy. But in many cases these treatments even fail to cure the cancer. Even when patients experience tumor regression, later relapse happens. The need to address not only preventative measures, but also more successful treatment strategies is necessarily required. Efforts along these lines are now being investigated through immunotherapy [4, 10, 11]. The theoretical study of tumor-immune dynamics has a long history. A good summary can be found in Adam and Bellomo.

Modeling of tumour growth dynamics is an active research field for biologists, mathematicians and engineers. Different approaches are used in the mathematical modeling of cancer and its control. Mathematical modelling of tumour growth is considered as one of the potentially powerful tools in the development of improved treatment regimens.

There are investigations of the tumour growth models by using cellular automata which can include very specific characteristics of the tumour, patient and drug effectively in the model [3 5]. Anderson and Chaplain [6] and Enderling et al. [7] also used both PDE's and the cellular automata approach to model tumour growth, angiogenesis and metastasis. Another different approach is the work of de Pillis and Radunskaya [8] in which they construct a general tumour growth model, using ordinary differential equations, which shows the dynamics of tumour growth by means of the numbers of tumour, healthy and immune cells.

In this present study, we have developed a three dimensional model based on

$$\frac{dx}{dt} = \alpha x(1-y)(1+z) - x^2 y$$

$$\frac{dy}{dt} = \beta y(1-z)(1+x) - y^2 z$$

$$\frac{dz}{dt} = \gamma z(1-x)(1+y) - z^2 x$$

where the parameters α, β and γ are arbitrary non-negative real numbers. Here $x(t)$ denotes the number of tumour cells at time t, $y(t)$ is the number of healthy host cells at time t, and $z(t)$ refers to the number of effector immune cells at time t in the single tumor-site compartment.

There is no harm to admit that these models is strongly idealized it demonstrates how the combination of a few proposed nonlinear interaction rules between the immune system and its targets are able to generate a considerable variety of different kinds of immune responses, many of which are observed both experimentally and clinically. In particular, solutions of the model equations correspond to states described by immunologist as *virgin state*, *immune state* and *state of tolerance*. This model replicates the so-called primary and secondary response; Moreover, it predicts the existence of a threshold level for the amount of pathogen germs or of transplanted tumor cells below which the host is able to eliminate the infectious organism or to reject the tumor graft. It is known that in some cases, such as leukaemia, the number of tumour cells in the blood stream is very important; this can be illustrated by ordinary differential equations. Therefore this model is important and encouraging for us to develop new drug administration techniques in cancer treatment by getting information about the effect of the administrated drug on a patient's metabolism.

2   Local Asymptotic Stability of Equilibria

Let us compute the equilibria of the system by solving $\dot{X} = F(X) = 0$, where $X = (x, y, z)^\top$ and $F = [f, g, h]^\top$ and $f(x, y, z) = \alpha x(1-y)(1+z) - x^2 y$, $g(x, y, z) = \beta y(1-z)(1+x) - y^2 z$ and $h(x, y, z) = \gamma z(1-x)(1+y) - z^2 x$. The equilibrium equation rewrites as

$$\begin{cases} x\left(\alpha(1 - y + z - yz) - xy\right) = 0, \\ y\left(\beta(1 - z + x - zx) - yz\right) = 0, \\ z\left(\gamma(1 - x + y - xy) - zx\right) = 0. \end{cases}$$

If α, β or γ is zero, then there are equilibrium lines in $\mathbb{R}^3$, with expression $x = y = 0$, $x = z = 0$ or $y = z = 0$. Thus, we assume that α, β and γ are nonzero. Four equilibria are obtained analytically:

- $x = y = z = 0$

- $x = 0$, $y = -1$, $z = \frac{\beta}{\beta - 1}$ if $\beta \neq 1$

- $x = \frac{\gamma}{\gamma - 1}$, $y = 0$, $z = -1$ if $\gamma \neq 1$

- $x = -1$, $y = \frac{\alpha}{\alpha - 1}$, $z = 0$ if $\alpha \neq 1$

One last equilibrium corresponding to the case $x \neq 0$, $y \neq 0$, $z \neq 0$ must be considered, but it has no analytical expression. It could be obtained by solving numerically

$$
\begin{cases}
1 - y + z - yz - xy/\alpha = 0\,, \\
1 - z + x - zx - yz/\beta = 0\,, \\
1 - x + y - xy - zx/\gamma = 0\,.
\end{cases}
$$

Here we shall explore the local asymptotic stability of the four fixed points as mentioned above.

2.1   Stability of the Origin

The jacobian $\partial F/\partial X$ about the equilibrium $(0,0,0)$ is

$$
\begin{pmatrix}
\alpha & 0 & 0 \\
0 & \beta & 0 \\
0 & 0 & \gamma
\end{pmatrix}
$$

Theorem 2.1. *The equilibrium $(0,0,0)$ is locally asymptotically stable if all the parameters α, β and γ are negative.*

Proof. The eigenvalues of the jacobian $\partial F/\partial X$ about the equilibrium $(0,0,0)$ are α, β and γ. All parameters are real and if they are negative then the equilibrium $(0,0,0)$ is locally asymptotically stable. □

A pair of 50 different initial values are taken where all the three parameters are taken as $\alpha = -0.1334, \beta = -0.1024$ and $\gamma = -0.9591$. The corresponding trajectory plots are given in the Fig. 1.
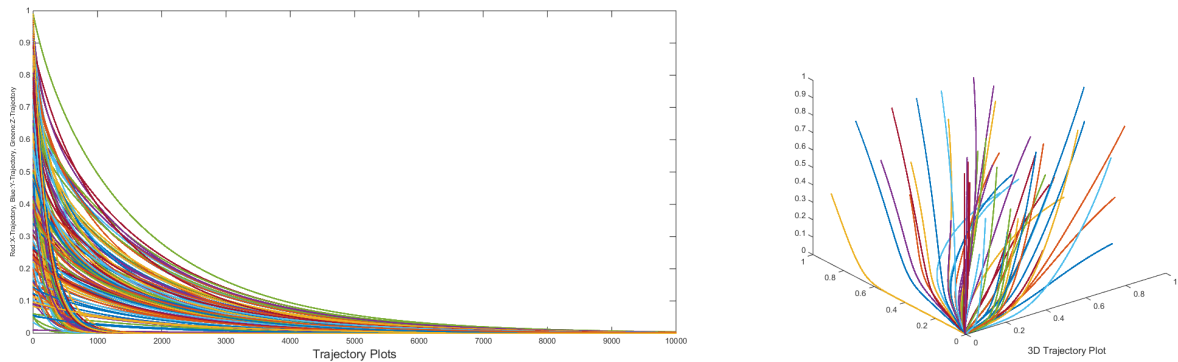

Figure 1: Trajectory plots which are attracting towards the origin for 50 different initial values with negative parameters.

Since the parameters α, β and γ in the model are meant to be positive and hence the equilibrium $(0,0,0)$ is practically not feasible.

A pair of 20 different initial values are taken from the neighbourhood of the fixed point $(0,0,0)$ where all the three parameters are taken as $\alpha = 0.7455, \beta = 0.7363$ and $\gamma = 0.5619$. The corresponding trajectory plots are given in the Fig. 2.
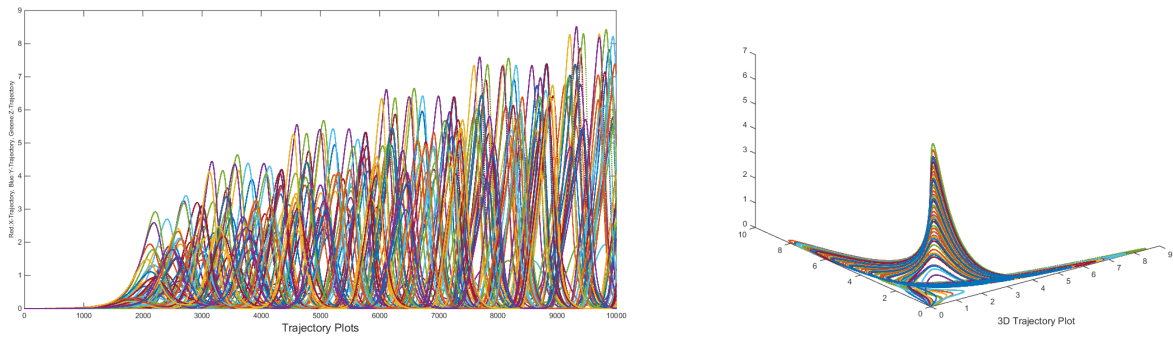
Figure 2: Trajectory plots which are repelling towards the origin for 20 different initial values with positive parameters $\alpha = 0.7455, \beta = 0.7363$ and $\gamma = 0.5619$.

2.2   Local Stability of $(0, -1, \frac{\beta}{\beta-1})$

The jacobian $\partial F/\partial X$ about the equilibrium $(0, -1, \frac{\beta}{\beta-1})$ is

$$\begin{pmatrix} 2\alpha\left(\frac{\beta}{\beta-1}+1\right) & 0 & 0 \\ \beta\left(\frac{\beta}{\beta-1}-1\right) & \frac{2\beta}{\beta-1}-\beta\left(\frac{\beta}{\beta-1}-1\right) & \beta-1 \\ -\frac{\beta^2}{(\beta-1)^2} & \frac{\beta\gamma}{\beta-1} & 0 \end{pmatrix}$$

Theorem 2.2. *The equilibrium $(0, -1, \frac{\beta}{\beta-1})$ is locally asymptotically stable if*

$$\alpha > \frac{1}{2}, \frac{2\alpha-1}{4\alpha-1} < \beta < \frac{1}{2}, 0 < \gamma < \frac{2\beta-1}{\beta^2-\beta}$$

A comprehensive list of parameters α, β and γ are fetched satisfying the condition for local asymptotic stability of the fixed point $(0, -1, \frac{\beta}{\beta-1})$. The parameters are plotted in the following Fig. 3.
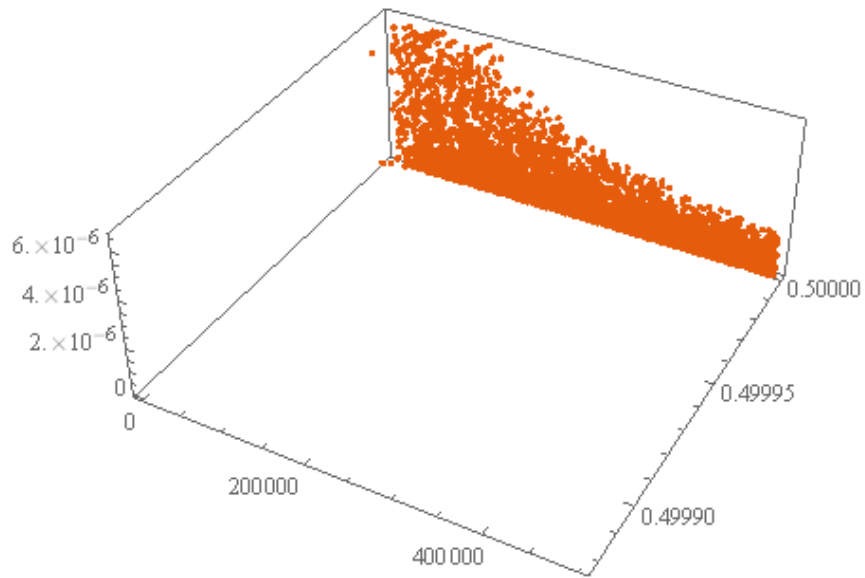
Figure 3: Parameter space (α, β, γ) for which the fixed point $(0, -1, \frac{\beta}{\beta-1})$ is attracting.

A pair of 50 different initial values are taken where all the three parameters are taken as $\alpha = -0.1334, \beta = -0.1024$ and $\gamma = -0.9591$. The corresponding attracting trajectory plots are given in the Fig. 4.
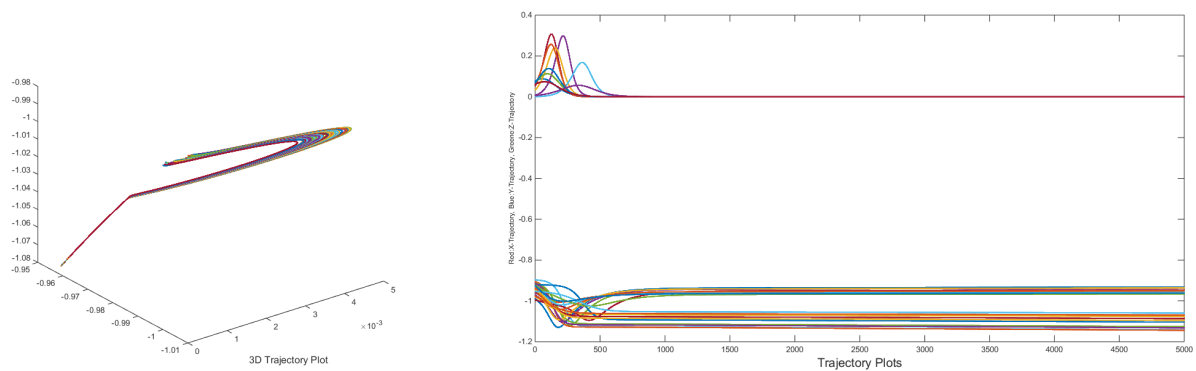

Figure 4: Trajectory plots which are attracting towards the fixed point $(0, -1, \frac{\beta}{\beta-1})$ for 50 different initial values.

A pair of 50 different initial values are taken where all the three parameters are taken as $\alpha = 0.9064, \beta = 0.3927$ and $\gamma = 0.0249$. The corresponding repelling trajectory plots are given in the Fig. 5.
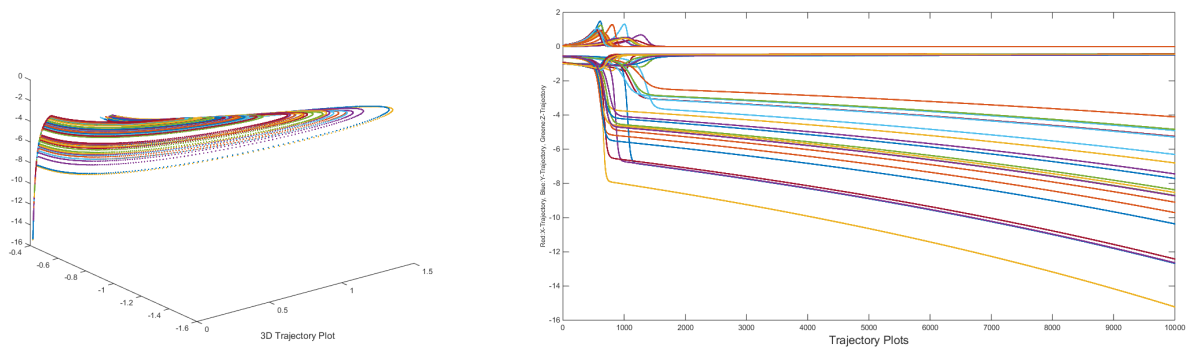
Figure 5: Trajectory plots which are repelling from the fixed point $(0, -1, \frac{\beta}{\beta-1})$ for 50 different initial values.

2.3 Local Stability of $(\frac{\gamma}{\gamma-1}, 0, -1)$

The jacobian $\partial F/\partial X$ about the equilibrium $(\frac{\gamma}{\gamma-1}, 0, -1)$ is

$$
\begin{pmatrix}
0 & -\frac{\gamma^2}{(\gamma-1)^2} & \frac{\alpha\gamma}{\gamma-1} \\
0 & 2\beta\left(\frac{\gamma}{\gamma-1}+1\right) & 0 \\
\gamma-1 & \gamma\left(\frac{\gamma}{\gamma-1}-1\right) & \frac{2\gamma}{\gamma-1}-\gamma\left(\frac{\gamma}{\gamma-1}-1\right)
\end{pmatrix}
$$

Theorem 2.3. *The equilibrium $(\frac{\gamma}{\gamma-1}, 0, -1)$ is locally asymptotically stable if*

$$
0 < \beta \le \frac{1}{2}, 0 < \gamma < \frac{\alpha+2}{2\alpha} - \frac{1}{2}\sqrt{\frac{\alpha^2+4}{\alpha^2}}
$$

A comprehensive list of parameters α, β and γ are fetched satisfying the condition for local asymptotic stability of the fixed point $(\frac{\gamma}{\gamma-1}, 0, -1)$. The parameters are plotted in the following Fig. 6.
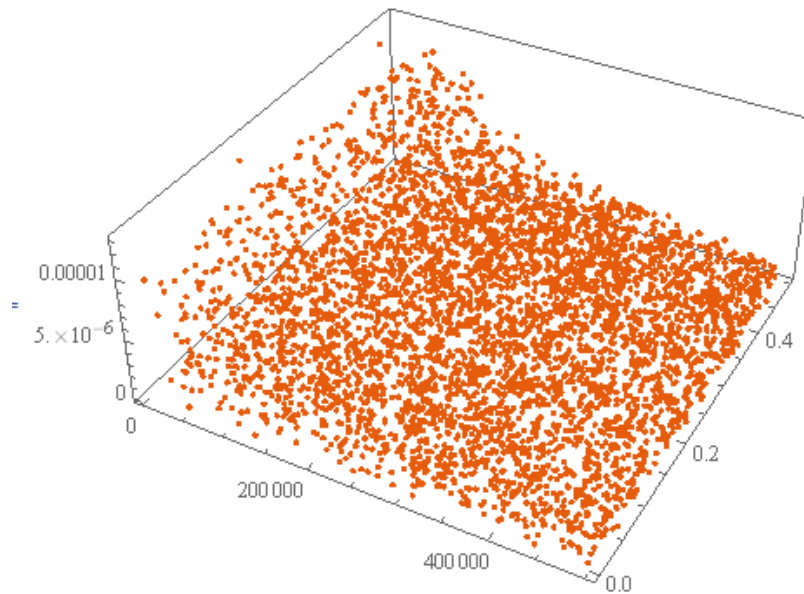
Figure 6: Parameter space (α, β, γ) for which the fixed point $(\frac{\gamma}{\gamma-1}, 0, -1)$ is attracting.

A pair of 50 different initial values are taken where all the three parameters are taken as $\alpha = -0.1334, \beta = -0.1024$ and $\gamma = -0.9591$. The corresponding trajectory plots are given in the Fig. 7.
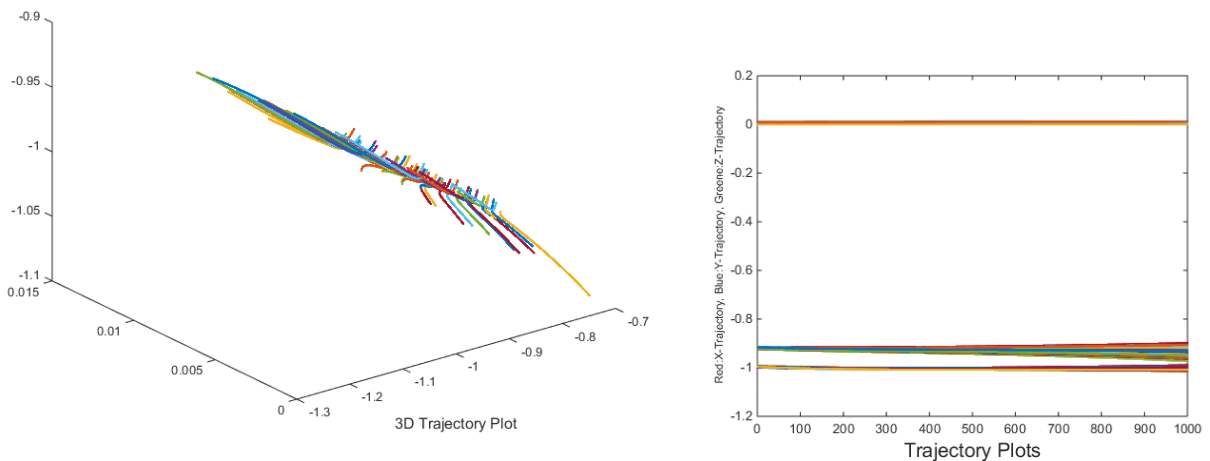

Figure 7: Trajectory plots which are attracting towards the fixed point $(0, -1, \frac{\beta}{\beta-1})$ for 50 different initial values.

The fixed point $(0, -1, \frac{\beta}{\beta-1})$ does repeal. When $(\alpha = 0.0350, \beta = 0.4402, \gamma = 0.4398)$ and $(\alpha = 0.775, \beta = 0.6184, \gamma = 0.9385)$ for all initial values taken from the neighbourhood of the fixed point $(0, -1, \frac{\beta}{\beta-1})$ the trajectories are repelling as shown in the Fig. 8 from top to bottom respectively .
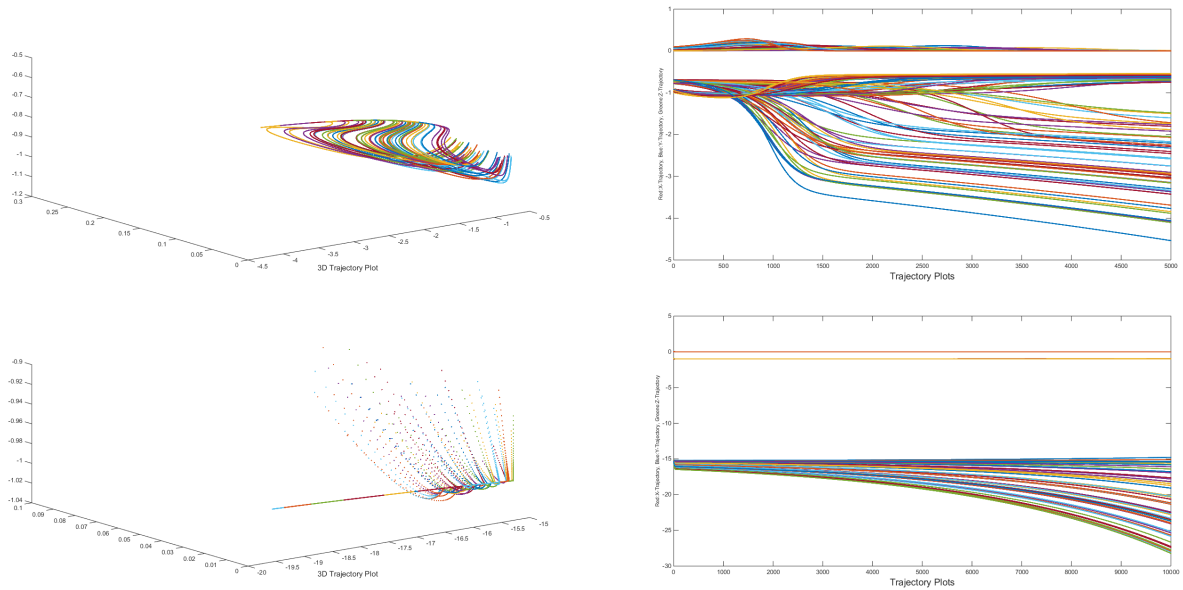
Figure 8: Trajectory plots which are repelling from the fixed point $(0, -1, \frac{\beta}{\beta-1})$ for 50 different initial values for both the example parameters as stated above from top to bottom respectively.

2.4   Local Stability of $(0, \frac{\alpha}{\alpha-1}, -1)$

The jacobian $\partial F/\partial X$ about the equilibrium $(0, \frac{\alpha}{\alpha-1}, -1)$ is

$$
\begin{pmatrix}
0 & 0 & 0 \\
\frac{2\alpha\beta}{\alpha-1} & \frac{2\alpha}{\alpha-1} + 2\beta & -\frac{\alpha\left(\frac{\alpha}{\alpha-1}+\beta\right)}{\alpha-1} \\
\frac{\alpha\gamma}{\alpha-1} + \gamma - 1 & -\gamma & \left(\frac{\alpha}{\alpha-1}+1\right)\gamma
\end{pmatrix}
$$

Theorem 2.4. *The equilibrium $(0, \frac{\alpha}{\alpha-1}, -1)$ is locally asymptotically stable if*

$$
\alpha = \frac{1}{2}, \frac{1}{2} < \beta < 1, 0 < \gamma < \frac{\frac{1}{4} - \frac{\beta}{2}}{\frac{\beta}{4} - \frac{1}{4}}
$$

A comprehensive list of parameters α, β and γ are fetched satisfying the condition for local asymptotic stability of the fixed point $(0, \frac{\alpha}{\alpha-1}, -1)$. The parameters are plotted in the following Fig. 9.
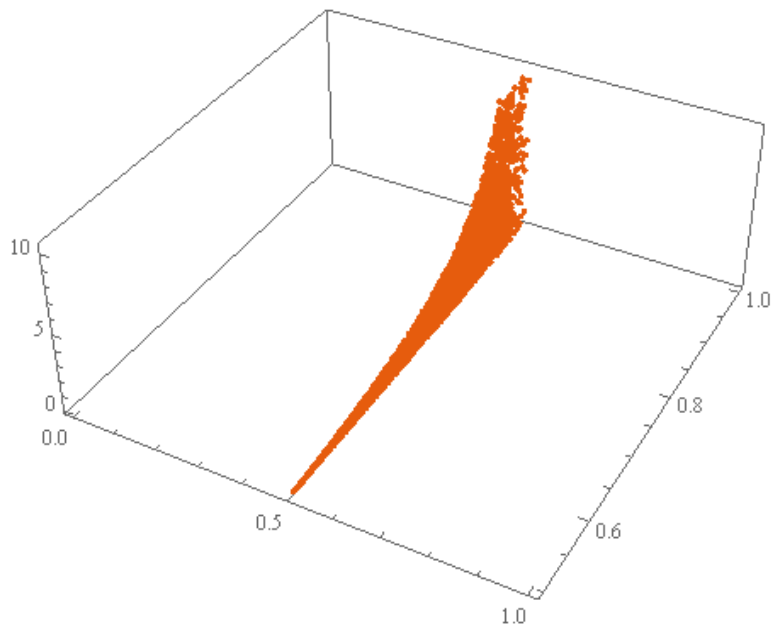
Figure 9: Parameter space (α, β, γ) for which the fixed point $(0, \frac{\alpha}{\alpha-1}, -1)$ is attracting.

A pair of 50 different initial values are taken where all the three parameters are taken as $\alpha = 0.5, , \beta = \frac{250054}{500001}$ and $\gamma = \frac{31}{78644}$. The corresponding trajectory plots are given in the Fig. 10.
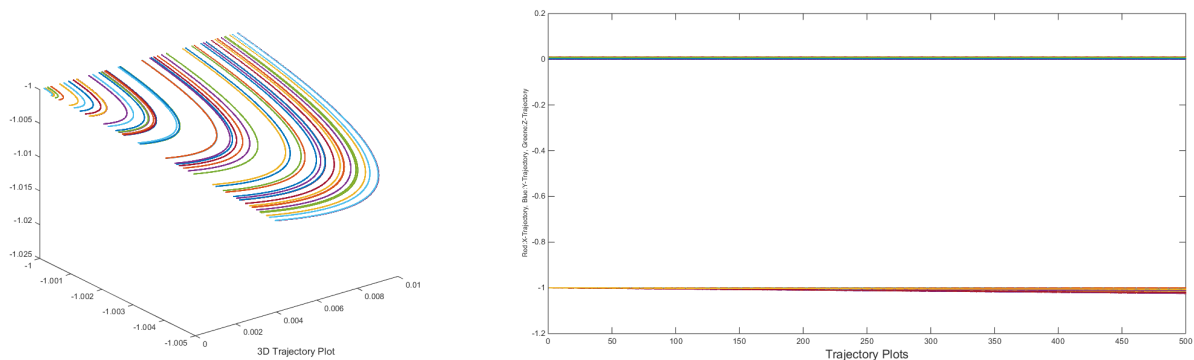

Figure 10: Trajectory plots which are attracting towards the fixed point $(0, \frac{\alpha}{\alpha-1}, -1)$ for 50 different initial values.

When $(\alpha = 0.8149, \beta = 0.3496, \gamma = 0.0216)$ and $(\alpha = 0.4049, \beta = 0.4824, \gamma = 0.0639)$ for all initial values taken from the neighbourhood of the fixed point $(0, \frac{\alpha}{\alpha-1}, -1)$ the trajectories are repelling as shown in the Fig. 8 from top to bottom respectively .
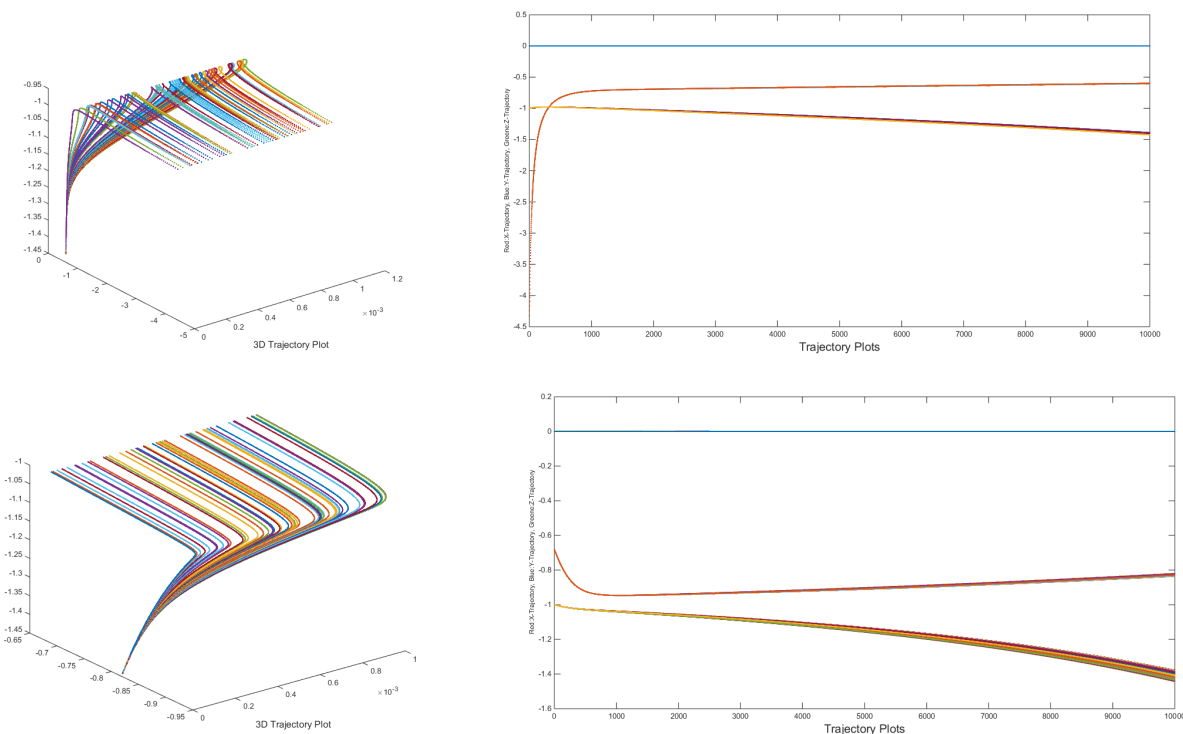
Figure 11: Trajectory plots which are repelling from the fixed point $(0, \frac{\alpha}{\alpha-1}, -1)$ for 50 different initial values for both the example parameters as stated above from top to bottom respectively.

3   Chaotic Solutions

In this section, we shall show that the system exhibits chaotic dynamics with the selected parameters. It has been observed that whenever the fixed point $(0, 0, 0)$ is repelling then chaos happens in the system for any initial values taken from the neighbourhood of the origin. This observation urges us to consider the following theorem.

Theorem 3.1. *The solution of the system is chaotic if all the parameters α, β and γ are positive.*

A region of parameters $(\alpha, \beta, \gamma) \subset \mathbb{R}^3$ is estimated, where the system possesses chaotic solutions. The region is plotted in the following Fig. 12.

Now we shall have a set of examples of parameters for which the system possesses chaos. The parameters and corresponding three dimensional chaotic trajectory for 50 differential initial values from the neighbourhood of the origin are shown in the Table 1. Note that different colors in the chaotic attractor correspond to 50 different set of initial values.
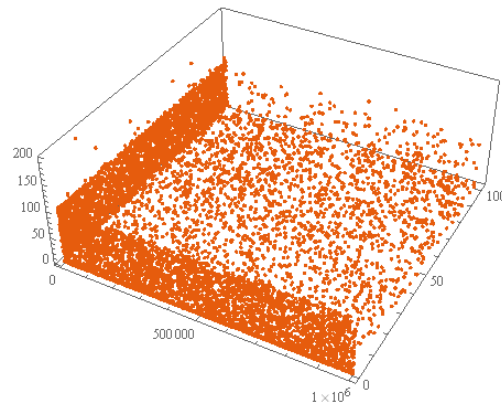
Figure 12: Region of parameters $(\alpha, \beta, \gamma) \subset \mathbb{R}^3$ for which the solution attains chaotic solutions.

Sl. No.	Parameters	Chaotic Trajectory Plot
1	$\alpha = 0.2834, \gamma = 0.6825, \gamma = 0.3581$ Repelling from the fixed point $(0,0,0)$	
2	$\alpha = 0.6658, \beta = 0.9733, \gamma = 0.6277$ Repelling from the fixed point $(0,0,0)$	
3	$\alpha = 0.3440, \beta = 0.5337, \gamma = 0.6278$ Repelling from the fixed point $(0,0,0)$	

Table 1: Parameters α, β and γ for which the system possesses chaotic solutions.
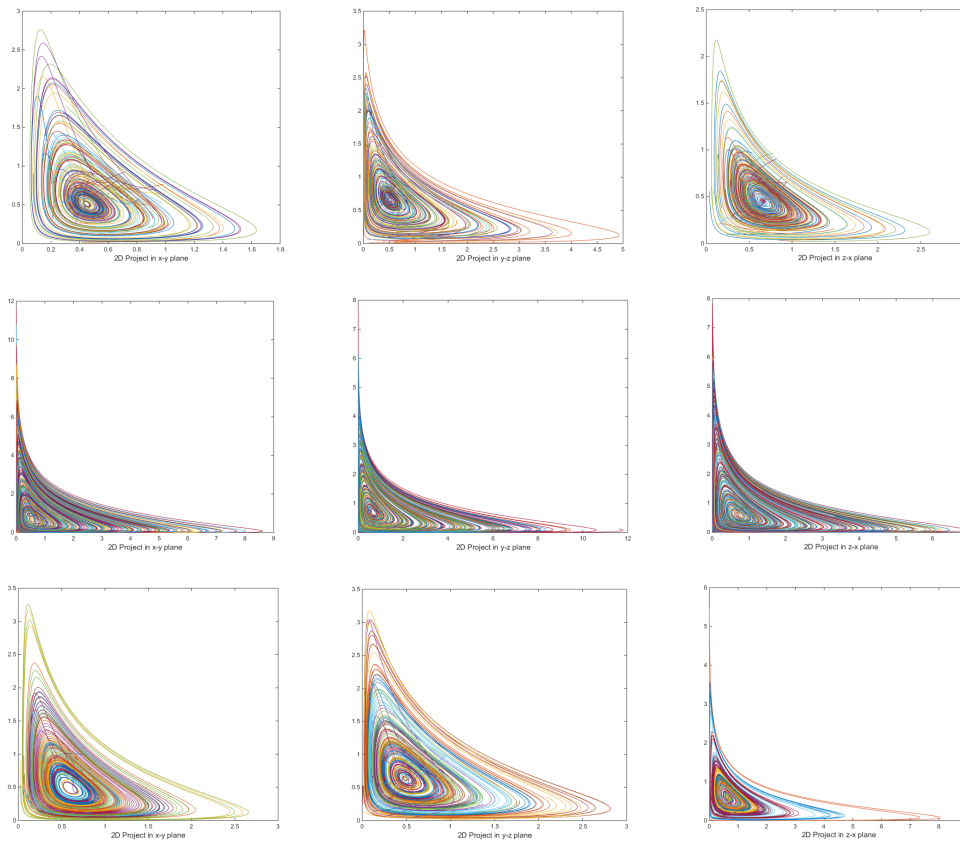
Figure 13: Projection of the chaotic attractor in xy, yz and zx planes of each of the three case as stated in the Table 1.

The two dimensional projections in the xy, yz and zx plane are plotted in the following Figure 13 for all the three chaotic attractors as stabled in the Table 1.

The trajectory plot up to 10^5 iterations are given for 50 different initial values for each of the set of parameters as given in the Table 1.

4 What Happens if all the parameters are same?

Although the issue about equality of the parameters α, β and γ might not attractive, still from a bird eye, we wish to gather an impression what happens to the system. Here we fix all the parameters to be same. Following we shall have the three dimensional trajectories with two dimensional projections in the xy, yz and zx plane. It is observed that the solution of the system remain chaotic.
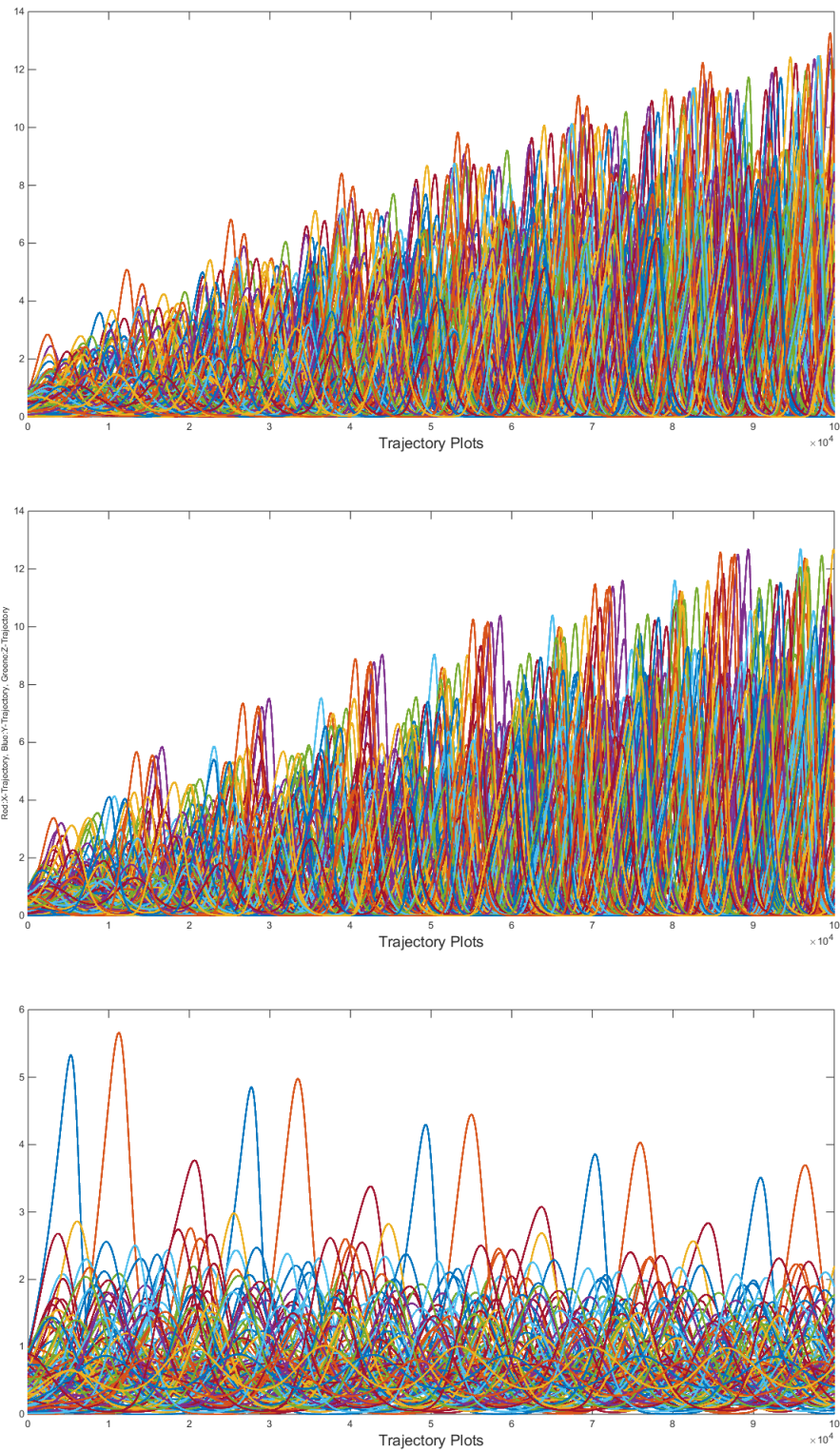
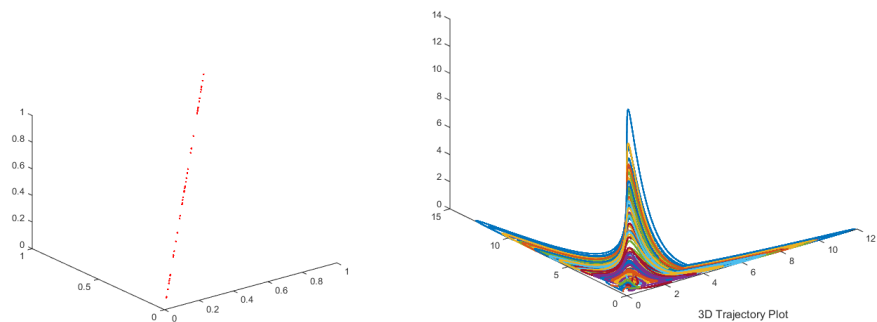Figure 14: Chaotic trajectory plots for the parameters as stated in the Table 1.

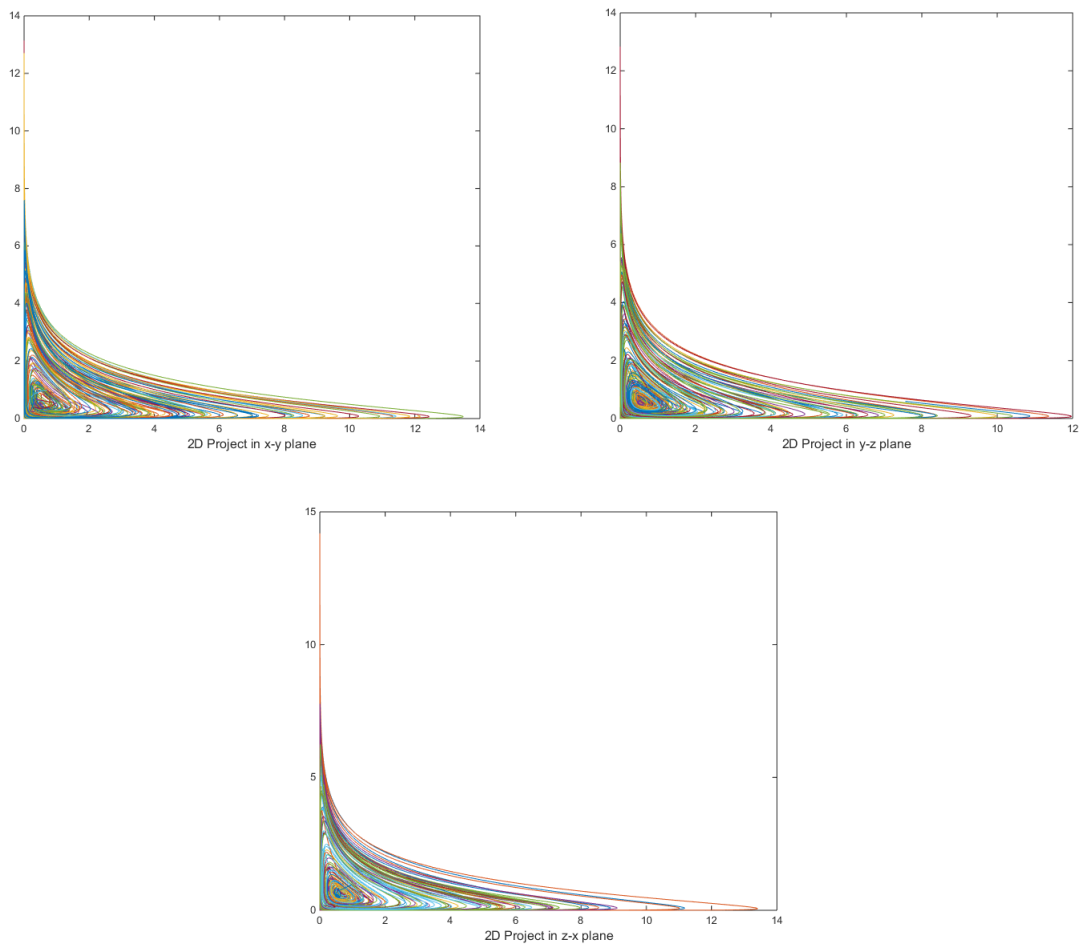Figure 15: Identical parameters and Chaotic trajectory plots.

Figure 16: Projection of the chaotic attractor as shown in Figure 15 in xy, yz and zx planes.

5 Conclusions and Future Endeavours

In this article, a new three dimensional chaotic model has been defined and analyzed computationally for the evolution of the cancer cells growth. The model is inspired by population dynamics and contains terms which refer to the interactions and competitions between tumour 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 for a range of positive parameters α, β and γ.

Moreover, we have confirmed the chaotic dynamics by computing the hurst exponent and fractal dimension. It is observed that all the three parameters are very sensitive. 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.

Acknowledgement

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