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Research paper

Nonlinear active control of a cancerous tumour

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Abstract

This paper deals with the control of a cancerous tumour growth. The model used is a Three-Dimensional Cancer Model (TDCM). The competition terms include tumour cells, healthy cells, and immune cells. Nature of the competition among the populations of tumour cells, healthy host cells, and immune cells results in a chaotic behaviour. In this paper, a nonlinear active control has been used to control the growth of a tumour. Effect of chemotherapy drug on the different cell populations has been studied. Our control objective is to control the tumour growth and minimize its population to a small value which can be considered as harmless.Along with the above objective, the normal cell population is also be maintained at a particular level. This work has been done completely inin-sillico environment. The simulation results are shown extensively to support the theoretical analysis and confirmed that the preliminary objectives of the paper are attained.

Keywords: *Tumour, immune, active control, chemotherapy.*

1. Introduction

The growth of cancerous tumour cells in living organisms involves a lot of complex biological interactions. A tumour is nothing but a result of uncontrolled cell growth. The adverse effect of cancerous tumour is well known to the human civilisation. Therefore, the scientific community is continuously searching for a better solution to combat the deadly disease. There are several approaches of treatment for the cure of a cancerous tumour such as surgery, radiotherapy, chemotherapy, and immunotherapy. Among these, chemotherapy is one of the widely used methods of treating the cancer patients. There are various mathematical models exist in the literature. These models explain the interaction among several competitive terms. With regular interaction with research oncologists, we have been trying to understand various aspects of tumour growth and impact of chemotherapeutic drugs on the growth of tumour cells. Some peculiar behaviours shown by Cancer progression such as tumour dormancy, creeping through is discussed extensively in [1].

There are several models of cell kill which show the killing of cancerous tumour cells in the presence of chemotherapy. In log-kill hypothesis, it was observed that killing of cells is proportional to the tumour population [15][2].Therefore, as per this hypothesis volume of large tumours decreases more rapidly, than the volume of smaller tumours for a fixed amount of drugs. But unfortunately, in the case of some diseases, like Hodgkin's disease and acute lymphoblast Leukemia, the result is contradictory to the hypothesis. In these cases, smaller tumours reduce faster than larger tumours of similar kind[15]. Eventually, another hypothesis called Norton-Simon hypothesis was evolved [15], in which the cell kill was observed to be in proportion with the tumour growth rate. As a matter of fact, before activation, the chemotherapy drugs must undergo metabolism by an enzyme. As per clinical observation, the amount of enzyme is fixed in our body; this process of metabolism gets saturated. Finally, in another hypothesis called E_{max}hypothesis [15], the cell kill was proportional to the saturable mass of a tumour[15] [3].

For these hypotheses, both constrained and unconstrained control techniques in open loop have been proposed in early works [4,5]. In some of the research works, application of feedback control having a quadratic performance criterion has been exclusively analysed [6]. The other arena of research in the literature largely includes optimal control considering a model of stochastic in nature [7], optimal singular control [8,9], a comparison between optimal controls using different kinds of models [7], etc. In some research of cancer treatment, a multi-objective optimal control model for the process of chemotherapy is used. In many control strategies cited above, effects of parametric variations and disturbance were not considered. So for obvious reason, robustness was not guaranteed at all. To attain the property of robustness, different control strategies were developed. Some of them are optimal linear regulation, nonlinear optimal control which is particularly based on variation of extremal, and H_∞ control technique [14].

In one of the recent works [10], it has been highlighted about the chaotic property exhibited by the cell populations. The growth control of a cancerous tumour has been studied in three-dimensional cancer model proposed by De Pillis and Radunskaya [1] using state space exact linearization [11] based on the Lie algebra[10].We know that the chemotherapy drug does also affect the fast-growing normal healthy cells. However, it is expected to maintain the normal cell concentration at a particular level after the course of chemotherapy. In the above work [10], a parametric entrainment control is used which directly affects the normal cell dynamics. It is well observed from simulation result given in [10], the normal cell population settles to a negative value after the application of control. Another issue is the presence of tumour cell at steady-state. Although, practically it is quite impossible to vanish the tumour volume, the steady-state performance can be improved. These two important issues are addressed and highlighted in this paper.

The paper is organised as follows. Some peculiar phenomena which help us to understand the complex biological interactions

pertaining to tumour growth are discussed in Section II. In Section III, the model to be used is discussed, supported by its theoretical background. The control of tumour growth using nonlinear active control is introduced in Section IV. The simulation results and discussion are included in Section V. Finally, some concluding remarks have been pointed out in Section VI.

2. Peculiar phenomena observed

There are several existing models available in the literature. These models are no doubt useful in providing a better understating of tumour growth and effect of chemotherapy. But they are not sufficient enough to showcase the qualitative aspects which are of interest to the research oncologists working in this field. To incorporate some of these qualitative behaviours, a model of three dimension proposed by De Pillis and Radunskaya [1] is used in this paper. In fact, the peculiar qualitative behaviourof our interest are explained in next subsections.

Jeff's phenomenon

It is clinically observed that there occurs a temporal oscillation in tumour size with the administration of chemotherapy [1]. This oscillation is apparently unsynchronised with the chemotherapy process. In case of some patients, it is observed that even after treatment the cancerous tumour continues to grow. After some time, when treatment is stopped, the tumour begins to decrease in size. It should be kept in mind that, this asynchronous reaction to chemotherapeutic drugs is not a result of drug resistance. In the model used, there is effect of thedrug on the normal cells, immune cells, as well as tumour cells. The size of tumour is asynchronous with drug administration. Over time, the phase and period of tumour volume change. This contributes to the oscillation in size of tumour size [1].

Tumour dormancy

This phenomenon has been a topic of interest in recent years among the researchers. There are evidences that a cancerous tumour may sometimes disappear or become no longer detectable [1]. But suddenly, it may reappear and grow alarmingly to a large mass which can be destructive in nature [1].

This is known as tumour dormancy. The effect of immune mechanism may lead to the oscillations in tumour size. The tumour dormancy has been incorporated in the mathematical modelling, considered in this paper.

Some nonlinear dynamics of immunogenic tumours exhibit "creeping through", when a tumour remains a relatively small period of time, and subsequently grows to very large size[1].

In the model used in this paper, immune cells and tumour cells interact with each other in a manner known as predator-prey. Tumour cells play the role of prey and immune cells play the role of predator.

The proliferation of cancerous tumour cells triggers the production of immune cells. Immune cells by nature try to decrease the population of tumour cells.

As a consequence, when tumour cell population decreases, immune cells population starts decreasing. This decreasing of immune cell population allows the tumour cells to grow once again. This cyclic behaviourmay continue indefinitely leading to a chaotic behaviour[10].

3. Model of tumour growth

The competitive terms used in the prescribed model are cancerous tumour cells, healthy normal cells, and immune cells. Let $T(t)$ denotes the number of tumour cells, $H(t)$ denotes the number of healthy normal cells, and, $I(t)$ denotes the number of immune cells at time t.

If the source of immune cells are considered to be outside of the system, then it is necessary to assume a constant influx rate, s.

In the absence of any tumour, the immune cells will die off at a per capita rate ofd_1, which results in the long term, population size of $\frac{s}{d_1}$.Then the system of ordinary differential equations describing the phenomena is as follows:

$$\begin{aligned}\frac{dT}{dt} &= r_1 T\left(1-\frac{T}{k_1}\right) - a_{12}TH - a_{13}TI\\ \frac{dH}{dt} &= r_2 H\left(1-\frac{H}{k_2}\right) - a_{21}TH\\ \frac{dI}{dt} &= s + \frac{r_3 TI}{T+k_3} - a_{31}TI - d_3 I\end{aligned} \quad (1)$$

But, for simplicity of mathematical analysis, it is considered that the effect of immune cells is not from outside the system. Therefore the term 's' can be dropped from the above set of ordinary differential equations.

The modified system can be written as follows.

$$\begin{aligned}\frac{dT}{dt} &= r_1 T\left(1-\frac{T}{k_1}\right) - a_{12}TH - a_{13}TI\\ \frac{dH}{dt} &= r_2 H\left(1-\frac{H}{k_2}\right) - a_{21}TH\\ \frac{dI}{dt} &= \frac{r_3 TI}{T+k_3} - a_{31}TI - d_3 I\end{aligned} \quad (2)$$

Where, r_1 is the rate at which cancerous tumour cells grow in the absence of effect from any other cell populations having maximum carrying capacity of k_1. a_{12} and a_{13} are the rate of cancerous tumour cell killing by healthy host cells and effecter immune cells respectively [10].

Whereas, $r_2$is the rate at which healthy normal cells grow having maximum carrying capacity ofk_2; a_{21} signifies the rate at which healthy host cells are inactivated by cancerous tumour cells. To keep the recognition process of tumour cells by effecter immune cells as simple as possible, it is considered that the stimulation of immune cells depends directly [10] on the number of cancerous tumour cells with positive constants $r_3$and k_3.

The effecter immune cells naturally die off at the rate of $d_3$and are inactivated by cancerous tumour cells at the rate of a_{31}.It is obvious to have an assumption that the rate of growth of cancerous tumour cell is more than that of healthy normal cells [10]. ($r_1 > r_2$)

To free the system of equations given in Equation (2) from dimensions, we introduce certain transformations listed below.

$$\begin{aligned}&x_1 = \frac{T}{k_1},\ x_2 = \frac{H}{k_2}, x_3 = \frac{I}{k_3}\\ &A_{12} = \frac{a_{12}k_2}{r_1},\ A_{21} = \frac{a_{21}k_1}{r_1}\\ &A_{13} = \frac{a_{13}k_3}{r_1}, A_{31} = \frac{a_{31}k_1}{r_1}\\ &R_2 = \frac{r_2}{r_1}, R_3 = \frac{r_3}{r_1}, D_3 = \frac{d_3}{r_1}\end{aligned} \quad (3)$$

Then, the non dimensional form of Equation (2) can be written as follows:

$$\begin{aligned}\frac{dx_1}{dt} &= x_1(1-x_1) - A_{12}x_1x_2 - A_{13}x_1x_3\\ \frac{dx_2}{dt} &= R_2x_2(1-x_2) - A_{21}x_1x_2\\ \frac{dx_3}{dt} &= \frac{R_3x_1x_3}{x_1+k_3} - A_{31}x_1x_3 - D_3x_3\end{aligned} \quad (4)$$

4. Control of a chaotic system

The cell populations before the application of chemotherapy drug show chaotic behaviour which is depicted in Fig.1.The relation between cancerous tumour cells and effecter immune cells exhibits a cyclic nature.

In particular, they interact in a predator-prey fashion.
To control this chaotic dynamics we have applied a nonlinear active control [11] which based on the Lyapunov stability theory [13].
Let us define our desired performances and error in states.
x_{d1} is the desired tumour volume in steady state.
x_{d2} is the healthy host cells in steady state.
x_{d3} is the effecter immune cells in steady state.

$$e_1 = x_1 - x_{d1}$$
$$e_2 = x_2 - x_{d2}$$
$$e_3 = x_3 - x_{d3} \quad (5)$$

Error dynamics can be written as

$$\dot{e}_1 = \dot{x}_1 - \dot{x}_{d1}$$
$$= x_1 - x_1^2 - A_{12}x_1x_2 - A_{13}x_1x_3 - \dot{x}_{d1}$$
$$\dot{e}_2 = \dot{x}_2 - \dot{x}_{d2}$$
$$= R_2x_2 - R_2x_2^2 - A_{21}x_1x_2 - \dot{x}_{d2}$$
$$\dot{e}_3 = \dot{x}_3 - \dot{x}_{d3}$$
$$= \frac{R_3x_1x_3}{x_1 + k_3} - A_{31}x_1x_3 - D_3x_3 - \dot{x}_{d3}$$

These equations can be reduced to

$$\dot{e}_1 = e_1 + x_{d1} - x_1^2 - A_{12}x_1x_2 - A_{13}x_1x_3 - \dot{x}_{d1}$$
$$\dot{e}_2 = R_2e_2 + R_2x_{d2} - R_2x_2^2 - A_{21}x_1x_2 - \dot{x}_{d2}$$
$$\dot{e}_3 = \frac{R_3x_1x_3}{x_1+k_3} - D_3e_3 - D_3x_{d3} - A_{31}x_1x_3 - D_3x_3 - \dot{x}_{d3} \quad (6)$$

We have chosen the control input in the structure given below.

$$u_1 = -x_{d1} + x_1^2 + A_{12}x_1x_2 + A_{13}x_1x_3 + \dot{x}_{d1} - g_1e_1$$
$$u_2 = -R_2x_{d2} + R_2x_2^2 + A_{21}x_1x_2 + \dot{x}_{d2} - g_2e_2$$
$$u_3 = -\frac{R_3x_1x_3}{x_1 + k_3} + D_3x_{d3} + A_{31}x_1x_3 - D_3x_3 - \dot{x}_{d3} - g_3e_3$$

After application of control input the system can be written as:

$$\frac{dx_1}{dt} = x_1(1 - x_1) - A_{12}x_1x_2 - A_{13}x_1x_3 + u_1$$
$$\frac{dx_2}{dt} = R_2x_2(1 - x_2) - A_{21}x_1x_2 + u_2$$
$$\frac{dx_3}{dt} = \frac{R_3x_1x_3}{x_1 + k_3} - A_{31}x_1x_3 - D_3x_3 + u_3$$

Where,g_1,g_2,g_3 are gain values which will be decided from the Lyapunov theory [13].
After application of these control inputs in the system dynamics, the error dynamics becomes

$$\dot{e}_1 = e_1 - g_1e_1$$
$$\dot{e}_2 = R_2e_2 - g_2e_2$$
$$\dot{e}_3 = -D_3e_3 - g_3e_3 \quad (7)$$

Let us consider a Lyapunov function candidate as,

$$V = \frac{1}{2}(e_1e_1^T + e_2e_2^T + e_3e_3^T)$$
$$\frac{dV}{de} = e_1\dot{e}_1 + e_2\dot{e}_2 + e_3\dot{e}_3$$
$$= e_1^2(1 - g_1) + e_2^2(R_2 - g_2) + e_3^2(-D_3 - k_3) \quad (8)$$

Negating both side of Equation (8) and writing in the matrix form:

$$-\frac{dV}{de} = e^T \begin{bmatrix} -(1-g_1) & 0 & 0 \\ 0 & -(R_2 - g_2) & 0 \\ 0 & 0 & D_3 + k_3 \end{bmatrix} e$$
$$= e^TQe$$

For stability, Q should be a positive definite matrix. To satisfy the conditions the gain values should be as follows:
$g_1 > 1$
$g_2 > R_2$
$g_3 > -D_3$ (9)

5. Results and discussion

For simulation purpose, we have used the value of the parameters, which are found to be relevant clinically, and are given as follows: $A_{12} = 1.5$, $A_{13} = 2.5, A_{21} = 1.5, R_2 = 0.6, A_{31} = 0.2$, $R_3 = 4.5$, $k_3 = 1$, $D_3 = 0.5$. The initial conditions of$T(0)$, $H(0)$, $and\ I(0)$ are considered as 0.1,0.1,and 0.1, respectively.
$x_{d1} = 0.01$,x_{d2}=0.8,$x_{d3} = 0.5$ are the desired values of the states at steady state.
It may be noted that all the parameters are dimensionless.

Simulation results of uncontrolled dynamics

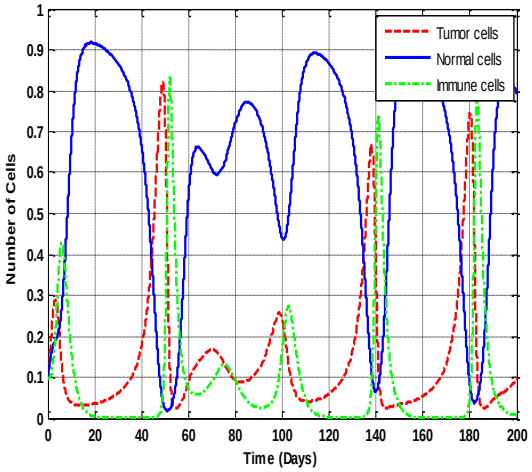

Fig.1. Time response of uncontrolled states

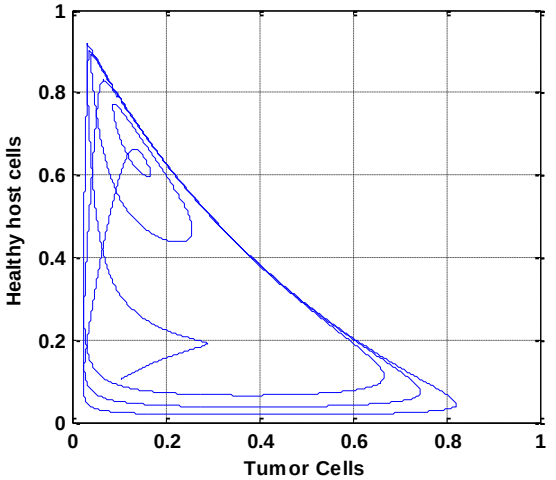

Fig.2. Phase plot between tumour cells and normal cells

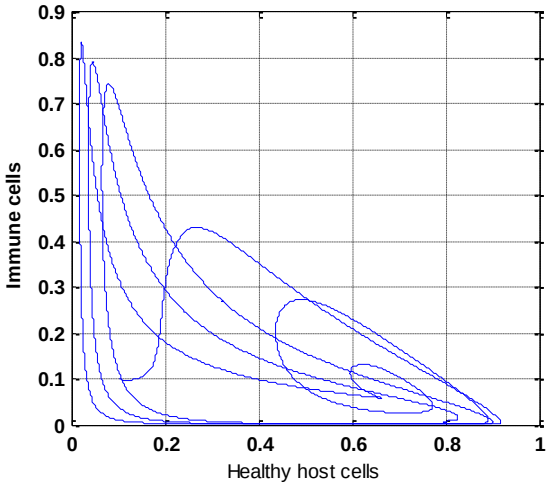

Fig.3. Phase plot between normal cells and immune cells

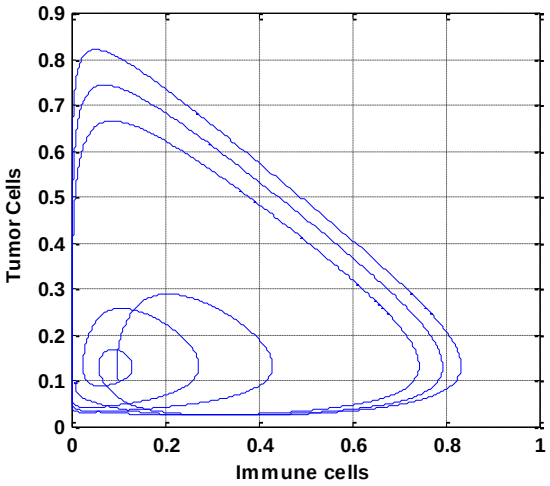

Fig.4. Phase plot between immune cells and normal cells

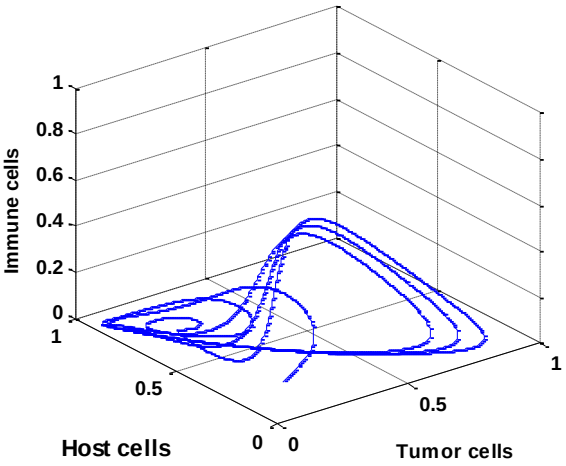

Fig.5. Phase plot between tumour cells, normal cells, and immune cells

Simulation results of controlled dynamics

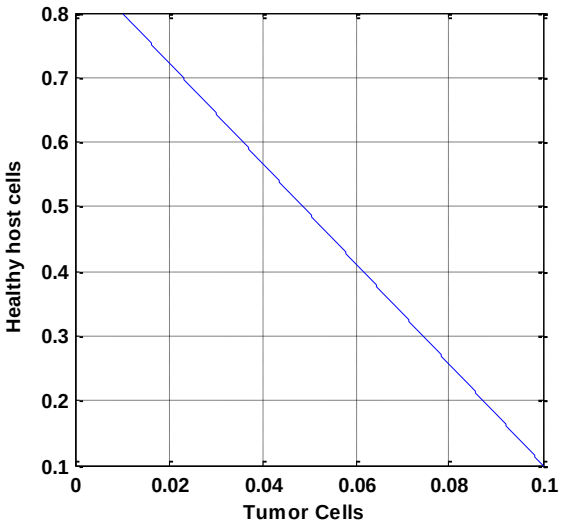

Fig.6. Phase plot between tumour cells and normal cells

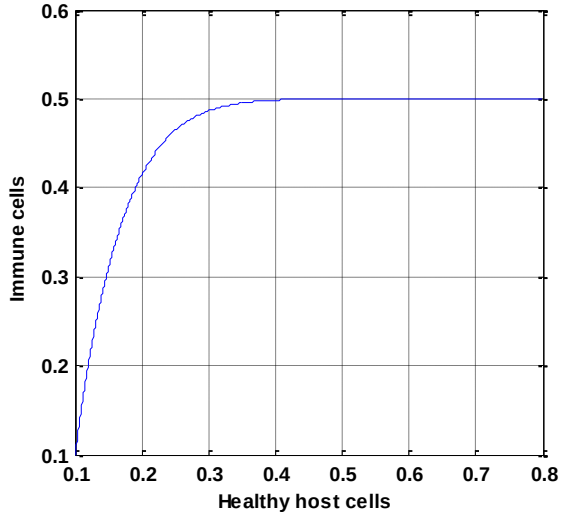

Fig.7. Phase plot between immune cells and normal cells

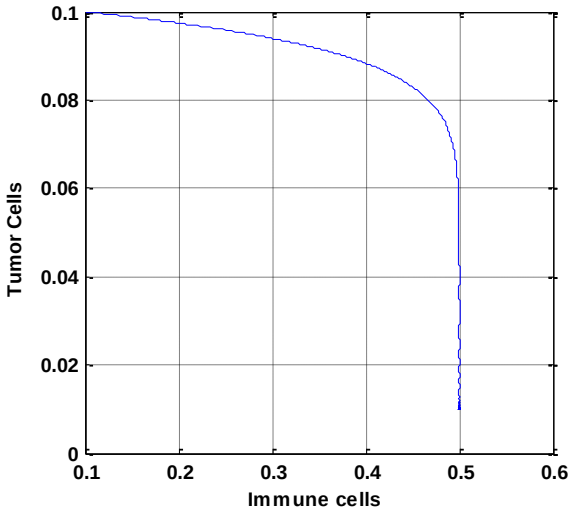

Fig.8. Phase plot between immune cells and tumour cells

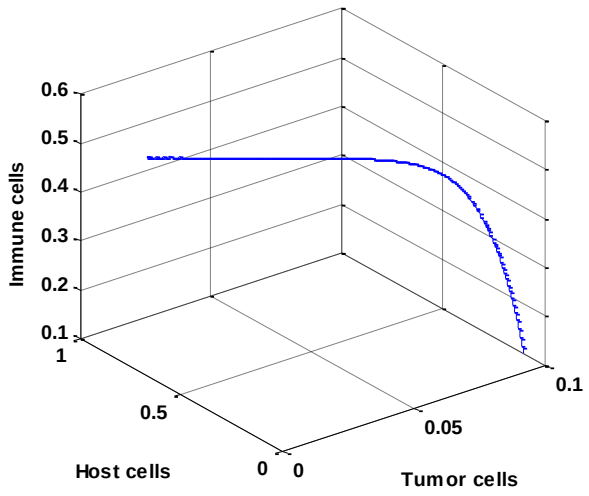

Fig.9. Phase plot between tumour cells, normal cells, and immune cells

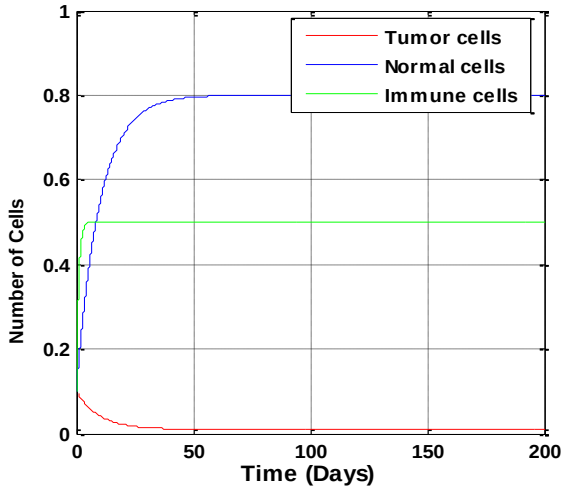

Fig.10. Time response of controlled states

Satisfying Equation (9), the gain values are chosen as $g_1 = 1.1, g_2 = 0.7, g_3 = 0.5$ and simulation results are obtained. It is spectacular from the Fig.10 that the states are converging to the desired values at steady-state. The chaotic behaviour shown by the cell populations in Fig.1 has been controlled by the nonlinear active control technique. We are in a position to obtain better steady-state response which is comparatively qualitative than other works. At steady-state, the tumour volume is almost diminished to a very smaller population which can be considered to be harmless. This gives rise to a notion that, the system has reached to the tumour free equilibrium point. In some research, the healthy host cell was not pondered upon. Here, we can visualise from Fig.10 that the healthy cells are maintained at a particular level which is more than the clinically safe value (> 0.75).As per the clinical requirement, the effecter immune cells are also maintained at a particular level which can be seen from Fig.10. Figures 2,3,4,5 show the phase plot of uncontrolled dynamics, whereas, Figs.6,7,8,9 show the phase plots of controlled dynamics.

6. Concluding remarks

In this research work, the chaotic dynamics of a tumour growth has been controlled effectively by the application of nonlinear active control. From the phase plots of uncontrolled dynamics the cyclic nature was observed which led to the chaos. The chaotic behaviour was controlled by the application of nonlinear active control which can be depicted from the phase plots and time response of controlled dynamics. Being well inside the clinical bounds, the parameters are chosen judiciously. The research will get a complete shape, when the results obtained in-sillico environment can be successfully implemented for in-vivo environment. The steady-staterequirementsare fulfilled and the results are quite convincing compared with other similar works. The uncertainties involved in the parameters and effect of disturbance are not considered in this paper. There is also evidence of measurement error. In future, the robustness issues will be a challenging direction in this field, when the system is subjected to the uncertainties and disturbances. Robust control techniques may be explored in this field.

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