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# An Analysis of the Dynamics of a Cancerous Tumour Model with Targeted Chemotherapy

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## Abstract

We have analyzed a model of Lotka-Volterra type interacting between immune cell-tumour cell-normal cells, where control policy is applied in terms of targeted chemotherapy. We determined conditions for the local stability of all the equilibrium points and global stability condition for the tumour free equilibrium point, including the feasibility of the solution. Further, we have discussed the possibility of Hopf bifurcation at each equilibrium point. Numerical simulation was carried out to observe the qualitative behaviour of the system as the control parameter is varied.

**Keywords:** Global Stability, Hopf Bifurcation, Lotka-Volterra Type, Targeted Chemotherapy

## 1. Introduction

Cancer, a dreaded disease for the last several decades, is characterized by uncontrolled and chaotic or unregulated growth of harmful cells. It is one of the major diseases that attack people belonging to all ethnicities throughout the world. Although cancer is often misconceived as a disease that comes with ageing it can occur in case of people of all ages including babies and children. Of course, statistically, it is found that the majority of the patients belong to the age group of over 55 years. From the scientific research carried out until now, it has been realized that Cancer is a disease in which abnormal cells increase overwhelmingly by the process of uncontrolled division and invade other tissues of the human body. Cancer can attack almost any part of the human body. Cancer is one of the leading causes of death worldwide. Despite its high death rates, nowadays, a large number of cancer patients can be cured with the help different types of treatment methods like surgery, radiotherapy, chemotherapy or immunotherapy, especially if the disease is detected in its early stage.

The goal of cancer treatment is to cure, control or palliation. Factors, which determine the treatment method to be undertaken from those mentioned above, are generally tumour type, location, size and the extent of the tumour. Other important factors which should be considered in determining the treatment plans are the patient's physiological status (eg., presence of co-morbid illnesses), psychological status and personal desires (eg., active treatment versus palliation of symptoms[1].

Each treatment type mentioned above has its advantages and disadvantages. Surgery is generally used for treating solid tumours that are contained in certain body organs like lung, liver etc. Before carrying out the surgery, it is seen whether the patient will be able to tolerate the surgery and anaesthesia, which is applied before the surgery. The main disadvantage of this method of treatment is that if the tumour is located in such parts where some of the tumour cells cannot be removed, then the left out tumour cells can cause recurrence of the disease. In such cases, surgery is generally followed with Radiotherapy so that the left out tumours can be eradicated[2].

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Radiotherapy is a type of treatment, which uses high doses of radiation that can kill tumour cells. However, the main disadvantage of this mode of treatment is that radiation not only kills tumour cells but also damage the surrounding tissues depending on how close those are to the tumour[3-5].

Chemotherapy is a mode of treatment in which different drugs are used to kill tumour cells. Either the main idea of chemotherapy is to eliminate or to reduce the number of malignant cells which are present in the primary and metastatic tumour or to stop or slow the tumour cells which grow and divide quickly. The main disadvantage of Chemotherapy is that apart from killing the tumour cells, it generally kills the healthy cells also and induces side effects, like hair loss, sore mouth, nausea, etc[6-10].

Immunotherapy is another mode of treatment in which effort is concentrated on boosting up the body's immune system to fight tumour cells. Immunotherapy too can cause side effects. Certain types of immunotherapy rev up the immune system, which can make feel flu like symptoms, such as chills, fever, fatigue, muscle aches and so on[11-15].

In comparison, targeted therapy focuses on the inner working of the cancer cells – the programming that sets them apart from normal cells. The main idea of targeted therapy is based on 'precision medicine'. It is a mode of treatment in which changes in cancer cells, which help them, divide, grow and spread is targeted. Either small-molecular drugs or monoclonal antibodies are generally used in this mode of therapy. Those drugs are used for the reason because those are tiny enough to penetrate the cells for targeting the inside mechanism which helps the cells to divide, grow and spread[16-19]. Monoclonal antibodies are also known as therapeutic antibodies, which are nothing but proteins that can be produced in the lab. These proteins are designed and produced in such a way so that they can be attached to specific targets within the cancer cells. Some monoclonal antibodies work in a way so that the cancer cells can be identified by the immune system to get those destroyed. Other types of monoclonal antibodies function in a way either to stop cancer cells from growing or causing them to self-destroy. Certain monoclonal antibodies can also stop signals that help form blood vessels for the spread of cancer, can deliver substances to cancer cells, which can kill them or can starve cancer cells of the hormones it needs to grow. Thus, though targeted therapy with monoclonal antibodies has many advantages, it has some drawbacks like those that cancer cells can become resistant to these antibodies[20,21-24]. For this reason, it may work best when used with other targeted therapies or with other cancer treatments, such as chemotherapy and radiation.

Till date, many authors have proposed many tumour cell growth models and has suggested various control policies that include treatment such as immunotherapy[11,14,25-27], chemotherapy[16,28-32], radiotherapy[4,5] and use of tumour cell targeting viruses etc.[2,33]. In 2003, de Pillis *et al.,*[30] constructed a mathematical model relating tumour growth and immune system iteration. In 2005, in[1], the authors developed a mathematical framework, which can be used to study the principles underlying the emergence and prevention of cancer cells treated with targeted small-molecule drugs. In this work, the authors considered a stochastic dynamical system, which was based on measurable parameters, such as the rate at which resistant mutants are generated and the turnover rate of tumour cells. In 2006, in[33], the authors presented a model of tumour therapy using oncolytic viruses that target tumour cells. In 2009, the authors' of[25] investigated the global dynamics to show under what conditions tumour clearance can be achieved. In 2006, in the paper[34] the authors developed a mathematical model, which considered four subpopulations of the haematopoietic system: progenitors, stem cells, differentiated cells and terminally differentiated cells. In 2012, the authors' of[14] proposed a model related to immunotherapy using transforming growth factor β (TGF-β). In 2017, in the paper[16] the authors proposed a model reflecting the effect of targeted chemotherapy with monoclonal antibodies. In 2003, de Pillis *et al.,*[30] constructed a mathematical model relating to tumour growth and immune system interaction. In this present paper, we propose a tumour model considering the immune cell, tumour cell and normal cell interaction with treatment in the form of targeted chemotherapy of the monoclonal antibody type. Our model is based on the following model proposed by de Pillis *et al.,* in[30], which is:

$$\begin{aligned}\frac{dI}{dt} &= s + \frac{\rho IT}{\alpha + T} - d_1 I \\ \frac{dT}{dt} &= r_1 T\left(1 - b_1 T\right) - c_2 IT - c_3 TN \\ \frac{dN}{dt} &= r_2 N\left(1 - N\right) - c_4 TN\end{aligned} \tag{1}$$

The subsequent part of this paper is structured as follows: In Section 2, model formulation is described mentioning the implication of the various terms and the parameters. In Section 3, we checked the positive invariance and boundedness of the solution of the model. Existence of the equilibrium points and their determination is done in Section 4. In Section 5, we checked the local stability of the equilibrium points. In Section 6, we investigated the possibility of the existence of Hopf bifurcation in the model by using Hurwitz criteria. The occurrence of Hopf bifurcation physically implies the existence of isolated periodic solutions. In Section 7, we constructed a Lyapunov Function to check the global stability of the locally stable tumour free equilibrium point within some parameter range. Numerical simulation is carried out in Section 8 and in Section 9, we drew our conclusions.

## 2. Model Formulation

We consider the tumour growth model suggested by de Pillis *et al.*,[30]. The model describes the interplay between immune cells, tumour cells and normal cells and is represented by a system of nonlinear ordinary differential equations. In contrast to[30], the Lotka-Volterra model is used to describe the interaction between immune cells, tumour cells, normal cells and drug administration. We assume that immune and tumour cells compete with each other in predator-prey fashion rule and tumour and normal cells compete for available resources. In addition, we amended the model by replacing Michaelis-Menten form $\frac{\rho IT}{\alpha+T}$ of the function in the immune system equation with the Lotka-Volterra form $c_1IT$. The reason for doing so is that the rate of change of tumour specific effector cells is difficult to measure experimentally. Therefore, the response function should be an increasing function of the number of tumour cells. Therefore, we assume that the larger the tumour, the greater the response of the immune system, and so, is not bounded above by some constant. Moreover, we apply control policy in term of targeted chemotherapy, which follows the logistic growth law with per capita decay rate after being injected. However, application of drug kills all types of cells but with different kill rates and it kills the normal cells, which grow and divide quickly to induce the side effects. To avoid these side effects we apply targeted chemotherapy, which can be attached to specific targets on the tumour cells, the attachment between drugs and tumour cells consume drugs, which are represented in the last equation by the term-kappa k TV, where, k denotes the combination rate of chemotherapy drug with tumour cells. Also, we introduce a parameter η to describe the effectiveness of the targeted chemotherapy.

Thus, based on de Pillis model, we construct the following mathematical model of immune-tumour–normal cells with targeted chemotherapy:

$$\begin{aligned}
\frac{dI}{dt} &= s+c_1IT-d_1I-a_1(1-\eta)VI \\
\frac{dT}{dt} &= r_1T\left(1-b_1T\right)-c_2IT-c_3TN-a_2VT \\
\frac{dN}{dt} &= r_2N\left(1-N\right)-c_4TN-a_3(1-\eta)VN \\
\frac{dV}{dt} &= \alpha V\left(1-\beta V\right)-d_2V-kTV
\end{aligned} \tag{2}$$

where I(t) represents the number of immune cells, T(t) represents the number of tumour cells, N(t) represents the number of normal cells and V(t) represents the amount of drug administered respectively at time t. The unit of cells is normalised by taking the carrying capacity of normal cells equal to one.

The source of the immune cells is considered to be outside of the system, so it is reasonable to assume a constant influx rate s. Furthermore, in the absence of any tumour, the cells die off at a per capita rate $d_1$, resulting in a long term population size of _ cells. As the tumour cells and normal cells cannot grow without bound, hence, we select tumour cells as well as the normal cells to follow a logistic growth law, with parameters $r_1$ and $r_2$ representing the per capita growth rates and representing the reciprocal carrying capacities of tumour cells. We consider drug administration in the form of targeted chemotherapy follows the logistic rule with drug administration rate α, maximum drug-carrying capacity $\frac{1}{\beta}$ and $d_2$ is the per capita decay rate after being injected.

The interaction between tumour cells and normal cells can result in the death of both cells, which are represented by $-c_3$ TN in the second equation and $-c_4$ NT in the third equation, where $c_3$ and $c_4$ denote the decay rate of tumour

cells due to normal cells and the decay rate of normal cells due to tumour cells. The interaction between tumour cells and immune cells, which are represented by $c_1IT$ and $-c_2IT$, where, $c_1$ and $c_2$ denoted the growth rate of immune cell in the presence of tumour cells and the decay rate of tumour cells due to immune cells. Chemotherapy kills immune cells, tumour cells and normal cells, which is represented by $-a_1(1-\eta)VI$,$-a_2VT$, $-a_3(1-\eta)VN$, where $a_1$, $a_2$, $a_3$ are decay rate of immune cells, tumour cells and normal cells due to chemotherapy, $\eta$ is the effectiveness of the targeted chemotherapy.

For numerical verification of our findings following parameter values are considered, which are taken from earlier cited works, which are mentioned in the table under the head 'source'.

## 3. Positive Invariance of Solutions

To have biological meaning, all values of four state variables must be non-negative. In this section, we will discuss the positive invariance of the solutions of the model.

Integrating the corresponding equations of the proposed model in the interval (0,t) we get,

$$N(t)=\frac{e^{\int_0^t (r_2-c_4T(\xi)-a_3V(\xi))d\xi}}{\int_0^t r_2 e^{\int_\theta^t (r_2-c_4T(\xi)-a_3V(\xi))d\xi} d\theta+N(0)}$$

$$T(t)=\frac{e^{\int_0^t (r_1-c_2I(\xi)-c_3N(\xi)-a_2V(\xi))d\xi}}{\int_0^t r_1 b_1 e^{\int_\theta^t (r_1-c_2I(\xi)-c_3N(\xi)-a_2V(\xi))d\xi} d\theta+T(0)}$$

$$I(t)=e^{\int_0^t -(c_1I(\xi)-d_1-a_1(1-\eta)V(\xi))\,d\xi}$$

$$(I(0)+\int_0^t s\, e^{\int_\theta^t (c_1I(\xi)-d_1-a_1(1-\eta)V(\xi))\,d\xi} d\theta)$$

$$V(t)=\frac{e^{\int_0^t (\alpha-d_2-kT(\xi))d\xi}}{\int_0^t \alpha\beta e^{\int_\theta^t (\alpha-d_2-kT(\xi))d\xi} d\theta+V(0)}$$

Implying $N(t)\geq 0$, $T(t)\geq 0$, $I(t)\geq 0$, $V(t)\geq 0$ for $t\geq 0$, provided that $N(0)\geq 0$, $T(0)\geq 0$, $I(0)\geq 0$ and $V(0)\geq 0$.

Thus, our proposed model is positively invariant which means that for given positive initial values, the solution always remain positive and this is essential from the biological point of view.

**Table 1.** Parameter values considered for the model

| Parameters | Meaning | Values | Source |
|---|---|---|---|
| S | The constant number of immune cells already present in the body | 0.05 | 30 |
| $d_1$ | The natural death rate of immune cells | 0.2 | 30 |
| $r_1$ | The intrinsic tumour growth rate | 0.4 | 30 |
| $r_2$ | The growth rate of normal cell | 0.35 | 30 |
| $1/b_1$ | The tumour population carrying capacity | 1/1.5 | 30 |
| $\beta$ | Maximum drug-carrying capacity | 0.7 | 30 |
| $d_2$ | The natural decay rate of drug | 0.05 | 30 |
| $a_1$ | Immune cell kill rate due to drug | 0.2 | 30 |
| $a_2$ | Tumour cell kill rate due to drug | 0.5 | 30 |
| $a_3$ | Normal cell kill rate due to drug | 0.25 | 30 |
| $c_1$ | The growth rate of immune cells due to tumour cells | 0.2 | 30 |
| $c_2$ | The decay rate of tumour cells due to immune cells | 0.3 | 30 |
| $c_3$ | The decay rate of tumour cells due to normal cells | 0.2 | 30 |
| $c_4$ | The decay rate of normal cells due to tumour cells | 0.25 | 30 |
| $\eta$ | Effectiveness of the targeted chemotherapy | 0.01 | 16 |
| k | Fractional tumour cells killed by chemotherapy | 0.01 | 16 |

## 4. Existence of Equilibrium Points

To obtain the fixed points of the system, we get:

- $E_1(N_1 = 1, T_1 = 0, I_1 = s/d_1, V_1 = 0)$, which is a tumour as well as the drug-free equilibrium point. This equilibrium point means that system is in a healthy stage.
- $E_2\left(N_2 = 1 - \frac{a_3(\alpha - d_2)(1-\eta)}{r_2\alpha\beta}, T_2 = 0, I_2 = \frac{s\alpha\beta}{d_1\alpha\beta + a_1(\alpha - d_2)(1-\eta)}, V_2 = \frac{\alpha - d_2}{\alpha\beta}\right)$,

  which is a tumour-free but not drug-free equilibrium point. This equilibrium point means that after drug administration, the growth of the tumour can be stopped.
- $E_3\left(N_3 = 1 - \frac{c_4 T_3}{r_2}, T_3, I_3 = \frac{s}{d_1 - c_1 T_3}, V_3 = 0\right)$ which is

  a drug-free equilibrium point.

  Here,

$$T_3 = \frac{r_1 - c_2 I_3 - c_3 N_3}{r_1 b_1} = \frac{1}{b_1} - \frac{c_2}{r_1 b_1}\left(\frac{s}{d_1 - c_1 T_3}\right) - \frac{c_3}{r_1 b_1}\left(\frac{r_2 - c_4 T_3}{r_2}\right)$$

Thus, for the existence of $T_3$ discriminant must be positive. This equilibrium point means that tumour persists when no drug is administered.

- The fourth co-existing equilibrium point is given by:

$$E_4\left(N_4 = \frac{r_2\alpha\beta - c_4\alpha\beta T_4 - a_3(1-\eta)(\alpha - d_2 - kT_4)}{r_2\alpha\beta},\right.$$

$$T_4, I_4 = \frac{s\alpha\beta}{d_1\alpha\beta + a_1(1-\eta)(\alpha - d_2 - kT_4) - c_1\alpha\beta T_4},$$

$$\left. V_4 = \frac{\alpha - d_2 - kT_4}{\alpha\beta}\right)$$

Here, $T_4$ is determined by the equation,

$$T_4 = \frac{1}{b_1} - \frac{c_2}{r_1 b_1}\left(\frac{s\alpha\beta}{d_1\alpha\beta + a_1(1-\eta)(\alpha - d_2 - kT_4) - c_1\alpha\beta T_4}\right)$$
$$- \frac{c_3}{r_1 b_1}\left(\frac{r_2\alpha\beta - c_4\alpha\beta T_4 - a_3(1-\eta)(\alpha - d_2 - kT_4)}{r_2\alpha\beta}\right)$$
$$- \frac{a_2}{r_1 b_1}\left(\frac{\alpha - d_2 - kT_4}{\alpha\beta}\right)$$

For the existence of $T_4$, the discriminate must be positive. This equilibrium is the endemic equilibrium point, where, normal cells, tumour cells and immune cells are present after drug administration.

Since N = 0 biologically means the death of the patient, so we discard the equilibrium points having N = 0.

## 5. Local Stability Analysis of the Equilibrium Points

To investigate the local stability of the biologically feasible equilibrium points, we will determine the eigenvalues of the Jacobian matrix at the corresponding equilibrium point.

- The Jacobian matrix of the system at the equilibrium points $E_1$ is:

$$J_{E_1} = \begin{pmatrix} -r_2.1 & -c_4.1 & 0 & -a_3(1-\eta) \\ 0 & r_1 - c_2 s/d_1 - c_3.1 & 0 & 0 \\ 0 & c_1 s/d_1 & -d_1 & -a_1(1-\eta)\, s/d_1 \\ 0 & 0 & 0 & \alpha - d_2 \end{pmatrix}$$

The eigenvalues are: $\lambda_{11} = -r_2$, $\lambda_{12} = r_1 - c_2 s/d_1 - c_3$, $\lambda_{13} = -d_1 < 0$ and $\lambda_{14} = \alpha - d_2 > 0$.

We observe that the eigenvalue $\lambda_{14}$ is positive (from the condition that the drug administration rate can't be less than or equal to the drug decay rate) which shows that the equilibrium point $E_1$ is an unstable saddle point.

- The Jacobian matrix of the system at equilibrium points $E_2$ is:

$$J_{E_2} = \begin{pmatrix} -r_2 + \frac{a_3(\alpha - d_2)(1-\eta)}{\alpha\beta} & -c_4\left(1 - \frac{a_3(\alpha - d_2)(1-\eta)}{r_2\alpha\beta}\right) & 0 & -a_3\left(1 - \frac{a_3(\alpha - d_2)(1-\eta)}{r_2\alpha\beta}\right) \\ 0 & r_1 \frac{c_3 s\alpha\beta}{d_1\alpha\beta + a_1(\alpha - d_2)(1-\eta)} - c_2\left(1 - \frac{a_3(\alpha - d_2)(1-\eta)}{r_2\alpha\beta}\right) - \frac{a_2(\alpha - d_2)}{\alpha\beta} & 0 & 0 \\ 0 & \frac{c_3 s\alpha\beta}{d_1\alpha\beta + a_1(\alpha - d_2)(1-\eta)} & -d_1 - \frac{a_1(\alpha - d_2)(1-\eta)}{\alpha\beta} & -\frac{a_3 s\alpha\beta(1-\eta)}{d_1\alpha\beta + a_1(\alpha - d_2)(1-\eta)} \\ 0 & -k\frac{(\alpha - d_2)}{\alpha\beta} & 0 & -\alpha + d_2 \end{pmatrix}$$

With the eigenvalues

$$\lambda_{21} = -r_2 + \frac{a_3(\alpha - d_2)(1-\eta)}{\alpha\beta}$$

$$\lambda_{22}=r_1-\frac{c_2 s\alpha\beta}{d_1\alpha\beta+a_1(\alpha-d_2)(1-\eta)}-c_3\left(1-\frac{a_3(\alpha-d_2)(1-\eta)}{r_2\alpha\beta}\right)-\frac{a_2(\alpha-d_2)}{\alpha\beta}$$

$$\lambda_{23}=-d_1-\frac{a_1(\alpha-d_2)(1-\eta)}{\alpha\beta}<0$$

$$\lambda_{24}=-\alpha+d_2<0$$

$E_2$ is stable if all the eigenvalues are less than zero. So, for the stability of $E_2$ we must have $\lambda_{21}<0$ and $\lambda_{22}<0$ as the other two eigenvalues are already negative as drug administration rate can't be negative and $0 < \eta < 1$.

$\lambda_{21}< 0$ gives, $\alpha<\frac{a_3(1-\eta)d_2}{a_3(1-\eta)-r_2\beta}$

Thus, we have,

$$1\le\frac{\alpha}{d_2}<\frac{a_3(1-\eta)}{a_3(1-\eta)-r_2\beta} \quad (3)$$

$$\lambda_{22}<0 \Rightarrow r_1-\frac{c_2 s\alpha\beta}{d_1\alpha\beta+a_1(\alpha-d_2)(1-\eta)} -c_3\left(1-\frac{a_3(\alpha-d_2)(1-\eta)}{r_2\alpha\beta}\right)-\frac{a_2(\alpha-d_2)}{\alpha\beta}<0 \quad (4)$$

So, the equilibrium point $E_2$ is stable if condition (3) and (4) are satisfied together.

- The Jacobian matrix of the system at equilibrium points $E_3$ is:

$$J_{E_3}=\begin{pmatrix} -r_2+c_4T_3 & -c_4\left(1-\frac{c_4T_3}{r_2}\right) & 0 & -a_3(1-\eta)\left(1-\frac{c_4T_3}{r_2}\right) \\ -c_3T_3 & r_1-2r_1b_1T_3-\frac{c_2s}{d_1-c_1T_3}-c_3(1-\frac{c_4T_3}{r_2}) & -c_2T_3 & -a_2T_3 \\ 0 & \frac{c_1s}{d_1-c_1T_3} & -d_1+c_1T_3 & \frac{-a_1(1-\eta)s}{d_1-c_1T_3} \\ 0 & 0 & 0 & \alpha-d_2-kT_3 \end{pmatrix}$$

We observe that the eigenvalue $\lambda_{34} = \alpha - d_2 - kT_3$ is always positive for the values in (Table 1). Therefore, the equilibrium point is an unstable point.

- The Jacobian matrix of the system at $E_4$ becomes:

$$J_{E_4}=\begin{pmatrix} A & -c_4N_4 & 0 & -a_3(1-\eta)N_4 \\ -c_3T_4 & B & -c_2T_4 & -a_2T_4 \\ 0 & c_1I_4 & C & -a_1(1-\eta)I_4 \\ 0 & -kV_4 & 0 & D \end{pmatrix}$$

where, $A=r_2 - 2r_2 N_4 - c_4 T_4 - a_3(1-\eta) V_4$,
$B=r_1 - 2r_1 b_1 T_4 - c_2 I_4 - c_3 N_4 - a_2 V_4$,
$C=-d_1 + c_1 T_4 - a_1 (1-\eta) V_4$,
$D= \alpha-2\alpha \beta V_4 - d_2$

The characteristic equation of $J_{E_4}$ is:

$=>\lambda^4-(A+B+C+D)\lambda^3+(AB+AC+AD+BC+BD+CD+c_1c_2I_4T_4-ka_2T_4V_4-c_3c_4N_4T_4)\lambda^2-\{ABC+ABD+ACD+BCD-k a_1c_2 T_4V_4(1-\eta) + c_1c_2I_4T_4(A+D) -k a_2 T_4 V_4 (A+C)- c_3 c_4 N_4 T_4 (C+D)-k a_3 c_3 N_4 T_4V_4 (1-\eta)\}\lambda+ \{ABCD+ c_1c_2 AD I_4 T_4 -k a_1 c_2 A T_4V_4 (1-\eta)-k a_2 AC T_4 V_4 - c_3c_4 CD N_4 T_4 -k a_3c_3 C (1-\eta) N_4T_4V_4\} =0$

$=> \lambda^4 + X\lambda^3 + Y\lambda^2 + Z\lambda + W=0$ (say)

By Routh-Hurwitz stability criteria, $E_4$ is stable when $X>0, Y>0, Z>0, XY>Z$ and $(XY-Z)Z - X_2 W>0$ .

Where,

$X>0 => r_2 -2r_2 N_4 - c_4 T_4 - a_3 (1-\eta) V_4 + r_1 -2 r_1 b_1 T_4 - c_2 I_4 - c_3 N_4 - a_2 V_4 -d_1 + c_1 T_4 -a_1 (1-\eta) V_4 + \alpha-2\alpha \beta V_4 -d_2<0$

$Y>0 => AB+AC+AD+BC+BD+CD+ c_1 c_2 I_4 T_4 > k a_2 T_4 V_4 + c_3c_4 N_4 T_4$

$Z>0 => ABC+ABD+ACD+BCD-k a_1c_2 T_4 V_4 (1-\eta) + c_1c_2 I_4 T_4 (A+D) <k a_2 T_4V_4(A+C) + c_3c_4 N_4 T_4 (C+D) +k a_3 c_3 N_4 T_4 V_4 (1-\eta)$

$XY>Z => (A+B+C+D)(AB+AC+AD+BC+BD+CD+c_1c_2I_4T_4 -k a_2 T_4V_4 - c_3c_4N_4 T_4) < \{ABC+ABD+ACD+BCD-k a_1c_2T_4V_4 (1-\eta) + c_1c_2 I_4T_4 (A+D)-k a_2 T_4V_4 (A+C)- c_3c_4 N_4T_4(C+D)-k a_3c_3N_4T_4V_4(1-\eta)\}$

$(XY-Z)Z - X^2W > 0 [- (A+B+C+D)(AB + AC + AD+BC + BD + CD + c_1c_2 I_4 T_4 - k a_2 T_4V_4- c_3c_4 N_4T_4) + \{ABC+ABD+ACD+BCD - k a_1c_2T_4V_4 (1-\eta) + c_1c_2I_4T_4 (A+D)- k a_2 T_4V_4(A+C)- c_3c_4 N_4 T_4 (C+D)- k a_3c_3 N_4T_4V_4 (1-\eta)\}] \{ABC+ABD+ACD+BCD - k a_1c_2T_4V_4 (1-\eta) + c_1c_2I_4T_4 (A+D)- k a_2T_4V_4 (A+C) - c_3c_4N_4T_4 (C+D)- k a_3c_3 N_4 T_4V_4 (1-\eta)\} + (A+B+C+D)^2 \{ABCD + c_1c_2 AD I_4T_4 - k a_1 c_2 A T_4 V_4 (1-\eta)- k a_2AC T_4V_4 - c_3c_4CD N_4T_4- k a_3c_3C (1-\eta) N_4 T_4V_4\} <0$

## 6. Possibility of Hopf Bifurcation at the Equilibrium Points

Mathematically, Hopf bifurcation occurs when a system has a pair of purely imaginary conjugate eigenvalues of the Jacobian matrix at an equilibrium point when the corresponding parameter value is changed. Physically occurrence of Hopf Bifurcation means the existence of a limit cycle, which is an isolated periodic solution of a non-linear system. Therefore, we are interested to study whether such a parameter value exists in our considered nonlinear system.

- In this section, we check for the possibility of Hopf bifurcation arising from the equilibrium point $E_1$. We evaluate the characteristic equation of the Jacobian matrix $J_{E_1}$ of the system which is found to $P(\lambda) = \lambda^4 + p_1\lambda^3 + p_2\lambda^2 + p_3\lambda + p_4$

where, $p_1 = -(-r_2 + r_1 - c_2 s/d_1 - c_3 - d_1 + \alpha - d_2)$

$p_2 = -(r_2 + d_1)(r_1 - c_2 s/d_1 - c_3) + r_2 d_1 - (r_2 + d_1)(\alpha - d_2) + (r_1 - c_2 s/d_1 - c_3)(\alpha - d_2)$

$p_3 = -\{r_2(r_1 - c_2 s/d_1 - c_3) d_1 - (r_2 + d_1)(r_1 - c_2 s/d_1 - c_3)(\alpha - d_2) + r_2 d_1(\alpha - d_2)\}$

And $p_4 = r_2(r_1 - c_2 s/d_1 - c_3) d_1(\alpha - d_2)$

By Hurwitz criteria if $(p_1p_2 - p_3) p_3 - p_4 p_1^2 = 0$, then Hopf bifurcation may occur at $E_1$[35]. Taking parameter values from (Table 1), the condition $(p_1p_2 - p_3) p_3 - p_4 p_1^2 = 0$, gives three values of the drug administration rate α out of which one value is negative and the other two are biologically meaningful values of α. Now we check for the possibility of Hopf bifurcation corresponding to these two biologically meaningful points. It is found that corresponding to these two values of α, the eigenvalues of the Jacobian matrix are real number and so, there is no Hopf bifurcation occurring at the equilibrium point $E_1$. The mathematical evidence is provided below.

- Here, Characteristic equation of the Jacobian matrix $J_{E_2}$

$P(\lambda) = \lambda^4 + q_1\lambda^3 + q_2\lambda^2 + q_3\lambda + q_4$

We apply the Hurwitz criteria,

$$(q_1q_2 - q_3) q_3 - q_4 q_1^2 = 0 \quad (5)$$

Where,

$$q_1 = -\{-r_2 + \frac{a_3(\alpha - d_2)(1-\eta)}{\alpha\beta} + r_1 - \frac{c_2 s\alpha\beta}{d_1\alpha\beta + a_1(\alpha - d_2)(1-\eta)} - c_3\left(1 - \frac{a_3(\alpha - d_2)(1-\eta)}{r_2\alpha\beta}\right) - \frac{a_2(\alpha - d_2)}{\alpha\beta} - d_1 - \frac{a_1(\alpha - d_2)(1-\eta)}{\alpha\beta} - \alpha + d_2\}$$

$$q_2 = \left(-r_2 + \frac{a_3(\alpha - d_2)(1-\eta)}{\alpha\beta}\right)\left(r_1 - \frac{c_2 s\alpha\beta}{d_1\alpha\beta + a_1(\alpha - d_2)(1-\eta)} - c_3\left(1 - \frac{a_3(\alpha - d_2)(1-\eta)}{r_2\alpha\beta}\right) - \frac{a_2(\alpha - d_2)}{\alpha\beta}\right) + \left(-r_2 + \frac{a_3(\alpha - d_2)(1-\eta)}{\alpha\beta}\right)$$

$$(-\alpha + d_2) + \left(r_1 - \frac{c_2 s\alpha\beta}{d_1\alpha\beta + a_1(\alpha - d_2)(1-\eta)} - c_3\left(1 - \frac{a_3(\alpha - d_2)(1-\eta)}{r_2\alpha\beta}\right) - \frac{a_2(\alpha - d_2)}{\alpha\beta}\right)(-\alpha + d_2) + \left(-r_2 + \frac{a_3(\alpha - d_2)(1-\eta)}{\alpha\beta}\right)\left(-d_1 - \frac{a_1(\alpha - d_2)(1-\eta)}{\alpha\beta}\right)$$

$$q_3 = \left(-r_2 + \frac{a_3(\alpha - d_2)(1-\eta)}{\alpha\beta}\right)\left(r_1 - \frac{c_2 s\alpha\beta}{d_1\alpha\beta + a_1(\alpha - d_2)(1-\eta)} - c_3\left(1 - \frac{a_3(\alpha - d_2)(1-\eta)}{r_2\alpha\beta}\right) - \frac{a_2(\alpha - d_2)}{\alpha\beta}\right)\left(d_1 + \frac{a_1(\alpha - d_2)(1-\eta)}{\alpha\beta}\right) + (\alpha - d_2)\left(-r_2 + \frac{a_3(\alpha - d_2)(1-\eta)}{\alpha\beta}\right)\left(r_1 - \frac{c_2 s\alpha\beta}{d_1\alpha\beta + a_1(\alpha - d_2)(1-\eta)} - c_3\left(1 - \frac{a_3(\alpha - d_2)(1-\eta)}{r_2\alpha\beta}\right) - \frac{a_2(\alpha - d_2)}{\alpha\beta}\right) + \left(-d_1 - \frac{a_1(\alpha - d_2)(1-\eta)}{\alpha\beta}\right)(\alpha - d_2)\left(r_1 - \frac{c_2 s\alpha\beta}{d_1\alpha\beta + a_1(\alpha - d_2)(1-\eta)} - c_3\left(1 - \frac{a_3(\alpha - d_2)(1-\eta)}{r_2\alpha\beta}\right) - \frac{a_2(\alpha - d_2)}{\alpha\beta}\right) + \left(-r_2 + \frac{a_3(\alpha - d_2)(1-\eta)}{\alpha\beta}\right)\left(-d_1 - \frac{a_1(\alpha - d_2)(1-\eta)}{\alpha\beta}\right)(\alpha - d_2)$$

$$q_4 = \left(-r_2 + \frac{a_3(\alpha - d_2)(1-\eta)}{\alpha\beta}\right)\left(r_1 - \frac{c_2 s\alpha\beta}{d_1\alpha\beta + a_1(\alpha - d_2)(1-\eta)}\alpha\beta - c_3\left(1 - \frac{a_3(\alpha - d_2)(1-\eta)}{r_2\alpha\beta}\right) - \frac{a_2(\alpha - d_2)}{\alpha\beta}\right)\left(-d_1 - \frac{a_1(\alpha - d_2)(1-\eta)}{\alpha\beta}\right)(-\alpha + d_2)$$

After solving the Equation (5), we get 12 values of the drug administration rate α. One value is negative, eight values are imaginary and three values are positive and out of these three positive values, two values are less than the natural decay rate of the drug. That is there are only one biologically meaningful values of α obtained on solving the condition 5. So, we check for the possibility of Hopf bifurcation corresponding to this biologically meaningful point. It is found that corresponding to this value of α, the eigenvalues of the Jacobian matrix are a real number which confirm that there is no Hopf bifurcation occurring at the equilibrium point $J_{E_2}$

- For the Jacobian matrix at $E_3$ one of the eigenvalue $\lambda_{34} = \alpha - d_2 - k T_3$ is always positive and the other three eigenvalues can be derived from the equation, $\lambda^3 + m_1\lambda^2 + m_2\lambda + m_3 = 0$

where, $m_1 = -\{(-r_2 + c_4 T_3) + (r_1 - 2 r_1 b_1 T_3 - c_2 I_3 - c_3 N_3) + (c_1 T_3 - d_1)\}$

$m_2 = (r_1 - 2 r_1 b_1 T_3 - c_2 I_3 - c_3 N_3)(c_1 T_3 - d_1) + c_1 c_2 I_3 T_3 + (-r_2 + c_4 T_3)(c_1 T_3 - d_1) + (-r_2 + c_4 T_3)(r_1 - 2 r_1 b_1 T_3 - c_2 I_3 - c_3 N_3) - c_3 c_4 N_3$

$= -\{(-r_2 + c_4 T_3)\{(r_1 - 2 r_1 b_1 T_3 - c_2 I_3 - c_3 N_3)(c_1 T_3 - d_1) + c_1 c_2 I_3 T_3\} - c_3 c_4 N_3 T_3 (c_1 T_3 - d_1)\}$

For valid values of $T_3$ i.e. where, $T_3$ is non-negative, we get $m_1 m_2 - m_3 \neq 0$. Thus, the Hurwitz criteria, $m_1 m_2 - m_3 = 0$ for the parameter values taken from the Table 1 is not satisfied as drug administration can't be negative. Hence, there is no Hopf bifurcation arising from $E_3$.

- The fourth co-existing equilibrium point is given by:

$$E_4\left(N_4=\frac{r_2\alpha\beta-c_4\alpha\beta T_4-a_3(1-\eta)(\alpha-d_2-kT_4)}{r_2\alpha\beta},\ T_4, I_4=\frac{s\alpha\beta}{d_1\alpha\beta+a_1(1-\eta)(\alpha-d_2-kT_4)-c_1\alpha\beta T_4},\ V_4=\frac{\alpha-d_2-kT_4}{\alpha\beta}\right)$$

Here, $T_4$ is determined by the Equation,

$$T_4=\frac{1}{b_1}-\frac{c_2}{r_1b_1}\left(\frac{s\alpha\beta}{d_1\alpha\beta+a_1(1-\eta)(\alpha-d_2-kT_4)-c_1\alpha\beta T_4}\right)-\frac{c_3}{r_1b_1}\left(\frac{r_2\alpha\beta-c_4\alpha\beta T_4-a_3(1-\eta)(\alpha-d_2-kT_4)}{r_2\alpha\beta}\right)-\frac{a_2}{r_1b_1}\left(\frac{\alpha-d_2-kT_4}{\alpha\beta}\right)$$

$\Rightarrow A_2T_4^{\,2}+B_2T_4+C_2=0$

where, $A_2=(c_3c_4\,\alpha\beta+a_2r_2k-r_1r_2b_1\alpha\beta-c_2a_3k(1-\eta))(c_1\alpha\beta+a_1k(1-\eta))$

$B_2=(r_1r_2\alpha\beta-c_3r_2\alpha\beta+(c_3a_3(1-\eta)-a_2r_2)(\alpha-d_2))(c_1\alpha\beta+a_1(1-\eta)k)-(c_3c_4\alpha\beta+a_2r_2k-r_1r_2b_1\alpha\beta-c_2a_3k(1-\eta))$

$(d_1\alpha\beta+a_1(1-\eta)(\alpha-d_2))$

$C_2=c_2r_2s\alpha^2\beta^2-(r_1r_2\alpha\beta-c_3r_2\alpha\beta+(c_3a_3(1-\eta)-a_2r_2)(\alpha-d_2))(d_1\alpha\beta+a_1(1-\eta)(\alpha-d_2))$

For the existence of the discriminate must be positive i.e. $B_2^{\,2}-4A_2C_2\geq 0$ which gives the following possible range for the drug administration rate α (for the parameter values in Table 1):

$\alpha\leq -4.35701$, $0.0089987\leq\alpha\leq 0.0292904$ and $\alpha\geq 4.44415$.

But all the above ranges are not biologically feasible as the first range gives the negative value of drug administration rate α, the second range shows that the drug administration rate α is lower than the natural decay rate for the drug and finally for the third range the value of $N_4$ becomes negative and so discarded.

Thus, for the parameter values taken from (Table 1), the equilibrium point $E_4$ does not exist and hence the possibility of Hopf bifurcation at $E_4$ does not arise.

## 7. Global Stability Analysis of the Tumour-Free Equilibrium Point $E_2$

In this section, we show that the tumour free equilibrium point $E_2$ is globally asymptotically stable if $N_{min}>\frac{r_1+r_2}{r_2+c_3}$, where, $N_{min}$ denotes the minimum number of normal cells.

To prove this, we construct a Lyapunov function of the form $W(N,T)=(N-N_2)^2+(T-T_2)^2$, which is positive definite and continuously differentiable for all positive bounded values of N and T. That is $W(N_2,T_2)=0$, and $W(N,T)>0\ \forall\ (N,T)$ in an isolated neighbourhood of $(N_2,T_2)$ [$N_2$ and $T_2$ corresponds to the equilibrium point $E_2$]

We have $\dot{W}=2(N-N_2)\dot{N}+2(T-T_2)\dot{T}$

$=2(N-N_2)(r_2N(1-N)-c_4TN-a_3(1-\eta)VN)+2(T-T_2)(r_1T(1-b_1T)-c_2IT-c_3TN-a_2VT)$

$\leq 2N(N-N_2)(r_2(1-N)-c_4T)+2T(T-T_2)(r_1(1-b_1T)-c_3N)$

$\leq 2N^2(r_2(1-N)-c_4T)+2T^2(r_1(1-b_1T)-c_3N)$ [Since $N-N_2\leq N$, $T_2=0$]

$\leq 2(r_2(1-N)-c_4T)+2(r_1(1-b_1T)-c_3N)$ [Since N, T≤1]

$\leq 2(r_2(1-N_{min})-c_4T_{min})+2(r_1(1-b_1T_{min})-c_3N_{min})$

$\leq (r_1+r_2)-(r_2+c_3)N_{min}-(r_1b_1+c_4)T_{min}$

where, $N_{min}$ and $T_{min}$ denotes the minimum normal cell and tumour cell population that can be present in the body respectively. It is easy to see that $T_{min}=0$.

Hence, $\dot{W}<0$ on imposing the condition

$$(r_1+r_2)-(r_2+c_3)N_{min}<0 \text{ i.e } N_{min}>\frac{r_1+r_2}{r_2+c_3}=K \text{ (say)}$$

Now when $t\to\infty$ and $N_{min}>K$, $T\to 0$ and under this limiting condition the equation corresponding to the drug administration becomes $\frac{dV}{dt}=\alpha V(1-\beta V)-d_2V$ with the limiting solution $V(t)\to\frac{\alpha-d_2}{\alpha\beta}=V^*$ (say)

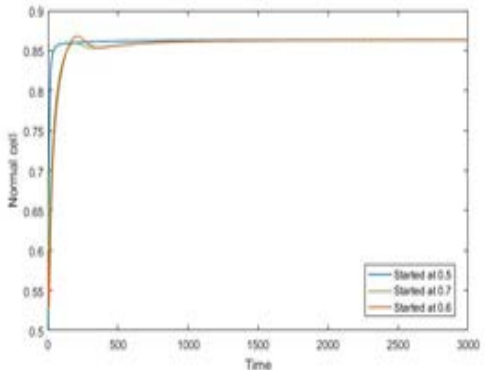
Again under the above limiting conditions, the equation corresponding to the immune cells becomes $\frac{dI}{dt}=s-d_1I-a_1(1-\eta)V^*I$ with the limiting solution $I(t)\to\frac{s\alpha\beta}{d_1\alpha\beta+a_1(\alpha-d_2)(1-\eta)}$

Therefore, imposing the condition $N_{min}>\frac{r_1+r_2}{r_2+c_3}$, the tumour-free equilibrium point $E_2$ can be made globally asymptotically stable if the conditions for its local stability are satisfied which was discussed in Section 5.

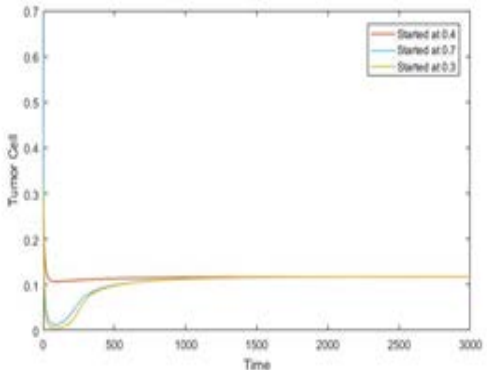
## 8. Numerical Simulation

Verification of our results has been done through numerical simulations viz. time series plots and phase diagrams. Considering the parameter values taken from

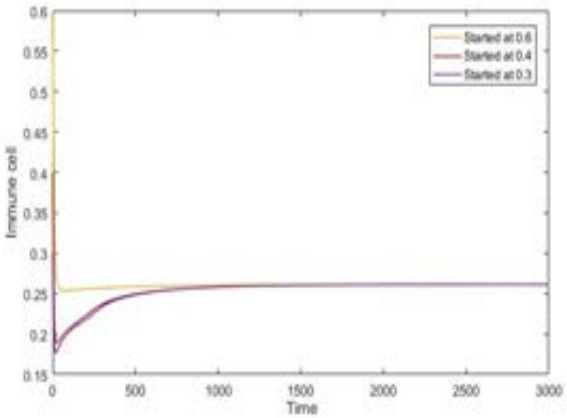
(Table 1) and the rate of drug administration to be α = .054, the trajectory of the system is drawn in the (Figure 1) for different initial points which show that the solution of the system approaches asymptotically to the coexisting equilibrium point $E_4$ = (0.86,0.117,0.26,0.075). Thus, if the rate of drug administration is α = .062, coexisting equilibrium point $E_4$ goes to tumour free equilibrium $E_2$ as shown in Figure 2(c).



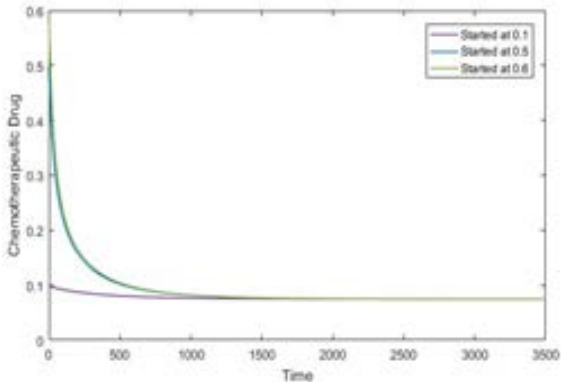

(a)




(b)

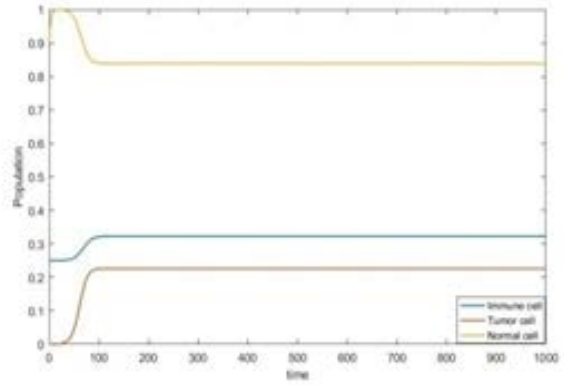



(c)

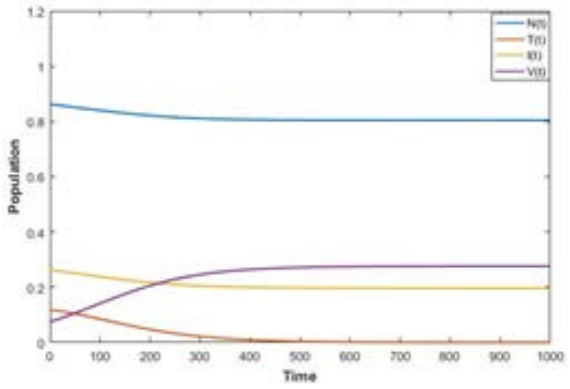



(d)

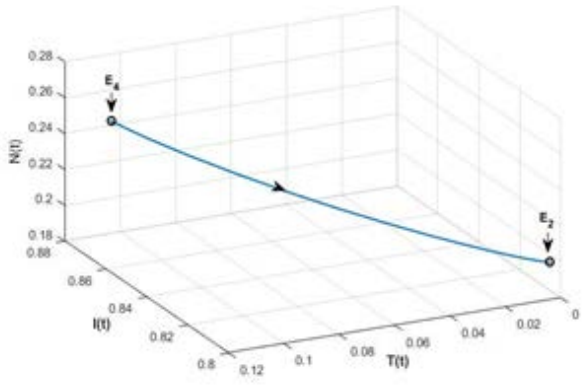
**Figure 1.** Time series of the solution of system (a) trajectories of Normal cells as a function of time, (b) trajectories of Tumour cells as a function of time, (c) trajectories of Immune cells as a function of time and (d) trajectories of drug administration as a function of time for the different initial condition.




(a)




(b)




(c)

**Figure 2.** (a) Time series solution of the system without treatment case, (b) with treatment case (c). This figure depicts the coexisting equilibrium $E_4$ goes to the globally stable equilibrium $E_2$.

## 9. Conclusion

In this paper, we have proposed a new nonlinear ordinary differential equation model involving immune-tumour-normal cells and studied the effect of targeted chemotherapy. We find that the equilibrium points of the system and derived the conditions for local stability at each of the equilibrium points. We also derived the condition for global stability of the tumour free equilibrium point by constructing a Lyapunov function. Local stability of an equilibrium point would imply that the disease would be eliminated only for short time (provided certain conditions are satisfied) whereas global stability implies that the disease finally dies out, again, of course under certain conditions. Using Hurwitz criterion and numerical calculation, it has been shown that no Hopf bifurcation can arise at each of the biologically feasible equilibrium points, which mean that there is no isolated periodic solution or limit cycle surrounding the equilibrium points, as certain considered parameter value change. Some numerical simulations were shown in support of the analytical results. In our numerical simulation, we found the value of drug administration for which the coexisting equilibrium is going for tumour free equilibrium. More particularly, it is seen that if the value of $\alpha = 0.062$, the tumour can be eradicated from the body. Of course, the study can be made more effective and realistic if we can use parameter values after estimating the feasible domain of the each of the parameters mentioned in Table 1 and then use different drug administration schedule depending on those biologically feasible parameter values. Moreover, incorporation of time lag in the immune cell-tumour cell interaction in the model can give better results. We will carry out these studies in our future research work.

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