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A STUDY ON A GENE THERAPY MODEL FOR THE COMBINED TREATMENT OF CANCER

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Abstract This paper addresses a gene therapy model under different cancer treatment combinations, considering effector cell and cancer cell populations. A gene therapy model has been modified by introducing radiotherapy and mAb drug treatment, respectively. The qualitative behaviour of the model under gene therapy, radio-genic therapy, and mAb-gene therapy is examined at each of the equilibrium points of the model. Analytical findings have been verified numerically. In addition, the system's dynamics have been investigated for different values of the treatment parameters. Our results reveal that the optimum level of immunotherapy can eradicate cancer cells from the body for the gene therapy model. Besides these findings, we have also found that combining radiotherapy, immunotherapy, and gene therapy could be a better cancer treatment strategy. For mAb-gene therapy, two scenarios have been presented in which the applied treatment can suppress cancer growth to zero.

Key words: mathematical modelling, cancer treatment, gene therapy, immunotherapy, radiotherapy, monoclonal antibody therapy (mAb), stability.

AMS Mathematics Subject Classification: 37M05, 37M10, 37N25, 92B05.

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1 Introduction

Cancer is caused by malignant tumours, which are uncontrollable growths of abnormal cells. In the initial stage, a tumour is not so dangerous; it becomes so when it invades other tissues and gains the ability to spread rapidly within the body. In the early 1990s, researchers developed mathematical models to explore the complex phenomenon of tumour-immune dynamics [1, 2, 4, 3]. Also, a few works [5, 6, 7, 8, 9] were carried out to observe the effect of different treatment procedures on tumour-immune dynamics. During this time, surgery, radiotherapy, chemotherapy, and immunotherapy were the primary treatment methods for cancer management. However, effective treatment depends on many factors, such as the tumour's response to the treatment, the stage and location of the tumour, the patient's immune response to the applied treatment, etc. So, combining two or more treatments has gained more interest in searching for effective cancer treatment. The current study separately represents a gene therapy model under radiotherapy and mAb therapy.

The prime aspect of surgery for cancer treatment is to remove the tumour physically through an operating procedure. In radiation treatment, an ionizing agent kills

cancer cells by depositing energy in the tissue sites [10, 11]. Chemotherapy is a cycle-based treatment protocol where chemical drugs are used to eradicate cancer; it also harms other healthy tissues of the body. The main target of immunotherapy in cancer treatment is to enhance or boost the patients' immune systems using external input to fight against cancer. At the present time, clinical oncologists are using gene therapy [11, 12, 13], and monoclonal antibody therapy (mAb) [15, 16, 14] for cancer treatment. Gene therapy is an effective cancer treatment that induces a well-engineered gene into the body's abnormal cells. In mAb therapy, external input is injected to activate the body's antibodies to attack the tumour directly.

Recently, a few reports have been published investigating the effects of various treatment strategies for cancer management. Belostotski and Freedman have modelled the radiotherapy treatment for cancer eradication with different control policies [17]. In [18], the authors have highlighted the importance of mathematical modelling in therapeutic success and developing efficient therapies for cancer treatment. de Pillis et al.[29] developed a mathematical model to investigate the effectiveness of mAb treatment on colorectal cancer growth. The authors of [19] proposed three models to understand the impact of radiation when the cancerous cells, the healthy cells, and the cells triggered by the immune cells interact. Considering targeted chemotherapy as a treatment for cancer, Liu and Liu constructed a model and found that targeted chemotherapy is a more effective treatment than regular chemotherapy to kill tumour cells [20]. Talkington et al. [21] explored the effect of adoptive immunotherapy for cancer treatment on four earlier mathematical models: Kuznetsov et al.[1], Kirschner and Panetta [6], Dong et al. [22], and Moore and Li [23]. Their results revealed that adoptive immunotherapy can successfully drive a patient from the large tumour fixed point to equilibrium with little or no tumour. A mathematical study by Ghosh and Banerjee [24] reported that antibodies also play a vital role in the cancer-immune system. A Caputo-type fractional-order mathematical model was proposed by Farayola et al. for cancer treatment via radiotherapy [25]. A practical scenario of a tumour clearance problem was described in [26] by considering a six-dimensional mathematical model under chemo-immunotherapy treatments.

In 2013, Tsygvintsev et al. [28] proposed a gene therapy model considering effector cells and cancerous cells. Tsygvintsev et al. [28] proposed their model using two nonlinear differential equations:

$$\frac{dI}{dt} = q(t)M + \frac{pI}{I+f} - dI + u(t),$$
$$\frac{dM}{dt} = r(t)M(1-bM) - a(t)\frac{IM}{g+M},$$

where $I(t)$ denotes the effector cell population and $M(t)$ denotes the cancerous cell population at time $t > 0$. They considered the parameters $q(t)$ for cancer antigenicity, $u(t)$ for immunotherapy, $r(t)$ for logistic cancer growth, and $a(t)$ for rate of cancer clearance by gene therapy to be varied with time. However, in our study, we keep $q(t)$ and $r(t)$ as constants, whereas $u(t)$ and $a(t)$ vary with time. Tsygvintsev et al. [28]

found that combining a high amount of immunotherapy and gene therapy could have a better result in clearing cancer from the body. Since a high dose of immunotherapy causes many side effects like nausea, fever, etc. Keeping these side effects in mind, we modified the Tsygvintsev et al. [28] model by introducing a new treatment parameter, γ, for radiotherapy following Isea and Lonngren [19]. We have also assumed that radiation energy is deposited directly into the cancer site to kill cancerous cells only. Therefore, the model under radiotherapy becomes

$$\begin{aligned}\frac{dI}{dt} &= qM + \frac{pI}{I+f} - dI + u,\\ \frac{dM}{dt} &= rM(1-bM) - \frac{aIM}{g+M} - \gamma M.\end{aligned}$$

Furthermore, another modification of the Tsygvintsev et al. [28] model is carried out with the inclusion of monoclonal antibody (mAb) therapy [29] for killing cancer cells directly. For this, we induce a new equation into the model [28] to describe mAb drug administration $C(t)$ at time t. The modified model takes the form

$$\begin{aligned}\frac{dI}{dt} &= qM + \frac{pI}{I+f} - dI + u,\\ \frac{dM}{dt} &= rM(1-bM) - \frac{aIM}{g+M} - kMC,\\ \frac{dC}{dt} &= -\eta C - \rho M\frac{C}{h+C} + v,\end{aligned}$$

where the term $-kMC$ in the second equation represents the death of cancer cells due to interaction with mAb. In the third equation, v denotes the initial amount of mAb drugs. The mAb protein in the body can be degraded via a natural process denoted by $-\eta C$. The term $-\rho M\frac{C}{h+C}$ represents the loss of available mAbs as they bind to cancer cells.

The rest of the paper is organized as follows: Section 2 discusses the qualitative analysis of the proposed model under the considered treatments. Then, the numerical simulations of our qualitative results are presented in section 3. Finally, section 4 summarises the present study.

2 Qualitative analysis

In this section, we will discuss the qualitative behaviour of our proposed model under different treatment combinations at the equilibrium points to understand the dynamical properties of the model. For this, we assume that all three equations of the system ensure positive and bounded solutions.

2.1 The model under gene therapy

The gene therapy model takes the form

$$\begin{aligned} \frac{dI}{dt} &= qM + \frac{pI}{I+f} - dI + u, \\ \frac{dM}{dt} &= rM(1-bM) - \frac{aIM}{g+M}. \end{aligned} \tag{1}$$

We first search the equilibrium points of the model (1) by setting $\frac{dI}{dt} = 0$ and $\frac{dM}{dt} = 0$. The equilibrium points of the system (1) are

1. Cancer free equilibria: $P_1(I_1, 0)$ and $P_2(I_2, 0)$, where I_1 and I_2 are calculated from the following equation

$$dI^2 - (p + u - df)I - uf = 0.$$

Solving above equation we get I_1 and I_2 as

$$I_1 = \frac{\chi_1 + \sqrt{\chi_2}}{2d}, \quad I_2 = \frac{\chi_1 - \sqrt{\chi_2}}{2d},$$

where

$$\chi_1 = p + u - df, \quad \chi_2 = (p + u - df)^2 + 4duf.$$

The equilibria P_1 and P_2 will exist only when $I_1 > 0$ and $I_2 > 0$ respectively.

2. Cancer infected equilibrium: $P^*(I^*, M^*)$, where

$$I^* = \frac{r(1 - bM^*)(g + M^*)}{a}, \quad M^* = \frac{dI^* - u - \frac{pI^*}{I^*+f}}{q}.$$

The equilibrium P^* will exist if $dI^* > u + \frac{pI^*}{I^*+f}$ and $M^* < \frac{1}{b}$.

Now, we will check the dynamics of the system (1) at the equilibria P_1, P_2 and P^*. For this, we obtain the Jacobian matrix by linearizing the system (1). The Jacobian matrix of the system (1) is

$$J = \begin{pmatrix} -d + \frac{pf}{(I+f)^2} & q \\ \frac{-aM}{g+M} & r(1-2bM) - \frac{agI}{(g+M)^2} \end{pmatrix}.$$

Corresponding to the cancer free equilibrium point $P_1(I_1, 0)$ the Jacobian matrix is

$$J(P_1) = \begin{pmatrix} -d + \frac{pf}{(I_1+f)^2} & q \\ 0 & r - \frac{aI_1}{g} \end{pmatrix}.$$

The eigenvalues of $J(P_1)$ are: $-d + \frac{pf}{(I_1+f)^2}$ and $r - \frac{aI_1}{g}$. Hence, P_1 is stable if $\frac{pf}{(I_1+f)^2} < d$ and $r < \frac{aI_1}{g}$; otherwise unstable.

Similarly, corresponding to the cancer free equilibrium point $P_1(I_1, 0)$ the Jacobian matrix is

$$J(P_2) = \begin{pmatrix} -d + \frac{pf}{(I_2+f)^2} & q \\ 0 & r - \frac{aI_2}{g} \end{pmatrix}.$$

The eigenvalues of $J(P_2)$ are: $-d + \frac{pf}{(I_2+f)^2}$ and $r - \frac{aI_2}{g}$. Hence, P_2 is stable if $\frac{pf}{(I_2+f)^2} < d$ and $r < \frac{aI_2}{g}$; otherwise unstable.

The Jacobian matrix at the cancer infected equilibrium $P^*(I^*, M^*)$ is

$$J(P^*) = \begin{pmatrix} -d + \frac{pf}{(I^*+f)^2} & q \\ \frac{-aM^*}{g+M^*} & r(1-2bM^*) - \frac{agI^*}{(g+M^*)^2} \end{pmatrix}.$$

The eigenvalues λ_1^* and λ_2^* of $J(P^*)$ are calculated from the characteristic equation

$$\lambda^2 + \Pi_1 \lambda + \Pi_2 = 0,$$

where

$$\begin{cases} \Pi_1 = d + \dfrac{agI^*}{(g+M^*)^2} - \dfrac{pf}{(I^*+f)^2} - r(1-2bM^*), \\ \Pi_2 = \left\{ r(1-2bM^*) - \dfrac{agI^*}{(g+M^*)^2} \right\} \left\{ -d + \dfrac{pf}{(I^*+f)^2} \right\} + \dfrac{aqM^*}{g+M^*}. \end{cases}$$

Therefore, the equilibrium P^* will be asymptotically stable if $\Pi_1 > 0$ and $\Pi_2 > 0$.

2.2 The model under radio-genic therapy

The radio-genic therapy model is

$$\begin{aligned} \frac{dI}{dt} &= qM + \frac{pI}{I+f} - dI + u, \\ \frac{dM}{dt} &= rM(1-bM) - \frac{aIM}{g+M} - \gamma M. \end{aligned} \tag{2}$$

By setting $\frac{dI}{dt} = 0$ and $\frac{dM}{dt} = 0$, we get the eqilibrium points of the system (2) as

1. Cancer free equilibria: $Q_1(I_1', M_1' = 0)$ and $Q_2(I_2', M_2' = 0)$, where I_1' and I_2' are calculated from the following equation

   $$dI^2 - (p + u - df)I - uf = 0.$$

   Solving above equation we get I_1' and I_2' as

   $$I_1' = \frac{\chi_1' + \sqrt{\chi_2'}}{2d}, \quad I_2' = \frac{\chi_1' - \sqrt{\chi_2'}}{2d},$$

   where

   $$\chi_1' = p + u - df, \quad \chi_2' = (p + u - df)^2 + 4duf.$$

   The equilibria Q_1 and Q_2 will exist only when $I_1' > 0$ and $I_2' > 0$ respectively.

2. Cancer infected equilibrium: $Q'(I', M')$, where

$$I' = \frac{\{r(1-bM')-\gamma\}(g+M')}{a}, \quad M' = \frac{dI'-u-\frac{pI'}{I'+f}}{q}.$$

The equilibrium Q' will exist if $dI' > u + \frac{pI'}{I'+f}$ and $rbM' + \gamma < r$.

To check the stability behaviour of the system (2), we calculated the Jacobian matrix of the system (2). The Jacobian matrix is

$$J' = \begin{pmatrix} -d + \frac{pf}{(I+f)^2} & q \\ \frac{-aM}{g+M} & r(1-2bM) - \frac{agI}{(g+M)^2} - \gamma \end{pmatrix}.$$

- The eigenvalues of the Jacobian matrix at equilibrium Q_1 are $-d + \frac{pf}{(I_1'+f)^2}$ and $r - \frac{aI_1'}{g} - \gamma$. Hence, Q_1 is stable only when $\frac{pf}{(I_1'+f)^2} < d$ and $r < \frac{aI_1'}{g} + \gamma$.

- Corresponding to the equilibrium Q_2, the eigenvalues are $-d + \frac{pf}{(I_2'+f)^2}$ and $r - \frac{aI_2'}{g} - \gamma$. Therefore, Q_2 is stable if $\frac{pf}{(I_2'+f)^2} < d$ and $r < \frac{aI_2'}{g} + \gamma$.

- Corresponding to the equilibrium Q', the eigenvalues of the Jacobian matrix are calculated from the equation

$$\lambda^2 + A_1\lambda + A_2 = 0,$$

where

$$\begin{cases} A_1 = d + \dfrac{agI'}{(g+M')^2} + \gamma - \dfrac{pf}{(I'+f)^2} - r(1-2bM'), \\ A_2 = \left\{ r(1-2bM') - \dfrac{agI'}{(g+M')^2} - \gamma \right\} \left\{ -d + \dfrac{pf}{(I'+f)^2} \right\} + \dfrac{aqM'}{g+M'}. \end{cases}$$

Therefore, the equilibrium Q' will be asymptotically stable if $A_1 > 0$ and $A_2 > 0$.

Now, we will derive the conditions for which the system (2) is globally asymptotically stable at cancer free equilibria Q_1 and Q_2.

Consider a Lyapunov function of the form

$$V(I, M) = (I - I_1' - I_1' ln \frac{I}{I_1'}) + (M - M_1').$$

Differentiating above equation with respect to t, we get

$$\begin{aligned}
\frac{dV}{dt} &= \left(1-\frac{I_1'}{I}\right)\frac{dI}{dt}+\frac{dM}{dt}\\
&= \left(1-\frac{I_1'}{I}\right)\left(qM+\frac{pI}{I+f}-dI+u\right)+\left(rM(1-bM)-\frac{aIM}{g+M}-\gamma M\right)\\
&= \left(1-\frac{I_1'}{I}\right)\left(qM+\frac{pI}{I+f}-\frac{pI_1'}{I_1'+f}-d(I-I_1')\right)+\\
&+\left(rM(1-bM)-\frac{aIM}{g+M}-\gamma M\right)\\
&= (I-I_1')\left(\frac{qM}{I}+\big(\frac{pI}{I+f}-\frac{pI_1'}{I_1'+f}\big)\frac{1}{I}-\frac{d}{I}(I-I_1')\right)+\\
&+\left(rM(1-bM)-\frac{aM}{g+M}(I-I_1')-\frac{aM}{g+M}I_1'-\gamma M\right)\\
&\le \left(\frac{qM}{I}(I-I_1')-\frac{d}{I}(I-I_1')^2\right)+\left(-rbM^2-\frac{aM}{g+M}(I-I_1')\right)+\\
&\qquad\qquad [\text{since}, I<I+f \quad \text{and} \quad I_1'<I_1'+f]\\
&+rM-\frac{aM}{g+M}I_1'-\gamma M\\
&\le \left(\frac{qM}{I}(I-I_1')-\frac{d}{I}(I-I_1')^2\right)+\left(-rbM^2-\frac{aM}{g+M}(I-I_1')\right)+\\
&+\big(r-\frac{a}{g+M}I_1'-\gamma\big)M\\
&= -X^TAX-B^TX
\end{aligned}$$

where

$$X^T=[I-I_1', M], \quad B^T=\Big[0,-r+\frac{aI_1'}{g+M}+\gamma\Big],$$

and

$$A=\begin{pmatrix} \frac{d}{I} & \frac{1}{2}\big(-\frac{q}{I}+\frac{a}{g+M}\big)\\ \frac{1}{2}\big(-\frac{q}{I}+\frac{a}{g+M}\big) & rb\end{pmatrix}.$$

By noting the second component of the vector B, we must have

$$\frac{aI_1'}{g+M}+\gamma > r,$$

for which $B^TX>0$.

Now, when $t\to\infty$ then from the system (2) we get

$$\frac{dI}{dt}\le u-dI \implies I(t)\le\frac{u}{d}+e^{-dt}I(0) \implies \lim_{t\to\infty} sup[I(t)]\le\frac{u}{d},$$

and

$$\frac{dM}{dt}\le rM(1-bM) \implies M(t)\le\frac{1}{b+M(0)e^{-rt}} \implies \lim_{t\to\infty} sup[M(t)]\le\frac{1}{b}.$$

Thus, if $I \leq \frac{u}{d}$, $M \leq \frac{1}{b}$, then $X^T AX > 0$ which shows that $\frac{dV}{dt} < 0$.

We calculated $\frac{dV(I,M)}{dt}$ to verify our above results numerically [considering various initial values, all parameters given in Table 1 and $\gamma = 0.1$]. Hence, by Lyapunov stability theorem, Q_1 is found to be globally asymptotically stable. Therefore, the cancer free equilibrium Q_1 is globally asymptotically stable if following conditions hold

$$\frac{aI_1'}{g+M} + \gamma > r, \quad I \leq \frac{u}{d}, \quad \text{and} \quad M \leq \frac{1}{b},$$

provided the equilibrium point Q_1 satisfy local stability conditions mentioned in the beginning of this section.

In the same way, we can derive the conditions for which the system (2) is globally asymptotically stable at the equilibrium Q_2.

2.3 The model under mAb-gene therapy

After the successful analysis of gene and redio-genic therapy model, now we are going to analyse the mAb-gene therapy model. The model takes the form

$$\begin{aligned} \frac{dI}{dt} &= qM + \frac{pI}{I+f} - dI + u, \\ \frac{dM}{dt} &= rM(1-bM) - \frac{aIM}{g+M} - kMC, \\ \frac{dC}{dt} &= -\eta C - \rho M \frac{C}{h+C} + v. \end{aligned} \tag{3}$$

The equilibrium points of the system (3) are

1. Cancer free equilibria: $R_1(\hat{I}_1, \hat{M}_1 = 0, \hat{C}_1 = \frac{v}{\eta})$ and $R_2(\hat{I}_2, \hat{M}_2 = 0, \hat{C}_2 = \frac{v}{\eta})$ where $\hat{I}_1$ and $\hat{I}_2$ are calculated from the following equation:

$$dI^2 - (p + u - df)I - uf = 0.$$

Solving above equation we get $\hat{I}_1$ and $\hat{I}_2$ as

$$\hat{I}_1 = \frac{\hat{\chi}_1 + \sqrt{\hat{\chi}_2}}{2d}, \quad \hat{I}_2 = \frac{\hat{\chi}_1 - \sqrt{\hat{\chi}_2}}{2d},$$

where

$$\hat{\chi}_1 = p + u - df, \quad \hat{\chi}_2 = (p + u - df)^2 + 4duf.$$

The equilibria R_1 and R_2 will exist only when $\hat{I}_1 > 0$ and $\hat{I}_2 > 0$ respectively.

2. Cancer infected equilibrium: $\hat{R}(\hat{I}, \hat{M}, \hat{C})$ where

$$\hat{I} = \frac{\{r(1-b\hat{M}) - k\hat{C}\}(g+\hat{M})}{a}, \quad \hat{M} = \frac{d\hat{I} - \frac{p\hat{I}}{\hat{I}+f} - u}{q},$$

and $\hat{C}$ will be calculated from the following equation

$$\eta C^2 - (v - \rho\hat{M} - \eta h)C - vh = 0.$$

The equilibrium $\hat{R}$ will exist if $d\hat{I} > \frac{p\hat{I}}{\hat{I}+f} + u$ and $rb\hat{M} + k\hat{C} < r$.

The Jacobian matrix of the system (3) is given below

$$\hat{J} = \begin{pmatrix} \frac{pf}{(I+f)^2} - d & q & 0 \\ -\frac{aM}{g+M} & r - 2rbM - \frac{agI}{(g+M)^2} - kC & -kM \\ 0 & -\frac{\rho C}{h+C} & -\eta - \frac{\rho hM}{(h+C)^2} \end{pmatrix}.$$

- The eigenvalues of the Jacobian matrix at the cancer free equilibrium R_1 are $-\eta$, $r - \frac{a\hat{I}_1}{g} - k\hat{C}_1$, and $\frac{pf}{(\hat{I}_1+f)^2} - d$. As $-\eta < 0$, hence this equilibrium becomes stable if $r < \frac{a\hat{I}_1}{g} + k\hat{C}_1$, and $\frac{pf}{(\hat{I}_1+f)^2} < d$; otherwise unstable.

- Corresponding to the another cancer free equilibrium R_2, the eigenvalues of the Jacobian matrix are $-\eta$, $r - \frac{a\hat{I}_2}{g} - k\hat{C}_2$, and $\frac{pf}{(\hat{I}_2+f)^2} - d$. As $-\eta < 0$, hence R_2 becomes stable only when $r < \frac{a\hat{I}_2}{g} + k\hat{C}_2$, and $\frac{pf}{(\hat{I}_2+f)^2} < d$; otherwise unstable.

- The eigenvalues of the Jacobian matrix at cancer infected equilibrium $\hat{R}$ are the roots of following equation

$$\lambda^3 + B_1\lambda^2 + B_2\lambda + B_3 = 0, \tag{4}$$

where

$$\begin{cases} B_1 = -b_{11} - b_{22} - b_{33}, \\ B_2 = b_{22}b_{33} + b_{11}b_{33} + b_{11}b_{22} - b_{32}b_{23} - b_{21}b_{12}, \\ B_3 = b_{11}b_{32}b_{23} + b_{12}b_{21}b_{33} - b_{11}b_{22}b_{33}, \end{cases}$$

with

$$\left.\begin{aligned} b_{11} = \frac{pf}{(\hat{I}+f)^2} - d, \qquad b_{12} = q, \qquad b_{21} = -\frac{a\hat{M}}{g+\hat{M}}, \\ b_{22} = r - 2rb\hat{M} - \frac{ag\hat{I}}{(g+\hat{M})^2} - k\hat{C}, \qquad b_{23} = -k\hat{M}, \\ b_{32} = -\frac{\rho\hat{C}}{h+\hat{C}}, \qquad b_{33} = -\eta - \frac{\rho h\hat{M}}{(h+\hat{C})^2}. \end{aligned}\right\}$$

According to Routh-Hurwitz rule, the roots of the equation (4) have negative real part if and only if

$$B_1 > 0, \qquad B_2 > 0, \qquad B_1B_2 - B_3 > 0. \tag{5}$$

Hence, for locally asymptotically stable at $\hat{R}$, (5) must hold otherwise it will be unstable.

Next, we establish the conditions for which the system (3) is globally stable at cancer-free equilibria R_1 and R_2. For this we construct a Lyapunov function as:

$$W(I,M,C) = (I - \hat{I}_1 - \hat{I}_1 ln\frac{I}{\hat{I}_1}) + (M - \hat{M}_1) + (C - \hat{C}_1 - \hat{C}_1 ln\frac{C}{\hat{C}_1}).$$

Now, differentiating above equation with respect to t and get

$$\begin{aligned}
\frac{dW}{dt} &= \left(1 - \frac{\hat{I}_1}{I}\right)\frac{dI}{dt} + \frac{dM}{dt} + \left(1 - \frac{\hat{C}_1}{C}\right)\frac{dC}{dt},\\
&= \left(1 - \frac{\hat{I}_1}{I}\right)\left(qM + \frac{pI}{I+f} - dI + u\right) + \left(rM(1-bM) - \frac{aIM}{g+M} - kMC\right) +\\
&\left(1 - \frac{\hat{C}_1}{C}\right)\left(- \eta C - \rho M\frac{C}{h+C} + v\right),\\
&= \left(1 - \frac{\hat{I}_1}{I}\right)\left(qM + \frac{pI}{I+f} - \frac{p\hat{I}_1}{\hat{I}_1+f} - d(I - \hat{I}_1)\right) + \left(rM(1-bM) - \frac{aIM}{g+M}\right.\\
&\left. - kMC\right) + \left(1 - \frac{\hat{C}_1}{C}\right)\left(- \eta(C - \hat{C}_1) - \rho M\frac{C}{h+C}\right),\\
&= (I - \hat{I}_1)\left(\frac{qM}{I} + (\frac{pI}{I+f} - \frac{p\hat{I}_1}{\hat{I}_1+f})\frac{1}{I} -\right.\\
&\left.\frac{d}{I}(I - \hat{I}_1)\right) + \left(rM(1-bM) - \frac{aM}{g+M}(I - \hat{I}_1)\right.\\
&\left. - \frac{aM}{g+M}\hat{I}_1 - kM(C - \hat{C}_1) - kM\hat{C}_1\right) + (C - \hat{C}_1)\left(\frac{-\eta}{C}(C - \hat{C}_1) - \rho M\frac{1}{h+C}\right),\\
&\leq \left(\frac{qM}{I}(I - \hat{I}_1) - \frac{d}{I}(I - \hat{I}_1)^2\right) + \left(- rbM^2 - \frac{aM}{g+M}(I - \hat{I}_1) - kM(C - \hat{C}_1)\right) +\\
&\left(\frac{-\eta}{C}(C - \hat{C}_1)^2 - \rho M\frac{1}{h+C}(C - \hat{C}_1)\right) + rM - \frac{aM}{g+M}\hat{I}_1 - kM\hat{C}_1,\\
&\qquad\qquad [\text{since}, I < I + f \quad \text{and} \quad \hat{I}_1 < \hat{I}_1 + f]\\
&\leq \left(\frac{qM}{I}(I - \hat{I}_1) - \frac{d}{I}(I - \hat{I}_1)^2\right) + \left(- rbM^2 - \frac{aM}{g+M}(I - \hat{I}_1) - kM(C - \hat{C}_1)\right) +\\
&\left(\frac{-\eta}{C}(C - \hat{C}_1)^2 - \rho M\frac{1}{h+C}(C - \hat{C}_1)\right) + \big(r - \frac{a}{g+M}\hat{I}_1 - k\hat{C}_1\big)M,\\
&= -Y^T DY - N^T Y,
\end{aligned}$$

where

$$Y^T = [I - \hat{I}_1, M, C - \hat{C}_1], \quad N^T = \big[0, -r + \frac{a\hat{I}_1}{g+M} + k\hat{C}_1, 0\big],$$

and

$$D = \begin{pmatrix} \frac{d}{I} & \frac{1}{2}\big(- \frac{q}{I} + \frac{a}{g+M}\big) & 0\\ \frac{1}{2}\big(- \frac{q}{I} + \frac{a}{g+M}\big) & rb & \frac{1}{2}\big(k + \frac{\rho}{h+C}\big)\\ 0 & \frac{1}{2}\big(k + \frac{\rho}{h+C}\big) & \frac{\eta}{C} \end{pmatrix}.$$

By noting the second component of the vector N, we must have

$$\frac{a\hat{I}_1}{g+M} + k\hat{C}_1 > r,$$

for which $N^T Y > 0$.

Now when $t \to \infty$ then from system (3) we get

$$\frac{dI}{dt} \leq u - dI \implies I(t) \leq \frac{u}{d} + e^{-dt}I(0) \implies \lim_{t\to\infty} sup[I(t)] \leq \frac{u}{d},$$

$$\frac{dM}{dt} \leq rM(1-bM) \implies M(t) \leq \frac{1}{b + M(0)e^{-rt}} \implies \lim_{t\to\infty} sup[M(t)] \leq \frac{1}{b},$$

and

$$\frac{dC}{dt} \leq v - \eta C \implies C(t) \leq \frac{v}{\eta} + e^{-\eta t}C(0) \implies \lim_{t\to\infty} sup[C(t)] \leq \frac{v}{\eta}.$$

Thus, if $I \leq \frac{u}{d}$, $M \leq \frac{1}{b}$ and $C \leq \frac{v}{\eta}$, then $Y^T DY > 0$ which shows that $\frac{dW}{dt} < 0$.

We calculated $\frac{dW(I,M,C)}{dt}$ to verify our above results numerically [considering various initial values, all parameters given in Table 1 and Table 2]. Hence, by Lyapunov stability theorem, R_1 is globally asymptotically stable. Therefore, the cancer-free equilibrium point R_1 is globally asymptotically stable if following conditions hold

$$\frac{a\hat{I}_1}{g+M} + k\hat{C}_1 > r, \quad I \leq \frac{u}{d}, \quad M \leq \frac{1}{b}, \quad \text{and} \quad C \leq \frac{v}{\eta},$$

provided that the equilibrium R_1 satisfies local stability conditions which were discussed in the beginning of this section.

In the same way, we can derive the conditions for which the system (3) is globally asymptotically stable at the equilibrium R_2.

3 Numerical simulation

In this section, we perform some numerical simulation of the proposed models under different treatment combinations using MATLAB [with the parameter values given in Table (1) and Table (2)]. The primary purpose of the numerical simulation is to visualize the change in the cell population's state with time and outline the impact of the variation of treatment efficacy on the growth of cancer cells. This is achieved by varying the values of the treatment parameters.

The set of parameters used to observe the dynamics of effector cells and cancerous cells for the gene therapy model (1) are: $q = 0.05$, $p = 0.1245$, $f = 10^{-3}$, $d = 0.03$, $r = 0.18$, $b = 10^{-9}$, and $g = 10^5$. The initial values used in these simulations are $I(0) = M(0) = 1000$.

Table 1: Parameter values for the simulation.

Parameter	**Definition**	**Value**	**Range**	**Source**
q	Cancer antigenicity	0.05 (1/time)	$[10^{-3}, 0.5]$	[28]
u	Immunotherapy term	1 (cell/time)	$[10^{-2}, 10^{2}]$	[28]
p	Proliferation rate of I	0.1245 (1/time)	0.1245	[28]
f	Half saturation for I proliferation term	10^{-3} (cells)	$[10^{-5}, 1]$	[28]
d	Half life of effector cells I	0.03 (1/time)	0.03	[28]
r	Cancer growth rate	0.18 (1/time)	$[10^{-1}, 2]$	[28]
b	Cancer cell capacity	10^{-9} (1/cells)	10^{-9}	[28]
a	Cancer clearance term	1 (1/cells)	$[10^{-2}, 10^{2}]$	[28]
g	Half-saturation for cancer clearance	10^{5} (cells)	10^{5}	[28]

Table 2: Parameter values for the simulation.

Parameters	Meaning	Values	Source
k	Rate of mAb-induced cancer death	5.5×10^{-1} L $mg^{-1}Day^{-1}$	[29]
η	Rate of mAb turnover and excretion	1.386×10^{-1} Day^{-1}	[29]
ρ	Rate of mAb-cancer cell complex formation	8.9×10^{-14} mg $Cells^{-1}L^{-1}Day^{-1}$	[29]
h	Concentration of mAbs for Half-maximal EGFR binding	4.45×10^{-5} mg L^{-1}	[29]

For the treatment parameters $u = 1$, and $a = 1$, the system (1) has two biologically feasible equilibria: $P_1(37.48, 0)$ which is cancer-free and $P^*(20174.56, 12082.25)$ which is cancer infected. The cancer-free equilibrium point P_1 is associated with eigenvalues -0.0299 and 0.1796; which implies that P_1 is a saddle-type unstable point. The eigenvalues associated with the cancer infected equilibrium point P^* are $-0.0055 \pm 0.0692i$. It indicates that P^* is a stable focus node. From Figure (1)(b) it can be observed that around point P^* the trajectories of the system (1) are in-going spirals as time increases, which suggests that the population of effector cells and cancer cells are going to be stable at point P^* (see Figure (1)(a)).

For the treatment parameters $u = 50$, and $a = 1$, there exist two biologically feasible equilibria for the system (1): $P_1(1670.82, 0)$ which is cancer-free and $P^*(19976.83, 10983.61)$ which is cancer infected. The point P_1 is associated with eigenvalues of -0.029 and 0.163, indicating P_1 is unstable. The eigenvalues associated with the point

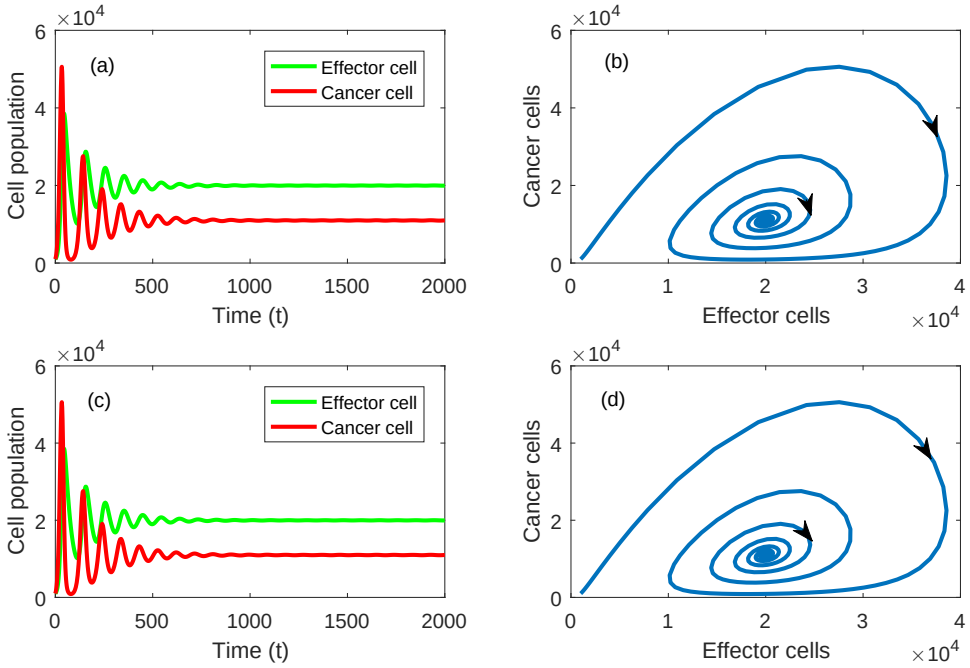

Figure 1: (a) Time series plot and (b) parametric plot of cell population for the immunotherapy term $u = 1$, and cancer clearance term $a = 1$. (c) Time series plot and (d) parametric plot of cell population for the immunotherapy term $u = 50$ and cancer clearance term $a = 1$.

P^* are $-0.0060 \pm 0.0661i$; implies that P^* is stable. From Figure (1)(d) it can be observed that around the point P^* the trajectories of the system (1) are in-going spirals as time increases, which suggests that the population of effector cells and cancer cells are going to be stable at point P^* (see Figure (1)(c)). From Figures of (1), we can see that there is no significant changes in the dynamics of the system (1) when we only increase the value of the immunotherapy term.

For the treatment parameters $u = 1$, and $a = 5$, there exhibits two biologically feasible equilibria for the system (1): $P_1(37.48, 0)$ which is cancer free and $P^*(3678.64, 2184.69)$ which is cancer infected. The cancer free equilibrium P_1 is associated with eigenvalues -0.029 and 0.178; which implies that P_1 is unstable. The cancer infected equilibrium is associated with eigenvalues $-0.0130 \pm 0.0711i$; indicating P^* is stable. It can also be observed from Figure (2)(b) that the trajectories of the system converge to P^* and Figure (2)(a) evidence that both the cell population are alive and stable at P^*.

For the treatment parameters $u = 50$, and $a = 5$, the system (1) has two biologically feasible equilibria: $P_1(1670.82, 0)$ which is cancer free and $P^*(3642.58, 1183.06)$ which is cancer infected. The eigenvalues corresponding to cancer free equilibrium P_1 are -0.029 and 0.096, indicating P_1 is unstable. The eigenvalues corresponding to the equilibrium P^* are $-0.0140 \pm 0.0514i$. Hence, P^* is stable. It can also be observed

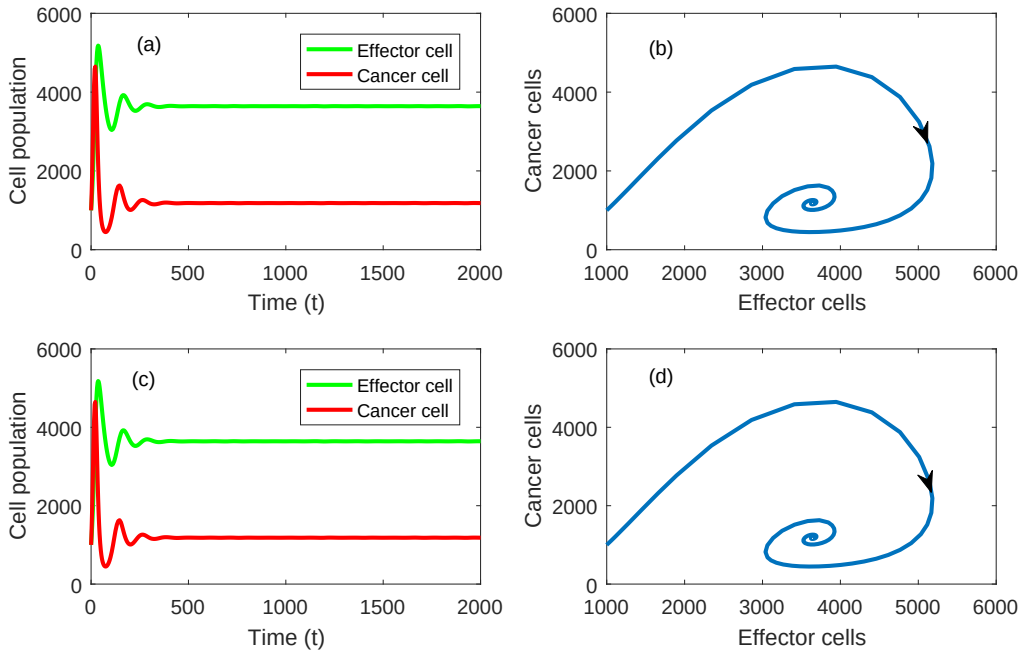

Figure 2: (a) Time series plot and (b) parametric plot of cell population for the immunotherapy term $u = 1$, and cancer clearance term $a = 5$. (c) Time series plot and (d) parametric plot of cell population for the immunotherapy term $u = 50$ and cancer clearance term $a = 5$.

from Figure (2)(d) that the trajectories of the system (1) converge to P^* and Figure (2)(c) evidence that both the cell population are alive and stable at P^*.

For the treatment parameters $u = 100$, and $a = 1$, there are two biologically feasible equilibria for the system (1): $P_1(3337.48, 0)$ which is cancer free and $P^*(19775.06, 9862.55)$ which is cancer infected. The cancer free equilibrium P_1 is associated with eigenvalues -0.029 and 0.147; which implies that P_1 is unstable. The cancer infected equilibrium is associated with eigenvalues $-0.0070 \pm 0.0630i$; indicating P^* is stable. It can also be observed from Figure (3)(b) that the trajectories of the system (1) converge to P^* and Figure (3)(a) evidence that both the cell population are alive and stable at P^*.

For the treatment parameters $u = 100$, $a = 5.5$ there exists only one biologically relevant equilibrium for the system (1) namely $P_1(3337.48, 0)$ which is cancer-free. The equilibrium P_1 is associated with eigenvalues -0.029 and -0.004, which indicates that P_1 is a stable node. Figure (3)(d) depicts that the trajectories of the system (1) converge to a point where the tumour cell population becomes zero i.e., to the point P_1. It can also be observed from Figure (3)(c) that the effector cell population incorporated with the treatment given can suppress the cancer growth to zero with time increases.

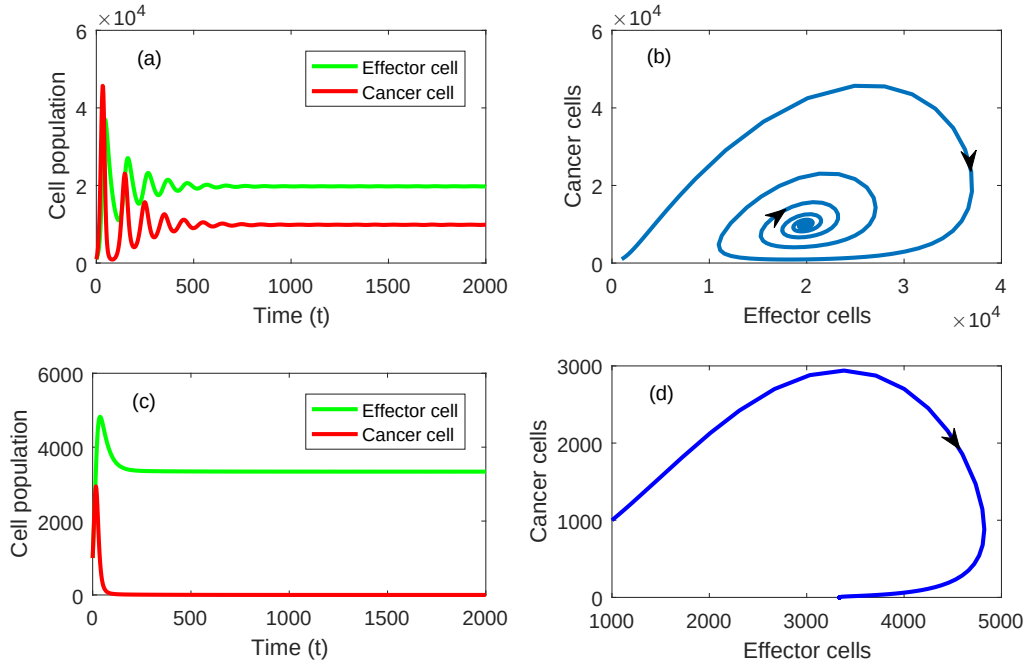

Figure 3: (a) Time series plot and (b) parametric plot of cell population for the immunotherapy term $u = 100$, and cancer clearance term $a = 1$. (c) Time series plot and (d) parametric plot of cell population for the immunotherapy term $u = 100$ and cancer clearance term $a = 5.5$.

From Figures of (3), it can be observed that if we inject an optimum amount of immunotherapy and a sufficient amount of gene therapy into the patient, the effector cells themselves can eradicate the cancer cells. However, the high dose of immunotherapy may cause some severe side effects. So, to reduce these side effects, we separately apply radiation and mAb therapy in the gene therapy model. In the next part of the simulation, we will present the effects of radiation and mAb therapy in the gene therapy model.

The set of parameters used to observe the dynamics of effector cells and cancerous cells for the radio-genic therapy model (2) are: $q = 0.05$, $p = 0.1245$, $f = 10^{-3}$, $d = 0.03$, $r = 0.18$, $b = 10^{-9}$, and $g = 10^5$. The initial values used in these simulations are $I(0) = M(0) = 1000$. The value of $\gamma = 0.1$ cell/time is estimated based on [19]. For the treatment parameters $u = 1$, $a = 1$, and $\gamma = 0.1$ cell/time, there exist two biologically relevant equilibria for the system (2) namely $Q_1(37.48, 0)$ which is cancer free and $Q'(8401.37, 5018.33)$ which is cancer infected. The cancer free equilibrium Q_1 is associated with eigenvalues -0.029 and 0.0796; indicating Q_1 is unstable. The cancer infected equilibrium Q' is stable as it is associated with eigenvalues $-0.0130 \pm 0.0470i$. Figure (4)(a) depicts that at point Q' both effector and cancer cells show damped oscillation behavior about zero rather than asymptotes to zero. It can also be observed from Figure (4)(b) that the trajectories of the system (2) converge to Q'.

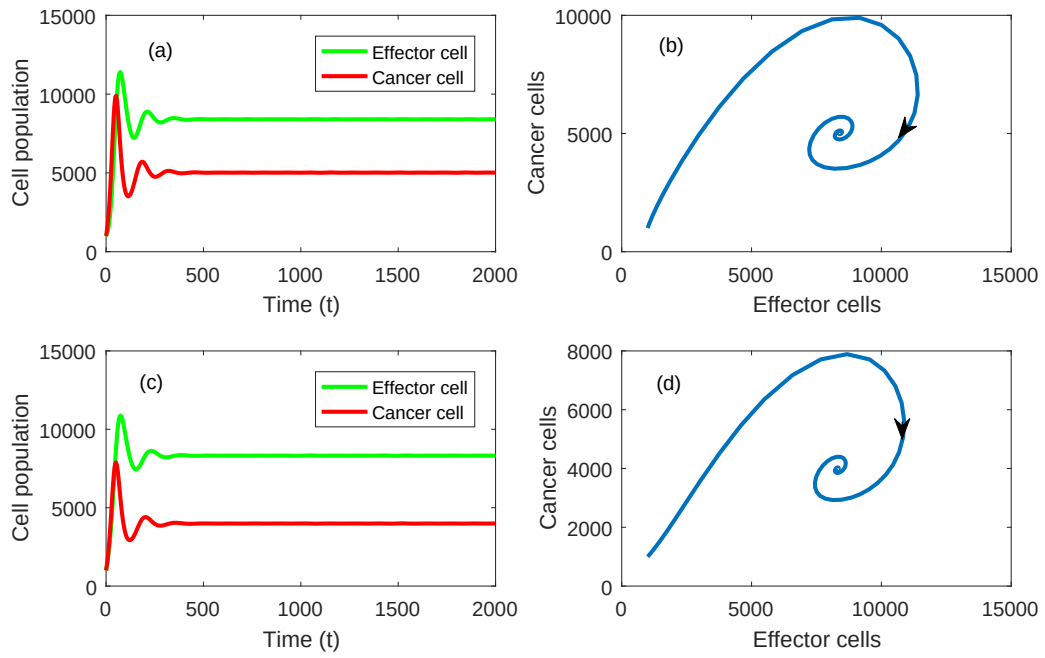

Figure 4: (a) Time series plot and (b) parametric plot of cell population for the immunotherapy term $u = 1$, cancer clearance term $a = 1$ and radiation dose $\gamma = 0.1$. (c) Time series plot and (d) parametric plot of cell population for the immunotherapy term $u = 50$, cancer clearance term $a = 1$ and radiation dose $\gamma = 0.1$ cell/time.

For the treatment parameters $u = 50$, $a = 1$, and $\gamma = 0.1$ cell/time, there exist two biologically relevant equilibria for the system (2) namely $Q_1(1670.82, 0)$ which is cancer free and $Q'(8319.04, 3988.93)$ which is cancer infected. The cancer free equilibrium Q_1 is unstable as it is associated with eigenvalues -0.029 and 0.063, whereas the cancer infected equilibrium Q' is stable as it is associated with eigenvalues $-0.0135 \pm 0.0416i$. It can also be observed from Figure (4)(d) that the trajectories of the system (2) converge to Q' and Figure (4)(c) evidence that both the cell population are alive and stable at Q'. For the treatment parameters $u = 1$, $a = 5$, and $\gamma = 0.1$ cell/time, there exist two biologically relevant equilibria for the system (2) namely $Q_1(37.48, 0)$ which is cancer free and $Q'(1615.14, 946.60)$ which is cancer infected. The cancer free equilibrium Q_1 is unstable as it is associated with eigenvalues of -0.029 and 0.078, whereas the cancer infected equilibrium Q' is stable as it is associated with eigenvalues $-0.0146 + 0.0460i$. It can also be observed from Figure (5)(b) that the trajectories of the system (2) converge to Q' and Figure (5)(a) evidence that both the cell population are still alive and stable at Q'.

For the treatment parameters $u = 50$, $a = 5$, and $\gamma = 0.1$ cell/time, there exists only one biologically relevant equilibrium for the system (2) namely $Q_1(1670.81, 0)$ which is cancer free. The equilibrium Q_1 is associated with eigenvalues -0.029 and -0.004. Hence Q_1 is a stable node. Figure (5)(c) represents that the effector cell population incorporated with the treatment given can suppress the cancer growth to zero with

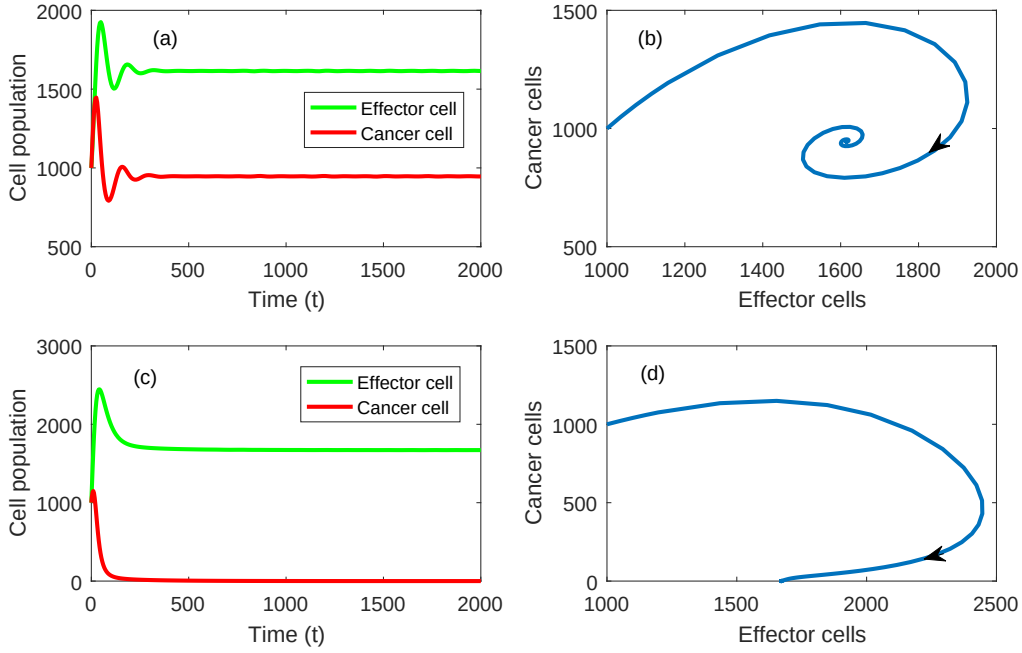

Figure 5: (a) Time series plot and (b) parametric plot of cell population for the immunotherapy term $u = 1$, cancer clearance term $a = 5$ and radiation dose $\gamma = 0.1$. (c) Time series plot and (d) parametric plot of cell population for the immunotherapy term $u = 50$, cancer clearance term $a = 5$ and radiation dose $\gamma = 0.1$ cell/time.

time increase. It can also be verified from Figure (5)(d) that the trajectories of the system (2) converge to a point where tumor cell population becomes zero i.e., to the point Q_1.

We have used Table (1) and Table (2) for simulating the mAb-gene therapy model. Here, we have assumed that the administration of mAb drugs is continual. The initial values used in these simulations are $I(0) = M(0) = 1000$, and $C(0) = 0.01$. We have also assumed that the value of v at time $t = 0$ is 0.01.
For the treatment parameters $u = 1$, $a = 1$ and in the presence of mAb drug, there exist two biologically relevant equilibria for the system, (3) namely $R_1(37.48, 0, 0.072)$ which is cancer free and $\hat{R}(15318.04, 9168.34, 0.072)$ which is cancer infected. The cancer free equilibrium R_1 is associated with eigenvalues -0.138, 0.14 and -0.029, which indicates that R_1 is unstable. The cancer infected equilibrium $\hat{R}$ is stable as it is associated with eigenvalues $-0.0100 \pm 0.0600i$ and -0.1400. It can also be observed from Figure (6)(c) that the trajectories of the system (3) converge to $\hat{R}$ and Figure (6)(a) evidence that both the cell population are still alive and stable at $\hat{R}$.

For the treatment parameters $u = 50$, $a = 5$, and in the presence of mAb drug, there exist two biologically relevant equilibria for the system, (3) namely $R_1(1670.82, 0, 0.072)$ which is cancer free and $\hat{R}(2825.79, 692.99, 0.072)$ which is cancer infected. The cancer free equilibrium R_1 is associated with eigenvalues -0.138, 0.06 and -0.029, indicat-

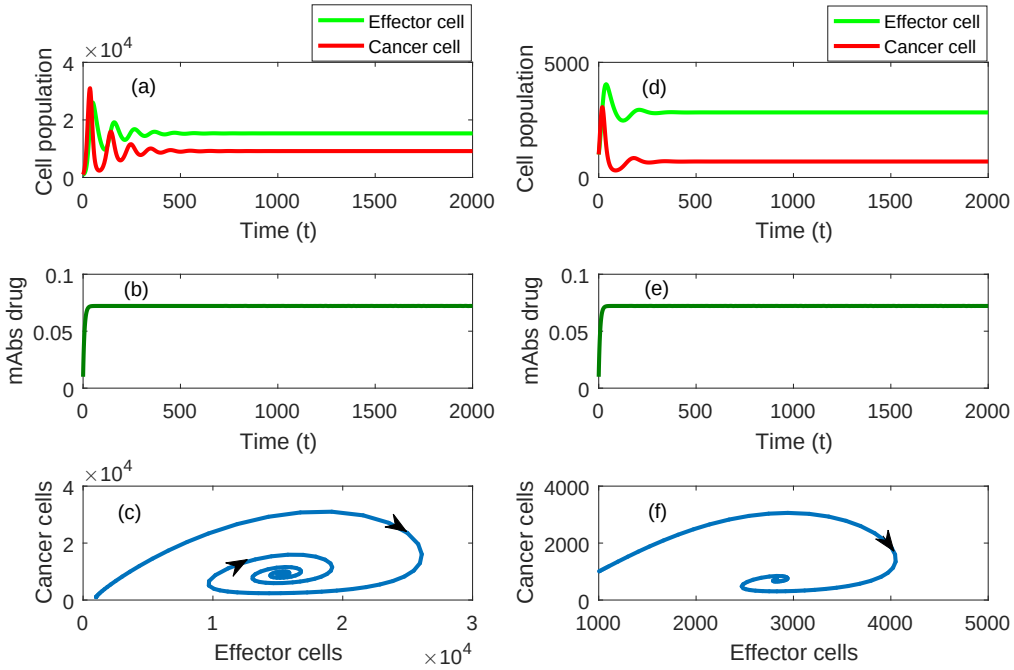

Figure 6: (a) Time series plot and (c) parametric plot of cell population for the immunotherapy term $u = 1$, and cancer clearance term $a = 1$. (d) Time series plot and (f) parametric plot of cell population for the immunotherapy term $u = 50$, and cancer clearance term $a = 5$. Time series plot of mAb drug is presented in (b) and (e).

ing R_1 is unstable. The eigenvalues corresponding to the cancer infected equilibrium $\hat{R}$ are $-0.0145 \pm 0.0355i$ and -0.1400, which implies that $\hat{R}$ is stable. It can also be observed from Figure (6)(f) that the trajectories of the system (3) converge to $\hat{R}$ and Figure (6)(d) evidence that both the cell population are still alive and stable at $\hat{R}$. For the treatment parameters $u = 50$, $a = 8.5$ and in the presence of mAb drugs, there exists only one biologically relevant equilibrium for the system, (3) namely $R_1(1670.82, 0, 0.072)$ which is cancer free. The equilibrium R_1 is a stable node as it is associated with eigenvalues -0.138, -0.0016 and -0.029. Figure (7)(a), (7)(b) represents that the effector cell population incorporated with the treatment given can suppress the cancer growth to zero with time increase and Figure (7)(c)) depicts that the trajectories of the system (3) converge to a point where the tumor cell population becomes zero i.e., to the point R_1.

For the treatment parameters $u = 85$, $a = 5$ and in the presence of mAb drugs, there exists only one biologically relevant equilibrium for the system, (3) namely $R_1(2837.48, 0, 0.072)$ which is cancer free. The equilibrium R_1 is a stable node as it is associated with eigenvalues -0.138, -0.0015 and -0.029. Figure (7)(d), (7)(e) represents that the effector cell population incorporated with the treatment given can suppress the cancer growth to zero with time increase and Figure (7)(f)) depicts that the trajectories of the system (3) converge to a point where the tumor cell population becomes zero i.e., to the point R_1.

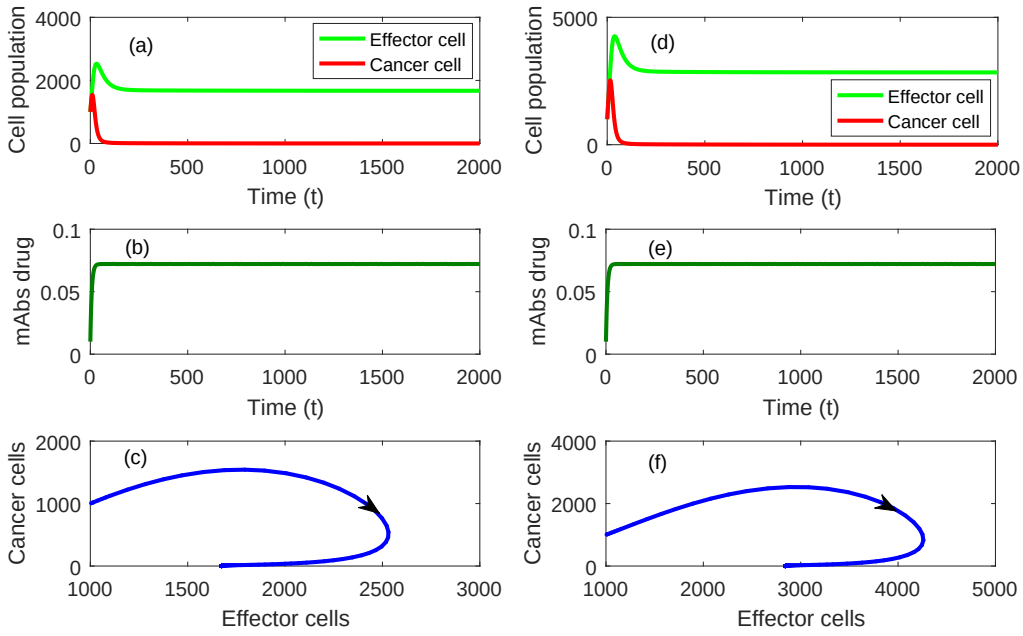

Figure 7: (a) Time series plot and (c) parametric plot of cell population for the immunotherapy term $u = 50$, and cancer clearance term $a = 8.5$. (d) Time series plot and (f) parametric plot of cell population for the immunotherapy term $u = 85$, and cancer clearance term $a = 5$. Time series plot of mAb drug is presented in (b) and (e).

4 Discussion and conclusion

This study introduces a cancer treatment model with non-linear ordinary differential equations under different treatment procedures. In the first, we have used gene therapy and immunotherapy as a combination treatment for cancer. The second treatment procedure applies a combination of radiotherapy, gene therapy, and immunotherapy. The third treatment procedure is related to a combined treatment process of gene therapy, immunotherapy and mAb therapy. Local stability at equilibrium points for each of the models has been discussed. The conditions for global stability at the tumour-free equilibria of the radio-genic therapy and mAb-gene therapy model have been derived. We have done the numerical simulation by keeping all the parameters constant and varying the treatment parameters of the models. Our theoretical and numerical findings suggest the following.

1. If the immunotherapy term $u = 100$ and the cancer clearance rate of gene therapy $a = 5.5$, the gene therapy model has only a cancer-free state. This means that if we inject the optimum level of immunotherapy and gene therapy so that the cancer clearance rate of gene therapy is $a = 5.5$, the patient can recover from the disease.

2. If radiation therapy is combined with immunotherapy and gene therapy, the patient will recover from the disease for the treatment parameters immunotherapy

term $u = 50$, cancer clearance rate of gene therapy $a = 5$, and radiation dose $\gamma = 0.1$.

3. For the case of combination treatment of mAb-gene therapy, the patient will recover from the disease if the treatment parameters immunotherapy term $u = 50$, and cancer clearance rate of gene therapy $a = 8.5$ or immunotherapy term $u = 85$, and cancer clearance rate of gene therapy $a = 5$.

In [28], the authors reported that the optimum amount of the treatment parameters u and a could clear the tumour. Here, we have found that instead of injecting the optimum level of the treatment parameters u and a, we could achieve better results by combining radiotherapy and mAb therapy with gene therapy. However, our study has been done based on a theoretical approach. Therefore, clinical verification is required before claiming that our findings are of major importance. Furthermore, finding the minimum amount of drugs for prescribed treatment to reduce cancer growth by incorporating an optimal control approach is also left out as future work.

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