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AN ANALYSIS OF A CANCER TREATMENT MODEL OF GENE THERAPY IN COMBINATION WITH TWO OTHER PRIMARY THERAPIES

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Abstract. Research on various sorts of cancer treatment is going on in case of cancer-immune system through mathematical models. In this study, we propose cancer treatment models with gene therapy alone and then gene therapy in combination with radiotherapy and monoclonal antibody therapy (mAbs) separately. Searching of equilibrium points and local stability analysis is completed both theoretically and numerically for each of the models. Numerical simulation for appropriate parameter values of each model is shown for better understanding of the treatment strategy to cure cancer. Our investigation reveals that gene therapy cannot eradicate cancer having high growth rate with lower immunotherapy drugs but it may work in a nice way if a patient tolerates higher dose of immunotherapy drugs. Further, we have observed that radiogenic therapy and mAbs-gene therapy showed better results in cancer eradication. The investigation shows that combination of monoclonal antibody therapy (mAbs) and gene therapy may perform in a better way to cure cancer than that of radiotherapy and gene therapy.

1. Introduction

Malignant growth is one of the primary causes of mortality within the world [1]. So, finding an efficient treatment against malignant growth may be a wide research area within the clinical sciences. If we look back to the history of cancer treatment; in eighteenth century, surgery was the mostly used treatment method for early stages of cancer. In 1895 radiation therapy was started, but it resulted in few cures. In twentieth century, there has been a sensational progression in chemotherapeutic treatment for cancer. Use of viruses were additionally seen as beneficial in controlling malignancies in human in an around 1956. Consequently, gene therapy, immunotherapy and monoclonal antibody therapies were developed for treatment of cancer patients during 1985 to 2000 [2]. At present, every day different types of treatments are adopted to conquer the disease. In our literature work [3] we found that the optimal combination of various therapies provide effective leads for cure of cancer. In the present investigation, we have combined gene therapy with radiotherapy and monoclonal antibody therapy separately to

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show the effectiveness of these two types of combinations. As cancer arises due to multiple genetical and other types of defects so it has always been difficult to eradicate existing tumours by correcting these defects altogether. Gene therapy aims to treat or prevent the malignant disease by using therapeutic information encoded in DNA sequences [4]. Also by generating a high concentration of an effector protein, gene therapy prevents cancer growth [5].

Radiation therapy is often highly effective for tumour eradication. Radiation is used to destroy malignant tumours either externally by X- rays and γ - rays or internally with the use of radioisotopes. Higher doses of radiation can produce better tumour control but it also damages normal tissues within the radiation field, which may severely influence the standard of life of the patient [5]. As of late, research has shown that the combination of gene and radiation therapy termed as radiogenic therapy increases cancer curability rate with less detrimental effect to the normal tissues. Clinical experiments have demonstrated that radiogenic therapy has many advantages and potential benefits over other treatment strategies. Because both have different toxicity profiles targeting different parts of the cell cycle in the best possible way. Gene therapy targets the S phase of the cell cycle while radiotherapy targets most radiosensitive M and G_2 phases. Radiations kill tumour cells and at the same time improves transfection proficiency and transgene reconciliation. Discharge of products from the radiation-damaged cells get incorporated with tumour antigens produced by immune effector cells drawing into immunocytes which mediate as an anti-tumour response causing significant clarification of neoplastic cell death [4].

It is commonly known that cancer cells are resistant to the body's immune system. But sometimes, the immune system attacks the cancer cells within the body by creating a sizable number of antibodies (a protein that sticks to a specific protein called an antigen) [11]. So, now a days researchers try to design such antibodies in the clinical lab which mainly target a neoplastic cell antigen. mAbs is one of such antibodies. Different types of mAbs namely naked mAbs (no drug or radioactive particle), conjugated mAbs (with chemotherapy drug or radioactive particle), bi-specific mAbs (two different proteins used at the same time) are developed for cancer treatment. Altogether, these antibodies are designed in such a way that they will be capable of binding with antigens easily on the surface of cancer cells rather than healthy cells; to restore, enhance the immune systems' attack on cancer cells, to spice up the immune response by strengthening immune system checkpoints or against cancer cells regrowth [12]. So, we have added gene therapy alongside mAbs for a better result with fewer side effects.

Many mathematical models are introduced by many authors to investigate efficient drug delivery processes to eradicate cancer. Tsygvintsev et al. [6] introduced a mathematical model of gene therapy by modifying the Kirschner and Panneta model [7]. They established stability condition of the model and estimated the treatment parameters at which cancer gets eradicated. They showed that high level of the TIL cell will clear the tumour. Local stability analysis and simulation

for various parameter set have been furnished for this model by Lestari et al. [8]. de Pillis et al. portrayed a mathematical model of colorectal cancer growth and showed the impact of two mAbs - cetuximab, panitumumAb [9]. In our study, we considered only the effect of cetuximab. It is already established that with the utilization of mAb treatment, cancer cells constantly mutated which frequently results in resistance or complete lack of responsiveness to the targeted therapy [11]. So, from the above analysis and theoretical observation of radiogenic therapy and mAbs therapy, we have introduced radiation effect and mAbs effect on the gene therapy model proposed by Tsygvntsev et al [6].

The paper is organized as follows: in section 2, we discussed model formulation. Local stability analysis and numerical simulation for our considered three different model is shown in section 3, section 4 and section 5, respectively. A comparative conclusion of the paper is given in section 6.

2. Model Formulation

The following considered model **(A)** is primarily based on Gene Therapy Model proposed by Tsygvintsev et. al [6]. The model deals with the dynamics of effector cell (including NK cells, Interleukin-2, LAK, Lymphocytes, T helper cells) and the cancerous Cells. $E(t)$ and $T(t)$ respectively denotes the number of effector cells and the number of cancerous cell at any time $t > 0$. The model proposed by Tsygvintsev et. al [6] is:

$$\begin{aligned} \frac{dE}{dt} &= cT - dE + \frac{pE}{E+f} + u_1 \\ \frac{dT}{dt} &= rT(1-bT) - \frac{aET}{g+T} \end{aligned} \qquad \textbf{(A)}$$

where, c is the cancer antigenicity, d is the half life of effector cells E, p is the proliferation rate of E, f is the Half-saturation for E proliferation term, u_1 is the immuno-therapy term, r is the cancer growth rate, b is the cancer cell capacity (logistic growth), a is the cancer clearance term, g is the half-saturation for cancer clearance.

TABLE 1. Parameter value for the model **(A)**

Parameters	Meaning	Values	interval	Source
c	cancer antigenicity	0.05 (1/time)	$[10^{-3}, 0.5]$	[6]
u_1	Immunotherapy term	1 (cell/time)	$[10^{-2}, 10^2]$	[6]
p	proliferation rate of E	0.1245 (1/time)	0.1245	[6]
f	half saturation for E proliferation term	10^{-3} (cells)	$[10^{-5}, 1]$	[6]
d	half life of effector cells E	0.03 (1/time)	0.03	[6]
r	cancer growth rate	0.18 (1/time)	$[10^{-1}, 2]$	[6]
b	cancer cell capacity	10^{-9} (1/cells)	10^{-9}	[6]
a	cancer clearance term	1 (1/cells)	$[10^{-2}, 10^2]$	[6]
g	Half-saturation, for cancer clearance	10^5 (cells)	10^5	[6]

Raul Isea et. al. proposed a mathematical model of cancer under radiotherapy [10]. The authors applied single dose of radiotherapy directly to the cancer cells to kill those without affecting the neighboring healthy cells or the immune system. Based on the Raul Isea et. al [10] model with the single dose of radiotherapy, we propose a model which is slight modification of the model **(A)** as follows:

$$\begin{aligned} \frac{dE}{dt} &= cT + \frac{pE}{E+f} - dE + u_1 \\ \frac{dT}{dt} &= rT(1-bT) - \frac{aET}{g+T} - \gamma T \end{aligned} \tag{B}$$

where, u_1 is the treatment term for external source of immune-effector cells and γ is the single dose of radiation treatment. We consider that radiation kills only cancerous cell.

Monoclonal antibody(mAbs) therapy is used broadly in various cancer treatment models, mainly when no other treatment works significantly [9]. So, we formulate a model based on de Pilli's mAbs treatment [9] which is slight modification of the model mentioned in **(A)**. We consider mAbs interact only with Cancerous cells which results in death of Cancerous cells. The model is as follows:

$$\begin{aligned} \frac{dE}{dt} &= cT + \frac{pE}{E+f} - dE + u_1 \\ \frac{dT}{dt} &= rT(1-bT) - \frac{aET}{g+T} - u_2MT \\ \frac{dM}{dt} &= -\eta M - \rho T\frac{M}{h+M} + V_M(t) \end{aligned} \tag{C}$$

where, the term $-u_2MT$ is the death rate of tumor-cells caused directly by tumor cells' interaction with mAbs. The term $V_M(t)$ represents mAb treatments. Because mAbs are not produced naturally in the body, no additional growth terms are included. The term $-\eta M$ represents the natural degradation of the mAb protein in the body. The term $-\rho T\frac{M}{h+M}$ represents the loss of available mAbs as they bind to tumor cells. mAbs have a very strong binding affinity for their target growth-factor receptors, and there are many growth factor receptors on every cell, so we assume that many mAbs are lost with each tumor cell. Also, we assume that the growth factor receptors are fully saturated when the mAb concentration is significantly higher than the growth factor receptor concentration. That is, we can approximate the number of mAbs lost with each tumor cell as the number of growth-factor receptors on that cell, as long as mAb concentration is not close to zero [9].

3. Stability Analysis of the model (A)

3.1. Equilibrium Points: We first search the equilibrium points of the above model without the dose of radiotherapy i.e the model

$$\begin{aligned} \frac{dE}{dt} &= cT + \frac{pE}{E+f} - dE + u_1 \\ \frac{dT}{dt} &= rT(1-bT) - \frac{aET}{g+T} \end{aligned} \tag{3.1}$$

For equilibrium points we have,

$$\frac{dE}{dt} = 0 \implies cT + \frac{pE}{E+f} - dE + u_1 = 0 \tag{3.2}$$

$$\frac{dT}{dt} = 0 \implies rT(1-bT) - \frac{aET}{g+T} = 0 \tag{3.3}$$

From equation (3.3),

$$T_1 = 0 \quad ; \quad T_2 = \tfrac{A_1+\sqrt{B_1}}{2rb} \quad ; \quad T_3 = \tfrac{A_1-\sqrt{B_1}}{2rb}$$

where, $A_1 = r(1-gb)$
$B_1 = (r(1-gb))^2 - 4(aE-rg)rb$

For, $T_1 = 0$ we have obtained from equation (3.2),

$$E_1 = \tfrac{A_2+\sqrt{B_2}}{2d} \quad \text{and} \quad E_2 = \tfrac{A_2-\sqrt{B_2}}{2d}$$

where, $A_2 = p + u_1 - df$
$B_2 = (p+u_1-df)^2 + 4du_1f$

Therefore, $P_1(E_1, T_1)$ and $P_2(E_2, T_1)$ are two equilibrium points.

For, $T_2 = \frac{A_1+\sqrt{B_1}}{2rb}$ we have obtained from equation (3.2),

$$E_3 = \tfrac{A_3+\sqrt{B_3}}{4rbd} \quad \text{and} \quad E_4 = \tfrac{A_3-\sqrt{B_3}}{4rbd}$$

where, $A_3 = (A_1 + \sqrt{B_1})c + 2rb(p + u_1 - df)$
$B_3 = ((A_1+\sqrt{B_1})c+2rb(p+u_1-df))^2+8rbdf((A_1+\sqrt{B_1})c+2u_1rb)$

Therefore, $P_2(E_3, T_2)$ and $P_3(E_4, T_2)$ are two equilibrium points.

For, $T_3 = \frac{A_1-\sqrt{B_1}}{2rb}$ we have obtained from equation (3.2),

$$E_5 = \tfrac{A_4+\sqrt{B_4}}{4rbd} \quad \text{and} \quad E_6 = \tfrac{A_4-\sqrt{B_4}}{4rbd}$$

where, $A_4 = (A_1 - \sqrt{B_1})c + 2rb(p + u_1 - df)$
$B_4 = ((A_1-\sqrt{B_1})c+2rb(p+u_1-df))^2+8rbdf((A_1-\sqrt{B_1})c+2u_1rb)$

Therefore, $P_5(E_5, T_3)$ and $P_6(E_6, T_3)$ are two equilibrium points.

From the above analysis we get six equilibrium points out of which $P_1(E_1, T_1)$, $P_2(E_2, T_1)$ are two cancer free equilibrium points and $P_3(E_3, T_2)$, $P_4(E_4, T_2)$, $P_5(E_5, T_3)$, $P_6(E_6, T_3)$ are four cancer infected equilibrium points.

3.2. Local Stability: Linearizing system (3.1) to obtain Jacobian as follows:

$$\mathbf{J} = \begin{bmatrix} -d + \frac{pf}{(E+f)^2} & c \\ \frac{-aT}{g+T} & r(1-2bT) - \frac{agE}{(g+T)^2} \end{bmatrix} \tag{3.4}$$

(1) Cancer free Jacobian matrix at cancer free equilibrium point $P_1(E_1, T_1)$

$$\mathbf{J_{P_1}} = \begin{bmatrix} -d + \frac{pf}{(E_1+f)^2} & c \\ 0 & r - \frac{aE_1}{g} \end{bmatrix} \tag{3.5}$$

Characteristic equation for (3.5) is

$$\lambda^2 - \alpha_1\lambda + \beta_1 = 0$$

where, $\alpha_1 = \frac{pf}{(E_1+f)^2} - d + r - \frac{aE_1}{g}$

$\beta_1 = (\frac{pf}{(E_1+f)^2} - d)(r - \frac{aE_1}{g})$

Therefore, $\lambda_{1,1} = \frac{\alpha_1 \pm \sqrt{\alpha_1^2 - 4\beta_1}}{2}$

(a) If $\beta_1 > 0$ and $\alpha_1^2 - 4\beta_1 \geq 0$ then the equilibrium points $P_1(E_1, T_1)$ in the form of nodes and if $\alpha_1 < 0$ then $P_1(E_1, T_1)$ asymptotically stable. If $\alpha_1 > 0$ then $P_1(E_1, T_1)$ is unstable.

(b) If $\beta_1 > 0$ and $\alpha_1^2 - 4\beta_1 < 0$ then the equilibrium points $P_1(E_1, T_1)$ in the form of spiral and if $\alpha_1 < 0$ then $P_1(E_1, T_1)$ asymptotically stable. If $\alpha_1 > 0$ then $P_1(E_1, T_1)$ is unstable.

(2) The eigen values of the Jacobian matrix at cancer free equilibrium point $P_2(E_2, T_1)$ are

$$\lambda_{2,1} = \frac{\alpha_2 \pm \sqrt{\alpha_2^2 - 4\beta_2}}{2}$$

where, $\alpha_2 = \frac{pf}{(E_2+f)^2} - d + r - \frac{aE_2}{g}$

$\beta_2 = (\frac{pf}{(E_2+f)^2} - d)(r - \frac{aE_2}{g})$

(a) If $\beta_2 > 0$ and $\alpha_2^2 - 4\beta_2 \geq 0$ then the equilibrium points $P_2(E_2, T_1)$ in the form of nodes and if $\alpha_2 < 0$ then $P_2(E_2, T_1)$ asymptotically stable. If $\alpha_2 > 0$ then $P_2(E_2, T_1)$ is unstable.

(b) If $\beta_2 > 0$ and $\alpha_2^2 - 4\beta_2 < 0$ then the equilibrium points $P_2(E_2, T_1)$ in the form of spiral and if $\alpha_2 < 0$ then $P_2(E_2, T_1)$ asymptotically stable. If $\alpha_2 > 0$ then $P_2(E_2, T_1)$ is unstable.

(3) The eigen values of the Jacobian matrix at cancer infected equilibrium point $P_3(E_3, T_2)$ are

$$\lambda_{3,2} = \frac{\alpha_3 \pm \sqrt{\alpha_3^2 - 4\beta_3}}{2}$$

where, $\alpha_3 = \frac{pf}{(E_3+f)^2} - d + r(1-2bT_2) - \frac{agE_3}{(g+T_2)^2}$

$$\beta_3 = (\tfrac{pf}{(E_3+f)^2} - d)(r(1-2bT_2) - \tfrac{agE_3}{(g+T_2)^2}) + \tfrac{caT_2}{g+T_2}$$

(a) If $\beta_3 > 0$ and $\alpha_3^2 - 4\beta_3 \geq 0$ then the equilibrium points $P_3(E_3, T_2)$ in the form of nodes and if $\alpha_3 < 0$ then $P_3(E_3, T_2)$ asymptotically stable. If $\alpha_3 > 0$ then $P_3(E_3, T_2)$ is unstable.

(b) If $\beta_3 > 0$ and $\alpha_3^2 - 4\beta_3 < 0$ then the equilibrium points $P_3(E_3, T_2)$ in the form of spiral and if $\alpha_3 < 0$ then $P_3(E_3, T_2)$ asymptotically stable. If $\alpha_3 > 0$ then $P_3(E_3, T_2)$ is unstable.

(4) The eigen values of the Jacobian matrix at cancer infected equilibrium point $P_4(E_4, T_2)$ are

$$\lambda_{4,2} = \tfrac{\alpha_4 \pm \sqrt{\alpha_4^2 - 4\beta_4}}{2}$$

where,
$$\alpha_4 = \tfrac{pf}{(E_4+f)^2} - d + r(1-2bT_2) - \tfrac{agE_4}{(g+T_2)^2}$$
$$\beta_4 = (\tfrac{pf}{(E_4+f)^2} - d)(r(1-2bT_2) - \tfrac{agE_4}{(g+T_2)^2}) + \tfrac{caT_2}{g+T_2}$$

(a) If $\beta_4 > 0$ and $\alpha_4^2 - 4\beta_4 \geq 0$ then the equilibrium points $P_4(E_4, T_2)$ in the form of nodes and if $\alpha_4 < 0$ then $P_4(E_4, T_2)$ asymptotically stable. If $\alpha_4 > 0$ then $P_4(E_4, T_2)$ is unstable.

(b) If $\beta_4 > 0$ and $\alpha_4^2 - 4\beta_4 < 0$ then the equilibrium points $P_4(E_4, T_2)$ in the form of spiral and if $\alpha_4 < 0$ then $P_4(E_4, T_2)$ asymptotically stable. If $\alpha_4 > 0$ then $P_4(E_4, T_2)$ is unstable.

(5) The eigen values of the Jacobian matrix at cancer infected equilibrium point $P_5(E_5, T_3)$ are

$$\lambda_{5,3} = \tfrac{\alpha_5 \pm \sqrt{\alpha_5^2 - 4\beta_5}}{2}$$

where,
$$\alpha_5 = \tfrac{pf}{(E_5+f)^2} - d + r(1-2bT_3) - \tfrac{agE_5}{(g+T_3)^2}$$
$$\beta_5 = (\tfrac{pf}{(E_5+f)^2} - d)(r(1-2bT_3) - \tfrac{agE_5}{(g+T_3)^2}) + \tfrac{caT_3}{g+T_3}$$

(a) If $\beta_5 > 0$ and $\alpha_5^2 - 4\beta_5 \geq 0$ then the equilibrium points $P_5(E_5, T_3)$ in the form of nodes and if $\alpha_5 < 0$ then $P_5(E_5, T_3)$ asymptotically stable. If $\alpha_5 > 0$ then $P_5(E_5, T_3)$ is unstable.

(b) If $\beta_5 > 0$ and $\alpha_5^2 - 4\beta_5 < 0$ then the equilibrium points $P_5(E_5, T_3)$ in the form of spiral and if $\alpha_5 < 0$ then $P_5(E_5, T_3)$ asymptotically stable. If $\alpha_5 > 0$ then $P_5(E_5, T_3)$ is unstable.

(6) The eigen values of the Jacobian matrix at cancer infected equilibrium point $P_6(E_6, T_3)$ are

$$\lambda_{6,3} = \frac{\alpha_6 \pm \sqrt{\alpha_6^2 - 4\beta_6}}{2}$$

where, $\alpha_6 = \frac{pf}{(E_6+f)^2} - d + r(1 - 2bT_3) - \frac{agE_6}{(g+T_3)^2}$

$$\beta_6 = (\frac{pf}{(E_6+f)^2} - d)(r(1 - 2bT_3) - \frac{agE_6}{(g+T_3)^2}) + \frac{caT_3}{g+T_3}$$

(a) If $\beta_6 > 0$ and $\alpha_6^2 - 4\beta_6 \geq 0$ then the equilibrium points $P_6(E_6, T_3)$ in the form of nodes and if $\alpha_6 < 0$ then $P_6(E_6, T_3)$ asymptotically stable. If $\alpha_6 > 0$ then $P_6(E_6, T_3)$ is unstable.

(b) If $\beta_6 > 0$ and $\alpha_6^2 - 4\beta_6 < 0$ then the equilibrium points $P_6(E_6, T_3)$ in the form of spiral and if $\alpha_6 < 0$ then $P_6(E_6, T_3)$ asymptotically stable. If $\alpha_6 > 0$ then $P_6(E_6, T_3)$ is unstable.

3.3. Simulation: The set of parameters were being used to see the dynamics of effector cells and cancerous cells for the model **(A)** is given in Table 2. The initial values used in these simulation are $E(0) = T(0) = 1000$. Based on the

TABLE 2. Parameter value for the model **(A)**

Parameters	c	u_1	p	f	d	r	b	a	g
Values	0.05	1	0.1245	10^{-3}	0.03	0.18	10^{-9}	1	10^5

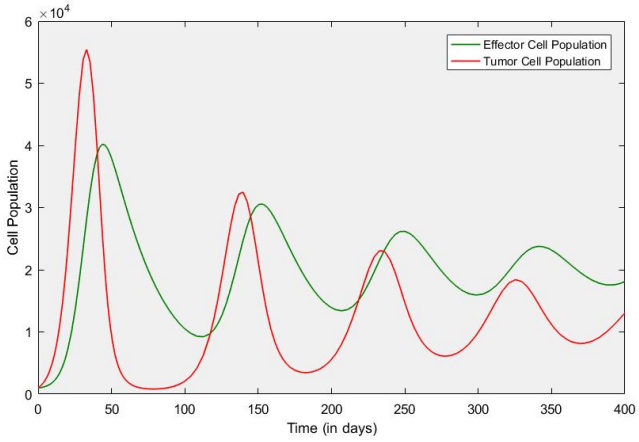


FIGURE 1. Gene therapy with low immunotherpeutic value, but high cancer growth

above parameter set, we get $P_1(37.4832, 0)$ and $P_3(20174.56, 12082.246)$ as two biologically valid equilibrium points. The equilibrium point P_1 is free of cancer and showed unstable result and has the type of saddle point. The equilibrium point

P_3 is cancer infected and it is asymptotically stable, incorporates a kind of inward spiral point i.e. at this point the trajectories are ingoing spirals as time increases, which suggests that the population of effector cells and tumor cells will develop in tandem for long time (Figure 1). That means the body with low immunity power or small treatment immunotherapeutic term cannot eradicated larger tumor from the body. So, we have to give large amount of treatment term u_1 and a or we shall required another treatment protocol.

4. Stability Analysis of The Model (B)

4.1. Equilibrium Points: For finding the equilibrium points of model **(B)** we have,

$$\frac{dE}{dt} = 0 \implies cT + \frac{pE}{E+f} - dE + u_1 = 0 \tag{4.1}$$

$$\frac{dT}{dt} = 0 \implies rT(1-bT) - \frac{aET}{g+T} - \gamma T = 0 \tag{4.2}$$

From equation (4.2),

$$T_1^* = 0 \quad ; \quad T_2^* = \tfrac{A_1^* + \sqrt{B_1^*}}{2rb} \quad ; \quad T_3^* = \tfrac{A_1^* - \sqrt{B_1^*}}{2rb}$$

where, $A_1^* = r - \gamma - grb$

$B_1^* = (r - \gamma - grb)^2 - 4rb(aE + \gamma g - rg)$

For, $T_1^* = 0$ we have obtained from equation (4.1),

$$E_1^* = \tfrac{A_2^* + \sqrt{B_2^*}}{2d} \quad \text{and} \quad E_2^* = \tfrac{A_2^* - \sqrt{B_2^*}}{2d}$$

where, $A_2^* = p + u_1 - df$

$B_2^* = (p + u_1 - df)^2 + 4du_1 f$

Therefore, $P_1^*(E_1^*, T_1^*)$ and $P_2^*(E_2^*, T_1^*)$ are two equilibrium points.

For, $T_2^* = \tfrac{A_1^* + \sqrt{B_1^*}}{2rb}$ we have obtained from equation (4.1),

$$E_3^* = \tfrac{A_3^* + \sqrt{B_3^*}}{2rbd} \quad \text{and} \quad E_4^* = \tfrac{A_3^* - B_3^*}{2rbd}$$

Therefore, $P_3^*(E_3^*, T_2^*)$ and $P_4^*(E_4^*, T_2^*)$ are two equilibrium points.

For, $T_3^* = \tfrac{A_1^* - \sqrt{B_1^*}}{2rb}$ we have obtained from equation (4.1),

$$E_5^* = \tfrac{A_4^* + \sqrt{B_4^*}}{2rdb} \quad \text{and} \quad E_6^* = \tfrac{A_4^* - \sqrt{B_4^*}}{2rdb}$$

Therefore, $P_5^*(E_5^*, T_3^*)$ and $P_6^*(E_6^*, T_3^*)$ are two equilibrium points.

From the above analysis we get six equilibrium points out of which $P_1^*(E_1^*, T_1^*), P_2^*(E_2^*, T_1^*)$ are two cancer free equilibrium points and $P_3^*(E_3^*, T_2^*), P_4^*(E_4^*, T_2^*), P_5^*(E_5^*, T_3^*), P_6^*(E_6^*, T_3^*)$ are four cancer infected equilibrium points.

4.2. Local Stability: Now we check stability analysis of the model at each of the equilibrium point.

Linearizing the model **(B)** to obtain Jacobian as follows:

$$\mathbf{J}^* = \begin{bmatrix} -d + \frac{pf}{(E+f)^2} & c \\ \frac{-aT}{g+T} & r(1-2bT) - \frac{agE}{(g+T)^2} - \gamma \end{bmatrix} \tag{4.3}$$

(1) Cancer free Jacobian matrix at cancer free equilibrium point $P_1^*(E_1^*, T_1^*)$

$$\mathbf{J_{P_1^*}} = \begin{bmatrix} -d + \frac{pf}{(E_1^*+f)^2} & c \\ 0 & r - \frac{aE_1^*}{g} - \gamma \end{bmatrix} \tag{4.4}$$

Characteristic equation for (4.4) is

$$\lambda^2 - \alpha_1^*\lambda + \beta_1^* = 0$$

where, $\alpha_1^* = \frac{pf}{(E_1^*+f)^2} - d + r - \frac{aE_1^*}{g} - \gamma$

$\beta_1^* = (\frac{pf}{(E_1^*+f)^2} - d)(r - \frac{aE_1^*}{g} - \gamma)$

Therefore, $\lambda_{1,1}^* = \frac{\alpha_1^* \pm \sqrt{(\alpha_1^*)^2 - 4\beta_1^*}}{2}$

(a) If $\beta_1^* > 0$ and $(\alpha_1^*)^2 - 4\beta_1^* \geq 0$ then the equilibrium points $P_1^*(E_1^*, T_1^*)$ in the form of nodes and if $\alpha_1^* < 0$ then $P_1^*(E_1^*, T_1^*)$ asymptotically stable. If $\alpha_1^* > 0$ then $P_1^*(E_1^*, T_1^*)$ is unstable.

(b) If $\beta_1^* > 0$ and $(\alpha_1^*)^2 - 4\beta_1^* < 0$ then the equilibrium points $P_1^*(E_1^*, T_1^*)$ in the form of spiral and if $\alpha_1^* < 0$ then $P_1^*(E_1^*, T_1^*)$ asymptotically stable. If $\alpha_1^* > 0$ then $P_1^*(E_1^*, T_1^*)$ is unstable.

(2) The eigen values of the Jacobian matrix at cancer free equilibrium point $P_2^*(E_2^*, T_1^*)$ are

$$\lambda_{2,1}^* = \frac{\alpha_2^* \pm \sqrt{(\alpha_2^*)^2 - 4\beta_2^*}}{2}$$

where, $\alpha_2^* = \frac{pf}{(E_2^*+f)^2} - d + r - \frac{aE_2^*}{g} - \gamma$

$\beta_2^* = (\frac{pf}{(E_2^*+f)^2} - d)(r - \frac{aE_2^*}{g} - \gamma)$

(a) If $\beta_2^* > 0$ and $(\alpha_2^*)^2 - 4\beta_2^* \geq 0$ then the equilibrium points $P_2(E_2, T_1)$ in the form of nodes and if $\alpha_2 < 0$ then $P_2(E_2, T_1)$ asymptotically stable. If $\alpha_2^* > 0$ then $P_2^*(E_2^*, T_1^*)$ is unstable.

(b) If $\beta_2^* > 0$ and $(\alpha_2^*)^2 - 4\beta_2^* < 0$ then the equilibrium points $P_2^*(E_2^*, T_1^*)$ in the form of spiral and if $\alpha_2^* < 0$ then $P_2^*(E_2^*, T_1^*)$ asymptotically stable. If $\alpha_2^* > 0$ then $P_2^*(E_2^*, T_1^*)$ is unstable.

(3) The eigen values of the Jacobian matrix at cancer infected equilibrium point $P_3^*(E_3^*, T_2^*)$ are

$$\lambda_{3,2}^* = \frac{\alpha_3^* \pm \sqrt{(\alpha_3^*)^2 - 4\beta_3^*}}{2}$$

where, $\alpha_3^* = \frac{pf}{(E_3^*+f)^2} - d + r(1-2bT_2^*) - \frac{agE_3^*}{(g+T_2^*)^2} - \gamma$

$\beta_3^* = (\frac{pf}{(E_3^*+f)^2} - d)(r(1-2bT_2^*) - \frac{agE_3^*}{(g+T_2^*)^2} - \gamma) + \frac{caT_2^*}{g+T_2^*}$

(a) If $\beta_3^* > 0$ and $(\alpha_3^*)^2 - 4\beta_3^* \geq 0$ then the equilibrium points $P_3^*(E_3^*, T_2^*)$ in the form of nodes and if $\alpha_3^* < 0$ then $P_3^*(E_3^*, T_2^*)$ asymptotically stable. If $\alpha_3^* > 0$ then $P_3^*(E_3^*, T_2^*)$ is unstable.

(b) If $\beta_3^* > 0$ and $(\alpha_3^*)^2 - 4\beta_3^* < 0$ then the equilibrium points $P_3^*(E_3^*, T_2^*)$ in the form of spiral and if $\alpha_3^* < 0$ then $P_3^*(E_3^*, T_2^*)$ asymptotically stable. If $\alpha_3^* > 0$ then $P_3^*(E_3^*, T_2^*)$ is unstable.

(4) The eigen values of the Jacobian matrix at cancer infected equilibrium point $P_4^*(E_4^*, T_2^*)$ are

$$\lambda_{4,2}^* = \frac{\alpha_4^* \pm \sqrt{(\alpha_4^*)^2 - 4\beta_4^*}}{2}$$

where, $\alpha_4^* = \frac{pf}{(E_4^*+f)^2} - d + r(1 - 2bT_2^*) - \frac{agE_4^*}{(g+T_2^*)^2} - \gamma$

$\beta_4^* = (\frac{pf}{(E_4^*+f)^2} - d)(r(1 - 2bT_2^*) - \frac{agE_4^*}{(g+T_2^*)^2} - \gamma) + \frac{caT_2^*}{g+T_2^*}$

(a) If $\beta_4^* > 0$ and $(\alpha_4^*)^2 - 4\beta_4^* \geq 0$ then the equilibrium points $P_4^*(E_4^*, T_2^*)$ in the form of nodes and if $\alpha_4^* < 0$ then $P_4^*(E_4^*, T_2^*)$ asymptotically stable. If $\alpha_4^* > 0$ then $P_4^*(E_4^*, T_2^*)$ is unstable.

(b) If $\beta_4^* > 0$ and $(\alpha_4^*)^2 - 4\beta_4^* < 0$ then the equilibrium points $P_4^*(E_4^*, T_2^*)$ in the form of spiral and if $\alpha_4^* < 0$ then $P_4^*(E_4^*, T_2^*)$ asymptotically stable. If $\alpha_4^* > 0$ then $P_4^*(E_4^*, T_2^*)$ is unstable.

(5) The eigen values of the Jacobian matrix at cancer infected equilibrium point $P_5^*(E_5^*, T_3^*)$ are

$$\lambda_{5,3}^* = \frac{\alpha_5^* \pm \sqrt{(\alpha_5^*)^2 - 4\beta_5^*}}{2}$$

where, $\alpha_5^* = \frac{pf}{(E_5^*+f)^2} - d + r(1 - 2bT_3^*) - \frac{agE_5^*}{(g+T_3^*)^2} - \gamma$

$\beta_5^* = (\frac{pf}{(E_5^*+f)^2} - d)(r(1 - 2bT_3^*) - \frac{agE_5^*}{(g+T_3^*)^2} - \gamma) + \frac{caT_3^*}{g+T_3^*}$

(a) If $\beta_5^* > 0$ and $(\alpha_5^*)^2 - 4\beta_5^* \geq 0$ then the equilibrium points $P_5^*(E_5^*, T_3^*)$ in the form of nodes and if $\alpha_5^* < 0$ then $P_5^*(E_5^*, T_3^*)$ asymptotically stable. If $\alpha_5^* > 0$ then $P_5^*(E_5^*, T_3^*)$ is unstable.

(b) If $\beta_5^* > 0$ and $(\alpha_5^*)^2 - 4\beta_5^* < 0$ then the equilibrium points $P_5^*(E_5^*, T_3^*)$ in the form of spiral and if $\alpha_5^* < 0$ then $P_5^*(E_5^*, T_3^*)$ asymptotically stable. If $\alpha_5^* > 0$ then $P_5^*(E_5^*, T_3^*)$ is unstable.

(6) The eigen values of the Jacobian matrix at cancer infected equilibrium point $P_6^*(E_6^*, T_3^*)$ are

$$\lambda_{6,3}^* = \frac{\alpha_6^* \pm \sqrt{(\alpha_6^*)^2 - 4\beta_6^*}}{2}$$

where, $\alpha_6^* = \frac{pf}{(E_6^*+f)^2} - d + r(1 - 2bT_3^*) - \frac{agE_6^*}{(g+T_3^*)^2} - \gamma$

$\beta_6^* = (\frac{pf}{(E_6^*+f)^2} - d)(r(1 - 2bT_3^*) - \frac{agE_6^*}{(g+T_3^*)^2} - \gamma) + \frac{caT_3^*}{g+T_3^*}$

(a) If $\beta_6^* > 0$ and $(\alpha_6^*)^2 - 4\beta_6^* \geq 0$ then the equilibrium points $P_6^*(E_6^*, T_3^*)$ in the form of nodes and if $\alpha_6^* < 0$ then $P_6^*(E_6^*, T_3^*)$ asymptotically

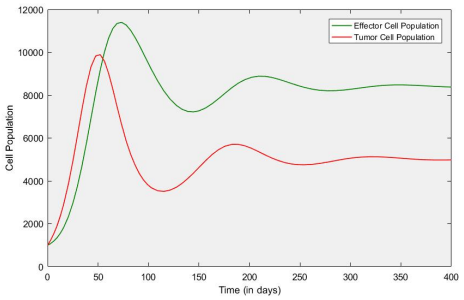
stable. If $\alpha_6^* > 0$ then $P_6^*(E_6^*, T_3^*)$ is unstable.

(b) If $\beta_6^* > 0$ and $(\alpha_6^*)^2 - 4\beta_6^* < 0$ then the equilibrium points $P_6^*(E_6^*, T_3^*)$ in the form of spiral and if $\alpha_6^* < 0$ then $P_6^*(E_6^*, T_3^*)$ asymptotically stable. If $\alpha_6^* > 0$ then $P_6^*(E_6^*, T_3^*)$ is unstable.

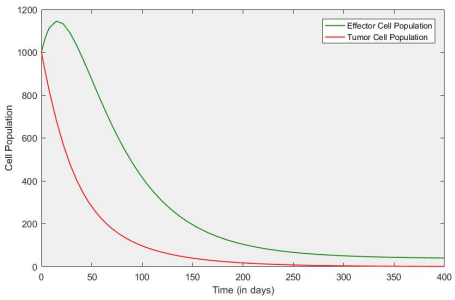
4.3. Simulation: The set of parameters were being used to see the dynamics of effector cells and cancerous cells for the model **(B)** is given in Table 3. The initial values used in these simulation are $E(0) = T(0) = 1000$.

TABLE 3. Parameter value for the model **(B)**

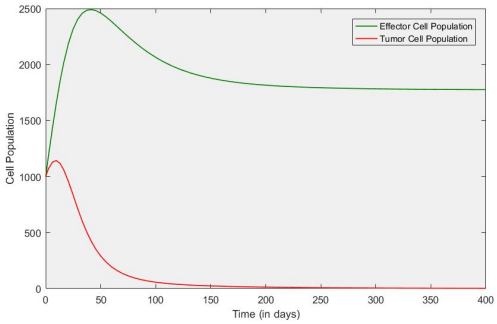
Parameters	c	u_1	p	f	d	r	b	a	g	$\gamma(estimated)$ based on [10]
Values for simulation 1	0.05	1	0.1245	10^{-3}	0.03	0.18	10^{-9}	1	10^5	0.1
Values for simulation 2	0.05	1	0.1245	10^{-3}	0.03	0.18	10^{-9}	1	10^5	0.195
Values for simulation 3	0.05	53	0.1245	10^{-3}	0.03	0.18	10^{-9}	5	10^5	0.1



(A) Simulation 1



(B) Simulation 2



(C) Simulation 3

FIGURE 2. Radiogenic therapy

Based on the parameter set of simulation 1, we have two biologically valid equilibrium points $P_1(37.4832, 0)$ and $P_3(8401.37, 5018.33)$. The cancer free equilibrium point P_1 is unstable and behaves as a saddle point in nature. The cancer infected equilibrium point P_3 is showed asymptotically stable result with inward spiral in nature. i.e. at this point both effector and tumor cells population showed damped oscillation behavior about zero rather than asymptotes to zero (Figure 2(A)). Based on the simulation 2, there is only one valid equilibrium point $P_1(37.4832, 0)$ and this point showed nodal sink nature with asymptotically stable behavior. That means the effector cell population incorporates with the treatment given can suppressed the tumor growth to zero with time increase (Figure 2(B)). Simulation 3, showed that the biologically valid equilibrium point $P_1(1770, 0)$ is asymptotically stable with nodal sink nature. That means tumor cells asymptotes to zero rather than oscillating about zero (Figure 2(C)).

5. Stability Analysis of The Model (C)

To find the equilibrium point of the system **(C)**, we have

$$\begin{aligned} cT + \frac{pE}{E+f} - dE + u_1 &= 0 \\ rT(1-bT) - \frac{aET}{g+T} - u_2MT &= 0 \\ -\eta M - \rho T\frac{M}{h+M} + V_M(t) &= 0 \end{aligned} \tag{5.1}$$

Solving above three equations, we get twelve equilibrium points and out of which one equilibrium point $P_1(1770.82, 0, 0.346)$ is biologically valid based on parameter Table 4.

The jacobian matrix at this point is

$$\mathbf{J}_{\mathbf{P_1^{**}}} = \begin{bmatrix} -d + \frac{pf}{(1770.82+f)^2} & c & 0 \\ 0 & r - \frac{1770.82a}{g} - 0.346u_2 & 0 \\ 0 & -\frac{0.346\rho}{h+0.346} & -\eta \end{bmatrix} \tag{5.2}$$

The characteristic equation for the above matrix is given by

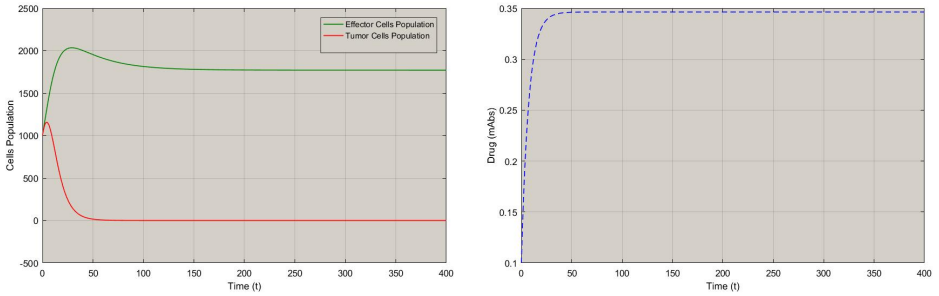
$$\lambda^3 - (X+Y+Z)\lambda^2 + (XZ+YZ+XY)\lambda - XYZ = 0 \tag{5.3}$$

where, $X = -d + \frac{pf}{(1770.82+f)^2}$; $Y = r - \frac{1770.82a}{g} - 0.346u_2$; $Z = -\frac{0.346\rho}{h+0.346}$.

Numerical simulation with the initial values $E(0) = T(0) = 1000$ and stability analysis showed that around this cancer-free equilibrium point P_1^{**}, the solution of the system (5.1) behaves asymptotically stable with nodal sink in nature. That means in this case also tumour cells asymptotes to zero rather than oscillating about zero (Figure 3(A)). Figure 3(B) shows the drug administration into the system in the form of mAbs, which is stable in approx 0.346, after some time of treatment.

TABLE 4. Parameter value for the model **(C)**

Parameters	Meaning	Values	Source
c	cancer antigenicity	0.05	[6]
u_1	Immunotherapy term	53	[6]
p	proliferation rate of E	0.1245	[6]
f	half saturation for E proliferation term	10^{-3}	[6]
d	half life of effector cells E	0.03	[6]
r	cancer growth rate	0.18	[6]
b	cancer cell capacity	10^{-9}	[6]
a	cancer clearance term	5	[6]
g	Half-saturation, for cancer clearance	10^5	[6]
u_2	Rate of mAb-induced tumor death	5.5×10^{-1}	[13]
η	Rate of mAb turnover and excretion	1.386×10^{-1}	[14]
ρ	Rate of mAb-tumor cell complex formation	8.9×10^{-14}	[15]
h	Concentration of mAbs for half-maximal EGFR binding	4.45×10^{-5}	[15]



(A) (B)

FIGURE 3. combination of mAbs and gene therapy

6. Discussion and Conclusion

Without numerical verification of the derived results, analytical studies can never be completed. In section 3, 4, 5; we presented numerical simulation of some important situations for each of our considered models of which we derived analytical results in corresponding sections.

In section 3, we considered treatment through gene therapy, in section 4 through a combination of gene and radiotherapy and lastly in section 5 through gene and mAbs therapy.

Figure 1 in section 3 shows that when only gene therapy is used as treatment method of a system with low treatment term and high cancer growth rate then tumor and immune cells compete with each other for a long time signifying that

cancer cannot be cured through this mechanism.

Figure 2(A) in section 4 shows that for low dosage of both radiotherapy ($\gamma = 0.1$) and immunotherapy ($u_1 = 1$) cancer cells and immune cells compete with each other for a long time signifying inefficiency of this treatment mechanism for considered parameter values. But the situation gets drastically changed when we increase the radiotherapy dose to a higher level ($\gamma = 0.195$). Figure 2(B) shows that in this case cancer cells get eradicated in time $t = 300$. But deficiency of this treatment mechanism is that along with the tumor cells it reduces the level of immune cells where the patient can be attack by other opportunistic diseases making the patients' survival difficult. Of course, this situation can be avoided for a set of selected values of the parameter which is shown in Figure 2(C). For radiotherapy dose ($\gamma = 0.1$), immunotherapy dose ($u_1 = 53$) and cancer clearence term ($a = 5$) cancer gets eradicated in time $t = 250$. Point to be noted in this case is that the immune cells maintain almost a constant level where the patient is safe.

Figure 3(A) and 3(B) in section 5 shows that cancer can be eradicated quickly ($t < 50$) if the treatment is carried out in combination of gene therapy and mAbs therapy and applying the parameter values given in Table 4. Added advantage of this treatment procedure is that the immune cells attained a higher level when cancer cells die out.

The above analyses have shown the theoretical behavior in case of different cancer treatment models. Oncologists may practice the above treatment strategies in the lab with any living body for a better result. This paper deals with the local stability and time series analysis of three different treatment models. The side effects of the above treatment policies and its control will be discussed in near future. This is our on-going research; the models with continuous radiotherapy, pulsed radiotherapy and optimal mAbs will be considered in our future works.

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