A study on cancer-obesity-treatment model with quadratic optimal control approach for better outcomes

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ABSTRACT

In this study, we propose a cancer-obesity-treatment model under the control parameters: IL-2 therapy, ACI therapy, and nutritional diet. We analyze the proposed model and examine the existence and stability of the equilibrium points for the cases: with and without treatment cases. Further, to reduce the number of cancer cells and minimize the toxicity effect of the drug dose on other healthy cells, we consider an optimal control problem over a finite time interval under the treatment control parameters. To understand the treatment effect, we present simulation results for our proposed model considering different treatment strategies: no treatment; only IL-2 therapy; a combination of IL-2 therapy and ACI therapy; and a combination of IL-2 therapy, ACI therapy, and nutritional diet. Our results demonstrate that we could achieve an optimal treatment schedule for cancer management by controlling all three treatment parameters.

1. Introduction

A tumor originates from any part of the body via abnormal growth of a single cell. It has a spreading tendency. Depending upon its spreading tendency, a tumor can be classified as benign (having no spreading tendency and not cancerous), premalignant (having the potential to become cancerous), and malignant (having rapid and uncontrolled spreading tendency and cancerous) [1,2]. Worldwide, millions of people die from cancer every year, and trends indicate that millions more will die from this disease. Therefore, scientific research (both clinical and theoretical) on cancer is crucial for the research community. The theoretical study of cancer through mathematical modeling is a valuable approach to shaping our understanding of tumor-immune dynamics. Significant research work [3–5] has been done to understand the tumor-immune dynamics.

Researching a suitable cancer treatment method is a broad research area in medical science. Chemotherapy [6], radiotherapy [7], and virotherapy [8] are widely used in the cancer eradication process. Immunotherapy is gaining more interest in cancer treatment as it has fewer side effects than other methods. The two types of immunotherapy are: one is passive (such as ACI and CAR-T cell therapy), where the external input of the immune system is used to attack tumor cells directly, and the other is active, where the external input enhances the immune system (such as IL-2 therapy, vaccine therapy) [9–11]. Moreover, scientific studies have reported that vitamin intervention and nutritional diet are also responsible for suppressing cancer formation [12,13]. Researchers claim that with the combination of various therapeutic approaches, cancer can be eradicated from the body optimally [14]. Mathematical modeling is making a significant contribution to the treatment of cancer. The reviewed work of Malinzi et al. [15] discussed some mathematical models related to different cancer treatment methods. de Pillis et al. [16] presented a mathematical

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model of tumor growth using mixed immunotherapy and chemotherapy. Freedman and Pinho developed a radiation treatment model [7] for cancer where the radiation affects normal cells proportionately. Bunimovich-Mendrazitsky et al. [17] analyzed a mathematical model of BCG immunotherapy for superficial bladder cancer. In [18], the authors explored the role of antibodies in controlling cancer growth. Makhlouf et al. [9] designed a treatment protocol considering chemotherapy, IL-2 cytokine therapy, $CD8^+T$, and $CD4^+T$ adoptive immunotherapy and investigated the effects of natural killer cells, circulating lymphocytes, $CD8^+T$ cells, and $CD4^+T$ cells on cancer cells. A modified nonlinear cancer model was analyzed in [8] using virotherapy and obtained the optimal dosage for long-term tumor eradication. The authors in [19] developed a cancer growth model incorporating chemotherapy and targeted drugs to investigate the impact of competition between cancer cells and healthy cells. Schlicke et al. [11] presented a mathematical model taking into account different treatment possibilities, and they analyzed the results derived from those possibilities after they were fitted to three patients with non-small cell lung cancer. The authors of [20] investigated a fractional-order tumor-immune-vitamin model (TIVM) under the Mittag-Leffler derivative and showed the effect of vitamins on tumor cell growth for different fractional orders.

The use of optimal control in a model of cancer treatment is not new. It is a well-known tool for studying treatment protocols with constraints. Sharma and Samanta [21] investigated the effects of chemotherapeutic and immunotherapeutic drugs in a tumor growth model [3], using quadratic optimal drug control. In [10], the author analyzed the combined effect of optimal treatment strategies by applying adoptive cellular immunotherapy and interleukin-2 therapy to a cancer treatment model. Rihan et al. [22] presented a delay differential model with optimal control to examine the interactions of the tumor cells and immune response cells with chemo-immunotherapy. Sweilam et al. [23] presented a fractional-order cancer treatment model and set up an optimal control problem for anti-angiogenic and immune cell therapies. A breast cancer fractional-order model was discussed in [24] in the presence of an immune-chemotherapeutic treatment process under control parameters: ketogenic diet, immune booster, and anti-cancer drugs. Das et al. [25] proposed and analyzed an optimal control problem for a delayed tumor-immune model in the presence of a multi-immuno-chemotherapeutic drug.

Several experimental studies have shown that obesity is a risk factor for different types of cancer. Theoretical studies [26–30] have also established that adipocytes, or fat cells, contribute to the growth of tumor cells. Thus, it is essential to investigate the role of obesity or fat cells in a cancerous system and find treatment protocols that control the excess growth of fat cells and cancer cells. In order to do this, Ku-Carrillo et al. [31] developed a cancer-obesity model that considers the immune system response and the effects of obesity on cancer growth. Furthermore, they extended their work [31] by introducing optimal chemotherapy treatment and establishing that losing weight can be helpful for chemotherapy treatment [32]. Yanti and Habibah [33] investigated the stability of the model [31] under chemotherapy. Arshad et al. [34] extended the model [31] to a fractional one and then investigated the role of obesity in the tumor-immune model. In [35], the authors found the optimal chemotherapy and immunotherapy treatment schedule for a cancer-obesity model with the Caputo time-fractional derivative. However, in the works mentioned above, the authors have not discussed the effect of nutritional diet on the model [31] that may directly control the fat cells of our body. In the current study, we propose and analyze a modified cancer-obesity model for tumor growth to discuss the optimal effect of nutritional diet along with two immuno-therapeutic treatments (IL-2 therapy and ACI therapy) on the model [31]. We aim to study the variation in tumor growth under control parameters: immune booster (IL-2 therapy), anti-cancer drugs (ACI therapy), and nutritional diet.

The rest of the paper is organized as follows: In Section "Model description", the formulated model is presented. In Section "Model without treatment", the stability of the model without treatment has been checked. Stability analysis of the model with treatment has been examined in Section "Model with treatment". The numerical simulation of our theoretical results has been carried out in Section "Optimal control". Finally, in Section "Numerical simulation", an optimal control problem has been set up for the treatment model by considering treatment parameters as the control inputs.

2. Model description

In this study, we consider a model initially proposed by Ku-Carrillo et al. [31]. The authors proposed their model based on the works of de Pillis and Radunskaya [6]. Ku-Carrillo et al. [31] studied the effect of obesity on the growth of cancer using the following set of ordinary differential equations:

$$
\left.
\begin{aligned}
\frac{dI}{dt} &= s + \frac{\rho IT}{\alpha + T + \mu F} - c_1 TI - d_1 I, \\
\frac{dT}{dt} &= r_1 T(1 - b_1 T) - c_2 IT - c_3 TN + c_5 TF, \\
\frac{dN}{dt} &= r_2 N(1 - b_2 N) - c_4 TN, \\
\frac{dF}{dt} &= r_3 F(1 - b_3 F) - c_6 TF,
\end{aligned}
\right\}
\tag{1}
$$

where $I(t)$ denotes the number of immune cells, $T(t)$ denotes the number of tumor cells, $N(t)$ denotes the number of normal cells, and $F(t)$ denotes the number of fat cells. The constant source rate of immune cells is 's'. The term $\frac{\rho IT}{\alpha + T + \mu F}$ is the stimulatory effect of immune cells on account of cancer and fat cells. 'd_1' is the natural death rate of the immune cells. It is assumed that tumor, normal, and fat cells can grow logistically with different growth rates r_1, r_2, and r_3 respectively. b_1, b_2, and b_3 represent the inverse of the carrying capacity for tumor cells, normal cells, and fat cells, respectively. The term '$c_5 TF$' denotes the contribution of fat cells to tumor growth. c_1, c_2, c_3, c_4, c_5, and c_6 are competition coefficients.

In [31], the authors have verified different scenarios reported in clinical studies, such as the effect of obesity on increasing cancer growth and the effect of a low or high caloric diet. Further, they analyzed the model with the use of optimal chemotherapeutic treatment [32] and observed that the effects of losing weight could be adjuvant to chemotherapy treatment.

In our study, we are interested in analyzing the model (1) for the particular sets of parameters used in combination treatment procedures. Since immunotherapy such as IL-2 therapy helps the body's immune system fight against cancer cells, the model (1) is extended to include an external source of immunotherapy treatment [3,4]. We add a new term $\delta(t)\sigma_1$ to represent the input rate of externally administered anti-tumor immune therapy, where $\delta(t)$ is the IL-2 therapy control parameter. Therefore, the first equation of (1) becomes

$$
\frac{dI}{dt} = s + \frac{\rho IT}{\alpha + T + \mu F} - c_1 TI - d_1 I + \delta(t)\sigma_1.
$$

Next, we modified the second equation of the system (1) with the use of ACI treatment therapy, which has an anti-tumor activity that can be achieved in conjunction with the high dosage of human recombinant IL-2 [15,22,25]. So, the term $-\gamma(t)T$ is added to the second equation, representing the tumor cells killed by an external injection of adoptive cellular immunotherapy, where $\gamma(t)$ is the time-dependent ACI treatment control parameter. Therefore, the second equation of (1) becomes

$$
\frac{dT}{dt} = r_1 T(1 - b_1 T) - c_2 IT - c_3 TN + c_5 TF - \gamma(t)T.
$$

Ku-Carrillo et al. [31] reported that fat cells contribute to cancer cell growth. They also showed that a low-calorie diet prevents the patient's condition from worsening compared to a high-calorie diet. So we are interested in controlling the growth of fat cells so that cancer cells grow under control via a nutritional diet [12,24]. Therefore, in the fourth

equation, we introduced a new term $-\beta(t)F$, where $\beta(t)$ denotes the nutritional diet control parameter, and hence the equation becomes

$$\frac{dF}{dt} = r_3 F(1 - b_3 F) - c_6 TF - \beta(t)F.$$

Therefore, the modified model becomes

$$
\left.
\begin{aligned}
\frac{dI}{dt} &= s + \frac{\rho IT}{\alpha + T + \mu F} - c_1 TI - d_1 I + \delta(t)\sigma_1, \\
\frac{dT}{dt} &= r_1 T(1 - b_1 T) - c_2 IT - c_3 TN + c_5 TF - \gamma(t)T, \\
\frac{dN}{dt} &= r_2 N(1 - b_2 N) - c_4 TN, \\
\frac{dF}{dt} &= r_3 F(1 - b_3 F) - c_6 TF - \beta(t)F,
\end{aligned}
\right\}
\tag{2}
$$

satisfying the known initial conditions $I(0) = I_0$, $T(0) = T_0$, $N(0) = N_0$, $F(0) = F_0$ and $\delta(t)$, $\gamma(t)$, and $\beta(t)$ are the time-dependent treatment control parameters. We also assume that all the parameter values are positive and the system (2) ensures positive solutions for the state equations $I(t)$, $T(t)$, $N(t)$ and $F(t)$. All parameters are taken from the paper [31].

3. Model without treatment

It is necessary to understand the dynamic behavior of the model in the absence of treatment before studying its effect on the model. In this section, we will check the system's behavior without treatment at each equilibrium point. For this, the model where $\delta(t) = 0$, $\gamma(t) = 0$, and $\beta(t) = 0$ becomes

$$
\left.
\begin{aligned}
\frac{dI}{dt} &= s + \frac{\rho IT}{\alpha + T + \mu F} - c_1 TI - d_1 I, \\
\frac{dT}{dt} &= r_1 T(1 - b_1 T) - c_2 IT - c_3 TN + c_5 TF, \\
\frac{dN}{dt} &= r_2 N(1 - b_2 N) - c_4 TN, \\
\frac{dF}{dt} &= r_3 F(1 - b_3 F) - c_6 TF.
\end{aligned}
\right\}
\tag{3}
$$

To find the equilibria of the system (3), we set $\frac{dI}{dt} = 0$, $\frac{dT}{dt} = 0$, $\frac{dN}{dt} = 0$ and $\frac{dF}{dt} = 0$.

The equilibrium points of the system (3) are

- Dead equilibrium:
  (i) $E_0(\frac{s}{d_1}, 0, 0, 0)$, (ii) $E_1(\frac{s}{d_1}, 0, 0, \frac{1}{b_3})$
- Disease-free equilibrium:
  (iii) $E_2(\frac{s}{d_1}, 0, \frac{1}{b_2}, 0)$, (iv) $E_3(\frac{s}{d_1}, 0, \frac{1}{b_2}, \frac{1}{b_3})$
- Disease-persistent equilibrium:
  (v) $E_5(\bar{I} = \frac{r_1(1 - b_1 \bar{T})}{c_2}, \bar{T}, 0, 0)$ where $\bar{T}$ will be calculated from the equation

  $$c_1 \bar{I} \bar{T}^2 - (s + \rho \bar{I} - c_1 \alpha \bar{I} - d_1 \bar{I})\bar{T} + (d_1 \alpha \bar{I} - s\alpha) = 0,$$

  and $\bar{T} < 1$. If $\bar{T} = 1$, then the size of the tumor is maximum. This equilibrium will exist for $b_1 \bar{T} < 1$.
  (vi) $E_6(\check{I} = \frac{r_1 \check{T}(1 - b_1 \check{T}) + c_5 \check{T}\check{F}}{c_2 \check{T}}, \check{T}, 0, \check{F} = \frac{r_3 - c_6 \check{T}}{r_3 b_3})$ where $\check{T}$ will be calculated from the equation

  $$c_1 \check{I} \check{T}^2 - (s + \rho \check{I} - c_1 \alpha \check{I} - c_1 \mu \check{I}\check{F} - d_1 \check{I})\check{T} + (d_1 \alpha \check{I} + d_1 \mu \check{I}\check{F} - s\alpha - s\mu\check{F}) = 0,$$

  also $\check{T} < 1$. If $\check{T} = 1$, then the size of the tumor is maximum. Equilibrium E_6 will exist for $b_1 \check{T} < 1$ and $c_6 \check{T} < r_3$.
- Co-axial equilibrium:
  (vii) The equilibrium $E_7(\tilde{I} = \frac{r_1(1 - b_1 \tilde{T}) - c_3 \tilde{N}}{c_2}, \tilde{T}, \tilde{N} = \frac{r_2 - c_4 \tilde{T}}{r_2 b_2}, 0)$ will exist for $b_1 \tilde{T} < 1$, $r_1(1 - b_1 \tilde{T}) > c_3 \tilde{N}$ and $r_2 > c_4 \tilde{T}$, where $\tilde{T}$ will be calculated from the equation

  $$c_1 \tilde{I} \tilde{T}^2 - (s + \rho \tilde{I} - c_1 \alpha \tilde{I} - d_1 \tilde{I})\tilde{T} + (d_1 \alpha \tilde{I} - s\alpha) = 0,$$

and $\tilde{T} < 1$. If $\tilde{T} = 1$, then the size of the tumor is maximum. (viii) The equilibrium $E_8(\hat{I} = \frac{r_1(1 - b_1 \hat{T}) - c_3 \hat{N} + c_5 \hat{F}}{c_2}, \hat{T}, \hat{N} = \frac{r_2 - c_4 \hat{T}}{r_2 b_2}, \hat{F} = \frac{r_3 - c_6 \hat{T}}{r_3 b_3})$ will exist for $b_1 \hat{T} < 1$, $r_1(1 - b_1 \hat{T}) > c_3 \hat{N}$, $r_2 > c_4 \hat{T}$ and $r_3 > c_6 \hat{T}$, where $\hat{T}$ will be calculated from the equation

$$c_1 \hat{I} \hat{T}^2 - (s + \rho \hat{I} - c_1 \alpha \hat{I} - c_1 \mu \hat{I}\hat{F} - d_1 \hat{I})\hat{T} + (d_1 \alpha \hat{I} + d_1 \mu \hat{I}\hat{F} - s\alpha - s\mu\hat{F}) = 0,$$

and $\hat{T} < 1$. If $\hat{T} = 1$, then the size of the tumor is maximum.

As $N = 0$ is tantamount to the death of a person, we are not considering those equilibria for stability analysis. In order to check local stability, we calculate the Jacobian of the system, which is given by

$$
\mathcal{J}_E =
\begin{pmatrix}
j_{11} & j_{12} & 0 & j_{14} \\
j_{21} & j_{22} & j_{23} & j_{24} \\
0 & j_{32} & j_{33} & 0 \\
0 & j_{42} & 0 & j_{44}
\end{pmatrix},
\tag{4}
$$

where $j_{11} = \frac{\rho T}{\alpha + \mu F + T} - c_1 T - d_1$, $j_{12} = \frac{(\alpha + \mu F)\rho I}{(\alpha + T + \mu F)^2} - c_1 I$, $j_{14} = -\frac{\rho \mu IT}{(\alpha + T + \mu F)^2}$, $j_{21} = -c_2 T$, $j_{22} = r_1 - 2r_1 b_1 T - c_2 I - c_3 N + c_5 F$, $j_{23} = -c_3 T$, $j_{24} = c_5 T$, $j_{32} = -c_4 N$, $j_{33} = r_2 - 2r_2 b_2 N - c_4 T$, $j_{42} = -c_6 F$ and $j_{44} = r_3 - 2r_3 b_3 F - c_6 T$.

The eigenvalues of the Jacobian (4) corresponding to the disease-free equilibrium E_2 are $-d_1$, $r_1 - \frac{sc_2}{d_1} - \frac{c_3}{b_2}$, $-r_2$ and r_3. Since, $r_3 > 0$ hence, E_2 is unstable. The eigenvalues of the Jacobian (4) at disease-free equilibrium E_3 are $-d_1$, $r_1 - \frac{c_2 s}{d_1} - \frac{c_3}{b_2} + \frac{c_5}{b_3}$, $-r_2$ and $-r_3$. Hence, for $r_1 + \frac{c_5}{b_3} < \frac{c_2 s}{d_1} + \frac{c_3}{b_2}$ the equilibrium E_3 becomes stable.

At $E_7(\tilde{I}, \tilde{T}, \tilde{N}, 0)$, the eigenvalues of the Jacobian (4) are $r_3 - c_6 \tilde{T}$ and the other three eigenvalues are the roots of the following cubic equation

$$\lambda^3 + P_1 \lambda^2 + P_2 \lambda + P_3 = 0, \tag{5}$$

where

$$
\begin{cases}
P_1 = -p_{11} - p_{22} - p_{33}, \\
P_2 = p_{22}p_{33} - p_{32}p_{23} + p_{11}p_{33} + p_{11}p_{22} - p_{21}p_{12}, \\
P_3 = p_{11}p_{23}p_{32} + p_{21}p_{12}p_{33} - p_{11}p_{22}p_{33},
\end{cases}
$$

with

$$
\left.
\begin{aligned}
p_{11} &= \frac{\rho \tilde{T}}{\alpha + \tilde{T}} - c_1 \tilde{T} - d_1, & p_{12} &= \frac{\alpha \rho \tilde{I}}{(\alpha + \tilde{T})^2} - c_1 \tilde{I}, & p_{21} &= -c_2 \tilde{T}, \\
p_{22} &= r_1 - 2r_1 b_1 \tilde{T} - c_2 \tilde{I} - c_3 \tilde{N}, & p_{23} &= -c_3 \tilde{N}, & p_{32} &= -c_4 \tilde{N}, \\
& & & & p_{33} &= r_2 - 2r_2 b_2 \tilde{N} - c_4 \tilde{T}.
\end{aligned}
\right\}
$$

According to Routh–Hurwitz rule, the roots of Eq. (5) have negative real part if and only if

$$P_1 > 0, \qquad P_2 > 0, \qquad P_1 P_2 - P_3 > 0. \tag{6}$$

Hence, for local asymptotical stability at E_7, the conditions $\frac{r_3}{c_6} < \tilde{T}$ and (6) must hold. Otherwise it will be unstable.

At co-axial equilibrium $E_8(\hat{I}, \hat{T}, \hat{N}, \hat{F})$, the characteristic values of the corresponding Jacobian matrix (4) are the roots of the following quartic equation

$$\lambda^4 + Q_1 \lambda^3 + Q_2 \lambda^2 + Q_3 \lambda + Q_4 = 0,$$

where

$$
\begin{cases}
Q_1 = -a - e - i - l, \\
Q_2 = ae - bd + ai + al + ei - fh + el - gk + il, \\
Q_3 = afh - aei + bdi - ael + bdl - cdk + agk - ail - eil + fhl + gik, \\
Q_4 = aeil - afhl - bdil + cdik - agik,
\end{cases}
$$

with Box I.

Box I.

$$a = \frac{\rho\hat{T}}{\alpha + \mu\hat{F} + \hat{T}} - c_1\hat{T} - d_1, \qquad b = \frac{(\alpha + \mu\hat{F})\rho\hat{I}}{(\alpha + \hat{T} + \mu\hat{F})^2} - c_1\hat{I}, \qquad c = -\frac{\rho\mu\hat{I}\hat{T}}{(\alpha + \hat{T} + \mu\hat{F})^2},$$

$$d = -c_2\hat{T}, \qquad e = r_1 - 2r_1 b_1 \hat{T} - c_2\hat{I} - c_3\hat{N} + c_5\hat{F}, \qquad f = -c_3\hat{T}, \qquad g = c_5\hat{T},$$

$$h = -c_4\hat{N}, \qquad i = r_2 - 2r_2 b_2\hat{N} - c_4\hat{T}, \qquad k = -c_6\hat{F}, \qquad l = r_3 - 2r_3 b_3\hat{F} - c_6\hat{T}.$$

Therefore, by Routh–Hurwitz rule, the equilibrium point E_8 will be locally asymptotically stable if

$$Q_1 > 0, \qquad Q_3 > 0, \qquad Q_4 > 0,$$

and
$$Q_1 Q_2 Q_3 > Q_3^2 + Q_1^2 Q_4.$$

4. Model with treatment

In this section, we will study the existence and stability behavior at various equilibrium points of the system (2) when treatments are present. In order to do the same, we set $\delta(t) = \delta$, $\gamma(t) = \gamma$, and $\beta(t) = \beta$. Hence the system (2) becomes

$$\begin{aligned}
\frac{dI}{dt} &= s + \frac{\rho IT}{\alpha + T + \mu F} - c_1 TI - d_1 I + \delta\sigma_1, \\
\frac{dT}{dt} &= r_1 T(1 - b_1 T) - c_2 IT - c_3 TN + c_5 TF - \gamma T, \\
\frac{dN}{dt} &= r_2 N(1 - b_2 N) - c_4 TN, \\
\frac{dF}{dt} &= r_3 F(1 - b_3 F) - c_6 TF - \beta F.
\end{aligned} \tag{7}$$

To find the equilibria of the system (7), we set $\frac{dI}{dt} = 0$, $\frac{dT}{dt} = 0$, $\frac{dN}{dt} = 0$ and $\frac{dF}{dt} = 0$. The equilibrium point of the system (7) are

- Dead equilibrium:
  (i) $E_0'\left(\frac{s+\delta\sigma_1}{d_1}, 0, 0, 0\right)$, (ii) $E_1'\left(\frac{s+\delta\sigma_1}{d_1}, 0, 0, \frac{r_3-\beta}{r_3 b_3}\right)$
- Disease-free equilibrium:
  (iii) $E_2'\left(\frac{s+\delta\sigma_1}{d_1}, 0, \frac{1}{b_2}, 0\right)$, (iv) $E_3'\left(\frac{s+\delta\sigma_1}{d_1}, 0, \frac{1}{b_2}, \frac{r_3-\beta}{r_3 b_3}\right)$
- Disease-persistent equilibrium:
  (v) $E_5'\left(\bar{I}' = \frac{r_1(1-b_1\bar{T}')-\gamma}{c_2}, \bar{T}', 0, 0\right)$ where $\bar{T}'$ will be calculated from the equation

  $$c_1\bar{I}'\bar{T}'^2 - (s + \rho\bar{I}' - c_1\alpha\bar{I}' - d_1\bar{I}' + \delta\sigma_1)\bar{T}' + (d_1\alpha\bar{I}' - s\alpha - \delta\alpha\sigma_1) = 0,$$

  and $\bar{T}' < 1$. If $\bar{T}' = 1$, then the size of the tumor is maximum. This equilibrium will exist for $b_1\bar{T}' < 1$.
  (vi) $E_6'\left(\check{I}' = \frac{r_1(1-b_1\check{T}')+c_5\check{F}'-\gamma}{c_2}, \check{T}', 0, \check{F}' = \frac{r_3-c_6\check{T}'-\beta}{r_3 b_3}\right)$ where $\check{T}'$ will be calculated from the equation

  $$c_1\check{I}'\check{T}'^2 - (s + \rho\check{I}' - c_1\alpha\check{I}' - c_1\mu\check{I}'\check{F}' - d_1\check{I}' + \delta\sigma_1)\check{T}'$$
  $$+ (d_1\alpha\check{I}' + d_1\mu\check{I}'\check{F}' - s\alpha - s\mu\check{F}' - \delta\alpha\sigma_1 - \delta\mu\sigma_1\check{F}') = 0,$$

  and $\check{T}' < 1$. If $\check{T}' = 1$, then the size of the tumor is maximum. Equilibrium E_6' will exist for $b_1\check{T}' < 1$ and $c_6\check{T}' < r_3$.
- Co-axial equilibrium:
  (vii) The equilibrium $E_7'\left(\tilde{I}' = \frac{r_1(1-b_1\tilde{T}')-c_3\tilde{N}'-\gamma}{c_2}, \tilde{T}', \tilde{N}' = \frac{r_2-c_4\tilde{T}'}{r_2 b_2}, 0\right)$ will exist for $b_1\tilde{T}' < 1$, $r_1(1-b_1\tilde{T}') > c_3\tilde{N}'+\gamma$ and $r_2 > c_4\tilde{T}'$, where $\tilde{T}'$ will be calculated from the equation

  $$c_1\tilde{I}'\tilde{T}'^2 - (s + \rho\tilde{I}' - c_1\alpha\tilde{I}' - d_1\tilde{I}' + \delta\sigma_1)\tilde{T}' + (d_1\alpha\tilde{I}' - s\alpha - \delta\alpha\sigma_1) = 0,$$

  and $\tilde{T}' < 1$. If $\tilde{T}' = 1$, then the size of the tumor is maximum.
  (viii) The equilibrium $E_8'\left(\hat{I}' = \frac{r_1(1-b_1\hat{T}')-c_3\hat{N}'+c_5\hat{F}'-\gamma}{c_2}, \hat{T}', \hat{N}' = \frac{r_2-c_4\hat{T}'}{r_2 b_2}, \hat{F}' = \frac{r_3-c_6\hat{T}'-\beta}{r_3 b_3}\right)$ will exist for $b_1\hat{T}' < 1$, $r_1(1 - b_1\hat{T}') > c_3\hat{N}'+\gamma$, $r_2 > c_4\hat{T}'$ and $r_3 > c_6\hat{T}'+\beta$, where $\hat{T}'$ will be calculated from the equation

  $$c_1\hat{I}'\hat{T}'^2 - (s + \rho\hat{I}' - c_1\alpha\hat{I}' - c_1\mu\hat{I}'\hat{F}' - d_1\hat{I}' + \delta\sigma_1)\hat{T}'$$
  $$+ (d_1\alpha\hat{I}' + d_1\mu\hat{I}'\hat{F}' - s\alpha - s\mu\hat{F}' - \delta\alpha\sigma_1 - \delta\mu\sigma_1\hat{F}') = 0,$$

and $\hat{T}' < 1$. If $\hat{T}' = 1$, then the size of the tumor is maximum.

As in the preceding section, we have done the local stability analysis of the system (7), excluding the equilibrium points where $N = 0$. The Jacobian matrix of the system (7) is given below:

$$\mathcal{J}_{E'}' = \begin{pmatrix} j'_{11} & j'_{12} & 0 & j'_{14} \\ j'_{21} & j'_{22} & j'_{23} & j'_{24} \\ 0 & j'_{32} & j'_{33} & 0 \\ 0 & j'_{42} & 0 & j'_{44} \end{pmatrix}, \tag{8}$$

where $j_{11} = \frac{\rho T}{\alpha+\mu F+T} - c_1 T - d_1$, $j_{12} = \frac{(\alpha+\mu F)\rho I}{(\alpha+T+\mu F)^2} - c_1 I$, $j_{14} = -\frac{\rho\mu IT}{(\alpha+T+\mu F)^2}$, $j_{21} = -c_2 T$, $j_{22} = r_1 - 2r_1 b_1 T - c_2 I - c_3 N + c_5 F - \gamma$, $j_{23} = -c_3 T$, $j_{24} = c_5 T$, $j_{32} = -c_4 N$, $j_{33} = r_2 - 2r_2 b_2 N - c_4 T$, $j_{42} = -c_6 F$, and $j_{44} = r_3 - 2r_3 b_3 F - c_6 T - \beta$.

The eigenvalues of the Jacobian matrix (8) at the disease-free equilibrium E_2' are $-d_1$, $r_1 - \frac{c_2(s+\delta\sigma_1)}{d_1} - \frac{c_3}{b_2} - \gamma$, $-r_2$ and $r_3 - \beta$. This equilibrium becomes stable if $r_1 < \gamma + \frac{c_2(s+\delta\sigma_1)}{d_1} + \frac{c_3}{b_2}$ and $r_3 < \beta$, otherwise unstable.

Corresponding to another disease-free equilibrium E_3', the eigenvalues of the Jacobian (8) are $-d_1$, $r_1 - \frac{c_2(s+\delta\sigma_1)}{d_1} - \frac{c_3}{b_2} + \frac{c_5(r_3-\beta)}{r_3 b_3} - \gamma$, $-r_2$ and $\beta - r_3$. Now, E_3' becomes stable if $r_1 - \frac{c_2(s+\delta\sigma_1)}{d_1} - \frac{c_3}{b_2} + \frac{c_5(r_3-\beta)}{r_3 b_3} - \gamma < 0 \implies r_1 + \frac{c_5(r_3-\beta)}{r_3 b_3} < \frac{c_2(s+\delta\sigma_1)}{d_1} + \frac{c_3}{b_2} + \gamma$ and $\beta < r_3$.

At $E_7'(\tilde{I}', \tilde{T}', \tilde{N}', 0)$, the eigenvalues are $r_3 - c_6\tilde{T}'$ and the other three eigenvalues are the roots of the following cubic equation

$$\lambda^3 + P_1'\lambda^2 + P_2'\lambda + P_3' = 0, \tag{9}$$

where

$$\begin{cases} P_1' = -p'_{11} - p'_{22} - p'_{33}, \\ P_2' = p'_{22}p'_{33} - p'_{32}p'_{23} + p'_{11}p'_{33} + p'_{11}p'_{22} - p'_{21}p'_{12}, \\ P_3' = p'_{11}p'_{23}p'_{32} + p'_{21}p'_{12}p'_{33} - p'_{11}p'_{22}p'_{33}, \end{cases}$$

with

$$\begin{aligned}
p'_{11} &= \frac{\rho\tilde{T}'}{\alpha+\tilde{T}'} - c_1\tilde{T}' - d_1, & p'_{12} &= \frac{\alpha\rho\tilde{I}'}{(\alpha+\tilde{T}')^2} - c_1\tilde{I}', & p'_{21} &= -c_2\tilde{T}', \\
p'_{22} &= r_1 - 2r_1 b_1\tilde{T}' - c_2\tilde{I}' - c_3\tilde{N}', & p'_{23} &= -c_3\tilde{T}', & p'_{32} &= -c_4\tilde{N}', \\
& & p'_{33} &= r_2 - 2r_2 b_2\tilde{N}' - c_4\tilde{T}'.
\end{aligned}$$

According to Routh–Hurwitz rule, the roots of Eq. (9) have negative real part if and only if

$$P_1' > 0, \qquad P_2' > 0, \qquad P_1'P_2' - P_3' > 0. \tag{10}$$

Hence, for local asymptotical stability at E_7', the conditions $\frac{r_3}{c_6} < \tilde{T}'$ and (10) must holds; otherwise it will be unstable.

At co-axial equilibrium $E_8'(\hat{I}', \hat{T}', \hat{N}', \hat{F}')$, the characteristics values of the corresponding Jacobian matrix (8) are the roots of the following

$$a' = \frac{\rho \hat{T}'}{\alpha + \mu \hat{F}' + \hat{T}'} - c_1 \hat{T}' - d_1, \qquad b' = \frac{(\alpha + \mu \hat{F}')\rho \hat{I}'}{(\alpha + \hat{T}' + \mu \hat{F}')^2} - c_1 \hat{I}', \qquad c' = -\frac{\rho \mu \hat{I}' \hat{T}'}{(\alpha + \hat{T}' + \mu \hat{F}')^2},$$

$$d' = -c_2 \hat{T}', \qquad e' = r_1 - 2r_1 b_1 \hat{T}' - c_2 \hat{I}' - c_3 \hat{N}' + c_5 \hat{F}' - \gamma, \qquad f' = -c_3 \hat{T}', \qquad g' = c_5 \hat{T}',$$

$$h' = -c_4 \hat{N}', \qquad i' = r_2 - 2r_2 b_2 \hat{N}' - c_4 \hat{T}', \qquad k' = -c_6 \hat{F}', \qquad l' = r_3 - 2r_3 b_3 \hat{F}' - c_6 \hat{T}' - \beta.$$

Therefore, by Routh–Hurwitz rule, the equilibrium point E_8' will be asymptotically stable if

$$Q_1' > 0, \qquad Q_3' > 0, \qquad Q_4' > 0,$$

and

$$Q_1' Q_2' Q_3' > Q_3'^2 + Q_1'^2 Q_4'.$$

Box II.

quartic equation

$$\lambda^4 + Q_1' \lambda^3 + Q_2' \lambda^2 + Q_3' \lambda + Q_4' = 0,$$

where

$$\begin{cases} Q_1' = -a' - e' - i' - l', \\ Q_2' = a'e' - b'd' + a'i' + a'l' + e'i' - f'h' + e'l' - g'k' + i'l', \\ Q_3' = a'f'h' - a'e'i' + b'd'i' - a'e'l' + b'd'l' - c'd'k' + \\ \qquad a'g'k' - a'i'l' - e'i'l' + f'h'l' + g'i'k', \\ Q_4' = a'e'i'l' - a'f'h'l' - b'd'i'l' + c'd'i'k' - a'g'i'k'. \end{cases}$$

with Box II.

4.1. Global stability at disease-free equilibrium $E_2'(I_2' = \frac{s+\delta\sigma_1}{d_1}, T_2' = 0, N_2' = \frac{1}{b_2}, F_2' = 0)$

In the above section, we have derived the local stability conditions of the system (7) at various equilibrium points. Local stability analysis describes stability behavior in the neighborhood of an equilibrium point. On the contrary, global stability analysis at a point describes the stability behavior of the system that happens further away from the equilibrium. So, in this section, we will derive the conditions for global stability at disease-free equilibrium. $E_2'(I_2' = \frac{s+\delta\sigma_1}{d_1}, T_2' = 0, N_2' = \frac{1}{b_2}, F_2' = 0)$ by the Lyapunov theorem. Also, from the biological point of view, it is necessary to show that the disease-free equilibrium is globally stable. We consider the Lyapunov function as

$$V(t) = \left(I - I_2' - I_2' \ln \frac{I}{I_2'} \right) + (T - T_2') + \left(N - N_2' - N_2' \ln \frac{N}{N_2'} \right) + (F - F_2').$$

Now, differentiating above equation with respect to t and we get

$$\frac{dV}{dt} = \left(1 - \frac{I_2'}{I}\right)\frac{dI}{dt} + \frac{dT}{dt} + \left(1 - \frac{N_2'}{N}\right)\frac{dN}{dt} + \frac{dF}{dt}$$

$$= \left(1 - \frac{I_2'}{I}\right)\left(s + \frac{\rho I T}{\alpha + T + \mu F} - c_1 T I - d_1 I + \delta \sigma_1 \right)$$

$$+ \left(r_1 T (1 - b_1 T) - c_2 I T - c_3 T N + c_5 T F - \gamma T \right)$$

$$+ \left(1 - \frac{N_2'}{N}\right)\left(r_2 N (1 - b_2 N) - c_4 T N \right)$$

$$+ \left(r_3 F (1 - b_3 F) - c_6 T F - \beta F \right)$$

$$= \left(\frac{I - I_2'}{I} \right)\left(\frac{\rho I T}{\alpha + T + \mu F} - c_1 T I - d_1 (I - I_2') \right)$$

$$+ \left(r_1 T (1 - b_1 T) - c_2 T (I - I_2') - c_2 T I_2' \right.$$

$$\left. - c_3 T (N - N_2') - c_3 T N_2' + c_5 T F - \gamma T \right)$$

$$+ \left(\frac{N - N_2'}{N} \right)\left(r_2 (N - N_2') - r_2 b_2 (N^2 - N_2'^2) - c_4 T N \right)$$

$$+ \left(r_3 F (1 - b_3 F) - c_6 T F - \beta F \right)$$

$$= \left(I - \frac{s + \delta\sigma_1}{d_1} \right)\left(\frac{\rho T}{\alpha + T + \mu F} - c_1 T - \frac{d_1}{I}\left(I - \frac{s + \delta\sigma_1}{d_1} \right) \right)$$

$$+ \left(-r_1 b_1 T^2 - c_2 T (I - \frac{s + \delta\sigma_1}{d_1}) - c_3 T (N - \frac{1}{b_2}) + c_5 T F \right)$$

$$+ \left(N - \frac{1}{b_2} \right)\left(r_2 (N - \frac{1}{b_2})(\frac{1 - N - \frac{1}{b_2}}{N}) - c_4 T \right)$$

$$+ \left(-r_3 b_3 F^2 - c_6 T F \right)$$

$$+ \left(r_1 T - c_2 T (\frac{s + \delta\sigma_1}{d_1}) - c_3 T \frac{1}{b_2} - \gamma T \right) + \left(r_3 F - \beta F \right)$$

Hence,

$$\frac{dV}{dt} = -Y^T M Y - P^T Y - Q^T Y, \tag{11}$$

where,

$$Y^T = [I - I_2', T, N - N_2', F], \qquad P^T = \left[0, -r_1 + c_2 \frac{s + \delta\sigma_1}{d_1} + c_3 \frac{1}{b_2} + \gamma, 0, 0 \right],$$

$$Q^T = \left[0, 0, 0, -r_3 + \beta \right],$$

and

$$M = \begin{pmatrix} \frac{d_1}{I} & \frac{1}{2}\left(c_1 + c_2 - \frac{\rho}{\alpha + T + \mu F} \right) & 0 & 0 \\ \frac{1}{2}\left(c_1 + c_2 - \frac{\rho}{\alpha + T + \mu F} \right) & r_1 b_1 & \frac{c_4}{2} & \frac{c_6 - c_5}{2} \\ 0 & \frac{c_4}{2} & 1 - \frac{1}{N} + \frac{1}{N b_2} & 0 \\ 0 & \frac{c_6 - c_5}{2} & 0 & r_3 b_3 \end{pmatrix}.$$

By noting the second component of the vector P and fourth component of the vector Q, we must have

$$-r_1 + c_2 \frac{s + \delta\sigma_1}{d_1} + c_3 \frac{1}{b_2} + \gamma > 0 \implies r_1 < c_2 \frac{s + \delta\sigma_1}{d_1} + c_3 \frac{1}{b_2} + \gamma,$$

and

$$-r_3 + \beta > 0 \implies r_3 < \beta.$$

for which $P^T Y > 0$ and $Q^T Y > 0$.

Furthermore, by considering the values of parameter set 1 given in Section "Numerical simulation", and if $I \le \frac{s}{d_1}$, $T \le \frac{1}{b_1}$, $N \le \frac{1}{b_2}$ and $F < \frac{1}{b_3}$, then all the minors of the matrix M are positive (all eigenvalues of M are also positive) and so $Y^T M Y > 0$. Now, it is clear that $\frac{dV}{dt} < 0$. Hence, we establish the following theorem:

Theorem 1. *The disease-free equilibrium $E_2'(I_2' = \frac{s+\delta\sigma_1}{d_1}, T_2' = 0, N_2' = \frac{1}{b_2}, F_2' = 0)$ will be globally asymptotically stable if the following conditions*

hold:

$$r_1 < c_2 \frac{s + \delta\sigma_1}{d_1} + c_3 \frac{1}{b_2} + \gamma, \quad r_3 < \beta, \quad I \leq \frac{s}{d_1}, \quad T \leq \frac{1}{b_1},$$

$$N \leq \frac{1}{b_2} \text{ and } F < \frac{1}{b_3}.$$

5. Optimal control

In this section, we apply optimal control theory to the system under treatment to look for an optimal drug administration protocol. We consider the modified model (2) with $\delta(t), \gamma(t)$ and $\beta(t)$ as time-dependent treatment control functions that should be minimized in order to reduce the spread of the disease. The objective function that must be minimized is given below:

$$\mathcal{J}(\delta, \gamma, \beta)$$
$$= \int_0^{T_f} [\alpha_1 T(t) + \alpha_2 F(t) - \alpha_3 I(t) - \alpha_4 N(t) + \alpha_5 \delta^2(t) + \alpha_6 \gamma^2(t) + \alpha_7 \beta^2(t)] dt, \tag{12}$$

where T_f is the final time and $\alpha_i, i = 1, \ldots, 7$ are relative weights to balance each term in the integrand in (12) and must be determined to reduce the growth of diseased cells (tumor and fat cells) and increase the number of immune and normal cells. Thus, we seek an optimal control δ^*, γ^* and β^* such that

$$\mathcal{J}(\delta^*, \gamma^*, \beta^*) = \min\{\mathcal{J}(\delta, \gamma, \beta) | (\delta, \gamma, \beta) \in \Delta\},$$

where the control set Δ is as

$$\Delta = \{(\eta_1, \eta_2, \eta_3) | \eta_i(t) \text{ is Lebesgue measurable, } 0 \leq \eta_i \leq \eta_{i\max} < 1,$$
$$i = 1, 2, 3\}. \tag{13}$$

If $\Omega(t, \Psi, u)$ denotes the integrand of $\mathcal{J}(\delta, \gamma, \beta)$, i.e.

$$\Omega(t, \Psi, u) = \alpha_1 T(t) + \alpha_2 F(t) - \alpha_3 I(t) - \alpha_4 N(t) + \alpha_5 \delta_1^2(t) + \alpha_6 \gamma_1^2(t) + \alpha_7 \beta_1^2(t), \tag{14}$$

where $\Psi = (I, T, N, F)$ and $u = (\delta_1, \gamma_1, \beta_1)$, we must show that Ω is a function bounded below. This will ensure that, Ω will have a minimum. For this purpose, first we investigate the convexity of Ω on Δ.

Suppose that u, v are distinct elements of Δ and $0 \leq \rho \leq 1$. We show that the following inequality holds

$$(1 - \rho)\Omega(t, \Psi, u) + \rho\Omega(t, \Psi, v) \geq \Omega(t, \Psi, (1 - \rho)u + \rho v), \tag{15}$$

where u, v are control vectors. Substituting (14) into (15) we get

$$(1 - \rho)\Omega(t, \Psi, u) + \rho\Omega(t, \Psi, v) - \Omega(t, \Psi, (1 - \rho)u + \rho v)$$
$$= (1 - \rho)\left(\alpha_1 T + \alpha_2 F - \alpha_3 I - \alpha_4 N + \alpha_5 \delta_1^2 + \alpha_6 \gamma_1^2 + \alpha_7 \beta_1^2\right)$$
$$+ \rho\left(\alpha_1 T + \alpha_2 F - \alpha_3 I - \alpha_4 N + \alpha_5 \delta_1^2 + \alpha_6 \gamma_1^2 + \alpha_7 \beta_1^2\right)$$
$$- \left(\alpha_1 T + \alpha_2 F - \alpha_3 I - \alpha_4 N + \alpha_5((1 - \rho)\delta_1 + \rho\delta_2)^2\right.$$
$$\left. + \alpha_6((1 - \rho)\gamma_1 + \rho\gamma_2)^2 + \alpha_7((1 - \rho)\beta_1 + \rho\beta_2)^2\right)$$
$$= \alpha_5 \rho(1 - \rho)(\delta_1 - \delta_2)^2 + \alpha_6 \rho(1 - \rho)(\gamma_1 - \gamma_2)^2 + \alpha_7 \rho(1 - \rho)(\beta_1 - \beta_2)^2$$
$$\geq 0.$$

Thus, inequality (15) holds and

$$\Omega(t, \Psi, u) = \alpha_1 T + \alpha_2 F - \alpha_3 I - \alpha_4 N + \alpha_5 \delta_1^2 + \alpha_6 \gamma_1^2 + \alpha_7 \beta_1^2$$
$$\geq \alpha_5 \delta_1^2 + \alpha_6 \gamma_1^2 + \alpha_7 \beta_1^2 \geq \tau(\delta_1^2 + \gamma_1^2 + \beta_1^2),$$

where $\tau = \min\{\alpha_6, \alpha_7, \alpha_8\}$. This shows that $\tau(\delta_1^2 + \gamma_1^2 + \beta_1^2)$ can be a lower bound for $\Omega(t, \Psi, u)$. Therefore, there exists an optimal control $(\delta^*, \gamma^*, \beta^*)$ to which $\Omega(t, \Psi, u)$ can be minimized.

Now, we define the Hamiltonian function of the system (2) as follows:

$$\mathcal{H} = \alpha_1 T + \alpha_2 F - \alpha_3 I - \alpha_4 N + \alpha_5 \delta^2 + \alpha_6 \gamma^2 + \alpha_7 \beta^2$$
$$+ \lambda_1 \left(s + \frac{\rho I T}{\alpha + T + \mu F} - c_1 T I - d_1 I + \delta(t)\sigma_1 \right)$$
$$+ \lambda_2 \left(r_1 T(1 - b_1 T) - c_2 I T - c_3 T N + c_5 T F - \gamma(t)T \right)$$
$$+ \lambda_3 \left(r_2 N(1 - b_2 N) - c_4 T N \right) + \lambda_4 \left(r_3 F(1 - b_3 F) - c_6 T F - \beta(t)F \right), \tag{16}$$

where $\lambda_i, i = 1, \ldots, 4$ are adjoint variables (Lagrange multipliers).

Theorem 2. *Suppose that $(\delta^*, \gamma^*, \beta^*) \in \Delta$ is an optimal control and the corresponding state variables are (I, T, N, F). Then, there exist adjoint variables $\lambda_i, i = 1, \ldots, 4$ that satisfy the following equations:*

$$\frac{d\lambda_1}{dt} = \alpha_3 - \lambda_1 \left(\frac{\rho T}{\alpha + T + \mu F} - c_1 T - d_1 \right) + \lambda_2 c_2 T,$$

$$\frac{d\lambda_2}{dt} = -\alpha_1 - \lambda_1 \left(\frac{\rho I(\alpha + \mu F)}{(\alpha + T + \mu F)^2} - c_1 I \right)$$
$$- \lambda_2(r_1 - 2r_1 b_1 T - c_2 I - c_3 N + c_5 F - \gamma(t)) + \lambda_3 c_4 N + \lambda_4 c_6 F,$$

$$\frac{d\lambda_3}{dt} = \alpha_4 + \lambda_2 c_3 T - \lambda_3(r_2 - 2r_2 b_2 N - c_4 T),$$

$$\frac{d\lambda_4}{dt} = -\alpha_2 + \lambda_1 \frac{\mu\rho I T}{(\alpha + T + \mu F)^2} - \lambda_2 c_5 T - \lambda_4(r_3 - 2r_3 b_3 F - c_6 T - \beta(t)),$$

with the transversality conditions $\lambda_i(T_f) = 0, i = 1, \ldots, 4$. Furthermore, the optimal values of control variables are as follows:

$$\delta^* = \min\left\{ \max\left\{ 0, -\frac{\lambda_1\sigma_1}{2\alpha_5} \right\}, 1 \right\},$$

$$\gamma^* = \min\left\{ \max\left\{ 0, \frac{\lambda_2 T}{2\alpha_6} \right\}, 1 \right\},$$

$$\beta^* = \min\left\{ \max\left\{ 0, \frac{\lambda_4 F}{2\alpha_7} \right\}, 1 \right\}.$$

Proof. Based on Hamiltonian function (16) and the Pontryagin's maximum principle [36–39], the Hamiltonian equations are obtained as

$$\frac{d\lambda_1}{dt} = -\frac{\partial \mathcal{H}}{\partial I} = \alpha_3 - \lambda_1 \left(\frac{\rho T}{\alpha + T + \mu F} - c_1 T - d_1 \right) + \lambda_2 c_2 T,$$

$$\frac{d\lambda_2}{dt} = -\frac{\partial \mathcal{H}}{\partial T} = -\alpha_1 - \lambda_1 \left(\frac{\rho I(\alpha + \mu F)}{(\alpha + T + \mu F)^2} - c_1 I \right)$$
$$- \lambda_2(r_1 - 2r_1 b_1 T - c_2 I - c_3 N + c_5 F - \gamma(t)) + \lambda_3 c_4 N + \lambda_4 c_6 F,$$

$$\frac{d\lambda_3}{dt} = -\frac{\partial \mathcal{H}}{\partial N} = \alpha_4 + \lambda_2 c_3 T - \lambda_3(r_2 - 2r_2 b_2 N - c_4 T),$$

$$\frac{d\lambda_4}{dt} = -\frac{\partial \mathcal{H}}{\partial F} = -\alpha_2 + \lambda_1 \frac{\mu\rho I T}{(\alpha + T + \mu F)^2}$$
$$- \lambda_2 c_5 T - \lambda_4(r_3 - 2r_3 b_3 F - c_6 T - \beta(t)),$$

where $\lambda_i(t), i = 1, \ldots, 4$ are called adjoint functions and transversality conditions are $\lambda_i(T_f) = 0, i = 1, \ldots, 4$. The optimal control functions are derived as follows:

$$\frac{\partial \mathcal{H}}{\partial \delta} = 0 \quad \Rightarrow 2\alpha_5 \delta + \lambda_1 \sigma_1 = 0 \quad \Rightarrow \delta = -\frac{\lambda_1 \sigma_1}{2\alpha_5},$$

$$\frac{\partial \mathcal{H}}{\partial \gamma} = 0 \quad \Rightarrow 2\alpha_6 \gamma - \lambda_2 T = 0 \quad \Rightarrow \gamma = \frac{\lambda_2 T}{2\alpha_6}, \tag{17}$$

$$\frac{\partial \mathcal{H}}{\partial \beta} = 0 \quad \Rightarrow 2\alpha_7 \beta - \lambda_4 F = 0 \quad \Rightarrow \beta = \frac{\lambda_4 F}{2\alpha_7}.$$

Using the bounds of the control variables, we have

$$\delta^* = \begin{cases} -\frac{\lambda_1 \sigma_1}{2\alpha_5}, & \text{if } 0 < -\frac{\lambda_1 \sigma_1}{2\alpha_5} < 1, \\ 0, & \text{if } -\frac{\lambda_1 \sigma_1}{2\alpha_5} \leq 0, \\ 1, & \text{if } -\frac{\lambda_1 \sigma_1}{2\alpha_5} \geq 1, \end{cases}$$

$$\gamma^* = \begin{cases} \frac{\lambda_2 T}{2\alpha_6}, & \text{if } 0 < \frac{\lambda_2 T}{2\alpha_6} < 1, \\ 0, & \text{if } \frac{\lambda_2 T}{2\alpha_6} \leq 0, \\ 1, & \text{if } \frac{\lambda_2 T}{2\alpha_6} \geq 1, \end{cases}$$

$$\beta^* = \begin{cases} \frac{\lambda_4 F}{2\alpha_7}, & \text{if } 0 < \frac{\lambda_4 F}{2\alpha_7} < 1, \\ 0, & \text{if } \frac{\lambda_4 F}{2\alpha_7} \leq 0, \\ 1, & \text{if } \frac{\lambda_4 F}{2\alpha_7} \geq 1. \end{cases}$$

By means of a new notation, we obtain

$$\delta^* = \min\left\{ \max\left\{ 0, -\frac{\lambda_1 \sigma_1}{2\alpha_5} \right\}, 1 \right\}, \quad \gamma^* = \min\left\{ \max\left\{ 0, \frac{\lambda_2 T}{2\alpha_6} \right\}, 1 \right\}, \tag{18}$$

$$\beta^* = \min\left\{ \max\left\{ 0, \frac{\lambda_4 F}{2\alpha_7} \right\}, 1 \right\}.$$

The second-order partial derivatives of the terms in the LHS of Eqs. (17) with respect to δ, γ and β

$$\frac{\partial^2 \mathcal{H}}{\partial \delta^2} = 2\alpha_5, \quad \frac{\partial^2 \mathcal{H}}{\partial \gamma^2} = 2\alpha_6, \quad \frac{\partial^2 \mathcal{H}}{\partial \beta^2} = 2\alpha_7, \quad \text{which are positive.}$$

This implies that the optimal problem is minimized at δ, γ, β.

We get the following optimal system:

$$\begin{cases} \frac{dI}{dt} = s + \frac{\rho I T}{\alpha + T + \mu F} - c_1 T I - d_1 I + \delta^* \sigma_1, \\ \frac{dT}{dt} = r_1 T (1 - b_1 T) - c_2 I T - c_3 T N + c_5 T F - \gamma^* T, \\ \frac{dN}{dt} = r_2 N (1 - b_2 N) - c_4 T N, \\ \frac{dF}{dt} = r_3 F (1 - b_3 F) - c_6 T F - \beta^* F, \end{cases} \tag{19}$$

$$\begin{cases} \frac{d\lambda_1}{dt} = \alpha_3 - \lambda_1 \left(\frac{\rho T}{\alpha + T + \mu F} - c_1 T - d_1 \right) + \lambda_2 c_2 T, \\ \frac{d\lambda_2}{dt} = -\alpha_1 - \lambda_1 \left(\frac{\rho I (\alpha + \mu F)}{(\alpha + T + \mu F)^2} - c_1 I \right) \\ \qquad\quad - \lambda_2 (r_1 - 2 r_1 b_1 T - c_2 I - c_3 N + c_5 F) \\ \qquad\quad - \gamma^*) + \lambda_3 c_4 N + \lambda_4 c_6 F, \\ \frac{d\lambda_3}{dt} = \alpha_4 + \lambda_2 c_3 T - \lambda_3 (r_2 - 2 r_2 b_2 N - c_4 T), \\ \frac{d\lambda_4}{dt} = -\alpha_2 + \lambda_1 \frac{\mu \rho I T}{(\alpha + T + \mu F)^2} - \lambda_2 c_5 T - \lambda_4 (r_3 - 2 r_3 b_3 F - c_6 T - \beta^*), \end{cases} \tag{20}$$

subject to the conditions

$$I(0) = I_0, \quad T(0) = T_0, \quad N(0) = N_0, \quad F(0) = F_0, \quad \lambda_i(T_f) = 0,$$
$$i = 1, \dots, 4.$$

6. Numerical simulation

In mathematical modeling, it is essential to verify theoretical results with the help of numerical simulations. So, in this section, we present numerical simulations of some essential theoretical results found in our investigation and provide practical explanations of those results. All the numerical verifications have been done using MATLAB-R2016a, Wolfram MATHEMATICA-12.3, and Maple-2021 software.

We consider parameters and units as arbitrary and choose two parameter sets, one having a low immune response and the other having a high immune response, for the numerical simulation of the without treatment model (3). All the parameter values and the initial values of the cell populations ($I_0 = 0$, $T_0 = 0.0001$, $N_0 = 1$, and $F_0 = 0.8$) are taken from the paper [31].
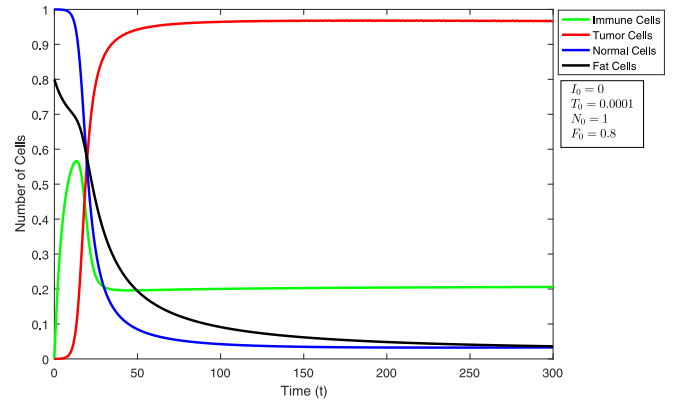

Fig. 1. Time series plot for the parameter set 1 with low immune response.

Parameter set 1: $s = 0.125$; $\rho = 0.75$; $\alpha = 0.3$; $\mu = 0.8$; $c_1 = 1$; $d_1 = 0.2$; $r_1 = 1.5$; $b_1 = 1$; $c_2 = 0.1$; $c_3 = 1$; $c_5 = 0.1$; $r_2 = 1$; $b_2 = 1$; $c_4 = 1$; $r_3 = 0.1$; $b_3 = 1.5$; $c_6 = 0.1$.

Parameter set 2: $s = 1.135$; $\rho = 0.75$; $\alpha = 0.3$; $\mu = 0.8$; $c_1 = 1$; $d_1 = 0.2$; $r_1 = 1.5$; $b_1 = 1$; $c_2 = 0.1$; $c_3 = 1$; $c_5 = 0.1$; $r_2 = 1$; $b_2 = 1$; $c_4 = 1$; $r_3 = 0.1$; $b_3 = 1.5$; $c_6 = 0.1$.

For the parameter set 1, there exists four biologically feasible equilibrium points for the system (3): See Box III.

The stability of the above four equilibria is as follows:

- The eigenvalues corresponding to disease-free equilibrium E_2 are -0.2000, -1.0000, 0.0437, 0.1000. It indicates that E_2 is a saddle-type critical point. Hence, around this point, the system shows unstable behavior. This equilibrium is regarded as a healthy equilibrium as there are no tumor and fat cells that can generate abnormal cells.
- Corresponding to the equilibria E_3, the eigenvalues are -0.2000, -0.1001, -1.0000, 0.5042; which indicates that E_3 is a saddle point, and the system is unstable around E_3. As fat cells are present at this equilibrium, there is a chance of the birth of abnormal cells.
- The equilibrium E_7 is a state where immune-tumor-normal cells co-exist. The eigenvalues associated with E_7 are -1.4422, -0.5678, -0.0124, 0.0043; which corresponds to an unstable saddle point. At this co-axial point, three types of cells compete with each other to survive, viz. immune-tumor-normal.
- The interior co-axial equilibrium E_8 is associated with eigenvalues -1.4883, -0.5815, -0.0109, -0.0045; which implies that the point E_8 is a stable node. It is to be noted that the point E_8 remains stable as long as the immune cells co-exist in the system up to a certain level. Fig. 1 depicts this situation where all the considered cell populations co-exist at E_8, and the tumor cell proliferates at a faster rate with its maximum carrying capacity. The system is stable at co-axial equilibrium E_8; however, due to inadequate immune responses of the system, the number of immune and normal cells gets reduced, and it indicates that if the immune cell population gets further reduced, the system becomes unstable at co-axial equilibrium E_8. Therefore, in this case, the patient needs external input to recover the system.

$$E_2 = \begin{vmatrix} I_2 = 0.6250 \\ T_2 = 0 \\ N_2 = 1 \\ F_2 = 0, \end{vmatrix} \quad E_3 = \begin{vmatrix} I_3 = 0.6250 \\ T_3 = 0 \\ N_3 = 1 \\ F_3 = 0.6667, \end{vmatrix} \quad E_7 = \begin{vmatrix} \tilde{I} = 0.2132 \\ \tilde{T} = 0.9574 \\ \tilde{N} = 0.0426 \\ \tilde{F} = 0, \end{vmatrix} \quad E_8 = \begin{vmatrix} \hat{I} = 0.2083 \\ \hat{T} = 0.9632 \\ \hat{N} = 0.0368 \\ \hat{F} = 0.0245. \end{vmatrix}$$
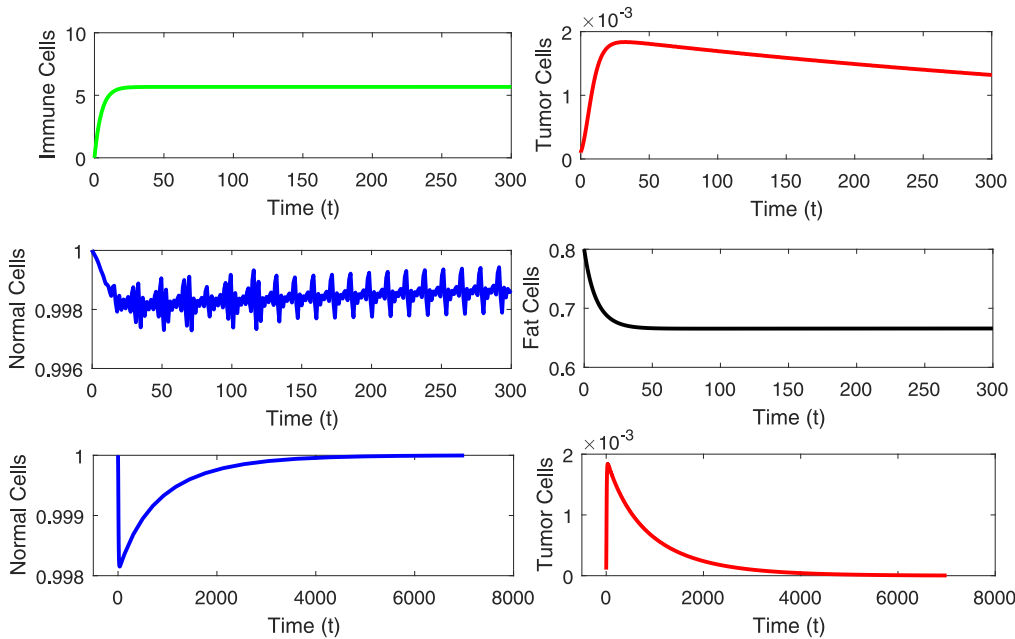
Box III.

Fig. 2. Time series plot for the parameter set 2 with high immune response.

For the parameter set 2, there exists two biologically feasible equilibrium points for the system (3):

$$E_2 = \begin{vmatrix} I_2 = 5.6750 \\ T_2 = 0 \\ N_2 = 1 \\ F_2 = 0, \end{vmatrix} \quad E_3 = \begin{vmatrix} I_3 = 5.6750 \\ T_3 = 0 \\ N_3 = 1 \\ F_3 = 0.6667. \end{vmatrix}$$

The nature of the stability of the above two equilibria is as follows:

- The eigenvalues corresponding to disease-free equilibrium E_2 are -0.2000, -1.0000, -0.0675, 0.1000; showing that it is an unstable saddle point. Hence, the healthy equilibrium point is not stable.
- The immune-normal-fat co-axial equilibrium E_3 is associated with eigenvalues -0.2000, -0.1001, -1.0000, -0.0008; which indicates that it is a asymptotically stable node. From Fig. 2, it can be observed that the tumor cells die off over a long period, whereas the normal and immune cells are stable at their required level in the presence of fat cells. Biologically, it implies that a system having high immunity may be able to clear the tumor from the system for a long time interval, and the system may become disease-free.

We have observed from Figures 1 and 2 that the system with a high immune response may suppress the tumor in contrast to the system with an inadequate immune response. Hence, for the simulation of the treatment case, we consider parameter set 1, which has low immunity, to understand the effect of external treatments. We have considered

three cases: (i) $\delta > 0$, $\gamma = 0$, $\beta = 0$, (ii) $\delta > 0$, $\gamma > 0$, $\beta = 0$, and (iii) $\delta > 0$, $\gamma > 0$, $\beta > 0$ along with $\sigma_1 = 0.3$.

Case (i) $\delta > 0$, $\gamma = 0$, $\beta = 0$:

For the value of treatment parameter $\delta = 0.25$, the system (7) exhibits four biologically valid equilibrium points, and these are given in Box IV.

The stability of the above four equilibria is as follows:

- The eigenvalues related to E_2' are -0.2000, -1.0000, 0.4000, 0.1000. Hence, E_2' is unstable saddle type.
- As corresponding to the equilibrium E_3', the eigenvalues are -0.2000, 0.4667, -1.0000, -0.1000; the equilibrium E_3' is an unstable saddle point.
- The eigenvalues related to E_7' where immune-tumor-normal co-exist are 0.0071, -1.3771, -0.5230, -0.1262. Hence, the equilibrium E_7' is also an unstable saddle point.
- The equilibrium E_8' is associated with eigenvalues -1.4796, -0.5574, -0.0168, -0.0076. Therefore, the equilibrium E_8' is an asymptotically stable node.

For the value of treatment parameter $\delta = 0.50$, the system (7) exhibits four biologically valid equilibrium points and these are given in Box V.

The stability of the above four equilibria is as follows:

- The eigenvalues related to E_2' are -0.2000, 0.3625, -1.0000, 0.1000, which corresponds to an unstable saddle point.
- The equilibrium E_3' is associated with eigenvalues -0.2000, 0.4292, -1.0000, -0.1000; indicating an unstable saddle type.

$$E_2' = \begin{vmatrix} I_2' = 1 \\ T_2' = 0 \\ N_2' = 1 \\ F_2' = 0, \end{vmatrix} \quad E_3' = \begin{vmatrix} I_3' = 1 \\ T_3' = 0 \\ N_3' = 1 \\ F_3' = 0.6667, \end{vmatrix} \quad E_7' = \begin{vmatrix} \tilde{I}' = 0.3559 \\ \tilde{T}' = 0.9288 \\ \tilde{N}' = 0.0712 \\ \tilde{F}' = 0, \end{vmatrix} \quad E_8' = \begin{vmatrix} \hat{I}' = 0.3415 \\ \hat{T}' = 0.9397 \\ \hat{N}' = 0.0603 \\ \hat{F}' = 0.0402. \end{vmatrix}$$

Box IV.

$$E_2' = \begin{vmatrix} I_2' = 1.3750 \\ T_2' = 0 \\ N_2' = 1 \\ F_2' = 0, \end{vmatrix} \quad E_3' = \begin{vmatrix} I_3' = 1.3750 \\ T_3' = 0 \\ N_3' = 1 \\ F_3' = 0.6667, \end{vmatrix} \quad E_7' = \begin{vmatrix} \tilde{I}' = 0.5139 \\ \tilde{T}' = 0.8972 \\ \tilde{N}' = 0.1028 \\ \tilde{F}' = 0, \end{vmatrix} \quad E_8' = \begin{vmatrix} \hat{I}' = 0.4821 \\ \hat{T}' = 0.9149 \\ \hat{N}' = 0.0851 \\ \hat{F}' = 0.0567. \end{vmatrix}$$

Box V.

$$E_2' = \begin{vmatrix} I_2' = 1.7500 \\ T_2' = 0 \\ N_2' = 1 \\ F_2' = 0, \end{vmatrix} \quad E_3' = \begin{vmatrix} I_3' = 1.7500 \\ T_3' = 0 \\ N_3' = 1 \\ F_3' = 0.6667, \end{vmatrix} \quad E_7' = \begin{vmatrix} \tilde{I}' = 0.6929 \\ \tilde{T}' = 0.8614 \\ \tilde{N}' = 0.1386 \\ \tilde{F}' = 0, \end{vmatrix} \quad E_8' = \begin{vmatrix} \hat{I}' = 0.6311 \\ \hat{T}' = 0.8886 \\ \hat{N}' = 0.1114 \\ \hat{F}' = 0.0742. \end{vmatrix}$$

Box VI.

- Corresponding to E_7', the eigenvalues are 1.4477, −0.5066, −0.0294, 0.0103, so, the critical point is again of unstable saddle type.
- The interior co-axial equilibrium E_8' is associated with eigenvalues −1.4696 −0.5339, −0.0243, −0.0085. Hence, around this equilibrium, the system (7) behaves in an asymptotically stable way.

For the value of treatment parameter $\delta = 0.75$, the system (7) exhibits four biologically valid equilibrium points and these are given in Box VI.

The stability of the above four equilibria is as follows:

- The eigenvalues corresponding to the equilibrium E_2' are −0.2000, 0.3250, −1.0000, 0.1000; which corresponds to an unstable saddle point.
- Corresponding to the equilibrium E_3', the eigenvalues are −0.2000, 0.3917, −1.0000, −0.1000; indicating to an unstable saddle point.
- The equilibrium E_7' is associated with eigenvalues −1.4373, −0.4635, −0.0349, 0.0139. Hence the equilibrium is of unstable saddle type.
- The eigenvalues corresponding to E_8' are −1.4575, −0.5109, −0.0258, −0.0158. Therefore, the system (7) behaves as an asymptotically stable system around this equilibrium.

From Fig. 3, it is clear that for the treatment parameter values of $\delta = 0.25, 0.5$, and 0.75, all four cell populations exist and compete to survive and stabilize at E_8. However, we observed that if we use only IL-2 therapy, the system could not clear the tumor cells. Hence, we require more external input. So, we introduce another external treatment parameter γ for ACI therapy in the following case.

Case (ii) $\delta > 0$, $\gamma > 0$, $\beta = 0$: Now, we will observe the dynamics of the system (7) in the presence of two treatment parameters, δ and γ.

For the treatment parameters $\delta = 0.25$ and $\gamma = 0.25$, there exist four equilibrium points as given in Box VII. The stability of the above four equilibria is as follows:

- The equilibrium E_2' is associated with eigenvalues −0.2000, 0.1500, −1.0000, 0.1000, indicating that it is an unstable saddle point.
- The immune-normal-fat co-existing critical point E_3' is associated with eigenvalues −0.2000, 0.2167, −1.0000, −0.1000; which corresponds to an unstable saddle point.
- Corresponding to E_7', eigenvalues are −0.0796 ± 0.0682i, −1.0068, 0.0879 which also indicates that E_7' is of unstable saddle type.
- Corresponding to E_8', eigenvalues are −0.0680 ± 0.0306i, −1.1255, −0.3462. Hence, around E_8' the system (7) shows the nature of an asymptotically stable inward spiral. Graphically, the existence and stability of the equilibrium E_8' can be observed from Fig. 4. Thus Fig. 4 demonstrates that for the parameter set 1 with treatment parameters $\delta = 0.25$ and $\gamma = 0.25$, the system could not clear the tumor at the required level, and the system still became tumor-persistent.

For the values of treatment parameters $\delta = 0.5$ and $\gamma = 0.25$, there are four biologically relevant equilibrium points as given in Box VIII. The stability of the above four equilibria is as follows:

- The eigenvalues corresponding to E_2' are −0.2000, 0.1125, −1.0000, 0.1000, showing the critical point is of unstable addle type.
- The equilibrium E_3' has corresponding eigenvalues as −0.2000, 0.1792, −1.0000, −0.1000; which indicates a saddle point.
- The eigenvalues associated with the critical point E_7' are −0.0803 ± 0.0811i, −1.0017, 0.0930; which corresponds to a saddle point.
- The co-existing equilibrium point E_8' has corresponding eigenvalues as −1.0996, −0.2098, −0.0333 ± 0.0274i which correspond to
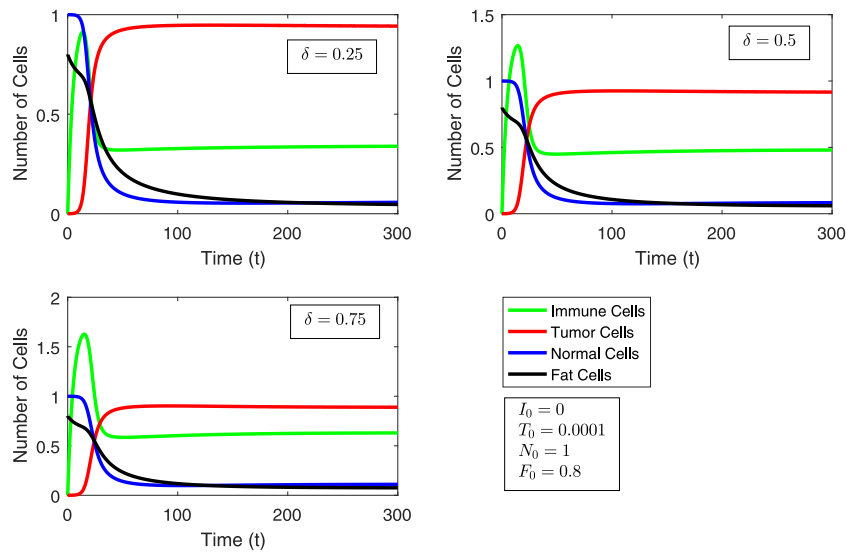
Fig. 3. Time series plot for the parameter set 1 with treatment parameter $\delta = 0.25$, 0.5 and 0.75.

$$E_2' = \begin{vmatrix} I_2' = 1 \\ T_2' = 0 \\ N_2' = 1 \\ F_2' = 0, \end{vmatrix} \quad E_3' = \begin{vmatrix} I_3' = 1 \\ T_3' = 0 \\ N_3' = 1 \\ F_3' = 0.6667, \end{vmatrix} \quad E_7' = \begin{vmatrix} \tilde{I}' = 1.8959 \\ \tilde{T}' = 0.1208 \\ \tilde{N}' = 0.8792 \\ \tilde{F}' = 0, \end{vmatrix} \quad E_8' = \begin{vmatrix} \hat{I}' = 0.6118 \\ \hat{T}' = 0.4509 \\ \hat{N}' = 0.5492 \\ \hat{F}' = 0.3661. \end{vmatrix}$$

Box VII.

$$E_2' = \begin{vmatrix} I_2' = 1.3750 \\ T_2' = 0 \\ N_2' = 1 \\ F_2' = 0, \end{vmatrix} \quad E_3' = \begin{vmatrix} I_3' = 1.3750 \\ T_3' = 0 \\ N_3' = 1 \\ F_3' = 0.6667, \end{vmatrix} \quad E_7' = \begin{vmatrix} \tilde{I}' = 2.1489 \\ \tilde{T}' = 0.0702 \\ \tilde{N}' = 0.9298 \\ \tilde{F}' = 0, \end{vmatrix} \quad E_8' = \begin{vmatrix} \hat{I}' = 0.8988 \\ \hat{T}' = 0.4002 \\ \hat{N}' = 0.5998 \\ \hat{F}' = 0.3999. \end{vmatrix}$$

Box VIII.
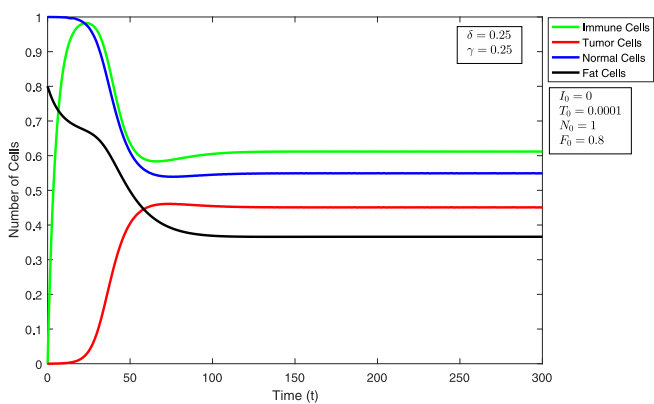
Fig. 4. Time series plot for the parameter set 1 with treatment parameter $\delta = 0.25$ and $\gamma = 0.25$.
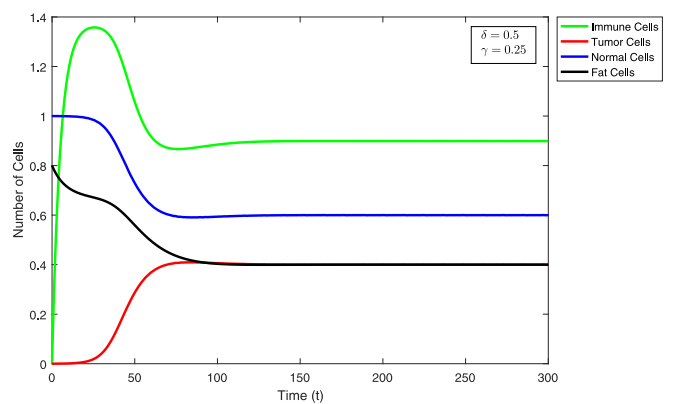
Fig. 5. Time series plot for the parameter set 1 with treatment parameter $\delta = 0.5$ and $\gamma = 0.25$.

a stable inward spiral. Graphically, the existence and stability of the equilibrium E_8' can be observed from Fig. 5. Thus Fig. 5

demonstrates that for the parameter set 1 with treatment parameter $\delta = 0.5$ and $\gamma = 0.25$, the system could not clear the tumor at the required level, and the system still becomes tumor-persistent.
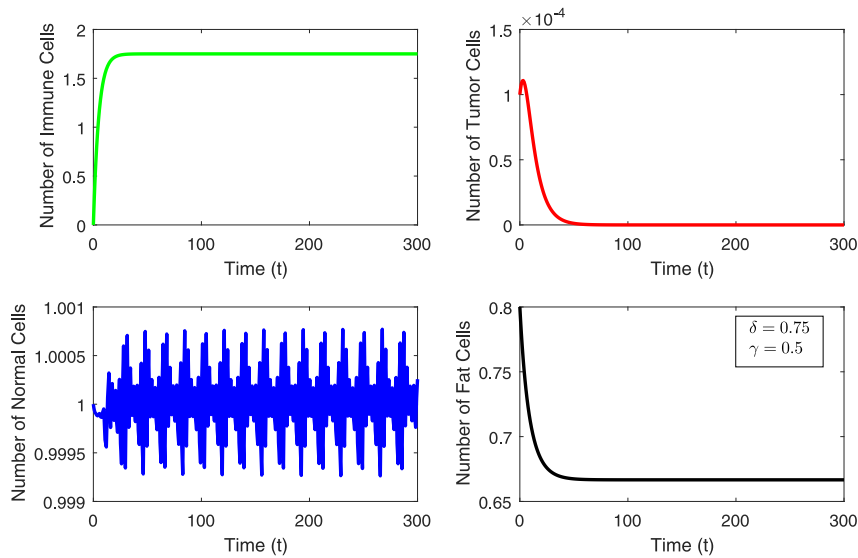
Fig. 6. Time series plot for the parameter set 1 with treatment parameter $\delta = 0.75$ and $\gamma = 0.5$.

For the values of treatment parameters $\delta = 0.75$ and $\gamma = 0.5$, there are two biologically relevant equilibrium points:

$$E_2' = \begin{vmatrix} I_2' = 1.7500 \\ T_2' = 0 \\ N_2' = 1 \\ F_2' = 0, \end{vmatrix} \quad E_3' = \begin{vmatrix} I_3' = 1.7500 \\ T_3' = 0 \\ N_3' = 1 \\ F_3' = 0.6667. \end{vmatrix}$$

The stability of the above two equilibria is as follows:

- The critical point E_2' is associated with eigenvalues -0.2000, -0.1750, -1.0000, 0.1000; which corresponds to an unstable saddle point.
- The corresponding eigenvalues of E_3' are -0.2000, -0.1083, -1.0000, -0.1000; which indicates a stable node. Graphically, the existence and stability of the equilibrium E_3' can be observed from Fig. 6. Thus, Fig. 6 demonstrates that for the parameter set 1 with treatment parameter $\delta = 0.75$ and $\gamma = 0.5$, the system could clear the tumor at the required level, and the system would still become tumor-free. However, at this point, it is important to note that the number of fat cells remains high, which may cause a rebirth of the tumor cells in the system. Hence, we may concentrate on controlling fat cells.

From Fig. 4, Figs. 5 and 6, it can be concluded that the increase in the treatment parameters δ and γ increases the tumor-reducing capability of the system. The system can eradicate tumors totally for values of $\delta = 0.75$ and $\gamma = 0.5$. However, a deficiency persists as the fat cells are still present, which can cause a reborn tumor. Hence, we introduced another external parameter, β, for a nutritional diet.

Now, we will observe the dynamics of the system (7) where all three treatment parameters δ, γ, and β are present.

Case (iii) $\delta > 0$, $\gamma > 0$, $\beta > 0$:

Considering the values of treatment parameters $\delta = 0.25$, $\gamma = 0.25$ and $\beta = 0.25$, there exist two biologically relevant equilibria:

$$E_2' = \begin{vmatrix} I_2' = 1 \\ T_2' = 0 \\ N_2' = 1 \\ F_2' = 0, \end{vmatrix} \quad E_7' = \begin{vmatrix} \tilde{I}' = 1.8959 \\ \tilde{T}' = 0.1208 \\ \tilde{N}' = 0.8792 \\ \tilde{F}' = 0. \end{vmatrix}$$

The stability of the above two equilibria is as follows:

- The equilibrium point E_2' has corresponding eigenvalues as -0.2000, 0.1500, -1.0000, -0.1500; which implies that E_2' is an unstable saddle point.
- The eigenvalues correspond to E_7' are $-0.0796 \pm 0.0682i$, -1.0068, -0.1621; which corresponds to a stable inward spiral. The graphical representation of the existence and stability of the system around the equilibrium E_7' is shown in Fig. 7. It can be observed that the tumor cells are still present in the system, whereas the fat cell population becomes zero.

For the values of treatment parameter $\delta = 0.5$, $\gamma = 0.5$, and $\beta = 0.25$, there are only one biologically relevant equilibrium point:

$$E_2' = \begin{vmatrix} I_2' = 1.3750 \\ T_2' = 0 \\ N_2' = 1 \\ F_2' = 0. \end{vmatrix}$$

- The equilibrium point E_2' has corresponding eigenvalues as -0.2000, -0.1375, -1.0000, -0.1500; which correspond to a stable node. The graphical representation of the existence and stability of the system around the equilibrium E_2' is shown in Fig. 8. It can be observed that both tumor cells and fat cells population become zero and the other healthy cells are stable at their maximum required level.

It is observed from figures 7 and 8 that with the use of all three external treatment inputs, the system gains more strength for tumor reducibility. Also, for the values of $\delta = 0.5$, $\gamma = 0.5$, and $\beta = 0.25$, the body acquires its healthy stage at which no tumor and fat cells are present.

Fig. 9 reveals that all trajectories of the system (7) converge to the disease-free equilibrium $E_2'(1.3750, 0, 1, 0)$, which suggests that it is globally asymptotically stable. Furthermore, it means that after applying an optimum amount of all three treatments, the patient's recovery is permanent, and the chances of the rebirth of the tumor are negligible.

The results and simulations of the optimal system are obtained from an iterative forward–backward algorithm based on the fourth-order Runge–Kutta method for $T_f = 100$, $h = 0.01$, $I(0) = 0$, $T(0) = 0.0001$, $N(0) = 1$, $F(0) = 0.8$, $\alpha_1 = \alpha_2 = 200$, $\alpha_3 = \alpha_4 = \alpha_5 = 1$, $\alpha_6 = \alpha_7 = 100$, $\lambda_i(T_f) = 0$, $i = 1, 2, 3, 4$, and the initial guesses for the control
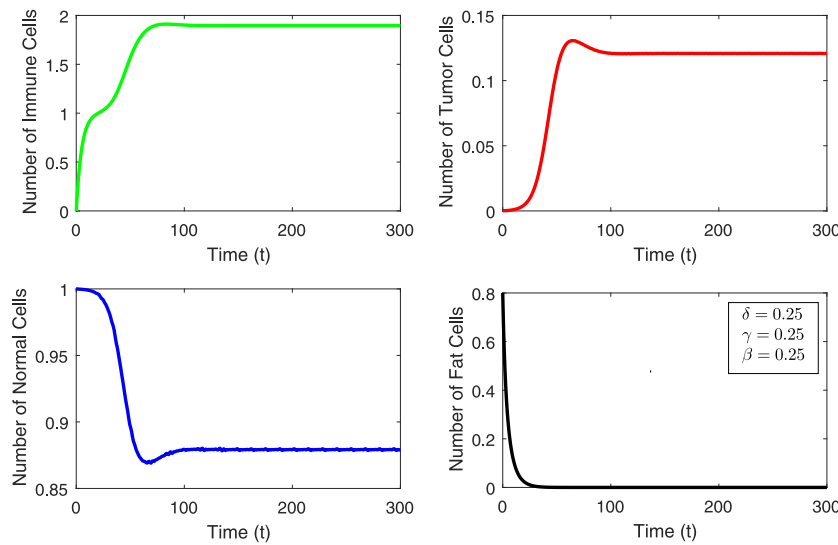
Fig. 7. Time series plot for the parameter set 1 with treatment parameter $\delta = 0.25$, $\gamma = 0.25$ and $\beta = 0.25$.
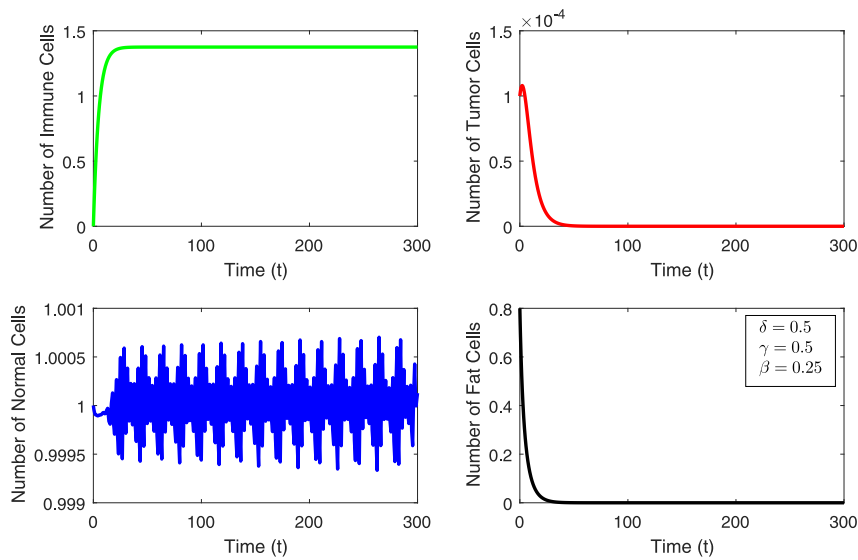

Fig. 8. Time series plot for the parameter set 1 with treatment parameter $\delta = 0.5$, $\gamma = 0.5$ and $\beta = 0.25$.

parameters as $\delta^*(0) = 1, \gamma^*(0) = 0.5, \beta^*(0) = 1$. The utilized algorithm is as follows:

Step 1. Choose an initial guess for the control parameters $\delta^*, \gamma^*, \beta^*$.

Step 2. Solve the system (19) using the usual Runge–Kutta method of the fourth order.

Step 3. From the resultant solutions of system (19), solve system (20) using the backward Runge–Kutta method.

Step 4. Update the control parameters $\delta^*, \gamma^*, \beta^*$ using system (18).

Step 5. Continue the procedure iteratively till the convergent solutions are achieved. In Fig. 10, we present the time series plot of immune cells (I), tumor cells (T), normal cells (N), and fat cells (F) with control of all the external treatment parameters. This figure shows that the number of tumor and fat cells is quickly driven to a much lower level. The number of immune and normal cells increases over time and stabilizes around a required level. Fig. 11 shows that the external input of treatment parameters $\gamma(t)$ for ACI-therapy and $\beta(t)$ for diet control are initially high for a short period and fall rapidly over time.

7. Conclusion

This study formulated a cancer-obesity-treatment model by considering four nonlinear differential equations. We first studied the model in the absence of any treatment. An existence and stability analysis has been performed. It is observed that immune cells may suppress tumor growth with a high immune response rate to tumor cells. However, in the case of a low immune response rate to the tumor cells, the system could not destroy tumor cells; in fact, tumor cells proliferate rapidly. Hence, we introduced an external treatment input to the system. We explained the conditions for stability of the equilibria for the case of the treatment model. Moreover, conditions for global stability at disease-free equilibrium $E_2'(I_2' = \frac{s+\delta\sigma_1}{d_1}, 0, N_2' = \frac{1}{b_2}, 0)$ have been derived. To understand the treatment effect on the system, we considered three cases: (i) $\delta > 0$, $\gamma = 0$, $\beta = 0$, (ii) $\delta > 0$, $\gamma > 0$, $\beta = 0$ and (iii) $\delta > 0$, $\gamma > 0$, $\beta > 0$.

- In case (i), it is impossible to eradicate tumors from the body using only IL-2 therapy.
- In the case of (ii), the combination of IL-2 therapy and ACI therapy can eradicate the tumor for the values of $\delta = 0.75$ and
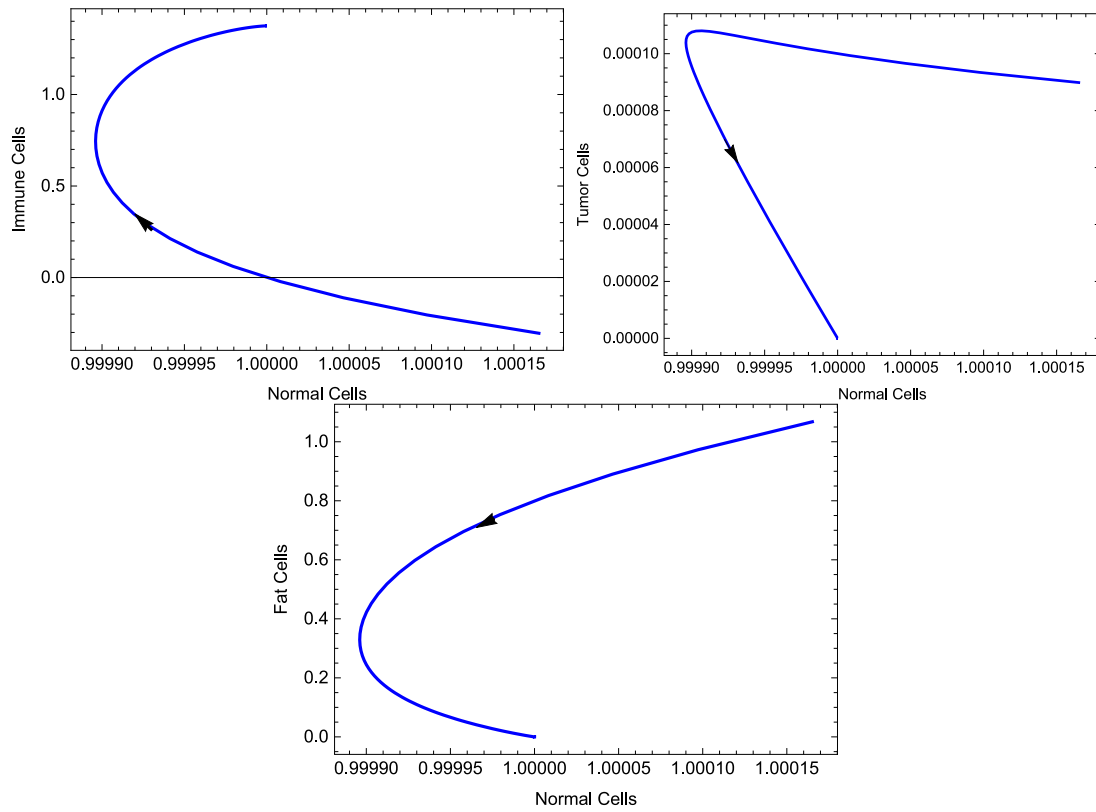
Fig. 9. Parametric plot of the system (7) around the equilibrium $E_2'(1.3750, 0, 1, 0)$ for $\delta = 0.5$, $\gamma = 0.5$, $\beta = 0.25$, using the parameter set 1 and initial values $I(0) = 0$, $T(0) = 0.0001$, $N(0) = 1$, $F(0) = 0.8$.
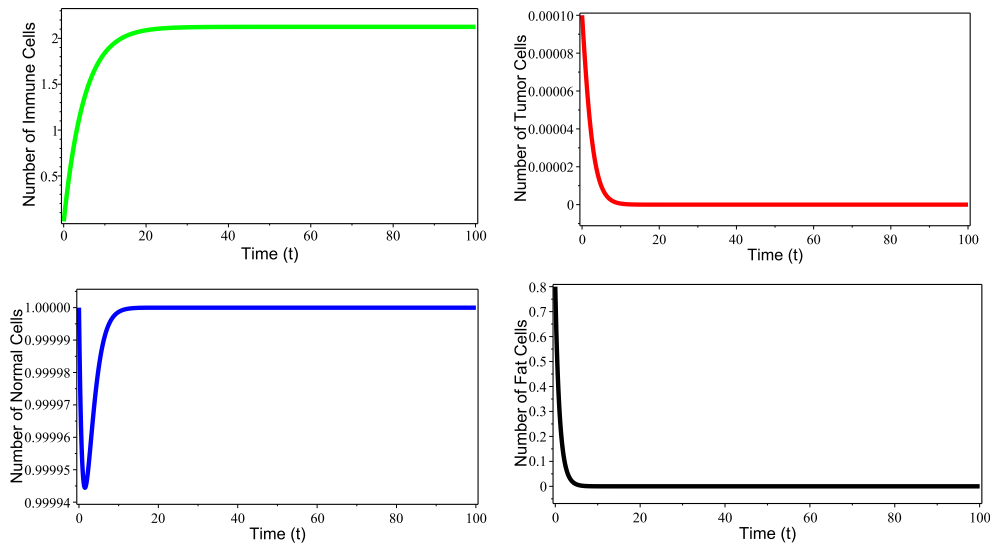

Fig. 10. Time series plot of the immune cells (I), tumor cells (T), normal cells (N), and fat cells (F) with control treatment parameter $\delta(t)$, $\gamma(t)$, and $\beta(t)$ using parameter set 1.

$\gamma = 0.5$. Nevertheless, in this case, fat cells are still present in the body, which may cause the rebirth of tumor cells in the long run. So, we introduce the diet parameter to control the growth of the fat cells.

- In case (iii), it is easily seen that the tumor cells and fat cells totally vanish from the body in long-term behavior for the values of treatment parameters $\delta = 0.5$, $\gamma = 0.5$, and $\beta = 0.25$. Here, it is observed that the normal cells oscillate around their maximum value of 1. This phenomenon is observed due to the overdose of prescribed treatment. Therefore, to control the oscillation, we

control the treatment parameters to reduce the side effects of the prescribed treatments on healthy cells.

- A control problem is constructed for the treatment model to minimize the cancerous cells during the treatment, keeping the normal cells above the required level. From Figs. 10 and 11, it can be concluded that normal cells can be stabilized using control theory on treatment parameters. Also, from Fig. 11, we obtained the maximum value of prescribed treatment as $\delta = 0.75$, $\gamma = 0.00025$, and $\beta = 0.75$ for which the tumor cells are reduced optimally. It is observed that optimal control is much more effective for reducing
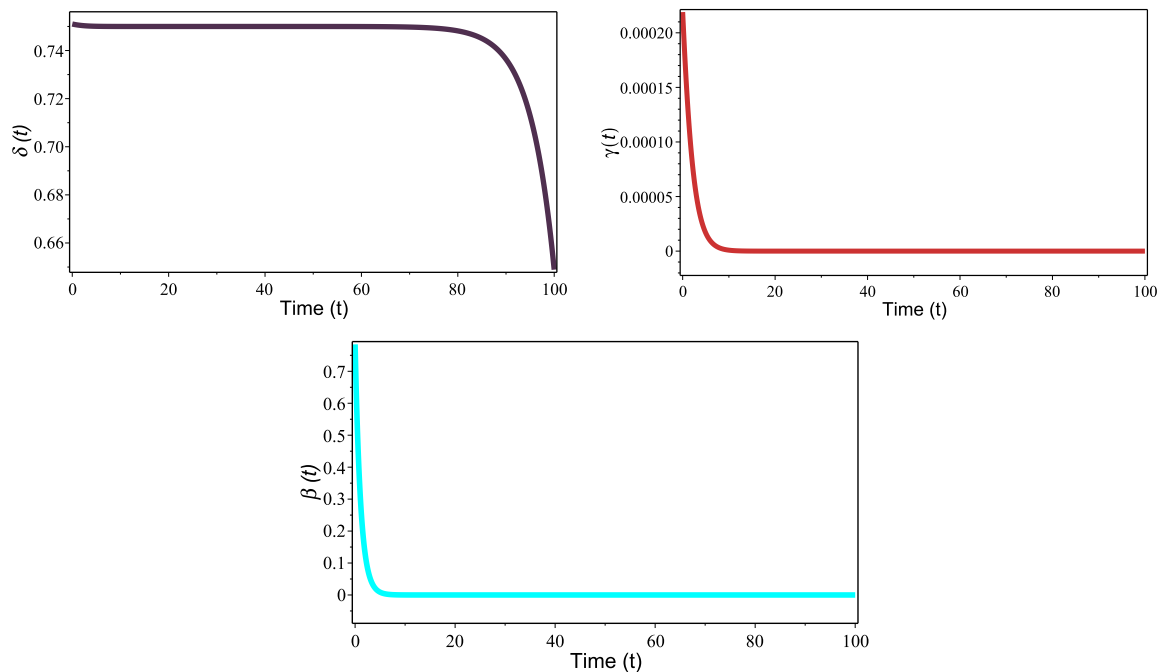
Fig. 11. The optimal control graph for treatment parameters $\delta(t)$, $\gamma(t)$, and $\beta(t)$ using the parameter set 1.

the number of tumor and fat cells, which is the main result of this paper. Also, early practice of all three treatment controls can lead to better results for tumor eradication.

We have used arbitrary parameter sets to simulate the model; it would be better if clinical data sets were used to fit the model. Time delay in the immune response to the tumor cells also plays an essential role in tumor-immune dynamics. So, the readers can extend the work using the delay factor in the immune response [2,10,40]. Another model refinement would include different immunotherapy control techniques such as gene therapy, CAR-T cell therapy, and molecular therapy. Such therapies are extensively studied in [9,19, 41] to find optimal treatment strategies for cancer management. The model can further be extended to fractional one using different fractional order derivatives to show their significant dynamical properties [42–45].

CRediT authorship contribution statement

Kaushik Dehingia: Conceptualization, Software, Writing manuscript. **Shao-Wen Yao:** Revision, Funding. **Khadijeh Sadri:** Writing- Reviewing final manuscript. **Anusmita Das:** Methodology, Review, Data Collection, Graphs sketching. **Hemanta Kumar Sarmah:** Graphs sketching, Visualization, Review final manuscript. **Anwar Zeb:** Supervision, Investigation, Review final manuscript, Validation. **Mustafa Inc:** Review final manuscript, Supervision, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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