Optimal control and global stability of the stomach cancer treatment model in the presence of obesity and psychological scare

M. F. Y. Al-Aboud
University of Tabriz

H. Kheiri*
University of Tabriz

G. Hojjati
University of Tabriz

S. Jawad
University of Baghdad

Abstract. In recent years, there has been a growing interest in developing mathematical models that can better inform treatment strategies for complex health conditions. In this work, we propose a novel model that integrates three critical elements: the rate of externally administered anti-tumor immune therapy, the time-dependent control of ACI treatment, and nutritional diet management. Our study aims to investigate the dynamical behavior of the proposed model, focusing on the stability of treatment outcomes. By employing a Lyapunov function, we derive the necessary and sufficient conditions for global stability, ensuring that our model can reliably predict long-term treatment effects.

Furthermore, we address the optimization of treatment regimens by formulating an optimal control problem, allowing us to identify the most effective strategies for reducing cancer cell populations. To validate our theoretical findings, we conduct numerical simulations that explore various treatment strategies within the framework of our model. The results of these simulations provide critical insights into how different approaches can be tailored to improve treatment efficacy for patients suffering from stomach cancer, particularly those facing the dual challenges of obesity and psychological distress.

AMS Subject Classification: 35F21, 92-10.
Keywords and Phrases: Stomach cancer; Optimal control; Ordinary differential equation; Dynamic systems; Stability

1   Introduction

Tumors originate from the abnormal proliferation of a single cell in any part of the body. They can be classified as benign (non-cancerous) or malignant (cancerous). Benign tumors may grow significantly but do not invade surrounding tissues or metastasize to other regions of the body. In contrast, malignant tumors have the ability to invade nearby tissues and can disseminate through the bloodstream and lymphatic system.

The unchecked and persistent growth of cancer cells is what leads to the disease. Unlike normal cells, which respond to regulatory signals, cancer cells continue to proliferate and invade healthy tissues, ultimately spreading throughout the body.

Cancers are categorized based on their cell origin into four primary types:

- Carcinomas develop from cells that line external and internal surfaces, with lung, breast, and colon cancers being the most prevalent.

- Sarcomas originate from supporting tissues such as bone, cartilage, fat, and muscle.

- Lymphomas arise in the lymphatic system and affect the body's immune tissues.

- Leukemias affect immature blood cells produced in the bone marrow.

Stomach cancer occurs when cells in the stomach proliferate abnormally. While tumors can form anywhere in the stomach, they most commonly arise in the glandular tissue lining its inner surface. Key signs and symptoms include abdominal pain or burning, heartburn, a feeling of fullness after small meals, nausea, loss of appetite or weight, abdominal swelling, fatigue or weakness, and the presence of blood in vomit or black stools [5, 10, 21].

Numerous approaches have been proposed in medical science for cancer treatment, including radiotherapy [11], chemotherapy [8], virotherapy [1], psychological panic factor [7], and immunotherapy [17]. Additionally, some researchers have explored the application of mathematical models to enhance cancer treatment strategies. For instance, DiPillis and et al. in [9] introduced a mathematical model that combines immunotherapy with chemotherapy to simulate tumor growth dynamics. In their study, Makhlouf et al. [17] developed a treatment protocol that integrates chemotherapy with IL2 cytokine therapy and both $CD8^+T$ and $CD4^+T$ adoptive immunotherapies, examining the roles of natural killer cells and circulating lymphocytes on the behavior of cancer cells. Furthermore, Schlicke et al. [23] proposed a mathematical framework that evaluates various treatment options and analyzes the outcomes based on data from three patients diagnosed with non-small cell lung cancer. Ahmad et al. [2] formulated a fractional order tumor-immune-vitamin model (TIVM) using the Mittag-Leffler derivative, investigating how different fractional orders of vitamins influence tumor cell proliferation. Optimal control strategies are frequently employed in cancer treatment models. Rihan et al. [22] introduced a delay differential model that utilizes optimal control to analyze the interactions between tumor cells and immune response cells in the context of chemo-immunotherapy. In another study, [25] outlined a fractional order model for cancer treatment, addressing an optimal control problem related to anti-angiogenic and immune cell therapies. Das et al. [4] developed an optimal control framework for a delayed tumor-immune model, incorporating a multi-immuno-chemotherapeutic drug. Additionally, experimental research has highlighted the significant impact of obesity

on various cancer types. This underscores the necessity to explore the influence of adipose tissue in cancer dynamics and to devise treatment protocols aimed at managing the excessive proliferation of both fat cells and cancer cells.

In this paper, we present a model focused on treating stomach cancer while considering the effects of obesity and psychological stress. After determining the equilibrium points, we analyze their local and global stability. Furthermore, we formulate an optimal control problem to derive an effective treatment strategy for stomach cancer in the context of obesity and psychological challenges.

The rest of the paper is organized as follows: In Section 2, the stomach cancer model with obesity and psychological scare is presented. We obtain the equilibrium points and then check the local and global stability of the model with treatment in Section 3. In section 4, we use an optimal control problem to look an optimal drug administration protocol for stomach cancer. The numerical simulation is presented in Section 5. Finally, some conclusions are given in Section 6.

2   Model description

In this paper, we consider a new model for the stomach cancer in presence of obesity and psychological care as follows:

$$
\begin{aligned}
\frac{dI}{dt} &= \frac{s}{1+pT} + \frac{CIT}{\alpha + T + \beta F} - d_1 I - e_1 IT + \gamma_1(t), \\
\frac{dT}{dt} &= r_1 T(1 - b_1 T) - e_2 IT - e_3 TN + e_5 TF - \gamma_2(t)T, \qquad (1) \\
\frac{dN}{dt} &= r_2 N(1 - b_2 N) - e_4 TN, \\
\frac{dF}{dt} &= r_3 F(1 - b_3 F) - e_6 TF - \gamma_3(t)F,
\end{aligned}
$$

where $I(t)$, $T(t)$, $N(t)$ and $F(t)$ are the numbers of immune cells, tumor cells, normal cells and fat cells at any given time t, respectively. Also

- s is the constatnt source of immune cells,

- p is psychological panic effect,

- The term $\dfrac{CIT}{\alpha + T + \beta F}$ 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 cells, normal cells and fat cells can grow logistically with different growth rates r_1, r_2 and r_3, respectively. Furthermore, 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 $e_5 TF$ denotes the contribution of fat cells to tumor growth,

- e_1, e_2, e_3, e_4, e_5 and e_6 are competition coefficients,

- $\gamma_1(t)$ present the input rate of externally administered anti-tumor immune therapy,

- $\gamma_2(t)$ is the time-dependent ACI treatment control parameter,

- $\gamma_3(t)$ denotes the nutritional diet control parameter.

Model 2 satisfies the nonnegative initial conditions $I(0) = I_0$, $T(0) = T_0$, $N(0) = N_0$ and $F(0) = F_0$.

2.1   Boundary and non-negativity of cells

In model (1), we assume that all the parameters are positive.

Theorem 2.1. *The region $\Omega+ = (I, T, N, F)I > 0, T \geq 0, N \geq, F \geq 0$ is a invariant set for model (1) positively.*

Proof. The existence and uniqueness of the solution of model (1) in $(0, \infty)$ is simply proved in [29]. On region $\Omega+$ we have

$$\frac{dI}{dt}\bigg|_{I=0} = \frac{s}{1+pT} + \gamma_1(t) > 0,$$
$$\frac{dT}{dt}\bigg|_{T=0} = 0, \qquad\qquad (2)$$
$$\frac{dN}{dt}\bigg|_{N=0} = 0,$$
$$\frac{dF}{dt}\bigg|_{F=0} = 0.$$

Now, if $(I(0), T(0), N(0), F(0)) \in \Omega+$, according to (2), (I, T, N, F) cannot escape from the hyperplanes of $I = 0, T = 0, N = 0$ and $F = 0$, and on each hyperplane, the vector field is tangent to that hyperplane or points toward the interior of region $\Omega+$; that is, the solution will remain in the region $\Omega+$, and therefore, this region is a positive invariant set. □

3   Dynamic behavior of the model

In this section, we investigate the existence and stability behavior at various equilibrium points of the system (1). To find the equilibrium points, by assuming $\gamma_1(t) = \gamma_1$, $\gamma_2(t) = \gamma_2$ and $\gamma_3(t) = \gamma_3$, we set

$$\frac{dI}{dt} = \frac{dT}{dt} = \frac{dN}{dt} = \frac{dF}{dt} = 0.$$

Hence, the equilibrium points $E_i(I, T, N, F)$, $i = 0, 1, ..., 7$ are as follows:

- $E_0\left(\frac{s + \gamma_1}{d_1}, 0, 0, 0\right).$

- $E_1\left(\frac{s + \gamma_1}{d_1}, 0, 0, \frac{r_3 - \gamma_3}{r_3 b_3}\right).$

- $E_2\left(\frac{s + \gamma_1}{d_1}, 0, \frac{1}{b_2}, 0\right).$

- $E_3\left(I, \dfrac{r_1 - e_2 I - \gamma_2}{r_1 b_1}, 0, 0\right)$, where I will be calculated from the equation

$$\frac{s}{1 + pT} + \frac{CIT}{\alpha + T + \beta F} - d_1 I - e_1 IT + \gamma_1 = 0.$$

This equilibrium point exists provided $e_2 I < r_1 - \gamma_2$.

- $E_4\left(\dfrac{s + \gamma_1}{d_1}, 0, \dfrac{1}{b_2}, \dfrac{r_3 - \gamma_3}{r_3 b_3}\right)$.

- $E_5\left(\dfrac{r_1(1 - b_1 T) + e_5 F - \gamma_2}{e_2}, T, 0, \dfrac{r_3 - e_6 T - \gamma_3}{r_3 b_3}\right)$, where T is obtained from the equation

$$\frac{s}{1 + pT} + \frac{CIT}{\alpha + T + \beta F} - d_1 I - e_1 IT + \gamma_1 = 0.$$

This equilibrium point exists for $e_6 T < r_3 - \gamma_3$ and $r_1(1 - b_1 T) + e_5 F > \gamma_2$.

- $E_6\left(\dfrac{r_1(1 - b_1 T) - e_3 N - \gamma_2}{e_2}, T, \dfrac{r_2 - e_4 T}{r_2 b_2}, 0\right)$ in which T is computed from

$$\frac{s}{1 + pT} + \frac{CIT}{\alpha + T} - d_1 I - e_1 IT + \gamma_1 = 0,$$

This equilibrium point exists provided $e_4 T < r_2$ and $r_1(1 - b_1 T) - e_3 N > \gamma_2$.

- $E_7\left(\dfrac{r_1(1 - b_1 T) - e_3 N + e_5 F - \gamma_2}{e_2}, T, \dfrac{r_2 - e_4 T}{r_2 b_2}, \dfrac{r_3 - e_6 T - \gamma_3}{r_3 b_3}\right)$, where T satisfies in

$$\frac{s}{1 + pT} + \frac{CIT}{\alpha + T + \beta F} - d_1 I - e_1 IT + \gamma_1 = 0.$$

This equilibrium point exists for $e_4 T < r_2$, $e_6 T < r_3 - \gamma_3$ and $r_1(1 - b_1 T) - e_3 N + e_5 F > \gamma_2$.

3.1 Local stability

In this subsection, we analyze the local stability of the system (1). Hence, we obtain the Jacobian matrix and then present the necessary and sufficient conditions for local stability at four equilibrium points. The Jacobian matrix of the model (1) is given by

$$
J = \begin{bmatrix}
j_{11} & j_{12} & 0 & j_{14} \\
j_{21} & j_{22} & j_{23} & j_{24} \\
0 & j_{32} & j_{33} & 0 \\
0 & j_{42} & 0 & j_{44}
\end{bmatrix},
\tag{3}
$$

where

$$
j_{11} = \frac{CT}{\alpha + T + \beta F} - d_1 - e_1 T,
$$

$$
j_{12} = -\frac{ps}{(1 + pT)^2} + \frac{CI(\alpha + \beta F)}{(\alpha + T + \beta F)^2} - e_1 I,
$$

$$
j_{14} = -\frac{\beta CIT}{(\alpha + T + \beta F)^2},
$$

$$
j_{21} = -e_2 T,
$$

$$
j_{22} = r_1(1 - 2b_1 T) - e_2 I - e_3 N + e_5 F - \gamma_2,
$$

$$
j_{23} = -e_3 T,
$$

$$
j_{24} = e_5 T,
$$

$$
j_{32} = -e_4 N,
$$

$$
j_{33} = r_2(1 - 2b_2 N) - e_4 T,
$$

$$
j_{42} = -e_6 F,
$$

$$
j_{44} = r_3(1 - 2b_3 F) - e_6 T - \gamma_3.
$$

Now, we get the eigenvalues of the Jacobi matrix at some equilibrium points.

CASE 1: The Jacobian matrix at the disease-free equilibrium E_2 is

$$J_{E_2} = \begin{bmatrix} -d_1 & -ps + \dfrac{(s+\gamma_1)(C-e_1\alpha)}{\alpha d_1} & 0 & 0 \\ 0 & r_1 - \dfrac{e_2(s+\gamma_1)}{d_1} - \dfrac{e_3}{b_2} - \gamma_2 & 0 & 0 \\ 0 & -\dfrac{e_4}{b_2} & -r_2 & 0 \\ 0 & 0 & 0 & r_3 - \gamma_3 \end{bmatrix}.$$

The eigenvalues of J_{E_2} are

$$\left\{ -d_1, \quad -r_2, \quad r_3 - \gamma_3, \quad r_1 - \frac{e_2(s+\gamma_1)}{d_1} - \frac{e_3}{b_2} - \gamma_2 \right\}.$$

Hence, the equilibrium point E_2 becomes locally stable if

$$r_3 < \gamma_3 \quad and \quad r_1 < \frac{e_2(s+\gamma_1)}{d_1} + \frac{e_3}{b_2} + \gamma_2,$$

otherwise E_2 is unstable.

CASE 2: For another disease-free equilibrium E_4, the Jacobian matrix is

$$J_{E_4} = \begin{bmatrix} -d_1 & j_{12} & 0 & 0 \\ 0 & j_{22} & 0 & 0 \\ 0 & -\dfrac{e_4}{b_2} & -r_2 & 0 \\ 0 & -e_6\dfrac{r_3 - \gamma_3}{r_3 b_3} & 0 & \gamma_3 - r_3 \end{bmatrix},$$

in which

$$j_{12} = -ps + \frac{\dfrac{\alpha C(s+\gamma_1)}{d_1} + \dfrac{\beta C(s+\gamma_1)(r_3-\gamma_3)}{d_1 r_3 b_3}}{\left(\alpha + \dfrac{\beta(r_3-\gamma_3)}{r_3 b_3}\right)^2} - \frac{e_1(s+\gamma_1)}{d_1},$$

$$j_{22} = r_1 - \frac{e_2(s+\gamma_1)}{d_1} - \frac{e_3}{b_2} + \frac{e_5(r_3-\gamma_3)}{r_3 b_3} - \gamma_2.$$

The eigenvalues of J_{E_4} are

$$\{ -d_1, \quad j_{22}, \quad -r_2, \quad \gamma_3 - r_3 \}.$$

This equilibrium point will be locally stable, provided

$$\gamma_3 < r_3 \qquad and \qquad r_1 + \frac{e_5(r_3 - \gamma_3)}{r_3 b_3} < \frac{e_2(s + \gamma_1)}{d_1} + \frac{e_3}{b_2} + \gamma_2,$$

CASE 3: For the equilibrium point E_6, the eigenvalues are $r_3 - e_6 T - \gamma_3$ and the roots of the following equation

$$\lambda^3 + P_1 \lambda^2 + P_2 \lambda + P_3 = 0, \tag{4}$$

in which

$$P_1 = -j_{11} - j_{22} - j_{33},$$
$$P_2 = -j_{23}j_{32} + j_{11}j_{33} + j_{22}j_{33} + j_{11}j_{22} - j_{12}j_{21},$$
$$P_3 = j_{32}j_{11}j_{23} - j_{11}j_{22}j_{33} + j_{12}j_{21}j_{33},$$

where

$$j_{11} = \frac{CT}{\alpha + T} - d_1 - e_2 T, \, j_{12} = -\frac{ps}{(1 + pT)^2} + \frac{\alpha CI}{(\alpha + T)^2} - e_1 I,$$
$$j_{14} = -\frac{\beta CIT}{(\alpha + T)^4}, \, j_{21} = -e_2 T,$$
$$j_{22} = r_1(1 - 2b_1 T) - e_2 I - e_3 N - \gamma_2, \, j_{23} = -e_3 T, \, j_{24} = e_5 T,$$
$$j_{32} = -e_4 N, \, j_{33} = -r_2 + e_4 T, \, j_{44} = r_3 - e_6 T - \gamma_3.$$

Using Routh–Hurwitz rule [19], the roots of (4) have negative real part if and only if

$$P_1 > 0, \qquad P_2 > 0, \qquad P_1 P_2 - P_3 > 0. \tag{5}$$

So, under the conditions (5) and $e_6 T > r_3 - \gamma_3$ the equilibrium point E_6 is locally stable, otherwise E_6 is unstable.

CASE 4: The eigenvalues of Jacobian matrix E_7 are obtained by solving the following equation

$$\lambda^4 + Q_1 \lambda^3 + Q_2 \lambda^2 + Q_3 \lambda + Q_4 = 0, \tag{6}$$

where

$Q_1 = -j_{11} - j_{22} - j_{33} - j_{44}$,

$Q_2 = j_{11}j_{22} + j_{11}j_{33} + j_{11}j_{44} - j_{12}j_{21} + j_{22}j_{33} - j_{32}j_{23} - j_{42}j_{24} + j_{22}j_{44} + j_{33}j_{44}$,

$Q_3 = j_{24}j_{33}j_{42} + j_{11}j_{24}j_{42} - j_{21}j_{14}j_{42} + j_{32}j_{23}j_{44} - j_{11}j_{23}j_{44} - j_{22}j_{33}j_{44}$
$\quad\quad - j_{11}j_{22}j_{44} + j_{12}j_{21}j_{44} + j_{32}j_{11}j_{23} - j_{11}j_{22}j_{33} + j_{12}j_{21}j_{33}$,

$Q_4 = -j_{42}j_{11}j_{24}j_{33} + j_{21}j_{14}j_{33}j_{42} - j_{11}j_{32}j_{23}j_{44} + j_{11}j_{22}j_{33}j_{44} - j_{12}j_{21}j_{33}j_{44}$.

Based on Routh–Hurwitz rule (6) have negative real part if and only if

$$Q_1 > 0, \quad\quad Q_3 > 0, \quad\quad Q_4 > 0, \quad\quad Q_1 Q_2 Q_3 > Q_3^2 + Q_1^2 Q_4. \quad (7)$$

The equilibrium point E_7 is locally stable under conditions (7), otherwise E_7 is unstable.

3.2 Global stability

Local stability describes the behavior of the model in the neighborhood of the equilibrium point; But global stability examines this property of the system at places far from the equilibrium point. In this subsection, we investigate the global stability of the equilibrium point

$$E_2\Big(I_2 = \frac{s + \gamma_1}{d_1}, T_2 = 0, N_2 = \frac{1}{b_2}, F_2 = 0\Big),$$

using the Lyapunov stability theorem [16]. Now, we consider the Lyapunov function as

$$V(t) = \Big(I - I_2 - I_2 \ln \frac{I}{I_2}\Big) + (T - T_2) + \Big(N - N_2 - N_2 \ln \frac{N}{N_2}\Big) + (F - F_2). \quad (8)$$

By differentiating from (8) respect to t, we get

$$\frac{dV}{dt} = \frac{dI}{dt} - I_2 \frac{\frac{dI}{dt}}{I} + \frac{dT}{dt} + \frac{dN}{dt} - N_2 \frac{\frac{dN}{dt}}{N} + \frac{dF}{dt}$$
$$= \Big(1 - \frac{I_2}{I}\Big)\frac{dI}{dt} + \frac{dT}{dt} + \Big(1 - \frac{N_2}{N}\Big)\frac{dN}{dt} + \frac{dF}{dt}. \quad (9)$$

Substituting (1) into (9), gives

$$\frac{dV}{dt} = \left(\frac{I - I_2}{I}\right)\left[\frac{s}{1 + pT} + \frac{CIT}{\alpha + T + \beta F} - e_1 IT - d_1(I - I_2) - s\right]$$
$$+ \left[r_1 T(1 - b_1 T) - e_2 T(I - I_2) - e_2 T I_2 - e_3 T(N - N_2) - e_3 T N_2 + e_5 TF - \gamma_2 T\right]$$
$$+ \left(\frac{N - N_2}{N}\right)\left[r_2(N - N_2) - r_2 b_2(N^2 - N_2^2) - e_4 TN\right]$$
$$+ \left[r_3 F(1 - b_3 F) - e_6 TF - \gamma_3 F\right]. \qquad (10)$$

Now, by simplification (10), we get

$$\frac{dV}{dt} = \left(I - \frac{s + \gamma_1}{d_1}\right)\left[\frac{s}{I(1 + pT)} + \frac{CT}{\alpha + T + \beta F} - e_1 T - \frac{d_1}{I}\left(I - \frac{s + \gamma_1}{d_1}\right) - \frac{s}{I}\right]$$
$$+ \left[-r_1 b_1 T^2 - e_2 T\left(I - \frac{s + \gamma_1}{d_1}\right) - e_3 T\left(N - \frac{1}{b_2}\right) + e_5 TF\right]$$
$$+ \left(N - \frac{1}{b_2}\right)\left[r_2(1 - b_2 N) - e_4 T\right]$$
$$+ (-r_3 b_3 F^2 - e_6 TF)$$
$$+ \left[r_1 T - e_2 T\left(\frac{s + \gamma_1}{d_1}\right) - e_3 \frac{T}{b_2} - \gamma_2 T\right] + (r_3 F - \gamma_3 F).$$

Let

$$Q^T = \begin{bmatrix} 0 & 0 & 0 & \gamma_3 - r_3 \end{bmatrix},$$
$$Y^T = \begin{bmatrix} I - I_2 & T & N - N_2 & F \end{bmatrix},$$
$$P^T = \begin{bmatrix} 0 & -r_1 + e_2\left(\frac{s + \gamma_1}{d_1}\right) + \frac{e_3}{b_2} + \gamma_2 & 0 & 0 \end{bmatrix},$$

and

$$M = \begin{bmatrix} \frac{d_1}{I} & \frac{1}{2}\left(e_1 + e_2 - \frac{C}{\alpha + T + \beta F} + \frac{sp}{I(1 + pT)}\right) & 0 & 0 \\ \frac{1}{2}\left(e_1 + e_2 - \frac{C}{\alpha + T + \beta F} + \frac{sp}{I(1 + pT)}\right) & r_1 b_1 & \frac{e_3}{4} & \frac{e_6 - e_5}{2} \\ 0 & \frac{e_3}{2} & r_2 b_2 & 0 \\ 0 & \frac{e_6 - e_5}{2} & 0 & r_3 b_3 \end{bmatrix}.$$

Therefore

$$\frac{dV}{dt} = -Y^T M Y - P^T Y - Q^T Y.$$

For the global stability, the second component of vector P and the fourth component of vector Q should be positive. So,

$$-r_1 + e_2 \left(\frac{s + \gamma_1}{d_1}\right) + \frac{e_3}{b_2} + \gamma_2 > 0 \implies r_1 < e_2 \left(\frac{s + \gamma_1}{d_1}\right) + \frac{e_3}{b_2} + \gamma_2, \tag{11}$$

and

$$\gamma_3 - r_3 > 0 \implies r_3 < \gamma_3. \tag{12}$$

Therefore, provided conditions (11) and (12), it results that $\dfrac{dV}{dt} < 0$ and we can state the following theorem.

Theorem 3.1. *The disease-free equilibrium point*

$$E_2 \left(I_2 = \frac{s + \gamma_1}{d_1}, T_2 = 0, N_2 = \frac{1}{b_2}, F_2 = 0\right),$$

is globally asymptotically stable if the following conditions hold

(1) $r_1 < e_2 \left(\dfrac{s + \gamma_1}{d_1}\right) + \dfrac{e_3}{b_2} + \gamma_2$.

(2) $r_3 < \gamma_3$.

4   Optimal control

The theory of optimal control provides the possibility to obtain an optimal treatment model for stomach cancer with obesity and psychological scare. For this goal, it should increase immune cells and normal cells, but reduce tumor cells and fat cells. So, we need to minimize the following objective function

$$J(\gamma_1, \gamma_2, \gamma_3) = \int_0^{T_f} \left[\alpha_1 T(t) + \alpha_2 F(t) - \alpha_3 I(t) - \alpha_4 N(t) + \alpha_5 \gamma_1^2(t) + \alpha_6 \gamma_2^2(t) + \alpha_7 \gamma_3^2(t)\right] dt, \tag{13}$$

where T_f is the final time and α_i $(i = 1, 2, ..., 7)$ are weights. Now, we seek an optimal control $(\gamma_1^*, \gamma_2^*, \gamma_3^*)$ such that

$$J(\gamma_1^*, \gamma_2^*, \gamma_3^*) = \min \left\{ J(\gamma_1, \gamma_2, \gamma_3) \mid (\gamma_1, \gamma_2, \gamma_3) \in \Delta \right\}, \qquad (14)$$

where

$$\Delta = \left\{ (\xi_1, \xi_2, \xi_3) \mid \ \xi_i(t) \ \text{is Lebesgue measurable}, \ 0 \le \xi_i \le \xi_{i_{\max}} \right\}.$$

Let

$$\Psi = (I, T, N, F), \qquad \tilde{\Gamma} = (\tilde{\gamma}_1, \tilde{\gamma}_2, \tilde{\gamma}_3),$$

and

$$\Omega(t, \Psi, \tilde{\Gamma}) = \alpha_1 T(t) + \alpha_2 F(t) - \alpha_3 I(t) - \alpha_4 N(t) + \alpha_5 \tilde{\gamma}_1^2(t) + \alpha_6 \tilde{\gamma}_2^2(t) + \alpha_7 \tilde{\gamma}_3^2(t).$$
$$(15)$$

Lemma 4.1. *The function $\Omega(t, \Psi, \tilde{\Gamma})$ is convex.*

Proof. Let $\tilde{\Gamma} = (\tilde{\gamma}_1, \tilde{\gamma}_2, \tilde{\gamma}_3)$, $\bar{\Gamma} = (\bar{\gamma}_1, \bar{\gamma}_2, \bar{\gamma}_3)$ and $0 \le \eta \le 1$. We must show that

$$(1 - \eta)\Omega(t, \Psi, \tilde{\Gamma}) + \eta\Omega(t, \Psi, \bar{\Gamma}) \ge \Omega(t, \Psi, (1 - \eta)\tilde{\Gamma} + \eta\bar{\Gamma}).$$

From (15), we obtain

$$(1 - \eta)\Omega(t, \Psi, \tilde{\Gamma}) + \eta\Omega(t, \Psi, \bar{\Gamma}) - \Omega(t, \Psi, (1 - \eta)\tilde{\Gamma} + \eta\bar{\Gamma})$$
$$= (1 - \eta)\Big[\alpha_1 T(t) + \alpha_2 F(t) - \alpha_3 I(t) - \alpha_4 N(t) + \alpha_5 \tilde{\gamma}_1^2(t) + \alpha_6 \tilde{\gamma}_2^2(t) + \alpha_7 \tilde{\gamma}_3^2(t)\Big]$$
$$+ \eta\Big[\alpha_1 T(t) + \alpha_2 F(t) - \alpha_3 I(t) - \alpha_4 N(t) + \alpha_5 \bar{\gamma}_1^2(t) + \alpha_6 \bar{\gamma}_2^2(t) + \alpha_7 \bar{\gamma}_3^2(t)\Big]$$
$$- \Big[\alpha_1 T(t) + \alpha_2 F(t) - \alpha_3 I(t) - \alpha_4 N(t) + \alpha_5 \big((1 - \eta)\tilde{\gamma}_1(t) + \eta\bar{\gamma}_1(t)\big)^2$$
$$+ \alpha_6 \big((1 - \eta)\tilde{\gamma}_2(t) + \eta\bar{\gamma}_2(t)\big)^2 + \alpha_7 \big((1 - \eta)\tilde{\gamma}_3(t) + \eta\bar{\gamma}_3(t)\big)^2\Big].$$

Hence,

$$(1 - \eta)\Omega(t, \Psi, \tilde{\Gamma}) + \eta\Omega(t, \Psi, \bar{\Gamma}) - \Omega(t, \Psi, (1 - \eta)\tilde{\Gamma} + \eta\bar{\Gamma})$$
$$= (1 - \eta)\Big[\alpha_5 \tilde{\gamma}_1^2(t) + \alpha_6 \tilde{\gamma}_2^2(t) + \alpha_7 \tilde{\gamma}_3^2(t)\Big] + \eta\Big[\alpha_5 \bar{\gamma}_1^2(t) + \alpha_6 \bar{\gamma}_2^2(t) + \alpha_7 \bar{\gamma}_3^2(t)\Big]$$
$$- \Big[\alpha_5 \big((1 - \eta)\tilde{\gamma}_1(t) + \eta\bar{\gamma}_1(t)\big)^2 + \alpha_6 \big((1 - \eta)\tilde{\gamma}_2(t) + \eta\bar{\gamma}_2(t)\big)^2 + \alpha_7 \big((1 - \eta)\tilde{\gamma}_3(t) + \eta\bar{\gamma}_3(t)\big)^2\Big].$$

Finally,

$$(1-\eta)\Omega(t,\Psi,\tilde{\Gamma}) + \eta\Omega(t,\Psi,\bar{\Gamma}) - \Omega(t,\Psi,(1-\eta)\tilde{\Gamma}+\eta\bar{\Gamma})$$

$$= \alpha_5\eta(1-\eta)\Big(\tilde{\gamma}_1(t) - \bar{\gamma}_1(t)\Big)^2 + \alpha_6\eta(1-\eta)\Big(\tilde{\gamma}_2(t) - \bar{\gamma}_2(t)\Big)^2$$

$$+ \alpha_7\eta(1-\eta)\Big(\tilde{\gamma}_3(t) - \bar{\gamma}_3(t)\Big)^2 \geq 0.$$

$\square$

Theorem 4.2. *The optimal control minimization problem* (13) *has an optimal solution.*

Proof. In Lemma 4.1, we proved that the function $\Omega(t,\Psi,\tilde{\Gamma})$ is convex. Now, it is enough to show that this function is bounded from below. This is hold by following

$$\Omega(t,\Psi,\Gamma) = \alpha_1 T(t) + \alpha_2 F(t) - \alpha_3 I(t) - \alpha_4 N(t) + \alpha_5\gamma_1^2(t) + \alpha_6\gamma_2^2(t) + \alpha_7\gamma_3^2(t)$$

$$\geq \alpha_5\gamma_1^2(t) + \alpha_6\gamma_2^2(t) + \alpha_7\gamma_3^2(t)$$

$$\geq \tau\Big(\gamma_1^2(t) + \gamma_2^2(t) + \gamma_3^2(t)\Big),$$

in which $\tau = \min\{\alpha_5, \alpha_6, \alpha_7\}$. $\square$

Definition 4.3. The Hamiltonian function of the system (1) and equation (13) is as follows

$$\mathcal{H} = \alpha_1 T(t) + \alpha_2 F(t) - \alpha_3 I(t) - \alpha_4 N(t) + \alpha_5\gamma_1^2(t) + \alpha_6\gamma_2^2(t) + \alpha_7\gamma_3^2(t)$$

$$+ \lambda_1\Big(\frac{s}{1+pT} + \frac{CIT}{\alpha+T+\beta F} - d_1 I - e_1 IT + \gamma_1(t)\Big)$$

$$+ \lambda_2\Big(r_1 T(1-b_1 T) - e_2 IT - e_3 TN + e_5 TF - \gamma_2(t)T\Big)$$

$$+ \lambda_3\Big(r_2 N(1-b_2 N) - e_4 TN\Big)$$

$$+ \lambda_4\Big(r_3 F(1-b_3 F) - e_6 TF - \gamma_3(t)F\Big), \tag{16}$$

where $\lambda_1, \lambda_2, \lambda_3, \lambda_4$ are Lagrange multipliers.

Theorem 4.4. *Suppose that $\left(\gamma_1^*(t), \gamma_2^*(t), \gamma_3^*(t)\right) \in \Delta$ be an optimal control for* (13). *Then, the adjoint Lagrange multipliers $\lambda_1, \lambda_2, \lambda_3, \lambda_4$ satisfy the following equations*

$$\frac{d\lambda_1}{dt} = \alpha_3 - \lambda_1 \left(\frac{CT}{\alpha + T + \beta F} - d_1 - e_1 T\right) + \lambda_2 e_2 T,$$

$$\frac{d\lambda_2}{dt} = -\alpha_1 - \lambda_1 \left(-\frac{ps}{(1+pT)^2} + \frac{(\alpha + \beta F)CI}{(\alpha + T + \beta F)^2} - e_1 I\right) + \lambda_3 e_4 N + \lambda_4 e_6 F$$
$$- \lambda_2 \left(r_1 - 2r_1 b_1 T - e_2 I - e_3 N + e_5 F - \gamma_2(t)\right),$$

$$\frac{d\lambda_3}{dt} = \alpha_4 + \lambda_2 e_3 T - \lambda_3 \left(r_2 - 2r_2 b_2 N - e_4 T\right),$$

$$\frac{d\lambda_4}{dt} = -\alpha_2 + \frac{\lambda_1 \beta CIT}{(\alpha + T + \beta F)^2} - \lambda_2 e_5 T - \lambda_4 \left(r_3 - 2r_3 b_3 F - e_6 T + \gamma_3(t)\right).$$

Furthermore

$$\lambda_i(T_f) = 0, \qquad i = 1, 2, 3, 4.$$

The optimal values of control variables are

$$\gamma_1^*(t) = \min\left\{\max\left\{0, -\frac{\lambda_1}{2\alpha_5}\right\}, 1\right\},$$

$$\gamma_2^*(t) = \min\left\{\max\left\{0, \frac{\lambda_2 T}{2\alpha_6}\right\}, 1\right\},$$

$$\gamma_3^*(t) = \min\left\{\max\left\{0, \frac{\lambda_4 F}{2\alpha_7}\right\}, 1\right\}.$$

Proof.   From the Hamiltonian function (16) and Pontryagin's principle [26], we have

$$\frac{d\lambda_1}{dt} = -\frac{d\mathcal{H}}{dI} = \alpha_3 - \lambda_1\left(\frac{CT}{\alpha + T + \beta F} - d_1 - e_1 T\right) + \lambda_2 e_2 T,$$

$$\frac{d\lambda_2}{dt} = -\frac{d\mathcal{H}}{dT} = -\alpha_1 - \lambda_1\left(-\frac{ps}{(1+pT)^2} + \frac{(\alpha + \beta F)CI}{(\alpha + T + \beta F)^2} - e_1 I\right) + \lambda_3 e_4 N + \lambda_4 e_6 F$$
$$- \lambda_2\big(r_1 - 2r_1 b_1 T - e_2 I - e_3 N + e_5 F - \gamma_2(t)\big),$$

$$(17)$$

$$\frac{d\lambda_3}{dt} = -\frac{d\mathcal{H}}{dN} = \alpha_4 + \lambda_2 e_3 T - \lambda_3\big(r_2 - 2r_2 b_2 N - e_4 T\big),$$

$$\frac{d\lambda_4}{dt} = -\frac{d\mathcal{H}}{dF} = -\alpha_2 + \frac{\lambda_1 \beta CIT}{(\alpha + T + \beta F)^2} - \lambda_2 e_5 T - \lambda_4\big(r_3 - 2r_3 b_3 F - e_6 T + \gamma_3(t)\big).$$

To obtain the solution of the optimal control problem, we compute the derivative of the Hamiltonian function $\mathcal{H}$ respect to γ_1, γ_2 and γ_3. So,

$$\frac{\partial \mathcal{H}}{\partial \gamma_1} = 2\alpha_5 \gamma_1(t) + \lambda_1 = 0 \Longrightarrow \gamma_1(t) = -\frac{\lambda_1}{2\alpha_5},$$

$$\frac{\partial \mathcal{H}}{\partial \gamma_2} = 2\alpha_6 \gamma_2(t) - \lambda_2 T = 0 \Longrightarrow \gamma_2(t) = \frac{\lambda_2 T}{2\alpha_6},$$

$$\frac{\partial \mathcal{H}}{\partial \gamma_3} = 2\alpha_7 \gamma_3(t) - \lambda_4 F = 0 \Longrightarrow \gamma_3(t) = \frac{\lambda_4 F}{2\alpha_7}.$$

Now, we obtain from bounds of the control variables

$$\gamma_1^*(t) = \begin{cases} -\dfrac{\lambda_1}{2\alpha_5}, & 0 < -\dfrac{\lambda_1}{2\alpha_5} < 1, \\[2mm] 0, & -\dfrac{\lambda_1}{2\alpha_5} \le 0, \\[2mm] 1, & -\dfrac{\lambda_1}{2\alpha_5} \ge 1. \end{cases}$$

$$\gamma_2^*(t) = \begin{cases} \dfrac{\lambda_2 T}{2\alpha_6}, & 0 < \dfrac{\lambda_2 T}{2\alpha_6} < 1, \\[2mm] 0, & \dfrac{\lambda_2 T}{2\alpha_6} \le 0, \\[2mm] 1, & \dfrac{\lambda_2 T}{2\alpha_6} \ge 1. \end{cases}$$

$$\gamma_3^*(t) = \begin{cases} \dfrac{\lambda_4 F}{2\alpha_7}, & 0 < \dfrac{\lambda_4 F}{2\alpha_7} < 1, \\ 0, & \dfrac{\lambda_4 F}{2\alpha_7} \leq 0, \\ 1, & \dfrac{\lambda_4 F}{2\alpha_7} \geq 1. \end{cases}$$

In other words

$$\gamma_1^*(t) = \min\left\{ \max\left\{ 0, -\frac{\lambda_1}{2\alpha_5} \right\}, 1 \right\},$$

$$\gamma_2^*(t) = \min\left\{ \max\left\{ 0, \frac{\lambda_2 T}{2\alpha_6} \right\}, 1 \right\},$$

$$\gamma_3^*(t) = \min\left\{ \max\left\{ 0, \frac{\lambda_4 F}{2\alpha_7} \right\}, 1 \right\}.$$

The second order derivatives of the Hamiltonian function are as follows

$$\frac{\partial^2 \mathcal{H}}{\partial \gamma_1^2} = 2\alpha_5, \qquad \frac{\partial^2 \mathcal{H}}{\partial \gamma_2^2} = 2\alpha_6, \qquad \frac{\partial^2 \mathcal{H}}{\partial \gamma_3^2} = 2\alpha_7.$$

Since $\alpha_5, \alpha_6, \alpha_7 > 0$, then the optimal control problem is minimized at $\gamma_1^*(t)$, $\gamma_2^*(t)$ and $\gamma_3^*(t)$. $\square$

5   Numerical simulation

In this section, we present the numerical simulation of the obtained theoretical results. All numerical computations have been performed in MATLAB 2017a programming environment on a 2.3Hz Intel core i7 processor laptop and 4GB of RAM. All the parameters and the initial values of the cells population are taken from [14] as follows

s	p	C	α	β	d_1	e_1	r_1	b_1
0.125	0.2	0.75	0.3	0.8	0.2	1	1.5	1
e_2	e_3	e_5	r_2	b_2	e_4	r_3	b_3	e_6
0.1	1	0.1	1	1	1	0.1	1.5	0.1
I_0	T_0	N_0	F_0	T_f				
0	0.0001	1	0.8	150				

To investigate the stability of equilibrium points based on treatment parameters, we consider the following three cases.

Case (i): $\gamma_1 > 0$, $\gamma_2 = \gamma_3 = 0$

(1) $\gamma_1 = 0.25$, $\gamma_2 = \gamma_3 = 0$
In this case, there are 8 equilibrium points. E_0, E_1, E_2, E_3, E_4, E_5 and E_6 are unstable saddle points and E_7 is asymptotically stable point. The results are given in Table 1.

(2) $\gamma_1 = 0.5$, $\gamma_2 = \gamma_3 = 0$
In this case, there are 8 equilibrium points. E_0, E_1, E_2, E_3, E_4 and E_5 are unstable saddle points, E_6 is saddle point and E_7 is asymptotically stable inward spiral point. The results are presented in Table 2.

(3) $\gamma_1 = 0.75$, $\gamma_2 = \gamma_3 = 0$
In this case, there are 8 equilibrium points. E_0, E_1, E_2, E_3, E_4 and E_5 are unstable saddle points, E_6 is saddle point and E_7 is asymptotically stable inward spiral point. Table 3 shows the numerical results.

Table 1: The stability of equilibrium points for $\gamma_1 = 0.25$, $\gamma_2 = 0$ and $\gamma_3 = 0$.

Equilibrium	I	T	N	F	Eigenvalues	Stability
E_0	1.875	0	0	0	$-0.2, 1.3125, 1, 0.1$	unstable saddl
E_1	1.875	0	0	0.6667	$-0.2, -0.1, 1.3792, 1$	unstable saddl
E_2	1.875	0	1	0	$-0.2, -1, 0.3125, 0.1$	unstable saddl
E_3	0.60312	0.9598	0	0	$-0.5318, -1.4963, 0.0402, 0.0040$	unstable saddl
E_4	1.875	0	1	0.6667	$-0.2, -0.1, -1, 0.3792$	unstable saddl
E_5	0.5919	0.9622	0	0.0252	$-1.4992, -0.5434, -0.0041, 0.0378$	unstable saddl
E_6	0.7102	0.8579	0.1420	0	$-1.4369, -0.4592, -0.0351, 0.0142$	unstable saddl
E_7	0.6438	0.8864	0.1136	0.0757	$-1.4580, -0.5077, -0.0257, -0.0165$	asymptotically st

To investigate the behavior of immune cells, tumor cells, normal cells and fat cells, we solve (1) with ode45 in Matlab software. Figure 1 shows the time series plot of these cells for $\gamma_1 = 0.75$, $\gamma_2 = 0$ and $\gamma_3 = 0$.

Table 2: The stability of equilibrium points for $\gamma_1 = 0.5$, $\gamma_2 = 0$ and $\gamma_3 = 0$.

Equilibrium	I	T	N	F	Eigenvalues	Stability
E_0	3.125	0	0	0	$-0.2, 1.1875, 1, 0.1$	unstable saddle
E_1	3.125	0	0	0.6667	$-0.2, -0.1, 1.2542, 1$	unstable saddle
E_2	3.125	0	1	0	$-0.2, -1, 0.1875, 0.1$	unstable saddle
E_3	1.0786	0.9289	0	0	$-0.4674, -1.4860, 0.0719, 0.0072$	unstable saddle
E_4	3.125	0	1	0.6667	$-0.2, -0.1, -1, 0.2542$	unstable saddle
E_5	1.0404	0.93359	0	0.04427	$-1.4921, -0.4895, -0.0072, 0.0664$	unstable saddle
E_6	4.6864	0.06272	0.93728	0	$-0.08196 \pm 0.12885i, -1, 0.0937$	saddle
E_7	1.2343	0.7822	0.2178	0.1452	$-0.0318 \pm 0.0154i, -1.4015, -0.4404$	asymptotically stable

Table 3: The stability of equilibrium points for $\gamma_1 = 0.75$, $\gamma_2 = 0$ and $\gamma_3 = 0$.

Equilibrium	I	T	N	F	Eigenvalues	Stability
E_0	4.375	0	0	0	$-0.2, 1.0625, 1, 0.1$	unstable saddle
E_1	4.375	0	0	0.6667	$-0.2, -0.1, 1.1292, 1$	unstable saddle
E_2	4.375	0	1	0	$-0.2, -1, 0.0625, 0.1$	unstable saddle
E_3	1.6115	0.8926	0	0	$-0.4004, -1.4696, 0.1074, 0.0107$	unstable saddle
E_4	4.375	0	1	0.6667	$-0.2, -0.1, -1, 0.1292$	unstable saddle
E_5	1.5195	0.90301	0	0.06466	$-1.4806, -0.4361, -0.0107, 0.0969$	unstable saddle
E_6	4.9191	0.01618	0.9838	0	$-0.09298 \pm 0.0503i, 0.9999, 0.09838$	saddle
E_7	2.0946	0.63036	0.36964	0.24643	$-0.0312 \pm 0.033i, -1.3014, -0.3994$	asymptotically stable

Case (ii): $\gamma_1, \gamma_2 > 0$, $\gamma_3 = 0$

(1) $\gamma_1 = 0.25$, $\gamma_2 = 0.25$, $\gamma_3 = 0$
In this case, there are 8 equilibrium points. E_0, E_1, E_2, E_3, E_4, E_5 and E_6 are unstable saddle points, and E_7 is asymptotically stable inward spiral point. The results are given in Table 4.

(2) $\gamma_1 = 0.5$, $\gamma_2 = 0.25$, $\gamma_3 = 0$
In this case, there are 7 equilibrium points. E_0, E_1, E_2, E_3, E_4 and E_5 are unstable saddle points and E_7 is asymptotically stable point. The results are presented in Table 5.

(3) $\gamma_1 = 0.75$, $\gamma_2 = 0.5$, $\gamma_3 = 0$
In this case, there are 6 equilibrium points. E_0, E_1, E_2 and E_5 are unstable saddle points, E_3 is saddle point and E_4 is asymptotically stable point. Table 6 shows the numerical results.
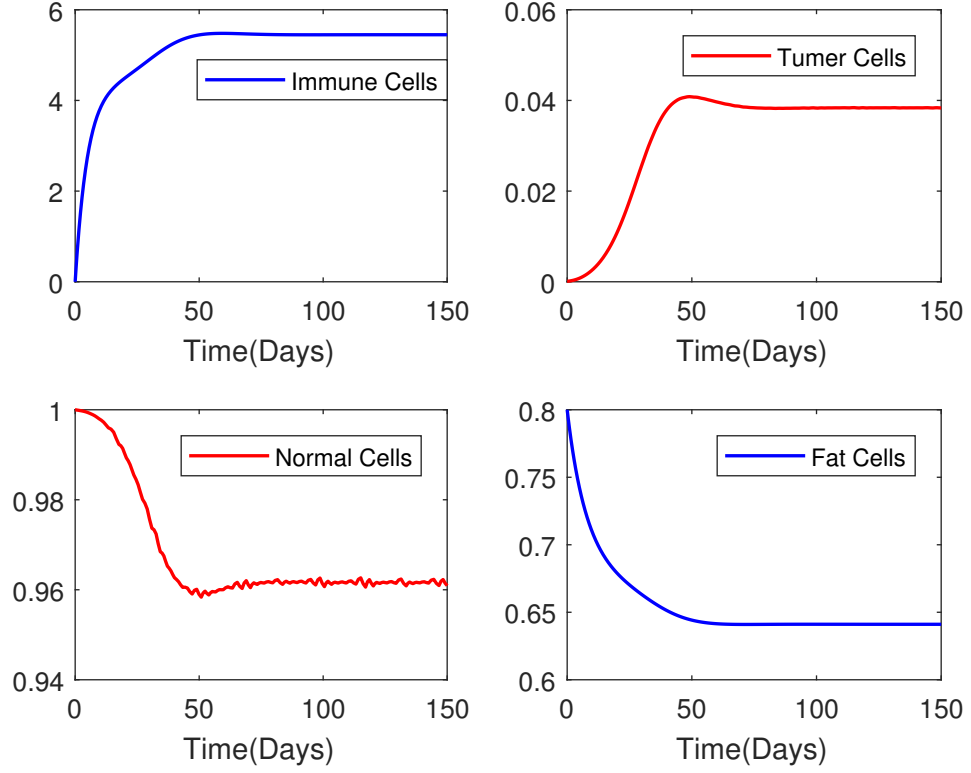
Figure 1: Time series plot of the immune cells, tumor cells, normal cells and fat cells for $\gamma_1 = 0.75$, $\gamma_2 = 0$ and $\gamma_3 = 0$.

The behavior of the immune cells, tumor cells, normal cells and fat cells is shown in Figure 2 for $\gamma_1 = 0.75$, $\gamma_2 = 0.5$ and $\gamma_3 = 0$.

Case (iii): $\gamma_1, \gamma_2, \gamma_3 > 0$

(1) $\gamma_1 = 0.25$, $\gamma_2 = 0.25$, $\gamma_3 = 0.25$

In this case, there are 4 equilibrium points. E_0, E_2 and E_3 are unstable saddle points and E_6 is asymptotically stable inward spiral point. The results are given in Table 7.

(2) $\gamma_1 = 0.5$, $\gamma_2 = 0.5$, $\gamma_3 = 0.25$

Table 4: The stability of equilibrium points for $\gamma_1 = 0.25$, $\gamma_2 = 0.25$ and $\gamma_3 = 0$.

Equilibrium	I	T	N	F	Eigenvalues	Stability
E_0	1.875	0	0	0	$-0.2, 1.0625, 1, 0.1$	unstable saddle
E_1	1.875	0	0	0.6667	$-0.2, -0.1, 1.1292, 1$	unstable saddle
E_2	1.875	0	1	0	$-0.2, -1, 0.0625, 0.1$	unstable saddle
E_3	0.8189	0.7783	0	0	$-0.3709, -1.2345, 0.2213, 0.0221$	unstable saddle
E_4	1.875	0	1	0.6667	$-0.2, -0.1, -1, 0.1292$	unstable saddle
E_5	0.7161	0.7947	0	0.1369	$-1.2529, -0.4373, -0.022, 0.2053$	unstable saddle
E_6	2.3407	0.0319	0.9682	0	$-0.08779 \pm 0.047i, -1, 0.0968$	saddle
E_7	1.3231	0.3253	0.6747	0.4498	$-0.0556 \pm 0.0386i, -1, -0.3267$	asymptotically stable

Table 5: The stability of equilibrium points for $\gamma_1 = 0.5$, $\gamma_2 = 0.25$ and $\gamma_3 = 0$.

Equilibrium	I	T	N	F	Eigenvalues	Stability
E_0	3.125	0	0	0	$-0.2, 0.9375, 1, 0.1$	unstable saddle
E_1	3.125	0	0	0.6667	$-0.2, -0.1, 1.0042, 1$	unstable saddle
E_2	3.125	0	1	0	$-0.2, -1, -0.0625, 0.1$	unstable saddle
E_3	1.5231	0.73179	0	0	$-0.2894, -1.2082, 0.2682, 0.0268$	unstable saddle
E_4	3.125	0	1	0.6667	$-0.2, -0.1, -1, 0.0042$	unstable saddle
E_5	1.268	0.7595	0	0.1603	$-1.2387, -0.3780, -0.0265, 0.2405$	unstable saddle
E_7	3.1062	0.0107	0.9893	0.6596	$-1, -0.2033, -0.004, -0.098$	asymptotically stable

Table 6: The stability of equilibrium points for $\gamma_1 = 0.75$, $\gamma_2 = 0.5$ and $\gamma_3 = 0$.

Equilibrium	I	T	N	F	Eigenvalues	Stability
E_0	4.375	0	0	0	$-0.2, 0.5625, 1, 0.1$	unstable saddle
E_1	4.375	0	0	0.6667	$-0.2, -0.1, 0.6292, 1$	unstable saddle
E_2	4.375	0	1	0	$-0.2, -1, -0.4375, 0.1$	unstable saddle
E_3	8.2303	0.1187	0	0	$-0.142 \pm 0.1616i, 0.8814, 0.0881$	saddle
E_4	4.375	0	1	0.6667	$-0.2, -0.1, -1, -0.3708$	asymptotically stable
E_5	2.3878	0.5284	0	0.3144	$-0.9364, -0.2064, -0.0585, 0.4716$	unstable saddle

In this case, there are 3 equilibrium points. E_0 and E_3 are unstable saddle points and E_2 is asymptotically stable point. The results are presented in Table 8.

Similar to the previous cases, the behavior of the immune cells, tumor cells, normal cells and fat cells is shown in Figure 3 for $\gamma_1 = 0.5$, $\gamma_2 = 0.5$ and $\gamma_3 = 0.25$.

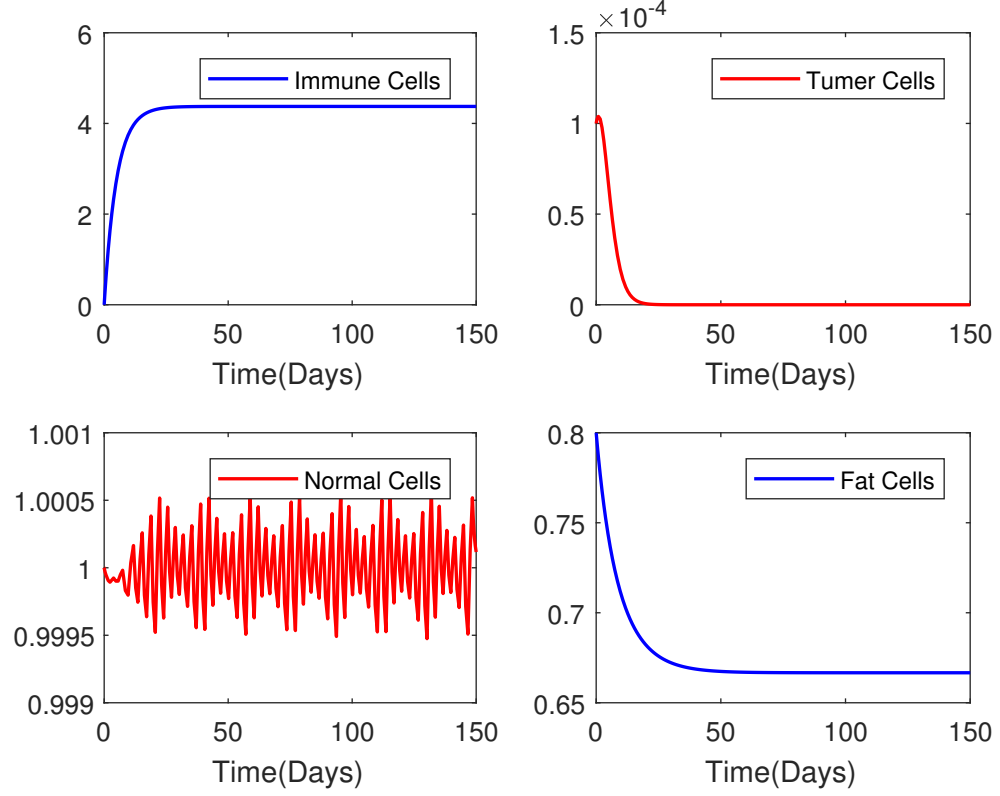**Case (iv):** $\gamma_1 = 0$, $\gamma_2, \gamma_3 > 0$

Figure 2: Time series plot of the immune cells, tumor cells, normal cells and fat cells for $\gamma_1 = 0.75$, $\gamma_2 = 0.5$ and $\gamma_3 = 0$.

Table 7: The stability of equilibrium points for $\gamma_1 = 0.25$, $\gamma_2 = 0.25$ and $\gamma_3 = 0.25$.

Equilibrium	I	T	N	F	Eigenvalues	Stability
E_0	1.875	0	0	0	$-0.2, 1.0625, 1, -0.15$	unstable saddle
E_2	1.875	0	1	0	$-0.2, -1, -0.0625, -0.15$	unstable saddle
E_3	0.8189	0.7783	0	0	$-0.3709, -1.2345, 0.2213, -0.2279$	unstable saddle
E_6	2.3407	0.03185	0.96815	0	$-0.08779 \pm 0.047i, -1, -0.1532$	asymptotically stable

(1) $\gamma_1 = 0$, $\gamma_2 = 0.25$, $\gamma_3 = 0.25$

Table 8: The stability of equilibrium points for $\gamma_1 = 0.5$, $\gamma_2 = 0.5$ and $\gamma_3 = 0.25$.

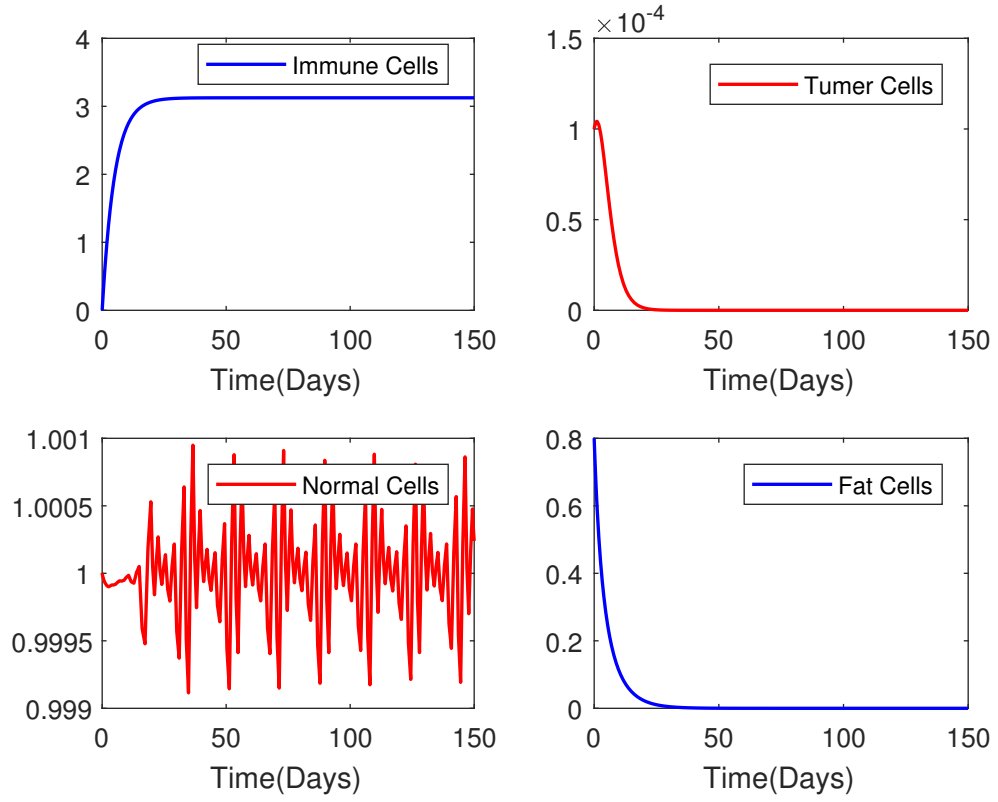| Equilibrium	I	T	N	F	Eigenvalues	Stability
E_0	3.125	0	0	0	$-0.2, 0.6875, 1, -0.15$	unstable saddle
E_2	3.125	0	1	0	$-0.2, -1, -0.3125, -0.15$	asymptotically stable
E_3	2.8239	0.4784	0	0	$-0.0822, -0.8528, 0.5216, -0.1978$	unstable saddle

Figure 3: Time series plot of the immune cells, tumor cells, normal cells and fat cells for $\gamma_1 = 0.5$, $\gamma_2 = 0.5$ and $\gamma_3 = 0.25$.

In this case, there are 4 equilibrium points. E_0, E_2 and E_3 are unstable saddle points and E_6 is asymptotically stable

inward spiral point. The results are given in Table 9.

(2) $\gamma_1 = 0$, $\gamma_2 = 0.5$, $\gamma_3 = 0.25$

In this case, there are 3 equilibrium points. E_0 and E_3 are unstable saddle points and E_2 is asymptotically stable point. The results are presented in Table 10.

(3) $\gamma_1 = 0$, $\gamma_2 = 0.75$, $\gamma_3 = 0.5$

In this case, there are 3 equilibrium points. E_0 and E_3 are unstable saddle points and E_2 is asymptotically stable point. Table 11 shows the numerical results.

Table 9: The stability of equilibrium points for $\gamma_1 = 0$, $\gamma_2 = 0.25$ and $\gamma_3 = 0.25$.

Equilibrium	I	T	N	F	Eigenvalues	Stability
E_0	0.625	0	0	0	$-0.2, 1.1875, 1, -0.15$	unstable saddle
E_2	0.625	0	1	0	$-0.2, -1, 0.1875, -0.15$	unstable saddle
E_3	0.2289	0.8181	0	0	$-0.4477, -1.2487, 0.1819, -0.2318$	unstable saddle
E_6	0.8618	0.3276	0.6724	0	$-0.0291, -0.2053, -1.0655, -0.1827$	asymptotically stable

Table 10: The stability of equilibrium points for $\gamma_1 = 0$, $\gamma_2 = 0.5$ and $\gamma_3 = 0.25$.

Equilibrium	I	T	N	F	Eigenvalues	Stability
E_0	0.625	0	0	0	$-0.2, 0.9375, 1, -0.15$	unstable saddle
E_2	0.625	0	1	0	$-0.2, -1, -0.0625, -0.15$	asymptotically stable
E_3	0.3328	0.6445	0	0	$-0.3065, -0.9929, 0.3555, -0.2144$	unstable saddle

Table 11: The stability of equilibrium points for $\gamma_1 = 0$, $\gamma_2 = 0.75$ and $\gamma_3 = 0.5$.

Equilibrium	I	T	N	F	Eigenvalues	Stability
E_0	0.625	0	0	0	$-0.2, 0.6875, 1, -0.4$	unstable saddle
E_2	0.625	0	1	0	$-0.2, -1, -0.3125, -0.4$	asymptotically stable
E_3	0.5497	0.4634	0	0	$-0.1761, -0.7270, 0.5366, -0.4463$	unstable saddle

In this case, the behavior of the immune cells, tumor cells, normal cells and fat cells is shown in Figure 4 for $\gamma_1 = 0$, $\gamma_2 = 0.75$ and
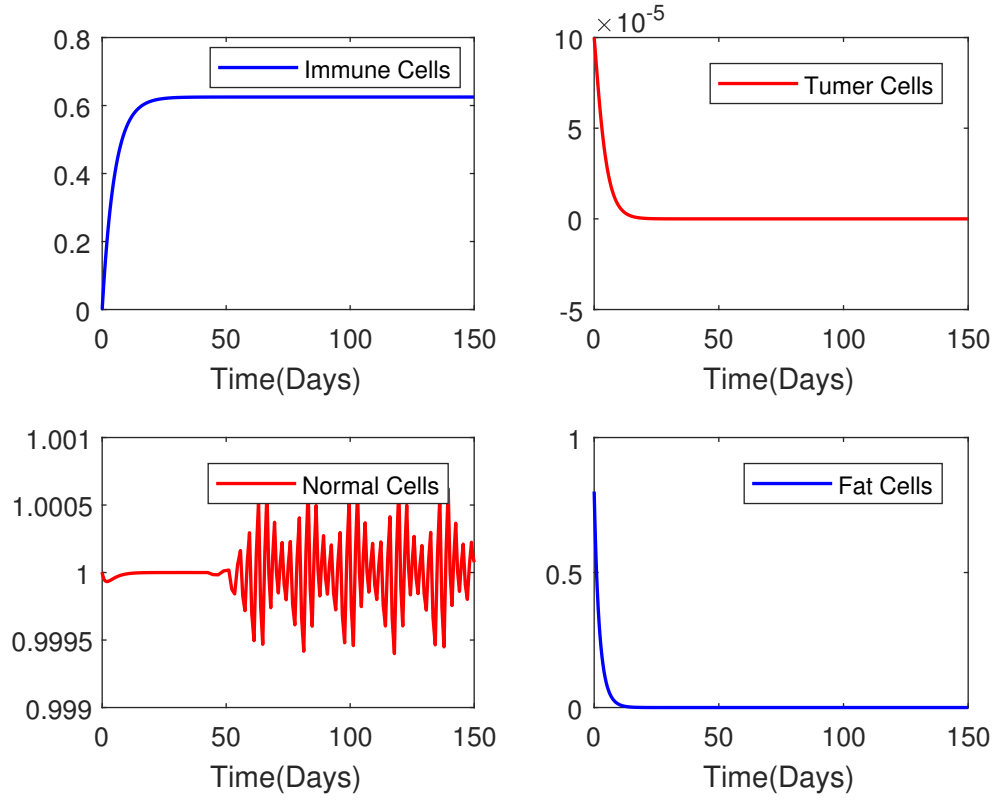
$\gamma_3 = 0.5.$

Figure 4: Time series plot of the immune cells, tumor cells, normal cells and fat cells for $\gamma_1 = 0$, $\gamma_2 = 0.75$ and $\gamma_3 = 0.5$.

Now, we use the following algorithm to solve the optimal control problem (13):

Step 1: Computing the optimal values $\gamma_1^*(t)$, $\gamma_2^*(t)$ and $\gamma_3^*(t)$

Step 2: Choose an initial guess for the control parameters γ_1^*, γ_2^* and γ_3^*.

Step 3: Solve (1) using ode45.

Step 4: Using the values obtained in the step 2, solve (17) using the backward method.

Step 5: Update the control parameters γ_1^*, γ_2^* and γ_3^* using Theorem [4.4].

The graphs of optimal control parameters are drawn in Figure [5] based on initial values $\alpha_1 = \alpha_2 = 200$, $\alpha_3 = \alpha_4 = \alpha_5 = 1$, $\alpha_6 = \alpha_7 = 100$, $\gamma_1^* = 0.75$, $\gamma_2^* = 0.00025$ and $\gamma_3^* = 0.75$.
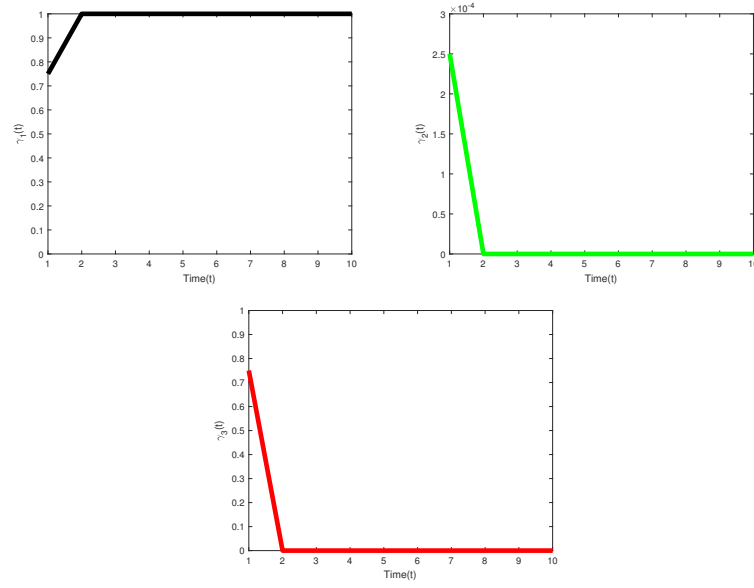

Figure 5: The optimal control graph for treatment parameters $\gamma_1^*(t)$, $\gamma_2^*(t)$ and $\gamma_3^*(t)$.

6   Conclusion

In this paper, we proposed a comprehensive model for treating stomach cancer in the context of obesity and psychological factors. We identified the equilibrium points of this model and assessed their local stability by analyzing the eigenvalues of the Jacobian matrix. Additionally, we derived the necessary and sufficient conditions for the global stability of the equilibrium point E_2.

To explore the optimal treatment strategies, we formulated and solved an optimal control problem, utilizing standard parameters for our numerical experiments. By varying the treatment parameters, we determined the stability types of the equilibrium points across eight different scenarios. In this work, optimal control was used to choose the optimal treatment for stomach cancer; this method can also be used to select the optimal treatment for other cancers. In future works, we will try to apply the effect of proper nutrition in the control of stomach cancer in a mathematical model and show its effectiveness with theoretical and numerical results.

7   Funding and Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript. No financial support was provided for this study

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Muhammad Faleh yoness Al-Aboud

Faculty of Mathematics, Statistics and Computer Science

Ph.D of Mathematics

University of Tabriz

Tabriz, Iran

E-mail: muhammedfaleh4444@gmail.com

Hossein Kheiri

Faculty of Mathematics, Statistics and Computer Science

Professor of Mathematics

University of Tabriz

Tabriz, Iran

E-mail: h-kheiri@tabrizu.ac.ir

Gholamreza Hojjati

Faculty of Mathematics, Statistics and Computer Science

Professor of Mathematics

University of Tabriz

Tabriz, Iran,

E-mail: ghojjati@yahoo.com

Shireen Jawad

Department of Mathematics

Associate Professor of Mathematics

University of Baghdad

Bghdad, Iraq

E-mail: shireenjawad82@gmail.com