THE ROLE OF OBESITY IN FRACTIONAL ORDER TUMOR-IMMUNE MODEL

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This work investigates the tumor-obesity model via a fractional operator to analyze the interactions between cancer and obesity, since fractional derivatives capture the long formation of cancerous tumor cells that might takes years to develop. It is known that fat cells enhance the development of cancerous tumor cells. To examine how the immune system is influenced due to fat cells, interactions of four types of cell population, namely tumor cells, immune cells, normal cells and fat cells are examined. We investigate the equilibrium points and discuss their stability analytically. Numerical simulations are carried out to verify the analytical results, demonstrating that a low fat diet results in a smaller tumor burden as compared to a high-caloric diet.

Keywords: Fractional-order tumor model, Caputo fractional derivative, Cancer, Obesity.

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1. Introduction

World Health Organization reported in 2014 that more than 1.9 billion adults who are 18 years old and older, were overweight. Half a million cancer deaths are reported every year and one in five is caused by obesity [8]. 2014 Cancer Progress Report of the American Association for Cancer Research (AACR) reveals that approximately 25% of the relative contribution to cancer has been obesity. Inactive life and poor diet result in a worse picture.

Adipose tissue enables the body to store energy as lipids, mostly triglycerides, for its future uses [2]. Subcutaneous and visceral tissues are two kinds of adipose tissue. Subcutaneous adipose tissues lie between muscle and skin. Visceral adipose tissues fill mainly the abdominal cavity. Abdominal visceral adipocytes release free fatty acids since they are more active when compared to abdominal subcutaneous adipocytes. In case of obesity, the adipocytes expand to abnormal volumes. Díaz et al. examines the interactions of chemokines, cytokines, macrophages and T-cells mathematically [9]. The effects of obesity on ovarian cancer are observed in the study [28]. Two epidemiological studies discussing the frequency of obesity in the region of Valencia is suggested in [18], [35]. In addition to the studies on obesity, some examples to mathematical models presenting tumor–immune interaction and cancer treatments can be mentioned. Firstly, we can mention the review on the dynamical models including some immune cells such as macrophages, cytotoxic T lymphocytes, natural killer cells, dendritic cells, regulatory T cells, and CD4+ T helper cells together with tumor cells [27]. In addition, anti-tumor reactivity is investigated and local/global bifurcations are analyzed [23]. A new mathematical interpretation to model lysis of a solid tumor is presented [26], whereas the reaction of the immune system is interpreted mathematically in case of multiple myeloma [15].

For mathematical investigation of cancer treatment, there are several nice works in the literature. For example, the role of immunity is discussed to fight with the cancer [36], whereas immunoediting is summarized in the review [20]. Adoptive cellular immunotherapy is applied to boost the immune system and to fight with tumor [21]. Contribution of BCG immunization is investigated for tumor–immune interaction [6]. Targeted chemotherapy is applied within-a-host model to eliminate tumor [25]. To determine drug response the comparison of the efficiency of a tumor

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model three dimensional (3D) spheres system with traditional 2D tumor spheres is demonstrated in [16]. Interactions between adaptive immune response and cancerous tumor cells are modeled and compared with the experimental data [33]. A dynamical model is proposed to test the success of chemotherapy, immunotherapy and vaccine therapy [11], while it has been extended by taking into account the reaction tie of the immune system [40]. A classifier has developed in [7] based on a convolutional neural network (CNN) simple architecture for tumor regression grading of rectal tumors after neoadjuvant chemoradiotherapy. As different from these studies, an optimal control problem has been constructed to set a chemotherapy strategy to cure minimize the number of tumor cells in the study [12]. To understand the effect of obesity on tumor population, Ku-Carrillo et al. proposes a mathematical model by extending the uncontrolled model in the study [12] so that the interaction between adipose cells and the immune system is investigated in [22].

In parallel to the classical integer models, the fractional models have attracted an increasing attention in mathematical biology over recent years. Fractional order models retain memory which is one of the main characteristics of fractional derivatives, while one of the features of immune response is to include memory. Recently, Pinto et al. [31] proposed a fractional order model incorporating latently infected cells, macrophages and CTLs for HIV infection. Bolton et al. [5] fits tumor growth data set by using fractional-order Gompertz model with an order of 0.68 much better than the classical integer-order Gompertz growth model. Karaman et al. [19] has shown that the fractional and continuous-time random-walk (CTRW) models lead to comparable results for low and high–grade pediatric brain tumors. A fractional order model of dengue fever outbreak is proposed in [14] showing that value of fractional order 0.77 is close to real data as compare to ordinary integer–order dengue model. A fractional order tumor model based on the connection between a growing immunogenic tumor and effector cells is investigated in [3]. In the study [38], a tumor–immune fractional order mathematical model incorporating three types of cells namely activated immune system cells, IL-2 (cytokine) and tumor cells is analyzed. Recently, cancer dormancy has been investigated in terms of a Caputo fractional derivative [37]. Moreover, two models with Caputo and conformable fractional derivative have been compared for tumor-immune interaction [4], whereas a fractional model consisting of helper CD4+ T, cytotoxic CD8+ T cells, cancer cells, dendritic cells and cytokine interleukin-2 (IL-2) cell are studied [39].

In this study, we examine the fractional order tumor-obesity model that consists of four types of cells: immune cells, cancer cells, normal cells and fat cells. The aim is to investigate the effect of fractional order derivative and parameters affecting the obesity. After stating the existence and uniqueness of the solution, we proceed with the proof of non-negative solutions. Then, we find the equilibrium points and discuss their stability theoretically. Then, we present some numerical results to observe the impact of immune response rate and low/high caloric diet in the system. The rest of the study is organized in the following way: In Sec. 2, some necessary definitions and formulation of the model are presented. Equilibrium points and stability conditions are obtained in Sec. 3. Then, we explain the discretization of the model in Sec. 4. Numerical simulations are presented in Sect. 5 to illustrate the applicability of theoretical predictions. The paper ends with the conclusion.

2. **Fractional tumor-obesity model**

We define left-sided fractional integral of order $q \in \mathbb{R}^+$ as follows [32, 17, 13]

$$I^q f(t) = \frac{1}{\Gamma(q)} \int_a^t (t-s)^{q-1} f(s) ds, \tag{1}$$

with $f : \mathbb{R}_+ \to \mathbb{R}$ provided that the expression on right hand side is well-defined where $t \in (a, b)$, $\Gamma(q)$ is the Euler Gamma function.

The Caputo fractional derivative $D^q f$ of order $0 < q < 1$ is given by

$$D^q f(t) = \frac{1}{\Gamma(1-q)} \int_a^t (t-s)^{-q} f'(s) ds, \tag{2}$$

provided that the expression on right hand side is well-defined.

In the study [22], the tumor-obesity model has been investigated containing the population immune cells $\mathcal{I}(t)$, tumor cells $\mathcal{T}(t)$, normal cells $\mathcal{N}(t)$ and fat cells $\mathcal{F}(t)$:

$$\begin{cases} \frac{d\mathcal{I}}{dt} = s + \frac{\rho\mathcal{I}\mathcal{T}}{\alpha+\mathcal{T}+\mu\mathcal{F}} - c_1\mathcal{I}\mathcal{T} - d\mathcal{I}, \\ \frac{d\mathcal{T}}{dt} = r_1\mathcal{T}(1-b_1\mathcal{T}) - c_2\mathcal{I}\mathcal{T} - c_3\mathcal{T}\mathcal{N} + c_5\mathcal{T}\mathcal{F}, \\ \frac{d\mathcal{N}}{dt} = r_2\mathcal{N}(1-b_2\mathcal{N}) - c_4\mathcal{T}\mathcal{N}, \\ \frac{d\mathcal{F}}{dt} = r_3\mathcal{F}(1-b_3\mathcal{F}) - c_6\mathcal{T}\mathcal{F}, \end{cases} \tag{3}$$

for $t \in (0, T]$. Here, the growth term for immune cells is represented by the following nonlinear function:

$$\frac{\rho\mathcal{I}\mathcal{T}}{\alpha+\mathcal{T}+\mu\mathcal{F}},$$

where ρ is immune response rate and α is immune threshold rate. Tumor cells and normal cells follow a logistic growth function $r_1\mathcal{T}(1-b_1\mathcal{T})$ and $r_2\mathcal{N}(1-b_2\mathcal{N})$, respectively, where r_1 and r_2 represent the growth rates of tumor cells and normal cells, respectively. Depending on the type/stage of the disease, r_1 may be bigger or smaller than r_2. We set $r_1 > r_2$, i.e., normal cells grow more slowly then tumor cells. Moreover, b_1 and b_2 represent the inverse carrying capacities of the tumor cells and normal cells, respectively with $b_1^{-1} \leq b_2^{-1} = 1$. On the other hand, as a consequence of the interaction of immune cells and tumor cells, there are two options: Tumor cells diminish or they cause inactive immune cell population presented using the following terms:

$$-c_1\mathcal{I}\mathcal{T} \quad \text{and} \quad -c_2\mathcal{I}\mathcal{T}.$$

Furthermore, there are two terms $-c_3\mathcal{T}\mathcal{N}$ and $-c_4\mathcal{T}\mathcal{N}$ representing the competition between tumor cells and normal cells, respectively. Here, we assume that $0 < c_3 < c_2$. This simply indicates that the immune system damages the tumor cell population more than the competition between tumor cells and normal cells.

The fractional order system possesses memory kernel which may be crucial for modeling of biological processes, as previous progression of the process can be model by fractional differential equations. Therefore fractional order models are appropriate to model the biological phenomena that cannot be described with integer order models as integer-order models are a special case of their fractional order counterparts. Cancer patients have diverse type of dispositions in the period of tumor progression that can be described better using fractional model as fractional order q can be adjusted to best fit the real data according to disease conditions of different patients. Therefore, in this study, we considered the following fractional order tumor-obesity model:

$$\left\{ \begin{array}{l} D^q\mathcal{I} = s^q + \frac{\rho^q\mathcal{I}\mathcal{T}}{\alpha^q+\mathcal{T}+\mu\mathcal{F}} - c_1^q\mathcal{I}\mathcal{T} - d^q\mathcal{I}, \\ D^q\mathcal{T} = r_1^q\mathcal{T}(1-b_1\mathcal{T}) - c_2^q\mathcal{I}\mathcal{T} - c_3^q\mathcal{T}\mathcal{N} + c_5^q\mathcal{T}\mathcal{F}, \\ D^q\mathcal{N} = r_2^q\mathcal{N}(1-b_2\mathcal{N}) - c_4^q\mathcal{T}\mathcal{N}, \\ D^q\mathcal{F} = r_3^q\mathcal{F}(1-b_3\mathcal{F}) - c_6^q\mathcal{T}\mathcal{F}, \end{array} \right\}, \tag{4}$$

$t \in (0, T]$, where description, units and values of the parameters are given in Table 1. Notice that the units of the model that is generalized by the fractional differential equations are different than the units of the classical integer-order model in the sense that these are expressed with respect to an intrinsic time variable depending on the fractional order q instead of the physical time. Therefore, a modified parameter depending on the fractional dimension has been used in the generalized model (4) to interpret the meaning of fractional order. When $q \to 1$ the generalized fractional tumor model in Eq. (4) reduces to the classical one given in Eq. (3).

The fractional order tumor model (4) can be written in the following form:

$$D^qU(t) = F(U(t)), \quad t \in (0, T], \; U(0) = U_0, \tag{5}$$

where

$$U = \begin{bmatrix} \mathcal{I} \\ \mathcal{T} \\ \mathcal{N} \\ \mathcal{F} \end{bmatrix}, \quad U_0 = \begin{bmatrix} \mathcal{I}_0 \\ \mathcal{T}_0 \\ \mathcal{N}_0 \\ \mathcal{F}_0 \end{bmatrix}, \quad F(U) = \begin{bmatrix} s^q + \frac{\rho^q\mathcal{I}\mathcal{T}}{\alpha^q+\mathcal{T}+\mu\mathcal{F}} - c_1^q\mathcal{I}\mathcal{T} - d^q\mathcal{I} \\ r_1^q\mathcal{T}(1-b_1\mathcal{T}) - c_2^q\mathcal{I}\mathcal{T} - c_3^q\mathcal{T}\mathcal{N} + c_5^q\mathcal{T}\mathcal{F} \\ r_2^q\mathcal{N}(1-b_2\mathcal{N}) - c_4^q\mathcal{T}\mathcal{N} \\ r_3^q\mathcal{F}(1-b_3\mathcal{F}) - c_6^q\mathcal{T}\mathcal{F} \end{bmatrix}.$$

We define the supremum norm as

$$\|F\| = \sup_{t\in(0,T]} |F(t)|,$$

TABLE 1. Parameter values for the model

Parameters	Description	Values (Units)	References
s	Immune source rate	0.125 (day^{-1}cells)	Estimated
ρ	Immune response rate	0.1 (day^{-1})	Estimated
α	Immune response initiated by tumor	0.3 (cells^{2})	[10]
b_1	Inverse of the carrying capacity of the tumor cells	1 (cells^{-1})	[10]
b_2	Inverse of the carrying capacity of the normal cells	1 (cells^{-1})	[10]
b_3	Inverse of the carrying capacity of the fat cells	0.5 (cells^{-1})	[22]
r_1	Growth rate of tumor cells	1.5 (day^{-1})	[10]
r_2	Growth rate of normal cells	0.9 (day^{-1})	Estimated
r_3	Growth rate of fat cells	0.1 (day^{-1})	[22]
c_1	Coefficient of the competition term	0.4 ($\text{day}^{-1}\text{cells}^{-1}$)	Estimated
c_2	Coefficient of the competition term	0.2 ($\text{day}^{-1}\text{cells}^{-1}$)	Estimated
c_3	Coefficient of the competition term	1 ($\text{day}^{-1}\text{cells}^{-1}$)	[10]
c_4	Coefficient of the competition term	0.8($\text{day}^{-1}\text{cells}^{-1}$)	Estimated
c_5	Coefficient of the competition term	0.1($\text{day}^{-1}\text{cells}^{-1}$)	[22]
c_6	Coefficient of the competition term	0.05($\text{day}^{-1}\text{cells}^{-1}$)	[22]
μ	Immune response initiated by tumor	0.8 (day^{-1})	Estimated
d	Death rate of immune cells	0.2 (day^{-1})	[10]

and the norm of the matrix $M = [m_{ij}(t)]$ as

$$\|M\| = \Sigma_{i,j} \sup_{t\in(0,T]} |m_{ij}(t)|.$$

Theorem 2.1. *The system (5) together with the initial condition $U(0) = U_0$ has a unique solution in the region $\Delta \times (0,T]$ if*

$$A^q \max\left\{\left(d^q + c_1^q\eta + \frac{2\rho^q\eta}{\alpha^q} e^{\frac{1}{1-(\frac{1}{\alpha^q}+\frac{\mu}{\alpha^q})\eta}}\right), (r_1^q + 2r_1^q b_1\eta + c_2^q\eta + c_3^q\eta + c_5^q\eta), (r_2^q + 2r_2^q b_2\eta + c_4^q\eta), (r_3^q + 2r_3^q b_3\eta + c_6^q\eta)\right\} < 1, \tag{6}$$

where $t \in (0,T]$, $A^q = \frac{T^q}{\Gamma(q+1)}$, and

$$\Delta = \{(\mathcal{I}, \mathcal{T}, \mathcal{N}, \mathcal{F}) : \max(|\mathcal{I}|, |\mathcal{T}|, |\mathcal{N}|, |\mathcal{F}|)\} \leq \eta.$$

Proof. The solution of system (5) has following form:

$$U(t) = U_0 + \frac{1}{\Gamma(q)}\int_0^t (t-s)^{q-1}F(U(s))ds = \Phi(U).$$

This gives the equality

$$\Phi(U_1) - \Phi(U_2) = \frac{1}{\Gamma(q)}\int_0^t (t-s)^{q-1}(F(U_1(s)) - F(U_2(s)))ds.$$

Hence, we have

$$\begin{aligned}\|\Phi(U_1) - \Phi(U_2)\| &= \frac{1}{\Gamma(q)}\left\|\int_0^t (t-s)^{q-1}(F(U_1(s)) - F(U_2(s)))ds\right\| \\ &\leq \frac{1}{\Gamma(q)}\int_0^t (t-s)^{q-1}\|(F(U_1(s)) - F(U_2(s)))\|ds \\ &\leq L\|U_1 - U_2\|,\end{aligned}$$

where

$$L = A^q \max\left\{\left(d^q + c_1^q\eta + \frac{2\rho^q\eta}{\alpha^q} e^{\frac{1}{1-(\frac{1}{\alpha^q}+\frac{\mu}{\alpha^q})\eta}}\right), (r_1^q + (2r_1^q b_1 + c_2^q + c_3^q + c_5^q)\eta), (r_2^q + (2r_2^q b_2 + c_4^q)\eta), (r_3^q + (2r_3^q b_3 + c_6^q)\eta)\right\}. \tag{7}$$

Thus, if $L < 1$, then the mapping $\Phi(U)$ is a contraction mapping and this yields that system (4) has a unique solution in the region $\Delta \times (0,T]$. □

Theorem 2.2. *The solution of the FDE (4) remains in $\mathbb{R}^4_+$.*

Proof. We observe that

$$D^q \mathcal{I}|_{I=0} = s^q, \quad D^q \mathcal{T}|_{T=0} = 0, \quad D^q \mathcal{N}|_{N=0} = 0, \quad D^q \mathcal{F}|_{F=0} = 0,$$

on each hyperplane bounding the non-negative orthant, the vector field points into $\mathbb{R}^4_+$. The solution will remain in $\mathbb{R}^4_+$ [30]. □

3. **Stability analysis generalized tumor-Obesity model**

We will investigate the conditions under which equilibrium points of the fractional order tumor-obesity model(4) exist and derive the analytical conditions for the stability of the equilibrium points.

3.1. **Equilibrium points**

There are three types of equilibrium points of the system (4) such as *Tumor Free Equilibrium*, *Dead Equilibrium* and *Coexisting Equilibrium*. To find them, we solve the following system for $\mathcal{I}(t), \mathcal{T}(t), \mathcal{N}(t), \mathcal{F}(t)$:

$$D^q \mathcal{I}(t) = 0,\ D^q \mathcal{T}(t) = 0,\ D^q \mathcal{N}(t) = 0,\ D^q \mathcal{F}(t) = 0.$$

- Tumor Free Equilibrium $E_0^q = (s^q/d^q, 0, 1, 1/b_3)$: The tumor cells are zero, but the normal cells survive.
- Dead Equilibrium:
  - Type 1 $E_1^q = (s^q/d^q, 0, 0, 1/b_3)$: Both tumor cells and normal cells die off.
  - Type 2 $E_2^q = (f(Z), Z, 0, h(Z))$: Only normal cells diminished and the tumor cells remain, where Z is a non-negative solution to the equation

$$Z + \frac{c_2^q}{r_1^q b_1^q} f(Z) - \frac{c_5^q}{r_1^q b_1^q} h(Z) = \frac{1}{b_1^q}, \tag{8}$$

with

$$f(Z) = \frac{s^q(\alpha^q + Z + \mu h(Z))}{(c_1^q Z + d^q)(\alpha^q + Z + \mu h(Z)) - \rho^q Z}, \tag{9}$$

and

$$h(Z) = \frac{1}{b_3} - \frac{c_6^q}{r_3^q b_3} Z. \tag{10}$$

Equation (8) yields a third order polynomial for Z as

$$B_1 Z^3 + B_2 Z^2 + B_3 Z + B_4 = 0, \tag{11}$$

where

$$\begin{aligned}
B_1 &= \left(c_1^q - \frac{\mu c_1^q c_6^q}{r_3^q b_3}\right)\left(1 + \frac{c_5^q c_6^q}{r_1^q b_1 r_3^q b_3}\right),\\
B_2 &= \left(1 + \frac{c_5^q c_6^q}{r_1^q b_1 r_3^q b_3}\right)\left(\alpha^q c_1^q + d^q - \rho^q + \frac{c_1^q \mu}{b_3} - \frac{d^q \mu c_6^q}{r_3^q b_3}\right) - \left(\frac{c_5^q}{r_1^q b_1 b_3} + \frac{1}{b_1}\right)\left(c_1^q - \frac{\mu c_1^q c_6^q}{r_3^q b_3}\right),\\
B_3 &= \frac{c_2^q}{r_1^q b_1}\left(s^q - \frac{s^q \mu c_6^q}{r_3^q b_3}\right) + \left(d^q \alpha^q + \frac{d^q \mu}{b_3}\right)\left(1 + \frac{c_5^q c_6^q}{r_1^q b_1 r_3^q b_3}\right)\\
&\quad - \left(\frac{c_5^q}{r_1^q b_1 b_3} + \frac{1}{b_1}\right)\left(\alpha^q c_1^q + d^q - \rho^q + \frac{c_1^q \mu}{b_3} - \frac{d^q \mu c_6^q}{r_3^q b_3}\right),\\
B_4 &= \frac{c_2^q}{r_1^q b_1}\left(s^q \alpha^q + \frac{s^q \mu}{b_3}\right) - \left(\frac{c_5^q}{r_1^q b_1 b_3} + \frac{1}{b_1}\right)\left(d^q \alpha^q + \frac{d^q \mu}{b_3}\right).
\end{aligned}$$

We define the discriminant of the polynomial in the Eq. (11) as

$$D(B) = 18 B_1 B_2 B_3 B_4 + B_2^2 B_3^2 - 4 B_4 B_2^3 - 4 B_3^3 B_1 - 27 B_4^2 B_1^2. \tag{12}$$

We note that if $D(B) > 0$, then all roots are real; if $D(B) < 0$, then one of the roots is real [34].

- Coexisting Equilibrium $E_3^q = (f(Z), Z, g(Z), h(Z)$: Both normal and tumor cells coexist, where Z is a non-negative solution of the equation

$$Z + \frac{c_2^q}{r_1^q b_1^q} f(Z) + \frac{c_3^q}{r_1^q b_1} g(Z) - \frac{c_5^q}{r_1^q b_1^q} h(Z) = \frac{1}{b_1^q}, \tag{13}$$

with

$$g(Z) = 1 - \frac{c_4^q}{r_2^q} Z. \tag{14}$$

The following third order polynomial for values of Z is derived from the Eq. (13):

$$C_1 Z^3 + C_2 Z^2 + C_3 Z + C_4 = 0, \tag{15}$$

where

$$\begin{aligned}
C_1 &= \left(c_1^q - \frac{\mu c_1^q c_6^q}{r_3^q b_3}\right)\left(r_2^q - \frac{c_3^q c_4^q}{r_1^q b_1} + \frac{r_2^q c_5^q c_6^q}{r_1^q b_1 r_3^q b_3}\right),\\
C_2 &= \left(c_1^q - \frac{\mu c_1^q c_6^q}{r_3^q b_3}\right)\left(\frac{r_2^q c_3^q}{r_1^q b_1} - \frac{r_2^q c_5^q}{r_1^q b_1 b_3} - \frac{r_2^q}{b_1}\right) + \left(r_2^q - \frac{c_3^q c_4^q}{r_1^q b_1} + \frac{r_2^q c_5^q c_6^q}{r_1^q b_1 r_3^q b_3}\right)\left(\alpha c_1^q + d^q - \rho^q + \frac{c_1^q \mu}{b_3} - \frac{d^q \mu c_6^q}{r_3^q b_3}\right),\\
C_3 &= \left(\frac{r_2^q c_3^q}{r_1^q b_1} - \frac{r_2^q c_5^q}{r_1^q b_1 b_3} - \frac{r_2^q}{b_1}\right)\left(\alpha c_1^q + d^q - \rho^q + \frac{c_1^q \mu}{b_3} - \frac{d^q \mu c_6^q}{r_3^q b_3}\right)\\
&\quad + \left(r_2^q - \frac{c_3^q c_4^q}{r_1^q b_1} + \frac{r_2^q c_5^q c_6^q}{r_1^q b_1 r_3^q b_3}\right)\left(d^q \alpha^q + \frac{d^q \mu}{b_3}\right) + \frac{c_2^q r_2^q}{r_1^q b_1}\left(s^q - \frac{s^q \mu c_6^q}{r_3^q b_3}\right),\\
C_4 &= \frac{c_2^q r_2^q}{r_1^q b_1}\left(s^q \alpha^q + \frac{s^q \mu}{b_3}\right) + \left(\frac{r_2^q c_3^q}{r_1^q b_1} - \frac{r_2^q c_5^q}{r_1^q b_1 b_3} - \frac{r_2^q}{b_1}\right)\left(d^q \alpha^q + \frac{d^q \mu}{b_3}\right).
\end{aligned}$$

3.2. Stability analysis

The Jacobian matrix of the system (4) evaluated at the equilibrium point $(\mathcal{I}^*, \mathcal{T}^*, \mathcal{N}^*, \mathcal{F}^*)$ is given by

$$J(\mathcal{I}^*, \mathcal{T}^*, \mathcal{N}^*, \mathcal{F}^*) = \begin{bmatrix} \omega_1 & \omega_2 & 0 & \omega_3 \\ -\omega_4 & \omega_5 & -\omega_6 & \omega_7 \\ 0 & -\omega_8 & \omega_9 & 0 \\ 0 & -\omega_{10} & 0 & \omega_{11} \end{bmatrix}, \tag{16}$$

where

$$\begin{aligned}
&\omega_1 = \frac{\rho^q \mathcal{T}^*}{\alpha^q + \mathcal{T}^* + \mu\mathcal{F}^*} - c_1^q \mathcal{T}^* - d^q, \quad \omega_2 = \frac{\rho^q \mathcal{I}^*(\alpha^q + \mu\mathcal{F}^*)}{(\alpha^q + \mathcal{T}^* + \mu\mathcal{F}^*)^2} - c_1^q \mathcal{I}^*, \quad \omega_3 = -\frac{\rho^q \mathcal{I}^* \mathcal{T}^*}{(\alpha^q + \mathcal{T}^* + \mu\mathcal{F}^*)^2},\\
&\omega_4 = c_2^q \mathcal{T}^*, \quad \omega_5 = r_1^q - 2r_1^q b_1 \mathcal{T}^* - c_2^q \mathcal{I}^* - c_3^q \mathcal{N}^* + c_5^q \mathcal{F}^*, \quad \omega_6 = c_3^q \mathcal{T}^*, \quad \omega_7 = c_5^q \mathcal{T}^*,\\
&\omega_8 = c_4^q \mathcal{N}^*, \quad \omega_9 = r_2^q - 2r_2^q b_2 \mathcal{N}^* - c_4^q \mathcal{T}^*,\\
&\omega_{10} = c_6^q \mathcal{F}^*, \quad \omega_{11} = r_3^q - 2r_3^q b_3 \mathcal{F}^* - c_6^q \mathcal{T}^*.
\end{aligned}$$

Using Matignon's results [29]

$$|arg(\lambda_i)| > \frac{q\pi}{2}, \quad (i = 1, 2, 3, 4), \tag{17}$$

where λ_1, λ_2, λ_3, λ_4 are the eigenvalues of the Jacobian matrix evaluated at the equilibrium points, we can discuss the local stability of the equilibrium points of the model (4).

Theorem 3.1. *The tumor free equilibrium point $E_0^q = (s^q/d^q, 0, 1, 1/b_3)$ of the system (4) is locally asymptotically stable if*

$$r_1^q + \frac{c_5^q}{b_3} < c_3^q + \frac{c_2^q s^q}{d^q}.$$

Proof. The Jacobian matrix at the tumor free equilibrium point E_0^q is given by

$$J(E_0^q) = \begin{bmatrix} \omega_1 & \omega_2 & 0 & 0 \\ 0 & \omega_5 & 0 & 0 \\ 0 & -\omega_8 & \omega_9 & 0 \\ 0 & -\omega_{10} & 0 & \omega_{11} \end{bmatrix}.$$

The eigenvalues of the Jacobian are

$$\begin{aligned}
\lambda_1 &= \omega_1 = -d^q < 0,\\
\lambda_2 &= \omega_5 = r_1^q - c_2^q \mathcal{I}^* - c_3^q \mathcal{N}^* + c_5^q \mathcal{F}^* = r_1^q - c_2^q \frac{s^q}{d^q} - c_3^q + \frac{c_5^q}{b_3^q},\\
\lambda_3 &= \omega_9 = r_2^q - 2r_2^q b_2 \mathcal{N}^* = -r_2^q < 0,\\
\lambda_4 &= \omega_{11} = r_3^q - 2r_3^q b_3 \mathcal{F}^* = -r_3^q < 0.
\end{aligned}$$

Tumor free equilibrium point E_0^q is locally asymptotically stable if $\lambda_2 < 0$ holds. Then, we reach the desired inequality. $\square$

Theorem 3.2. *The dead equilibrium of Type 1 $E_1^q = (s^q/d^q, 0, 0, 1/b_3)$ of the system (4) is a saddle point.*

Proof. The Jacobian matrix at the equilibrium point E_1^q is given by

$$J(E_1^q) = \begin{bmatrix} \omega_1 & \omega_2 & 0 & 0 \\ 0 & \omega_5 & 0 & 0 \\ 0 & 0 & \omega_9 & 0 \\ 0 & -\omega_{10} & 0 & \omega_{11} \end{bmatrix}.$$

The eigenvalues of the Jacobian are

$$\begin{aligned} \lambda_1 &= \omega_1 = -d^q, \\ \lambda_2 &= \omega_5 = r_1^q - c_2^q \mathcal{I}^* + c_5^q \mathcal{F}^* = r_1^q - \frac{c_2^q s^q}{d^q} + \frac{c_5^q}{b_3}, \\ \lambda_3 &= \omega_9 = r_2^q, \\ \lambda_4 &= \omega_{11} = r_3^q - 2r_3^q b_3 \mathcal{F}^* = -r_3^q. \end{aligned}$$

We observe that $\lambda_1 < 0$, $\lambda_4 < 0$ are automatically satisfied, while $\lambda_2 < 0$ if $r_1^q + \frac{c_5^q}{b_3} < \frac{c_2^q s^q}{d^q}$. However, $\lambda_3 = r_2^q > 0$. It follows that the equilibrium point E_1^q is a saddle point. $\square$

Theorem 3.3. *The dead equilibrium of Type 2 $E_2^q = (\mathcal{I}^*, \mathcal{T}^*, 0, \mathcal{F}^*)$ is locally asymptotically stable if the coefficients of the characteristic polynomial of the Jacobian in (16) evaluated at E_2^q satisfy*

$$A_1 > 0,\ A_3 > 0,\ A_4 > 0 \ \text{and}\ \eta = A_1 A_2 A_3 - (A_3^2 + A_1^2 A_4) > 0, \tag{18}$$

for all $q \in (0, 1)$, where

$$\begin{aligned} A_1 &= -(\omega_{11} + \omega_5 + \omega_9 + \omega_1), \\ A_2 &= (\omega_1\omega_{11} + \omega_1\omega_5 + \omega_2\omega_4 + \omega_{11}\omega_5 + \omega_{10}\omega_7 + \omega_1\omega_9 + \omega_{11}\omega_9 + \omega_5\omega_9), \\ A_3 &= (-\omega_1\omega_{11}\omega_5 - \omega_{11}\omega_2\omega_4 - \omega_{10}\omega_3\omega_4 - \omega_1\omega_{10}\omega_7 - \omega_1\omega_{11}\omega_9 \\ &\quad - \omega_1\omega_5\omega_9 - \omega_2\omega_4\omega_9 - \omega_{11}\omega_5\omega_9 - \omega_{10}\omega_7\omega_9), \\ A_4 &= \omega_1\omega_{11}\omega_5\omega_9 + \omega_{11}\omega_2\omega_4\omega_9 + \omega_{10}\omega_3\omega_4\omega_9 + \omega_1\omega_{10}\omega_7\omega_9. \end{aligned}$$

Proof. Eigenvalues of the Jacobian in (16) evaluated at E_2^q are found through the following characteristic equation:

$$P_{E_2}(\lambda) = \lambda^4 + A_1\lambda^3 + A_2\lambda^2 + A_3\lambda + A_4 = 0.$$

By the Routh–Hurwitz criteria [1], we obtain the required conditions.

$\square$

Theorem 3.4. *The coexisting equilibrium point $E_3^q = (\mathcal{I}^*, \mathcal{T}^*, \mathcal{N}^*, \mathcal{F}^*)$ is locally asymptotically stable if the coefficients of the characteristic polynomial of the Jacobian in (16) evaluated at E_3^q satisfy*

$$A_1 > 0,\ A_3 > 0,\ A_4 > 0 \ \text{and}\ \eta = A_1 A_2 A_3 - (A_3^2 + A_1^2 A_4) > 0, \tag{19}$$

for all $q \in (0, 1)$, where

$$\begin{aligned} A_1 &= -(\omega_{11} + \omega_5 + \omega_9 + \omega_1), \\ A_2 &= (\omega_1\omega_{11} + \omega_1\omega_5 + \omega_2\omega_4 + \omega_{11}\omega_5 + \omega_{10}\omega_7 + \omega_1\omega_9 + \omega_{11}\omega_9 + \omega_5\omega_9 - \omega_6\omega_8), \\ A_3 &= (-\omega_1\omega_{11}\omega_5 - \omega_{11}\omega_2\omega_4 - \omega_{10}\omega_3\omega_4 - \omega_1\omega_{10}\omega_7 - \omega_1\omega_{11}\omega_9 - \omega_1\omega_5\omega_9 + \omega_1\omega_6\omega_8 \\ &\quad - \omega_2\omega_4\omega_9 - \omega_{11}\omega_5\omega_9 + \omega_{11}\omega_6\omega_8 - \omega_{10}\omega_7\omega_9), \\ A_4 &= \omega_1\omega_{11}\omega_5\omega_9 - \omega_1\omega_{11}\omega_6\omega_8 + \omega_{11}\omega_2\omega_4\omega_9 + \omega_{10}\omega_3\omega_4\omega_9 + \omega_1\omega_{10}\omega_7\omega_9. \end{aligned}$$

Proof. The characteristic equation of the Jacobian in (16) evaluated at E_3^q is given by

$$P_{E_3}(\lambda) = \lambda^4 + A_1\lambda^3 + A_2\lambda^2 + A_3\lambda + A_4 = 0. \tag{20}$$

By the Routh-–Hurwitz criteria [1], we derive the required condition. $\square$

Before discretization of the model (4), we discuss the numerical stability for different values of b_3 and ρ.

Effect of varying carrying capacity of fat cells b_3

We are interested in the intersection of the following immune-nullcline (N_I) and tumor-nullcline (N_T) to examine the impact of low fat diet on tumor cell population at co-existing equilibrium:

$$N_I := \{(I,T) : I = \frac{s^q(\alpha^q + T + \mu h(T))}{(c_1^q T + d^q)(\alpha^q + T + \mu h(T)) - \rho^q T} = f(T)\},$$

$$N_T := \{(I,T) : I = \frac{1}{c_2^q}(r_1(1 - b_1 T) - c_3^q g(T) + c_5^q h(T)) = j(T)\},$$

where $h(T)$ and $g(T)$ are defined in Eqn. (10) and (14), respectively.

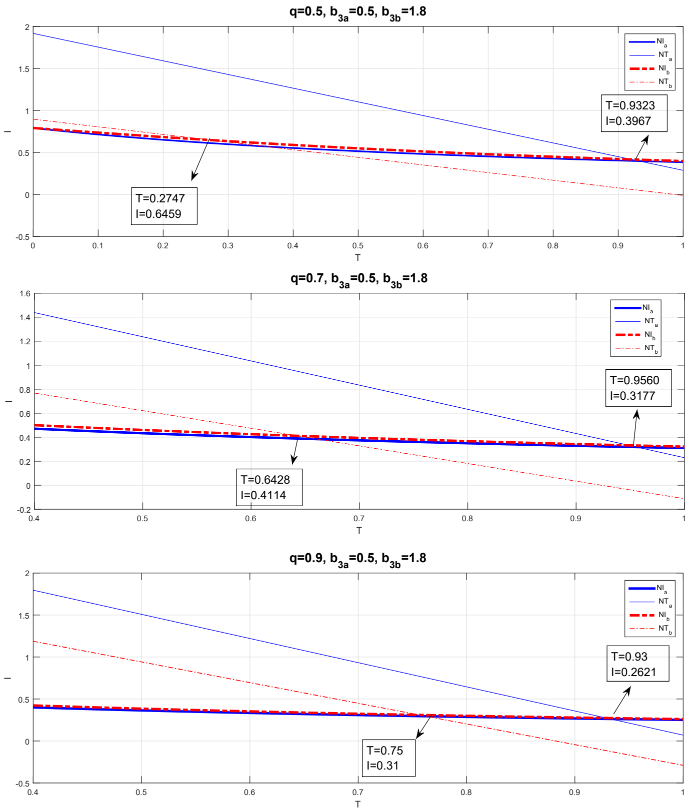

FIGURE 1. Case $N_I - N_T$: Effect of varying carrying capacity of fat cells for $q = 0.5$ (*top*), $q = 0.7$ (*middle*) and $q = 0.9$ (*bottom*) with $b_3 = 0.5$, $b_3 = 1.8$.

We observe from Fig. 1 that shifting the T-nullcline by changing b_3 reduces the number of tumor cells at the equilibrium point. This clinically means that with a low caloric diet, the co-existing equilibrium moves towards the state from a high tumor burden to a smaller tumor burden. As we increase the order of fractional derivative, the equilibrium points move towards a high tumor burden.

Effect of varying immune response ρ

As the immune response rate is increased from 0.1 to 1.2, the co-existing equilibrium point approaches the state corresponding to a smaller tumor burden as depicted in Fig. 2, while the number of immune cells increases accordingly. As we increase the order of fractional derivative, both the number of tumor cells and immune cells increase.

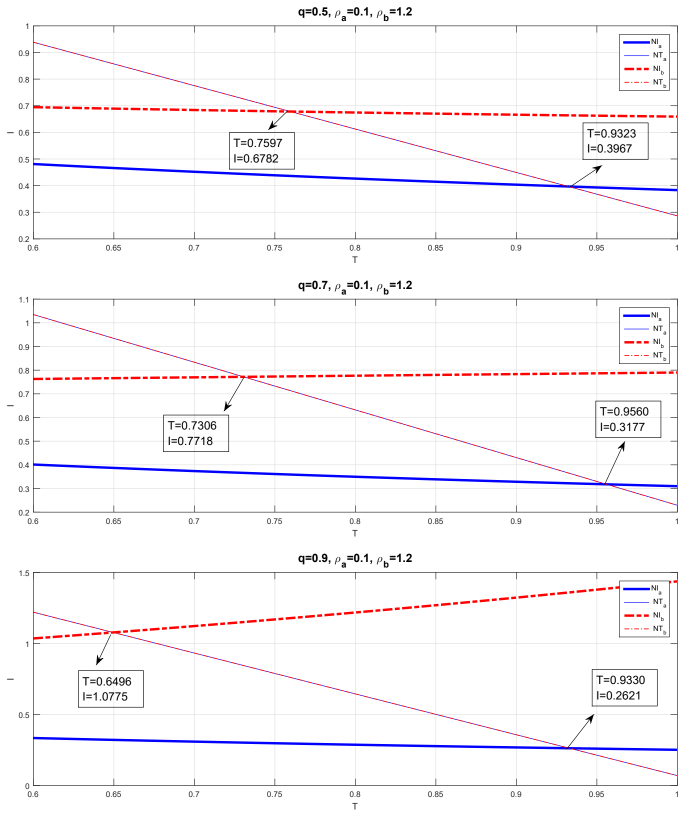

FIGURE 2. Case $N_I - N_T$: Effect of varying immune response rate for $q = 0.5$ (top), $q = 0.7$ $(middle)$ and $q = 0.9$ $(bottom)$ with $\rho = 0.1$, $\rho = 1.2$

4. **Discretization of the model**

In this section, we explain the discretization of the tumor model. There are no general methods to solve system of fractional differential equations analytically. We use $L1$-discretization formula to obtain the numerical solution following the study [24].

In order to discretize the fractional order tumor model (4), we write it as follows:

$$
{}_0D_t^q \chi(t) = \psi(\chi(t)), \quad t > 0, \quad \chi(0) = \chi_0, \tag{21}
$$

where

$$
\chi = \begin{bmatrix} \mathcal{I} \\ \mathcal{T} \\ \mathcal{N} \\ \mathcal{F} \end{bmatrix}, \ \chi_0 = \begin{bmatrix} \mathcal{I}_0 \\ \mathcal{T}_0 \\ \mathcal{N}_0 \\ \mathcal{F}_0 \end{bmatrix}, \ \psi(\chi) = \begin{bmatrix} s^q + \frac{\rho^q \mathcal{I}\mathcal{T}}{\alpha^q + \mathcal{T} + \mu\mathcal{F}} - c_1^q \mathcal{I}\mathcal{T} - d^q \mathcal{I} \\ r_1^q \mathcal{T}(1 - b_1\mathcal{T}) - c_2^q \mathcal{I}\mathcal{T} - c_3^q \mathcal{T}\mathcal{N} + c_5^q \mathcal{T}\mathcal{F} \\ r_2^q \mathcal{N}(1 - b_2\mathcal{N}) - c_4^q \mathcal{T}\mathcal{N} \\ r_3^q \mathcal{F}(1 - b_3\mathcal{F}) - c_6^q \mathcal{T}\mathcal{F} \end{bmatrix}.
$$

Let $t_n = n\Delta t$ for $n = 0, 1, \cdots, N$ where $\Delta t = \frac{t_f}{N}$ is the time step increment. The operator ${}_0\mathbb{D}_t^q f(t)$ is an approximation to the left Caputo derivative ${}_0D_t^q f(t)$ and it is given by

$$
\begin{aligned}
{}_0\mathbb{D}_{t_k}^q f(t) &= \frac{1}{\Gamma(1-q)} \sum_{j=1}^{k} \frac{f_j - f_{j-1}}{\Delta t} \int_{t_{j-1}}^{t_j} \frac{1}{(t_k - s)^q}\, ds \\
&= \underbrace{\frac{\Delta t^{-q}}{\Gamma(2-q)}}_{:=B_0} \sum_{j=1}^{k} (f_j - f_{j-1}) \underbrace{\left((k-j+1)^{1-q} - (k-j)^{1-q}\right)}_{:=A_{k,j}}.
\end{aligned}
$$

Then, the equation (21) can be discretized at $t = t_k$ as

$$
B_0\, A_{k,k}\, \chi_k = B_0\, A_{k,k}\, \chi_{k-1} - B_0 \sum_{j=1}^{k-1} (\chi_j - \chi_{j-1})\, A_{k,j} + \psi(\chi_k).
$$

5. **Numerical simulations**

In this section, we present some numerical results. The initial conditions are set as

$$
\mathcal{I}_0 = s^q/d^q, \quad \mathcal{T}_0 = 1, \quad \mathcal{N}_0 = 0, \quad \mathcal{F}_0 = 0.8,
$$

to study the equilibrium point E_2^q, while they are fixed as

$$
\mathcal{I}_0 = s^q/d^q, \quad \mathcal{T}_0 = 0.0001, \quad \mathcal{N}_0 = 1, \quad \mathcal{F}_0 = 0.8
$$

to examine the equilibrium point E_3^q. We present time evolution of the model for values of $q = 0.9, 0.7, 0.5$ and check the stability conditions stated in Section 3.**2**. We try to understand the effect of fat cells in the model by varying b_3 and q. Further, we investigate the effect of immune response rate ρ.

5.1. **Case I: Results associated with the equilibrium point E_2^q**

We find the equilibrium point E_2^q by setting $r_2 = 0.7$, $b_3 = 0.5$ and $b_3 = 1$, and list the results in Table 2-3, respectively. For a high caloric diet ($b_3 = 0.5$), as we decrease the value of the parameter q, the number of immune cells increases, while the number of tumor cells and fat cells decrease. For a low caloric diet ($b_3 = 1.8$), the same behavior is observed. However, the number of tumor cells and fat cells are smaller and the number of immune cells are larger than the case with $b_3 = 0.5$. This shows that fractional order q is an important parameter because it might change the number of cells. By varying the carrying capacity of fat cells (b_3), we investigate the effect of diet on tumor cells. We can observe that the low caloric diet prevents the growth of tumor and it leads the tumor to shrink. In Fig. 3, the number of cells are compared with respect to the low and high caloric diet for different values of fractional order q. We observe that the solutions converge to the equilibrium points showing the validity of our theoretical results.

TABLE 2. Case 1: Equilibrium point E_2^q with $r_2 = 0.7$ and $b_3 = 0.5$

Equilibrium point	A_1	A_2	A_3	A_4	η	Eigenvalues
$E_2^{0.9} = (0.2454, 1.0376, 0, 0.8879)$	2.3010	1.3081	0.1843	0.0069	0.4841	(-1.5168,-0.5992,-0.0617,-0.1234)
$E_2^{0.7} = (0.3037, 1.0349, 0, 0.7259)$	2.3213	1.4159	0.2129	0.0133	0.0093	(-1.4346,-0.6923,-0.0881,-0.1062)
$E_2^{0.5} = (0.3814, 1.0088, 0, 0.5733)$	2.3188	1.4347	0.2193	0.0088	0.6338	(-1.4062,-0.7124,-0.1346,-0.0656)

TABLE 3. Case 1: Equilibrium point E_2^q with $r_2 = 0.7$ and $b_3 = 1$

Equilibrium point	A_1	A_2	A_3	A_4	η	Eigenvalues
$E_2^{0.9} = (0.2568, 0.9987, 0, 0.4648)$	2.1877	1.1524	0.1394	0.0047	0.3095	(-1.4641,-0.5704,-0.0616,-0.0916)
$E_2^{0.7} = (0.3206, 0.9812, 0, 0.3960)$	2.1700	1.1966	0.1428	0.0047	0.3281	(-1.3716,-0.6502,-0.0878,-0.0603)
$E_2^{0.5} = (0.4055, 0.9387, 0, 0.3362)$	2.1307	1.1523	0.1207	0.4472e-04	0.2801	(-1.3352,-0.6593,-0.1333,-0.0029)

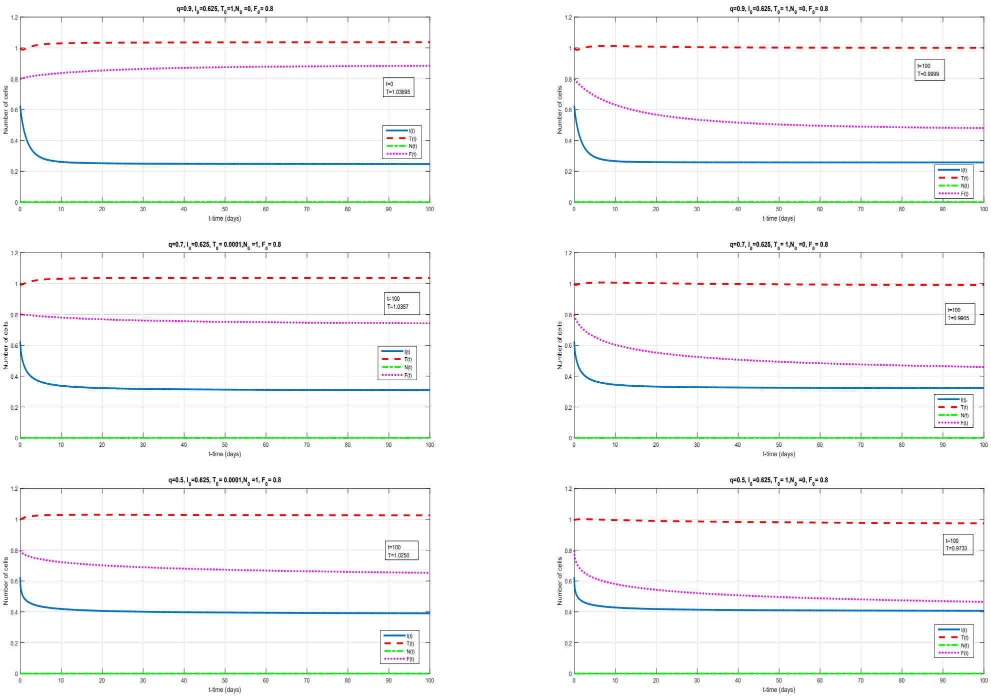

FIGURE 3. Case 1: Equilibrium point E_2^q for $q = 0.9$ (*top*), $q = 0.7$ (*middle*) and $q = 0.5$ (*bottom*) with $b_3 = 0.5$ (*left*), $b_3 = 1$ (*right*) and $r_2 = 0.7$.

5.2. Case 2: Results associated with the co-existing equilibrium with low immune response rate

We continue with the equilibrium point E_3^q by fixing the immune response rate as $\rho = 0.1$ with $b_3 = 0.5$ and $b_3 = 1.8$ in Table 4-5, respectively. Similar to the previous case, we can observe that varying the fractional order q greatly affects the number of cells. As the fractional order q is decreased, the number of immune cells and normal cells increases, while the number of tumor cells and fat cells decrease. In Fig. 4, the effect of low caloric diet is more visible. In other words, it leads to a smaller tumor cell population. A low caloric diet associated with the order $q = 0.5$ leads tumor to eradicate in the final time step. However, for this choice of parameters, the number of normal cells is smaller than the number of tumor cells.

TABLE 4. Case 2: Equilibrium points E_3^q with $b_3 = 0.5$, $\rho = 0.1$

Equilibrium point	A_1	A_2	A_3	A_4	η	Eigenvalues
$E_3^{0.9} = (0.2621, 0.9330, 0.1608, 1)$	2.1403	1.1869	0.1839	0.0077	0.3978	(-1.4585,-0.5650,-0.0584 ± 0.0220i)
$E_3^{0.7} = (0.3177, 0.9560, 0.1196, 0.8230)$	2.1971	1.3010	0.2061	0.0097	0.4997	(-1.4014,-0.6702,-0.0627 ± 0.0105i)
$E_3^{0.5} = (0.3967, 0.9323, 0.1210, 0.6815)$	2.3215	1.6129	0.3776	0.0269	1.1266	(-1.3359,-0.7401,-0.0700,-0.1755)

TABLE 5. Case 2: Equilibrium points E_3^q with $b_3 = 1.8$, $\rho = 0.1$

Equilibrium point	A_1	A_2	A_3	A_4	η	Eigenvalues
$E_3^{0.9} = (0.3100, 0.7563, 0.3197, 0.3304)$	1.9513	1.1224	0.2259	0.0116	0.3996	(-1.3088,-0.4829,-0.0798 ± 0.0197i)
$E_3^{0.7} = (0.4114, 0.6428, 0.4080, 0.3357)$	1.9202	1.2062	0.2927	0.0216	0.5127	(-1.1883,-0.5435,-0.0942 ± 0.0283i)
$E_3^{0.5} = (0.6459, 0.2747, 0.7411, 0.4477)$	3.3302	3.8530	1.8145	0.2950	16.7184	(-1.8391,-0.7937,-0.3487 ± 0.0970i)

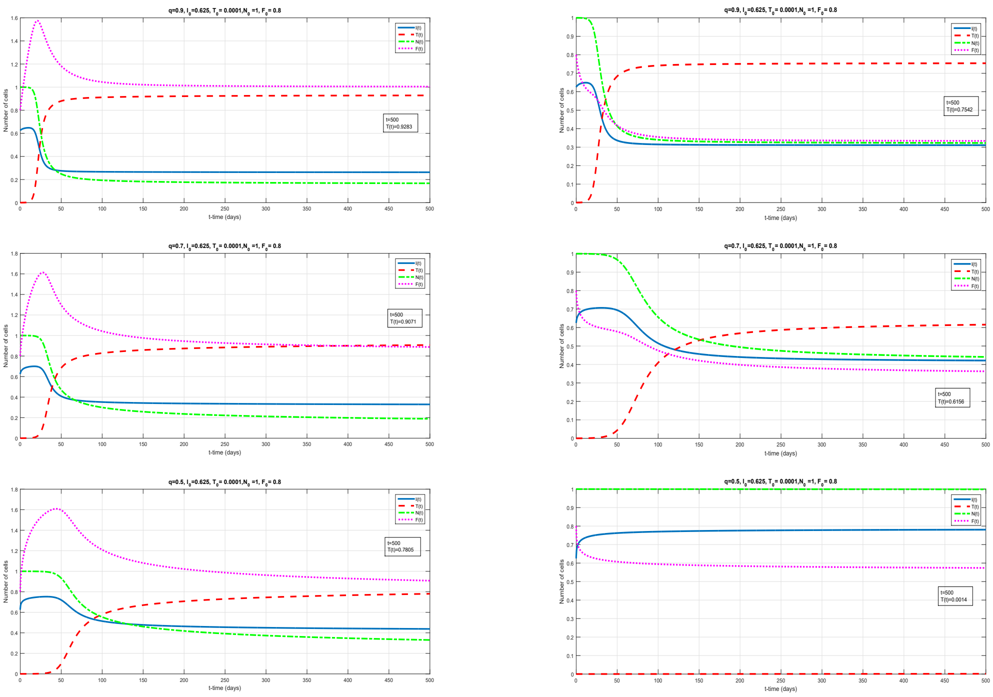

FIGURE 4. Case 2: Equilibrium point E_3^q for $q = 0.9$ (*top*), $q = 0.7$ (*middle*) and $q = 0.5$ (*bottom*) with $b_3 = 0.5$ (*left*), $b_3 = 1.8$ (*right*) $\rho = 0.1$.

5.3. Case 3: Results associated with the co-existing equilibrium with high immune response rate

Next, we examine the effect of high immune response by taking $\rho = 2$ with $b_3 = 0.5$ in Table 6 and $b_3 = 1.5$ in Table 7. The effect of the parameter ρ is very obvious, that is, the number of immune cells converge to 2 for $q = 0.9$ and it decreases up to 1 for $q = 0.5$. It causes more tumor cells to be destroyed. From Fig. 5, we observe that a low caloric diet leads to a sharp decrease in the number of tumor cells. For a low caloric diet, tumor cells stabilizes to 0.1727, 0.1822, 0.0613 for $q = 0.9, 0.7, 0.5$, respectively which are lower values compared with the case when patient is gaining weight. In Fig. 5, it can be seen that a low caloric diet helps to control the number of tumor cells and it is accelerated by smaller values of q.

TABLE 6. Case 3: Equilibrium points E_3^q with $b_3 = 0.5$, $\rho = 1.2$

Equilibrium point	A_1	A_2	A_3	A_4	η	Eigenvalues
$E_3^{0.9} = (1.0775, 0.6496, 0.4158, 1.3038)$	1.5389	0.6612	0.0981	0.0053	0.0776	(-1.2055,-0.1980,-0.0677 $\pm$ 0.0830i)
$E_3^{0.7} = (0.7718, 0.7306, 0.3272, 1.1005)$	1.6863	0.8419	0.1679	0.0121	0.1758	(-1.2156,-0.3026,-0.0841 $\pm$ 0.0853i)
$E_3^{0.5} = (0.6782, 0.7597, 0.2838, 0.9257)$	1.8675	1.1095	0.2793	0.0260	0.4102	(-1.2031,-0.4496,-0.1074 $\pm$ 0.0962i)

TABLE 7. Case 3: Equilibrium points E_3^q with $b_3 = 1.8$, $\rho = 1.2$

Equilibrium point	A_1	A_2	A_3	A_4	η	Eigenvalues
$E_3^{0.9} = (1.7471, 0.1727, 0.8447, 0.5041)$	1.2194	0.4507	0.0881	0.0062	0.0314	(-0.9310, -0.0809 $\pm$ 0.1894i,-0.1265)
$E_3^{0.7} = (1.0872, 0.1822, 0.8322, 0.4932)$	1.4067	0.6503	0.1390	0.0116	0.0850	(-0.9478,-0.1245 $\pm$ 0.1339i,-0.2098)
$E_3^{0.5} = (0.8397, 0.0613, 0.9422, 0.5315)$	1.6925	0.9063	0.1852	0.0118	0.2159	(-0.9515, -0.0473,-0.4064,-0.2873)

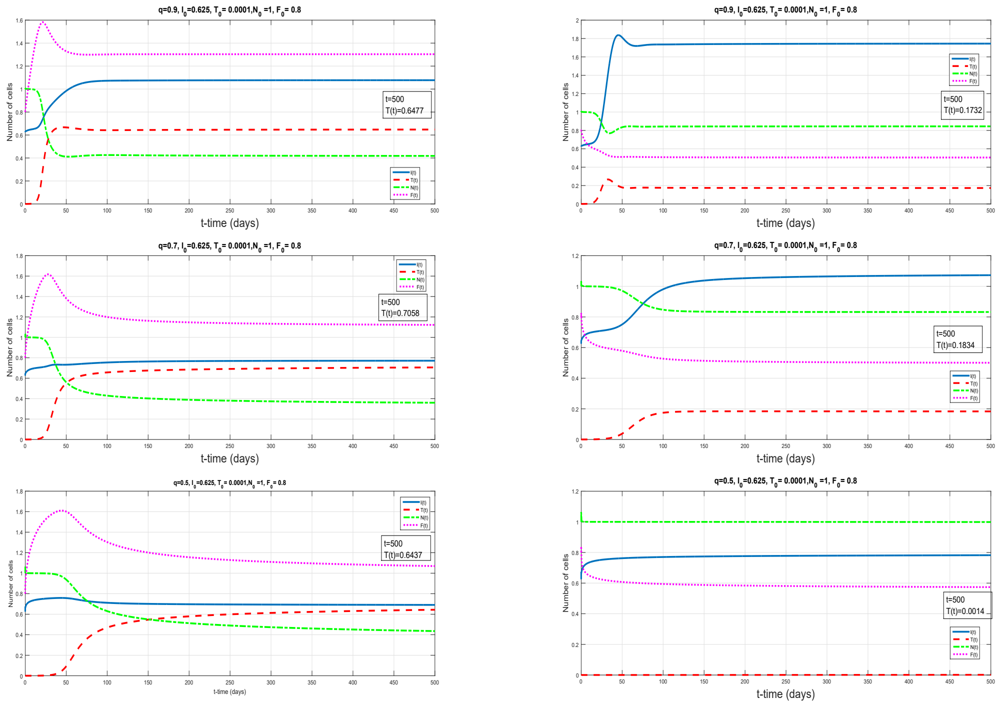

FIGURE 5. Case 3: Equilibrium point E_3^q for $q = 0.9$ (*top*), $q = 0.7$ (*middle*) and $q = 0.5$ (*bottom*) with $b_3 = 0.5$ (*left*), $b_3 = 1.8$ (*right*), $\rho = 1.2$.

6. **Summary and conclusion**

In this study, we investigate the effect of obesity in a generalized cancer tumor growth model. Integer order models can be limited and they may not reproduce the results obtained from the real data. Fractional derivatives have advantage that the order q can be varied for a better data fit depending on the progression of different cancers. In order to examine the effect of fractional order q on tumor–obesity model, we present several numerical simulations for different values of the fractional order q. Our simulation results demonstrate that varying the fractional order greatly affects the behavior of tumor, immune, normal and fat cells. By perturbing the parameters b_3, ρ in the system, an increase in the number of immune cells and a decrease in the number of tumor cells are observed in case of a low caloric diet. As the order of fractional derivative goes to zero, a smaller tumor population is achieved. We showed that the numerical results are in good agreement with theory, indicating the validity of the numerical and theoretical analysis.

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