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# FRACTIONAL ORDER MODEL OF IMMUNE CELLS INFLUENCED BY CANCER CELLS

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**Abstract.** In this paper, we study the mathematical model of interaction cancer cells and immune system cells presented Castiglione and Piccoli. As the interaction between cancer cells and the immune system is weak, when the immune system of the body begins to decrease, the cancer cells get stronger and increase rapidly. Helper CD4+ T and cytotoxic CD8+ T cells, cancer cells, dendritic cells and cytokine interleukin-2 (IL-2) cells are involved in the mathematical model of this competition in the living body. As can be seen in the literature, since the cancer cells have memory structure, fractional models describe the struggle between the cancer cells and immune system give more meaningful results than classical models as closer to the reality. The main motivation of the present work is to generalize the model in Castiglione and Piccoli [*J. Theor. Biol.* **247** (2007) 723–732] by using Caputo fractional derivative. The main aim is to analyze the behaviors of system cells by changing of the fractional parameter. In this sense, we study on the stability analysis of treatment free and the fixed points of the prescribed model. To get the numerical solutions, we apply the Adam-Bashforth-Moulton (ABM) algorithm and also illustrate the results by the graphics held by Matlab program. We have reached the excellent result that cancer cells decrease as $\theta$ diminishes in this process.

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## 1. Introduction

Cancer refers to a quite number of different diseases characterized by DNA damage that causes abnormal cell growth. The malignant cancer cells have two important roles: first, they can no longer be divisible or differentiated normally; second, they can invade surrounding tissues and go to distant places in the body [26]. The healthy body is well equipped to defend itself against cancer. Cancer can occur when the immune system and other defense mechanisms fail [26]. The characteristic features of cancer are the rapid, uncontrolled proliferation of cells and independent propagation in which secondary focus (metastases) occurs from the origin region. This propagation happens by circulation of blood or lymphatic fluid, through unintentional transplantation from one site to another during surgery, and neighborhood. As a result, cancer cells are different from normal cells in terms of cell size, shape, number, differentiation, function, and ability to move to distant tissues [26].

*Keywords and phrases:* Immune cells influenced by cancer cells, helper CD4+ T and cytotoxic CD8+ T cells, interleukin-2 (IL-2).

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Tumors caused by uncontrolled cleavage and development in cells can be recognized by the immune system. One of the normal functions of the immune system is to recognize and remove the malignant cells that acts in the living body. Numerous antigens that form the immune response have been shown in many experimentally generated tumors and in some cancer cases [22].

First, these antigens are restricted to two main groups according to their expression patterns: tumor-specific antigens found in tumor cells and not found in any normal cells; and the tumor-associated antigens in tumor cells and some normal cells. However, this classification is not excellent because it has been found that many antigens that are thought to be tumor specific are also expressed by some normal cells. Modern classification of tumor antigens is based on the molecular structures and sources [22].

The first attempts to simplify and characterize tumor antigens are based on the production of specific monoclonal antibodies for tumor cells and the identification of antigens recognized by these antibodies. One of the important developments in this field is the development of techniques to identify tumor antigens recognized by cytotoxic T lymphocytes (CTLs), because CTLs are the main immune defense mechanisms against tumors. CTLs recognize peptides originating from cytoplasmic proteins bound to the class I major histocompatibility complex (MHC-1) molecules.

Neoplastic transformation is caused by genetic changes some of which are seen as non-self by the immune system and cause cell surface antigen expression, The products of the modified protooncogenes and tumor suppressor genes are synthesized in the cytoplasm of tumor cells and, like any other cytosolic protein, can enter the pathway of MHC-1 antigen processing and be recognized by CD8+ T cells. Since these altered proteins are not present in normal cells, they do not induce self-tolerance. Some cancer patients have CD4+ and CD8+ T cells that respond to products of mutated oncogenes such as circulating RAS, p53, and BCR-ABL proteins [22].

Cytotoxic T lymphocytes have been shown to have a good anti-tumor effect on cytotoxic T cells that react against tumor antigens in experimentally generated tumors. CTLs in humans play a protective role against virus-associated neoplasms, and CTLs have been shown to be present in the blood of cancer patients and in tumor infiltrations. CD4+ T cells typically recognize the 12–16 aa peptides whose length presented by MHC class II molecules. These cells play a central role in the initiation and maintenance of adaptive immune responses. The contribution of CD4+ T cells to anti-tumor immunity is complex [40]. CD4+ T cells help the activation and proliferation of CD8+ T cells [8]. Although it has been demonstrated that both cell-mediated and humoral immunity has anti-tumor activity, the basic mechanism of tumor immunity is the killing of tumor cells by CD8+ CTLs. Cellular immune responses that protect against tumors are typically linked to CD8+ T cells. However, CD4+ T cells also play a central role [40]. Human CD4+ T cells can recognize tissue-specific antigens, common tumor antigens, and viral antigens caused by tumor transformation [40]. Natural killer (NK) cells are lymphocytes that are capable of spontaneously destroying cells that are infected with a pathogen or that exhibit foreign symptoms such as tumor cells [29]. NK cells are particularly effective against cells that show decreased MHC expression. Following activation by IL-2, NK cells can disrupt various human tumors in vitro [29].

Dendritic cells (DC) are central regulators of the adaptive immune response and are required for T cell mediated cancer immunity. In particular, anti-tumoral responses are based on the initiation of tumor antigens to lymph nodes to activate cytotoxic T lymphocytes. DC maturation is required to provide co-stimulatory signals to T cells, but DC maturation occurs in tumors, and it is insufficient to generate strong immunity especially in the light of suppressive mechanisms in tumors [15].

Cytokine interleukin-2 (IL-2) is a four $\alpha$-helix bundle cytokine of size 15.5 kDa. It is generated mainly by CD4+ T cells as a result of the antigen stimulation response. However, NK is also produced by T cells, CD8+ cells, mast cells, and DCs. IL-2 has a strong T cell growth factor effect. It can also induce natural killer (NK) cells, increase their cytolytic effects, and support many other immune system components needed to remove auto reactive cells and maintain homeostasis. IL-2 administration has been reported to cause apparently curative and persistent regressions in cancer patients [10].

Considering that there are many potential anti-tumor mechanisms, the strongest evidence for the presence of immune control is the increased frequency of cancer in immunocompromised hosts. Approximately 5% of people with congenital immunodeficiency develop cancer and this prevalence is 200 times greater than those with immunocompatibility. The incidence of malignancy is increased in immunocompromised transplant recipients

and AIDS patients [22]. The main problem in tumor biology is to understand factors affecting tumor growth rate and the role of these factors in clinical course and response to therapy. The original transformed cell (approximately 10 μm in diameter) should be folded in half by at least 30 populations to create 109 cells (approximately 1 g in weight) which are the smallest clinically detectable mass [22]. However, in order to create a tumor with a maximum size of 1012 cells (approximately 1 kg in weight) which is in comply with the life, only 10 additional cleavage cycles are required. These are the minimum estimates based on the assumption that all strains of transformed cells retain their cleavage ability and that there is no loss of cells in the replicative pool.

The growth rate of a tumor is determined by three main factors: the duration of tumor cells doubling, the fraction of tumor cells in the replicative pool, and the rate of spillage and loss of cells in the growing lesion. As cell cycle control is eliminated in most tumors, tumor cells enter the cycle more easily and without the usual limitations. In contrast, dividing cells do not have to complete the cycle faster than normal cells. In fact, the total cell cycle time of most tumors is the same or longer as the equivalent normal cell. So, it can be said that tumor growth is not related to shortening of cell cycle time. The cell cycle of fast growing tumors is high, which emphasizes the high rates of proliferation and apoptosis. Therefore, proliferation rate should be higher than apoptosis for tumor growth [22].

In the recent years, an increasing interest has been shown by the researchers to introduce mathematical models for diseases because the diseases lead to serious social problems [7, 21, 30, 32, 34, 35, 37]. In this sense, some references related to immune system and tumor growth models can be given [11, 20, 23, 33]. de Pillis *et al.* [33] analyzed the model of competition of tumor and the immune system. Many of tumor growth models concern natural killer cells, CD4+ T cells, CD8+ T cells in the immune system cells. There are a few models dealing with dendritic cells (DC) and IL-2 whereas DC play a crucial role at the beginning the cancer and coordinating of the immune system cells such as T cells. Dendritic cells are the most important cells that allow the release of antigens [22]. IL-2 induces the increase of T-lymphocyte cells stimulate by the antigens and also activates macrophages that swallow foreign substances in the body. That's why, DC and IL-2 are the most important part of the immune system. In addition, memory T cells are made up of active effect T cells and the duty in the body is to detect the antigens and give an immunological response in a short time when they meet the antigenic stimuli [24]. Castiglione and Piccoli [9] proposed the ordinary differential equation (ODE) model that involves the immune system cells, DC and IL-2.

Fractional calculus is a powerful tool to describe the memory and hereditary properties of the complex natural phenomena [3, 13, 17–19, 31]. The well-known Riemann-Liouville, Grünwald-Letnikov and Caputo operators have been successfully used to model the anomalous structures in many real world applications. Note that the characteristic property of differential equations (classical and fractional) is the need of specified initial or boundary conditions to guarantee the uniqueness of the solutions [14]. In this sense, Caputo fractional derivative is more preferred than the Riemann-Liouville because it leads to physically interpretable initial conditions. Therefore, we generalize the model studied in [9] by using Caputo fractional derivative. Adam-Bashforth-Moulton type predictor-corrector scheme is one of the basic methods for solving fractional derivatives and it has an important place in the Caputo derivative because the initial conditions are required. The main motivation of this work is to research numerical solutions of fractional model which describes the behavior immune system under the effect of cancer cells. For this purpose, we apply the ABM algorithm and illustrate the results by graphics and give stability analysis of treatment free and fixed points of the model.

## 2. Preliminaries

**Definition 2.1.** Caputo derivatives are given in [36] as:

$$ {}_0^C D_t^\theta g(t) = \frac{1}{\Gamma(k-\theta)} \int_0^t (t-\lambda)^{k-\theta-1} g^{(k)}(\lambda)\, \mathrm{d}\lambda $$

where $g(t)$ is a function and $\theta$, $(k-1<\theta<k, k\in Z)$ is the order of the derivative.

ABM type predictor-corrector scheme to solve nonlinear fractional differential equations (FDE) was first proposed by Diethelm *et al.* [12]. Recently, Baskonus *et al.* [4, 5] have applied this method to economic systems and some equations, Mekkaoui *et al.* [27] have investigated the chaotic systems. The problem is based upon the following initial-value problem:

$$\begin{aligned} D_t^{\theta} z(t) &= w(t, z(t)), \qquad 0 \le t \le T \\ z^{(k)}(0) &= z_0^{(k)}, \qquad k = 0, 1, \ldots, m-1, \end{aligned} \tag{2.1}$$

where $m = [\theta]$. The equation in equation (3.8) is equivalent to the Volterra integral equation

$$z(t) = \sum_{k=0}^{[\theta]-1} z_0^{(k)} \frac{t^k}{k!} + \frac{1}{\Gamma(\theta)} \int_0^t (t-s)^{\theta-1} w(s, z(s))\, \mathrm{d}s. \tag{2.2}$$

The ABM type predictor–corrector method is applied to get the numerical integration in equation (2.2):

$$z_{\ell}(t_{m+1}) = \sum_{k=0}^{m-1} z_0^{(k)} \frac{t^k}{k!} + \frac{\ell^{\theta}}{\Gamma(\theta+2)} w(t_{m+1}, z_{\ell}^{p}(t_{m+1})) + \frac{\ell^{\theta}}{\Gamma(\theta+2)} \sum_{j=0}^{m} x_{j,m+1} w(t_{m+1}, z_{\ell}(t_{m+1})) \tag{2.3}$$

where

$$x_{j,m+1} = \begin{cases} m^{\theta+1} - (m-\theta)(m+1), & j = 0, \\ (m-j+2)^{\theta+1} + (m-j)^{\theta+1} - 2(m-j+1)^{\theta+1}, & 1 \le j \le m, \\ 1, & j = m+1. \end{cases}$$

The predictor is given as follow:

$$z_{\ell}^{p}(t_{m+1}) = \sum_{k=0}^{[\theta]-1} z_0^{(k)} \frac{t^k}{k!} + \frac{1}{\Gamma(\theta)} \sum_{j=0}^{m} y_{j,m+1} w(t_j, z_{\ell}(t_j)), \tag{2.4}$$

where

$$y_{j,m+1} = \frac{\ell^{\theta}}{\theta} (m-j+1)^{\theta} - (m-j)^{\theta}, \; 0 \le j \le n.$$
$$\ell = \frac{T}{M}, t_m = mh, m = 0, 1, 2, \ldots, M.$$

## 3. Fractional order model and free equilibrium point

In this section, we propose the mathematical model of the relation between cancer cells and immune system with Caputo FD. In addition, we explain the reality of the problem dynamics. Our fractional model is given as follows:

$$\begin{aligned} {}_0^C D_t^{\theta}\, E &= \alpha_0^{\theta} + \beta_0^{\theta} DE \left(1 - \frac{E}{p_0^{\theta}}\right) - c_0^{\theta}\, E, \\ {}_0^C D_t^{\theta}\, F &= \alpha_1^{\theta} + \beta_1^{\theta} I (M+D) F \left(1 - \frac{F}{p_1^{\theta}}\right) - c_1^{\theta} F, \end{aligned}$$

$$
\begin{aligned}
{}_0^C D_t^\theta\ M &= \beta_2^\theta M\left(1-\frac{M}{p_2^\theta}\right)-d_2^\theta MF,\\
{}_0^C D_t^\theta\ D &= -d_3^\theta DF,\\
{}_0^C D_t^\theta\ I &= \beta_4^\theta DE-e_4^\theta IF-c_4^\theta I.
\end{aligned}
\tag{3.1}
$$

where $E, F, M, D, I$ denote CD4+ T cells, CD8+ T cells, myeloid cells, dendritic cells and IL-2, respectively.

The first equation shows the concentration of CD4+ T cells and the term $\alpha_0^\theta - c_0^\theta E$ represents natality and natural fatality rate of cells, respectively. The term $\beta_0^\theta DE(1-\frac{E}{p_0^\theta})$ represents helper CD4+ T cells upon presentation of dendritic cells, $p_0^\theta$ is the carrying capacity of CD4+ T cells. Dendritic cells are syringe into the host cells long since loaded. The second equation describes the concentration of CD8+ T cells and $\alpha_1^\theta - c_1^\theta F$ denotes natality and natural fatality rate of cells, respectively. The term $\beta_1^\theta I(M+D)F(1-\frac{F}{p_1^\theta})$ models the interaction between CD8+ T cells and cancer cells, dendritic cells and $p_1^\theta$ is the carrying capacity of CD8+ T cells. The third equation deals with the myeloid (tumor) cells and the term $\beta_2^\theta M(1-\frac{M}{p_2^\theta})$ represents reproduction and saturation of tumor cells, $p_2^\theta$ is the carrying capacity of myeloid cells. We suppose that growth of tumor cells is of logistic type and the law is based on experimental data [28]. The term $-d_2^\theta MF$ represents the rate of tumor killed by CD8+ T cells. The fourth equation models the concentration of dendritic cells and the term $-d_3^\theta DF$ represents the rate of dendritic cells (behave as an activatoron CD8+ T cells) killed by CD8+ T cells. The last equation models dynamics of IL-2 and the term $\beta_4^\theta DE$ represents IL-2 increased due to dendritic and CD4+ T cells. $-e_4^\theta IF$ represents the rot of IL-2 after the immune system response and $-c_4^\theta I$ represents the rate of death cells.

To obtain free equilibrium points for fractional derivative model (3.1), firstly we write as follow:

$$\alpha_0^\theta + \beta_0^\theta DE\left(1-\frac{E}{p_0^\theta}\right)-c_0^\theta E=0, \tag{3.2}$$

$$\alpha_1^\theta + \beta_1^\theta I(M+D)F\left(1-\frac{F}{p_1^\theta}\right)-c_1^\theta F=0, \tag{3.3}$$

$$\beta_2^\theta M\left(1-\frac{M}{p_2^\theta}\right)-d_2^\theta MF=0, \tag{3.4}$$

$$-d_3^\theta DF=0, \tag{3.5}$$

$$\beta_4^\theta DE-e_4^\theta IF-c_4^\theta I=0. \tag{3.6}$$

For the obtaining equilibrium points, from equation (3.5) $DF=0$ because of $d_3^\theta>0$. But $F$ is not equal 0 because of $\alpha_1^\theta>0$ and we get $D=0$. If we substitute $D=0$, in the equations (3.2) and (3.6), we get $E=\frac{\alpha_0^\theta}{c_0^\theta}$ and $I=0$, respectively. If we substitute $I=0$, in equation (3.3), we get $F=\frac{\alpha_1^\theta}{c_1^\theta}$.

From equation (3.4) $M[\beta_2^\theta(1-\frac{M}{p_2^\theta})-d_2^\theta F]=0$ with $F=\frac{\alpha_1^\theta}{c_1^\theta}$ and $I=0$. $M[\beta_2^\theta(1-\frac{M}{p_2^\theta})-d_2^\theta F]=0$ has two solutions $M=0$ and $M=p_2^\theta[1-\frac{\alpha_1{}^\theta d_2^\theta}{\beta_2^\theta c_2^\theta}]$. So, the system has two equilibrium points $P_1=(E_1,F_1,M_1,D_1,I_1)$

and $P_2 = (E_2, F_2, M_2, D_2, I_2)$ defined by

$$E_{1,2} = \frac{\alpha_0^\theta}{c_0^\theta}, \quad F_{1,2} = \frac{\alpha_1^\theta}{c_1^\theta}, \; D_{1,2} = 0, \quad I_{1,2} = 0, \tag{3.7}$$

$$M_1 = 0, \; M_2 = p_2^\theta \left[1 - \frac{\alpha_1^\theta d_2^\theta}{\beta_2^\theta c_2^\theta}\right] . \tag{3.8}$$

Hence, we obtain

$$P_1 = \left(\frac{\alpha_0^\theta}{c_0^\theta}, \frac{\alpha_1^\theta}{c_1^\theta}, 0, 0, 0\right) \quad \text{and} \quad P_2 = \left(\frac{\alpha_0^\theta}{c_0^\theta}, \frac{\alpha_1^\theta}{c_1^\theta}, p_2^\theta \left[1 - \frac{\alpha_1^\theta d_2^\theta}{\beta_2^\theta c_2^\theta}\right], 0, 0\right). \tag{3.9}$$

Looking at equilibrium points, we can conclude that the tumor cells don't disappear over time at $P_1$ and disappear at $P_2$.

The stability of $P_1$ and $P_2$ can be deduced by the eigenvalues of the system Jacobian matrix $J(P)$.

$$\text{J(P)=} \begin{pmatrix} \beta_0^\theta D(1 - 2E/p_0^\theta) - c_0^\theta & 0 & 0 & \beta_0^\theta E(1 - E/p_0^\theta) & 0 \\ 0 & b_1^\theta I(M + D)(1 - 2F/p_1^\theta) - c_1^\theta & \beta_1^\theta IF(1 - F/p_1^\theta) & \beta_1^\theta F(1 - F/p_1^\theta) & \beta_1^\theta F(M + D)(1 - F/p_1^\theta) \\ 0 & -d_2^\theta M & \beta_2^\theta(1 - 2M/p_2^\theta) - d_2^\theta F & 0 & 0 \\ 0 & -d_3^\theta D & 0 & -d_3^\theta F & 0 \\ \beta_4^\theta D & -e_4^\theta I & 0 & \beta_4^\theta E & -e_4^\theta F - c_4^\theta \end{pmatrix}$$

We can say that, the stability of equilibrium points depend on $\alpha_1^\theta d_2^\theta - \beta_2^\theta c_1^\theta$. Thus, if $\alpha_1^\theta d_2^\theta > \beta_2^\theta c_1^\theta$, $P_1$ is stable and $P_2$ is unstable. If $\alpha_1^\theta d_2^\theta < \beta_2^\theta c_1^\theta$, $P_1$ is unstable and $P_2$ is stable. It means that if $\alpha_1^\theta d_2^\theta > \beta_2^\theta c_1^\theta$, namely natality and fatality rate of CD8+ T cells is greater than the rate of tumor reproduction, tumor cells are killed by CD8+ T cells. In this case, tumor-free equilibrium point and immune system is enough to fight tumor cells. We find that by using the parameters in [9] the eigenvalues

$$\lambda_1^{(1)} = -c_0^\theta, \lambda_2^{(1)} = -c_1^\theta, \lambda_3^{(1)} = \frac{-(\alpha_1^\theta d_2^\theta - \beta_2^\theta c_1^\theta)}{c_1^\theta},$$

$$\lambda_4^{(1)} = \frac{-\alpha_1^\theta d_3^\theta}{c_1^\theta}, \lambda_5^{(1)} = \frac{-(\alpha_1^\theta e_4^\theta + c_1^\theta c_4^\theta)}{c_1^\theta} \tag{3.10}$$

and

$$\lambda_1^{(1)} = -c_0^\theta, \lambda_2^{(1)} = -c_1^\theta, \lambda_3^{(1)} = \frac{(\alpha_1^\theta d_2^\theta - \beta_2^\theta c_1^\theta)}{c_1^\theta},$$

$$\lambda_4^{(1)} = \frac{-\alpha_1^\theta d_3^\theta}{c_1^\theta}, \lambda_5^{(1)} = \frac{-(\alpha_1^\theta e_4^\theta + c_1^\theta c_4^\theta)}{c_1^\theta}. \tag{3.11}$$

Because all parameter are positive, we conclude that $P_1$ is unstable and $P_2$ is stable.

## 4. Application of method and numerical results

Several numerical methods are suggested to solve fractional differential equations. In this section, we obtain the numerical solutions of prescribed model using the ABM algorithm as follows:

$$\begin{aligned}
E_{m+1} &= E_0 + \frac{\ell^\theta}{\Gamma(\theta+2)}\left(\alpha_0^\theta + \beta_0^\theta D_{m+1}^p E_{m+1}^p\left(1-\frac{E_{m+1}^p}{p_0^\theta}\right) - c_0^\theta E_{m+1}^p\right) \\
&\quad + \frac{\ell^\theta}{\Gamma(\theta+2)}\sum_{j=0}^{m} x_{j,m+1}\left(\alpha_0^\theta + \beta_0^\theta D_j E_j\left(1-\frac{E_j}{p_0^\theta}\right) - c_0^\theta E_j\right), \\
F_{m+1} &= F_0 + \frac{\ell^\theta}{\Gamma(\theta+2)}\left(\alpha_1^\theta + \beta_1^\theta I_{m+1}^p\left(M_{m+1}^p + D_{m+1}^p\right)F_{m+1}^p\left(1-\frac{F_{m+1}^p}{p_1^\theta}\right) - c_1^\theta F_{m+1}^p\right) \\
&\quad + \frac{\ell^\theta}{\Gamma(\theta+2)}\sum_{j=0}^{m} x_{j,m+1}\left(\alpha_1^\theta + \beta_1^\theta I_j\left(M_j + D_j\right)F_j\left(1-\frac{F_j}{p_1^\theta}\right) - c_1^\theta F_j\right), \\
M_{m+1} &= M_0 + \frac{\ell^\theta}{\Gamma(\theta+2)}\left(\beta_2^\theta M_{m+1}^p\left(1-\frac{M_{m+1}^p}{p_2^\theta}\right) - d_2^\theta M_{m+1}^p F_{m+1}^p\right) \\
&\quad + \frac{\ell^\theta}{\Gamma(\theta+2)}\sum_{j=0}^{m} x_{j,m+1}\left(\beta_2^\theta M_j\left(1-\frac{M_j}{p_2^\theta}\right) - d_2^\theta M_j F_j\right), \\
D_{m+1} &= D_0 + \frac{\ell^\theta}{\Gamma(\theta+2)}\left(-d_3^\theta D_{m+1}^p F_{m+1}^p\right) + \frac{\ell^\theta}{\Gamma(\theta+2)}\sum_{j=0}^{m} x_{j,m+1}\left(-d_3^\theta D_j F_j\right), \\
I_{m+1} &= I_0 + \frac{\ell^\theta}{\Gamma(\theta+2)}\left(\beta_4^\theta D_{m+1}^p E_{m+1}^p - e_4^\theta I_{m+1}^p F_{m+1}^p - c_4^\theta I_{m+1}^p\right) \\
&\quad + \frac{\ell^\theta}{\Gamma(\theta+2)}\sum_{j=0}^{m} x_{j,m+1}\left(\beta_4^\theta D_j E_j - e_4^\theta I_j F_j - c_4^\theta I_j\right)
\end{aligned} \tag{4.1}$$

where

$$\begin{aligned}
E_{m+1}^p &= E_0 + \frac{1}{\Gamma(\theta)}\sum_{j=0}^{m} y_{j,m+1}\left(\alpha_0^\theta + \beta_0^\theta D_j E_j\left(1-\frac{E_j}{p_0^\theta}\right) - c_0^\theta E_j\right), \\
F_{m+1}^p &= F_0 + \frac{1}{\Gamma(\theta)}\sum_{j=0}^{m} y_{j,m+1}\left(\alpha_1^\theta + \beta_1^\theta I_j\left(M_j + D_j\right)F_j\left(1-\frac{F_j}{p_1^\theta}\right) - c_1^\theta F_j\right), \\
M_{m+1}^p &= M_0 + \frac{1}{\Gamma(\theta)}\sum_{j=0}^{m} y_{j,m+1}\left(\beta_2^\theta M_j\left(1-\frac{M_j}{p_2^\theta}\right) - d_2^\theta M_j F_j\right), \\
D_{m+1}^p &= D_0 + \frac{1}{\Gamma(\theta)}\sum_{j=0}^{m} y_{j,m+1}\left(-d_3^\theta D_j F_j\right), \\
I_{m+1}^p &= I_0 + \frac{1}{\Gamma(\theta)}\sum_{j=0}^{m} y_{j,m+1}\left(\beta_4^\theta D_j E_j - e_4^\theta I_j F_j - c_4^\theta I_j\right).
\end{aligned} \tag{4.2}$$

To plot the graphics, we assume the initial values $E_0 = 0$, $F_0 = 0$, $M_0 = 1$, $D_0 = 10$, $I_0 = 0$ only for convenience. Physical parameters of the system are $\alpha_0 = 10^{-4}$, $\beta_0 = 10^{-1}$, $p_0 = 1$, $c_0 = 0.005$, $\alpha_1 = 10^{-4}$, $\beta_1 = 10^{-2}$, $p_1 = 1$, $c_1 = 0.005$, $\beta_2 = 0.02$, $p_2 = 1$, $d_2 = 0.1$, $d_3 = 0.1$, $\beta_4 = 10^{-2}$, $e_4 = 10^{-7}$, $c_4 = 10^{-2}$ and the graphics are obtained for the fractional order nonlinear system (3.1) with $0.7 \leq \theta < 1$. As we understand

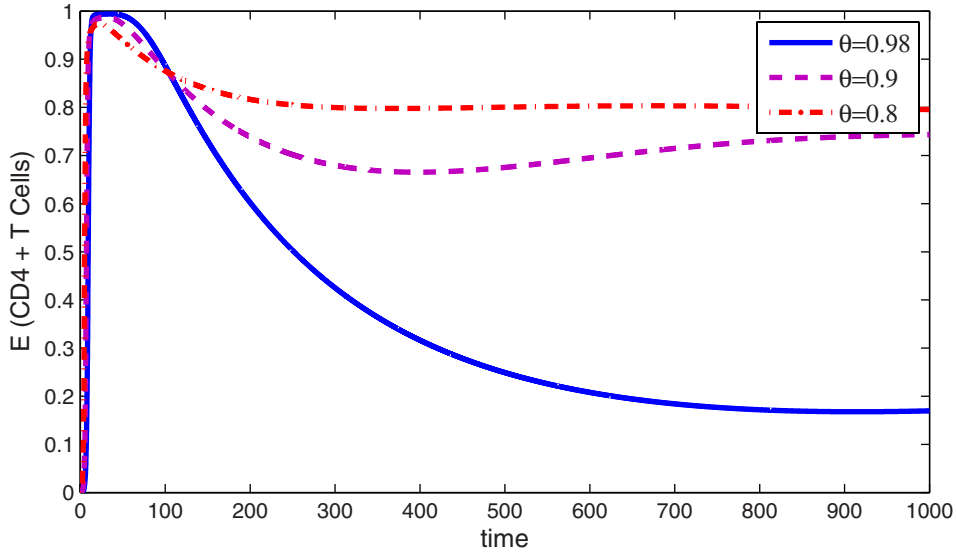


FIGURE 1. Numerical simulations for CD4+ T cells which interact with tumor cells at time $t$.

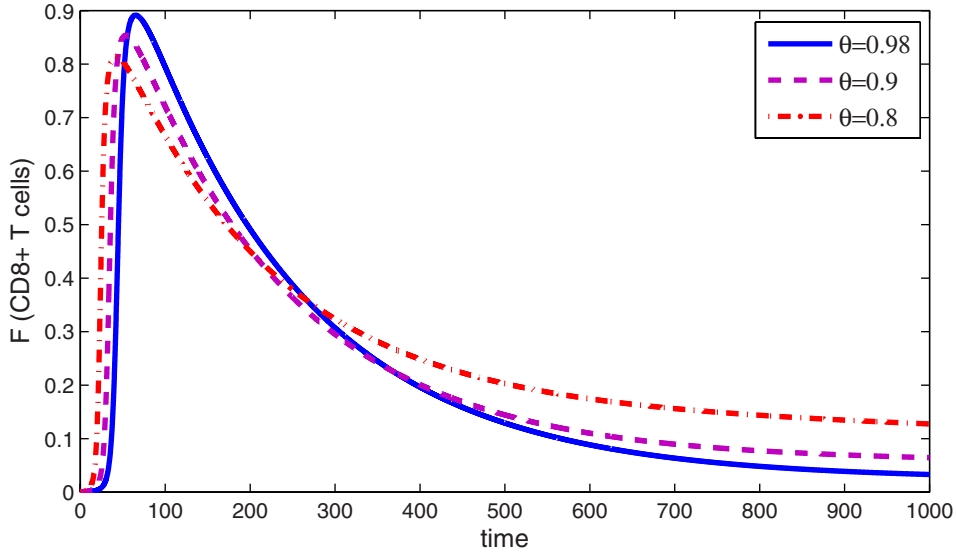


FIGURE 2. Numerical simulations for CD8+ T cells which interact with tumor cells at time $t$.

from the initial values, we offer dendritic cells and tumor cells to the system. Based on our observations, the immune system cells respond to the dendritic cells. That is, CD4+ T cells, CD8+ T cells and IL-2 have reacted to tumor cells. Approximately 100 hours later, the immune system cells take their maximum values CD4+ T cells in Figure 1 and CD8+ T cells in Figure 2, while the tumor cells receive the smallest value in Figure 3. After a while, the cells of the immune system (CD4+ T cells, CD8+ T cells and IL-2) begin to decrease because the tumor cells decrease. Once the cells of immune system reduce to a certain point, the tumor cells begin to grow and all of this process can be seen in Figures 1–6.

Also when $\theta = 0.98$, we see that in Figure 1 and 2, the cells of immune system (CD4+ T cells and CD8+ T cells) are suddenly grow and then rapidly decrease so the tumor cells almost grow to its starting point at last in

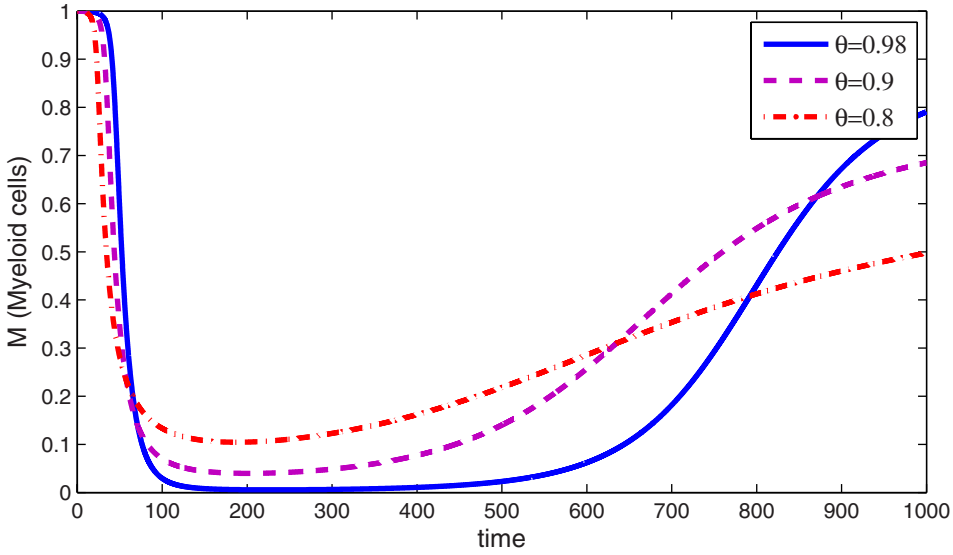


FIGURE 3. Numerical simulations for myeloid (tumor) cells which interact with tumor cells at time $t$.

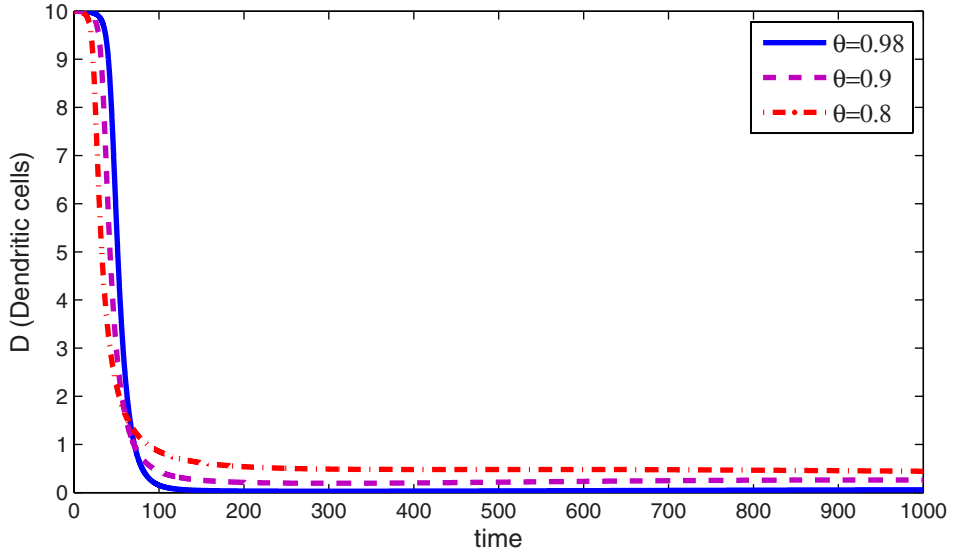


FIGURE 4. Numerical simulations for dendritic cells which interact with tumor cells at time $t$.

Figure 3. In Figures 1 and 2 when $\theta = 0.9$ and $\theta = 0.8$, memory T cells, become more active than when $\theta = 0.98$ hence in Figure 3 when $\theta = 0.8$, the tumor cells grow half as much as the initial point. One can observe that dynamical behavior of fractional order nonlinear system (3.1) in Figure 6. In accordance with real life, when the immune system is strong, we see that cancer cells grow less in Figures 1–6.

As seen in [1, 2, 6, 16, 25, 38, 39], one can observe that in Figures 1–6 of FDE system (3.1) reach a fixed point in longer time.

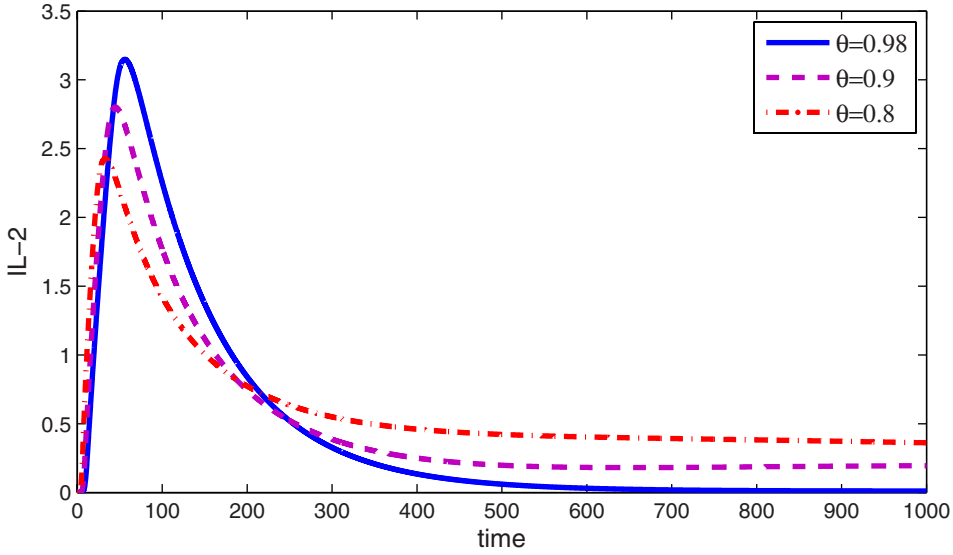


FIGURE 5. Numerical simulations IL-2 which interact with tumor cells at time $t$.

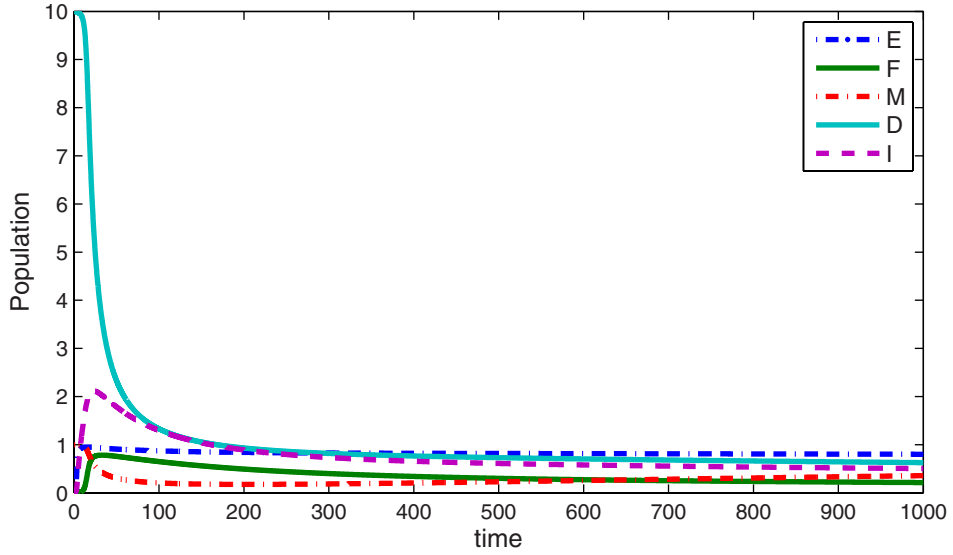


FIGURE 6. Dynamical behavior of system in (3.1) at $\theta = 0.7$.

## 5. Concluding remarks

In the present work, the integer order model [9] has been generalized by using Caputo fractional derivative because the immune system and also the cancer cells have memory features. This model is specialized in dendritic cells and IL-2 because they are important parts of the immune system. Moreover, the model examines how CD4+ T cells and CD8+ T cells fight with tumor cells. Then investigated free equilibrium points and stability of the model with no treatment and we find two equilibrium points which one of is stable and the other is unstable. This study is given numerical solution of the model with Adam-Bashforth-Moulton algorithm for fractional order model, this numerical solution is newly implemented for the system in (3.1) and given some graphs to

visualize this solution. As shown in the graphs the interaction between cancer cells and immune system cells is very strict, the change in one of the cells affects the other kind of cells.

The effectiveness of the cells of immune system are increasing in contrast, the effectiveness of tumor cells are decreasing for different values of $\theta$. It is seen that the small change in $\theta$ has great results and the approximate solution depend on the fractional order $\theta$. It has two reasons, either of them is the Caputo fractional derivative is appropriate real-life problem that is, it gives good results in such problems, the other is Caputo fractional derivative is non-local derivative.

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