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New Fractional Cancer Mathematical Model via IL-10 Cytokine and Anti-PD-L1 Inhibitor

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Abstract: In this study, we explore a recent biological model created to analyze the behavior of cancer cells by administering a dose of a drug containing anti-PD-L1 and IL-10 with the Caputo and Atangana–Baleanu derivative in the Caputo sense (ABC). Using the Caputo derivative in order to examine the stability of the non-linear system, we are able to demonstrate that it is existent and unique, and to introduce several numeric data obtained for the fractional values in MATLAB by using the Adams–Bashforth–Moulton (ABM) method. Additionally, by using the predictor–corrector approach, the numerical results from the system with ABC derivative will be produced. As a result, it has been observed that immune system cells that are exposed to single-dose drug with fractional order effectively combat cancer cells. The tumor cells decrease by 70.44% and 80.16% for the system generalized by the Caputo and ABC derivative, respectively, for the order $\alpha = 0.42$.

Keywords: anti-PD-L1; cancer; IL-10; fractional nonlinear system

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1. Introduction

There is no doubt that cancer is becoming a more popular topic for recent research, as the numbers of people contracting this disease are rising and the deaths that are caused by it are increasing as well. The function of the immune system, the body's defense system, is to recognize and kill cancer cells by stopping their progress. However, cancer cells may escape the notice of the immune system because the interaction between the PD-L1 proteins located on the surface of cancer cells and the PD-1 molecules located on the surface of T lymphocytes is impacted by a debilitation in the activation of lymphocytes; this leads to a halt in the immune response. Lately, sights have been set on enabling the immune system to recognize and eliminate cancer cells by use of anti-PD-L1 inhibitors in order to prevent cancer cells from escaping the immune system. Specifically, immune checkpoint inhibitors, anti-PD-L1, are designed to enhance the effectiveness of T cell activation by blocking negative pathways that are associated with T cell activation [1–5]. As for the IL-10 cytokine, it provides the immune system with the opportunity to fight the cancer cells more effectively by enhancing the number and efficiency of CD8+T cells [6,7]. Aside from this, the use of IL-10 is also beneficial for controlling the growth of tumors [8].

Mathematical modeling, also referred to as the reinterpretation of real-world problems with equations, is currently one of the tools used by scientists to predict the onset of diseases that cause problems.

There are many mathematical models that are very close to the reality, but they still cannot precisely describe reality. Thus, in order to provide better fit to real-world data, there is a need to build more accurate models that are able to account for this. Numerous studies have shown that fractional-order derivative modeling of real-life processes is more accurate and reliable when compared to the integer or classical order circumstances [9–18]. Caputo fractional derivatives are also useful when dealing with real-life issues since they allow the application of boundary conditions and beginning conditions to be incorporated into the analysis. There are many important features of fractional analysis, including the ability to

describe and analyze problems that arise in the fields of physics [19], biology [20], engineering [21–24], as well as other science disciplines through mathematical modeling [25–35]. In recent times, we have encountered models that involve the use of fractional derivatives to mathematically analyze complex biological processes involving hereditary properties and memory effects, such as diseases [36–45] that are being produced by fractional derivative.

There are many academics who are currently working on developing the theory of fractional calculus by creating various types of fractional derivative operators with the non-singular kernels in order to prevent classical fractional differential operators from exhibiting singularities as a result of the kernel. Recently, authors from diverse disciplines of mathematics constructed and explored mathematical models employing AB-fractional derivative by utilizing the non-singular kernel found in the Atangana–Baleanu fractional derivative operators.

The purpose of this work is to investigate the relationship between IL-10, anti-PD-L1, CD8+T cells, and cancer cells by means of the mathematical model configured with fractional analysis. Another objective is to comprehend how an immune system strengthened by components can thwart the development of cancer cells.

The interplay amongst CD8+T and CD4+T cells, cancer cells, and IL-2 with Caputo derivative was analyzed by [38]. Bringing IL-12 and anti-PD-L1 into consideration, a study concerning the reciprocal action of the immune system and cancerous cells was introduced by [39]. A vaccine model incorporating cancerous cells with IL-12 and IL-2 was perused by [46]. A mathematical model of the treatment modality combining radiation and anti-PD-L1 in the framework of cancer was established by [47]. Here, two significant radiobiological elements, namely, cell mending and cell reconstruction, are considered by the model given in [41]. The fact that the Caputo fractional derivative value and the coefficient of cancer cell multiplication are relatively more susceptible amongst the model elements was proven when the sensitivity analysis is studied. The co-infection model of cancer and hepatitis dynamics is investigated using Atangana–Baleanu in the Caputo sense [48].

The model, given by [49], which will be investigated with the fractional derivative in this article, is as follows:

$$\frac{dT}{dt} = a + bI_{10}CT\left(1 - \frac{T}{p}\right) - cT \tag{1}$$

$$\frac{dC}{dt} = dC\left(1 - \frac{C}{q}\right) - eCTI_{10} - zCTZ \tag{2}$$

$$\frac{dI_{10}}{dt} = -fI_{10} \tag{3}$$

$$\frac{dZ}{dt} = -\gamma Z \tag{4}$$

where T, C, I_{10}, Z denote CD8+T cells, cancer cells, IL-10, and anti-PD-L1, respectively. In Equation (1), which demonstrates the change in CD8+T cells with time, the term $a - cT$ denotes the formation and death of T cells, respectively; the term $bI_{10}CT\left(1 - \frac{T}{p}\right)$ denotes the growth of CD8+T cells in consequence of the interaction of CD8+T cells with the IL-10 and cancer cells. In Equation (2), which demonstrates the change in cancer cells with time, the term $dC\left(1 - \frac{C}{q}\right)$ denotes the growth of cancer cells; and the term $-eCTI_{10} - zCTZ$ represents the decrease in cancer cells with the effect of the IL-10 and the anti-PD-L1. In Equation (3), which demonstrates the change in the IL-10 cytokine with time, the term $-fI_{10}$ denotes the decrease in the IL-10 cytokine. In Equation (4), which defines the anti-PD-L1 dynamic with time, the term $-\gamma Z$ models the decrease in the anti inhibitor thought to be existent in the dynamic.

The study is formed with the following section: basic tools and model in the Caputo sense are briefly mentioned in Sections 2 and 3, respectively. Section 3 also underpins the existence and uniqueness of the solution and stability analysis for Equations (9)–(12). The system with the Caputo fractional derivative and ABC derivative are numerically explained

to look over the whole effect in Section 4. Finally, the study concludes by discussing the attained results.

2. Basic Tools

This section provides a reminder of some fundamental definitions and properties.

Definition 1 ([9]). *Let $\alpha \in (a-1, a), \alpha \in Z^+$, the Riemann–Liouville (RL) fractional derivative is given by*

$$ {}_0D_t^{\alpha} f(t) = \frac{1}{\Gamma(a-\alpha)} \left(\frac{d}{ds}\right)^a \int_0^t (t-s)^{a-\alpha-1} f(s) ds. $$

Definition 2 ([9]). *Let $\alpha \in (a-1, a), \alpha \in Z^+$, the Caputo fractional derivative is given by*

$$ {}_0^C D_t^{\alpha} f(t) = \frac{1}{\Gamma(a-\alpha)} \int_0^t (t-s)^{a-\alpha-1} f^{(a)}(s) ds. \tag{5} $$

Definition 3. *The Sobolev space of order 1 in (a, b) is given by*

$$ H^1(a, b) = \{f \in L^2(a, b) : u' \in L^2(a, b)\}. $$

Let $\alpha \in [0, 1]$, $f \in H^1(a, b)$, $a < b$ be a function. $B(\alpha)$ is a normalization function with $B(0) = B(1) = 1$ and is of the following form

$$ B(\alpha) = 1 - \alpha + \frac{\alpha}{\Gamma(\alpha)}, $$

E_α is the Mittag–Leffler function, defined by its series representation as

$$ E_{\alpha,\beta}(z) = \sum_{k=0}^{\infty} \frac{z^k}{\Gamma(\alpha k + \beta)}, \alpha, \beta > 0. $$

Definition 4. *The AB derivative in Caputo sense of f is given [10]*

$$ {}_a^{ABC} D_t^{\alpha} [f(t)] = \frac{B(\alpha)}{1-\alpha} \int_a^t f'(s) E_\alpha \left[-\alpha \frac{(t-s)^\alpha}{1-\alpha}\right] ds, \tag{6} $$

Definition 5. *The AB derivative in RL type of order α of f is given by [10]:*

$$ {}_a^{ABR} D_t^{\alpha} [f(t)] = \frac{B(\alpha)}{1-\alpha} \frac{d}{dt} \int_a^t f(s) E_\alpha \left[-\alpha \frac{(t-s)^\alpha}{1-\alpha}\right] ds. \tag{7} $$

Definition 6. *The fractional integral associated to the AB fractional derivative is defined by [10]:*

$$ {}_a^{AB} I_t^{\alpha} [f(t)] = \frac{1-\alpha}{B(\alpha)} f(t) + \frac{\alpha}{B(\alpha)\Gamma(\alpha)} \int_a^t f(s)(t-s)^{\alpha-1} ds. \tag{8} $$

3. Model in Caputo Sense

In this section, generalization of the model given by Equations (1)–(4) with Caputo fractional derivative and ABC derivative, respectively, will be made by using a dimensional representation.

The original Caputo fractional order model is given by the following

$$
\begin{aligned}
{}_0^C D_t^{\alpha_1}(T) &= a^{\alpha_1} + b^{\alpha_1} I_{10} C T\left(1 - \frac{T}{p^{\alpha_1}}\right) - c^{\alpha_1} T && (9)\\
{}_0^C D_t^{\alpha_2}(C) &= d^{\alpha_2} C\left(1 - \frac{C}{q^{\alpha_2}}\right) - e^{\alpha_2} C T I_{10} - z^{\alpha_2} C T Z && (10)\\
{}_0^C D_t^{\alpha_3}(I_{10}) &= -f^{\alpha_3} I_{10} && (11)\\
{}_0^C D_t^{\alpha_4}(Z) &= -\gamma^{\alpha_4} Z, && (12)
\end{aligned}
$$

and the original model with ABC sense is given by the following

$$
\begin{aligned}
{}_0^{ABC} D_t^{\alpha_1}(T) &= a^{\alpha_1} + b^{\alpha_1} I_{10} C T\left(1 - \frac{T}{p^{\alpha_1}}\right) - c^{\alpha_1} T && (13)\\
{}_0^{ABC} D_t^{\alpha_2}(C) &= d^{\alpha_2} C\left(1 - \frac{C}{q^{\alpha_2}}\right) - e^{\alpha_2} C T I_{10} - z^{\alpha_2} C T Z && (14)\\
{}_0^{ABC} D_t^{\alpha_3}(I_{10}) &= -f^{\alpha_3} I_{10} && (15)\\
{}_0^{ABC} D_t^{\alpha_4}(Z) &= -\gamma^{\alpha_4} Z && (16)
\end{aligned}
$$

where the initial conditions are $T(0) = 0, C(0) = 1, I_{10}(0) = 4, Z(0) = 2$, and $i \in \{1, 2, 3, 4\}$, $\alpha_i \in [0, 1]$. $\alpha_i = \alpha$ will be assumed in the following sections.

3.1. Stability Analysis of the Model in Caputo Fractional Derivative

The stability analysis will be given for the model, which is rearranged using the Caputo fractional derivative and the dimension so that the right–left sides have the same size.

$C = 0$, $C = q^{\alpha}$ are obtained by solving equations where the left-hand sides of Equations (9)–(12) are set to 0.

Let P_1, P_2 be the equilibrium points of Equations (9)–(12). The Jacobian matrix of this system is computed as follows:

$$
J(P) = \begin{pmatrix}
b^{\alpha} I_{10} C - 2b^{\alpha} I_{10} C \frac{T}{p^{\alpha}} - c^{\alpha} & -e^{\alpha} C I_{10} - z^{\alpha} C Z & 0 & 0\\
b^{\alpha} I_{10} T\left(1 - \frac{T}{p^{\alpha}}\right) & d^{\alpha} - 2d^{\alpha} \frac{C}{q^{\alpha}} - e^{\alpha} T I_{10} - z^{\alpha} T Z & 0 & 0\\
b^{\alpha} C T\left(1 - \frac{T}{p^{\alpha}}\right) & -e^{\alpha} C T & -f^{\alpha} & 0\\
0 & -e^{\alpha} C T & 0 & -\gamma^{\alpha}
\end{pmatrix}.
$$

As a result, the eigenvalues of the matrix $J(P_1)$ produced by substituting the P_1 in the Jacobian matrix equilibrium point are determined to be $\lambda_j^{(1)}, j \in \{1, 2, 3, 4\}$ as follows:

$$
\lambda_1^{(1)} = -c^{\alpha}, \lambda_2^{(1)} = d^{\alpha}, \lambda_3^{(1)} = -f^{\alpha}, \lambda_4^{(1)} = -\gamma^{\alpha}.
$$

The eigenvalues $\lambda_j^{(2)}, j \in \{1, 2, 3, 4\}$ of the $J(P_2)$ matrix obtained in the same manner are as follows:

$$
\lambda_1^{(2)} = -c^{\alpha}, \lambda_2^{(2)} = -d^{\alpha}, \lambda_3^{(2)} = -f^{\alpha}, \lambda_4^{(2)} = -\gamma^{\alpha}.
$$

The stability of the system is dependent on the tumor's growth rate when we utilize the values in Table 1, as shown from the 2nd components (d^{α} and $-d^{\alpha}$) of the eigenvalue vectors. Looking at the equation of $\lambda_2^{(1)}$ and $\lambda_2^{(2)}$, the first of these values is positive, whereas the second is negative. As a result, we declare that P_1 is unstable, while P_2 is stable. In other words, for the eigenvalues derived from the solution of the characteristic equation of $det\left(J(P_2) - \lambda_j^{(2)} I\right) = 0$, for $j \in \{1, 2, 3, 4\}$, P_2 is asymptotically stable since $\left|arg\left(\lambda_j^{(2)}\right)\right| > \frac{\alpha\pi}{2}$.

Table 1. The (1)–(4) system's parameter value as expressed by $c = cells$ and $h = hour$ [49].

Parameter	Meaning	Value (Unit)
a	the initial density of CD8+T cells	0.0001 ($ch^{-1}mm^{-3}$)
b	the reproduction rate of CD8+T	0.39 ($c^{-1}h^{-1}mm^3$)
c	the death ratio of CD8+T cells	0.0005 (h^{-1})
p	the carrying capacity of CD8+T cells	1 (cmm^{-3})
d	the tumor growth ratio	0.02 ($ch^{-1}mm^{-3}$)
q	the carrying capacity of cancer cells	1 (cmm^{-3})
e	the death ratio of cancer cells under the effect of IL-10	0.15 (h^{-1})
z	the death ratio of cancer cells under the effect of anti-PD-L1	1 ($c^{-1}h^{-1}mm^3$)
f	the decay rates of IL-10	0.01 (h^{-1})
γ	the decay rates of anti-PD-L1	0.001925 (h^{-1})

Using Table 1, it is seen that the tumor concentration at the two equilibria makes a significant difference. In terms of biology, the tumor-free equilibrium point exists when $C = 0$. In this instance, the tumor is successfully fought by the immune system, therefore, no therapy is required. Treatment is required at the other equilibrium point where $C = q$ is attained since the tumor concentration is nearly at its carrying capacity.

3.2. The Existence and Uniqueness of Solution in Caputo Fractional Derivative

Let positive parameters, the initial conditions $T(0) \geqslant 0, C(0) \geqslant 0, I_{10}(0) \geqslant 0, Z(0) \geqslant 0$ where $0 < \alpha \leq 1$ for system given by Equations (9)–(12). Hence the system is the following:

$$\begin{aligned} D^{\alpha}Y(t) =& B_1Y(t) + C(t)B_2Y(t) + I_{10}(t)C(t)B_3Y(t) + I_{10}(t)C(t)Y(t) \\ &+ B_4Y(t) + T(t)Z(t)B_5Y(t) + \phi. \end{aligned} \tag{17}$$

where $t \in [0, \alpha]$ and

$$y(t) = \begin{pmatrix} C(t) \\ T(t) \\ I_{10}(t) \\ Z(t) \end{pmatrix}, y(0) = \begin{pmatrix} C(0) \\ T(0) \\ I_{10}(0) \\ Z(0) \end{pmatrix}, \phi = \begin{pmatrix} a^{\alpha} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, B_1 = \begin{pmatrix} -c^{\alpha} & 0 & 0 & 0 \\ 0 & d^{\alpha} & 0 & 0 \\ 0 & 0 & -f^{\alpha} & 0 \\ 0 & 0 & 0 & -\gamma^{\alpha} \end{pmatrix}, B_2 = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & \frac{-d^{\alpha}}{q^{\alpha}} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix},$$

$$B_3 = \begin{pmatrix} b^{\alpha} & 0 & 0 & 0 \\ -e^{\alpha} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, B_4 = \begin{pmatrix} \frac{-b^{\alpha}}{p^{\alpha}} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}, B_5 = \begin{pmatrix} 0 & 0 & 0 & 0 \\ 0 & -z^{\alpha} & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}.$$

Definition 7 ([12–14]). *$C^*[0, \alpha]$ is the class of continuous functions on the interval $[0, \alpha]$ and the class of continuous column vector $Y(t)$ and its components $T(t)$, $C(t)$, $I_{10}(t)$, $Z(t)$. The norm of $Y \epsilon C^*[0, \alpha]$ is displayed by a*

$$\|Y\| = \sup_t \left|Ye^{-Kt}T(t)\right| + \sup_t \left|Ye^{-Kt}C(t)\right| + \sup_t \left|Ye^{-Kt}I_{10}(t)\right| + \sup_t \left|Ye^{-Kt}Z(t)\right|$$

when $t > \tau \geq 0$, we say $C^*_{\tau}[0, \alpha]$, $C_{\tau}[0, \alpha]$.

Definition 8. *The initial value problem in Equation (17) has a solution as $Y \in C^*[0, \alpha]$ if*

- *$(t, Y(t)) \in A, t \epsilon [0, \alpha]$ where $A = [0, \alpha] \times L$, $L = \{(T, C, I_{10}, Z) \in R^4_+ : |T| \leq t_1,\ |C| \leq c, |I_{10}| \leq i_{10}, |Z| \leq z\}$; t_1, c, i_{10}, z are positive constants.*
- *$Y(t)$ is satisfied in Equation (17).*

Theorem 1. *There is only unique solution $Y \in C^*[0, \alpha]$ to the initial value problem Equation (17).*

Proof. By using the properties of fractional calculus and Equation (17),

$$\begin{aligned} I^{1-\alpha}\frac{d}{dt}Y(t) &= B_1Y(t)+C(t)B_2Y(t)+I_{10}(t)C(t)B_3Y(t)+I_{10}(t)C(t)T(t)+B_4Y(t) \\ &\quad +T(t)Z(t)B_5Y(t)+\phi. \end{aligned}$$

Using I^{α},

$$\begin{aligned} Y(t) &= Y(0)+I^{\alpha}[B_1Y(t)+C(t)B_2Y(t)+I_{10}(t)C(t)B_3Y(t)+I_{10}(t)C(t)T(t)+B_4Y(t) \\ &\quad +T(t)Z(t)B_5Y(t)+\phi]. \end{aligned} \tag{18}$$

Let $F : C^*[0,\alpha] \to C^*[0,\alpha]$. Hence,

$$\begin{aligned} FY(t) &= Y(0)+I^{\alpha}[B_1Y(t)+C(t)B_2Y(t)+I_{10}(t)C(t)B_3Y(t)+I_{10}(t)C(t)T(t)+B_4Y(t) \\ &\quad +T(t)Z(t)B_5Y(t)+\phi]. \end{aligned} \tag{19}$$

Later,

$$\begin{aligned} e^{-KT}(FY-FX) &= e^{-Kt}I^{\alpha}[B_1(Y-X)+C(t)B_2(Y-X)+I_{10}(t)C(t)B_3(Y-X) \\ &\quad +I_{10}(t)C(t)T(t)B_4(Y-X)+T(t)Z(t)B_5(Y-X)+\phi] \\ &\leq \frac{1}{\Gamma(\alpha)}\int_0^t (t-s)^{\alpha-1}e^{-K(t-s)}(Y(s)-X(s))\times e^{-Ks}(B_1+cB_2+i_{10}cB_3 \\ &\quad +i_{10}ct_1B_4+t_1zB_5)ds \\ &\leq (B_1+cB_2+i_{10}cB_3+i_{10}ct_1B_4+t_1zB_5)\times\frac{1}{K^{\alpha}}\|Y-X\|\frac{1}{\Gamma(\alpha)}\int_0^t s^{\alpha-1}ds. \end{aligned}$$

We acquire

$$\|FY-FX\| \leq (B_1+cB_2+i_{10}cB_3+i_{10}ct_1B_4+t_1zB_5)\times\frac{1}{K^{\alpha}}\|Y-X\|.$$

If K is chosen below $K^{\alpha} \geq B_1+cB_2+i_{10}cB_3+i_{10}ct_1B_4+t_1zB_5$, obtained such that

$$\|FY-FX\| < \|Y-X\|.$$

Thus, Equation (18) is said to have a unique solution $X \in C^*[0,\alpha]$. Through F, shown by Equation (19), which appears to have a fixed point. Then, the following is obtained by using Equation (18)

$$\begin{aligned} e^{-Kt}Y'(t) &= e^{-Kt}\left[\frac{t^{\alpha-1}}{\Gamma(\alpha)}[B_1Y(0)+C(0)B_2Y(0)+I_{10}(0)C(0)B_3Y(0)+I_{10}(0)C(0)T(0)B_4Y(0)\right. \\ &+ T(0)Z(0)B_5Y(0)+\phi]+I^{\alpha}\Big(B_1Y'(t)+C'(t)B_2Y(t)+C(t)B_2Y'(t) \\ &+ I'_{10}(t)C(t)B_3Y(t)+I_{10}(t)C'(t)B_3Y(t)+I_{10}(t)C(t)B_3Y'(t)+I'_{10}(t)C(t)T(t)B_4Y(t) \\ &+ I_{10}(t)C'(t)T(t)B_4Y(t)+I_{10}(t)C(t)T'(t)B_4Y(t)I_{10}(t)C(t)T(t)B_4Y'(t)+T'(t)Z(t)B_5Y(t) \\ &+ \left.T(t)Z'(t)B_5Y(t)+T(t)Z(t)B_5Y'(t)\Big)\right]. \end{aligned}$$

From Equation (18), it can be said that $Y' \in C^*_{\tau}[0,\alpha]$. Using Equation (18), inscribed

$$\begin{aligned} \frac{dY(t)}{dt} &= \frac{d}{dt}I^{\alpha}[B_1Y(t)+C(t)B_2Y(t)+I_{10}(t)C(t)B_3Y(t)+I_{10}(t)C(t)T(t)+B_4Y(t) \\ &\quad +T(t)Z(t)B_5Y(t)+\phi], \end{aligned}$$

hereby,

$$I^{1-\alpha}\frac{dY(t)}{dt} = I^{1-\alpha}\frac{d}{dt}I^{\alpha}[B_1Y(t)+C(t)B_2Y(t)+I_{10}(t)C(t)B_3Y(t)+I_{10}(t)C(t)T(t) + B_4Y(t)+T(t)Z(t)B_5Y(t)+\phi].$$

Hence, the following is obtained:

$$D^{\alpha}Y(t) = B_1Y(t)+C(t)B_2Y(t)+I_{10}(t)C(t)B_3Y(t)+I_{10}(t)C(t)T(t)+B_4Y(t) + T(t)Z(t)B_5Y(t)+\phi.$$

and

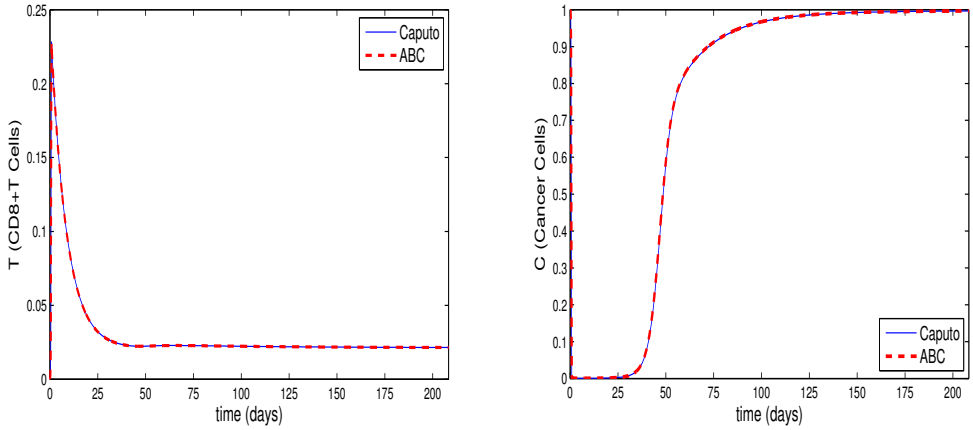
$$Y(0) = Y_0+I^{\alpha}[B_1Y(0)+C(0)B_2Y(0)+I_{10}(0)C(0)B_3Y(0)+I_{10}(0)C(0)T(0)+B_4Y(0) + T(0)Z(0)B_5Y(0)+\phi] = X_0.$$

Hence, it can be seen that the initial value problem Equation (17) is equivalent to Equation (18). □

4. Comparing Numerical Results of Model with Caputo Derivate and ABC Derivative

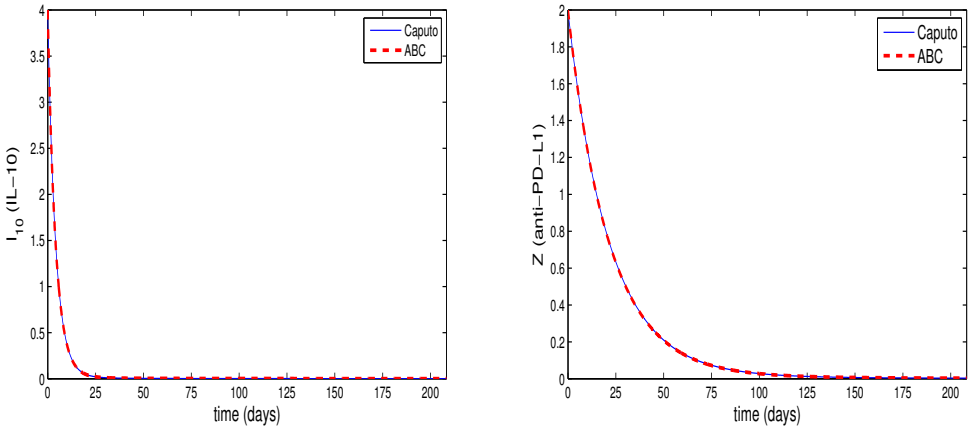
Figures 1a–d, 2a–d and 3a–d are drawn from the solution of the Equations (9)–(12). The solution is composed by the use of Caputo fractional derivative and the Equations (13)–(16), which is formed by the use of ABC derivative for fractional order $\alpha = 1, 0.93, 0.76, 0.59, 0.42$. The ABM method is used to obtain the solution to Equations (9)–(12) and the predictor–corrector method is used to find the solution to Equations (13)–(16). Moreover, the system's tumor burden has been attempted to be taken into account when choosing the fractional order.

The Figure 1a–d show that the tumor burden in the system has not diminished and that the cancer cells have reached their initial value. By synchronously examining Figures 2b and 3b derived for tumor cells, along with Figures 2a and 3a derived for CD8+T cells, it is observed that CD8+T cells peak at the point when the number of tumor cells is at minimum. After a time interval, CD8+T cells also show a decrease due to the decrease in the number of tumor cells; thus, the tumor cells, taking advantage of the deficiency of the immune system, start regrowing. This conclusion is in accordance with the fact that the patients whose immune systems are supressed have a greater risk of developing cancer. Furthermore, tumor congregation diminishes in intensity when the activity of the immune system is enhanced, mitigating the strain of tumors on the system.



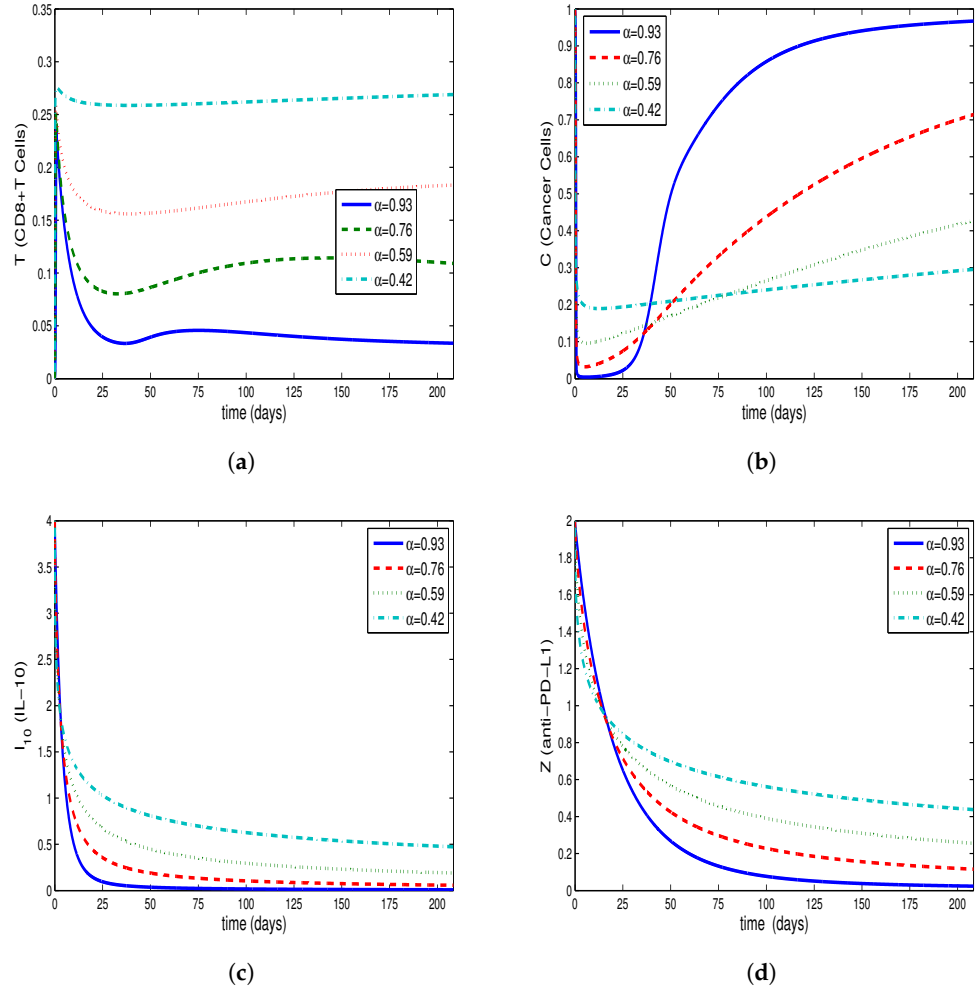
(**a**) (**b**)

Figure 1. *Cont.*



(**c**) (**d**)

Figure 1. Numerical simulations of the system given by Equations (9)–(12) with Caputo fractional derivative and Equations (13)–(16) with ABC fractional derivative for $\alpha = 1$.



(**a**) (**b**)

(**c**) (**d**)

Figure 2. Numerical simulations of the system given by Equations (9)–(12) with Caputo fractional derivative according to time.

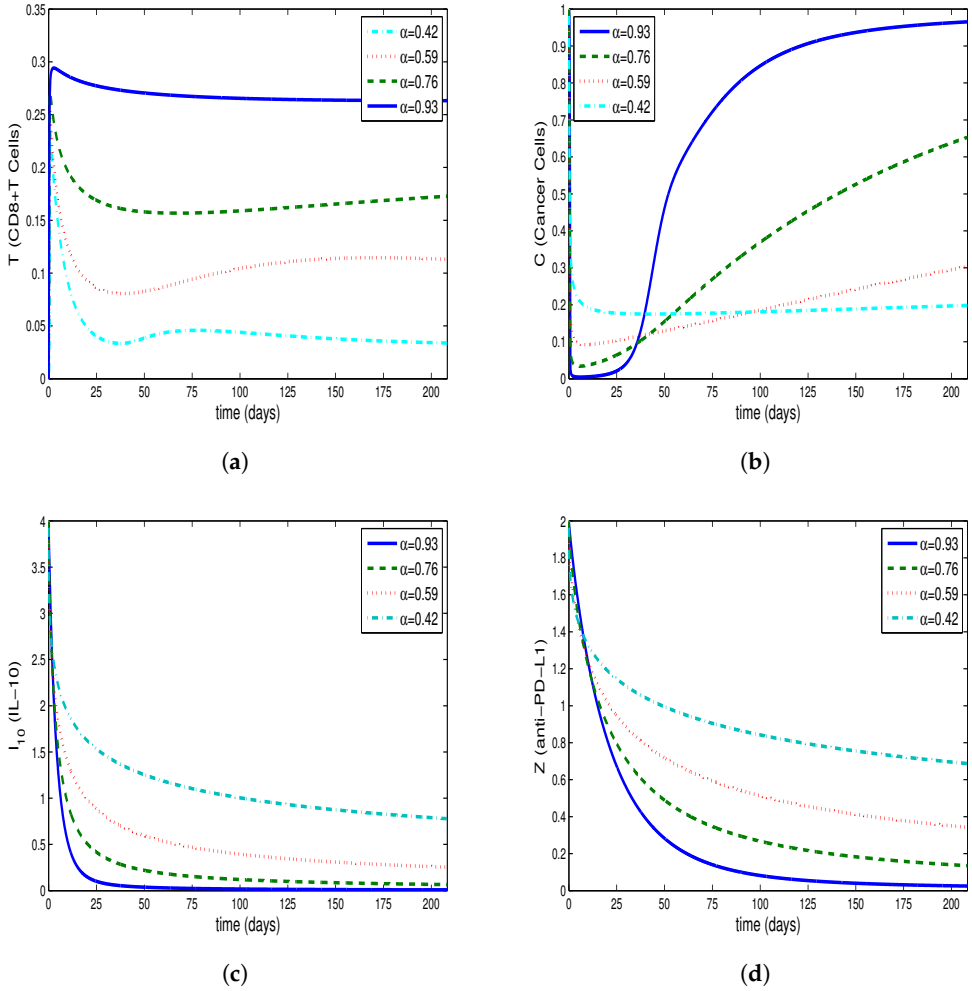


Figure 3. Numerical simulations of the system given by Equations (13)–(16) with ABC fractional derivative according to time.

As shown in Figures 2c,d and 3c,d, the half-lives of the single-dose IL-10 cytokine and anti-PD-L1 inhibitor after being delivered to the system cause them to demonstrate decline up to a specific point. Moreover, these figures reveal that α, which represents the situation where IL-10 and anti-PD-L1 remain at the highest level, is the lowest value amongst all the assessed values.

Additionally, for the relevant values of $\alpha = 1, 0.93, 0.76, 0.59, 0.42$, the tumor cells decline by 0.33%, 3.29%, 28.57%, 57.26%, and 70.44%, respectively, for the system generalized by the Caputo derivative, and 0.33%, 3.47%, 34.71%, 69.66%, and 80.16%, respectively for the system generalized by the ABC derivative, compared to the initial value.

5. Concluding Remarks

Equations (1)–(4), generalized by the Caputo and ABC derivatives, are examined. It is seen that tumor cells show a reduction from 0.33% to 70.44% and from 0.33% to 80.16%, respectively. It is observed that the order representing the situation which elongates the time interval between the decreasing and regrowth of tumor cells is a fractional order $\alpha = 0.42$. The obtained result is compatible with the fact that the system generalized by the fractional derivative is more appropriate for daily life issues involving memory and genetic factors.

Subsequent to the stability analysis of the system with the Caputo derivative, the existence–uniqueness problem concerning the solution of the system is scrutinized.

It is recognized that the number of cancer cells is decreased by 70.44% in comparison with the initial level for the system given by Equations (9)–(12). The value of α for the system given by Equations (13)–(16), for the situation where it declines by 80.16%, is 0.42. Therefore, it is deduced that the CD8+T cells fight cancer cells more efficiently under the influence of IL-10 and anti-PD-L1 by means of the solutions of the systems generalized by Caputo and ABC derivative. We can state that the system with the ABC derivative puts up a more effective struggle compared to the system with the Caputo derivative.

In addition, it is observed that the order representing the situation, where the time interval until the cancer cells regrow to their initial value is elongated, is also of fractional order $\alpha = 0.42$ in these novel systems designed by fractional derivative. The obtained result evidences that a more efficient struggle is given against cancer in the event that the influence of the derivative on the system declines.

Tables 2 and 3 show the cell concentrations of different cells in the same time interval for the systems generalized by Caputo or ABC derivatives. According to Tables 2 and 3, the IL-10 and anti-PD-L1 concentrations are higher for ABC derivatives, although the CD8+T cells remain on the same level of concentration synchronously for both of the generalized systems. This leads to a striking result, demonstrating that the cancer cells decrease by a higher rate in comparison with their initial value in ABC as against Caputo derivative. High tumor burden in the systems given by Equations (9)–(12) and Equations (13)–(16) can be associated with a fractional order α close to 1 via Figures 1a–d, 2a–d and 3a–d.

Table 2. The concentration of variables of system at for order α Caputo fractional derivative.

α	CD8+T Cells	Tumor Cells	IL-10	Anti-PD-L1
1	0.0214	0.9967	0.0008	0.003
0.93	0.0335	0.9671	0.008	0.0236
0.76	0.1091	0.7143	0.0571	0.1152
0.59	0.1832	0.4274	0.1892	0.2553
0.42	0.2689	0.2956	0.4728	0.4376

Table 3. The concentration of variables of system at for order α ABC derivative.

α	CD8+T Cells	Tumor Cells	IL-10	Anti-PD-L1
1	0.0214	0.9967	0.0008	0.003
0.93	0.0338	0.9653	0.0082	0.0246
0.76	0.1129	0.6529	0.0654	0.1348
0.59	0.1728	0.3034	0.2532	0.3425
0.42	0.2632	0.1984	0.7779	0.6872

The system given by Equations (9)–(12) and Equations (13)–(16), which have been analyzed using the fractional derivative, also demonstrate that IL-10 and anti-PD-L1, which are given in a single dose, have a significant impact on the elimination of cancer cells. When a specific protocol is followed with repeated dose applications and treatments, the effectiveness of the drug is accepted.

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