



Analysis of a Fractional Tumor–Immune Interaction Model With Exponential Kernel

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Abstract. In this paper, a tumor-immune interaction model has been analyzed via Caputo-Fabrizio fractional derivative operator with exponential kernel. Existence of solution of the model has been established with a fixed-point method and then it demonstrated the uniqueness of solution also. The stability of the model has been analyzed with the help of Hyers-Ulam stability approach and then numerical solution by using the Adam-Basford method. The results are further examined in detail with simulations for different fractional derivative values.

1. Introduction

Diseases have always existed throughout the history of humanity and have often resulted in death for humans. Many diseases often pass from animals to humans through bacteria and viruses. Carrier individuals can transmit bacteria or virus to the other people and this may eventually turn into a pandemic. Antonine pandemic, which is known as Flower or Measles in colloquial language, is thought to have caused the death of an estimated 5 million people in 165-180 AD. In the mid-500s, the Justinian Plague (1st Plague Outbreak), which was caused by the *Yersinia pestis* bacteria strain, resulted in the death of 30-50 million people. Many other similar outbreaks have occurred throughout the history. Among these, the most common causes of death are the yellow fever epidemic (late 1800s), Spanish Flu (1918-1919), and HIV/AIDS (1981-still ongoing). In the 21st century, a remarkable soaring occurred in epidemic diseases. Since the beginning of 2000s, virus-borne epidemics such as SARS, Swine flu, Ebola, and MERS are causing threats to countries, continents and even the whole world. One of the most important recent examples is the coronavirus, which is called COVID-19, that continues today and already caused death of many peoples.

Countries are forced to allocate big budgets for the treatment of pandemic diseases. While some have treatment, for some others there is only the possibility of slowing down, postponing or delaying the disease. Nowadays, cancer, which has many varieties, is one of the most important diseases that threatens humanity, apart from viruses. There are almost 100 types of cancer detected so far. Tubers that are formed by excessive proliferation of cells and tend to grow in any tissue or organ of the body are called tumors. Tumors are

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usually divided into two different types, namely benign and malign. Malign tumors are defined as cancer in the literature. There has been considerable progress in the treatment of such malignant tumors. Studies have shown that cytokine interleukin-2 (IL-2) strengthens the immune system and thus can be used with immunotherapy treatment against tumors. This treatment method is one of the important developments in cancer treatment. The immune system cannot always separate tumor cells from other cells. That is, the spread and progression of tumor cells throughout the body can be quite fast. But with immunotherapy treatment, our original cells can be fulfilled or increased.

A model, which represents a tumor-immune interaction with time lag, has been premised by Kuznetsov et al. [4]. In this study, the proposed model will be analyzed with the help of fractional derivative operators.

Noteworthy research on this subject are as follows: Kirschner and Panetta [5] thought they could strengthen the immune system with interleukin-2 (IL-2). On the other hand, mathematics that developed on this subject researched the effect of immunotherapy with the model and made some suggestions on how the tumor can be eliminated. Khajanchi and Banerjee [6] performed a research on the stability of a tumor-immune interaction model, which was proposed by Kuznetsov. Moreover, in order to verify their evidence, the system parameters have been altered and numerical simulations were suggested. Banerjee and Sarkar [7] carried out a qualitative analysis of the system of differential equations, including a tumor-immune interaction mathematical model. Thanks to this approach, they provided a new perspective to the model and developed control strategies to cope with the big oscillations. Wei and Lin [8] have established a mathematical analysis that would determine the minimum dose required for the immunotherapy treatment to get the maximum benefit. They also claimed that the proposed numerical method could be applied to a class of mathematical models for periodic drug treatments. Robertson-Tessi et al. [9] analyzed the mathematical model of the interactions between the growing tumor and the immune system. Ledzewicz et al. [10] have suggested a mathematical model for cancer-immune system interactions. They conducted research on the regression of cancer with chemotherapy and thus the necessity to move it to a region where it controls cancer. In addition, there are many studies in the literature on mathematical modeling and its fractional derivatives [11–21].

Considering the crucial studies related to tumor-immune interaction in the literature, we shall analyze the proposed tumor-immune interaction mathematical model by extending it to the fractional derivative operator. This study is divided into six different sections as follows: In the first section, a literature review of the mathematical model is carried out and significant information on the subject is given. The literature, which will be used in the study, such as essential definitions, theorems and lemma etc. are presented in the second section. In the third section, the model and its new version by means of the fractional derivative operator are examined. Also in this section, the existence and uniqueness solutions of the model are studied. In the fourth section, the stability of the model is presented with the Hyers-Ulam stability theorem. In the fifth section, the numerical solutions of the model are examined. The simulations are given for different fractional derivative values. Moreover, the detailed analyzes were carried out and interpreted by making comparisons with the help of graphics. The last section is devoted for a conclusion.

2. Preliminaries

In this section, fundamental definitions and results shall be given and they are related to fractional derivatives and integral operators [22–26].

Definition 2.1. *The well-known fractional order Caputo derivative is defined as follows [22],*

$${}_a^C D_t^\vartheta \phi(t) = \frac{1}{\Gamma(m - \vartheta)} \int_a^t \frac{\phi^{(m)}(\omega)}{(t - \omega)^{\vartheta+1-m}} d\omega, \quad m - 1 < \vartheta < m \in N, \quad (1)$$

with $\phi \in H^1(a, b)$, $b > a$.

Definition 2.2. The Riemann-Liouville fractional integral is defined as [26]:

$$J^{\vartheta} \phi(t) = \frac{1}{\Gamma(\vartheta)} \int_a^t \phi(\omega)(t - \omega)^{\vartheta-1} d\omega. \tag{2}$$

Definition 2.3. The Sobolev space of order 1 in (a, b) is defined as [23]:

$$H^1(a, b) = \{u \in L^2(a, b) : u' \in L^2(a, b)\}. \tag{3}$$

Definition 2.4. Let $f \in H^1(a, b)$, $b > a$, $\rho \in (0, 1)$ then, the definition of the new Caputo fractional derivative is [24],

$${}^{CF} \mathfrak{D}_t^{\rho}(\phi(t)) = \frac{\rho M(\rho)}{1 - \rho} \int_a^t \frac{d\phi(\omega)}{d\omega} \exp\left[-\rho \frac{t - \omega}{1 - \rho}\right] d\omega, \tag{4}$$

where $M(\rho)$ is a normalization function. Also, $M(0) = M(1) = 1$. If the function does not belong to $H^1(a, b)$, above definition is also written as below

$${}^{CF} \mathfrak{D}_t^{\rho}(\phi(t)) = \frac{\rho M(\rho)}{1 - \rho} \int_a^t (\phi(t) - \phi(\omega)) \exp\left[-\rho \frac{t - \omega}{1 - \rho}\right] d\omega. \tag{5}$$

Also, Losada and Nieto [25] proposed that the new Caputo derivative (CF) of order $0 < \rho < 1$ can be reformulated as below,

Definition 2.5. The Caputo-Fabrizio (CF) derivative with fractional order ρ is as below [25],

$${}^{CF} \mathfrak{D}_{\star}^{\rho}(\phi(t)) = \frac{1}{1 - \rho} \int_0^t \phi'(\omega) \exp\left[-\rho \frac{t - \omega}{1 - \rho}\right] d\omega. \tag{6}$$

Remark 2.6. The Laplace transform of the new Caputo fractional derivative with s variable

$$\begin{aligned} LT[\mathfrak{D}_t^{\rho}(\phi(t))] &= \frac{1}{1 - \nu} \int_0^{\infty} \exp(-st) \int_0^t \frac{d\phi(x)}{d\omega} \exp\left[-\rho \frac{t - \omega}{1 - \rho}\right] d\omega dt \\ &= \frac{(sLT(\phi(t)) - f(0))}{s + \nu(1 - s)}. \end{aligned} \tag{7}$$

Definition 2.7. Let $0 < \rho < 1$. The fractional integral of order ρ of a function f is defined by [24],

$${}^{CF} I^{\rho} \phi(t) = \frac{2(1 - \rho)}{(2 - \rho)M(\rho)} u(t) + \frac{2\rho}{(2 - \rho)M(\rho)} \int_0^t u(s) ds, \quad t \geq 0. \tag{8}$$

Definition 2.8. The function $f(t, y)$ satisfies a Lipschitz condition in the variable y on a set $D \subset \mathbb{R}^2$ if a constant $L > 0$ exists with [26]

$$|f(t, y_1) - f(t, y_2)| \leq L|y_1 - y_2|, \tag{9}$$

whenever $(t, y_1), (t, y_2)$ are in D . L is a Lipschitz constant.

Definition 2.9. Let $f(t, x)$ be piecewise continuous in t and satisfies the Lipschitz condition [26]

$$\|f(t, x) - f(t, \hat{x})\| \leq L\|x - \hat{x}\|, \quad \forall x, \hat{x} \in \mathbb{R}^n \tag{10}$$

then, the function $f(t, x)$ is said to be Lipschitz in x , and the positive constant L is called a Lipschitz constant.

3. The Mathematical Model and Its Derivation

3.1. Classical model

The following mathematical model is a system of differential equations containing two main populations by Kuznetsov et al.[4]. These populations are effector cells and tumor cells.

$$\begin{aligned} \frac{dE(t)}{dt} &= s + \frac{pE(t)T(t)}{g + T(t)} - mE(t)T(t) - dE(t), \\ \frac{dT(t)}{dt} &= aT(t)(1 - bT(t)) - nE(t)T(t). \end{aligned} \tag{11}$$

The tumor-immune dynamics model in [5] takes into consideration three different populations. Firstly, $X(t)$ identifies activated immune system cells. Secondly, $Y(t)$ identifies tumor cells. And thirdly, $Z(t)$ identifies the interleukin-2 ($IL-2$) this portion properly concentration in the single tumor region compartment model. This model is given as follows.

$$\begin{aligned} \frac{dX(t)}{dt} &= \gamma Y(t) - \theta_2 X(t) + \frac{\zeta_1 X(t)Z(t)}{\eta_1 + Z(t)} + \kappa_1, \\ \frac{dY(t)}{dt} &= \mu_2(1 - \beta Y(t))Y(t) - \frac{\alpha X(t)Y(t)}{\eta_2 + Y(t)}, \\ \frac{dZ(t)}{dt} &= \frac{\zeta_2 X(t)Y(t)}{\eta_3 + Y(t)} - \theta_3 Z(t) + \kappa_2. \end{aligned} \tag{12}$$

with the initial conditions:

$$X(0) = X_0, \quad Y(0) = Y_0, \quad Z(0) = Z_0$$

All the parameters given below are available in [5].

Table 1: Values of the parameters of the system (12)

Parameter	Value
γ	[0, 0.05]
θ_2	0.03
ζ_1	0.1245
η_1	2×10^7
μ_2	0.18
β	1×10^{-9}
α	1
η_3	10
ζ_2	5
θ_3	1×10^3

3.2. Existence of solution to the fractional model

In this section, existence of solution shall be examined for a fractional tumor-immune interaction mathematical model by using a fixed point technique. When the system (12) is written via the CF fractional derivative, we have the following form:

$$\begin{aligned}
 {}_t^{\text{CF}}\mathfrak{D}_0^\rho X(t) &= \gamma Y(t) - \theta_2 X(t) + \frac{\zeta_1 X(t)Z(t)}{\eta_1 + Z(t)} + \kappa_1, \\
 {}_t^{\text{CF}}\mathfrak{D}_0^\rho Y(t) &= \mu_2(1 - \beta Y(t))Y(t) - \frac{\alpha X(t)Y(t)}{\eta_2 + Y(t)}, \\
 {}_t^{\text{CF}}\mathfrak{D}_0^\rho Z(t) &= \frac{\zeta_2 X(t)Y(t)}{\eta_3 + Y(t)} - \theta_3 Z(t) + \kappa_2,
 \end{aligned}
 \tag{13}$$

with non-negative initial conditions

$$X_0 = X(0), \quad Y_0 = Y(0), \quad Z_0 = Z(0).$$

The system (13) can be written using the definition (2.6) as follows:

$$\begin{aligned}
 X(t) - X(0) &= \frac{2(1 - \rho)}{2M(\rho) - \rho M(\rho)} \left(\gamma Y(t) - \theta_2 X(t) + \frac{\zeta_1 X(t)Z(t)}{\eta_1 + Z(t)} + \kappa_1 \right) \\
 &\quad + \frac{2\rho}{2M(\rho) - \rho M(\rho)} \int_0^t \left(\gamma Y(\omega) - \theta_2 X(\omega) + \frac{\zeta_1 X(\omega)Z(\omega)}{\eta_1 + Z(\omega)} + \kappa_1 \right) d\omega, \\
 Y(t) - Y(0) &= \frac{2(1 - \rho)}{2M(\rho) - \rho M(\rho)} \left(\mu_2(1 - \beta Y(t))Y(t) - \frac{\alpha X(t)Y(t)}{\eta_2 + Y(t)} \right) \\
 &\quad + \frac{2\rho}{2M(\rho) - \rho M(\rho)} \int_0^t \left(\mu_2(1 - \beta Y(\omega))Y(\omega) - \frac{\alpha X(\omega)Y(\omega)}{\eta_2 + Y(\omega)} \right) d\omega, \\
 Z(t) - Z(0) &= \frac{2(1 - \rho)}{2M(\rho) - \rho M(\rho)} \left(\frac{\zeta_2 X(t)Y(t)}{\eta_3 + Y(t)} - \theta_3 Z(t) + \kappa_2 \right) \\
 &\quad + \frac{2\rho}{2M(\rho) - \rho M(\rho)} \int_0^t \left(\frac{\zeta_2 X(\omega)Y(\omega)}{\eta_3 + Y(\omega)} - \theta_3 Z(\omega) + \kappa_2 \right) d\omega.
 \end{aligned}
 \tag{14}$$

For simplicity of the kernels, one can write as follows,

$$\begin{aligned}
 \mathfrak{Q}_1(t, X) &= \gamma Y(t) - \theta_2 X(t) + \frac{\zeta_1 X(t)Z(t)}{\eta_1 + Z(t)} + \kappa_1, \\
 \mathfrak{Q}_2(t, Y) &= \mu_2(1 - \beta Y(t))Y(t) - \frac{\alpha X(t)Y(t)}{\eta_2 + Y(t)}, \\
 \mathfrak{Q}_3(t, Z) &= \frac{\zeta_2 X(t)Y(t)}{\eta_3 + Y(t)} - \theta_3 Z(t) + \kappa_2.
 \end{aligned}
 \tag{15}$$

and

$$\begin{aligned}
 \Phi_1 &= -\theta_2 + \frac{\zeta_1 \mathfrak{S}_3}{\eta_1 + \mathfrak{S}_3} \\
 \Phi_2 &= \mu_2 + \mu_2 \beta c_1 + \alpha \mathfrak{S}_1 c_2 \\
 \Phi_3 &= \theta_3.
 \end{aligned}$$

It is assumed that $C: X(t), Y(t), Z(t), X^*(t), Y^*(t), Z^*(t) \in L[0, 1]$ are continuous functions, so that $\|X(t)\| \leq \mathfrak{S}_1, \|Y(t)\| \leq \mathfrak{S}_2$ and $\|Z(t)\| \leq \mathfrak{S}_3$, respectively.

Theorem 3.1. *The kernels $\mathfrak{Q}_1, \mathfrak{Q}_2, \mathfrak{Q}_3$ satisfy the Lipschitz condition if the assumption C is true and are contractions provided that $\Phi_i < 1$ for $i = 1, 2, 3$.*

Proof. First, we proof that $\mathfrak{Q}_1(t, X)$ satisfies the Lipschitz condition. Let $X(t)$ and $X^*(t)$ be two functions. Then,

$$\begin{aligned} \|\mathfrak{Q}_1(t, X) - \mathfrak{Q}_1(t, X^*)\| &= \left\| \left(\gamma Y - \theta_2 X + \frac{\zeta_1 X Z}{\eta_1 + Z} + \kappa_1 \right) \right. \\ &\quad \left. - \left(\gamma Y - \theta_2 X^* + \frac{\zeta_1 X^* Z}{\eta_1 + Z} + \kappa_1 \right) \right\| \\ &\leq \left(-\theta_2 + \frac{\zeta_1 Z}{\eta_1 + Z} \right) \|X - X^*\| \\ &\leq \left(-\theta_2 + \frac{\zeta_1 \mathfrak{E}_3}{\eta_1 + \mathfrak{E}_3} \right) \|X - X^*\| \\ &= \Phi_1 \|X - X^*\|. \end{aligned} \tag{16}$$

Next, we proof that $\mathfrak{Q}_2(t, Y)$ satisfies the Lipschitz condition. Let $Y(t)$ and $Y^*(t)$ be two functions. Then,

$$\begin{aligned} \|\mathfrak{Q}_2(t, Y) - \mathfrak{Q}_2(t, Y^*)\| &= \left\| \left(\mu_2(1 - \beta Y)Y - \frac{\alpha X Y}{\eta_2 + Y} \right) \right. \\ &\quad \left. - \left(\mu_2(1 - \beta Y^*)Y^* - \frac{\alpha X Y^*}{\eta_2 + Y^*} \right) \right\| \\ &\leq \left(\mu_2 + \mu_2 \|(Y + Y^*)\| \right) \|Y - Y^*\| \\ &\quad + \left\| \frac{\alpha X}{\eta_2 + Y} - \frac{\alpha X}{\eta_2 + Y^*} \right\| \times \|Y - Y^*\| \\ &\leq \left(\mu_2 + \mu_2 \beta \|(Y + Y^*)\| \right) \|Y - Y^*\| \\ &\quad + \left\| \frac{\alpha X}{\eta_2 + Y} - \frac{\alpha X}{\eta_2 + Y^*} \right\| \times \|Y - Y^*\| \\ &\leq \left(\mu_2 + \mu_2 \beta c_1 + \alpha \mathfrak{E}_1 c_2 \right) \|Y - Y^*\| \\ &= \Phi_2 \|Y - Y^*\|. \end{aligned} \tag{17}$$

Finally, we proof that $\mathfrak{Q}_3(t, Z)$ satisfies the Lipschitz condition. Let $Z(t)$ and $Z^*(t)$ be two functions. Then,

$$\begin{aligned} \|\mathfrak{Q}_3(t, Z) - \mathfrak{Q}_3(t, Z^*)\| &= \left\| \left(\frac{\zeta_2 X Y}{\eta_3 + Y} - \theta_3 Z + \kappa_2 \right) \right. \\ &\quad \left. - \left(\frac{\zeta_2 X Y}{\eta_3 + Y} - \theta_3 Z^* + \kappa_2 \right) \right\| \\ &= \Phi_3 \|Z - Z^*\|. \end{aligned} \tag{18}$$

Considering equations (16)-(18), the kernels $\mathfrak{Q}_i, i = 1, 2, 3$ are satisfying the Lipschitz conditions, and they are contractions with $\Phi_i < 1, i = 1, 2, 3$. This completes the proof.

□

By using the kernels $\mathfrak{Q}_i, i = 1, 2, 3$ and the initial conditions $X(0) = Y(0) = Z(0) = 0$, we rewrite the system given by equation (8) as follows:

$$\begin{aligned} X(t) &= \frac{2(1 - \rho)}{2M(\rho) - \rho M(\rho)} \mathfrak{Q}_1(t, X(t)) + \frac{2\rho}{2M(\rho) - \rho M(\rho)} \int_0^t \mathfrak{Q}_1(\omega, X(\omega)) d\omega, \\ Y(t) &= \frac{2(1 - \rho)}{2M(\rho) - \rho M(\rho)} \mathfrak{Q}_2(t, Y(t)) + \frac{2\rho}{2M(\rho) - \rho M(\rho)} \int_0^t \mathfrak{Q}_2(\omega, Y(\omega)) d\omega, \\ Z(t) &= \frac{2(1 - \rho)}{2M(\rho) - \rho M(\rho)} \mathfrak{Q}_3(t, Z(t)) + \frac{2\rho}{2M(\rho) - \rho M(\rho)} \int_0^t \mathfrak{Q}_3(\omega, Z(\omega)) d\omega, \end{aligned} \tag{19}$$

Then, we have a system of equations defined by means of recursive formulas as follows:

$$\begin{aligned} X_n(t) &= \frac{2(1-\rho)}{2M(\rho)-\rho M(\rho)} \mathfrak{L}_1(t, X_{n-1}(t)) + \frac{2\rho}{2M(\rho)-\rho M(\rho)} \int_0^t \mathfrak{L}_1(\omega, X_{n-1}(\omega))d\omega, \\ Y_n(t) &= \frac{2(1-\rho)}{2M(\rho)-\rho M(\rho)} \mathfrak{L}_2(t, Y_{n-1}(t)) + \frac{2\rho}{2M(\rho)-\rho M(\rho)} \int_0^t \mathfrak{L}_2(\omega, Y_{n-1}(\omega))d\omega, \\ Z_n(t) &= \frac{2(1-\rho)}{2M(\rho)-\rho M(\rho)} \mathfrak{L}_3(t, Z_{n-1}(t)) + \frac{2\rho}{2M(\rho)-\rho M(\rho)} \int_0^t \mathfrak{L}_3(\omega, Z_{n-1}(\omega))d\omega, \end{aligned} \tag{20}$$

Also, the difference of each equation can be written as follows:

$$\begin{aligned} (X_{n+1} - X_n)(t) &= \frac{2(1-\rho)}{2M(\rho)-\rho M(\rho)} (\mathfrak{L}_1(t, X_n(t)) - \mathfrak{L}_1(t, X_{n-1}(t))) \\ &\quad + \frac{2\rho}{2M(\rho)-\rho M(\rho)} \int_0^t (\mathfrak{L}_1(\omega, X_n(\omega)) - \mathfrak{L}_1(\omega, X_{n-1}(\omega)))d\omega, \end{aligned} \tag{21}$$

$$\begin{aligned} (Y_{n+1} - Y_n)(t) &= \frac{2(1-\rho)}{2M(\rho)-\rho M(\rho)} (\mathfrak{L}_2(t, Y_n(t)) - \mathfrak{L}_2(t, Y_{n-1}(t))) \\ &\quad + \frac{2\rho}{2M(\rho)-\rho M(\rho)} \int_0^t (\mathfrak{L}_2(\omega, Y_n(\omega)) - \mathfrak{L}_2(\omega, Y_{n-1}(\omega)))d\omega, \end{aligned} \tag{22}$$

$$\begin{aligned} (Z_{n+1} - Z_n)(t) &= \frac{2(1-\rho)}{2M(\rho)-\rho M(\rho)} (\mathfrak{L}_3(t, Z_n(t)) - \mathfrak{L}_3(t, Z_{n-1}(t))) \\ &\quad + \frac{2\rho}{2M(\rho)-\rho M(\rho)} \int_0^t (\mathfrak{L}_3(\omega, Z_n(\omega)) - \mathfrak{L}_3(\omega, Z_{n-1}(\omega)))d\omega, \end{aligned} \tag{23}$$

Theorem 3.2. *The tumor-immune interaction mathematical model (13) has a solution if the following inequality is achieved:*

$$\Theta = \max\{\Phi_i\} < 1, \quad i = 1, 2, 3. \tag{24}$$

Proof. Let us consider the following equations,

$$\mathfrak{M}_{1n}(t) = X_{n+1}(t) - X_n(t), \quad \mathfrak{M}_{2n}(t) = Y_{n+1}(t) - Y_n(t), \quad \mathfrak{M}_{3n}(t) = Z_{n+1}(t) - Z_n(t).$$

We start with $\mathfrak{M}_{1n}(t)$,

$$\begin{aligned} \|\mathfrak{M}_{1n}(t)\| &\leq \frac{2(1-\rho)}{2M(\rho)-\rho M(\rho)} \|\mathfrak{L}_1(t, X_n(t)) - \mathfrak{L}_1(t, X(t))\| \\ &\quad + \frac{2\rho}{2M(\rho)-\rho M(\rho)} \int_0^t \|\mathfrak{L}_1(\omega, X_n(\omega)) - \mathfrak{L}_1(\omega, X(\omega))\|d\omega \\ &\leq \left(\frac{2-2\rho}{M(\rho)(2-\rho)} + \frac{2\rho}{M(\rho)(2-\rho)} \right) \Phi_1 \|X_n - X\| \\ &\leq \left(\frac{2-2\rho}{M(\rho)(2-\rho)} + \frac{2\rho}{M(\rho)(2-\rho)} \right)^n \Theta^n \|X - X_1\|. \end{aligned} \tag{25}$$

Next, we show for $\mathfrak{M}_{2n}(t)$,

$$\begin{aligned} \|\mathfrak{M}_{2n}(t)\| &\leq \frac{2(1-\rho)}{2M(\rho)-\rho M(\rho)} \|\mathfrak{L}_2(t, Y_n(t)) - \mathfrak{L}_2(t, Y(t))\| \\ &\quad + \frac{2\rho}{2M(\rho)-\rho M(\rho)} \int_0^t \|\mathfrak{L}_2(\omega, Y_n(\omega)) - \mathfrak{L}_2(\omega, Y(\omega))\| d\omega \\ &\leq \left(\frac{2-2\rho}{M(\rho)(2-\rho)} + \frac{2\rho}{M(\rho)(2-\rho)} \right) \Phi_2 \|Y_n - Y\| \\ &\leq \left(\frac{2-2\rho}{M(\rho)(2-\rho)} + \frac{2\rho}{M(\rho)(2-\rho)} \right)^n \Theta^n \|Y - Y_1\|. \end{aligned} \tag{26}$$

Finally, we show for $\mathfrak{M}_{3n}(t)$,

$$\begin{aligned} \|\mathfrak{M}_{3n}(t)\| &\leq \frac{2(1-\rho)}{2M(\rho)-\rho M(\rho)} \|\mathfrak{L}_3(t, Z_n(t)) - \mathfrak{L}_3(t, Z(t))\| \\ &\quad + \frac{2\rho}{2M(\rho)-\rho M(\rho)} \int_0^t \|\mathfrak{L}_3(\omega, Z_n(\omega)) - \mathfrak{L}_3(\omega, Z(\omega))\| d\omega \\ &\leq \left(\frac{2-2\rho}{M(\rho)(2-\rho)} + \frac{2\rho}{M(\rho)(2-\rho)} \right) \Phi_3 \|Z_n - Z\| \\ &\leq \left(\frac{2-2\rho}{M(\rho)(2-\rho)} + \frac{2\rho}{M(\rho)(2-\rho)} \right)^n \Theta^n \|Z - Z_1\|. \end{aligned} \tag{27}$$

So, it can be said that, we can find $\mathfrak{M}_{in}(t) \rightarrow 0, i = 1, 2, 3$, as $n \rightarrow \infty$. This completes the proof.

□

3.3. Uniqueness of solution to fractional model

In this section, we shall show the uniqueness of solution of the tumor-immune interaction mathematical model.

Theorem 3.3. *The tumor-immune interaction mathematical model (13) has a unique solution if the following inequality hold true:*

$$\left(\frac{2-2\rho}{M(\rho)(2-\rho)} + \frac{2\rho}{M(\rho)(2-\rho)} \right) \Phi_i \leq 1, \quad i = 1, 2, 3. \tag{28}$$

Proof. Let us assume that the system (13) has solutions $X(t), Y(t), Z(t)$, as well as $\tilde{X}(t), \tilde{Y}(t), \tilde{Z}(t)$. Then, the system can also be written as,

$$\begin{aligned} \tilde{X}(t) &= \frac{2-2\rho}{M(\rho)(2-\rho)} \mathfrak{L}_1(t, \tilde{X}(t)) + \frac{2\rho}{M(\rho)(2-\rho)} \int_0^t \mathfrak{L}_1(\omega, \tilde{X}(\omega)) d\omega, \\ \tilde{Y}(t) &= \frac{2-2\rho}{M(\rho)(2-\rho)} \mathfrak{L}_2(t, \tilde{Y}(t)) + \frac{2\rho}{M(\rho)(2-\rho)} \int_0^t \mathfrak{L}_2(\omega, \tilde{Y}(\omega)) d\omega, \\ \tilde{Z}(t) &= \frac{2-2\rho}{M(\rho)(2-\rho)} \mathfrak{L}_3(t, \tilde{Z}(t)) + \frac{2\rho}{M(\rho)(2-\rho)} \int_0^t \mathfrak{L}_3(\omega, \tilde{Z}(\omega)) d\omega, \end{aligned} \tag{29}$$

When the norm is taken for both the systems of equations above, firstly

$$\begin{aligned}
 \|X(t) - \tilde{X}(t)\| &\leq \frac{2-2\rho}{M(\rho)(2-\rho)} \left\| \left(\gamma Y(t) - \theta_2 X(t) + \frac{\zeta_1 X(t)Z(t)}{\eta_1 + Z(t)} + \kappa_1 \right) \right. \\
 &\quad \left. - \left(\gamma Y(t) - \theta_2 \tilde{X}(t) + \frac{\zeta_1 \tilde{X}(t)Z(t)}{\eta_1 + Z(t)} + \kappa_1 \right) \right\| \\
 &\quad + \frac{2\rho}{M(\rho)(2-\rho)} \int_0^t \left\| \left(\gamma Y(\omega) - \theta_2 X(\omega) \right. \right. \\
 &\quad \left. \left. + \frac{\zeta_1 X(\omega)Z(\omega)}{\eta_1 + Z(\omega)} + \kappa_1 \right) - \left(\gamma Y(\omega) - \theta_2 \tilde{X}(\omega) + \frac{\zeta_1 \tilde{X}(\omega)Z(\omega)}{\eta_1 + Z(\omega)} + \kappa_1 \right) \right\| d\omega \\
 &\leq \frac{2-2\rho}{M(\rho)(2-\rho)} \left[-\theta_2 + \frac{\zeta_1 \mathfrak{S}_3}{\eta_1 + \mathfrak{S}_3} \right] \|X - \tilde{X}\| \\
 &\quad + \left[-\theta_2 + \frac{\zeta_1 \mathfrak{S}_3}{\eta_1 + \mathfrak{S}_3} \right] \frac{2\rho}{M(\rho)(2-\rho)} \|X - \tilde{X}\| \\
 &\leq \frac{2-2\rho}{M(\rho)(2-\rho)} \Phi_1 \|X - \tilde{X}\| + \frac{2\rho \Phi_1}{M(\rho)(2-\rho)} \|X - \tilde{X}\|.
 \end{aligned} \tag{30}$$

Secondly,

$$\begin{aligned}
 \|Y(t) - \tilde{Y}(t)\| &\leq \frac{2-2\rho}{M(\rho)(2-\rho)} \left\| \left(\mu_2(1 - \beta Y(t))Y(t) - \frac{\alpha X(t)Y(t)}{\eta_2 + Y(t)} \right) \right. \\
 &\quad \left. - \left(\mu_2(1 - \beta \tilde{Y}(t))\tilde{Y}(t) - \frac{\alpha X(t)\tilde{Y}(t)}{\eta_2 + \tilde{Y}(t)} \right) \right\| \\
 &\quad + \frac{2\rho}{M(\rho)(2-\rho)} \int_0^t \left\| \left(\mu_2(1 - \beta Y(\omega))Y(\omega) - \frac{\alpha X(\omega)Y(\omega)}{\eta_2 + Y(\omega)} \right) \right. \\
 &\quad \left. - \left(\mu_2(1 - \beta \tilde{Y}(\omega))\tilde{Y}(\omega) - \frac{\alpha X(\omega)\tilde{Y}(\omega)}{\eta_2 + \tilde{Y}(\omega)} \right) \right\| d\omega \\
 &\leq \frac{2-2\rho}{M(\rho)(2-\rho)} \left[\mu_2 + \mu_2 \beta c_1 + \alpha \mathfrak{S}_1 c_2 \right] \|Y - \tilde{Y}\| \\
 &\quad + \left[\mu_2 + \mu_2 \beta c_1 + \alpha \mathfrak{S}_1 c_2 \right] \frac{2\rho}{M(\rho)(2-\rho)} \|Y - \tilde{Y}\| \\
 &\leq \frac{2-2\rho}{M(\rho)(2-\rho)} \Phi_2 \|Y - \tilde{Y}\| + \frac{2\rho \Phi_2}{M(\rho)(2-\rho)} \|Y - \tilde{Y}\|.
 \end{aligned} \tag{31}$$

Lastly,

$$\begin{aligned}
 \|Z(t) - \tilde{Z}(t)\| &\leq \frac{2-2\rho}{M(\rho)(2-\rho)} \left\| \left(\frac{\zeta_2 X(t)Y(t)}{\eta_3 + Y(t)} - \theta_3 Z(t) + \kappa_2 \right) - \left(\frac{\zeta_2 X(t)Y(t)}{\eta_3 + Y(t)} - \theta_3 \tilde{Z}(t) + \kappa_2 \right) \right\| \\
 &\quad + \frac{2\rho}{2M(\rho) - \rho M(\rho)} \int_0^t \left\| \left(\frac{\zeta_2 X(\omega)Y(\omega)}{\eta_3 + Y(\omega)} - \theta_3 Z(\omega) + \kappa_2 \right) \right. \\
 &\quad \left. - \left(\frac{\zeta_2 X(\omega)Y(\omega)}{\eta_3 + Y(\omega)} - \theta_3 \tilde{Z}(\omega) + \kappa_2 \right) \right\| d\omega \\
 &\leq \frac{2-2\rho}{M(\rho)(2-\rho)} [\theta_3] \|Z - \tilde{Z}\| + [\theta_3] \frac{2\rho}{2M(\rho) - \rho M(\rho)} \|Z - \tilde{Z}\| \\
 &\leq \frac{2-2\rho}{M(\rho)(2-\rho)} \Phi_3 \|Z - \tilde{Z}\| + \frac{2\rho \Phi_3}{2M(\rho) - \rho M(\rho)} \|Z - \tilde{Z}\|.
 \end{aligned} \tag{32}$$

The following inequality can be written,

$$\begin{aligned} & \left(\frac{2-2\rho}{M(\rho)(2-\rho)}\Phi_1 + \frac{2\rho\Phi_1}{2M(\rho)-\rho M(\rho)} - 1 \right) \|X - \tilde{X}\| \geq 0. \\ & \left(\frac{2-2\rho}{M(\rho)(2-\rho)}\Phi_2 + \frac{2\rho\Phi_2}{2M(\rho)-\rho M(\rho)} - 1 \right) \|Y - \tilde{Y}\| \geq 0. \\ & \left(\frac{2-2\rho}{M(\rho)(2-\rho)}\Phi_3 + \frac{2\rho\Phi_3}{2M(\rho)-\rho M(\rho)} - 1 \right) \|Z - \tilde{Z}\| \geq 0. \end{aligned} \tag{33}$$

Thus, $\|X - \tilde{X}\| = \|Y - \tilde{Y}\| = \|Z - \tilde{Z}\| = 0$. This implies $X(t) = \tilde{X}(t), Y(t) = \tilde{Y}(t), Z(t) = \tilde{Z}(t)$. Thus, the model has a unique solution. \square

4. Stability Analysis

In this section, we shall examine the stability of the tumor-immune interaction mathematical model (13). First of all, the following definition should be given.

Definition 4.1. The system (13) is Hyers-Ulam stable [29] if there exists constants $\Theta_i > 0, i = 1, 2, 3$ satisfying for every $v_i > 0, i = 1, 2, 3$,

$$\begin{aligned} & \left| X(t) - \frac{2-2\rho}{M(\rho)(2-\rho)} \mathfrak{L}_1(t, X(t)) + \frac{2\rho}{M(\rho)(2-\rho)} \int_0^t \mathfrak{L}_1(\omega, X(\omega))d\omega \right| \leq v_1, \\ & \left| Y(t) - \frac{2-2\rho}{M(\rho)(2-\rho)} \mathfrak{L}_2(t, Y(t)) + \frac{2\rho}{M(\rho)(2-\rho)} \int_0^t \mathfrak{L}_2(\omega, Y(\omega))d\omega \right| \leq v_2, \\ & \left| Z(t) - \frac{2-2\rho}{M(\rho)(2-\rho)} \mathfrak{L}_3(t, Z(t)) + \frac{2\rho}{M(\rho)(2-\rho)} \int_0^t \mathfrak{L}_3(\omega, Z(\omega))d\omega \right| \leq v_3, \end{aligned}$$

There exist, $\bar{X}(t), \bar{Y}(t), \bar{Z}(t)$ are satisfying,

$$\begin{aligned} \bar{X}(t) &= \frac{2-2\rho}{M(\rho)(2-\rho)} \mathfrak{L}_1(t, \bar{X}(t)) + \frac{2\rho}{M(\rho)(2-\rho)} \int_0^t \mathfrak{L}_1(\omega, \bar{X}(\omega))d\omega, \\ \bar{Y}(t) &= \frac{2-2\rho}{M(\rho)(2-\rho)} \mathfrak{L}_2(t, \bar{Y}(t)) + \frac{2\rho}{M(\rho)(2-\rho)} \int_0^t \mathfrak{L}_2(\omega, \bar{Y}(\omega))d\omega, \\ \bar{Z}(t) &= \frac{2-2\rho}{M(\rho)(2-\rho)} \mathfrak{L}_3(t, \bar{Z}(t)) + \frac{2\rho}{M(\rho)(2-\rho)} \int_0^t \mathfrak{L}_3(\omega, \bar{Z}(\omega))d\omega, \end{aligned} \tag{34}$$

such that

$$|X(t) - \bar{X}(t)| \leq \sigma_1 v_1, |Y(t) - \bar{Y}(t)| \leq \sigma_2 v_2, |Z(t) - \bar{Z}(t)| \leq \sigma_3 v_3.$$

Theorem 4.2. The fractional system (13) is Hyers-Ulam stable with assumption C.

Proof. In Theorem 3.3, $X(t), Y(t), Z(t)$ were shown to have a unique solution. Let $\bar{X}(t), \bar{Y}(t), \bar{Z}(t)$ be an approximate solution of system (13) satisfying the system (19). Then, we can say that

$$\begin{aligned}
 \|X(t) - \bar{X}(t)\| &\leq \frac{2(1-\rho)}{2M(\rho) - \rho M(\rho)} \left\| \left(\gamma Y(t) - \theta_2 X(t) + \frac{\zeta_1 X(t) Z(t)}{\eta_1 + Z(t)} + \kappa_1 \right) \right. \\
 &\quad \left. - \left(\gamma Y(t) - \theta_2 \bar{X}(t) + \frac{\zeta_1 \bar{X}(t) Z(t)}{\eta_1 + Z(t)} + \kappa_1 \right) \right\| \\
 &\quad + \frac{2\rho}{2M(\rho) - \rho M(\rho)} \int_0^t \left\| \left(\gamma Y(\omega) - \theta_2 X(\omega) + \frac{\zeta_1 X(\omega) Z(\omega)}{\eta_1 + Z(\omega)} + \kappa_1 \right) \right. \\
 &\quad \left. - \left(\gamma Y(\omega) - \theta_2 \bar{X}(\omega) + \frac{\zeta_1 \bar{X}(\omega) Z(\omega)}{\eta_1 + Z(\omega)} + \kappa_1 \right) \right\| d\omega \\
 &\leq \frac{2(1-\rho)}{2M(\rho) - \rho M(\rho)} \left[-\theta_2 + \frac{\zeta_1 \mathfrak{S}_3}{\eta_1 + \mathfrak{S}_3} \right] \|X - \bar{X}\| \\
 &\quad + \left[-\theta_2 + \frac{\zeta_1 \mathfrak{S}_3}{\eta_1 + \mathfrak{S}_3} \right] \frac{2\rho}{2M(\rho) - \rho M(\rho)} \|X - \bar{X}\| \\
 &\leq \frac{2(1-\rho)}{2M(\rho) - \rho M(\rho)} \Phi_1 \|X - \bar{X}\| + \frac{2\rho \Phi_1}{2M(\rho) - \rho M(\rho)} \|X - \bar{X}\| \\
 &\leq \left(\frac{2(1-\rho)}{2M(\rho) - \rho M(\rho)} + \frac{2\rho}{2M(\rho) - \rho M(\rho)} \right) \Phi_1 \|X - \bar{X}\|.
 \end{aligned} \tag{35}$$

When we take $v_1 = \Phi_1$, $\Theta_1 = \frac{2(1-\rho)}{2M(\rho) - \rho M(\rho)} + \frac{2\rho}{2M(\rho) - \rho M(\rho)}$, we have

$$\|X(t) - \bar{X}(t)\| \leq v_1 \Theta_1.$$

Secondly,

$$\begin{aligned}
 \|Y(t) - \bar{Y}(t)\| &\leq \frac{2(1-\rho)}{2M(\rho) - \rho M(\rho)} \left\| \left(\mu_2(1 - \beta Y(t)) Y(t) - \frac{\alpha X(t) Y(t)}{\eta_2 + Y(t)} \right) \right. \\
 &\quad \left. - \left(\mu_2(1 - \beta \bar{Y}(t)) \bar{Y}(t) - \frac{\alpha X(t) \bar{Y}(t)}{\eta_2 + \bar{Y}(t)} \right) \right\| \\
 &\quad + \frac{2\rho}{2M(\rho) - \rho M(\rho)} \int_0^t \left\| \left(\mu_2(1 - \beta Y(\omega)) Y(\omega) - \frac{\alpha X(\omega) Y(\omega)}{\eta_2 + Y(\omega)} \right) \right. \\
 &\quad \left. - \left(\mu_2(1 - \beta \bar{Y}(\omega)) \bar{Y}(\omega) - \frac{\alpha X(\omega) \bar{Y}(\omega)}{\eta_2 + \bar{Y}(\omega)} \right) \right\| d\omega \\
 &\leq \frac{2(1-\rho)}{2M(\rho) - \rho M(\rho)} \left[\mu_2 + \mu_2 \beta c_1 + \alpha \mathfrak{S}_1 c_2 \right] \|Y - \bar{Y}\| \\
 &\quad + \left[\mu_2 + \mu_2 \beta c_1 + \alpha \mathfrak{S}_1 c_2 \right] \frac{2\rho}{2M(\rho) - \rho M(\rho)} \|Y - \bar{Y}\| \\
 &\leq \frac{2(1-\rho)}{2M(\rho) - \rho M(\rho)} \Phi_2 \|Y - \bar{Y}\| + \frac{2\rho \Phi_2}{2M(\rho) - \rho M(\rho)} \|Y - \bar{Y}\| \\
 &\leq \left(\frac{2(1-\rho)}{2M(\rho) - \rho M(\rho)} + \frac{2\rho}{2M(\rho) - \rho M(\rho)} \right) \Phi_2 \|Y - \bar{Y}\|.
 \end{aligned} \tag{36}$$

When we take $v_2 = \Phi_2$, $\Theta_2 = \frac{2(1-\rho)}{2M(\rho) - \rho M(\rho)} + \frac{2\rho}{2M(\rho) - \rho M(\rho)}$, we have

$$\|Y(t) - \bar{Y}(t)\| \leq v_2 \Theta_2.$$

Lastly,

$$\begin{aligned}
 \|Z(t) - \bar{Z}(t)\| &\leq \frac{2(1-\rho)}{2M(\rho) - \rho M(\rho)} \left\| \left(\frac{\zeta_2 X(t)Y(t)}{\eta_3 + Y(t)} - \theta_3 Z(t) + \kappa_2 \right) \right. \\
 &\quad \left. - \left(\frac{\zeta_2 X(t)Y(t)}{\eta_3 + Y(t)} - \theta_3 \bar{Z}(t) + \kappa_2 \right) \right\| \\
 &\quad + \frac{2\rho}{2M(\rho) - \rho M(\rho)} \int_0^t \left\| \left(\frac{\zeta_2 X(\omega)Y(\omega)}{\eta_3 + Y(\omega)} - \theta_3 Z(\omega) + \kappa_2 \right) \right. \\
 &\quad \left. - \left(\frac{\zeta_2 X(\omega)Y(\omega)}{\eta_3 + Y(\omega)} - \theta_3 \bar{Z}(\omega) + \kappa_2 \right) \right\| d\omega \tag{37} \\
 &\leq \frac{2(1-\rho)}{2M(\rho) - \rho M(\rho)} [\theta_3] \|Z - \bar{Z}\| + [\theta_3] \frac{2\rho}{2M(\rho) - \rho M(\rho)} \|Z - \bar{Z}\| \\
 &\leq \frac{2(1-\rho)}{2M(\rho) - \rho M(\rho)} \Phi_3 \|Z - \bar{Z}\| + \frac{2\rho\Phi_3}{2M(\rho) - \rho M(\rho)} \|Z - \bar{Z}\| \\
 &\leq \left(\frac{2(1-\rho)}{2M(\rho) - \rho M(\rho)} + \frac{2\rho}{2M(\rho) - \rho M(\rho)} \right) \Phi_3 \|Z - \bar{Z}\|.
 \end{aligned}$$

When we take $v_3 = \Phi_3$, $\Theta_3 = \frac{2(1-\rho)}{2M(\rho) - \rho M(\rho)} + \frac{2\rho}{2M(\rho) - \rho M(\rho)}$, we have

$$\|Z(t) - \bar{Z}(t)\| \leq v_3 \Theta_3.$$

Considering the above inequalities, it is clear that the system (13) is Hyers-Ulam stable. It means that (35), (36) and (37) inequalities are stable under given conditions. This shows us that the model is provided with Hyers-Ulam stability. So that the proof is completed. \square

5. Numerical Scheme

A method is presented for applying numerical solutions of fractional differential equations to the Caputo-Fabrizio fractional derivative in [28].

$${}_0^{CF} \mathfrak{D}_t^\rho x(t) = (f(t, x(t))), \tag{38}$$

or

$$(f(t, x(t))) = \frac{M(\rho)}{1-\rho} \int_0^t x'(\tau) \exp\left[-\frac{\rho}{1-\rho}(t-\tau)\right] d\tau. \tag{39}$$

When the above equation is written with the help of the mean integral theorem,

$$x(t) - x(0) = \frac{1-\rho}{M(\rho)} f(t, x(t)) + \frac{\rho}{M(\rho)} \int_0^t f(\tau, x(\tau)) d\tau. \tag{40}$$

Therefore,

$$x(t_{n+1}) - x(0) = \frac{1-\rho}{M(\rho)} f(t_n, x(t_n)) + \frac{\rho}{M(\rho)} \int_0^{t_{n+1}} f(t, x(t)) dt, \tag{41}$$

and

$$x(t_n) - x(0) = \frac{1-\rho}{M(\rho)} f(t_{n-1}, x(t_{n-1})) + \frac{\rho}{M(\rho)} \int_0^{t_n} f(t, x(t)) dt, \quad (42)$$

which on subtraction yields

$$x(t_{n+1}) - x(t_n) = \frac{1-\rho}{M(\rho)} \{f(t_n, x(t_n)) - f(t_{n-1}, x_{n-1})\} + \frac{\rho}{M(\rho)} \int_0^{t_n} f(t, x(t)) dt, \quad (43)$$

where

$$\begin{aligned} \int_{t_n}^{t_{n+1}} f(t, x(t)) dt &= \int_{t_n}^{t_{n+1}} \left\{ \frac{f(t_n, x_n)}{h} (t - t_{n-1}) - \frac{f(t_{n-1}, x_{n-1})}{h} (t - t_n) \right\} dt \\ &= \frac{3h}{2} f(t_n, x_n) - \frac{h}{2} f(t_{n-1}, x_{n-1}). \end{aligned} \quad (44)$$

Thus,

$$\begin{aligned} x(t_{n+1}) - x(t_n) &= \frac{1-\rho}{M(\rho)} [f(t_n, x_n) - f(t_{n-1}, x_{n-1})] + \frac{3\rho h}{2M(\rho)} f(t_n, x_n) \\ &\quad - \frac{\rho h}{2M(\rho)} f(t_{n-1}, x_{n-1}), \end{aligned} \quad (45)$$

which implies that

$$x(t_{n+1}) - x(t_n) = \left(\frac{1-\rho}{M(\rho)} + \frac{3\rho h}{2M(\rho)} \right) f(t_n, x_n) + \left(\frac{1-\rho}{M(\rho)} + \frac{3\rho h}{2M(\rho)} \right) f(t_{n-1}, x_{n-1}). \quad (46)$$

Hence,

$$x_{n+1} = x_n + \left(\frac{1-\rho}{M(\rho)} + \frac{3\rho h}{2M(\rho)} \right) f(t_n, x_n) + \left(\frac{1-\rho}{M(\rho)} + \frac{3\rho h}{2M(\rho)} \right) f(t_{n-1}, x_{n-1}), \quad (47)$$

which is the corresponding two-step Adams-Bashforth method for the Caputo-Fabrizio fractional derivative.

Theorem 5.1. Let $x(t)$ be a solution of ${}_a^{CF} \mathfrak{D}_t^\rho(x(t)) = f(t, x(t))$, where f is a continuous function bounded for the Caputo-Fabrizio fractional derivative [28],

$$x_{n+1} = x_n + \left(\frac{1-\rho}{M(\rho)} + \frac{3\rho h}{2M(\rho)} \right) f(t_n, x_n) + \left(\frac{1-\rho}{M(\rho)} + \frac{\rho h}{2M(\rho)} \right) f(t_{n-1}, x_{n-1}) + R_\rho^n, \quad (48)$$

where $\|R_\rho^n\| \leq M$.

5.1. Numerical Scheme for the model

The fractional tumor-immune interaction mathematical model via the CF derivative was introduced in system (13) as below,

$$\begin{aligned}
 X(t) - X(0) &= \frac{1 - \rho}{M(\rho)} \left(\gamma Y(t) - \theta_2 X(t) + \frac{\zeta_1 X(t) Z(t)}{\eta_1 + Z(t)} + \kappa_1 \right) \\
 &\quad + \frac{\rho}{M(\rho)} \int_0^t \left(\gamma Y(\omega) - \theta_2 X(\omega) + \frac{\zeta_1 X(\omega) Z(\omega)}{\eta_1 + Z(\omega)} + \kappa_1 \right) d\omega, \\
 Y(t) - Y(0) &= \frac{1 - \rho}{M(\rho)} \left(\mu_2 (1 - \beta Y(t)) Y(t) - \frac{\alpha X(t) Y(t)}{\eta_2 + Y(t)} \right) \\
 &\quad + \frac{\rho}{M(\rho)} \int_0^t \left(\mu_2 (1 - \beta Y(\omega)) Y(\omega) - \frac{\alpha X(\omega) Y(\omega)}{\eta_2 + Y(\omega)} \right) d\omega \\
 Z(t) - Z(0) &= \frac{1 - \rho}{M(\rho)} \left(\frac{\zeta_2 X(t) Y(t)}{\eta_3 + Y(t)} - \theta_3 Z(t) + \kappa_2 \right) \\
 &\quad + \frac{\rho}{M(\rho)} \int_0^t \left(\frac{\zeta_2 X(\omega) Y(\omega)}{\eta_3 + Y(\omega)} - \theta_3 Z(\omega) + \kappa_2 \right) d\omega.
 \end{aligned} \tag{49}$$

Thus,

$$\begin{aligned}
 X_{n+1} - X(0) &= \frac{1 - \rho}{M(\rho)} \left(\gamma Y(t_n) - \theta_2 X(t_n) + \frac{\zeta_1 X_n(t_n) Z(t_n)}{\eta_1 + Z(t_n)} + \kappa_1 \right) \\
 &\quad + \frac{\rho}{M(\rho)} \int_0^{t_{n+1}} \left(\gamma Y(t) - \theta_2 X(t) + \frac{\zeta_1 X(t) Z(t)}{\eta_1 + Z(t)} + \kappa_1 \right) dt, \\
 Y_{n+1} - Y(0) &= \frac{1 - \rho}{M(\rho)} \left(\mu_2 (1 - \beta Y_n(t_n)) Y_n(t_n) - \frac{\alpha X(t_n) Y_n(t_n)}{\eta_2 + Y_n(t_n)} \right) \\
 &\quad + \frac{\rho}{M(\rho)} \int_0^{t_{n+1}} \left(\mu_2 (1 - \beta Y(t)) Y(t) - \frac{\alpha X(t) Y(t)}{\eta_2 + Y(t)} \right) dt, \\
 Z_{n+1} - Z(0) &= \frac{1 - \rho}{M(\rho)} \left(\frac{\zeta_2 X(t_n) Y(t_n)}{\eta_3 + Y(t_n)} - \theta_3 Z_n(t_n) + \kappa_2 \right) \\
 &\quad + \frac{\rho}{M(\rho)} \int_0^{t_{n+1}} \left(\frac{\zeta_2 X(t) Y(t)}{\eta_3 + Y(t)} - \theta_3 Z(t) + \kappa_2 \right) dt.
 \end{aligned} \tag{50}$$

and

$$\begin{aligned}
 X_n - X(0) &= \frac{1 - \rho}{M(\rho)} \left(\gamma Y(t_{n-1}) - \theta_2 X(t_{n-1}) + \frac{\zeta_1 X_{n-1}(t_{n-1}) Z(t_{n-1})}{\eta_1 + Z(t_{n-1})} + \kappa_1 \right) \\
 &\quad + \frac{\rho}{M(\rho)} \int_0^{t_{n+1}} \left(\gamma Y(t) - \theta_2 X(t) + \frac{\zeta_1 X(t) Z(t)}{\eta_1 + Z(t)} + \kappa_1 \right) dt, \\
 Y_n - Y(0) &= \frac{1 - \rho}{M(\rho)} \left(\mu_2 (1 - \beta Y_{n-1}(t_{n-1})) Y_{n-1}(t_{n-1}) - \frac{\alpha X(t_{n-1}) Y_{n-1}(t_{n-1})}{\eta_2 + Y_{n-1}(t_{n-1})} \right) \\
 &\quad + \frac{\rho}{M(\rho)} \int_0^{t_{n+1}} \left(\mu_2 (1 - \beta Y(t)) Y(t) - \frac{\alpha X(t) Y(t)}{\eta_2 + Y(t)} \right) dt, \\
 Z_n - Z(0) &= \frac{1 - \rho}{M(\rho)} \left(\frac{\zeta_2 X(t_{n-1}) Y(t_{n-1})}{\eta_3 + Y(t_{n-1})} - \theta_3 Z_{n-1}(t_{n-1}) + \kappa_2 \right) \\
 &\quad + \frac{\rho}{M(\rho)} \int_0^{t_{n+1}} \left(\frac{\zeta_2 X(t) Y(t)}{\eta_3 + Y(t)} - \theta_3 Z(t) + \kappa_2 \right) dt
 \end{aligned} \tag{51}$$

with the system (50) and (51), the following equation system is obtained.

$$\begin{aligned}
 X_{n+1} - X(0) &= \frac{1 - \rho}{M(\rho)} \left\{ \left(\gamma Y(t_n) - \theta_2 X(t_n) + \frac{\zeta_1 X_n(t_n) Z(t_n)}{\eta_1 + Z(t_n)} + \kappa_1 \right) \right. \\
 &\quad \left. - \left(\gamma Y(t_{n-1}) - \theta_2 X(t_{n-1}) + \frac{\zeta_1 X_{n-1}(t_{n-1}) Z(t_{n-1})}{\eta_1 + Z(t_{n-1})} + \kappa_1 \right) \right\} \\
 &\quad + \frac{\rho}{M(\rho)} \int_{t_n}^{t_{n+1}} \left(\gamma Y(t) - \theta_2 X(t) + \frac{\zeta_1 X(t) Z(t)}{\eta_1 + Z(t)} + \kappa_1 \right) dt, \\
 Y_{n+1} - Y(0) &= \frac{1 - \rho}{M(\rho)} \left\{ \left(\mu_2 (1 - \beta Y_n(t_n)) Y_n(t_n) - \frac{\alpha X(t_n) Y_n(t_n)}{\eta_2 + Y_n(t_n)} \right) \right. \\
 &\quad \left. - \left(\mu_2 (1 - \beta Y_{n-1}(t_{n-1})) Y_{n-1}(t_{n-1}) - \frac{\alpha X(t_{n-1}) Y_{n-1}(t_{n-1})}{\eta_2 + Y_{n-1}(t_{n-1})} \right) \right\} \\
 &\quad + \frac{\rho}{M(\rho)} \int_{t_n}^{t_{n+1}} \left(\mu_2 (1 - \beta Y(t)) Y(t) - \frac{\alpha X(t) Y(t)}{\eta_2 + Y(t)} \right) dt, \\
 Z_{n+1} - Z(0) &= \frac{1 - \rho}{M(\rho)} \left\{ \left(\frac{\zeta_2 X(t_n) Y(t_n)}{\eta_3 + Y(t_n)} - \theta_3 Z_n(t_n) + \kappa_2 \right) \right. \\
 &\quad \left. - \left(\frac{\zeta_2 X(t_{n-1}) Y(t_{n-1})}{\eta_3 + Y(t_{n-1})} - \theta_3 Z_{n-1}(t_{n-1}) + \kappa_2 \right) \right\} \\
 &\quad + \frac{\rho}{M(\rho)} \int_{t_n}^{t_{n+1}} \left(\frac{\zeta_2 X(t) Y(t)}{\eta_3 + Y(t)} - \theta_3 Z(t) + \kappa_2 \right) dt.
 \end{aligned} \tag{52}$$

where

$$\begin{aligned}
 &\int_{t_n}^{t_{n+1}} \left(\gamma Y(t) - \theta_2 X(t) + \frac{\zeta_1 X(t) Z(t)}{\eta_1 + Z(t)} + \kappa_1 \right) dt \\
 &= \int_{t_n}^{t_{n+1}} \left\{ \frac{\mathfrak{Q}_1(t_n, X_n)}{h} (t - t_{n-1}) - \frac{\mathfrak{Q}_1(t_{n-1}, X_{n-1})}{h} (t - t_n) \right\} \\
 &= \frac{3h}{2} \mathfrak{Q}_1(t_n, B_{T_n}) - \frac{h}{2} \mathfrak{Q}_1(t_{n-1}, B_{T_{n-1}}), \\
 &\int_{t_n}^{t_{n+1}} \left(\mu_2 (1 - \beta Y(t)) Y(t) - \frac{\alpha X(t) Y(t)}{\eta_2 + Y(t)} \right) dt \\
 &= \int_{t_n}^{t_{n+1}} \left\{ \frac{\mathfrak{Q}_2(t_n, Y_n)}{h} (t - t_{n-1}) - \frac{\mathfrak{Q}_2(t_{n-1}, Y_{n-1})}{h} (t - t_n) \right\} \\
 &= \frac{3h}{2} \mathfrak{Q}_2(t_n, Y_n) - \frac{h}{2} \mathfrak{Q}_2(t_{n-1}, Y_{n-1}), \\
 &\int_{t_n}^{t_{n+1}} \left(\frac{\zeta_2 X(t) Y(t)}{\eta_3 + Y(t)} - \theta_3 Z(t) + \kappa_2 \right) dt \\
 &= \int_{t_n}^{t_{n+1}} \left\{ \frac{\mathfrak{Q}_3(t_n, Z_n)}{h} (t - t_{n-1}) - \frac{\mathfrak{Q}_3(t_{n-1}, Z_{n-1})}{h} (t - t_n) \right\} \\
 &= \frac{3h}{2} \mathfrak{Q}_3(t_n, Z_n) - \frac{h}{2} \mathfrak{Q}_3(t_{n-1}, Z_{n-1}).
 \end{aligned} \tag{53}$$

Therefore,

$$\begin{aligned}
 X_{n+1} - X_n &= \frac{1-\rho}{M(\rho)} \left\{ \mathfrak{L}_1(t_n, X_n) - \mathfrak{L}_1(t_{n-1}, X_{n-1}) \right\} \\
 &\quad + \frac{3\rho h}{2M(\rho)} \mathfrak{L}_1(t_n, X_n) - \frac{\rho h}{2M(\rho)} \mathfrak{L}_1(t_{n-1}, X_{n-1}), \\
 Y_{n+1} - Y_n &= \frac{1-\rho}{M(\rho)} \left\{ \mathfrak{L}_2(t_n, Y_n) - \mathfrak{L}_2(t_{n-1}, Y_{n-1}) \right\} \\
 &\quad + \frac{3\rho h}{2M(\rho)} \mathfrak{L}_2(t_n, Y_n) - \frac{\rho h}{2M(\rho)} \mathfrak{L}_2(t_{n-1}, Y_{n-1}), \\
 Z_{n+1} - Z_n &= \frac{1-\rho}{M(\rho)} \left\{ \mathfrak{L}_3(t_n, Z_n) - \mathfrak{L}_3(t_{n-1}, Z_{n-1}) \right\} \\
 &\quad + \frac{3\rho h}{2M(\rho)} \mathfrak{L}_3(t_n, Z_n) - \frac{\rho h}{2M(\rho)} \mathfrak{L}_3(t_{n-1}, Z_{n-1}),
 \end{aligned} \tag{54}$$

which implies that,

$$\begin{aligned}
 X_{n+1} &= X_n + \left(\frac{1-\rho}{M(\rho)} + \frac{3\rho h}{2M(\rho)} \right) \mathfrak{L}_1(t_n, X_n) + \left(\frac{1-\rho}{M(\rho)} + \frac{\rho h}{2M(\rho)} \right) \mathfrak{L}_1(t_{n-1}, X_{n-1}), \\
 Y_{n+1} &= Y_n + \left(\frac{1-\rho}{M(\rho)} + \frac{3\rho h}{2M(\rho)} \right) \mathfrak{L}_2(t_n, Y_n) + \left(\frac{1-\rho}{M(\rho)} + \frac{\rho h}{2M(\rho)} \right) \mathfrak{L}_2(t_{n-1}, Y_{n-1}), \\
 Z_{n+1} &= Z_n + \left(\frac{1-\rho}{M(\rho)} + \frac{3\rho h}{2M(\rho)} \right) \mathfrak{L}_3(t_n, Z_n) + \left(\frac{1-\rho}{M(\rho)} + \frac{\rho h}{2M(\rho)} \right) \mathfrak{L}_3(t_{n-1}, Z_{n-1}),
 \end{aligned}$$

According to Theorem 4.1, we get,

$$\begin{aligned}
 X_{n+1} &= X_n + \left(\frac{1-\rho}{M(\rho)} + \frac{3\rho h}{2M(\rho)} \right) \mathfrak{L}_1(t_n, X_n) + \left(\frac{1-\rho}{M(\rho)} + \frac{\rho h}{2M(\rho)} \right) \mathfrak{L}_1(t_{n-1}, X_{n-1}) + {}^1R_\rho^n, \\
 Y_{n+1} &= Y_n + \left(\frac{1-\rho}{M(\rho)} + \frac{3\rho h}{2M(\rho)} \right) \mathfrak{L}_2(t_n, Y_n) + \left(\frac{1-\rho}{M(\rho)} + \frac{\rho h}{2M(\rho)} \right) \mathfrak{L}_2(t_{n-1}, Y_{n-1}) + {}^2R_\rho^n, \\
 Z_{n+1} &= Z_n + \left(\frac{1-\rho}{M(\rho)} + \frac{3\rho h}{2M(\rho)} \right) \mathfrak{L}_3(t_n, Z_n) + \left(\frac{1-\rho}{M(\rho)} + \frac{\rho h}{2M(\rho)} \right) \mathfrak{L}_3(t_{n-1}, Z_{n-1}) + {}^3R_\rho^n,
 \end{aligned}$$

where

$$\|{}^iR_\rho^n\|_\infty < \frac{\rho}{M(\rho)} (n+1)! h^{n+1}, \quad i = 1, 2, 3.$$

The numerical simulations for the system (13) are performed for each function below. The behavior of the model is analyzed in detail using fractional order derivative for different ρ values. The parameters used in the simulations are $\gamma = 0.05, \theta_2 = 0.03, \zeta_1 = 0.1245, \eta_1 = 2 \times 10^7, \eta_2 = 1 \times 10^5, \mu_2 = 0.18, \beta = 1 \times 10^{-9}, \alpha = 1, \theta_3 = 10, \zeta_2 = 5, \eta_3 = 1 \times 10^3$ with initial conditions $X(0) = Y(0) = Z(0) = 1/\beta$

5.2. Numerical simulation

In this section, simulations for the model are presented. Numerical results were obtained with the approach proposed in the previous section and presented with graphics. Numerical results are shown for different fractional derivative values. Firstly, the simulation of X, Y and Z for $\rho = 1$ is presented in Figure 1.

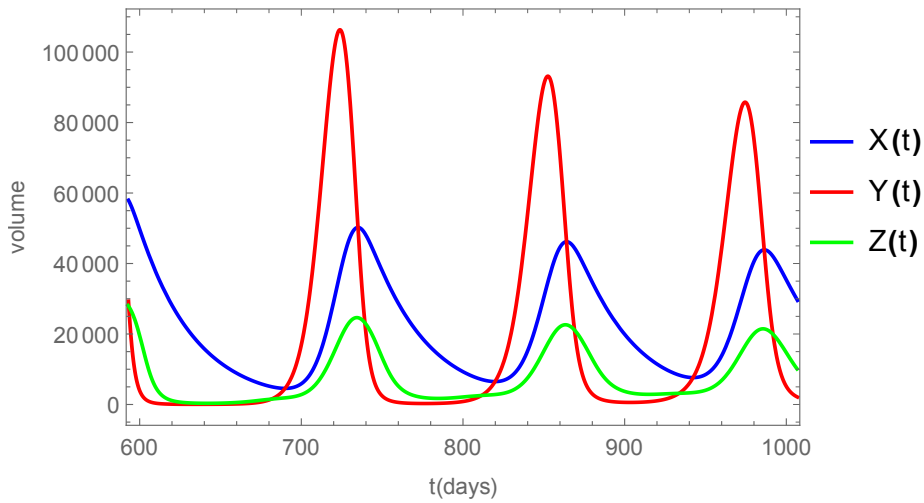


Figure 1: Numerical simulation of solutions for $\rho = 1$.

In Figure 1, simulation of the X , Y and Z functions for $\rho = 1$ is presented. The activated immune system cells identified by $X(t)$ and the interleukin-2 (IL-2) concentration cells in the single tumor region compartment have similar variability, whereas the tumor cells identified by $Y(t)$ have two-fold increases over time.

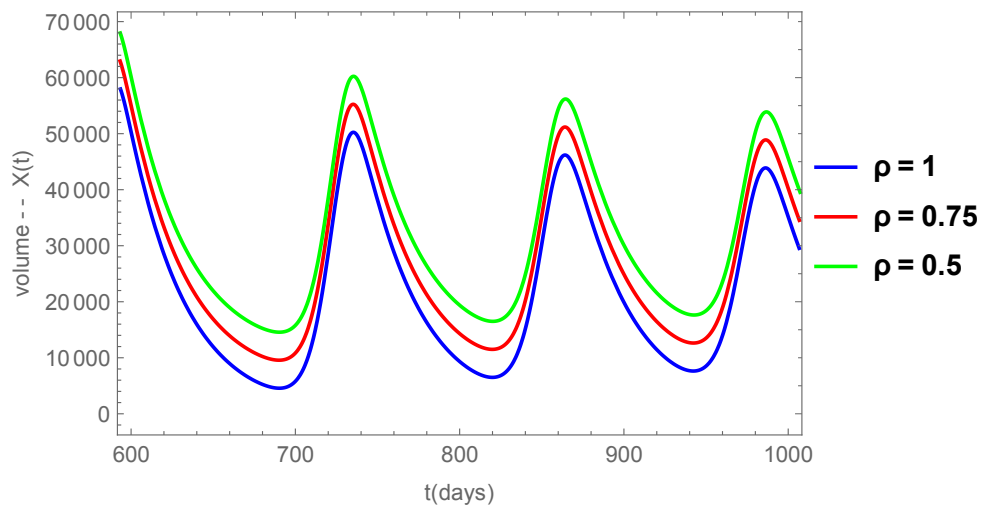


Figure 2: Numerical simulation of solutions $X(t)$ for different value of ρ .

In Figure 2, for different values of ρ the simulation of activated immune system cells, which is identified by $X(t)$, is presented. As it can easily be seen, as ρ values decrease, the number of cells increases. While the increase in the number of cells is less than the increase in $Y(t)$ cells, it is more than the increase in $Z(t)$ cells.

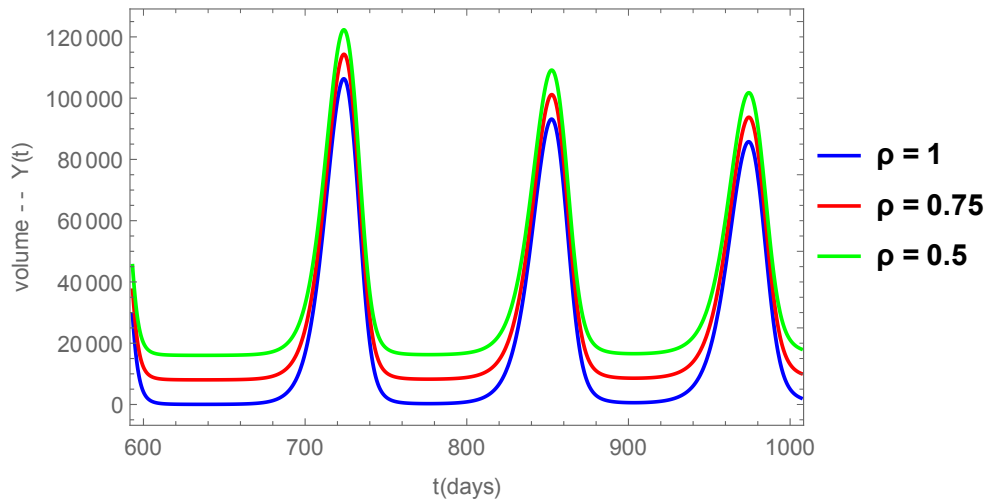


Figure 3: Numerical simulation of solutions $Y(t)$ for different value of ρ .

In Figure 3, the simulation of tumor cells, which is identified by $Y(t)$, is presented for the different values of ρ . Though the increase in the numbers of cell is maximum in some time periods, it is quite high in the time periods when the numbers of cell are lower than $X(t)$.

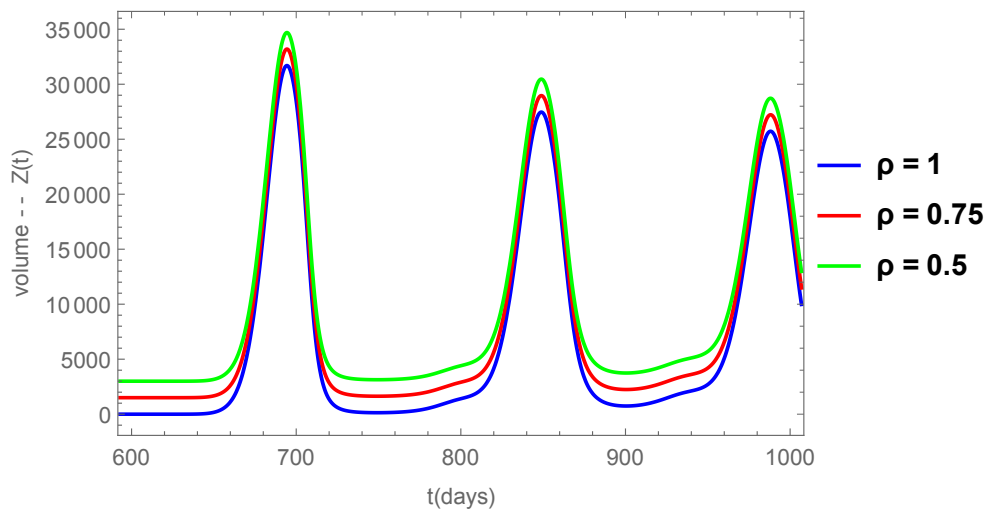


Figure 4: Numerical simulation of solutions $Z(t)$ for different value of ρ .

In Figure 4, the simulation of the concentration cells of interleukin-2 (IL-2) in the single tumor region compartment, which is defined by $Z(t)$, is presented for the different values of ρ . Even though the time intervals, in which the numbers of cell increase, are the same as $X(t)$ and $Y(t)$, they have still the lowest number of cells.

6. Conclusion

In this study, a tumor-immune interaction model was analyzed with the non-singular Caputo-Fabrizio fractional derivative. Existence and uniqueness of solutions of the mathematical model were carried out and their stability was also examined. The numerical solutions of the model were presented with the Adam-Basford numerical method, which was applied to the fractional derivative operator. The method

has been tested for the values of different order fractional derivative and good results have been obtained for the problem. Furthermore, in order to observe the behavior of the model, simulations are performed and presented in the Figures 1-4.

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