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Research Article

Fractional-Order Mathematical Modeling and Stability Analysis of Tumor-Immune System Relation Including Chemotherapy Drug Effect

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Abstract

Worldwide, cancer is the second most common cause of death. Chemotherapy is a widely used strategy to tumor treatment that is particularly effective in controlling the growth of cancerous tumors and their size. We created a fractional-order mathematical model that illustrates tumor growth in the presence of chemotherapy to obtain a more profound comprehension of the complexities of chemotherapy mechanisms. This all-inclusive paradigm addresses both the impacts of medication therapy and the immune system's reaction. We demonstrated the positivity and boundedness of the solutions by looking at their existence and uniqueness in order to demonstrate the biological significance of the system. Our approach involves identifying equilibrium points and investigating stability requirements within a range of model parameters in order to characterize the dynamic features of this differential equation model. Additionally, we ran numerical simulations with various parameter values.

To illustrate the memory effect of the fractional derivative, we also simulated the system's dynamic behavior for various orders of fractional derivatives. To put it another way, we came to the conclusion that the chemotherapeutic treatment is quite effective on populations and that the memory effect happens when ϑ, decreases from 1. The purpose of this research is to assist physicians in adopting the appropriate safety measures when diagnosing and treating cancer.

Kemoterapi İlaç Etkisi Dahil Tümör-Bağışıklık Sistemi İlişkisinin Kesirli Mertebeden Matematiksel Modellenmesi ve Kararlılık Analizi

Anahtar Kelimeler
Varlık-teklik, Sayısal çözümler, Kararlılık, Sayısal simülasyon, Kesirli mertebeden türev

Özet

Kanser dünya çapında ikinci en sık ölüm nedenidir. Kemoterapi, özellikle kanserli tümörlerin büyümesinin ve boyutlarının kontrol edilmesinde etkili olan, tümör tedavisinde yaygın olarak kullanılan bir stratejidir. Kemoterapi mekanizmalarının karmaşıklığının daha derinlemesine anlaşılmasını sağlamak için kemoterapi varlığında tümör büyümesini gösteren kesirli dereceli bir matematiksel model oluşturduk. Bu her şeyi kapsayan paradigma, hem ilaç tedavisinin etkilerini hem de bağışıklık sisteminin tepkisini ele alır. Sistemin biyolojik önemini ortaya koymak için çözümlerin varlığına ve tekliğine bakarak çözümlerin pozitifliğini ve sınırlılığını ortaya koyduk. Yaklaşımımız, bu diferansiyel denklem modelinin dinamik özelliklerini karakterize etmek için denge noktalarının belirlenmesini ve bir dizi model parametresi dahilinde stabilite gereksinimlerinin araştırılmasını içerir. Ek olarak çeşitli parametre değerleriyle sayısal simülasyonlar yürüttük.

Kesirli türevin hafıza etkisini göstermek için, ayrıca kesirli türevlerin çeşitli dereceleri için sistemin dinamik davranışını da simüle ettik. Başka bir deyişle, kemoterapötik tedavinin popülasyonlar üzerinde oldukça etkili olduğu ve hafıza etkisinin ϑ, 1'den düştüğünde ortaya çıktığı sonucuna vardık. Bu araştırmanın amacı, kanseri tedavi etmek ve teşhis koyarken uygun güvenlik önlemlerini alma konusunda hekimlere yardımcı olmaktır.

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1. Introduction

The term "cancer" is broad and encompasses a variety of disorders that might potentially affect any region of the body. A wide range of illnesses collectively referred to as cancer are defined by unchecked cell division. Unrestricted cell proliferation in cancer leads to the creation of malignant tumors that can spread to distant sections of the body. One of the most noticeable characteristics of cancer is the quick development of aberrant cells that multiply uncontrollably and eventually invade neighboring bodily parts. Subsequently, these cells may disperse to other remote regions of the body. It is often acknowledged that cancer is one of the deadliest diseases in the modern world. Despite great efforts, a permanent treatment for cancer remains unattainable due to its complicated nature, making the battle against cancer challenging. The prevalence of cancer has not decreased despite developments in science and technology. Cancer continues to be a major contributor to death rates worldwide. Ten million individuals lost their lives to cancer in 2020. Over the next 20 years, the World Health Organization (WHO) projects a startling 70% increase in new cancer cases (World Health Organization, 2015). According to the WHO, minimizing the disease's risk factors can prevent 30% to 50% of cancer cases. Furthermore, early detection, proper care, and therapy can stop cancer from spreading. The likelihood of recovering from different forms of cancer is greatly increased by early detection and effective therapy. Numerous researchers have investigated the interactions between the immune system, particularly effector cells, tumor cells. The field of evolutionary biology and ecology offers new perspectives that can greatly increase our understanding of clinical behavior. Controlling the progression of tumors requires attention, underlining the extraordinary importance of cancer research [1–5]. Mathematical modeling serves as a valuable tool for understanding interactions between various components in the tumor microenvironment. Mathematical modeling has been used to explain the relationship between these components, as seen in references [6-9]. One of the most common types of treatments used to treat cancer is chemotherapy. Chemotherapy frequently has a significant impact on halting the spread of cancer. There are many mathematical models that include the effect of chemotherapy on the relationship between the immune system and tumor cells. For example, In [10], Özköse et al. They examined the relationship between cancer and effector cells, taking into account the effect of chemotherapy drugs, and made predictions about the future behavior of the cancer. In this article, the use of stem cells in cancer treatment together with chemotherapy. is demonstrated mathematically. In our study, we considered immune cells instead of effector cells. Immune cells instead of effector cells were taken into account in the parameters. In [11] the authors aimed to identify areas of most significant variation in the cellular population within the tumor. Taking into account the entire range of values, they obtained parameters characterizing the effectiveness of the disruptive drug based on the proposed treatment approach. In [12], Song et.al. They developed a mathematical model to mimic tumor growth in the context of chemotherapy in order to gain a better grasp of the mechanisms underlying treatment. Our system's dimensional consistency is guaranteed since the measurement units on the right and left sides of the equations are consistent. This has been achieved by changing the parameters in the equations on the right-hand side, for example by increasing them to 9.

In our study, unlike the studies in the literature, we specifically focused on the effect of chemotherapy drug concentration on the destruction of tumor cells. Thus, medical scientists adjust the dose of chemotherapy drug accordingly and plan the treatment accordingly.

Motivated by the aforementioned research, we created a mathematical model in this work that uses fractional derivatives in Caputo to investigate the relationship between immune cells, tumor cells and chemotherapy drugs. It is more advantageous to use mathematical modeling that includes Caputo fractional order derivatives. Because there is a memory effect in mathematical modeling that includes fractional order derivatives, and it is easier and takes less time for the system to reach stability than mathematical modeling that includes integer order derivatives. There are multiple definitions for fractional order derivatives. It is common to apply both the the Riemann-Liouville and the Caputo definitions. The Caputo derivative has been applied to enhance comprehension of the characteristics of the physical state and expand its relevance to practical problems, as it alone necessitates initial conditions given by the integer order derivative. For a problem to be interpreted physically, the derivative of the constant must be equal to zero. For this reason, it is more appropriate to use the Caputo fractional derivative to physically interpret the initial conditions. Additionally, the Laplace transform of the Caputo derivative requires physically interpretable initial conditions. These features have made the Caputo derivative more preferred in practice. We have also seen how important chemotherapy drugs are in the fight against cancer. Thus, by carrying out an insightful and guiding study for scientists dealing with medicine and biology, the importance of mathematical modeling containing fractional order derivatives in the treatment of cancer diseases has been emphasized.

2. Preliminaries

To help you understand this content, we have included some introductory explanations of fractional calculus in this section [15].

Definition 1. Order ϑ fractional integral is represented by

$$I^{\vartheta}f(t)=\int_0^t \frac{(t-s)^{\vartheta-1}}{\Gamma(\vartheta)}f(s)\,ds,$$

where $t>0,\ \vartheta>0$, the fractional derivative is defined by

$$D^{\vartheta}f(t)=I^{n-\vartheta}D^{n}f(t)\left(D=\frac{d}{dt}\right),$$

where $\vartheta\in(n-1,n),\ t>0,\ \ \Gamma$ is the Gamma function.

Definition 2.

$${}_0^C D_t^{\vartheta}f(t)=\begin{cases}\dfrac{1}{\Gamma(n-\vartheta)}\displaystyle\int_0^t \frac{\left({}^{d}/_{dt}\right)^{n}f(\tau)}{(t-\tau)^{\vartheta-n+1}}, & 0\le n-1<\vartheta<n, \qquad n=[\vartheta],n\in N,\\ \left(\dfrac{d}{dt}\right)^{n}f(t), & \vartheta=n,n\in N.\end{cases} \tag{1}$$

provides an explanation of the Caputo fractional derivative of $f\colon(0,\infty)\to\mathcal{R}$, of order $\vartheta>0$.

Definition 3. The function $f(t)$ of order $\vartheta>0$'s Laplace transform (LT) of the Caputo operator is explained by

$$L\left[{}_0^C D_t^{\vartheta}f(t)\right]=s^{\vartheta}F(s)-\sum_{v=0}^{n-1}f^{v}(0)s^{\vartheta-v-1}\,f^{v}(0). \tag{2}$$

Definition 4. The definition of the gamma function is $Re(z)>0$ utilizing the integral

$$\Gamma(z)=\int_0^{\infty}e^{-t}t^{z-1}\,dt.$$

Among the basic properties of the gamma function is

$$\Gamma(z+1)=z\Gamma(z),$$
$$\Gamma(n+1)=n!$$

for $z\in\mathbb{C},n\in N_0$. The gamma function has singular poles at $z=-n(n=0,1,2,\dots)$.

Definition 5. The Laplace transform (LT) of the function $f(t)=t^{\vartheta_1-1}E_{\vartheta,\vartheta_1}\left(\pm wt^{\vartheta}\right)$ is described as

$$L\left[t^{\vartheta_1-1}E_{\vartheta,\vartheta_1}\left(\pm wt^{\vartheta}\right)\right]=\frac{s^{\vartheta-\vartheta_1}}{s^{\vartheta}\pm w}, \tag{3}$$

where $E_{\vartheta,\vartheta_1}$ is Mittag-Leffler function.

Theorem 1 [15,16]**.** Examine the fractional order scheme that follows:

$$\frac{d^{\vartheta}X}{dt^{\vartheta}}=f(X),\quad X(0)=X_0, \tag{4}$$

with $X\in\mathcal{R}^n$ and $\vartheta\in(0,1]$. The system's (4) equilibrium points are the equation's solutions $f(X^*)=0$, and these equilibrium points:

(1) Asymptotically stable ⇔ all the eigenvalues $\lambda_i,i=1,2,\dots,n$ of the Jacobian matrix $J(X^*)$ satisfy that $|\arg(\lambda_i)|>\frac{\vartheta\pi}{2}$.

(2) Stable ⇔ it is asymptotically stable or the eigenvalues $\lambda_i,i=1,2,\dots,n$ of $J(X^*)$ that satisfy $|\arg(\lambda_i)|=\frac{\vartheta\pi}{2}$ if have the same geometric multiplicity and algebraic multiplicity.

(3) Unstable ⇔ eigenvalues λ_i for some $i=1,2,\dots,n$ of $J(X^*)$ satisfy $|\arg(\lambda_i)|<\frac{\vartheta\pi}{2}$.

3. Mathematical Modelling

It is possible to forecast how cancer cells will grow and spread as well as how chemotherapy medications will affect these cells using mathematical models. Many diseases can be treated and their ability to spread inhibited by mathematical models. Our goal is to use these mathematical models to track the disease's progress while also advancing science by watching how the disease affects individuals. Many individuals die from cancer, a disease that has become more common over time. We take into consideration three subclasses: immune system cells, tumor cells, and chemotherapy drugs in order to analyze the impact of these drugs and the spread of cancer cells on these cells. Tumor cell T, immune system cell I, chemotherapy medication D, and population as a whole are denoted. The following is the suggested fractional order model:

$$\begin{aligned} D^{\vartheta}T(t) &= {s_1}^{\vartheta}T\left(1-\frac{T}{k_1}\right)-{\theta_1}^{\vartheta}TI-{d_1}^{\vartheta}T-{\theta_2}^{\vartheta}DT, \\ D^{\vartheta}I(t) &= {s_2}^{\vartheta}I\left(1-\frac{I}{k_2}\right)-{\theta_3}^{\vartheta}DI(t)-{d_2}^{\vartheta}I(t), \\ D^{\vartheta}D(t) &= -\gamma^{\vartheta}D+V^{\vartheta}(t). \end{aligned} \tag{5}$$

with initial settings $T(0)=T_0\geq 0, I(0)=I_0\geq 0, D(0)=D_0\geq 0$.

Table 1 provides a summary of the parameter descriptions. To make sure they comply with the model's features (5), these values are extracted from [10,19]. It is important to note that we take all parameters to be non-negative [10, 19].

This section may be divided into subheadings. It should provide a concise and precise description of the experimental results, their interpretation, as well as the experimental conclusions that can be drawn.

Table 1. The biological significance of the numerical quantities and parameters

Parameters	Meaning	Value	Unit	Source
T_0	Density of free tumors	1	mm^3/cells	[10]
I_0	Immunity cells initial concentration	1	mm^3/cells	[10]
D_0	Chemotherapy Concentration Drug	1	mm^3/cells	[10]
γ	Decay rate of chemotherapy drug	6.4	(1/day)	[10]
d_2	The natural death rate of Immune system cells	0.07	[19]	[19]
s_1	Logistic growth rate of Tumor cells	0.18	(1/day)	[10]
k_1	The carrying capacity of tumor cells	10	(1/cells)	[19]
θ_1	The rate of tumor cell death brought on by immune system cell attack	0.9	(1/day)	[10]
d_1	Natural death rate of Tumor cells	0.03	(1/day)	[10]
θ_2	Fractional tumor cells killed by chemotherapy	0.9	(1/cells)	[10]
θ_3	Decay rate of immune system cells killed by chemotherapy	0.9	(1/cells)	[10]
$V(t)$	Chemotherapy drug inflow and outflow with time dependence	1	(1/day)	[10]
s_2	Logistic growth rate of immune System Cells	0.4	(cells/day)	[19]
k_2	The Carrying capacity of immune system	20	(1/cells)	[19]

4. Existence and Uniqueness

Now let's evaluate system (5) with its original configuration $T(0)=T_0,\ I(0)=I_0,\ D(0)=D_0$. For the system (5), the formula is:

$$D^{\vartheta}X(t)=B_1X(t)+T(t)B_2X(t)+I(t)B_3X(t)+V,$$
$$X(0)=X_0\,, \tag{6}$$

where

$$X(t)=\begin{pmatrix}T(t)\\I(t)\\D(t)\end{pmatrix},\ X(0)=\begin{pmatrix}T(0)\\I(0)\\D(0)\end{pmatrix},$$

$$B_1=\begin{pmatrix}{s_1}^{\vartheta}-{d_1}^{\vartheta}&0&0\\0&{s_2}^{\vartheta}-{d_2}^{\vartheta}&0\\0&0&-\gamma^{\vartheta}\end{pmatrix},\ B_2=\begin{pmatrix}-\frac{{s_1}^{\vartheta}}{k_1}&-{\theta_1}^{\vartheta}&-{\theta_2}^{\vartheta}\\0&0&0\\0&0&0\end{pmatrix},\ B_3=\begin{pmatrix}0&0&0\\0&-\frac{{s_2}^{\vartheta}}{k_2}&0\\0&0&0\end{pmatrix},V=\begin{pmatrix}0\\0\\V^{\vartheta}(t)\end{pmatrix}.$$

Definition 7 [15]**.** Let $C^*[0,\tau^*]$ be the class of continuous column $X(t)$ whose components $T,I,D\in C^*[0,\tau^*]$ are the class of continuous functions on the interval $[0,\tau^*]$. The norm of $X\in C^*[0,\tau^*]$ is given by

$$\|X\|=\sup_t|e^{-Nt}T(t)|+\sup_t|e^{-Nt}I(t)|+\sup_t|e^{-Nt}D(t)|,$$

where N is a natural number and when $t>\delta\geq m$, we write $C_{\delta}^*[0,\tau^*]$ and $C_{\delta}[0,\tau^*]$.

Definition 8 [15]**.** $X\in C^*[0,\tau^*]$ is a solution of *IVP* (6) if

(1) $\big(t,X(t)\big)\in D, t\in[0,\tau^*]$ where $D=[0,\tau^*]\times K, K=\{(T,I,D)\in\mathcal{R}_+^3\colon |T|\leq p,|I|\leq r,|D|\leq w\}$,

$p,r,w\in\mathcal{R}_+$ are constants.

(2) $X(t)$ satisfies (6).

Theorem 2. The unique solution for the IVP (6) is $X\in C^*[0,\tau^*]$.

Proof. The equation in (6) can be stated as follows due to the inherent characteristics of the fractional calculus:

$$I^{1-\vartheta}\frac{d}{dt}X(t)=B_1X(t)+T(t)B_2X(t)+I(t)B_3X(t)+V.$$

Operating by I^{ϑ} we achieve

$$X(t)=X(0)+I^{\vartheta}(B_1X(t)+T(t)B_2X(t)+I(t)B_3X(t)+V). \tag{7}$$

Let us now $F\colon C^*[0,\tau^*]\to C^*[0,\tau^*]$ described by

$$FX(t)=X(0)+I^{\vartheta}(B_1X(t)+T(t)B_2X(t)+I(t)B_3X(t)+V). \tag{8}$$

Then

$$e^{-Nt}\|FX-FY\|=e^{-Nt}I^{\vartheta}\Big(B_1(X(t)-Y(t))+T(t)B_2\big(X(t)-Y(t)\big)+I(t)B_3\big(X(t)-Y(t)\big)\Big),$$
$$\leq\left|\tfrac{1}{\Gamma(\vartheta)}\int_0^t(t-s)^{\vartheta-1}e^{-N(t-s)}\big(X(s)-Y(s)\big)e^{-Ns}ds\right|(B_1+pB_2+rB_3),$$
$$\leq(B_1+pB_2+rB_3)\left|\tfrac{1}{\Gamma(\vartheta)}\int_0^t(u)^{\vartheta-1}e^{-N(u)}\right|\|X-Y\|,$$
$$\leq\frac{(B_1+pB_2+rB_3)\left|\frac{\gamma(\vartheta,Nt)}{\Gamma(\vartheta)}\right|}{N^{\vartheta}}\|X-Y\|,$$

where $\gamma(\vartheta,Nt)$ is the lower incomplete gamma function and $u=t-s$. Since N is an arbitrary, we accept that $N^{\vartheta}\geq B_1+pB_2+rB_3$, then we get $\|FX-FY\|\leq\|X-Y\|$. In (8), operator F has a fixed point. Therefore, (7) has a special solution. $X\in C^*[0,\tau^*]$.

In (7), we have

$$X(t) = X(0) + \frac{t^{\vartheta}}{\Gamma(\vartheta+1)}\big(B_1X(0) + T(0)B_2X(0) + I(0)B_3X(0)\big)$$
$$+I^{\vartheta+1}\big(B_1X'(t) + T'(t)B_2X(t) + T(t)B_2X'(t) + I'(t)B_3X(t) + I(t)B_3X'(t)\big).$$
$$e^{-Nt}X'(t) = e^{-Nt}\frac{t^{\vartheta}}{\Gamma(\vartheta)}(B_1X(0) + S(0)B_2X(0) + I(0)B_3X(0) + V)$$
$$+I^{\vartheta}\big(B_1X'(t) + T'(t)B_2X(t) + T(t)B_2X'(t) + I'(t)B_3X(t) + I(t)B_3X'(t)\big).$$

The assumption $X' \in C_{\delta}^{*}[0,\tau^{*}]$. From (7) we have

$$\frac{dX(t)}{dt} = \frac{d}{dt}I^{\vartheta}(B_1X(t) + T(t)B_2X(t) + I(t)B_3X(t) + V).$$

Operating by $I^{1-\vartheta}$ we get

$$I^{1-\vartheta}\frac{dX(t)}{dt} = I^{1-\vartheta}\frac{d}{dt}I^{\vartheta}(B_1X(t) + T(t)B_2X(t) + I(t)B_3X(t) + V).$$
$$D^{\vartheta}X(t) = (B_1X(t) + T(t)B_2X(t) + I(t)B_3X(t) + V),$$

and

$$X(0) = X_0 + I^{\vartheta}(B_1X(t) + T(t)B_2X(t) + I(t)B_3X(t) + V).$$

Consequently, Equation (7) and IVP (6) are equal.

5. Equilibria and Their Stabilities

The following formula can be used to find the equilibrium positions in system (5):

$$\begin{aligned} D^{\vartheta}T(t) &= {s_1}^{\vartheta}T\left(1-\frac{T}{k_1}\right) - {\theta_1}^{\vartheta}TI - {d_1}^{\vartheta}T - {\theta_2}^{\vartheta}DT = 0,\\ D^{\vartheta}I(t) &= {s_2}^{\vartheta}I\left(1-\frac{I}{k_2}\right) - {\theta_3}^{\vartheta}DI(t) - {d_2}^{\vartheta}I(t) = 0,\\ D^{\vartheta}D(t) &= -\gamma^{\vartheta}D + V^{\vartheta}(t)=0. \end{aligned} \tag{9}$$

Then the equilibrium points are:

$$\begin{aligned} E_1 &= \big(0,0,V^{\vartheta}\gamma^{-\vartheta}\big),\\ E_2 &= \big(0,\gamma^{-\vartheta}k_2s_2^{-\vartheta}\big(-\gamma^{\vartheta}d_2^{\vartheta} + \gamma^{\vartheta}s_2^{\vartheta} - V^{\vartheta}\theta_3^{\vartheta}\big),V^{\vartheta}\gamma^{-\vartheta}\big),\\ E_3 &= \big(\gamma^{-\vartheta}k_1s_1^{-\vartheta}\big(-\gamma^{\vartheta}d_1^{\vartheta} + \gamma^{\vartheta}s_1^{\vartheta} - V^{\vartheta}\theta_2^{\vartheta}\big),0,V^{\vartheta}\gamma^{-\vartheta}\big),\\ E_4 &= \big(\gamma^{-\vartheta}k_1s_1^{-\vartheta}s_2^{-\vartheta}\big(-\gamma^{\vartheta}d_1^{\vartheta}s_2^{\vartheta} + \gamma^{\vartheta}s_1^{\vartheta}s_2^{\vartheta} + \gamma^{\vartheta}d_2^{\vartheta}k_2\theta_1^{\vartheta} - \gamma^{\vartheta}k_2s_2^{\vartheta}\theta_1^{\vartheta} - V^{\vartheta}s_2^{\vartheta}\theta_2^{\vartheta}\\ &\quad + V^{\vartheta}k_2\theta_1^{\vartheta}\theta_3^{\vartheta}\big),\gamma^{-\vartheta}k_2s_2^{-\vartheta}\big(-\gamma^{\vartheta}d_2^{\vartheta} + \gamma^{\vartheta}s_2^{\vartheta} - V^{\vartheta}\theta_3^{\vartheta}\big),V^{\vartheta}\gamma^{-\vartheta}\big). \end{aligned}$$

Theorem 3. Let E_1 be the model (5) equilibrium points. Pretend that

$${s_1}^{\vartheta} - {d_1}^{\vartheta} < {\theta_2}^{\vartheta}V^{\vartheta}\gamma^{-\vartheta}$$

and

$${s_2}^{\vartheta} - {d_2}^{\vartheta} < {\theta_3}^{\vartheta}V^{\vartheta}\gamma^{-\vartheta}$$

then E_1 is locally asymptotically stable.

Proof. Model (5)'s Jacobian matrix, as determined at equilibrium point E_1, is provided by

$$J(E_1) = \begin{pmatrix} {s_1}^{\vartheta} - {d_1}^{\vartheta} - {\theta_2}^{\vartheta}V^{\vartheta}\gamma^{-\vartheta} & 0 & 0\\ 0 & {s_2}^{\vartheta} - {d_2}^{\vartheta} - {\theta_3}^{\vartheta}V^{\vartheta}\gamma^{-\vartheta} & 0\\ 0 & 0 & -\gamma^{\vartheta} \end{pmatrix},$$

the characteristic equation

$$|J(E_1) - \lambda I| = 0$$

states that,

$$\left(-\gamma^{\vartheta}-\lambda\right)\left[\left(s_1{}^{\vartheta}-d_1{}^{\vartheta}-\theta_2{}^{\vartheta}V^{\vartheta}\gamma^{-\vartheta}-\lambda\right)\left(s_2{}^{\vartheta}-d_2{}^{\vartheta}-\theta_3{}^{\vartheta}V^{\vartheta}\gamma^{-\vartheta}-\lambda\right)\right]=0,$$

eigenvalues of $J(E_1)$ are:

$$\lambda_1=-\gamma^{\vartheta},$$
$$\lambda_2=s_1{}^{\vartheta}-d_1{}^{\vartheta}-\theta_2{}^{\vartheta}V^{\vartheta}\gamma^{-\vartheta},$$
$$\lambda_3=s_2{}^{\vartheta}-d_2{}^{\vartheta}-\theta_3{}^{\vartheta}V^{\vartheta}\gamma^{-\vartheta}.$$
$$\lambda_i<0,|\arg(\lambda_i)|=\pi>\frac{\vartheta\pi}{2},i=1,2,3.$$

The equilibrium point is E_1, which is locally asymptotically stable according to Theorem 1.

Theorem 4. The equilibrium point E_2 of the model (5) is asymptotically stable if

$$s_1{}^{\vartheta}-d_1{}^{\vartheta}<\theta_1{}^{\vartheta}\left(\gamma^{-\vartheta}k_2s_2^{-\vartheta}\left(-\gamma^{\vartheta}d_2^{\vartheta}+\gamma^{\vartheta}s_2^{\vartheta}-V^{\vartheta}\theta_3^{\vartheta}\right)+\theta_2{}^{\vartheta}V^{\vartheta}\gamma^{-\vartheta}\right)$$

and

$$s_2{}^{\vartheta}-d_2{}^{\vartheta}<2\gamma^{-\vartheta}s_2^{-\vartheta}\left(-\gamma^{\vartheta}d_2^{\vartheta}+\gamma^{\vartheta}s_2^{\vartheta}-V^{\vartheta}\theta_3^{\vartheta}\right)+\theta_3{}^{\vartheta}V^{\vartheta}\gamma^{-\vartheta}.$$

Proof. Model (5)'s Jacobian matrix, as determined at equilibrium point E_2, is provided by

$$J(E_2)=\begin{pmatrix}a_{11}&0&0\\0&a_{22}&a_{23}\\0&0&-\gamma\end{pmatrix},$$

$$a_{11}=s_1{}^{\vartheta}-d_1{}^{\vartheta}-\theta_1{}^{\vartheta}\left(\gamma^{-\vartheta}k_2s_2^{-\vartheta}\left(-\gamma^{\vartheta}d_2^{\vartheta}+\gamma^{\vartheta}s_2^{\vartheta}-V^{\vartheta}\theta_3^{\vartheta}\right)-\theta_2{}^{\vartheta}V^{\vartheta}\gamma^{-\vartheta}\right),$$
$$a_{22}=s_2{}^{\vartheta}-d_2{}^{\vartheta}-2\gamma^{-\vartheta}s_2^{-\vartheta}\left(-\gamma^{\vartheta}d_2^{\vartheta}+\gamma^{\vartheta}s_2^{\vartheta}-V^{\vartheta}\theta_3^{\vartheta}\right)-\theta_3{}^{\vartheta}V^{\vartheta}\gamma^{-\vartheta},$$
$$a_{23}=-\theta_3{}^{\vartheta}\gamma^{-\vartheta}k_2s_2^{-\vartheta}\left(-\gamma^{\vartheta}d_2^{\vartheta}+\gamma^{\vartheta}s_2^{\vartheta}-V^{\vartheta}\theta_3^{\vartheta}\right).$$

The characteristic equation $|J(E_2)-\lambda I|=0$ states that

$$\left(-\gamma^{\vartheta}-\lambda\right)\left[\left(s_1{}^{\vartheta}-d_1{}^{\vartheta}-\theta_1{}^{\vartheta}\left(\gamma^{-\vartheta}k_2s_2^{-\vartheta}\left(-\gamma^{\vartheta}d_2^{\vartheta}+\gamma^{\vartheta}s_2^{\vartheta}-V^{\vartheta}\theta_3^{\vartheta}\right)-\theta_2{}^{\vartheta}V^{\vartheta}\gamma^{-\vartheta}\right)-\lambda\right)\left(s_2{}^{\vartheta}-d_2{}^{\vartheta}\right.\right.$$
$$\left.\left.-2\gamma^{-\vartheta}s_2^{-\vartheta}\left(-\gamma^{\vartheta}d_2^{\vartheta}+\gamma^{\vartheta}s_2^{\vartheta}-V^{\vartheta}\theta_3^{\vartheta}\right)-\theta_3V^{\vartheta}\gamma^{-\vartheta}-\lambda\right)\right]=0,$$

we get

$$\lambda_1=-\gamma^{\vartheta},$$
$$\lambda_2=s_1{}^{\vartheta}-d_1{}^{\vartheta}-\theta_1{}^{\vartheta}\left(\gamma^{-\vartheta}k_2s_2^{-\vartheta}\left(-\gamma^{\vartheta}d_2^{\vartheta}+\gamma^{\vartheta}s_2^{\vartheta}-V^{\vartheta}\theta_3^{\vartheta}\right)-\theta_2{}^{\vartheta}V^{\vartheta}\gamma^{-\vartheta}\right),$$
$$\lambda_3=s_2{}^{\vartheta}-d_2{}^{\vartheta}-2\gamma^{-\vartheta}s_2^{-\vartheta}\left(-\gamma^{\vartheta}d_2^{\vartheta}+\gamma^{\vartheta}s_2^{\vartheta}-V^{\vartheta}\theta_3^{\vartheta}\right)-\theta_3{}^{\vartheta}V^{\vartheta}\gamma^{-\vartheta}.$$
$$\lambda_i<0,|\arg(\lambda_i)|=\pi>\frac{\vartheta\pi}{2},i=1,2,3.$$

The equilibrium point is E_2, which is locally asymptotically stable according to Theorem 1.

Theorem 5. The equilibrium point E_3 of the model (5) is asymptotically stable if

$$s_1{}^{\vartheta}-d_1{}^{\vartheta}<2\gamma^{-\vartheta}\left(-\gamma^{\vartheta}d_1^{\vartheta}+\gamma^{\vartheta}s_1^{\vartheta}-V^{\vartheta}\theta_2^{\vartheta}\right)+\theta_2{}^{\vartheta}V^{\vartheta}\gamma^{-\vartheta}$$

and

$$s_2{}^{\vartheta}-d_2{}^{\vartheta}<\theta_3{}^{\vartheta}V^{\vartheta}\gamma^{-\vartheta}.$$

Proof. Model (5)'s Jacobian matrix, as determined at equilibrium point E_3, is provided by

$$J(E_3)=\begin{pmatrix}a_{11}&a_{12}&a_{13}\\0&a_{22}&0\\0&0&-\gamma\end{pmatrix},$$

$$a_{11}=s_1{}^{\vartheta}-d_1{}^{\vartheta}-2\gamma^{-\vartheta}\left(-\gamma^{\vartheta}d_1^{\vartheta}+\gamma^{\vartheta}s_1^{\vartheta}-V^{\vartheta}\theta_2^{\vartheta}\right)-\theta_2{}^{\vartheta}V^{\vartheta}\gamma^{-\vartheta},$$
$$a_{12}=-\theta_1\gamma^{-\vartheta}k_1s_1^{-\vartheta}\left(-\gamma^{\vartheta}d_1^{\vartheta}+\gamma^{\vartheta}s_1^{\vartheta}-V\theta_2^{\vartheta}\right),$$
$$a_{13}=-\theta_2\gamma^{-\vartheta}k_1s_1^{-\vartheta}\left(-\gamma^{\vartheta}d_1^{\vartheta}+\gamma^{\vartheta}s_1^{\vartheta}-V\theta_2^{\vartheta}\right),$$

$$a_{22} = {s_2}^{\vartheta} - {d_2}^{\vartheta} - {\theta_3}^{\vartheta} V^{\vartheta} \gamma^{-\vartheta}.$$

The characteristic equation

$$|J(E_3) - \lambda I| = 0$$

states that,

$$\left(-\gamma^{\vartheta} - \lambda\right)\left[\left({s_1}^{\vartheta} - {d_1}^{\vartheta} + 2d_1^{\vartheta} - 2s_1^{\vartheta} + 2\gamma^{-\vartheta} V^{\vartheta} \theta_2^{\vartheta} - {\theta_2}^{\vartheta} V^{\vartheta} \gamma^{-\vartheta} - \lambda\right)\left({s_2}^{\vartheta} - {d_2}^{\vartheta} - {\theta_3}^{\vartheta} V^{\vartheta} \gamma^{-\vartheta} - \lambda\right)\right] = 0,$$

we get

$$\lambda_1 = -\gamma^{\vartheta},$$
$$\lambda_2 = {s_1}^{\vartheta} - {d_1}^{\vartheta} - 2\gamma^{-\vartheta}\left(-\gamma^{\vartheta} d_1^{\vartheta} + \gamma^{\vartheta} s_1^{\vartheta} - V^{\vartheta} \theta_2^{\vartheta}\right) - {\theta_2}^{\vartheta} V^{\vartheta} \gamma^{-\vartheta},$$
$$\lambda_3 = {s_2}^{\vartheta} - {d_2}^{\vartheta} - {\theta_3}^{\vartheta} V^{\vartheta} \gamma^{-\vartheta}.$$
$$\lambda_i < 0, |\arg(\lambda_i)| = \pi > \frac{\vartheta \pi}{2}, i = 1,2,3.$$

The equilibrium point is E_3 , which is locally asymptotically stable according to Theorem 1.

Theorem 6. The co-existence equilibrium point E_4 of the model (5) is asymptotically stable if

$${s_1}^{\vartheta} - {d_1}^{\vartheta} < 2\gamma^{-\vartheta} s_2^{-\vartheta}\left(-\gamma^{\vartheta} d_1^{\vartheta} s_2^{\vartheta} + \gamma^{\vartheta} s_1^{\vartheta} s_2^{\vartheta} + \gamma^{\vartheta} d_2^{\vartheta} k_2 \theta_1^{\vartheta} - \gamma^{\vartheta} k_2 s_2^{\vartheta} \theta_1^{\vartheta} - V^{\vartheta} s_2^{\vartheta} \theta_2^{\vartheta} + V^{\vartheta} k_2 \theta_1^{\vartheta} \theta_3^{\vartheta}\right)$$
$$+{\theta_1}^{\vartheta} \gamma^{-\vartheta} k_2 s_2^{-\vartheta}\left(-\gamma^{\vartheta} d_2^{\vartheta} + \gamma^{\vartheta} s_2^{\vartheta} - V^{\vartheta} \theta_3^{\vartheta}\right) + \theta_2^{\vartheta} V^{\vartheta} \gamma^{-\vartheta}$$

and

$${s_2}^{\vartheta} - {d_2}^{\vartheta} < 2\gamma^{-\vartheta}\left(-\gamma^{\vartheta} d_2^{\vartheta} + \gamma^{\vartheta} s_2^{\vartheta} - V^{\vartheta} \theta_3^{\vartheta}\right)\theta_3^{\vartheta} V^{\vartheta} \gamma^{-\vartheta}.$$

Proof. Model (5)'s Jacobian matrix, as determined at co-existence equilibrium point E_4 , is provided by

$$J(E_4) = \begin{pmatrix} a_{11} & a_{12} & a_{13} \\ 0 & a_{22} & a_{23} \\ 0 & 0 & -\gamma \end{pmatrix},$$

$$a_{11} = {s_1}^{\vartheta} - {d_1}^{\vartheta} - 2\gamma^{-\vartheta} s_2^{-\vartheta}\left(-\gamma^{\vartheta} d_1^{\vartheta} s_2^{\vartheta} + \gamma^{\vartheta} s_1^{\vartheta} s_2^{\vartheta} + \gamma^{\vartheta} d_2^{\vartheta} k_2 \theta_1^{\vartheta} - \gamma^{\vartheta} k_2 s_2^{\vartheta} \theta_1^{\vartheta} - V^{\vartheta} s_2^{\vartheta} \theta_2^{\vartheta} + V^{\vartheta} k_2 \theta_1^{\vartheta} \theta_3^{\vartheta}\right)$$
$$-{\theta_1}^{\vartheta} \gamma^{-\vartheta} k_2 s_2^{-\vartheta}\left(-\gamma^{\vartheta} d_2^{\vartheta} + \gamma^{\vartheta} s_2^{\vartheta} - V^{\vartheta} \theta_3^{\vartheta}\right) - \theta_2^{\vartheta} V^{\vartheta} \gamma^{-\vartheta},$$
$$a_{12} = -\theta_1 \gamma^{-\vartheta} k_1 s_1^{-\vartheta} s_2^{-\vartheta}\left(-\gamma^{\vartheta} d_1^{\vartheta} s_2^{\vartheta} + \gamma^{\vartheta} s_1^{\vartheta} s_2^{\vartheta} + \gamma^{\vartheta} d_2^{\vartheta} k_2 \theta_1^{\vartheta} - \gamma^{\vartheta} k_2 s_2^{\vartheta} \theta_1^{\vartheta} - V^{\vartheta} s_2^{\vartheta} \theta_2^{\vartheta} + V^{\vartheta} k_2 \theta_1^{\vartheta} \theta_3^{\vartheta}\right),$$
$$a_{13} = -\theta_2 \gamma^{-\vartheta} k_1 s_1^{-\vartheta} s_2^{-\vartheta}\left(-\gamma^{\vartheta} d_1^{\vartheta} s_2^{\vartheta} + \gamma^{\vartheta} s_1^{\vartheta} s_2^{\vartheta} + \gamma^{\vartheta} d_2^{\vartheta} k_2 \theta_1^{\vartheta} - \gamma^{\vartheta} k_2 s_2^{\vartheta} \theta_1^{\vartheta} - V^{\vartheta} s_2^{\vartheta} \theta_2^{\vartheta} + V^{\vartheta} k_2 \theta_1^{\vartheta} \theta_3^{\vartheta}\right),$$
$$a_{22} = {s_2}^{\vartheta} - {d_2}^{\vartheta} < 2\gamma^{-\vartheta}\left(-\gamma^{\vartheta} d_2^{\vartheta} + \gamma^{\vartheta} s_2^{\vartheta} - V^{\vartheta} \theta_3^{\vartheta}\right)\theta_3^{\vartheta} V^{\vartheta} \gamma^{-\vartheta},$$
$$a_{23} = {\theta_3}^{\vartheta} \gamma^{-\vartheta} k_2 s_2^{-\vartheta}\left(-\gamma^{\vartheta} d_2^{\vartheta} + \gamma^{\vartheta} s_2^{\vartheta} - V^{\vartheta} \theta_3^{\vartheta}\right).$$

The characteristic equation

$$|J(E_4) - \lambda I| = 0$$

states that,

$$\left(-\gamma^{\vartheta} - \lambda\right)\Big[\Big(\big({s_1}^{\vartheta} - {d_1}^{\vartheta} + 2d_1^{\vartheta} - 2s_1^{\vartheta} - 2s_2^{-\vartheta} d_2^{\vartheta} k_2 \theta_1^{\vartheta} - 2k_2 \theta_1^{\vartheta}$$
$$- 2\gamma^{-\vartheta} V^{\vartheta} \theta_2^{\vartheta} - 2\gamma^{-\vartheta} s_2^{-\vartheta} V^{\vartheta} k_2 \theta_1^{\vartheta} \theta_3^{\vartheta} + {\theta_1}^{\vartheta} k_2 s_2^{-\vartheta} d_2^{\vartheta} - {\theta_1}^{\vartheta} k_2 + {\theta_1}^{\vartheta} \gamma^{-\vartheta} k_2 s_2^{-\vartheta} V^{\vartheta} \theta_3^{\vartheta}$$
$$- \theta_2^{\vartheta} V^{\vartheta} \gamma^{-\vartheta}\big) - \lambda\Big)\left({s_2}^{\vartheta} - {d_2}^{\vartheta} + \left(2d_2^{\vartheta} - 2s_2^{\vartheta} + 2\gamma^{-\vartheta} V^{\vartheta} \theta_3^{\vartheta}\right)\theta_3^{\vartheta}\, V^{\vartheta} \gamma^{-\vartheta} - \lambda\right)\Big] = 0,$$

we get

$$\lambda_1 = -\gamma^{\vartheta},$$
$$\lambda_2 = \big({s_1}^{\vartheta} - {d_1}^{\vartheta} - 2\gamma^{-\vartheta} s_2^{-\vartheta}\left(-\gamma^{\vartheta} d_1^{\vartheta} s_2^{\vartheta} + \gamma^{\vartheta} s_1^{\vartheta} s_2^{\vartheta} + \gamma^{\vartheta} d_2^{\vartheta} k_2 \theta_1^{\vartheta} - \gamma^{\vartheta} k_2 s_2^{\vartheta} \theta_1^{\vartheta} - V^{\vartheta} s_2^{\vartheta} \theta_2^{\vartheta} + V^{\vartheta} k_2 \theta_1^{\vartheta} \theta_3^{\vartheta}\right)$$
$$- {\theta_1}^{\vartheta} \gamma^{-\vartheta} k_2 s_2^{-\vartheta}\left(-\gamma^{\vartheta} d_2^{\vartheta} + \gamma^{\vartheta} s_2^{\vartheta} - V^{\vartheta} \theta_3^{\vartheta}\right) - \theta_2^{\vartheta} V^{\vartheta} \gamma^{-\vartheta}\big),$$
$$\lambda_3 = {s_2}^{\vartheta} - {d_2}^{\vartheta} - 2\gamma^{-\vartheta}\left(-\gamma^{\vartheta} d_2^{\vartheta} + \gamma^{\vartheta} s_2^{\vartheta} - V^{\vartheta} \theta_3^{\vartheta}\right)\theta_3^{\vartheta}\, V^{\vartheta} \gamma^{-\vartheta}.$$
$$\lambda_i < 0, |\arg(\lambda_i)| = \pi > \frac{\vartheta \pi}{2}, i = 1,2,3.$$

The co-existence equilibrium point is E_4, which is locally asymptotically stable according to Theorem 1.

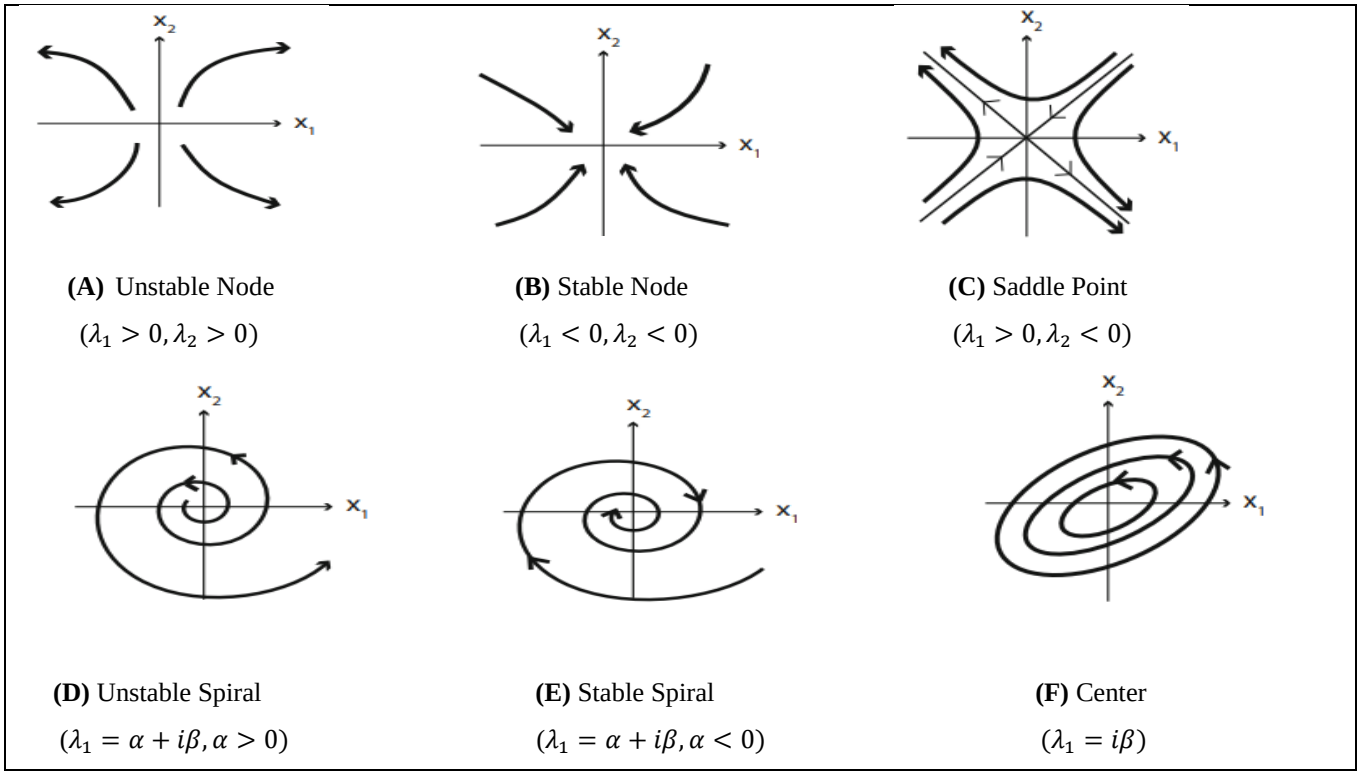

Figure 1. Phase Portrait for System (5)

Since $\lambda_i < 0, i = 1,2,3$, it has a stable node graph; see Fig.1(B).

6.Positivity and Boundedness

Lemma 1 (Generalized Mean Value Theorem)**.** Assume that $w(t) \in C[a,b]$ and ${}_0^C D_t^{\vartheta} w(t) \in C[a,b]$ for $0 < \vartheta \leq 1$, then

$$w(t) = w(a) + \frac{1}{\Gamma(\vartheta)} {}_0^C D_t^{\vartheta} w(\tau)(t-a)^{\vartheta},$$

where $0 \leq \tau \leq t, \ \forall t \in (a,b]$.

Remark 1. If $w \in C[0,b]$ and ${}_0^C D_t^{\vartheta}\big(w(t)\big) \geq 0, \ \forall t \in (0,b]$, then the function $w(t)$ is non-increasing for all $t \in [0,b]$.

Theorem 5. The solution of model (5) along with initial settings is bounded in $\mathcal{R}_+^3$.

Proof. Noting that $\mathcal{R}_+^3$ is positivity invariant, the non negative region.

From system (5), we get

$$\begin{aligned} D^{\vartheta} T(t)_{T=0} &= 0 \geq 0, \\ D^{\vartheta} I(t)_{I=0} &= 0 \geq 0, \\ D^{\vartheta} D(t)_{D=0} &= V^{\vartheta}(t) \geq 0. \end{aligned} \tag{10}$$

If $\big(T(0), I(0), D(0)\big) \in \mathcal{R}_+^3$, The solution of model (5) is therefore unable to escape the hyperplanes $T = 0, I = 0,$ $D = 0$ in accordance with system (10) and Remark 1. This means that the region $\mathcal{R}_+^3$ is a collection of positive invariants.

Theorem 6.

For the system (5), the region $P = \{T(t), I(t), D(t) \in \mathcal{R}_+^3, \ 0 < T(t) + I(t) + D(t) \leq V^{\vartheta}(t)C\}$ is an invariant set that is positive.

Proof. From model (5) we have

$$D^{\vartheta} N(t) = {s_1}^{\vartheta} T\left(1 - \frac{T}{k_1}\right) - {\theta_1}^{\vartheta} TI - {d_1}^{\vartheta} T - {\theta_2}^{\vartheta} DT + {s_2}^{\vartheta} I\left(1 - \frac{I}{k_2}\right) - {\theta_3}^{\vartheta} DI(t) - {d_2}^{\vartheta} I(t) - \gamma^{\vartheta} D + V^{\vartheta}(t).$$

This gives

$$D^{\vartheta}N(t) \leq V^{\vartheta}(t) + N.$$

When we use the preceding equation with the Laplace Transform, we have

$$S^{\vartheta}L(N) \leq \frac{V^{\vartheta}(t)}{S} + L(N),$$

this further provides,

$$L(N) \leq \frac{S^{-1}V^{\vartheta}(t)}{(S^{\vartheta}-1)}.$$

When we use the previous equation $N \leq V^{\vartheta}(t)t^{\vartheta}E_{\vartheta,\vartheta+1}(t^{\vartheta})$ with the Laplace Transform.

From Mittag Leffler function definition, we can infer if $T_0, I_0, D_0 \in \mathcal{R}_+^3$, then

$$N(t) \leq V^{\vartheta}(\mathrm{t})E_{\vartheta,\vartheta+1}(t^{\vartheta}),$$

$$N(t) \leq V^{\vartheta}(\mathrm{t})C,\ C > 0.$$

This suggests that because $N(t)$ is bounded, $T(t)$, $I(t)$ and $D(t)$, are also bounded.

7. Numerical Scheme

We examine the dynamics of the proposed fractional order model (5) using the Caputo fractional operator. The suggested nonlinear fractional order system is numerically modeled using the Adams type estimator-corrector approach [25–29]. In relation to the Caputo operator of order ϑ, the following Cauchy type ODE is considered:

$$ {}_0^C D_t^{\vartheta}\phi(t) = \phi\big(t,\phi(t)\big), \phi^{(b)}(0) = \phi_0^b, 0 < \vartheta < 1, 0 < t \leq \tau\,, \tag{11}$$

where $b = 0,1,\ldots,n-1$, and $n = [\vartheta]$. Eq. (11) can be turned to the Volterra equation:

$$\phi(t) = \sum_{b=0}^{n-1} \phi_0^{(b)} \frac{t^b}{b!} + \frac{1}{\Gamma(\vartheta)}\int_0^t (t-s)^{\vartheta-1}\phi(s,\phi(s))ds. \tag{12}$$

Considering the numerical solutions of the model with the proposed predictor-corrector scheme associated with the Adam-Bashforth-Moulton algorithm [26], we can take $h = {}^{\tau}/_{N}$, $t_z = zh$, and $z = 0,1,\ldots,N \in Z^+$, by letting $\phi_z \approx \phi(t_z)$, the accompanying corrector formula [29], which is as follows, can be used to discretize it:

$$\begin{aligned}
T_{q+1} = {} & \sum_{z=0}^{q-1} T_0^{(z)} \frac{t_{q+1}^z}{z!} + \frac{h^{\vartheta}}{\Gamma(\vartheta+2)}\sum_{z=0}^{q}\big(p_{z,q+1}\big)\left(s_1{}^{\vartheta}T_z\left(1-\frac{T_z}{k_1}\right) - \theta_1{}^{\vartheta}T_z I_z - d_1{}^{\vartheta}T_z - \theta_2{}^{\vartheta}D_z T_z\right) \\
& + \frac{h^{\vartheta}}{\Gamma(\vartheta+2)}\sum_{z=0}^{q}\big(p_{q+1,q+1}\big)\left(s_1{}^{\vartheta}T_{q+1}^{PF}\left(1-\frac{T_{q+1}^{PF}}{k_1}\right) - \theta_1{}^{\vartheta}T_{q+1}^{PF}I_{q+1}^{PF} - d_1{}^{\vartheta}T_{q+1}^{PF}\right. \\
& \left. - \theta_2{}^{\vartheta}D_{q+1}^{PF}T_{q+1}^{PF}\right), \\
I_{q+1} = {} & \sum_{z=0}^{q-1} I_0^{(z)} \frac{t_{q+1}^z}{z!} + \frac{h^{\vartheta}}{\Gamma(\vartheta+2)}\sum_{z=0}^{q}\big(p_{z,q+1}\big)\left(s_2{}^{\vartheta}I_z\left(1-\frac{I_z}{k_2}\right) - \theta_3{}^{\vartheta}D_z I_z - d_2{}^{\vartheta}I_z\right) \\
& + \frac{h^{\vartheta}}{\Gamma(\vartheta+2)}\sum_{z=0}^{q}\big(p_{q+1,q+1}\big)\left(s_2{}^{\vartheta}I_{q+1}^{PF}\left(1-\frac{I_{q+1}^{PF}}{k_2}\right) - \theta_3{}^{\vartheta}D_{q+1}^{PF}I_{q+1}^{PF} - d_2{}^{\vartheta}I_{q+1}^{PF}\right), \\
D_{q+1} = {} & \sum_{z=0}^{q-1} R_0^{(z)} \frac{t_{q+1}^z}{z!} + \frac{h^{\vartheta}}{\Gamma(\vartheta+2)}\sum_{z=0}^{q}(p_{z,q+1})\left(-\gamma^{\vartheta}D_z + V^{\vartheta}(t)\right) \\
& + \frac{h^{\vartheta}}{\Gamma(\vartheta+2)}\sum_{z=0}^{q}\big(p_{q+1,q+1}\big)\left(-\gamma^{\vartheta}D_z + V^{\vartheta}(t)\right),
\end{aligned}$$

where

$$\begin{aligned}
T_{q+1}^{PF} = {} & \sum_{z=0}^{q-1} T_0^{(z)} \frac{t_{q+1}^z}{z!} + \frac{h^{\vartheta}}{\Gamma(\vartheta+1)}\sum_{z=0}^{q}(j_{z,q+1})\left(s_1{}^{\vartheta}T_z\left(1-\frac{T_z}{k_1}\right) - \theta_1{}^{\vartheta}T_z I_z - d_1{}^{\vartheta}T_z - \theta_2{}^{\vartheta}D_z T_z\right), \\
I_{q+1}^{PF} = {} & \sum_{z=0}^{q-1} I_0^{(z)} \frac{t_{q+1}^z}{z!} + \frac{h^{\vartheta}}{\Gamma(\vartheta+1)}\sum_{z=0}^{q}(j_{z,q+1})\left(s_2{}^{\vartheta}I_z\left(1-\frac{I_z}{k_2}\right) - \theta_3{}^{\vartheta}D_z I_z - d_2{}^{\vartheta}I_z\right),
\end{aligned}$$

$$D_{q+1}^{PF} = \sum_{z=0}^{q-1} D_0^{(z)} \frac{t_{q+1}^z}{z!} + \frac{h^\vartheta}{\Gamma(\vartheta+1)} \sum_{z=0}^{q} (j_{z,q+1}) \left(-\gamma^\vartheta D_z + V^\vartheta(t)\right),$$

and

$$p_{z,q+1} = \begin{cases} q^{\vartheta+1} - (q-\vartheta)(q+1)^\theta, & if\ z = 0, \\ (q-z+2)^{\vartheta+1} + (q-z)^{\vartheta+1} - 2(q-z+1)^{\vartheta+1}, & if\ 1 \le z \le q, \\ 1, & if\ z = q+1, \end{cases} \tag{13}$$

where

$$j_{z,q+1} = (q+1-z)^\vartheta - (q-z)^\vartheta.$$

8. Numeric Simulation

In this part, the Adams-Bashforth-Moulton Predictor-Corector method [27] is used to derive numerical solutions for system (5) using the parameters listed in Table 1. Numerical simulations are utilized to investigate the impact of the modifications. Depending on the system parameters (5) and different values of the fractional derivative of ϑ, the behavior of the system is examined. Table 1 gives the parameter values for the numerical simulations.

The fluctuation of cancer cells over time for various fractional derivatives is shown in Figure 2. It is observed that tumor cells decrease over time and reach stability on approximately the 5th day. In the case of the Caputo fractional derivative, as ϑ decreases from 1, it takes longer for tumor cells to reach stability. Figure 3 shows how immune system cells evolve over time for various fractional derivatives. It is observed that the immune system cells proliferate rapidly, reaching stability in approximately the 30th day, and in the integer-ordered state, it takes less time to reach the equilibrium point. The amount of immune system cells appears to decrease as the fractional derivative decreases from 1 to 0 (not equal to zero). Figure 4 shows how the chemotherapeutic drug concentration changes over time for various fractional derivatives. Figure 4 shows that the chemotherapy drug concentration decreases over time and reaches stability after approximately day 2. Here again, it takes less time for the fractional derivative to reach stability in the integer case.

Moreover, by varying the ϑ parameter while keeping other parameters constant, the fluctuation of the concentration of immune system cells, tumor cells and chemotherapy drug over time has been examined in Figures 5,6,7. The value of ϑ is 0.90. Figure 5 shows that as γ (the rate of degradation of chemotherapy drug) decreases, the number of tumor cells increases, reaching stability after approximately day 5. This is a situation we encounter in real life as well. Because the chemotherapy drug fights cancer. When the concentration of the drug decreases, the number of cancer cells increases. As shown in Figure 6, as γ (the degradation rate of the chemotherapy drug) decreases, there is a corresponding decrease in immune cells at γ =1.4 and γ =2.4, and an increase in immune cells at γ =4.4 and γ =6.4. This is a situation that also exists biologically. Because if the breakdown rate of the chemotherapy drug decreases, immune cells cannot fight cancer and decrease. From Figure 7, it is clearly seen that when γ (degradation rate of chemotherapy drug) decreases, the concentration of chemotherapy drug increases. In Figure 8, the effects of the s_1 parameter (logistic growth rate of tumor cells) on tumor cells are examined. It is seen that as s_1 decreases, the number of tumor cells decreases and the tumor cells reach stability on approximately the 5th day. This is also valid biologically. Because as the logistic growth rate, that is, the reproduction rate, of tumor cells increases, the proportion of tumor cells also increases.

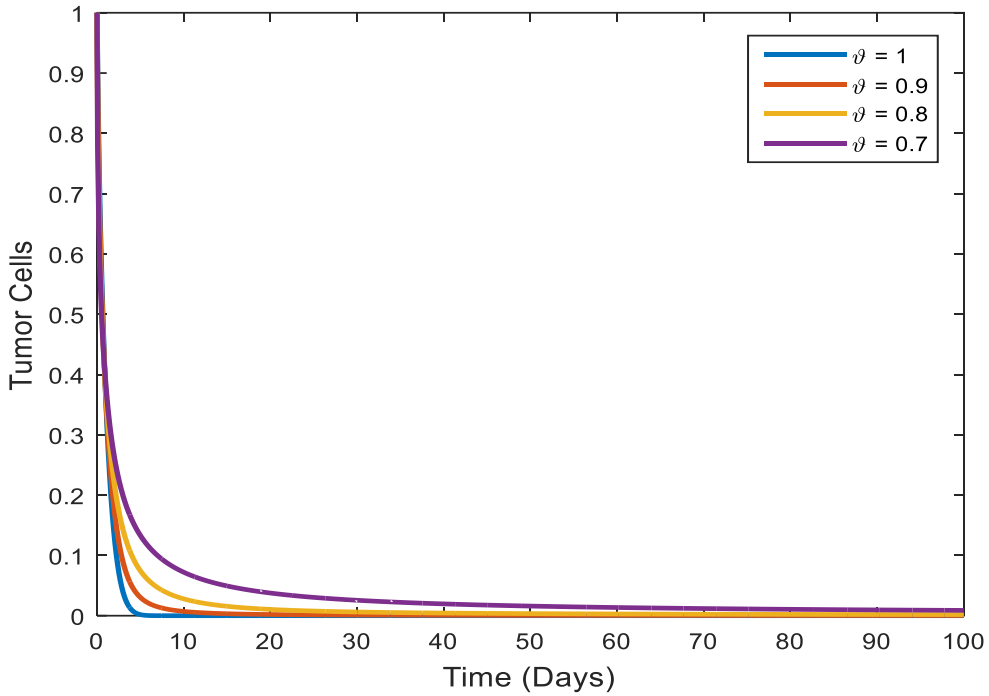

Figure 2. Tumor cell changes over time for different fractional order derivatives

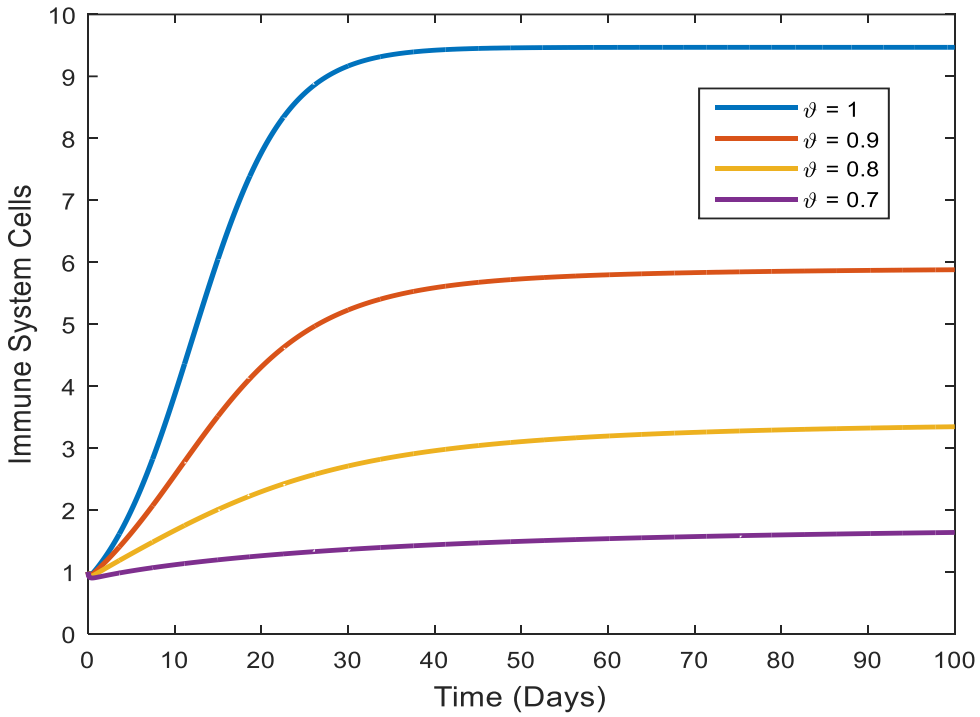

Figure 3. Immune system cells changes over time for different fractional order derivatives

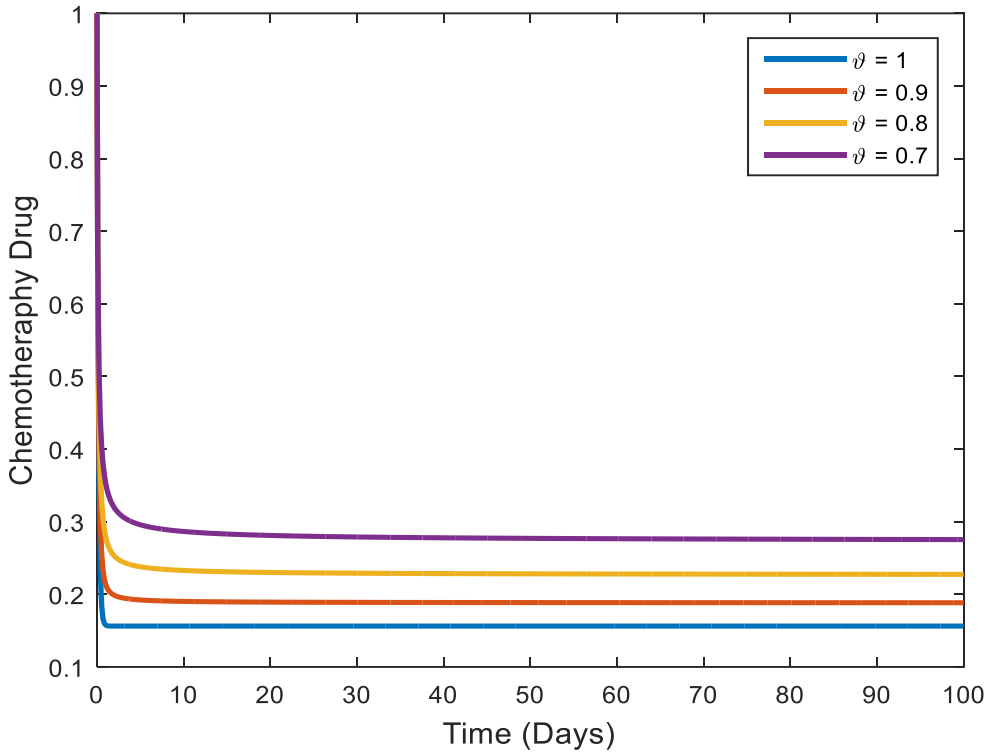

Figure 4. Chemotherapy drug changes over time for different fractional order derivatives

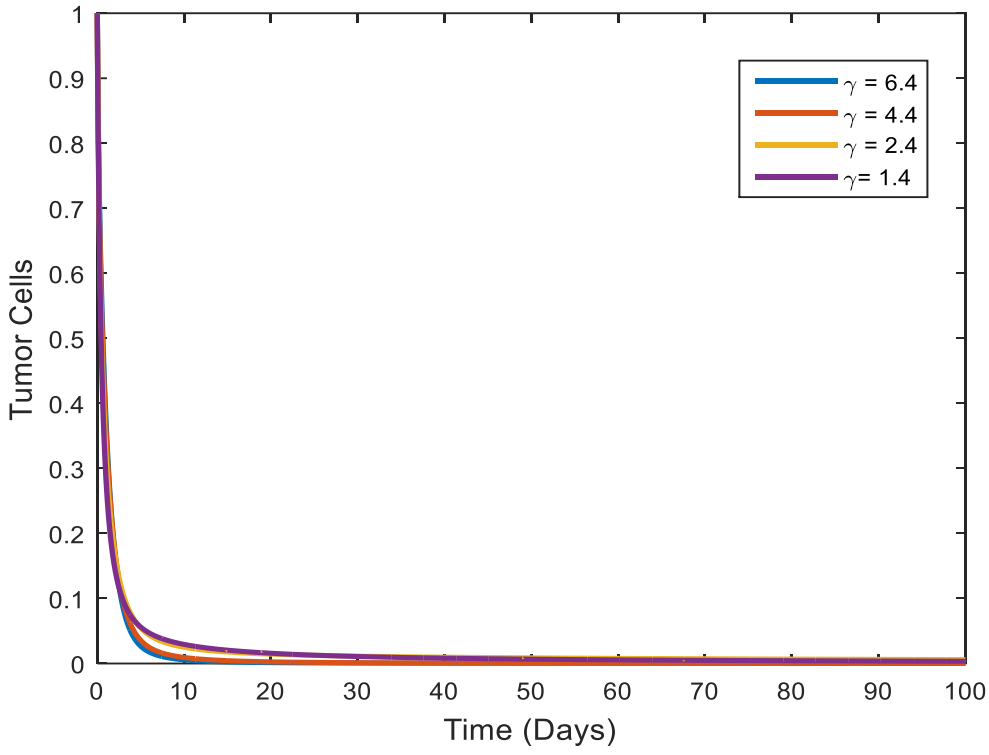

Figure 5. Tumor cells changes over time for the various γ values and ϑ=0.9

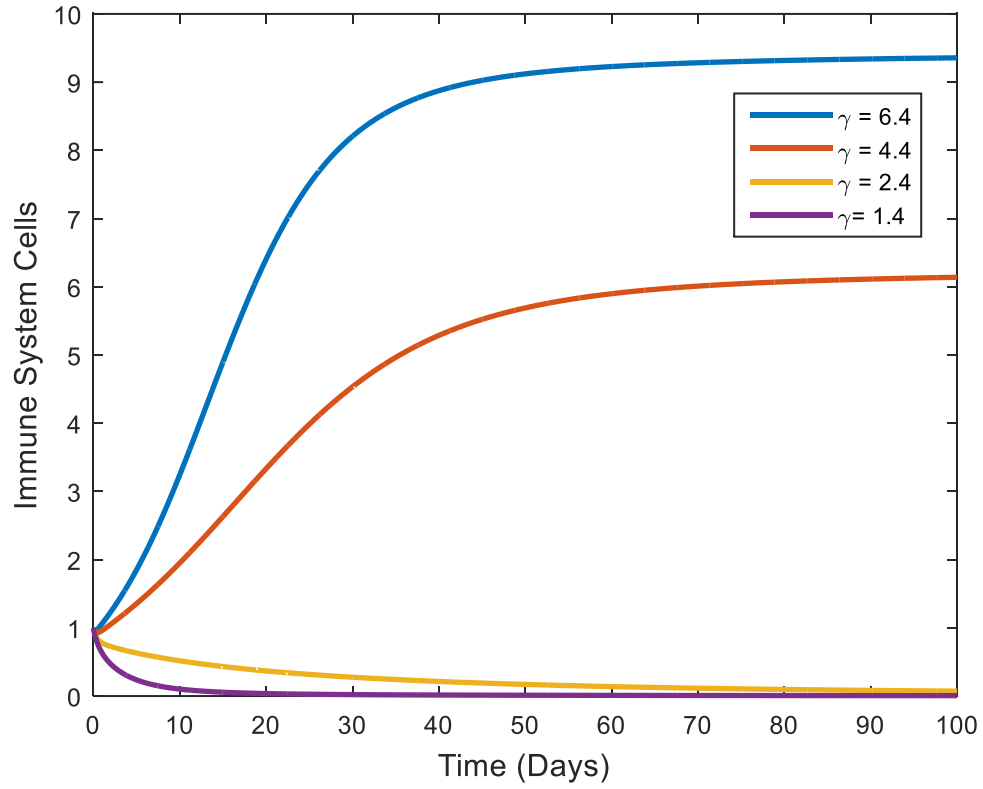

Figure 6. Immune system cells changes over time for the various γ values and ϑ=0.9

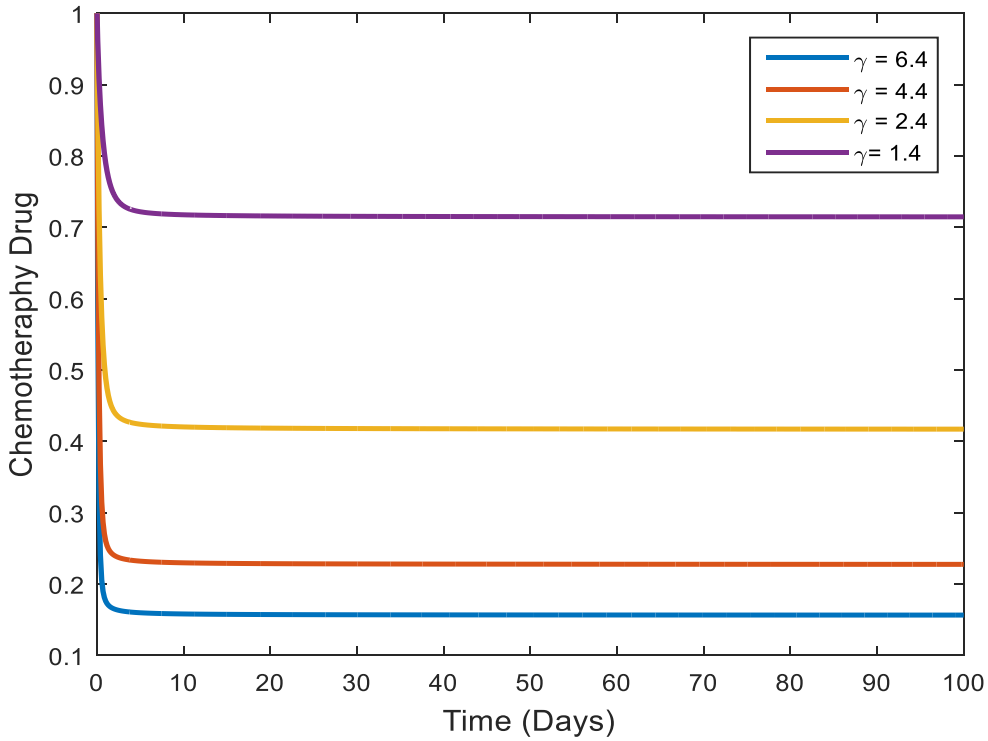

Figure 7. Chemoterapy drug changes over time for the various γ values and ϑ=0.9

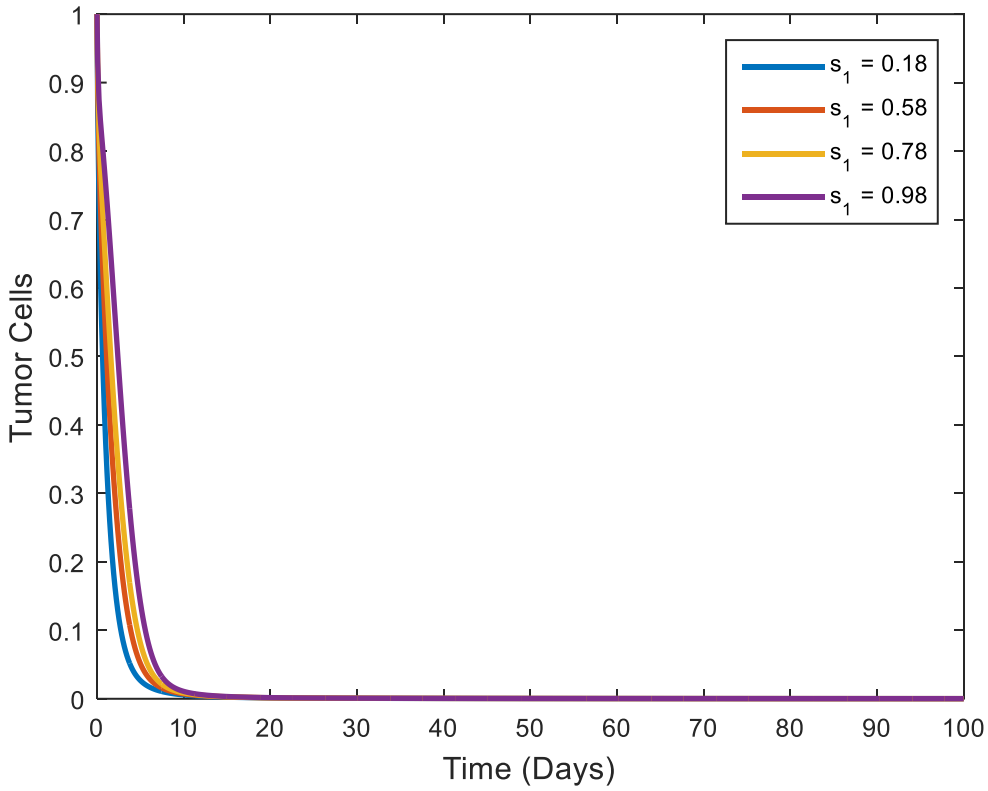

Figure 8. Tumor cells changes over time for the various s_1 values and ϑ=0.9

9. Discussion and Conclusion

The system of fractional differential equations (5) with Caputo fractional derivative, which represents the Caputo fractional graded cancer-immune system model, is discussed in this article. It has been determined that, under certain particular conditions, the equilibrium points of model (5) have been asymptotically stable by examining the local asymptotic stability of the tumor-free and tumor infection fixed points of the system. The existence and uniqueness of the model are then looked at. To confirm the theoretical outcomes, numerical simulations are also obtained. For this model, numerical simulations are provided that account for various fractional orders and parameter values. To look into the behavior of the system and see what happens when the fractional derivative is changed, shapes have been created for a range of ϑ values. In summary, the fractional model provides a better fit to the experimental data than the integer order model. The majority of research on biological system modeling has focused on integer-order ordinary differential equations. The dynamics of diseases have been better understood through the use of mathematical models based on integer order ordinary differential equations. Fractional-order differential equation models, on the other hand, have greater benefits than integer-order mathematical models. Unlike integer order models, fractional order models take the memory effect into account. This specific characteristic would make sense because memory is one of the immune system's core functions. In terms of both biology and mathematics, the immune system is one of the most intriguing systems. The majority of immune effectors perform several tasks due to its acknowledged multifunctional and multipathway nature. Furthermore, the immune system is more resilient since several effectors normally carry out each activity. Because fractional order differential equations are intrinsically linked to systems that possess memory in tumor-immune interactions, they are used. These models' non-local characteristics, which are absent from differential operators of integer order, are their most essential property. We refer to the feature that a model's subsequent stage is dependent upon all of its previous stages in addition to its current state. Conversely, fractional derivatives are crucial for explaining how memory affects dynamical systems. The use of fractional order differential equations aids in the reduction of modeling errors brought on by overlooked parameters. Nonetheless, it has proven possible to effectively use fractional calculus in conjunction with instantaneous time to accomplish realistic representation of a physical process. It also depends on the past events' history.

Despite the fact that the fractional derivative has no physical meaning, fractional order models can be supported by demonstrating that they fit experimental data more closely than integer order models. Drawing on the preceding discourse, the aim of this research is to examine a fractional-order mathematical framework and substantiate it by demonstrating its

superiority over the integer-order model in fitting actual data. Comments on biological science are provided. Memory trace and hereditary features are taken into consideration to demonstrate the advantages of fractional order modeling. Based on the analytical results, it has been concluded that the Caputo fractional derivative yields more accurate results than the integer order derivativeIn other words, compared to integer order derivatives, fractional order derivatives stabilize faster. According to our research, a high drug concentration results in a notable reduction in tumor cell count. Therefore, the concentration of chemotherapy drugs is important while treating cancer. Examined the outcomes of the simulation demonstrated how the alteration in ϑ impacted the system's dynamic behavior.

Consequently, it has been shown that there have been considerable variations in the quantity of immune system cells, tumor cells, and chemotherapy medication concentration. We believe that scholars in the domains of mathematics and medicine will greatly benefit from this work. We believe that this multidisciplinary work will pave the way for more research along these lines and provide insight into how this data might be used in the future for the mathematical modelling of cancer.

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