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On dynamics of fractional-order oncolytic virotherapy models

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Abstract

In this paper, we provide a mathematical model with a fractional-order to investigate the dynamics of oncolytic virotherapy. We focus on how the dynamics of oncolytic virotherapy models can rely on the burst size of the virus. The burst size of a virus is the number of new viruses released from the lysis of an infected cell. Different viruses have different burst sizes. The numerical simulations confirm that the fractional-order differential models have the ability can provide accurate descriptions of oncolytic virotherapy models and capture the memory of the dynamics.

Keywords: Fractional calculus, oncolytic virotherapy, immune innate response, equilibrium points, local stability.

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1. Introduction

Oncolytic viruses are viruses that can selectively replicate in cancer cells but leave healthy normal cells unharmed. In oncolytic viral therapy, oncolytic viruses infect tumor cells and replicate themselves in tumor cells; upon analysis of infected tumor cells, new virion particles burst out and proceed to infect additional tumor cells. This idea was initially tested in the middle of the last century and merged with renewed ones over the last 30 years due to the technological advances in virology and in the use of viruses as vectors for gene transfer. Over the last decade, great efforts have been made for understanding dynamics and molecular mechanics of viral cytotoxicity of oncolytic viruses. Those efforts provided an interesting possible alternative therapeutic approach to help cure cancer patients. However, the outcomes of virotherapy depends in a complex way on interactions between viruses and tumor cells [4].

During the last two decades, several mathematical models have been applied to understanding oncolytic virotherapy. For example, Wu et al. [18] and Wein et al. [15] proposed and analyzed some partial differential equations models to study some aspects of cancer virotherapy. For ordinary differential equations models, Wodarz in [17] and [16], Komarova and Wodarz [9], Novozhilov et al. [11], Bajzer et al.

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[2], and Tian [14] studied ODE models. Tian [14] analyzed a mathematical model for oncolytic virotherapy that includes burst size. Most of biological systems have long-range temporal memory. Modeling such systems by fractional models provides the systems with a long-time memory and extra degrees of freedom. Despite of the fact that differential equations with integer-orders have long been used in modeling cancer [3, 8], the fractional-order differential equations (FODEs) have been recently used to model many biological phenomena. One of the advantages of using FODEs to model such phenomena is that models become more consistent with the biological model. This is due to the fact that fractional order derivatives can capture the memory and hereditary properties of those models [13]. Also, it is worth mentioning that classical mathematical models with integer-orders ignore the intermediate cellular interactions and memory effects. For example, the kinetic of the viral decline in patients responding to interferon-is characterized by bi-phase shape following a delay about 8-9 hours, likely to be the sum of interferon α-pharmacokinetics and pharmacodynamics as well as the intracellular delay of the ciral life cycle [11]. Therefore, modeling of the biological systems by fractional order differential equations has more advantages than classical integer-order mathematical modeling, in which such effects are neglected.

In this paper, we study dynamics of a fractional-order oncolytic virotherapy model discussed in [14]. The focus here is on describing dynamics of oncolytic models when fraction-order derivatives are implemented. We also aim to show how can fractional-order models give more insight into the memory of the derivative and hence to the memory of the dynamics incoded. The organization of the paper is as follows. In Section 2, we provide a very brief preliminary to fractional calculus. In Section 3, we study the fractional-order oncolytic virotherapy model by focusing on the formulation of the fractional-order model, parameters, and the invariant. In section Section 4 we summarized the main stability results for model (3.2). In Section 5 we provide numerical simulations to the solutions using Matlab and we compare solutions obtained from applying fractional derivatives to the results obtained from the integer derivative. We discuss parameter values and provide numerical simulations with biological interpretations. Conclusions are given in Section Section 6.

2. Preliminaries

This section contains some preliminary definitions from fractional calculus and the associated notation. We first give the definition of fractional-order integration and fractional order. Let $L^1 = L^1[a, b]$ be the class of Lebesgue integrable functions on $[a, b]$, $a < b < \infty$. The fractional integral of order $\nu \in \mathbb{R}^+$ of the function $f(t), t > 0$ $(f : \mathbb{R} \to \mathbb{R})$ is defined by

$$I_a^\nu = \frac{1}{\Gamma(\nu)} \int_q^t (t-s)^{\nu-1} f(s) ds, \ t > 0, \tag{2.1}$$

where $\Gamma(.)$ is the Gamma function.

The fractional derivative of order $\alpha \in (n-1, n)$ of the function $f(t)$ is defined by several ways, the most common ones are:

(i) Riemann-Liouville fractional derivative: Take the fractional integral of order $(n-\alpha)$ and then apply the n^{th} derivative

$$D_\alpha^a f(t) = D_\alpha^a I_{n-\alpha}^a,$$

where $D_n^* = \frac{d^n}{dt^n}, n = 1, 2, \ldots;$

(ii) Caputo's fractional derivative: Start with a n^{th} derivative of the function, then take a fractional integral of order $(n-\alpha)$

$$D_\alpha^a f(t) = I_{n-\alpha}^a D_n^a f(t), n = 1, 2, \ldots.$$

We notice that the definition of time-fractional derivative of a function $f(t)$ at $t = t_n$ involves an integration and calculating time-fractional derivative that requires all the past history, that is, all the values of $f(t)$ from $t = 0$ to $t = t_n$. Caputo's definition, which is a modification of the Riemann-Liouville definition, has the advantage of dealing properly with initial value problems and it solves the problem of the derivative of constants. For more properties of the fractional derivatives and integrals we refer to [12].

3. A model of oncolytic virotherapy

The basic model under study was proposed and studied by Tian [14], the integer-order model is given by

$$\begin{aligned} \frac{dx}{dt} &= \lambda x(1-\frac{x+y}{K}) - \beta x v, \\ \frac{dy}{dt} &= \beta x v - \delta y, \\ \frac{dv}{dt} &= b\delta y - \beta x v - \gamma v, \end{aligned} \tag{3.1}$$

where x stands for uninfected tumor cells, y for infected tumor cells, and v for free viruses. The parameter λ is the tumor growth rate, K is the carrying capacity of tumor cell population, β is the infected rate of the virus, δ is the death rate of infected tumor cells, b is the burst size, αy models the release of virions by infected tumor cells, and γv is the clearance rate of free virus particles. This model emphasizes the rule of burst size of viruses in virus replication ability. The burst size of a virus is the number of new viruses released from a lysis of an infected cell. Viruses of same type have almost the same burst size.

After non-dimensionalizing the system by setting $\tau = \delta t$, $x = Kx^*$, $y = Ky^*$,$v = Kv^*$, $r = \frac{\lambda}{\delta}$, $a = \frac{\beta K}{\delta}$, and $c = \frac{\gamma}{\delta}$ and dropping the stars over variables,and replacing the ordinary derivative by the Caputo fractional derivative, the fractional-order version of the model is given by

$$\begin{aligned} D_t^\alpha x &= r^\alpha x(1-x-y) - a^\alpha x v, \\ D_t^\alpha y &= a^\alpha x v - y, \\ D_t^\alpha v &= b^\alpha y - a^\alpha x v - c^\alpha v, \end{aligned} \tag{3.2}$$

where D_t^α is the Caputo fractional derivative and $0 < \alpha \leqslant 1$. We assume that all parameters are nonnegative. Next, we prove that the positive invariant domain of system (3.2) is

$$D = \{(x, y, v) : x \geqslant 0, y \geqslant 0, v \geqslant 0, 0 \leqslant x + y \leqslant 1\}.$$

This is a biological meaningful range of variables.

Theorem 3.1. *Assume that the parameters* r, s, b, *and* c *are all positive and real and denote* $\mathbb{R}^3_+ = \{X \in \mathbb{R}^3 : X \geqslant 0\}$ *and let* $X(t) = (x(t), y(t), v(t))^t$. *Then for any* $X(0) > 0$, *the solution* $X(t)$ *of* (3.2) *on* $t \geqslant 0$ *will remain in* $\mathbb{R}^3_+$. *Moreover, if* $0 < x(0) + y(0) < 1$, *then* $\limsup t \longrightarrow +\infty v(t) \leqslant (\frac{b}{c})^\alpha$.

Proof. We will prove this result by contradiction. Assume that the there exists t^* at which of the components of the solution will be zero and all other components are positive.

If $x(t^*) = 0$ holds, then $y(t) > 0$, $v(t) > 0$ when $t \in [0, t^*]$ and $x(t) > 0$ when $t \in [0, t^*)$. Now $D_t^\alpha x(t) > -a^\alpha m_1 x$, where $m_1 = \min_{t\in[0,t^*]} v(t)$, $t \in [0, t^*]$. Hence,

$$x(t) > x(0)E_\alpha(-a m_1 t^\alpha),\ t \in [0, t^*],$$

where $E_\alpha(t) = \sum_{k=0}^{\infty} \frac{t^k}{\Gamma(k\alpha+1)}$ is the Mittag Leffler function. Since $x(0) > 0$, then $x(t^*) > 0$ which is a contradiction.

If $y(t^*) = 0$ holds, then $x(t) > 0$, $v(t) > 0$ when $t \in [0, t^*]$ and $y(t) > 0$ when $t \in [0, t^*)$. From the second equation of the system (3.2) we have $D_t^\alpha y(t) > -y(t)$, $t \in [0, t^*]$ which implies

$$y(t) > y(0)E_\alpha(-t^\alpha),\ t \in [0, t^*].$$

Since $y(0) > 0$, we get $y(t^*) > 0$ which is a contradiction.

If $v(t^*) = 0$ holds, then $x(t) > 0$, $y(t) > 0$ when $t \in [0, t^*]$ and $v(t) > 0$ when $t \in [0, t^*)$. Letting

$m_2 = \min_{t\in[0,t^*]} x(t)$, $t \in [0, t^*]$ and $k = a^\alpha m_2 + c^\alpha$, we get $D_t^\alpha v(t) > -kv(t)$, $t \in [0, t^*]$ which implies

$$v(t) > v(0)E_\alpha(-kt^\alpha),\ t \in [0, t^*].$$

Since $v(0) > 0$, we get $v(t^*) > 0$ which is a contradiction.

Similar arguments can be used to check the other cases; if two components are zero simultaneously at t^* and if all of the components are zero simultaneously at t^*.

Now adding the first two equations in (3.2) we get

$$D_t^\alpha\{x(t) + y(t)\} = r^\alpha x(1 - x - y) - y \leqslant r^\alpha x(1 - (x + y)) \leqslant r^\alpha(1 - (x + y)).$$

Since $x(0) \leqslant 1$, by the comparison theorem, we have $x(t) \leqslant 1$. Also, since $0 \leqslant x(0) + y(0) \leqslant 1$, by comparison theorem, we have $0 \leqslant x(t) + y(t) \leqslant 1$ for $t \geqslant 0$. It also follows that $0 \leqslant y(t) \leqslant 1$.

Under the assumptions of nonnegativity of the solution components $x(t)$ and $y(t)$ and being smaller than 1, we have

$$x(t) + y(t) \leqslant (x(0) + y(0))E_\alpha(-r^\alpha t^\alpha) + (1 - E_\alpha(-r^\alpha t^\alpha)),$$

and so $\limsup_{t\longrightarrow\infty}(x(t) + y(t)) \leqslant 1$. The last equation of (3.2) then leads to

$$D_t^\alpha = b^\alpha y - a^\alpha xv - c^\alpha v \leqslant b^\alpha - c^\alpha v,$$

so

$$v(t) \leqslant v(0)E_\alpha(-c^\alpha t^\alpha) + \frac{b^\alpha}{c^\alpha}(1 - E_\alpha(-c^\alpha t^\alpha)).$$

Hence

$$\limsup_{t\longrightarrow\infty} v(t) \leqslant (\frac{b}{c})^\alpha.$$ □

4. Equilibria and stability

To evaluate the equilibrium points we set

$$D_t^\alpha x = 0,\ \ D_t^\alpha y = 0,\ \ D_t^\alpha v = 0.$$

The system (3.2) has always two equilibrium points in the positive invariant domain D, namely, $E_0 = (0, 0, 0)$ and $E_1(1, 0, 0)$. When $b > 1 + (\frac{c}{a})^\alpha$ it has a new equilibrium point in addition to E_0 and E_1. The third equilibrium point is given by

$$E_2 = (\frac{c^\alpha}{a^\alpha(b^\alpha - 1)}, \frac{r^\alpha c^\alpha(a^\alpha b^\alpha - a^\alpha - c^\alpha)}{a^\alpha(b^\alpha - 1)(a^\alpha b^\alpha - a^\alpha + r^\alpha c^\alpha)}, \frac{r^\alpha(a^\alpha b^\alpha - a^\alpha - c^\alpha)}{a^\alpha(a^\alpha b^\alpha - a^\alpha + r^\alpha c^\alpha)}).$$

The Jacobian matrix of system (3.2) is as follows

$$\begin{pmatrix} r^\alpha - 2r^\alpha x - r^\alpha y - a^\alpha v & -r^\alpha x & -a^\alpha x \\ a^\alpha v & -1 & a^\alpha x \\ -a^\alpha v & b^\alpha & -a^\alpha x - c^\alpha \end{pmatrix}.$$

The Jacobian matrices at E_0, E_1, and E_2 are given as

$$\begin{pmatrix} r^\alpha & 0 & 0 \\ 0 & -1 & 0 \\ 0 & b^\alpha & -c^\alpha \end{pmatrix},\ \begin{pmatrix} -r^\alpha & -r^\alpha & a^\alpha \\ 0 & -1 & a^\alpha \\ 0 & b^\alpha & -(a^\alpha + c^\alpha) \end{pmatrix},\ \text{and}\ \begin{pmatrix} -\frac{(rc)^\alpha}{a^\alpha(b-1)^\alpha} & -\frac{(rc)^\alpha}{a^{alpha}(b-1)^\alpha} & -\frac{c^\alpha}{(b-1)^\alpha} \\ \frac{r^\alpha(a^\alpha b^\alpha - a^\alpha - c^\alpha)}{(ab)^\alpha - a^\alpha + (rc)^\alpha} & -1 & \frac{c^\alpha}{b^\alpha - 1} \\ -\frac{r^\alpha(a^\alpha b^\alpha - a^\alpha - c^\alpha)}{(ab)^\alpha - a^\alpha + (rc)^\alpha} & b^\alpha & -\frac{(bc)^\alpha}{b^\alpha - 1} \end{pmatrix},$$

respectively. Stability analysis shows that the nave equilibrium E_0 is unstable (because of the positivity of r). However, the memory state E_1 is (globally) asymptotically stable if $b^\alpha < 1 + (\frac{c}{a})^\alpha$ and in this case the virotherapy always fails, and unstable if $b^\alpha > 1 + (\frac{c}{a})^\alpha$. Here, $\mathcal{B}_1 = 1 + (\frac{c}{a})^\alpha$ is the first threshold value for the burst size. The memory E_1 is also unstable at $\mathcal{B}_1$. The proof is analogous to the integer-order derivative case in [14] .

To state the result about stability of E_2 we need to know the second threshold value. Let us first define a function $\Phi(x)$,

$$\Phi(x) = -a^{3\alpha}x^4 + a^{2\alpha}(3c^\alpha + c^{2\alpha} + r^\alpha - a^\alpha - (ac)^\alpha + 1)x^3 + (ac)^\alpha(3(rc)^\alpha + 3a^\alpha + rc^{2\alpha} + 3(ac)^\alpha + r^\alpha + r^{2\alpha} - a^{2\alpha})x^2 + c^{2\alpha}(3(ar)^\alpha + 2(acr)^\alpha + r^{2\alpha}c^\alpha + 2a^{2\alpha})x + r^\alpha c^{3\alpha}(r^\alpha + a^\alpha).$$

So we can see that

$$H(b) = \frac{(rc)^\alpha \Phi(b^\alpha - 1)}{a^{2\alpha}(b^\alpha - 1)^3((ab)^\alpha - a^\alpha + (rc)^\alpha)}.$$

This function can be derived from one of the Routh-Hurwitz stability conditions ($H_2 > 0$) [1]. The second threshold $\mathcal{B}_2$ is given by

$$\mathcal{B}_2 = \min\{b > \mathcal{B}_1 : H(b) = 0\}. \tag{4.1}$$

The equilibrium E_2 is locally asymptotically stable when $\mathcal{B}_1 < b < \mathcal{B}_2$, [14]. The characteristic equation of the linearized system of (3.2) at E_2 is

$$P(\lambda) = \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3,$$

where

$$a_1 = \frac{(rc)^\alpha + (ab)^\alpha - a^\alpha + (abc)^\alpha}{a^\alpha(b^\alpha - 1)}, \quad a_2 = \frac{(rc)^\alpha((bc)^\alpha + b^\alpha - 1)}{a^\alpha(b^\alpha - 1)^2} + \frac{(rc)^\alpha((ab)^\alpha - a^\alpha - c^\alpha)(r^\alpha - a^\alpha)}{a^\alpha(b^\alpha - 1)((ab)^\alpha - a^\alpha + (rc)^\alpha)},$$

and

$$a_3 = \frac{(rc)^\alpha((ab)^\alpha - a^\alpha - c^\alpha)}{a^\alpha(b-1)^\alpha}.$$

The discriminant of $P(\lambda)$ is given by

$$D(P) = \begin{vmatrix} 1 & a_1 & a_2 & a_3 & 0 \\ 0 & 1 & a_1 & a_2 & a_3 \\ 3 & 2a_1 & a_2 & 0 & 0 \\ 0 & 3 & 2a_1 & a_2 & 0 \\ 0 & 0 & 3 & 2a_1 & a_2 \end{vmatrix}.$$

That is, $D(P) = 18a_1a_2a_3 + (a_1a_2)^2 - 4a_3a_1^3 - 4a_2^3 - 27b_3^2$.

According to the stability conditions in [12, 14] we have the following proposition.

Proposition 4.1. *E_2 is locally asymptotically stable if all eigenvalues of the Jacobian matrix at E_2 satisfy*

$$|\arg(\lambda_i)| > \frac{\alpha\pi}{2}, \ i = 1, 2, 3.$$

Considering the stability conditions in [1], the following proposition can be stated.

Proposition 4.2.

1. *If $\mathcal{B}_1 < b < \mathcal{B}_2$, then E_2 is asymptotically stable.*
2. *If $D(P) > 0$ and the conditions of the Routh-Hurwitz are satisfied, i.e., $a_1 > 0$, $a_3 > 0$, and $a_1a_2 > a_3$, then E_2 is locally asymptotically stable.*
3. *If $D(P) < 0$, $a_1 > 0$,$a_2 > 0$, $a_1a_2 > a_3$, $\alpha \in (0, 1)$, then E_2 is locally asymptotically stable.*
4. *If $D(P) < 0$, $a_1 \geqslant 0$,$a_2 \geqslant 0$, $a_3 > 0$, $\alpha \in (0.5, \frac{2}{3})$, then E_2 is locally asymptotically stable.*

5. *If* $D(P) < 0$, $a_1 < 0$,$a_2 < 0$, $\alpha > \frac{2}{3}$, *then* E_2 *is unstable.*

Given a biological FODEs system

$$D^{\alpha}Y = F(t, Y, P), \tag{4.2}$$

where $t \in [0, T]$, $0 < \alpha \leqslant 1$, $Y(0) = Y_0$, and $Y(t) = [x(t), y(t), v(t)]^T$. Also P is the set of parameters appear in model (3.2). If $F(t, Y)$ satisfies Lipschitz condition

$$\|F(t, Y_1(t), P) - (t, Y_2(t), P)\| \leqslant k\|Y_1(t) - Y_2(t)\|, \tag{4.3}$$

where Y is the solution for the perturbed system, then system (3.2) has a unique solution provided that the Lipschitz condition (4.2) is satisfied and

$$\frac{KT^{\alpha}}{\Gamma(\alpha+1)} < 1.$$

5. Simulation and discussion

We use Matlab to demonstrate our results about fractional-order of the oncolytic virothrapy. The code used here implements predictor-corrector method proposed by Diethelm and Freed in [7]. Stability properties of this method is discussed in [5]. To demonstrate the dynamical behavior of model (3.2) we use data of parameter values from [14] to perform numerical simulations of the dynamics of the system. To illustrate the affect of the fractional-order derivative, we use different values of α as shown in the figures. The parameter values are $r = 0.36$, $a = 0.11$, and $c = 0.2$. By considering $b = 9$, the following equilibrium points can be obtained for model (3.2)

$$E_0 = (0, 0, 0, 0), E_1 = (1, 0, 0), E_2 = (0.\overline{6}, 0.0730, 2.5729).$$

It is known that the burst size is not affected by the choice of the initial conditions [14]. Stability analysis shows that equilibrium point E_0 is unstable. Figure 1 shows that E_1 is locally asymptotically stable equilibrium point of the system. This is consistent with the analytic results that is obtained from studying the model analytically.

For our models, based on the above data, there are two threshold values for the burst size; $\mathcal{B}_1 = 5$ and $\mathcal{B}_2 = 27.766$. If the burst size is between the thresholds, then the virotherapy is partially successful due to E_1 being unstable and E_2 being asymptotically stable. When the burst size b is smaller than $\mathcal{B}_1$ the virotherapy fails due to the fact that there will not be enough newly produced viruses to infect tumor cells. The threshold $\mathcal{B}_1$ has a transcritical bifurcation with respect to the equilibrium E_1 and the threshold $\mathcal{B}_2$ has a Hopf bifurcation. If the burst size is greater than $\mathcal{B}_2$ there is a family periodic solutions to the system for $\alpha = 1$. For α close to 1, the amplitude of the oscillation decays as time increases. However, as the fractional-order α gets closer and closer to 1 the solution behavior looks much similar to the periodic solution at $\alpha = 1$.

When $b = 25$ and $\alpha = 1$, periodic solutions around the equilibrium point E_2 appear. For a fractional-derivative close to 1, oscillations appear with an amplitude that decays as time increases. Note that in the figures of this paper we use the word 'relative' to label the horizontal axis. The reason is that for the sake of simplicity and demonstration we conduct numerical simulations based on the nondimensionalized model rather than the original one. Therefore, the units of the tumor cells, infected tumor cells, and viruses are not absolute numbers. For instance, the quantity of tumor cells in all figures is the portion of tumor cells over the tumor carrying capacity. Other quantities including 'relative time' have similar interpretation.

Figure 1 shows that E_1 is locally asymptotically stable when $b = 4$. In fact, this is true for all values of $b < 5$. It is unstable for $b > 5$.

Figure 2 shows E_1 is locally unstable since $b = 25 > \mathcal{B}_{\infty} = 5$. The virotherapy treatment will eventually reach the equilibrium E_2 after a damped oscillation when $b = 25$. There will be a similar behavior for all values of b between 5 and 27.766. Figure 3 shows periodic solutions rising from Hopf bifurcation. We notice that the dynamical behavior of the system becomes very sensitive to small changes in the order of

the fractional derivative (e.g. the damped oscillators can be observed). Also, one can notice the sensitivity of the model to changes in the value of burst size (amplitude changes significantly due to this change). For example, we need a fractional derivative that is as close to 1 as possible to get a similar behavior to the integer-order case (e.g. $\alpha = .999$) in Figure 3. It is worth mentioning that the solution in Figure 3 is Lyapunov stable. Figure 3 shows that E_2 is locally unstable.

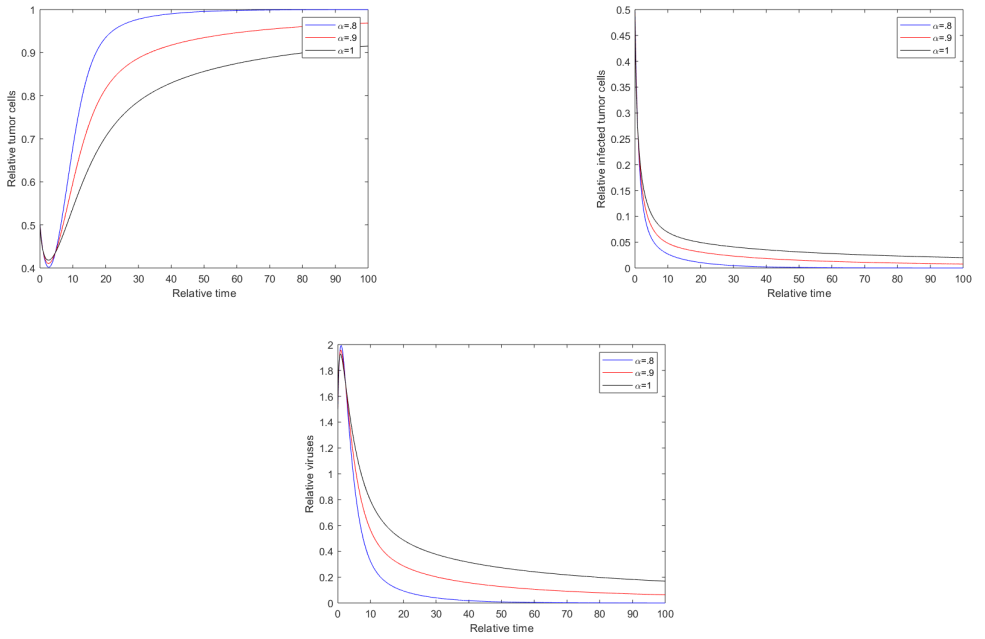

Figure 1: Dynamics of virotherapy when $b = 4$ and initial values $x = 0.5$, $y = 0.5$, and $v = 1.5$, for $\alpha = 1$, $\alpha = .8$, and $\alpha = .9$.

Figure 2 shows E_1 is locally unstable since $b = 9 > \mathcal{B}_1 = 2.82$.

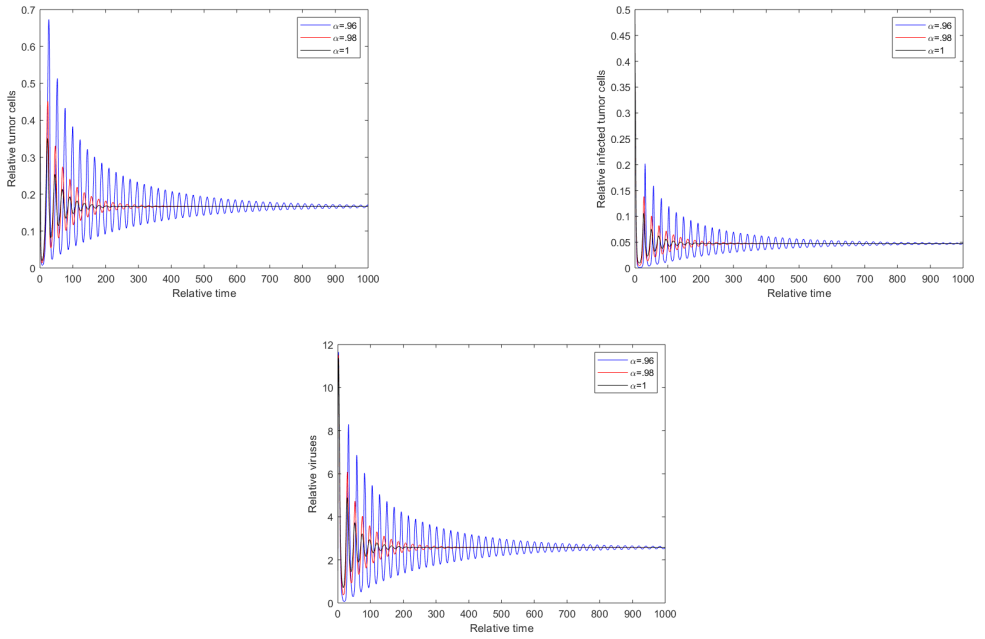

Figure 2: Damped oscillators when $b = 27$ and initial values $x = 0.5$, $y = 0.5$, and $v = 1.5$, for $\alpha = .96$, $\alpha = .98$, and $\alpha = 1$.

The equilibrium point E_2 is asymptotically stable as long as $b \in (2.82, 19.012)$. Figure 3 shows this fact

for $b = 9$.

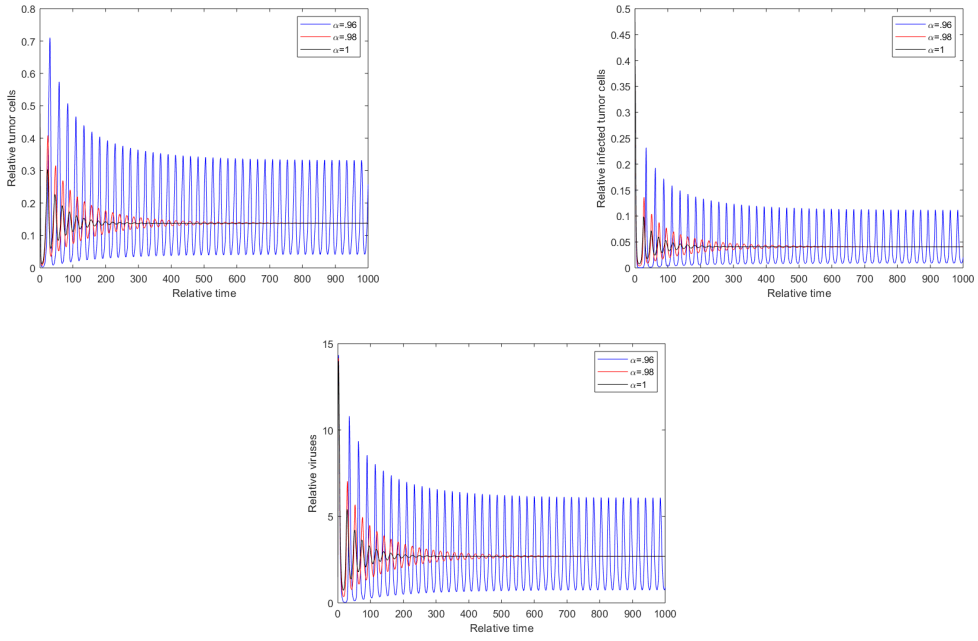

Figure 3: Dynamics of model when $b = 28$ and initial values $x = 0.5$, $y = 0.5$, and $v = 1.5$, for $\alpha = .96$, $\alpha = .98$, and $\alpha = 1$.

Figure 4 shows the dynamics for tumor cells vs the infected ones.

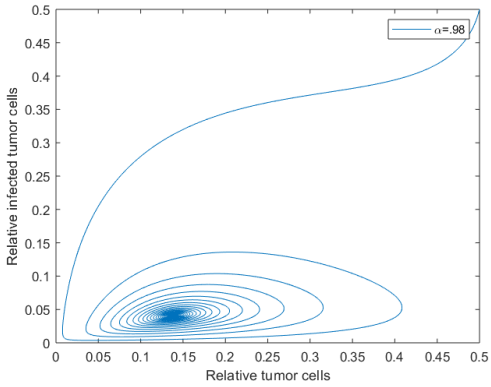

Figure 4: Dynamics of Tumor cells vs infected tumor cells of the model when $\alpha = .98$.

6. Conclusion

A fractional-order Oncolytic Virotherapy model was studied in the work. The main goal was to show that the fractional-order derivative can play an important rule in understanding the memory of the derivatives and can be an efficient tool of studying dynamics of different oncolytic virotherapy models. Since fractional-order models possess memory, FODE gives us a more realistic way to model oncolytic virotherapy and study their dynamics. The presence of a fractional derivative in a differential equation can lead to an increase in the complexity of the observed behavior. On the other hand, it can show how the solution is continuously dependent on all the previous states.

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