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Stability analysis of a fractional virotherapy model for cancer treatment

Análisis de estabilidad de un modelo fraccionario para el tratamiento de cáncer

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Abstract. This paper presents a stability analysis of a differential equations model related to the cancer treatment with an oncolytic virus in its classical and fractional version via Caputo derivatives. Numerical simulations of three possible scenarios are presented and support the discussions on the advantages of using fractional modeling.

Key words and phrases. Fractional Modeling, Fractional Differential Equation, Oncolitic Virus.

2020 Mathematics Subject Classification. 26A33, 92B05.

Resumen. Este artículo presenta un análisis de estabilidad de un modelo de ecuaciones diferenciales ordinarias para el tratamiento de cáncer usando virus oncológicos siendo consideradas las versiones clásica y fraccionaria. Usando diferentes valores para el orden de la derivada fraccionaria de Caputo, se presentan y discuten tres escenarios para tal tratamiento.

Palabras y frases clave. Modelación fraccionaria, Ecuación diferencial Fraccionaria, Virus Oncológico.

1. Introduction

Cancer is a major global cause of mortality and treatments have many side effects for the patient. A new form of treatment, without damaging healthy cells, uses viruses to fight tumors. The so-called oncolytic viruses are viruses

modified through genetic engineering to destroy cancer cells and induce immune responses [7]. Therapy using oncolytic viruses offers several important advantages over traditional approaches such as greater therapeutic selectivity since only cancer cells will suffer damage; prevents normal tissues from being exposed to excessive doses of chemotherapy and radiation therapy; ability to destroy cancer cells that have metastasized and lytic death of cancer cells provides a pro-inflammatory microenvironment and the potential for induction of an anticancer vaccine response [34].

With continuous advancements in treatment methods, studies have found that the virus has great potential for cancer treatment [4]. Many advances have been made and we mention some of them.

The first oncolytic virus drug approved was T-Vec virus (*Talimogene laherparepvec*), created by modifying the virus herpes simplex type 1 (HSV-1) armed with GM-CSF, approved in the USA, in October 2015, in Europe, in January 2016, and Australia, in May of the same year. T-Vec stops tumor growth, prolonging patient survival [13].

The use of oncolytic viruses against glioblastoma with Zika virus (ZIKV) is currently being studied in mice. Preliminary results showed that ZIKV infected and killed glioblastoma stem cells, completely eradicating the tumor or giving the patient greater life expectancy. Thus, genetically modified strains may have therapeutic efficacy for adult patients with glioblastoma [20, 51].

Oncolytic viruses have demonstrated promise in treating diverse tumor types, including hepatocellular and pancreatic carcinomas, mesotheliomas, myelomas, squamous cell carcinomas of the head and neck, and breast cancers [50]. For example, hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third most common cause of cancer-related death worldwide and is a highly aggressive type of cancer and numerous oncolytic viruses are being tested in preclinical HCC models, with good direct evidence and anti-tumor efficacy [22].

There are various papers dealing with mathematical models applied to the dynamics of the oncolytic viruses on tumor cells. For example, [10] studied an ordinary differential equation (ODE) model to verify the potent efficacy of modified M1 virus; in [26] a mathematical model for treatment of cancer is presented using oncolytic virotherapy in the presence of immune effectors; [23] developed a mathematical model dealing with the interactions between the oncolytic virus, the tumor cells, the normal cells, and the antitumoral and antiviral immune responses; in [12] a mathematical model is presented with a combined therapy using oncolytic virus and a checkpoint inhibitor and evaluated the efficacy of the combination therapy; a mathematical model describing the interaction between tumor cells and an oncolytic virus is presented in [19]

where they use experimental data to obtain optimized parameters; a theoretical study giving a mathematical model that describes the dynamics of cancer treatment with the oncolytic viruses is presented in [27].

The construction of a mathematical model that describes a natural phenomenon is not an easy task, but scenarios that such a model can present are very important [17]. Usually, the closer we get to a better description of a real problem, the greater are the number of variables involved and the complexity of the equations [21]. The mathematical modeling of complex phenomena using nonlinear differential equations is a hot topic in the present era, due to extensive applications and the need for dealing with real-world problems raised in day-to-day life [30, 49]. Recently, many researchers pointed out and also illustrated that the integer-order differential operators are not always appropriate tools to model the complex and nonlinear phenomena [31, 40].

In this sense, the fractional (non-integer) derivative, which is as old as the classical (integer) derivative, has demonstrated its relevance in modeling real phenomena. In recent decades, many articles cite the contribution of fractional modeling to better describe and understand real phenomena [5, 42, 48]. Despite not having a physical and geometric interpretation for fractional derivatives [37], fractional differential equations are related to systems with memories, since they are generally non-local operators, that is, the calculation of the fractional temporal derivative at a given point requires all previous points [11]. Memory processes exist in many biological systems [6, 11, 29, 32, 36]. The advantage that fractional models have is that they can describe the evolution over time of tumors taking into account their history, attribute that may improve ODE-based tumor models [1]. Also, fractional differential equations can help us reduce errors arising from the parameters of modeling real-life phenomena (multiscale nature and better fitting to data) [2, 3, 25, 35]. Finally, the paper [25] brings another reason to choose fractional modeling to describe tumor growth and treatment: Fractality (connections between fractional calculus and fractal structures, revealing patterns in nature, such as tumor growth).

For these reasons, we propose the fractional version of a classic model with ordinary differential equations, which describes the interaction between populations of cancer cells, cancerous infected by viral particles, and viral particles in the fight against cancer by oncolytic viruses. The advantage of this model is that it lists through a seemingly simple system all the relevant biological facts that are known about various terms of tumor dynamics with oncolytic treatment and it is possible to carry out a general analysis of the resulting system. In this way, all results are a consequence of the stated biological assumptions. Oncolytic viruses specifically infect cancer cells, replicate in them, kill them, and spread to other tumor cells. It is a promising treatment. The goal of therapy is to reduce this population, stabilizing it at low levels. Supported by numerical and analytical results, our studies indicate that fractional

modeling, in addition to recovering the classic version, can describe a greater number of scenarios and models better reality.

Over time, several definitions of fractional operators, techniques for analytical and numerical solutions emerged [15, 28, 41, 43]. The well-known Riemann-Liouville, Grünwald-Letnikov, and Caputo operators have been successfully used to model the anomalous structures in many biological systems applications. We opted for the Caputo Fractional Derivative as a fractional operator in this work because its initial conditions are physically interpretable and it is quite recurrent in the literature [38]. For the numerical simulations we use the Grünwald-Letnikov method for fractional differential equations [33] since it is easier to implement [44].

The paper is organized as follows. In Section 2, we present the model. In Sections 3 and 4, we discuss its predictions and results in the light of clinical oncology pratice. Finally, Section 5 we present our concluding remarks.

2. Mathematical model

The simple mathematical model proposed in [45, 46, 47], describes in a simplified way the dynamics of tumor infection. The understanding of the possible scenarios of this model is decisive for the success of the therapy. The model assumes that tumor cells grow and are infected by viruses. The infected tumor cells stop dividing, produce new viruses and eventually die. We present the model:

$$\begin{cases} \dfrac{dx}{dt} = \overline{r}x\left(1 - \dfrac{x+y}{w}\right) - \overline{d}x - \overline{\beta}xv \\ \dfrac{dy}{dt} = \overline{\beta}xv - \left(\overline{d} + \overline{a}\right)y \\ \dfrac{dv}{dt} = \overline{k}y - \overline{u}v \end{cases}, \tag{1}$$

where the variable x represents the number of tumor cells not infected by the virus, y the number of tumor cells infected by the virus, and v the viral particles. The amount of cancer cells in each instant t is given by $x + y$. The growth of uninfected cells is described by the logistic equation, with $\overline{r}$ the intrinsic growth rate and w the carrying capacity of the total amount of cancer cells. In biological terms, this means that the cancer cells divide and that this results in exponential growth at small tumor cell densities, but that growth is slowed down as the tumor reaches larger sizes and runs out of space, nutrients, and other resources required for growth. The parameter $\overline{d}$ represents the natural mortality rate of cancer cells, infected or not. Uninfected cancer cells become infected in proportion to $\overline{\beta}xv$. In addition to the natural mortality rate, infected

cancer cells have a mortality rate $\overline{a}$ due to the virus. Viral particles grow at a rate of $\overline{k}$ and decay at a rate of $\overline{u}$.

To obtain the fractional version of the model (1) we must analyze carefully the dimensions of the variables and parameters. Following [5, 16], the dimension of $\dfrac{d}{dt}$ is time^{-1}, in the fractional version the dimension of $\dfrac{d^\alpha}{dt^\alpha}$, $0 < \alpha \leq 1$, is time$^{-\alpha}$, so that both sides of each equation have the same dimension we take a parameter τ in dimension time that results $\dfrac{1}{\tau^{1-\alpha}}\dfrac{d^\alpha}{dt^\alpha}$ in the unit time^{-1}. Then, the fractional version is given by:

$$\begin{cases} \dfrac{1}{\tau^{1-\alpha}} D^\alpha x(t) = \overline{r}x\left(1 - \dfrac{x+y}{w}\right) - \overline{d}x - \overline{\beta}xv \\ \dfrac{1}{\tau^{1-\alpha}} D^\alpha y(t) = \overline{\beta}xv - \left(\overline{d} + \overline{a}\right) y \\ \dfrac{1}{\tau^{1-\alpha}} D^\alpha v(t) = \overline{k}y - \overline{u}v \end{cases},$$

where D^α is the Caputo derivative of order α, $0 < \alpha \leq 1$.

Let us consider $m = \tau^{1-\alpha}\overline{m}$ for each parameter, then we can rewrite the model as:

$$\begin{cases} D^\alpha x(t) = rx\left(1 - \dfrac{x+y}{w}\right) - dx - \beta xv \\ D^\alpha y(t) = \beta xv - (d+a)\, y \\ D^\alpha v(t) = ky - uv \end{cases}. \tag{2}$$

The meaning of each parameter is similar to that of the integer order model given by (1).

3. Stability analysis

We present the stability analysis to the fractional model (2). The equilibrium points are given by:

$$E_1 = (0,0,0),$$
$$E_2 = \left(\frac{w(r-d)}{r}, 0, 0\right),$$
$$E_3 = (\overline{x}, \overline{y}, \overline{v}),$$

with

$$\overline{x} = \frac{(d+a)u}{k\beta}, \quad \overline{y} = \frac{u\left[wk\beta(r-d) - ru(d+a)\right]}{k\beta\left(ru + wk\beta\right)}, \quad \overline{v} = \frac{wk\beta(r-d) - ru(d+a)}{\beta(ru + wk\beta)},$$

and $E_2 > 0$, if $r > d$ and $E_3 > 0$, if $wk\beta(r-d) > ru(d+a)$.

In the equilibrium points E_1 and E_2 there are not viral particles and the equilibrium point E_1 shows an absence of total cancer cells, while E_2 shows only a population of cancer cells not infected by the virus. The equilibrium point E_3 shows the coexistence of the three populations.

To study the stability of the equilibrium points, we present the following result:

Theorem 3.1. *Let λ_i, $i = 1, 2$ and 3, be the roots of the characteristic polynomial equation (eigenvalues) associated with the Jacobian matrix of the model* (2) *at the equilibrium point studied. If*

$$|\arg(\lambda_i)| > \alpha\frac{\pi}{2},$$

the equilibrium point is locally stable [24].

The Jacobian matrix of (2) evaluated at E_1 is:

$$J(E_1) = \begin{pmatrix} r-d & 0 & 0 \\ 0 & -(d+a) & 0 \\ 0 & k & -u \end{pmatrix},$$

and, consequently, the eigenvalues are

$$\lambda_1 = r - d, \quad \lambda_2 = -(d+a) < 0 \quad \text{and} \quad \lambda_3 = -u < 0. \tag{3}$$

Theorem 3.2. *The equilibrium point E_1 of model* (2) *is locally stable if, and only if, $r < d$.*

This is, the tumor will only be fully cleared if the intrinsic growth rate of the cancer cells is less than the natural death rate.

The Jacobian matrix of (2) evaluated at E_2 is:

$$J(E_2) = \begin{pmatrix} -r+d & -r+d & -\beta\dfrac{w(r-d)}{r} \\ 0 & -(d+a) & \beta\dfrac{w(r-d)}{r} \\ 0 & k & -u \end{pmatrix},$$

and then, the characteristic equation of $J(E_2)$ is:

$$[\lambda - (d-r)]\left[(\lambda+d+a)(\lambda+u) - k\beta\frac{w(r-d)}{r}\right] = 0. \tag{4}$$

Therefore, one of the eigenvalues is $\lambda_1 = d - r$, and solving

$$\lambda^2 + (d+a+u)\lambda + (d+a)u - k\beta\frac{w(r-d)}{r} = 0,$$

we obtain two other eigenvalues given by

$$\lambda_{2,3} = \frac{-(d+a+u) \pm \sqrt{\Delta}}{2},$$

where

$$\begin{aligned}\Delta &= (d+a+u)^2 - 4\left[(d+a)u - k\beta\frac{w(r-d)}{r}\right] \\ &= (d+a-u)^2 + 4k\beta\frac{w(r-d)}{r}.\end{aligned}$$

We have $E_2 > 0$, if $r > d$ and, consequently, $\Delta > 0$, and the eigenvalues λ_2 and λ_3 are real.

Therefore,

$$\lambda_2 = \frac{-(d+a+u) - \sqrt{\Delta}}{2} < 0.$$

For $\lambda_3 = \dfrac{-(d+a+u) + \sqrt{\Delta}}{2} < 0$, it must occur $(d+a+u)^2 > \Delta$. So,

$$\begin{aligned} d^2 + a^2 + u^2 + 2ad + 2au + 2du > d^2 + a^2 + u^2 + 2ad - 2au - 2du \\ + 4k\beta\frac{w(r-d)}{r} \Rightarrow \\ 4au + 4du > 4k\beta\frac{w(r-d)}{r} \Rightarrow \frac{(a+d)u}{k\beta} > \frac{w(r-d)}{r} \\ r - d < \frac{ru(a+d)}{k\beta w}. \end{aligned} \tag{5}$$

Theorem 3.3. *The equilibrium point E_2 of the model (2) is locally stable if, and only if, $0 < r - d < \dfrac{ru(a+d)}{k\beta w}$.*

The Jacobian matrix of (2) calculated in $E_3 = (\overline{x}, \overline{y}, \overline{v})$ is:

$$J(E_3) = \begin{pmatrix} r - \dfrac{2\overline{x}r}{w} - \dfrac{r\overline{y}}{w} - d - \beta\overline{v} & -\dfrac{r\overline{x}}{w} & -\beta\overline{x} \\ \beta\overline{v} & -(d+a) & \beta\overline{x} \\ 0 & k & -u \end{pmatrix}.$$

The value M is given by

$$\begin{aligned}-M &= r - \frac{2\overline{x}r}{w} - \frac{r\overline{y}}{w} - d - \beta\overline{v} \\ &= r - \frac{ru[wk\beta(r-d) - ru(d+a)]}{wk\beta(ru+wk\beta)} - d - \beta k\frac{wk\beta(r-d) - ru(d+a)}{k\beta(ru+wk\beta)} \\ &- \frac{2ru(d+a)}{wk\beta} \\ &= -\frac{ru(d+a)}{wk\beta},\end{aligned}$$

and of $N = d + a$, and then the characteristic equation associated with $J(E_3)$ is:

$$\lambda^3 + (M+N+u)\lambda^2 + \left[MN + Mu + Nu - k\beta\overline{x} + \frac{\beta r}{w}\overline{xv}\right]\lambda + MNu + \beta^2 k\overline{xv} - k\beta M\overline{x} + \frac{u\beta r}{w}\overline{xv} = 0. \quad (6)$$

As $k\beta M\overline{x} = MNu$ and $k\beta\overline{x} = Nu$, we can rewrite the equation as:

$$\lambda^3 + (M+N+u)\lambda^2 + \left[MN + Mu + \frac{\beta r}{w}\overline{xv}\right]\lambda + \beta^2 k\overline{xv} + \frac{u\beta r}{w}\overline{xv} = 0. \quad (7)$$

Let us write $a_1 = M+N+u$, $a_2 = MN+Mu+\frac{\beta r}{w}\overline{xv}$ and $a_3 = \beta^2 k\overline{xv}+\frac{u\beta r}{w}\overline{xv}$. Thus, all the coefficients of (6) are real and positive, so, by Descartes' rule of signs, there is no positive root. In other words, we can have three negative roots or one negative root and a pair complex conjugate.

Given a characteristic polynomial equation of the third degree of the form $\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0$, by the Routh-Hurwitz stability criterion, the equilibrium point is stable if, and only if, $a_1 > 0$, $a_3 > 0$ and $a_1a_2 > a_3$ [8]. We can now state the following theorems:

Theorem 3.4. *The characteristic equation associated with the Jacobian matrix evaluated at the equilibrium point E_3 of the model* (2)*, when it exists, has three real and negative roots or one negative real root and a pair of complex conjugate roots.*

Theorem 3.5. *The equilibrium point E_3 of integer order model* (2)*, $\alpha = 1$, is locally stable if, and only if, $a_1a_2 > a_3$.*

And the stability theorem for the fractional case is given by:

Theorem 3.6. *The equilibrium point E_3 of model (2), with $0 < \alpha < 1$, is locally stable if one of the following occurs:*

- *$a_1a_2 > a_3$, that is, the three eigenvalues are negative (λ_1, λ_2, $\lambda_3 < 0$),*
- *$\lambda_1 < 0$, $|\arg(\lambda_2)| > \frac{\alpha\pi}{2}$ and $|\arg(\lambda_3)| > \frac{\alpha\pi}{2}$.*

4. Numerical simulations

For the numerical simulations we use the Grünwald-Letnikov method for fractional differential equations [33]. The parameters were based on the articles by [45, 46, 47] with the initial conditions: $x_0 = 4$, $y_0 = 1$ and $v_0 = 1$. Since τ does not affect the stability of the equilibrium points, in the simulatations we set $\tau = 1$.

For the situation that we do not have treatment, $k = 0$ (there is no virus replication), the tumor grows until it reaches its carrying capacity (see Figure 1).

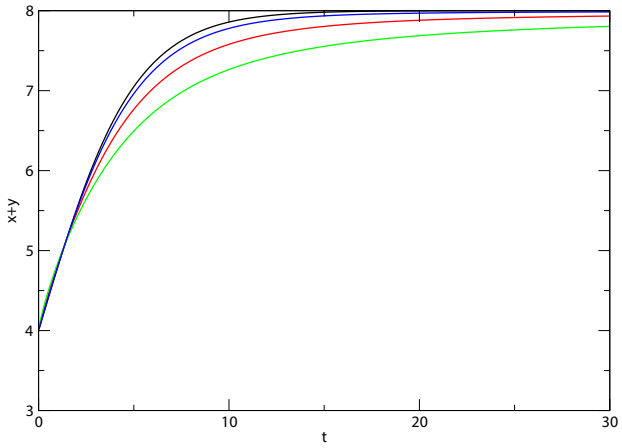

FIGURE 1. The growth curves for cancer cell population, for $k = 0$ (without virus replication), $r = 0.5$, $w = 10$, $d = 0.1$, $\beta = 1.5$, $a = 0.2$ and $u = 0.1$, with $\alpha = 1$ (black line), $\alpha = 0.97$ (blue line), $\alpha = 0.9$ (red line) e $\alpha = 0.8$ (green line).

As observed by [39], in the classical model, the population goes to the carrying capacity faster than expected. On the other hand, it is one of the advantages of the fractional model, as noted, the lower the order of the derivative the slower is the convergence to the carrying capacity. This slower convergence towards the carrying capacity is consistent with the growth of some types of cancer tumors [14], which is highly relevant to the study, as long as this model includes competition between tumor cells for vital resources and predicts that it takes longer to reach the maximum size of a tumor.

Next, we present three simulations (S1, S2 and S3) varying the parameters a, β e k (see Table 1). These parameters are influential in the interaction between populations [47].

	S1	S2	S3
r	0.5	0.5	0.5
w	10	10	10
d	0.1	0.1	0.1
β	0.1	1.5	0.1
a	1	0.2	1
k	0.04	0.04	0.2
u	0.1	0.1	0.1

TABLE 1. Parameters of the model (2).

4.1. Simulation 1 (S1)

With the parameters of S1 given in Table 1, the point E_1 is unstable, therefore, $r > d$. The E_2 equilibrium point is stable, as it satisfies Theorem 3.3. And there is no equilibrium point E_3. We have much smaller k and β constants when compared to the mortality rate a of cells infected due to the virus.

From Figure 2, observe that smaller values of α are associated with faster growth of cancer cells, however, this occurs only at the beginning of the dynamics, and then these values are associated with a slower convergence for the E_2 equilibrium point.

Fractional modeling, with an order of lower derivatives, can characterize tumors that in a short period of time grow quickly and then tend to the carrying capacity more slowly.

4.2. Simulation 2 (S2)

For model (2) with the parameters of S2, we will analyze the equilibrium point E_3. The characteristic equation associated with the Jacobian matrix is:

$$\lambda^3 + 0.425\lambda^2 + 0.01866\lambda + 0.01125 = 0.$$

So, the eigenvalues are given by:

$$\lambda_1 = -0.4406,$$

$$\lambda_{2,3} = 0.00781 \pm 0.1596i.$$

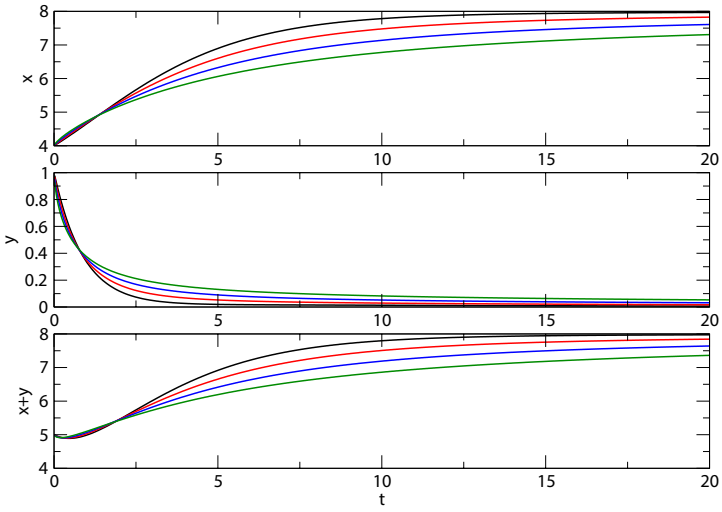

FIGURE 2. Dynamics of cancer cells, for simulation 1, different values of α, $\alpha = 1$ (black line); $\alpha = 0.9$ (red line); $\alpha = 0.8$ (blue line) and $\alpha = 0.7$ (green line).

From Theorem 3.6 the equilibrium point E_3 is stable for the model of order α, if

$$\alpha < \frac{2}{\pi} \arctan \frac{0.1596}{0.00781} \simeq 0.968.$$

In Figures 3, 4 and 5 we present the dynamic of cancer cells considering different values of α.

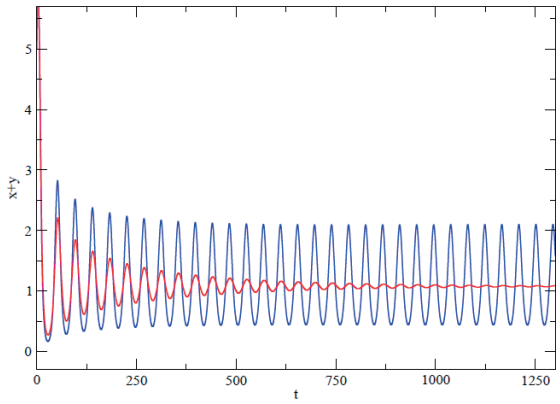

FIGURE 3. Dynamics of cancer cells, for simulation 2, with $\alpha = 0.97$ (blue line) and $\alpha = 0.96$ (red line).

In Figure 3 it is possible to observe that for $\alpha = 0.97$ the equilibrium point E_3 is unstable and for $\alpha = 0.96$ is stable, which is consistent with the result, since

$$\alpha = 0.96 < \frac{2}{\pi} \arctan \frac{0.1596}{0.00781} = 0.968.$$

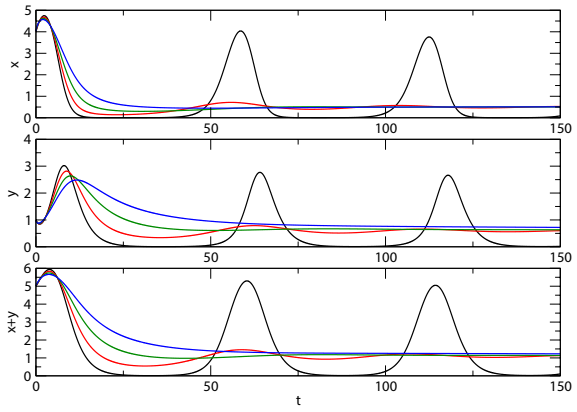

FIGURE 4. Dynamics of cancer cells, for simulation 2, with $\alpha = 1$ (black line), $\alpha = 0.9$ (red line); $\alpha = 0.8$ (green line) and $\alpha = 0.7$ (blue line).

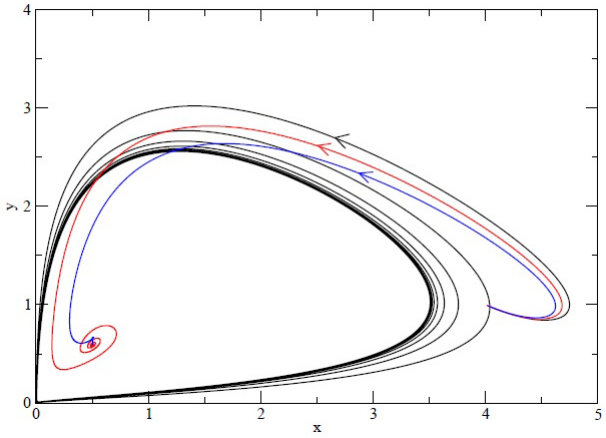

FIGURE 5. Phase portrait: uninfected cancer cells × infected cancer cells, for simulation 2 and $\alpha = 1$ (black line); $\alpha = 0.9$ (red line) e $\alpha = 0.8$ (blue line).

In Figure 5, for $\alpha = 1$ (black line), it is observed that the number of uninfected cancer cells oscillates periodically in time. And the same is true of infected cancer cells. And this is represented by the figure in which the phase portrait is very similar to a centre (black line). However, for $\alpha = 0.9$ and 0.8, there is the damping of oscillations over the equilibrium point, the phase portrait resembles a stable spiral.

When comparing the results (see Figures 3, 4 and 5) for different values of α, it is possible to observe that stability is related to the order of the fractional derivative and we observe also that, as the order of the derivative decreases, there is greater damping of the system with losses of oscillations.

4.3. Simulation 3 (S3)

For the model (2) with the parameters of S3, the point E_1 is unstable, because $r > d$. By Theorem 3.3 the equilibrium point E_2 is also unstable. Now let us analyze the point $E_3 = (5.5, 0.5, 1)$.

The characteristic equation associated with the Jacobian matrix at this point is:

$$\lambda^3 + 1.475\lambda^2 + 0.3575\lambda + 0.07375 = 0,$$

and the eigenvalues are:

$$\lambda_1 = -0.04745, \quad \lambda_2 = -0.24504 \quad \text{and} \quad \lambda_3 = -1.18251.$$

As the three eigenvalues are negative, the equilibrium point E_3 is stable for all order α, $0 < \alpha \leq 1$. This fact is in agreement with Theorem 3.5, because $a_1 a_2 = 0.5273125 > 0.01375 = a_3$.

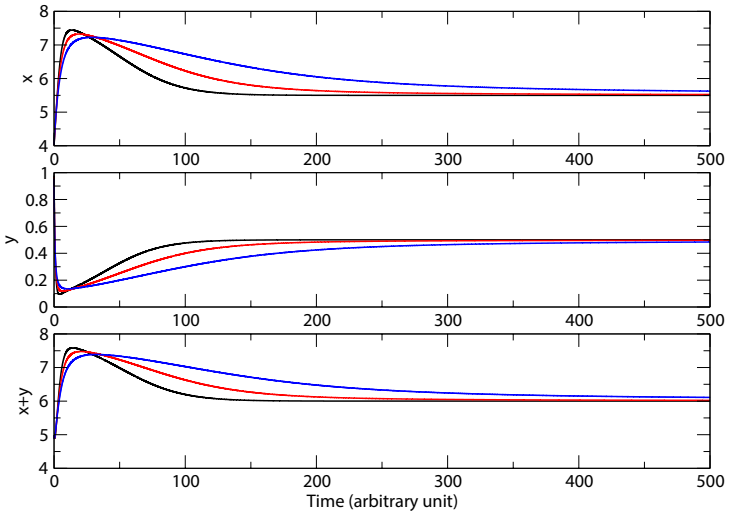

FIGURE 6. Dynamics of uninfected cancer cells (x), infected (y) and total ($x + y$) during the time parameters for the simulation 3 (S3), with order $\alpha = 1$ (black line); $\alpha = 0.9$ (red line) and $\alpha = 0.8$ (blue line).

We observed that there are no oscillations of the cancer cells over time and, when decreasing the order of the fractional derivative, the uninfected cancer cells go more slowly to the equilibrium point.

5. Discussion and conclusion

Clinical trials in the treatment of various types of cancer using oncolytic viruses have shown a significant reduction in tumor size and prolonged patient survival rates [9]. Since this therapy has significant potential benefits in the fight against cancer, there has been much interest in constructing and analyzing mathematical models of the effects of virotherapy. So, we take a simple model with ordinary differential equations that describe the dynamics of tumor treatment with virotherapy and generalize using the Caputo Derivative in order to capture the effect of memory present in biological systems, the fractality and, the multiscale nature that fit better the data.

We explore the stability analysis and numerical simulations of the model and the work showed that the fractional derivative of Caputo provides a better model. For the three different sets of parameters for some values of the order of the derivative, it was possible to find scenarios that represent tumor

control, which best describes the tumor dynamics with the oncolytic virus. It was demonstrated that in the fractional-order dynamics the model is more stable than its equivalent in the integer-order since the stability domain in the fractional-order model is greater than the corresponding domain for the integer-order model. We also observed that the order derivative fractional dampens the behavior of oscillations over the equilibrium point (Figures 3, 4, and 5). Thus, a more reliable model can be obtained by choosing the relevant fractional order according to the actual data.

As pointed out in [18] there are two primary ways to interpret biologically the presence of long period orbits (as can be observed in the Figure 3) in oncolytic virotherapy: complete tumor eradication or tumor remission. The fractional model, compared to the classical one, describes a wider range of scenarios, especially the case in which there is tumor remission.

Our results reinforce the current vision that Fractional Calculus is a very powerful tool in Biomathematics since it incorporates the memory effect and may reduce errors arising from simplifications made in the usual modeling.

Our results corroborate with the literature and highlight that a scenario of total tumor eradication is difficult and that treatment with an oncolytic virus can usually cause tumor control. As future work, we intend to study virotherapy using mathematical models combined with other treatments and through clinical data to obtain the order of the derivative that best describes the scenario.

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