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On a mathematical model of the influence of memory on cancer treatment using gene therapy

Modelagem matemática da influência de memória no tratamento do câncer por terapia gênica

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ABSTRACT

Cancer is one of the diseases that causes the most deaths in the world. Gene therapy is a recent alternative technique that has shown good clinical results in the treatment of gene changes and mutations caused by cancer. In this work, we will study the effects of gene therapy treatment by adding the hypothesis of the existence of immunological memory to the dynamics of cancer propagation through the introduction of multi-fractional order derivatives in the mathematical modeling for the problem. From a theoretical point of view, we will prove that the problem is well-posed in Hadamard's sense. We present numerical simulations for different scenarios, which demonstrate evidence that patients' previous contact with the virus involved in gene therapy can harm the effectiveness of the treatment.

Keywords: Gene therapy; Mathematical modeling; Caputo fractional derivatives; Memory

RESUMO

O câncer é uma das doenças que mais causa mortes no mundo. A terapia gênica é uma técnica alternativa recente e que tem demonstrado bons resultados clínicos no tratamento das alterações e mutações gênicas causadas pelo câncer. Neste trabalho, estudaremos os efeitos do tratamento por terapia gênica adicionando a hipótese da existência de memória imunológica a dinâmica de propagação do câncer, através da introdução das derivadas de ordem multi-fracionária na modelagem matemática para o problema. Do ponto de vista teórico, provaremos que o problema é bem posto no sentido de Hadamard. Apresentamos simulações numéricas para distintos cenários, os quais demonstram evidências de que o contato prévio dos pacientes com o vírus atuante na terapia gênica pode prejudicar a eficácia do tratamento.

Palavras-chave: Terapia gênica; Modelagem matemática; Derivadas fracionária de Caputo; Memória

1 INTRODUCTION

Cancer is a deadly illness of the present era, resulting from the uncontrolled proliferation of abnormal cells in the body Tsygvintsev et al. (2012). Chemotherapy is a well-known treatment for cancer that works to reduce the size of the primary tumor, slow down its growth, and destroy any cancer cells that may have spread throughout the body of the patient. Radiotherapy is a common form of treatment for cancer, which seeks to destroy cancer cells through radiation. This approach targets rapidly growing cancer cells, but can also have a significant impact on the reproduction of healthy cells. Both radiotherapy and surgery are commonly used before and after operations, and can cause a range of side effects, which can further weaken the patient Dokuyucu et al. (2018).

An alternative to the more traditional treatments is gene therapy Rabinowich et al. (1996), which has been found to be effective in clinical trials. This treatment involves introducing genetic material (DNA or RNA) into cells, with the aim of achieving various objectives Tsygvintsev et al. (2012); Zhao et al. (2012). One possibility is to replace defective or missing genes with healthy ones Tsygvintsev et al. (2012). Another approach being explored is to introduce genes into tumors, which can be activated by drugs given to the patient Zhao et al. (2012). The most common form of gene therapy, however, is to enhance the immune system's response to cancer, thus increasing the ability of immune cells to fight cancer cells Rabinowich et al. (1996).

Verifying the efficacy of a novel therapy such as gene therapy through clinical trials necessitates the recruitment and organization of a large number of patients, which takes time and resources, in addition to the cost of the materials involved Gabhann et al. (2010); Rabinowich et al. (1996); Zhao et al. (2012). Mathematical modeling is a great aid to clinical experiments. It enables the testing of hypotheses that generate a vast array of evidence at no cost, which, when combined with clinical experiments, can significantly advance cancer research Dokuyucu et al. (2018); Gabhann et al. (2010). Thus, the combination of mathematical modeling and clinical experiments can be a powerful tool in the fight against cancer Gabhann et al. (2010).

Many gene therapies employ viruses that have been genetically mutated from existing viruses, such as the T-Vec virus[1] which is a modified form of herpes simplex virus type 1. Additionally, there are promising studies that are utilizing mutations of the Zika virus for cancer treatment Tontonoz, Matthew (2015). Since these viruses have been around for a while, it is reasonable to question how much of an impact the immunological memory associated with them has on the efficacy of oncological treatments using them (positively or negatively).

Main contributions and paper organization: This work contributes to potential clinical tests by exploring a mathematical model of cancer treatment with gene therapy that incorporates memory into the system through fractional-order derivatives. We show that the model has a unique continuous solution that continuously depends on the initial data, the parameters, and the amount of memory. The numerical simulation with and without memory of both cancer cells and the virus used in oncological treatment are presented in Section 3, showing that the best scenario occurs when memory is present. Consequently, one of the research avenues is to introduce memory in individuals with a family history of cancer.

2 GENE VIROTHERAPY MODEL

At each instant $t \geq 0$, the quantities $x(t)$, $y(t)$, and $v(t)$ represent the number of uninfected and growing cancer cells, cancer cells already infected by the virus, and viral particles, respectively. The total tumor cell population during viral therapy is the sum of infected and uninfected tumor cells, $x(t) + y(t)$. The aim of the therapy should be to reduce this population to a low level. If it is decreased below a certain threshold in the model, the tumor population can be considered eliminated.

The virus related to gene therapy has an effect on the body and targets cancer cells. We will look at a model that is an extension of the Lotka-Volterra equations[2], which takes into account the immunological impact of memory effects on the results of gene therapy Du et al. (2013). This memory is described by derivatives of fractional order of Caputo type Diethelm (2010), given by

[1]This was the first oncological virus medicine approved for useTontonoz, Matthew (2015)

[2]The Lotka-Volterra equations are also known as predator-prey equations. They are a system of first-order differential equations that describe the dynamics of a biological system in which two species interact, one species as predator and the other as prey Wodarz & Komarova (2014).

$$
\begin{aligned}
D^{\alpha_1}x(t) &= r^{\alpha_1}x(t)\left(1-\frac{x(t)+y(t)}{\omega}\right) - d^{\alpha_1}x(t) - \beta^{\alpha_1}x(t)v(t)\\
D^{\alpha_2}y(t) &= \beta^{\alpha_2}x(t)v(t) - (d^{\alpha_2}+a^{\alpha_2})y(t)\\
D^{\alpha_3}v(t) &= k^{\alpha_3}y(t) - \mu^{\alpha_3}v(t)\,,
\end{aligned}
\tag{1}
$$

with initial conditions

$$
x(0) = x_0 \geq 0\,, y(0) = y_0 \geq 0\,, v(0) = v_0 \geq 0\,. \tag{2}
$$

Equation (1) describes the development of a tumor in a cell population that has been treated with gene therapy. The parameters r, ω, d represent, respectively, the growth rate, support capacity, and mortality rate of cancer cells. β describes the effectiveness of the process, including the rate at which viral particles encounter uninfected cells, the rate of virus entry, and the rate of successful infection. Infected cancer cells have a mortality rate, which is composed of the sum of the natural death rate d and the virus-infected death rate a. Therefore, the average lifespan of an infected cell is $1/(d+a)$. k is the rate of virus reproduction by infected cells and $k/(d+a)$ is the total amount of viral particles that are produced from an infected cell. Finally, μv is the virus decay rate. The parameters in the model are raised to powers of the respective Caputo fractional derivatives D^{α_j} of order $\alpha_j \in [0,1]$, to $j = 1,2,3$, in order to maintain the temporal scale of the dynamics Diethelm (2010).

2.1 Well-posedness

In this subsection, we will present results of well-posedness, that is, existence, uniqueness, permanence, and continuous dependence of a solution, initial data, and model parameters.

For that fate, let $U(t) = (x(t), y(t), v(t))^T$ be the vector that represents a possible solution for the model (1). The first auxiliary result in this context is the following lemma.

Lemma 2.1. *Let $F(t, U(t))$ be the vector function that represents the right-hand side of the model* (1)*. Then $F(t, U(t))$ is continuous with respect to t and Lipschitz continues with respect to $U(t)$, for $t \in [0, T]$, whatever $T > 0$.*

Proof. Since the model (1) is composed of sums and products of continuous functions, it follows that $F(t, U(t))$ is a continuous function with respect to t in the interval $[0, T]$.

Furthermore, the Jacobian matrix of the model (1) is given by

$$J(t,U(t)) = \begin{bmatrix} r^{\alpha_1}(1-(2x(t)+y(t))/w) - d^{\alpha_1} - \beta^{\alpha_1}v(t) & -r^{\alpha_1}x(t)/w & -\beta^{\alpha_1}x(t) \\ -\beta^{\alpha_2}x(t) & -(d^{\alpha_2}-a^{\alpha_2}) & -\beta^{\alpha_2}x(t) \\ 0 & k^{\alpha_3} & -\mu^{\alpha_3} \end{bmatrix}.$$

As a consequence, each coordinate of $J(t,U(t))$ is continuous. Therefore, it follows from the Weierstrass Theorem (see Sotomayor (1979)) that there is a constant $M > 0$, independent of $t \in [0,T]$ and $U(t)$, such that $\|J(t,U(t))(t)\| \leq M$. Now, applying the Mean Value Theorem (see Sotomayor (1979)) follows the Lipschitz continuity of $F(t,U(t))$.

The following result ensures the consistency of the solution to model (1) with initial conditions (2), meaning that all components of $U(t)$ remain nonnegative, as the problem being studied suggests. To do this, we define the region $\Omega_+ := \{U(t) := (x(t),y(t),v(t))^T : \text{ all components of } U(t) \text{ are non-negative}\}$. We will use the arguments of Santos et al. (2017) to demonstrate that Ω_+ is an invariant region. This means that if the initial conditions (2) are located in Ω_+, then the solution $U(t)$ of the model (1) will remain in Ω.

Proposition 2.1. *The region Ω_+ is a positive invariant set for a solution of the model* (1) *with initial conditions.*

Proof. Denote by H_+^j the set whose j-th coordinate[3] belongs to Ω_+, for $j = 1,\cdots,3$.

Then, the vector field relative to the model (1) restricted to H_+^j, for $j = 1,\cdots,3$, has the form

$$f_1(x(t),y(t),v(t)) = (r^{\alpha_1}x(t)(1-x(t)/w) - d^{\alpha_1}x(t),0,0)$$
$$f_2(x(t),y(t),v(t)) = (0,-(d^{\alpha_2}+a^{\alpha_2}),0)\,, \quad f_3(x(t),y(t),v(t)) = (0,0,-\mu^{\alpha_3})\,.$$

Using the properties of the Laplace transform applied to fractional calculus and the definition of the Mittag-Leffler function (see Diethelm (2010); Santos et al. (2017)),

[3]For example, $H_+^1 := \{(x(t),0,0) : , x(t) \geq 0\}$.

we obtain that, over H_+^j, for $j = 1, \cdots, 3$,

$$(x(t), 0, 0) = (t^{\alpha_1} E_{\alpha_1, \alpha_1+1}(r^{\alpha_1} t^{\alpha_1}) x(0) + E_{\theta_1,1}(-d^{\alpha_1} t^{\alpha_1}) x(0), 0, 0) \tag{3}$$

$$(0, y(t), 0) = (0, E_{\alpha_2,1}(-(d^{\alpha_2} + a^{\alpha_2}) t^{\alpha_2}) y(0), 0) \tag{4}$$

$$(0, 0, v(t)) = (0, 0, E_{\alpha_3,1}(-\mu^{\alpha_3} t^{\alpha_3}) v(0)) \,. \tag{5}$$

Therefore, any solution of the model (1) remains in H_+^j, given that the initial conditions (2) belong to H_+^j, for $j = 1 \cdots, 3$, respectively. Thus, H_+^j is a positively invariant set.

Now, it is necessary to show that the solution $U(t)$ remains in Ω_+. Suppose by contradiction that this does not happen. In other words, suppose that some of the coordinates of $U(t)$ are not in Ω_+, for some $t_* \in [0, T]$. Due to the continuity of $F(t, U(t))$ with respect to t given by Lemma 2.1, there must exist an interval around t_* such that at least one of the coordinates of $U(t)$ does not belong to Ω_+, in this range. Assume that this happens for the first of the coordinates (if it happens with the others, the argument is analogous). As $x(0) > 0$ and due to the continuity of $x(\cdot)$, with respect to t, there must exist a $\hat{t} > 0$, such that $x(\hat{t}) = 0$. We can still assume that t^* is sufficiently close to $\hat{t}$ and thus $x(t^*) < x(\hat{t})$. On the other hand, from (3) it follows that $D^{\alpha_1} x(t)|_{t=\hat{t}} \geq 0$. Therefore, the Mean Value Theorem for noninteger derivatives (see Odibat & Shawagfeh (2007)) implies that $x(t^*) - x(\hat{t}) \geq 0$, for t^* sufficiently close to $\hat{t}$. A contradiction. Thus, $U(t) \in \Omega_+$, for all $t \geq 0$.

In what follows, we will prove that the model (1) with initial conditions (2) has a unique solution.

Theorem 2.1. *Assume that the hypotheses of Lemma 2.1 are true. Then, there is a unique continuous and nonnegative solution $U(t)$ for the model* (1)-(2)*, for all $t \in [0, T]$. Such a solution continuously depends on the initial data* (2)*, the model parameters and the orders of the derivatives $\alpha_j \in]0, 1]$, for $j = 1, \cdots, 3$.*

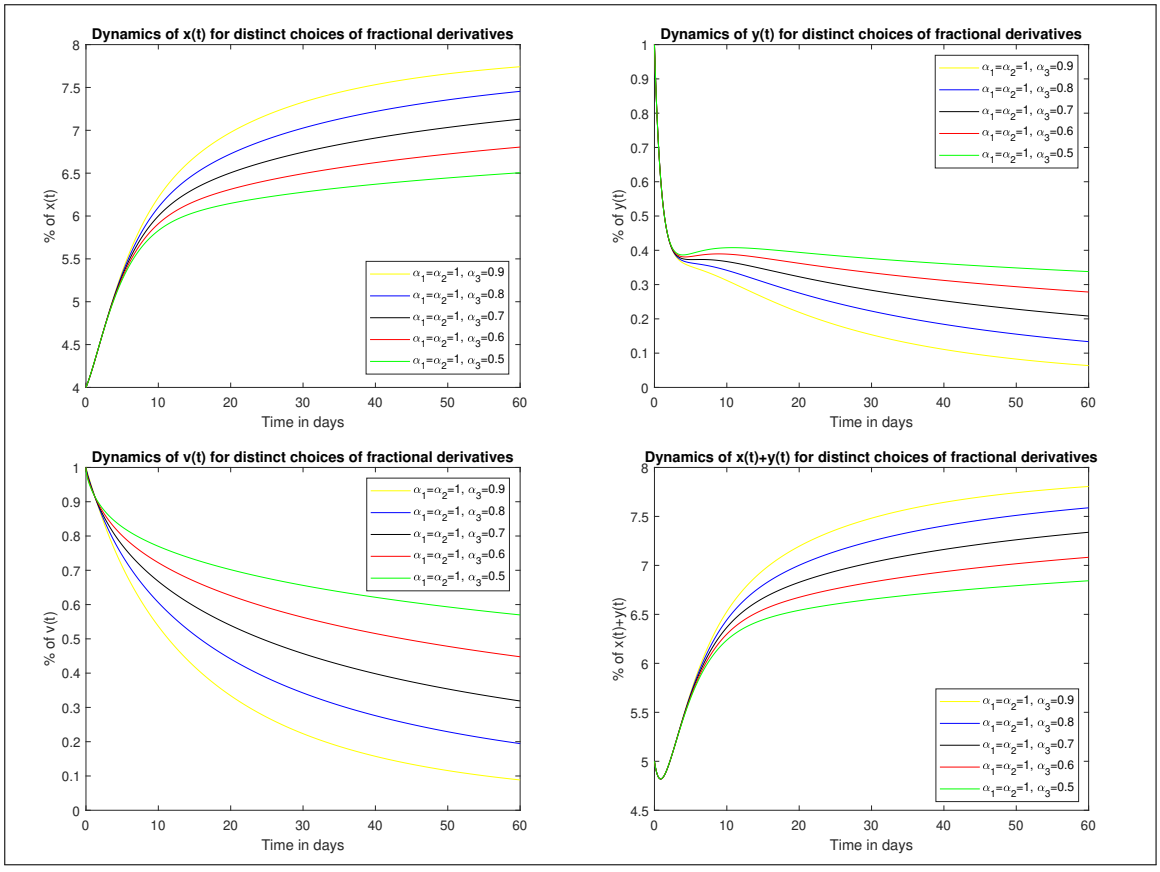
Proof. It follows from Lemma 2.1 that $F(t, U(t))$ is continuous with respect to t and Lipschitz continues with respect to $U(t)$, for any $t \in [0, T]$. Therefore, (Diethelm, 2010, Theorems 8.7 - 8.11), implies the existence of a unique continuous solution in $[0, T]$ for the model (1)-(2). The continuous dependence of the initial data, the parameters and

the orders of the derivatives follows from the results in (Diethelm, 2010, Theorems 8.7 - 8.11).

3 NUMERICAL SIMULATIONS

In this contribution, we will present simulations in which the solution of the model (1) with initial conditions (2) is approximated by a trapezoidal type rule for fractional differential equations proposed and studied in Garrappa (2015), using a mesh with a uniform size of $h = 10^{-4}$. For all simulations, the initial conditions were set to $x(0) = 4$, $y(0) = 1$, and $v(0) = 1$, while the parameters $r = 0.5$, $\omega = 10$, $d = 0.1$, $\beta = 0.1$, $a = 1$, $k = 0.04$, and $\mu = 0.1$ were kept constant.

Figure 1 – Effect of different memories of the virus ($\alpha_3 \in]0, 1]$) on the dynamics of the solution of x, y, v and $x + y$



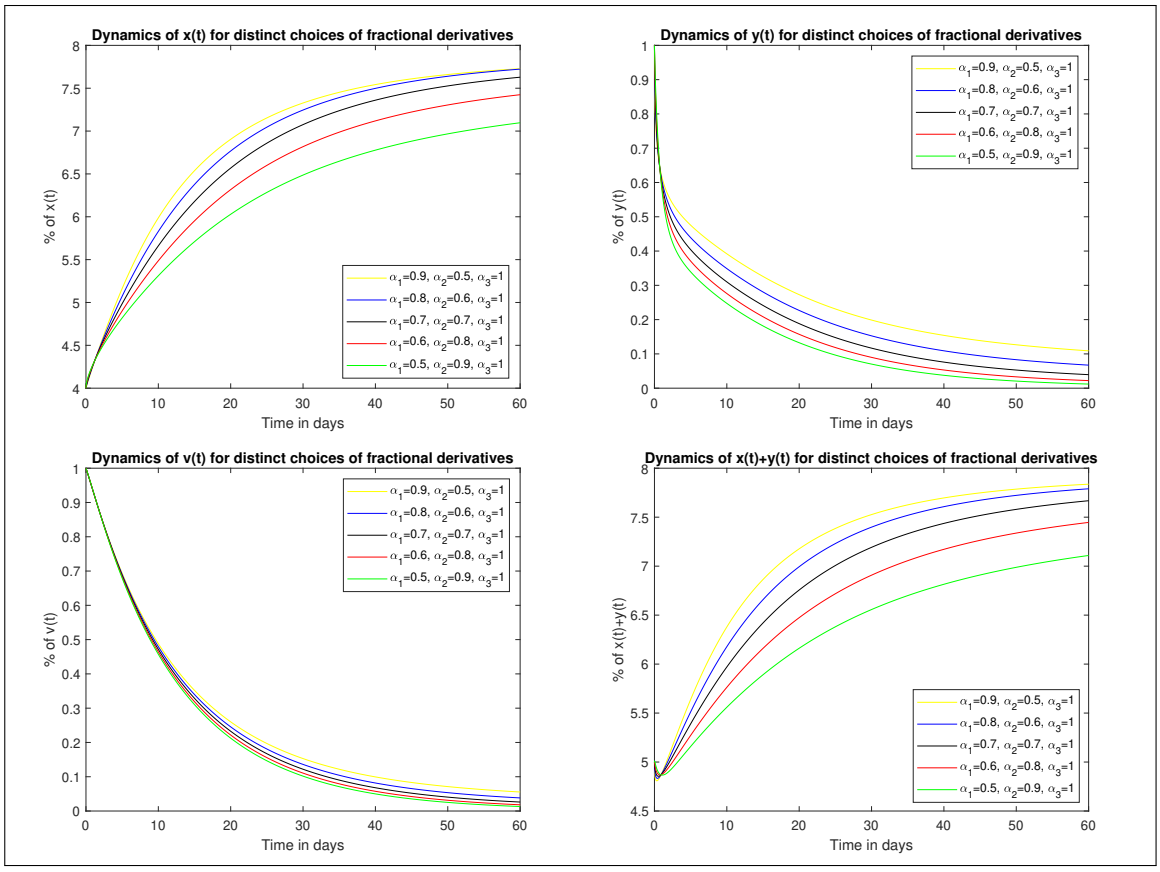
Source: the author (2024)

Simulated scenario 1: Figure 1 illustrates a situation in which the patient had not been exposed to the virus before, which means that cells $x(t)$ and $y(t)$ had no immunological memory. Consequently, the derivatives were set to the order

$\alpha_1 = \alpha_2 = 1$. On the other hand, the virus had been "trained" to combat cancer cells, so only $v(t)$ had different levels of immunological memory. The values of α_3 are shown in Figure 1.

The results in Figure 1 lead to the conclusion that the cancer cells affected by the virus $x(t)$ obtained the lowest percentage when the virus has higher levels of memory and higher percentages when $v(t)$ has lower memory, that is, when the fractional derivative approaches 1. On the other hand, $y(t)$ presents an opposite dynamic: the greater the memory of the virus, the fewer cancer cells unaffected by the virus, and the more memory $v(t)$ has, the greater the number of cells $y(t)$. The virus dynamics performs best when the fractional derivative is 0.5, that is, the larger the memory, the greater the number of viruses.

Figure 2 – Effect of different memories on the dynamics of the solution of x, y, v and $x + y$



Source: the author (2024)

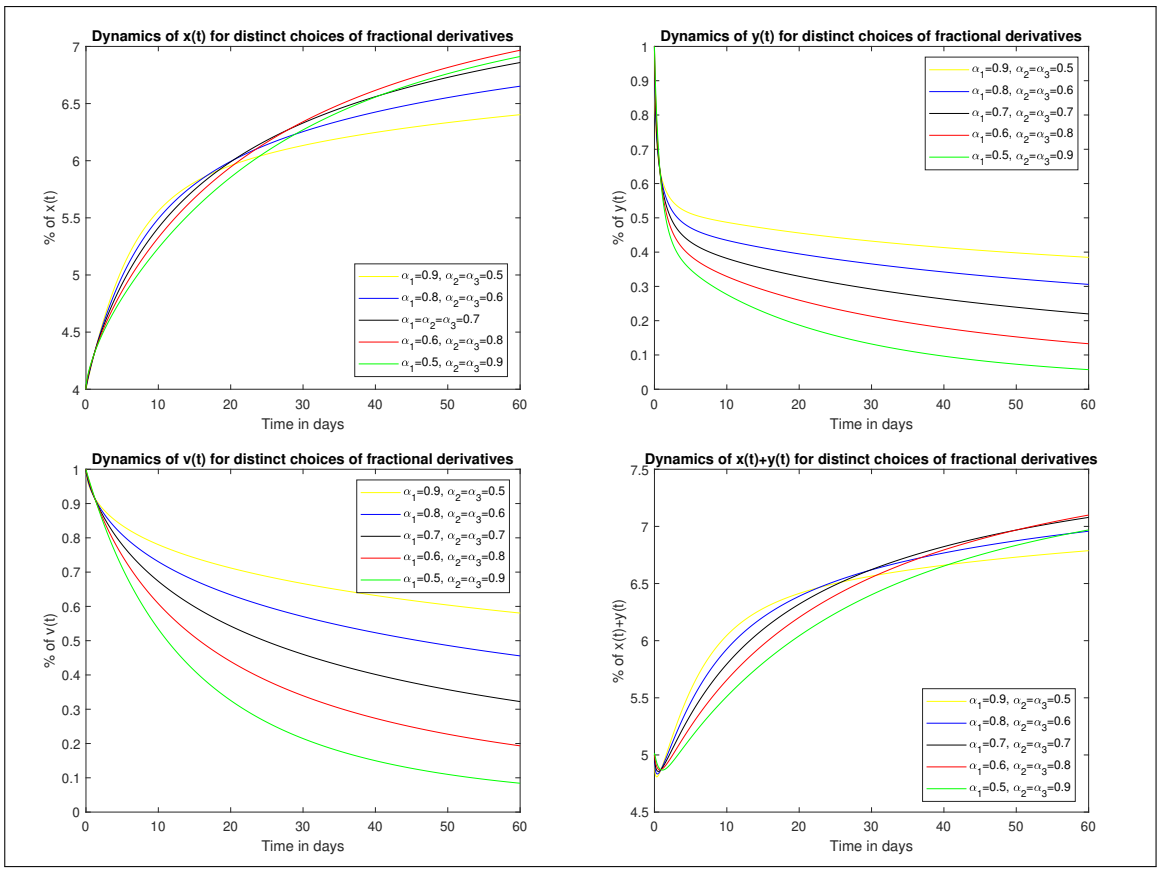
Simulated scenario 2: In Figure 2, we illustrate a situation in which the patient had already encountered the virus, meaning that cells $x(t)$ and $y(t)$ have immunological memory (α_1 and α_2 are not necessarily 1). However, the virus had not been exposed to

cancer cells before, so $v(t)$ does not have any immunological memory ($\alpha_1 = 1$), as shown in Figure 2.

Looking at the results in Figure 2, we arrive at the conclusion that cells $x(t)$ and $y(t)$ had a higher percentage when cells $x(t)$ have less memory and cells $y(t)$ have more memory. Similarly, $x(t)$ and $y(t)$ had a lower percentage when cells $x(t)$ have greater memory and cells $y(t)$ have less memory. The virus $v(t)$ suffered a slight influence resulting from the different memories of cells $x(t)$ and $y(t)$. However, there was a smaller decrease when cells $x(t)$ have less memory and cells $y(t)$ have more memory.

Simulated scenario 3: In Figure 3, we can observe a simulation of a situation in which the patient had already been exposed to the virus and had received immunological training to combat cancer cells. This is represented by cells $x(t)$, $y(t)$ and the virus $v(t)$, all of which have immunological memory ($\alpha_j \neq 1$ for all $j = 1, 2, 3$).

Figure 3 – Effect of different memories on the dynamics of the solution of x, y, v and $x + y$



Source: the author (2024)

In this simulation, it is evident that the most advantageous situation is when cells $x(t)$ have less memory and cells $y(t)$ and the virus have more memory. When the

memory of cells $x(t)$ increases and the derivative of the dynamics of cells $y(t)$ and the virus $v(t)$ comes closer to 1 ($\alpha_2 \to 1$ and $\alpha_3 \to 1$), the result is more cells $x(t)$, fewer cells $y(t)$, and a lower percentage of virus.

4 CONCLUSIONS

The simulated scenarios presented in Figure 1, Figure 2 and Figure 3 demonstrate that the presence of different memory levels leads to a complex behavior of the related dynamics. It is evident that when cancer cells possess memory in addition to the virus, the situation is more advantageous than when the virus has memory and cancer cells do not. Consequently, the potential for introducing prior memory into individuals with the probability of having hereditary cancer can be explored. A further examination is currently being conducted and will be reported in forthcoming work.

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