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Dynamical Analysis of Chemotherapy Optimal Control using Mathematical Model Presented by Fractional Differential Equations, Describing Effector Immune and Cancer Cells Interactions.

Mehdi Shahbazi^{1*}, G Hussian Erjaee¹, and Hoda Erjaee²

¹Mathematics Department, Shiraz University, Shiraz, Iran.

²Department of Basic Science, Shiraz University, Shiraz, Iran.

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*For Correspondence

Mathematics Department,
Shiraz University, Shiraz, Iran.

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ABSTRACT

Evaluation of chemotherapy treatment in cancer cells is important because of its damaging side effects. For controlling chemotherapy treatment in cancer cells an accurate and comprehensive mathematical model could be useful. Many mathematical models have been used to show the benefits of immune system on controlling the growth of a tumor and the detrimental effects of chemotherapy on both the tumor cell and the immune cell populations. In this article, we offer a novel mathematical model presented by fractional differential equations. This model will then be used to analyze the bifurcation and stability of the complex dynamics which occur in the local interaction of effector-immune cell and tumor cells in a solid tumor. We will also investigate the optimal control of combined chemo-immunotherapy. We argue that our fractional differential equations model will be superior to its ordinary differential equations counterpart in facilitating understanding of the natural immune interactions to tumor and of the detrimental side-effects which chemotherapy may have on a patient's immune system.

INTRODUCTION

The response to treatment in a tumor is dependent on many factors; some of these factors included are severity of the tumor, application of the treatment and the ability of patient's own immune system. Over the past decades, mathematical modeling has been developed to evaluate the growth of a tumor and predict the treatment processing. These models can facilitate to control a tumor by predicting its size. In addition, it is possible to evaluate the effect of the body's natural immune system on tumor cells by these models. They can also help to determine optimal drug treatments or the timing of surgery (e.g., cf. [4-24] and the references therein). After the implicit understanding that chemotherapy has damaging side effects, variety of models have been applied in cancer growth with chemotherapy, these models have been investigated to minimize the total amount of drugs which are used in chemotherapy (See for example [1], [2] and references therein).

In the tumor growth model presented by Pillis [4], an explicit representation of the immune system is included, as well as chemotherapy treatment. This allows not only to incorporate the beneficial effects of the immune system on controlling the growing tumor, but also to track directly the detrimental effects of chemotherapy on both the tumor cell and the immune cell populations. The count of circulating

lymphocytes in a patient's bloodstream is a common clinical practice which is used to reflect the strength of the patient's overall immune health.

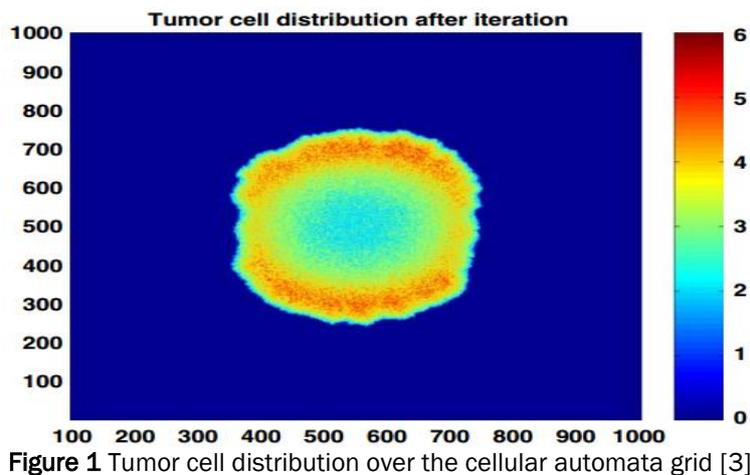


Figure 1 Tumor cell distribution over the cellular automata grid [3]

It is understood that this procedure does not provide a complete profile of the patient's immune health but, it is accepted as one measure. Therefore, in this model two immune components are included: effector-immune cells and circulating lymphocytes. The effector immune cells actively target and destroy tumor cells, while, as stated, the circulating lymphocytes serve as a way to monitor the additional damaging side-effects of chemotherapy [4].

Ordinary differential equations (ODE) and partial differential equations in the form of heat diffusion and statistical equations are just some of the mathematical tools that have been used in deriving these models. In this article, we extend the ODE system presented by de Pillis *et al.* [4] with using a fractional differential equation (FDE). By using this model we will be able to investigate the optimal control on combination of chemo-immunotherapy. We claim that our FDE model will be better than its ODE counterpart, who facilitates to understand the response of natural immune interactions in a tumor and also it helps to identify the possible damaging side-effects of chemotherapy on a patient's immune system. Indeed, some of the advantages of our FDE model over previous ones are represented as following. First of all, as it is explained by Andrew Einstein [22], some of the cells in various body organs, for example, breast cells, have a rugged surface. Using ordinary calculus cannot be properly understood because of this nature of the cells. Although, study these cells using fractional calculus may be amenable. In another words, there are some busted points in the surface of these cells where the ordinary (classical) derivative can't explain them. In this kind of domains, fractional differentiation can be used because, the smoothness property of the domain which is necessary for classical derivatives may not be essential in fractional derivatives. Second, in the definition of the classical derivative of a function only two points in the neighborhood of a point is used. In the definition of the fractional derivative all the points in a neighborhood of a point are used. In this case, more accurate results are obtained in subsequent applications because of using all the accessible information. *Non-local property* is the term used for this situation which closely reflects reality, and this is primary reason that explains why FDE is increasingly applied to dynamical systems.

In this article, for the circulating lymphocyte population which shows the patient health, we will introduce a FDE model. In this model, the interaction of tumor cell and effector-immune populations in tumor latency is inserted into circulating lymphocyte population which shows a combined FDA model. Moreover, to discuss the dynamical behavior of this model the fixed point and their stability characteristics are determined. We will use Grunwald-Letnikov discretization method to find the solution of this FDE system [23 & 24], then we will find the results by using software tools such as MATLAB™. Note that chemotherapy is not considered in this FDE model. In the second model in the form of FDE, chemotherapy drug concentration is added to the tumor-immune interactions and we will consider the same three cells populations as in the first FDE. Now, similar to the way in which it can be done in classical ODE systems, we will discuss the dynamic behavior of the system and determine the stability of the various feasible fixed points. One of the main goals in using fractional order instead of classical integer order derivative in our model is to obtain more accurate results in optimally control application of chemotherapy and to minimize the total tumor while constraining the immune state to stay above a specified threshold. For this optimality, similar to linear optimal control method used by de Pillis *et al.* [4], we will also use it for our FDE model. Obviously, in the processing of this optimality we need to solve our FDE system numerically. To facilitate

this solution, as in above first FDE system, we will apply Grunwald-Letnikov method to discretize the model and then use MATLAB™ software to find the results.

As we stated before, we will expect more accurate results in solving our FDE systems as compared to the results found by classical ODE methods.

Preliminaries and Dynamics of FDE Model

The first model that we have considered in this section is a three cells population model describing the interaction between the tumor cell (T) plus the effector-immune cell (N) with the circulation lymphocyte population (C), which measures the patient health. If we suppose these three cells evolve with independent variable time, then we can present our model in the form of FDE as follows:

$$\begin{aligned} D^\alpha T &= aT(1-bT) - c_1NT, \\ D^\alpha N &= \alpha_1 - fN + g \frac{T}{h+T} N - pNT, \\ D^\alpha C &= \alpha_2 - \beta C. \end{aligned} \quad (1)$$

This model is similar to the classical ODE models presented by de Pillis and Radunskaya^[17] and de Pillis et al.^[4]. Here, we use the same order derivatives $\alpha \in (0, 1]$ for all three equations with given positive initial values $T(0) = T_0$, $N(0) = N_0$ and $C(0) = C_0$. Before any justification of these three equations, we should clarify the definition of fractional derivative, D^α , which is used here. Following the Caputo's definition for FDE^[23], this derivative is defined by $D^\alpha x(t) = J^{n-\alpha} D^n x(t)$, where $0 < \alpha \leq 1$ and J^n is the n^{th} -order Riemann-Liouville integral operator defined by

$$J^n x(t) = \frac{1}{\Gamma(n)} \int_0^t (t-\tau)^{n-1} x(\tau) d\tau$$

with $t > 0$ and $n = \min\{k \in \mathbb{N} : k > \alpha\}$ which is one for $0 < \alpha \leq 1$. Therefore, as we stated above, for the fractional derivative order $0 < \alpha \leq 1$ the smoothness property of the domain is not essential in this fractional derivative.

Here, we have summarized the explanations of three equations in model (1) as follows. In the first equation, the tumor cell population is assumed to grow logistically, while tumor cells are killed by the immune cells through a mass-action dynamic^[18]. In the second equation, the immune cells have a constant source rate α_1 , while death is proportional to the population of immune cells through the term $-fN$. Immune cells are also recruited by tumor cells through a Kuznetsov term, $g(T/(h+T))N$ which serves to provide a saturation effect^[25]. Additionally, immune cells are inactivated through contact with tumor cells according to a mass-action dynamic. The immune-tumour cell complex of the third equation has a constant source rate α_2 and a proportional death term $-\beta C$. Here, all of the parameters are similar to those presented in^[18] so that we can compare our results with those found by other classical ODE models. These values are given in Table 1. These parameters were chosen to be within ranges that are allowed for reasonable dynamics as well as convergence of the optimal control algorithm.

Similar to the classical ODE systems, we can analyze the dynamical behavior of system (1) and determine the stability of its various feasible fixed points. Hence, we first find the fixed points of this system. To find this, from the last equation in (1) we obtain $C = \alpha_2/\beta$, and from the first equation we get $T = 0$ and $a(1-bT) - c_1N = 0$. Now, from the second equation with $T = 0$ we find $N = \alpha_1/f$. Therefore, one of the feasible fixed points will be $(\bar{T}, \bar{N}, \bar{C}) = (0, \alpha_1/f, \alpha_2/\beta)$. By calculating the Jacobian of the system we have

$$DF(\bar{T}, \bar{N}, \bar{C}) = \begin{bmatrix} -2ab\bar{T} + a - c_1\bar{N} & -c_1\bar{T} & 0 \\ -p\bar{N} + g\bar{N}h/(h+\bar{T})^2 & -f - p\bar{T} + g\bar{T}/(h+\bar{T}) & 0 \\ 0 & 0 & -\beta \end{bmatrix}.$$

Evaluating the eigenvalues of this Jacobian matrix at evaluated fixed point yields $\lambda_1 = a - c_1\alpha_1/f$, $\lambda_2 = -f$ and $\lambda_3 = -\beta$. Obviously, with the parameter values given in Table1, λ_2 and λ_3 are negative but $\lambda_1 = 4.21 \times 10^{-3}$ is positive which means this fixed point, with $T = 0$, is unstable.

Now, for the second fixed point with $N = \alpha_1 / (f - gT / (h + T) + pT)$, from the first equation in (1) we get $a(1 - bT)((f + pT)(h + T) - gT) - c_1\alpha_1(h + T) = 0$. Plugging the parameter values from Table 1 into this third degree equation and solving it by MATLAB™, yields three solutions on which just one of them is positive and acceptable, and the other two are negative which is physiologically unacceptable. With this acceptable positive value of T we will get two other related components of the second fixed point $(\bar{T}, \bar{N}, \bar{C}) = (9.8039 \times 10^{13}, 6.1199, 6.25 \times 10^{10})$. The above Jacobian matrix at this point has three negative eigenvalues $\lambda_1 = -0.004324$, $\lambda_2 = -1960.809617$ and $\lambda_3 = -0.0012$. Consequently, system (1) has two fixed points on which the first one with $T = 0$ is unstable and the second one with a large value of T is stable.

Table 1: Parameter Values.

Parameters	Units	Description	Estimated Values
a	Day ⁻¹	Tumor growth rate	4.31×10^{-3}
b	Cell ⁻¹	$1/b$ is tumor carrying capacity	1.02×10^{-14}
c_1	Cell ⁻¹ . Day ⁻¹	Fractional tumor cell kill by effectors cells	3.41×10^{-10}
f	Day ⁻¹	Death rate of effector cells	4.12×10^{-2}
G	Day ⁻¹	Maximum effector cell recruitment rate by tumor cells	1.5×10^{-3}
H	Cells ²	Steepness coefficient of the effector cell recruitment curve	2.02×10^1
K_C, K_N	Day ⁻¹	Fractional effector cell and circulating lymphocyte kill by chemotherapy	6.0×10^{-1}
K_T	Day ⁻¹	Fractional tumor cell kill by chemotherapy	8.0×10^{-1}
P	Cell ⁻¹ . Day ⁻¹	Effector cell inactivation rate by tumor cells	2×10^{-11}
α_1	Cell ⁻¹ . Day ⁻¹	Constant source of effector cells	1.2×10^4
α_2	Cell ⁻¹ . Day ⁻¹	Constant source of circulating lymphocytes	7.5×10^8
β	Day ⁻¹	Death rate of circulating lymphocytes	1.2×10^{-2}
γ	Day ⁻¹	Rate of chemotherapy drug decay	9.0×10^{-1}

Therefore, in the absence of medical treatment with $T_0 > 0$ the tumor cell populations will grow up to its maximum possible value. At this point, the tumor needed to be controlled by treatment. If we do not control the tumor, the effector-immune cells are not able to renovate. The right hand side in the second equation of system (1) has negative derivative which proofs this fact that while the tumor cell is growing up the effect of the body immune system is converging to zero. This circumstance is also illustrated, as the results of numerical solutions to the system (1), in the next section.

Discretization and Numerical Solutions of FDE Model

As we discussed above, linear stability analysis of system (1) was similar to that of its ODE counterpart. However, to solve FDE system (1) first we need to discretize it. Among the several

discretization methods that are available for the fractional derivative D^α , we have used the one that is granted by Grünwald-Letnikov [23 & 24]. In this method $D^\alpha x(t)$ is approximated by

$$D^\alpha x(t) = \lim_{l \rightarrow 0} l^{-\alpha} \sum_{j=0}^{\lceil t/l \rceil} (-1)^j \binom{\alpha}{j} x(t - jl). \quad (2)$$

Here, l is the step size and $\lceil t \rceil$ denotes the integer part of t . Under this discretization method $D^\alpha x(t)$ in system (1) can be replaced by $\sum_{j=0}^{\lceil t_n/l \rceil} c_j^\alpha x(t_{n-j})$, where $t_n = nl$ and c_j^α are the Grünwald-Letnikov coefficients which is defined by:

$$c_j^\alpha = l^{-\alpha} (-1)^j \binom{\alpha}{j}, \quad j = 0, 1, 2, \dots$$

These coefficients can also be evaluated recursively as:

$$c_0^\alpha = l^{-\alpha} \text{ and } c_j^\alpha = \left(1 - \frac{1+\alpha}{j}\right) c_{j-1}^\alpha, \quad j = 1, 2, 3, \dots \quad (3)$$

Using formula (2), system (1) is discretized as follows:

$$\begin{aligned} \sum_{j=0}^n c_j^\alpha T_{n-j} &= aT_n(1 - bT_n) - c_1 N_n T_n \\ \sum_{j=0}^n c_j^\alpha N_{n-j} &= \alpha_1 - fN_n + g \frac{T_n}{h + T_n} N_n - pN_n T_n \\ \sum_{j=0}^n c_j^\alpha C_{n-j} &= \alpha_2 - \beta C_n. \end{aligned} \quad (4)$$

Simple calculation on (4) yields the following recursive formulas:

$$\begin{aligned} T_n &= \frac{\sum_{j=1}^n c_j^\alpha T_{n-j}}{a(1 - bT_n) - c_1 N_n - c_0^\alpha}, \\ N_n &= \frac{\alpha_1 - \sum_{j=1}^n c_j^\alpha N_{n-j}}{f - g \frac{T_n}{h + T_n} + pT_n + c_0^\alpha}, \\ C_n &= \frac{\alpha_2 - \sum_{j=1}^n c_j^\alpha C_{n-j}}{\beta + c_0^\alpha}. \end{aligned} \quad (5)$$

We have used MATLAB™ software to solve this discretized system (5) with initial values $T_0 = 10^7$, $N_0 = 3 \times 10^5$, $C_0 = 6.25 \times 10^{10}$ and the results are illustrated in Figures 2-4. In these figures, we consider different values of fractional order derivative $0.90 < \alpha \leq 1$. As we can see, the normalized values of tumor cells will grow up to its maximum capacity within the long range of time, while the population of natural effector-immune cells is converging to zero. Note that the values of circulation lymphocytes remain without change with respect to the time. As we discussed analytically, these behaviors show the instability of any fixed point of the system with $T = 0$.

It is clear from Figures 2-4 that the decreasing and increasing rates of T and N , respectively, are slighter while the value of α will be closer to 0.90. Comparing to the results for classical order, $\alpha = 1$ (Figure 2), we claim that these rates are more consistent with the natural reaction of the body immune

system. The main reason is the non-local property of FDE. The effect of this property to the results is clear from the discretized system (1) in recursive formulas (5) (look at the summations in the top of the fractions) on which, for the calculation of each unknown valuables in n th point, we have used all possible carrying information by the previous points from $j=1$ to $j=n-1$. Hence, the numerical results of system (5) are more accurate comparing to those found by classical ODE counterparts [4 & 17].

In the next section we will consider three cells population model, as system (1), together with the effect of chemotherapy presented by a system of FDE.

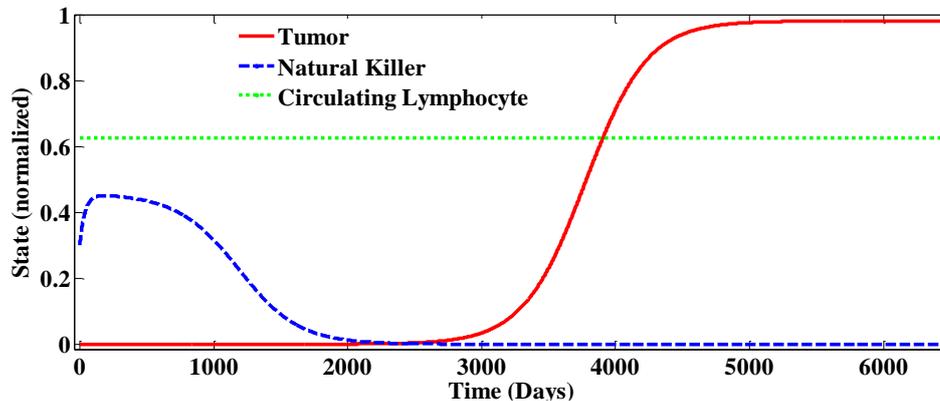


Figure 2 Normalized results (T, N and C) of numerical solutions of system (1) for positive initial values given in the text with fractional derivative order $\alpha=1$.

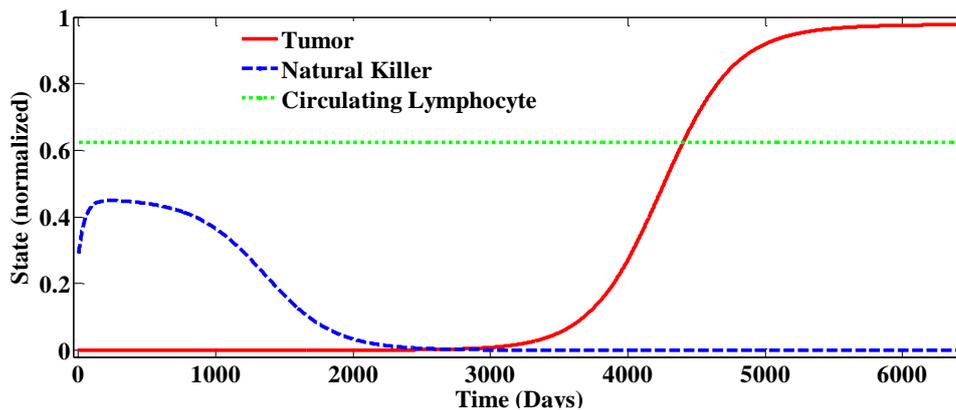


Figure 3: Normalized results (T, N and C) of numerical solutions of system (1) for positive initial values given in the text with fractional derivative order $\alpha=0.98$.

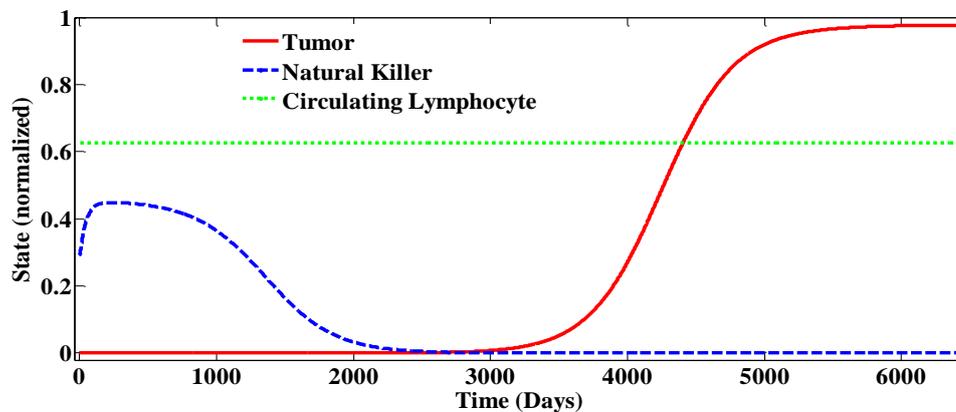


Figure 4: Normalized results (T, N and C) of numerical solutions of system (1) for positive initial values given in the text with fractional derivative order $\alpha=0.95$.

FDE Model with Chemotherapy Treatment

In this section, we consider the same system (1) with three cells population model along with a chemotherapy treatment describing the growth, death, and interactions of each cells. We can present such a system in the form of FDE as follows:

$$\begin{aligned}
 D^\alpha T &= aT(1 - bT) - c_1 NT - K_T MT, \\
 D^\alpha N &= \alpha_1 - fN + g TN/(h + T) - pNT - K_N MN, \\
 D^\alpha C &= \alpha_2 - \beta C - K_C MC, \\
 D^\alpha M &= -\gamma M + V_M.
 \end{aligned} \tag{6}$$

In this model, from the first to the third equations, the effect of chemotherapy to the three cells are shown by the terms consisting of the multiplication of each cell to the drug concentration M with the constant rates K_T , K_N and K_C , respectively. These constant rates are given in Table 1. The variation of drug concentration is shown by the fourth equation with an outside treatment source, V_M , and the term $-\gamma M$ that shows the drug decays out of the system.

To understand the dynamic of system (6), similar to the system (1), we will first find the fixed points and then analyze their stability types. Noting that the fixed points can be evaluated by replacing the left hand side of equations in system (6) to the zero, from the fourth equation we get $M = V_M / \gamma$ and from the third equation we get $C = \alpha_2 / (\beta + (K_C V_M) / \gamma)$. Combining these two we get $C = (\alpha_2 \gamma) / (\gamma \beta + K_C V_M)$. From the first equation of (6) we get $T = 0$ and $a(1 - bT) - c_1 N - K_T M = 0$. Now, by replacing $T = 0$ in the second equation we find $N = \alpha_1 / (f + K_N M)$ or $N = \alpha_1 \gamma / (\gamma f + K_N V_M)$. Hence, one of the fixed points will be $(\bar{T}, \bar{N}, \bar{C}, \bar{M}) = (0, \alpha_1 \gamma / (\gamma f + K_N V_M), \alpha_2 \gamma / (\gamma \beta + K_C V_M), V_M / \gamma)$. For analyzing the stability of this fixed point, we should find the eigenvalues of Jacobian matrix, but $DF(\bar{T}, \bar{N}, \bar{C}, \bar{M}) =$

$$\begin{bmatrix}
 -2ab\bar{T} + a - c_1\bar{N} - K_T\bar{M} & -c_1\bar{T} & 0 & -K_T\bar{T} \\
 -p\bar{N} + g\bar{N}h/(h + \bar{T})^2 & -f - p\bar{T} - K_N\bar{M} + g\bar{T}/(h + \bar{T}) & 0 & -K_N\bar{M} \\
 0 & 0 & -\beta - K_C\bar{M} & -K_C\bar{M} \\
 0 & 0 & 0 & -\gamma
 \end{bmatrix}. \tag{7}$$

Calculating the eigenvalues of this Jacobian matrix at this fixed point, we get $\lambda_1 = a - (c_1 \alpha_1 \gamma / (\gamma f + K_N V_M)) - (K_T V_M / \gamma)$, $\lambda_2 = -f - (K_N V_M / \gamma)$, $\lambda_3 = -\beta - (K_C V_M / \gamma)$ and $\lambda_4 = -\gamma$. Since all parameters exist in these eigenvalues are positive, the signs of λ_2 , λ_3 and λ_4 are negative, but the sign of λ_1 depend upon the value of V_M . We have discussed the case of no treatment, $V_M = 0$, in last section. However, for the case $V_M > 0$, for example for the value $V_M = 1$, the fixed point will be $(\bar{T}, \bar{N}, \bar{C}, \bar{M}) = (0, \alpha_1 \gamma / (\gamma f + K_N), \alpha_2 \gamma / (\gamma \beta + K_C), 1 / \gamma)$ with all negative eigenvalues. This means that if we apply the drug to the system continually, then the fixed point with $T = 0$ will remain stable. Obviously, the case $T = 0$ with the existence of positive treatment source ($V_M = 1$) cannot be an interesting case. On the other hand, evaluating the other fixed point with non-zero tumor cells population and $V_M = 1$, we will get negative values which is biologically unacceptable. So, in order to find the best values for V_M on which the tumor cell populations is decreasing down to zero, while the effector-immune and circulation lymphocyte cell populations are increasing to their possible maximum

values, we need to apply an optimal control. In this case, in next section we will apply the linear optimal control to the system (6).

Linear Optimal Control on Chemotherapy Treatment

In this optimal control, we are minimizing the value of V_M subject to the equations of system (6). That is,

$$\text{Minimizing: } J(V_M) = \int_0^\tau (T(t) + \varepsilon V_M(t)) dt, \quad (8)$$

Subject to: Four FDE in system (6).

To solve this optimization problem, first we need to clarify the existence of the solutions. To do this, we follow the same arguments that have been done by De Pillis and Radunskaya in^[17] and the results from Fleming and Rishel in^[26]. We should just note that here in system (6); we are dealing with fractional derivatives while the derivatives in the above referred articles are just the ordinary derivatives. However, in fractional derivative, since the properties that exist for $\alpha = 1$ are also satisfied for any $0 < \alpha < 1$, there is no difference between the optimal control theorems in both cases.

Now, for the existence solution of (8), first we note that the solutions are bounded with respect to the finite time. This is clear, since the following sub system of (6) has bounded solutions.

$$\begin{aligned} D^\alpha T &= aT & D^\alpha N &= \alpha_1 + gN \\ D^\alpha C &= \alpha_2 & D^\alpha M &= 1. \end{aligned}$$

Therefore, acceptable (positive) solutions of system (6) are bounded from above. Next, we state the existence solution theorem for optimal problem (8) without the proof^[18 & 26].

Theorem 1 Optimization problem (8) has a solution $\min_{V_M \in [0,1]} J(V_M) = J(V_M^*)$ in admissible control

set $U = \{V_M \text{ is piecewise continues } / 0 \leq V_M \leq 1, \forall t \in [0, \tau]\}$, with some initial value $T(0) = T_0$, $N(0) = N_0$, $C(0) = C_0$ and $M(0) = M_0$, if the following conditions are satisfied.

First, the set U should be nonempty, closed and bounded. Second, right hand side functions in system (6) are all continues, bounded above by a sum of the bounded control and the state, and can be written as a linear function of V_M with some coefficients depending on time and the state. And third, the integrand of $J(V_M)$ is convex on U and is bounded below by some linear combination of V_M^2 .

Now, we are ready to state the characterization of linear optimal control theorem, with the proof, using Pontryagin's Maximum Principle^[27].

Theorem 2 Suppose an optimal control V_M^* and the solutions of system (6) that minimize the function

$J(V_M) = \int_0^\tau (T(t) + \varepsilon V_M(t)) dt$ are given. Then there exist adjoin variables λ_i for $i = 1, 2, 3, 4$ that satisfy to the following system

$$\begin{aligned} \dot{\lambda}_1 &= \lambda_1 [2abT + c_1N + k_T M - a] + \lambda_2 [pN - g(h/(h+T)^2)N] - 1, \\ \dot{\lambda}_2 &= \lambda_1 c_1 T + \lambda_2 [f - g(T/(h+T)) + pT + k_N M], \\ \dot{\lambda}_3 &= \lambda_3 [\beta + k_C M], \\ \dot{\lambda}_4 &= \lambda_1 k_T T + \lambda_2 k_N N + \lambda_3 k_C C + \lambda_4 \gamma. \end{aligned} \quad (9)$$

Here, $\lambda_i(\tau) = 0$ for all $i = 1, 2, 3, 4$. Moreover, the optimal V_M^* is given by

$$V_M^* = \begin{cases} 0 & \text{if } \varepsilon + \lambda_4 > 0 \\ 1 & \text{if } \varepsilon + \lambda_4 < 0 \\ -\frac{P(T, N, M)}{Q(T, N)} & \text{if } \varepsilon + \lambda_4 = 0 \end{cases}$$

Where

$$Q(T, N) = K_T^2 T - \lambda_1 (K_T^2 abT^2 + c_1 K_N^2 NT) + \lambda_2 \left(\alpha_1 K_N^2 - K_T^2 NT \left(p - \frac{gh}{(h+T)^2} + \frac{2ghT}{(h+T)^3} \right) \right), \quad (10)$$

$$P(T, N, M) = \left[\lambda_1 \frac{\partial \mu_1}{\partial T} + \lambda_2 \frac{\partial \mu_2}{\partial T} + (K_T - K_N) c_1 N - K_T (a - K_T M) \right] \dot{T} + \left[\lambda_1 \frac{\partial \mu_1}{\partial N} + \lambda_2 \frac{\partial \mu_2}{\partial N} + c_1 (K_T - K_N) T \right] \dot{N} + \mu_1 \dot{\lambda}_1 + \mu_2 \dot{\lambda}_2 - \gamma Q M. \quad (11)$$

In this case, the Hamiltonian of the system is given by

$$H = T + \varepsilon V_M + \lambda_1 [aT(1 - bT) - c_1 NT - K_T MT] + \lambda_2 \left[\alpha_1 - fN + g \frac{T^\eta}{h + T^\eta} N - pNT - K_N MN \right] + \lambda_3 [\alpha_2 - \beta C - K_C MC] + \lambda_4 [-\gamma M + V_M(t)]. \quad (12)$$

The switching function in this case is $\phi = \frac{\partial H}{\partial V_M} = \varepsilon + \lambda_4$. Since there is no explicit dependence on V_M in the switching function, the possibility of singular arcs arises. The optimal control is given by

$$V_M = \begin{cases} 0 & \text{if } \varepsilon + \lambda_4 > 0 \\ 1 & \text{if } \varepsilon + \lambda_4 < 0 \\ \text{singular} & \text{if } \varepsilon + \lambda_4 = 0. \end{cases}$$

In the regions where the switching function is not zero, we have bang-bang control. In order to address the issue of singular arcs, we suppose the switching function is zero on an interval (t_1, t_2) . This implies that all the derivatives of λ_4 must vanish in that interval. We can use this fact to determine the optimal control in such regions.

For the explanation to follow, we recall that $\dot{\lambda}_3 = \lambda_3 [\beta + K_C M]$. Since $M(t) \geq 0$ and $\lambda_3(t_f) = 0$, we can conclude that $\lambda_3(t) = 0$ on the entire time interval. Setting the first three time derivatives of the switching function to zero, and using $\lambda_3 = 0$, we obtain

$$\begin{aligned} \phi' = 0 &= \lambda_1 K_T T + \lambda_2 K_N N - \gamma \varepsilon, \\ \phi'' = 0 &= \lambda_1 (K_T abT^2 + c_1 K_N NT) + \lambda_2 \left(\alpha_1 K_N - \frac{K_T ghTN}{(h+T)^2} + K_T pNT \right) - K_T T, \\ \phi''' = 0 &= \lambda_1 \mu_1 + \lambda_2 \mu_2 - (K_T T (a - c_1 N - K_T M) + c_1 K_N NT). \end{aligned} \quad (13)$$

Where

$$\mu_1(T, N, M) = T^2 [K_T ab(a - K_T M) + c_1 (p - ab)(K_T - K_N) N] + c_1 K_N T (2\alpha_1 - fN - K_N MN) - \frac{c_2 K_T ghT^2 N}{(h+T)^2} + \frac{c_2 g K_N NT^2}{h+T}. \quad (14)$$

$$\begin{aligned} \mu_2(T, N, M) &= -\frac{\alpha_1 K_N gT}{(h+T)} - \frac{ghT}{(h+T)^2} (K_T abTN + c_1 K_N N^2 + K_T \alpha_1), \\ &\quad - \frac{ghK_T N}{(h+T)^3} (h - T) (aT(1 - bT) - c_1 NT - K_T MT), \\ &\quad + c_1 pN^2 T (K_N - K_T) + \alpha_1 K_N f + \alpha_1 pT (K_N + K_T), \\ &\quad + K_T pNT (a - K_T M) + \alpha_1 K_N^2 M. \end{aligned} \quad (15)$$

From $\phi' = 0$ and $\phi'' = 0$, we can solve for λ_1 and λ_2 in terms of the state. We get

$$\lambda_1 = \frac{K_N K_T N T - \gamma \varepsilon (\alpha_1 K_N \frac{K_T g h T N}{(h+T)^2} + K_T p N T)}{K_N K_T a b T^2 N + c_1 K_N^2 N^2 T - K_T T (\alpha_1 K_N \frac{K_T g h T N}{(h+T)^2} + K_T p N T)}, \quad (16)$$

$$\lambda_2 = \frac{\gamma \varepsilon (K_T a b T^2 + c_1 K_N N T) - K_T^2 T^2}{K_N K_T a b T^2 N + c_1 K_N^2 N^2 T + K_T T (\alpha_1 K_N \frac{K_T g h T N}{(h+T)^2} + K_T p N T)}. \quad (17)$$

Now, we know all four adjoint variables in terms of the state in a singular region. To determine the control, we need to find the fourth derivative of the switching function. We then get a linear equation in V_M whose coefficients are functions of T , N and M . We see that $\phi'''' = 0 = Q(T, N)V_M + P(T, N, M)$ or

$$V_M = -\frac{P(T, N, M)}{Q(T, N)}$$

where

$$Q(T, N) = K_T^2 T - \lambda_1 (K_T^2 a b T^2 + c_1 K_N^2 N T) + \lambda_2 \left(\alpha_1 K_N^2 - K_T^2 N T \left(p - \frac{g h}{(h+T)^2} + \frac{2 g h T}{(h+T)^3} \right) \right) \quad (18)$$

$$P(T, N, M) = \left[\lambda_1 \frac{\partial \mu_1}{\partial T} + \lambda_2 \frac{\partial \mu_2}{\partial T} + (K_T - K_N) c_1 N - K_T (a - K_T M) \right] \dot{T} + \left[\lambda_1 \frac{\partial \mu_1}{\partial N} + \lambda_2 \frac{\partial \mu_2}{\partial N} + c_1 (K_T - K_N) T \right] \dot{N} + \mu_1 \dot{\lambda}_1 + \mu_2 \dot{\lambda}_2 - \gamma Q M. \quad (19)$$

Here, \dot{T} , \dot{N} , $\dot{\lambda}_1$ and $\dot{\lambda}_2$ are given by the relevant expressions for the time derivative in the state and adjoint equations and

$$\frac{\partial \mu_1}{\partial T} = 2T(K_T a b (a - K_T M) + c_1 (p - a b) (K_N - K_T) N) + c_1 K_N T (2\alpha_1 - f N - K_N M N) + c_1 g K_N N T \frac{(2h + T)}{(h + T)^2} - c_1 g h K_T N T \frac{2h}{(h+T)^3}, \quad (20)$$

$$\frac{\partial \mu_1}{\partial N} = c_1 (p - a b) (K_T - K_N) T^2 - c_1 K_N^2 M T - \frac{c_1 g h K_T T^2}{(h+T)^2} + \frac{c_1 g K_N T^2}{h+T}, \quad (21)$$

$$\frac{\partial \mu_2}{\partial T} = -\frac{g h (\alpha_1 K_N + K_T a b N T)}{(h + T)^2} + p c_1 N^2 (K_N - K_T) + p \alpha_1 (K_N + K_T) - g h (\alpha_1 K_T + c_1 K_N N^2) \frac{(h - T)}{(h + T)^3} + p K_T N (a - K_T M) - \frac{g h K_T N (a - a b T - c_1 N - K_T M) (T - 4 h T + h^2)}{(h+T)^4}, \quad (22)$$

and

$$\frac{\partial \mu_2}{\partial N} = -g h \frac{T}{(h + T)^2} (K_T a b T + 2 c_1 K_N N) + 2 c_1 p N T (K_N - K_T) + K_T p T (a - K_T M) - g h K_T \frac{T(h-T)}{(h+T)^3} (a(1 - bT) - 2 c_1 N - K_T M). \quad (23)$$

Since, we know λ_1 and λ_2 in terms of the state variables T and N , we know Q purely in terms of T and N . For the singular control to be minimizing the Generalized Legendre Clebsch condition needs to be satisfied, that is $Q(T, N)$ would have to be non-negative on this interval [4]. The results are shown in Figure 5. Note that $Q(T, N)$ is only negative in a very specific region. In this region, we can guarantee that there are no singular minimizing arcs, so the control is bang-bang. In other regions, the potential for singular arcs has not been ruled out, but in fact arises in most practical situations, since most of the T - N plane meets the criterion $Q(T, N) \geq 0$ [4].

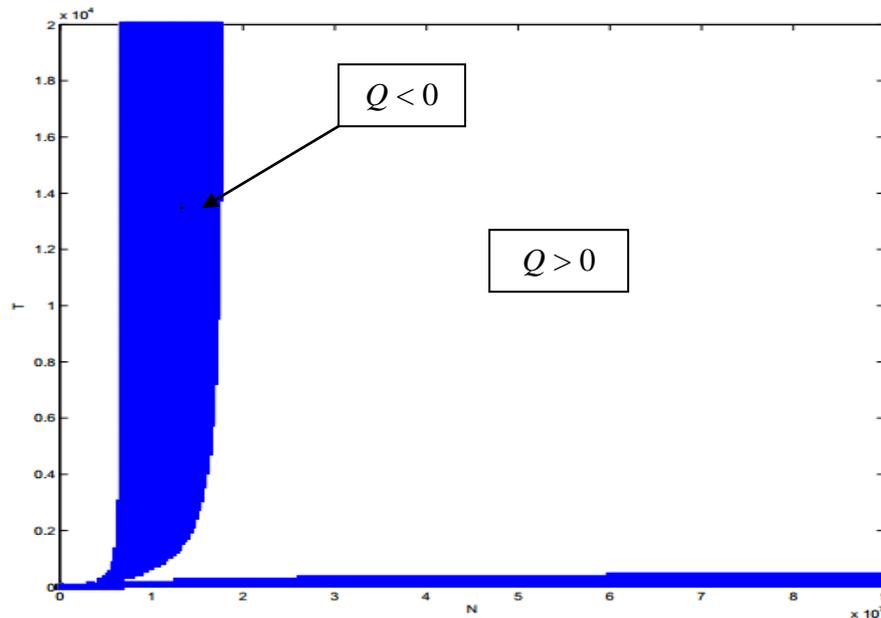


Figure 5: Plot of $Q(T,N)$. Here, Q is denoted by Q Min the graphic. Q is negative in the shaded region. This says that the singular control is minimizing in the un-shaded regions.

In writing system (9) we may consider the columns of Jacobian matrix (7). Now for solving optimization problem (8), we should first solve system (9) with some values of T, N, C and M . Here, to be consistent with other results in [4 & 17], we start with $T = 10^7, N = 3 \times 10^5, C = 6.25 \times 10^{10}$ and $M = 0$. Then, by finding the value V_M^* and plugging into the system (6), instead of V_M , we are ready to solve this system with the same starting point T, N, C and M as above. The similar discretization method that we have done for FDE system (1) can be applied here for system (6) to get

$$\begin{aligned}
 \sum_{j=0}^n c_j^\alpha T_{n-j} &= aT_n(1-bT_n) - c_1N_nT_n - K_T M_n T_n, \\
 \sum_{j=0}^n c_j^\alpha N_{n-j} &= \alpha_1 - fN_n + gT_n N_n(h+T_n) - pN_n T_n - K_N M_n N_n, \\
 \sum_{j=0}^n c_j^\alpha M_{n-j} &= \alpha_2 - \beta C_n - K_C M_n C_n, \\
 \sum_{j=0}^n c_j^\alpha M_{n-j} &= -\gamma M_n + V_M(t).
 \end{aligned}
 \tag{24}$$

Now, by simple calculation on (24), we get the following recursive formula.

$$\begin{aligned}
 T_n &= \sum_{j=1}^n c_j^\alpha T_{n-j} / \left(a(1-bT_n) - c_1N_n - K_T M_n - c_0^\alpha \right), \\
 N_n &= \left(\alpha_1 - \sum_{j=1}^n c_j^\alpha N_{n-j} \right) / \left(f + gT_n / (h+T_n) - pT_n - K_N M_n + c_0^\alpha \right), \\
 C_n &= \left(\alpha_2 - \sum_{j=1}^n c_j^\alpha C_{n-j} \right) / \left(\beta - K_C M_n + c_0^\alpha \right), \\
 M_n &= \left(V_M - \sum_{j=1}^n c_j^\alpha M_{n-j} \right) / \left(\gamma + c_0^\alpha \right).
 \end{aligned}
 \tag{25}$$

By solving this system for some customary time, say $t \in [0, 9]$, we arrive at the new point with a new set of values T, N, C and M . Then, this new set of values will serve as a new starting point with initial values $\lambda_i = 0$ for all $i = 1, 2, 3, 4$ for solving system (9), in the next iteration, to find a new optimal value

of V_M^* . These iterations will continue up to the time $t = 100$ (days). Indeed, using MATLAB™ to solve these two joint systems (9 and 11), as the solution of optimal problem (8), the results are illustrated in Figures 6-11 for different values of fractional derivative $0.90 < \alpha \leq 1$. Figure 6 represents the results for $\alpha = 1$. In this figure, the results are in complete agreement with those found by using the classical systems of ODE counterparts [4 & 17]. However, in Figures 7 and 8 the results for the values $0.90 < \alpha < 1$ are somehow different from Figure 6. We claim that these results are in more agreement with the nature of the chemotherapy treatment. The amount of the medicine that has been used in each period of time (each 9 days) is completely visible at the starting iterations, and shows a oscillatory pattern that is converging to zero in a long range of time. Almost the same pattern can be seen for the tumor cell populations. This oscillatory pattern is more visible in Figures 10 and 11, and also shows the amount of controlled medicine in each period of time (each 9 days) for $\alpha = 0.98$ and 0.95, respectively. On the other hand, in Figure 9 which demonstrates evaluated optimal values of V_M^* for $\alpha = 1$ in different periods of time, no such oscillatory pattern can be seen. We can have similar discussion for decreasing pattern of natural effector-immune and circulation lymphocyte cell populations in Figures 6-8. We emphasize that the reason for the accuracy of FDE is the non-local property of these equations. This means that the next state of a system not only depends upon its current state but also upon its historical states starting from the initial time. To see this, pay attention to the summation terms in the right hand side of system (25).

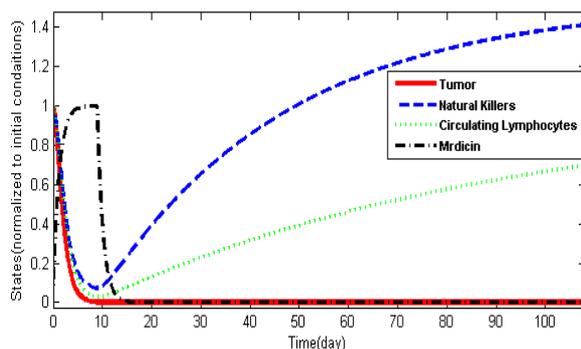


Figure 6 Normalized results (T, N, C and M) of numerical solutions of optimization problem (8) for fractional order derivative $\alpha = 1$.

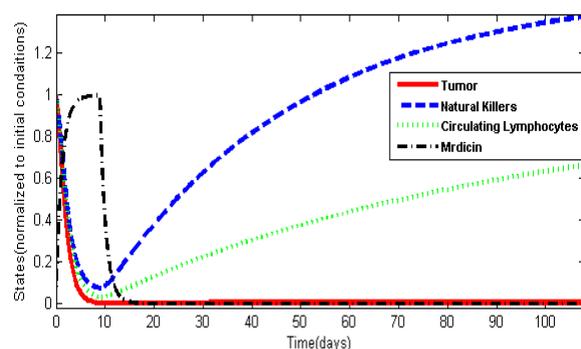


Figure 7 Normalized results (T, N, C and M) of numerical solutions of optimization problem (8) for fractional order derivative $\alpha = 0.98$.

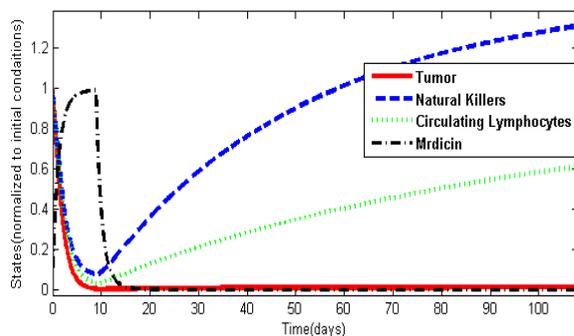


Figure 8 Normalized results (T, N, C and M) of numerical solutions of optimization problem (8) for fractional order derivative $\alpha = 0.95$.

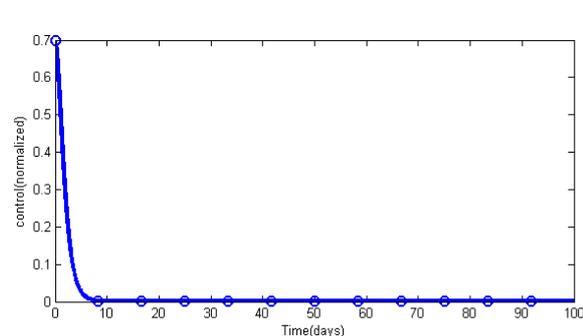


Figure 9 Normalized results of controlled medicine V_M^* found by numerical solutions of system (9) for each time period (each 9 days) related to the fractional order derivative $\alpha = 1$.

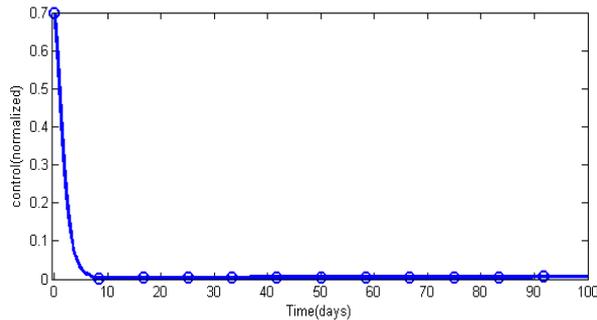


Figure 10 Normalized results of controlled medicine V_M^* found by numerical solutions of system (9) for each time period (each 9 days) related to the fractional order derivative $\alpha = 0.98$.

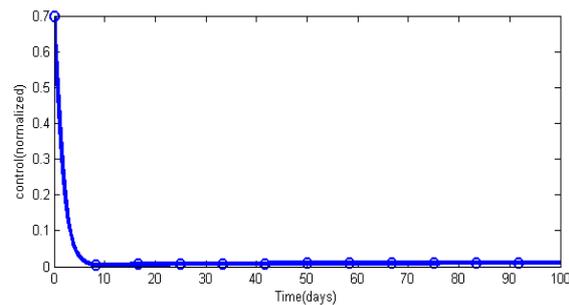


Figure 11 Normalized results of controlled medicine V_M^* found by numerical solutions of system (9) for each time period (each 9 days) related to the fractional order derivative $\alpha = 0.95$.

CONCLUSION

In this article, we introduced a three cells population model describing the interaction between the tumor and the effector-immune cells together with the circulation lymphocyte population, without any treatment, in the form of FDE. As we have seen, the local stability analyses of the fixed points for this FDE system were the same as its counterpart ODE system. These analyses were agreed with numerical results of discretized FDE system using Grünwald-Letnikov method. As we have expected the tumor cell population were increasing up to its maximum values by any positive initial value. Hence, a more reliable FDE system with chemotherapy treatment was considered. In order to find the best amount of medicine on which the tumor cell population is decreasing, while other two variables, the effector-immune cells and circulation lymphocyte population are increasing, we conducted a linear optimal control. We could adapt the same existence and characteristic optimal control theorems as in ODE systems for our FDE system. We claim that due to the non-local property of FDE, the results found by this system were more accurate as we compare to the results found by counterpart ODE models. We also claimed that the results would be more accurate when we use the lower value of α in the interval $(0.9, 1]$. However, we should note that by choosing any smaller values α , we will encounter a larger amount of errors in calculations. In these two FDE systems that we have introduced here, experimentally, we have found that the best value of α for the best results is 0.95.

REFERENCES

1. A Matveev, A Savkin. Application of optimal control theory to analysis of cancer chemotherapy regimens. *Systems and Control Lett.* 2002;46:311–321.
2. KR Fister, JC Panetta. Optimal control applied to competing chemotherapeutic cell-kill strategies. *SIAM J Appl Math.* 2003;63(6):1954–1971.
3. DG Mallet, LG De Pillis. A cellular automata model of tumor-immune system interactions. *J Theoretical Biol.* 2006;239:334–350
4. LG de Pillis, W Gu, KR Fister, T Head, K Maples, T Neal, A Murugan, K Yoshida. Chemotherapy for tumors: An analysis of the dynamics and a study of linear and linear optimal controls, *Mathematical Biosci.* 2006;S0025-5564:83-86.
5. D Peixoto. Modelling hematopoiesis in health and disease. *Mathematical and Computer Modelling*, Accepted 21 April 2010.
6. H Enderling, MAJ Chaplain, ARA Anderson, JS Vaidya. A mathematical model of breast cancer development, local treatment and recurrence. *J Theor Biol.* 2007;246:245–259.
7. E Bavafaye-Haghighi, MJ Yazdanpanah, B Kalaghchi, and H Soltanian-Zadeh. Multiscale cancer modeling: In the line of fast simulation and chemotherapy. *Mathematical and Computer Modelling.* 2009;49:1449-1464.
8. H Enderling, ARA Anderson, MAJ Chaplain, AJ Munro and JS Vaidya. Mathematical modelling of radiotherapy strategies for early breast cancer. *J Theoretical Biol.* 2006;241:158–171.
9. JP Whiteley, DJ Gavaghan. Non-linear modeling of breast tissue. *Mathematical Med Biol.* 2007;24:327–345.

10. DD Dionysiou, GS Stamatakos, NK Uzunoglu, SN Konstantina, A Marioli. A four-dimensional simulation model of tumor response to radiotherapy in vivo: parametric validation considering radiosensitivity, genetic profile and fractionation. *J Theor Biol.* 2004;230:1–20.
11. CE Kelly, RD Leek, HM Byrne, SM Cox, Harris AL, CE Lewis. Modelling macrophage infiltration into a vascular tumours. *J Theor Med.* 2002;4:21–38.
12. SD Webb, JA Sherratt, RG Fish. Cells behaving badly: a theoretical model for the Fas/FasL system in tumour immunology. *Math Biosci.* 2002;179:113–129.
13. F Castiglione, B Piccoli. Cancer immunotherapy, mathematical modeling and optimal control. *J Theoretical Biol.* 2007;247:723–732.
14. Z Szymanska. Analysis of immunotherapy models in the context of cancer dynamics. *Int J App Math Comput Sci.* 2003;13(3):407–418.
15. U Ledzewicz, T Brown, H Schattler. Comparison of optimal controls for a model in cancer chemotherapy with I1 and I2 type objectives. *Optimization Methods and Software.* 2004;19(3-4):339–350.
16. U Ledzewicz, H Schattler. Drug resistance in cancer chemotherapy as an optimal control problem. *Discrete and Continuous Dynamical Systems Series B.* 2006;6(1):129–150.
17. LG de Pillis, AE Radunskaya. A mathematical tumor model with immune resistance and drug therapy: an optimal control approach. *J Theor Med.* 2001;3:79–100.
18. LG de Pillis, AE Radunskaya. The dynamics of an optimally controlled tumor model: A case study. *Mathematical and Computer Modelling.* 2003;37(11):1221–1244.
19. A Matzavinos, MAJ Chaplain, VA Kuznetsov. Mathematical modelling of the spatio-temporal response of cytotoxic T-lymphocytes to a solid tumour. *Mathematical Med Biol.* 2004;21:1–34.
20. A Matzavinos, MAJ Chaplain. Mathematical Modelling of Spatio-temporal Phenomena in Tumour Immunology. *Tutorial Mathematical Biosci.* 2006;111:131-183.
21. VA Kuznetsov, GD Knott. Modeling tumor re-growth and immunotherapy, *Math Compute Modelling.* 2001;33:1275–1287.
22. Einstein A. Mount Sinai School of Medicine, Annual Publication of the American Institute of Physics; 1998.
23. I Podlubny. *Fractional differential equations*, New York: Academic Press; 1999.
24. KB Oldham, J Spanier. *The fractional calculus*, New York: Academic Press; 1974.
25. VA Kuznetsov. A mathematical model for the interaction between cytotoxic lymphocytes and tumor cells, Analysis of the growth, stabilization and regression of the B cell lymphoma in mice chimeric with respect to the major histocompatibility complex, *Biomed. Sci.*, 1991;2:465–476.
26. Wendell H. Fleming and Raymond W. Rishel, *Deterministic and Stochastic Optimal Control.* Springer-Verlag; 1975.
27. L Pontryagin, VG Boltyanskii, RV Gamkrelidze, EF Mishchenko. *The Mathematical Theory of Optimal Processes*, Gordon and Breach; 1962.