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Research paper

Dynamical behaviour of fractional order tumor-immune model with targeted chemotherapy treatment

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Abstract

In this study, we discussed the fractional order model of tumor-immune system based on Liu's model. We examine the dynamic behaviour of tumor growth and investigate the conditions of tumor removal mathematically. We discussed qualitative analysis on the mathematical model and defined the existence and uniqueness conditions. Local stability is also checked for tumor-free equilibrium point. We give facts about that tumor growth rate, source rate of immune cells, and death rate of immune cells play vital role in tumor dynamics. Numerical simulations are demonstrated to reveal the analytical results.

Keywords: *Caputo derivative; Fractional differential equation; Stability; Tumor-immune model.*

1. Introduction

The system of ordinary differential equations occurring in mechanics, physics, engineering, biological sciences, economics, and many more fields of sciences may be classified into either linear or nonlinear formulated as initial or boundary value problems. The nonlinear systems of equation are more difficult to obtain a exact or analytical solution. At present, there exist several theoretical and experimental problems in mechanical engineering which are still unsolved.

As part of the natural process of the body, the cells are replaced by a process of continuous division and growth. Once any type of cancer occurs, cells reproduce in an arbitrary manner. Then, chemotherapy interferes with the ability to divide and reproduce a cancer cell. Literature shows that mechanical advances can momentarily reduce the free light-chain load, and without effective chemotherapy i.e., targeted chemotherapy they are probably not able to significantly improve the system. On the other hand, the responsibility of mechanical approaches collectively with targeted chemotherapy is still being discovered.

In the real world, tumor is one of the major infectious diseases which affect the public health system. Primary tumor growth is a complex process, involving many interactions between the tumors and surrounding tissues. Literature of tumor treatment shows that the treatments traditionally used to fight against tumor are surgery, radiotherapy and chemotherapy. Unfortunately, these treatments kill normal cells as well as tumor cells. Afterward, immunotherapy is introduced [1-3]. It is based on the generally-accepted hypothesis that the immune system is the best tool humans have for fighting disease [3].

The fractional derivative has been widely applied in many research areas which have been perceived an enormous growth in the last four decades. For examples, the models approaching the backgrounds of economics, physics, circuits, heat transfer, diffusion, electro-chemistry, and even biology are always apprehensive with fractional derivative [4-7]. In fact, fractional derivative based approaches establish more advanced and updated models of engineering systems than the ordinary derivative-based approaches do in many applications. The theories of fractional derivatives generalize the idea of ordinary derivatives to some extent. The literature shows that there is no field that has remained untouched by fractional derivatives.

In this part of the manuscript, we develop a fractional order mathematical model of tumor-immune system with targeted chemotherapy [8]. Basically, the mathematical model is based on interactions between tumor cells (T), effector cells (N), circulating lymphocytes (C), which is presented with the help of Caputo derivative by the following system of nonlinear ordinary differential equations,

$$ {}_{0}^{C}D_{t}^{\alpha}T = rT\left(1-\frac{T}{K}\right) - E_{k}NT - C_{k}MT \tag{1a} $$

$$ {}_{0}^{C}D_{t}^{\alpha}N = s_{1} + M_{T}\left(\frac{T}{s+T}\right)N - d_{E}N - E_{I}TN - C_{E}(1-\varepsilon)MN \tag{1b} $$

$$ {}_{0}^{C}D_{t}^{\alpha}C = s_{2} - d_{c}C - C_{c}(1-\varepsilon)MC \tag{1c} $$

$$ {}_{0}^{C}D_{t}^{\alpha}M = T_{M} - d_{d}M - \alpha TM \tag{1d} $$

$$ \text{with } T(0)=T_{0},\ N(0)=N_{0},\ C(0)=C_{0} \text{ and } M(0)=M_{0}. \tag{2} $$

Where, M is the concentration of chemotherapeutics drugs in tissue. r is the tumor growth rate, K is the tumor carrying capacity, E_K is the fractional tumor cells killed by effector cells, C_K is the fractional tumor cells killed by targeted chemotherapy, s_1 is the constant source of effector cells, M_T is the maximum effector cells recruitment rate by tumor cells, s is the steepness coefficient of the effector cells recruitment, d_E is the death rate of effector cells, E_I is the effector cells inactivation rate by tumor cells, C_E is the fractional effector cells killed by targeted chemotherapy, s_2 is the

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constant source of circulating lymphocyte cells, d_c is the death rate of circulating lymphocyte cells, C_c is the fractional circulating lymphocyte cells killed by targeted chemotherapy, ε is the efficacy of targeted chemotherapy, d_d is the decay rate of chemotherapy, T_M is the chemotherapy treatment, α is the grouping rate of chemotherapy drug with tumor cells.

2. Analysis of the model

2.1. Non-negativity and boundedness of populations

To establish the key theorem of non-negativity, first we assume $x(t)=[T(t), N(t), C(t), M(t)]^T$, and $\Re_+^4=\{x\in\Re^4 : x\geq 0\}$. We also require the following generalized mean value theorem and corollary [4, 8].

Theorem 1 ([4]). *Suppose that* $f(x)\in C[a,b]$ *and Caputo derivative* ${}_a^C D_t^\alpha f(x)\in C(a,b]$ *for* $a<\alpha\leq a+1$, *then we have*

$$f(x)=f(a)+\frac{1}{\Gamma(\alpha)}\left({}_a^C D_t^\alpha f\right)(\tau)(x-a)^\alpha \qquad (3)$$

with $a\leq\tau\leq x$, $\forall x\in(a,b]$.

Corollary 1. *Let* $f(x)\in C[a,b]$ *and* ${}_0^C D_t^\alpha f(x)\in C(a,b]$ *for* $0<\alpha\leq 1$.

- *If* ${}_0^C D_t^\alpha f(x)\geq 0$, $\forall x\in(a,b)$, *then* $f(x)$ *is increasing function for each* $x\in[a,b]$.
- *If* ${}_0^C D_t^\alpha f(x)\leq 0$, $\forall x\in(a,b)$, *then* $f(x)$ *is decreasing function for each* $x\in[a,b]$.

Theorem 2. *The solution of system (1) will be unique and in* $\Re_+^4$, *if the initial condition (2) are non-negative on* $t\geq 0$. *Additionally, they are bounded.*

Proof. In 2007, Lin [9] discussed the solution of general system of fractional order ordinary differential equation in Theorem 2.2, which shows that the solution of system (1) always be unique. Consequently, we have to simplify the nonnegative $\Re_+^4$ is a positively invariant region. From system (1), we get

${}_0^C D_t^\alpha T=rT\left(1-\frac{T}{K}\right)\geq 0$,

and ${}_0^C D_t^\alpha N=s_1>0$, ${}_0^C D_t^\alpha C=s_2>0$, ${}_0^C D_t^\alpha M=T_M>0$. (4)

By Corollary 1, the solution of model (1) will be remain in $\Re_+^4$. Moreover, from system (1), we can write

$${}_0^C D_t^\alpha T=rT\left(1-\frac{T}{K}\right)-E_kNT-C_kMT,$$

Therefore,

$${}_0^C D_t^\alpha T-rT\left(1-\frac{T}{K}\right)<0. \qquad (5)$$

Thus, by Corollary 1, the tumor cell population (T) is decreases with increase of time. Similarly, we can define the remaining populations are tending to constants or zero with increase of time. Hence, all the populations are bounded.

2.2. Equilibrium points

To evaluate the equilibrium points of model (1), let
${}_0^C D_t^\alpha T=0$, ${}_0^C D_t^\alpha N=0$, ${}_0^C D_t^\alpha C=0$, ${}_0^C D_t^\alpha M=0$.

By easy calculation, we can determine two types of equilibrium solution:
(I) Tumor free equilibrium point:

$$E_0=(T_0,N_0,C_0,M_0)$$

$$E_0=\left(0,\frac{s_1 d_d}{d_d d_E+C_E(1-\varepsilon)T_M},\frac{s_2 d_d}{d_d d_c+C_c(1-\varepsilon)T_m},\frac{T_M}{d_d}\right) \qquad (6)$$

(II) Coexisting equilibrium point:

$$E^*=(T^*,N^*,C^*,M^*),$$

where, $N^*=\left[\frac{\frac{r}{k}(d_d+\alpha T^*)(k-T^*)-C_KT_M}{E_K(d_d+\alpha T^*)}\right]$, $C^*=\frac{s_2(d_d+\alpha T^*)}{d_c(d_d+\alpha T^*)+C_c(1-\varepsilon)T_M}$,

$M^*=\frac{T_M}{(d_d+\alpha T^*)}$, and T^* is determined by the equation

$$F(T^*)=s_1+\frac{M_T T^*}{(s+T^*)}\left[\frac{\frac{r}{k}(d_d+\alpha T^*)(k-T^*)-C_KT_M}{E_K(d_d+\alpha T^*)}\right]-d_E\left[\frac{\frac{r}{k}(d_d+\alpha T^*)(k-T^*)-C_KT_M}{E_K(d_d+\alpha T^*)}\right]$$
$$-E_IT^*\left[\frac{\frac{r}{k}(d_d+\alpha T^*)(k-T^*)-C_KT_M}{E_K(d_d+\alpha T^*)}\right]$$
$$-\frac{C_E(1-\varepsilon)T_M}{(d_d+\alpha T^*)}\left[\frac{\frac{r}{k}(d_d+\alpha T^*)(k-T^*)-C_KT_M}{E_K(d_d+\alpha T^*)}\right]=0 \qquad (7)$$

2.3. Stability of the tumor-free equilibrium solution

Now, we discuss the stability of the tumor free equilibrium point. Many researchers studied the Routh–Hurwitz stability criteria for fractional order systems [7-10], and describe the necessary and sufficient condition $|\arg(\lambda_i)|>\alpha\frac{\pi}{2}$, for various models.

Theorem 3. *The tumor free equilibrium solution (*E_0*) is locally asymptotically stable if all eigenvalues* λ_i *of the Jacobian matrix* $J(E_0)$ *for model (1), satisfy* $|\arg(\lambda_i)|>\alpha\frac{\pi}{2}$, *whenever* $r<(E_KN_0+C_KM_0)$.

Proof. To locate the stability at E_0, first we determine the Jacobian matrix of the model (1),

$$J(E_0)=\begin{pmatrix} r-E_KN_0-C_KM_0 & 0 & 0 & 0 \\ \frac{M_T}{s}N_0-E_IN_0 & -d_E-C_E(1-\varepsilon)M_0 & 0 & -C_E(1-\varepsilon)N_0 \\ 0 & 0 & -d_c-C_c(1-\varepsilon)M_0 & -C_c(1-\varepsilon)C_0 \\ -\alpha M_0 & 0 & 0 & -d_d \end{pmatrix}. \qquad (8)$$

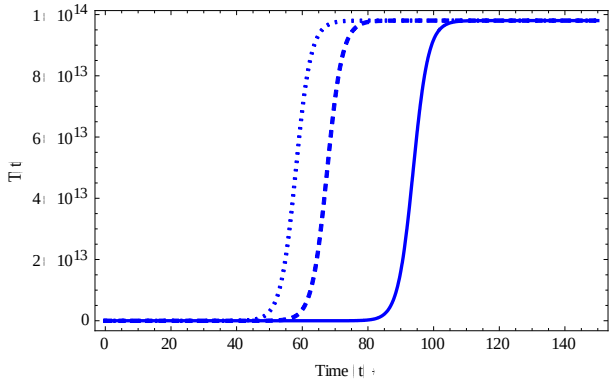
Next, we calculate the characteristic polynomial of $J(E_0)$ to get

$$P(\lambda)\equiv(\lambda-r+E_KN_0+C_KM_0)(\lambda+d_E+C_E(1-\varepsilon)M_0)$$
$$(\lambda+d_c+C_c(1-\varepsilon)M_0)(\lambda+d_d)=0.$$

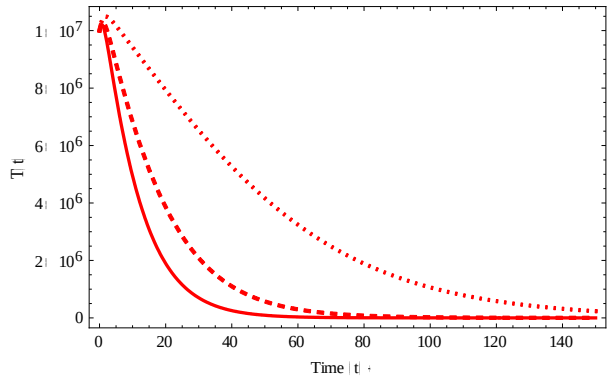
Consequently, the characteristic polynomial illustrate that all eigenvalues of model (1) at E_0 are $(r-E_KN_0-C_KM_0)$, $(-d_E-C_E(1-\varepsilon)M_0)$, $(-d_c-C_c(1-\varepsilon)M_0)$ and $-d_d$. As we know all the parameter values are positive and efficacy of the targeted chemotherapy is $0\leq\varepsilon\leq 1$. Therefore, all four eigenvalues are always negative if and only if $r<(E_KN_0+C_KM_0)$, in that case the equilibrium point is locally asymptotically stable.
According to Routh-Hurwitz criteria, the all roots of the characteristic equation have negative real parts if and only if $|\arg(\lambda_i)|>\alpha\frac{\pi}{2}$, which shows the necessary and sufficient condition for tumor free equilibrium solution.

3. Numerical Simulation

In this part, we define the numerical simulation to confirm the analytic results achieved in the last segment. Initially, we have collected all the parameter values from Liu et al. [8].



(a)



(b)

Fig. 1: Simulation of system (1): Plot of tumor cells vs. time for various value of chemotherapy treatment (T_M), **(a). Blue** - Dotted ($T_M = 0.40$), Dashed ($T_M = 0.44$), Straight ($T_M = 0.48$), **(b). Red** - Dotted ($T_M = 0.52$), Dashed ($T_M = 0.56$), Straight ($T_M = 0.60$), with initial values $T(0) = 10^7$, $N(0) = 3\times10^5$, $C(0) = 6.25\times10^{10}$ and $M(0) = 0.45$.

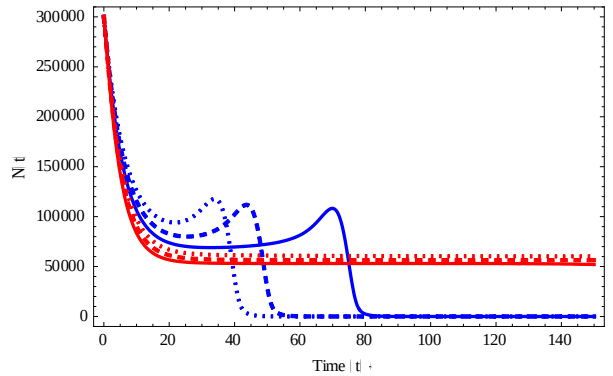


Fig. 2: Simulation of system (1): Plot of Effector immune cells vs. time for various value of chemotherapy treatment (T_M), Blue Dotted ($T_M = 0.40$), Blue Dashed ($T_M = 0.44$), Blue Straight ($T_M = 0.48$), Red Dotted ($T_M = 0.52$), Red Dashed ($T_M = 0.56$), Red Straight ($T_M = 0.60$), with initial values $T(0) = 10^7$, $N(0) = 3\times10^5$, $C(0) = 6.25\times10^{10}$ and $M(0) = 0.45$.

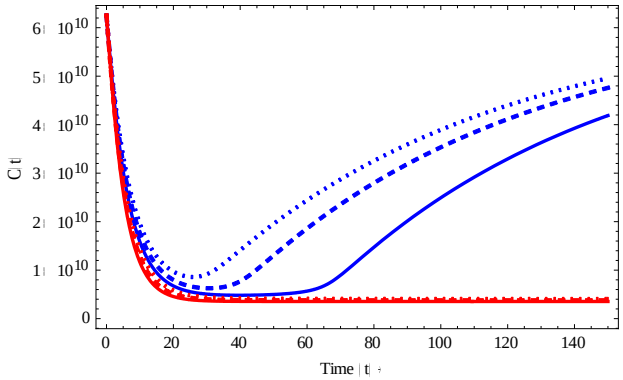


Fig. 3: Simulation of system (1): Plot of Circulating lymphocyte cells vs. time for various value of chemotherapy treatment (T_M), Blue Dotted ($T_M = 0.40$), Blue Dashed ($T_M = 0.44$), Blue Straight ($T_M = 0.48$), Red Dotted ($T_M = 0.52$), Red Dashed ($T_M = 0.56$), Red Straight ($T_M = 0.60$), with initial values $T(0) = 10^7$, $N(0) = 3\times10^5$, $C(0) = 6.25\times10^{10}$ and $M(0) = 0.45$.

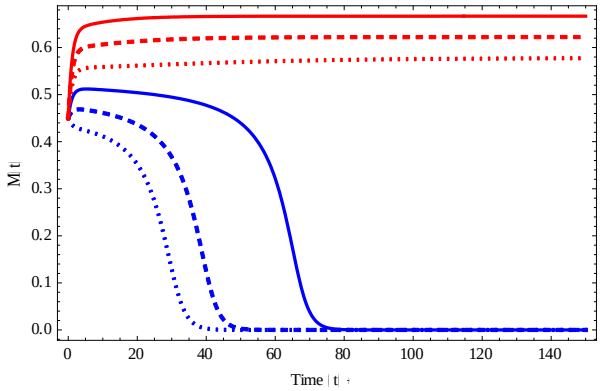


Fig. 4: Simulation of system (1): Plot of concentration of chemotherapy drugs in tissue vs. time for various value of chemotherapy treatment (T_M), Blue Dotted ($T_M = 0.40$), Blue Dashed ($T_M = 0.44$), Blue Straight ($T_M = 0.48$), Red Dotted ($T_M = 0.52$), Red Dashed ($T_M = 0.56$), Red Straight ($T_M = 0.60$), with initial values $T(0) = 10^7$, $N(0) = 3\times10^5$, $C(0) = 6.25\times10^{10}$ and $M(0) = 0.45$.

For model (1), we have taken $r = 0.431\,\text{day}^{-1}$, $K = 9.80\times10^{13}$ cells, $E_K = 3.41\times10^{-10}$ cells^{-1}day^{-1}, $C_K = 0.80\,\text{day}^{-1}$, $M_T = 1.50\times10^{-2}\,\text{day}^{-1}$, $s_1 = 1.20\times10^4$ cells day^{-1}, $d_E = 4.12\times10^{-2}\,\text{day}^{-1}$, $C_E = 0.60\,\text{day}^{-1}$, $E_1 = 2.00\times10^{-11}$ cells^{-1}day^{-1}, $C_c = 0.60\,\text{day}^{-1}$, $d_c = 1.20\times10^{-2}\,\text{day}^{-1}$, $s_2 = 7.50\times10^8$ cells day^{-1}, $d_d = 0.9\,\text{day}^{-1}$ and $\alpha = 3.20\times10^{-9}\,\text{day}^{-1}$. And, the chemotherapy treatment parameter is taken as $0 \le T_M \le 1$ and efficacy of chemotherapy is $0 \le \varepsilon \le 1$.

4. Conclusion

In this article, we establish a system of Caputo sense fractional order mathematical model of tumor-immune system with targeted chemotherapy. The author explained the non-negative solutions and boundedness as an essential part of any population dynamics model. The authors have defined all the equilibrium points for the proposed model. By using stability analysis on an anticipated fractional order system, we obtained a sufficient condition on the parameters for the stability of the tumor free equilibrium solution. The numerical simulations have performed for various values of chemotherapy treatment (T_M).

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