GRÜNWALD-LETNIKOV SCHEME FOR SYSTEM OF CHRONIC MYELOGENOUS LEUKEMIA FRACTIONAL DIFFERENTIAL EQUATIONS AND ITS OPTIMAL CONTROL OF DRUG TREATMENT

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Abstract. In this article, a mathematical model describing the growth or terminating myelogenous leukemia blood cancer's cells against naive T-cell and effective T-cell population of body, presented by fractional differential equations. We use this model to analyze the stability of the dynamics, which occur in the local interaction of effector-immune cell and tumor cells. We will also investigate the optimal control of combined chemo-immunotherapy. We claim that our fractional differential equations model is 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.

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1. Introduction

Chronic myelogenous leukemia (CML) is a kind of blood cancer and occurs in adults about 15 percent [1]. The age average for blood cancer patients ranges between 45-55 years old. The occurrence rate is one or three among per 100,000 individuals [1]. In this field, researchers such as Fokas [2] and Adimy [3] have presented CML models in 1991 and 2005, respectively. A mathematical model has also presented by Afenya and Bentil in 1998 [4] for blood cancer. Recently, the models used for analyzing the cancer reaction against drug therapy could assist physicians in cancer treatment. Therefore, using optimized control methods, which minimized damages to body, the drug dose can be optimized. In this article, the ordinary differential equations (ODE) which presented by Moore and Li for brain blood cancer [5] is re-derived by using fractional order equations (FDE). We expect that our FDE model will be superior to its ODE 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. Therefore, in this article, at first we will introduce a FDE model to present the interaction between naive T cells, effectors T cells, and CML cancer cells in cancer dormancy and then we will discuss about the dynamic behavior of the first system and determine the stability type of the various feasible fixed points. For drug optimality, as similar to the targeted therapy (such as imatinib) and broad cytotoxic therapy (such as cytarabine) methods used by Moore and Li [5], we implement the processors in our FDE model. To find the solutions of this FDE system, we discretize the system by using Grunwald-Letnikov discretization method [6, 7], then the results will be obtain by software tools such as MATLAB^{TM}. As is said, we expect more accurate results in solving FDE systems in comparison with the results by classical ODE counterpart.

2. PRELIMINARIES

In this section, the ODE presented by Moore and Li for brain blood cancer (CML) [5] is explained by using FDE. Therefore, we consider the following system with three cells populations along with a chemotherapy treatment describing the

growth, death and interactions of each cells;

$$
\begin{aligned}
&D_t^{\alpha} T_n = s_n - u_2(t) d_n T_n - k_n T_n \left(\frac{C}{C+\eta} \right), \\
&D_t^{\alpha} T_e = \alpha_n k_n T_n \left(\frac{C}{C+\eta} \right) + \alpha_e T_e \left(\frac{C}{C+\eta} \right) - u_2(t) d_e T_e - \gamma_e C T_e, \\
&D_t^{\alpha} C = (1 - u_1(t)) r_c C ln \left(\frac{C_{max}}{C} \right) - u_2(t) d_c C - \gamma_c C T_e.
\end{aligned} \tag{1}
$$

In this system $T_n(0)$, $T_e(0)$ and $C(0)$ are known initial values and time dependent drug efficacies which incorporated by u_1(t) and u_2(t). All of the parameter values in the above equations are assumed to be positive. The structure of the equations guarantees non negative solutions for the state variables, T_n(t), T_e(t) and C(t). The effect of the targeted drug represents by the control function $u_1(t)$, which shows the production of cancer cells. We assume this drug affects only cancer cells and not the other cells, so $u_1(t)$ appears only in the first equation. The $u_2(t)$ term uses to incorporate treatment by a broad chemotherapy, such as cytarabine or hydroxyurea or a combination of such drugs, which is cytotoxic to all three-cell populations. The negative terms in the above equations represent losses from the cell populations while the positive terms are source terms for the cell populations [8]. In our model with controls, we let $C(t)$ denote the cancer cell population, T_n(t) the naive T cell population and T_e(t) the effector T cell population at time t. In the first equation of system (1), the populations of naive T-Cell cells are generated with a constant factor s_n, while the cells death is proportional to $-d_n T_n$ and Michaelis-Menten term $k_n \left(\frac{C}{C+\eta} \right)$. In the two equation of this system, the effective cells are constructed by using Michaelis-Menten term, while the cells death is proportional to $-d_e T_e$ and$-\gamma_e C T_e$. In the three equation, the populations of C cells are generated with $r_c ln \left(\frac{C_{max}}{C} \right)$. While the cells death is proportional to $-d_c C$ and $-\gamma_c T_e$. The lower case parameters (s_n, α_n, etc.) in the above equations are all constants, as is C_{max}. Definitions for these parameters appear in Table 1. Setting $u_1(t) \equiv 0$ and $u_2(t) \equiv 1$ in the above equations would give the same model described for the dynamics of the disease without treatment [5]. Therefore, we can

present our model in the form of FDE as follows.

$$
\begin{aligned}
&D_t^{\alpha} T_n = s_n - d_n T_n - k_n T_n \left(\frac{C}{C+\eta}\right),\\
&D_t^{\alpha} T_e = \alpha_n k_n T_n \left(\frac{C}{C+\eta}\right) + \alpha_e T_e \left(\frac{C}{C+\eta}\right) - d_e T_e - \gamma_e C T_e,\\
&D_t^{\alpha} C = r_c C ln \left(\frac{C_{max}}{C}\right) - d_c C - \gamma_c C T_e.
\end{aligned} \tag{2}
$$

Firstly, we find the fixed points for system (2) and then their stability should be analyzed. Here, we use the same values for the parameters as in [5] and is appear in Table 1. To determine the dynamical behavior of the cell populations near the

TABLE 1. Parameter Estimated Values for Patient A and B.

Parameters	$\mathbf{s_n}$	$\mathbf{d_n}$	$\mathbf{d_e}$	$\mathbf{d_c}$	$\mathbf{k_n}$	η	$\alpha_{\mathbf{n}}$	$\alpha_{\mathbf{e}}$	$\mathbf{C}_{\mathbf{m}ax}$	$\mathbf{r_c}$	$\gamma_{\mathbf{e}}$	$\gamma_{\mathbf{c}}$
Patient A	0.29	0/35	0.40	0.012	0.066	140	0.39	0.65	160000	0.011	0.79	0.058
Patient B	0.071	0/05	0.012	0.68	0.063	43	0.56	0.53	190000	0.23	0.0077	0.047

fixed points, we need to determine the linearization of system (2). This linearization yields

(3)

$$
DF = \begin{bmatrix}
-1-(1.26)\left(\frac{C}{C+6.622}\right) & 0 & \frac{-(8.3437)T_n}{(C+6.622)^2}\\
0.9418\left(\frac{C}{C+6.622}\right) & 10.6\left(\frac{C}{C+6.622}\right) - 0.24 - C & \frac{(6.2365)T_n}{(C+6.622)^2} - \frac{(70.19)T_e}{(C+6.622)^2} - T_e\\
0 & -\gamma_c C & (4.6)\ln\left(\frac{29260}{C}\right) - 18.2 - T_e
\end{bmatrix}.
$$

Substituting fixed point P_1= (1, 0, 0) in this matrix, we get

$$
DF(P_1) = \begin{bmatrix}
-1 & 0 & -0.19027\\
0 & -0.24 & 0.1422\\
0 & 0 & -18.2
\end{bmatrix}.
$$

By easy calculation, the eigenvalues of this Jacobian matrix will be found as $\lambda_1 = -1$, $\lambda_2 = -0.24$ and $\lambda_3 = -18.2$. It is clear that λ_1, λ_2 and λ_3 all have negative (real) sign. Therefore, P_1 is a stable point. For the second fixed point P_2= $(\overline{T_n}, \overline{T_e}, \overline{C})$ (if exists), we may use a similar analysis.

Now, to solve FDE system (1), at first we discretize this equations. Among the several discretization methods which are available for the fractional derivative D_t^{α},

we use the one that have generated by Grunwald-Letnikov [6, 7]. In this method $D_t^\alpha x(t)$ is approximated by

$$D_t^\alpha x(t)=\lim_{l\to 0}\frac{1}{l^\alpha}\sum_{j=0}^{[\frac{t}{l}]}(-1)^j\binom{\alpha}{j}x\left(t-jl\right), \tag{4}$$

where, l is the step size and $[t]$ is the integer part of t. Using this method for system (1), $D_t^\alpha x(t)$ is replaced by $\sum_{j=0}^{[\frac{t_n}{l}]}c_j^\alpha x(t_{n-j})$, where $t_n = nl$ and c_j^α is Grunwald-Letnikov coefficients defined by

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

We may calculate c_j^α with the following recursive formula:

$$c_j^\alpha=\left(1-\frac{1+\alpha}{j}\right)c_{j-1}^\alpha \quad j=0,1,2,\ldots \quad c_0^\alpha=l^\alpha \tag{5}$$

Now, Using (5), system (1) can be discretize as follows:

$$\begin{aligned}
(T_n)_n&=\frac{s_n-\sum_{j=1}^n c_j^\alpha(T_n)_{n-j}}{c_0+d_nu_2(t)+k_n\left(\frac{C_n}{C_n+\eta}\right)},\\
(T_e)_n&=\frac{\alpha_nk_n(T_n)_n\left(\frac{C_n}{C_n+\eta}\right)-\sum_{j=1}^n c_j^\alpha(T_e)_{n-j}}{c_0+d_eu_2(t)+\gamma_eC_n-\alpha_e\left(\frac{C_n}{C_n+\eta}\right)},\\
(C)_n&=\frac{-\sum_{j=1}^n c_j^\alpha C_{n-j}}{c_0-(1-u_1(t))r_cln\left(\frac{C_{max}}{C_n}\right)+d_cu_2(t)+\gamma_c(T_e)_n}.
\end{aligned} \tag{6}$$

We solve this system with some values of T_n, T_e and C. Here, to be consistence with other results in [8], we start with $T_n = 1510$, $T_e = 10$ and $C= 10000$. The results are depicted in Figures 1 and 2 for different values of fractional derivative $0.90 < \alpha \leq 1$. In these figures, the results are in complete agreement with those found by using the classical systems of ODE counterparts [8]. Figures 2 and 4 compares the behavior of CML cell population after solving for without Treatment, one control (u_1) and for two controls (u_1 and u_2), for patients A and B, respectively. However, the CML cell population plot for $0.90 < \alpha \leq 1$ is shown in Figure 1 and 2 for $\alpha = 1, 0.95$. It is expected that the results of Figures 1 and 2 will be more consistent for $\alpha = 0.95$ with drug therapy nature. We claim that these results are in more agreements with the nature of the chemotherapy treatment. From these reults the amount of the medicine that has been used in each period of time (each

1 days) is completely visible at the starting iterations, and shows a suitable pattern that is converges to zero in entire therapy period (250 days).

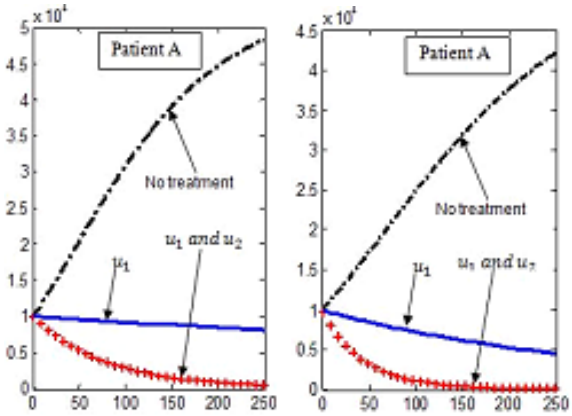

FIGURE 1. results **C** of numerical solution of system (1) for positive initial values given by the text with fractional derivative $\alpha = 1$ (left hand), $\alpha = 0.95$ (right hand) for patients A.

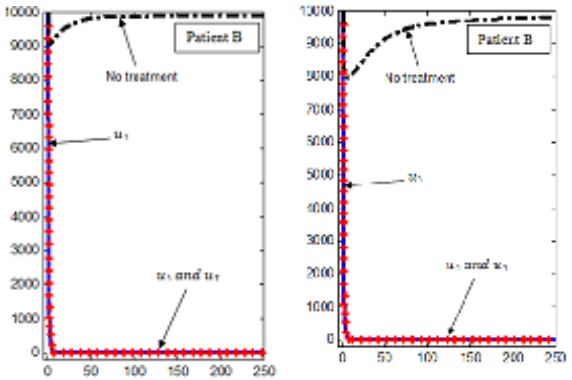

FIGURE 2. results **C** of numerical solution of system (1) for positive initial values given by the text with fractional derivative $\alpha = 1$ (left hand), $\alpha = 0.95$ (right hand) for patients B.

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