International Journal of Innovation Scientific Research and Review
Vol. 04, Issue, 03, pp.2494-2504, March 2022
Available online at http://www.journalijisr.com
SJIF Impact Factor 4.95

IJISRR

ISSN: 2582-6131

Research Article

NUMERICAL SIMULATION OF MATHEMATICAL MODEL FOR CANCER TREATMENTS BY STEM CELLS AND CHEMOTHERAPY USING CAPUTO-FABRIZIO FRACTIONAL DERIVATIVE

[1,] * M. Abubakar, [2]M. Abdulhameed, [1]A. M. Kwami, [3]A. Abdullahi, [4]S. Markus, [1]D. G. Yakubu

[1]Department of Mathematical Sciences, Abubakar Tafawa Balewa University, Bauchi, Nigeria.
[1,2]School of Science and Technology, The Federal Polytechnic Bauchi, Nigeria.
[3]Department of Mathematics, Federal University Kashere, Gombe State, Nigeria.
[4]Department of Mathematical Sciences, University of Maiduguri, Borno State, Nigeria.

Received 17th January 2022; Accepted 18th February 2022; Published online 31st March 2022

ABSTRACT

The high rate of mortality caused by cancer diseases has attracted much attention from various disciplines to come up with better preventive measures and treatment strategies that will lessen cancer development and increase survival rate. Several comprehensive mathematical analyses were carried out using the well-known Banach fixed point theorem/contracting principle to study the behaviour and stability of the cancer disease models. With these models a lot of numerical estimates of biological knowledge of the parameters have been obtained, a number of phenomena interpreted, and predictions were made in order to gain further knowledge of cancer development and possible treatment. In this study, simulation of the cancer mathematical model using Caputo-Frabrizio fractional derivative to see the effects of the combined treatment of cancer disease by stem cells and chemotherapy were performed. From the graphical representation of results presented one can clearly see the effects of the application of the stem cells and the chemotherapy involved in the treatment of cancer tumor. In the past, most of the cancer treatment were done by conventional chemotherapy, radiotherapy, hormone therapy, molecularly targeted therapies and surgery which were used either singly or in combination with one another or other therapies and all played vital role except the side effects that these therapies incur in the normal tissues and organs. Thus, from the recent research carried out by some researchers, it is now clear that in many cases they do not represent complete cure. Hence, the need to address not only the preventative measures of cancer disease, but also more successful treatment can be achieved using combination of stem cells and chemotherapy.

Keywords: Chemotherapy, Immune system, Mathematical model, Stem cell, differential equation.

INTRODUCTION

Cancer is a no communicable disease but destroys life and causes death worldwide, where new cases and death from the disease keep rising despite the advancement in science and technology [1]. Numerous types of cancer exist in both male and female genders worldwide depending on the geographical locations, atmosphere and nature of the intake of that location [2]. The common among them include breast and cervical cancer which are common cancers in the world and the most frequent cancer among women, prostate cancer and liver cancer are common in men, colorectal cancer which is common cancer in men and in women globally [3,4]. Some of the common signs and symptoms of cancer may include pyrexia, ail, tiredness, changes in skin appearance (redness, sores that would not heal, jaundice, darkening), unplanned weight loss or weight gain, lumps or tumors (mass), inconvenient swallowing, changes and difficulties with bowel or bladder function, never – ceasing cough or throatiness, curtly of breath, chest pains, bleeding and discharges that can't be explained [5, 6]. Cell mutations and other factors that assist in damaging the DNA eventually leads to cancer [7], and these factors include air pollution, smoking, heavy alcohol drinking, eating a poor diet, obesity, exposure to chemicals, and other toxins [8]. And if these triggering factors are prevented it will go a long way in minimizing the risk of effecting with cancer. Chemotherapy, immunotherapy, radiotherapy and surgery are well known clinical procedures used in treating or managing cancer which depend upon the patient's condition, location of the tumor, and the stage of cancer. Evidence has shown that the combination of more than one therapies for the treatment of advanced-stage cancer is a veritable option because therapies target different methods of tumor cell survival and their combined effect is highly desirable [9]. It has been for decades that biological processes are being modeled mathematically based on the advances in technology and availability of related data which provide means of a better understanding of the processes. Different kinds of differentials equation have served as a tool in modeling hematological processes in which [10] developed a reduced system of delay differential equation from an aged structured partial differential equation model that describe a better transition between chronic and acute phases of myeogenous leukemia by incorporating self – renewing population and non-constant cell cycle durations, but the model does not incorporate feedback controls on apoptosis which seems to be important for myelogenous leukemia appearance. For better understanding of the dynamic of acute leukemia and in particular find theoretical conditions for the efficient drug delivery, [11] have investigated and obtained a nonlinear system with distributed delays mathematical model of leukemia cells dynamic. [12] have added on Adimy *et al.,* (2008) and [13] model of cell dynamic where they separate the cell development phase into a structure of numerous sub-compartments by showing the overall dynamical system of the equation can be condensed to two coupled nonlinear equations with four internal sub-systems involving distributed delays. [14] propose a couple of PDE model that was transformed into a non-linear distributed delay system for healthy and cancerous cell dynamics in Acute Myeloid Leukemia. [15] developed a mathematical model system of two age-structured partial differential equations which was reduced to a delay differential-difference system by

***Corresponding Author: M. Abubakar,**
1Department of Mathematical Sciences, Abubakar Tafawa Balewa University, Bauchi, Nigeria.

integrating system over age and using the characteristics method that helps in understanding the uncontrolled proliferation of blood cells in some hematological disorders. Moreover, [16] have developed a multi-stage acute myeloid leukemia model by converting the PDE model to a nonlinear time-delay model through the construction of linear Lyapunov functionals which guarantee global exponential stability with a given decay rate. [17] developed and analyze a nonlinear time-delay mathematical model that was coupled to a differential-difference system that describes the coexistence between the population of an ordinary and leukemic cell. The model explains the invasion of the bone marrow by unhealthy cells that are characterized by fast self – renewing dynamics. Many authors, have improved on [17] by modifying the coupling manner of the healthy and mutated cells to investigate some biological concerns on cancer stem cells dormancy. [18] and [19] have re-explore the steadiness of "0" and positive equilibriums for both healthy and unhealthy hematopoiesis via Lyapunov – Krasovskii Functional (LKFs) and Quadratic Functional respectively. To add to the existing mathematical model that was aimed at the improvement in cancer treatment [19] developed and explored an age-structured model that describes the coexistence between mutated and ordinary stem cells by transforming the PDE into a nonlinear time-delay system governing the dynamics of healthy cells, coupled to a nonlinear differential-difference system describing dynamics of unhealthy cells to achieve; the case where therapy aims to eradicate cancer cells while preserving healthy cells; a less demanding, more realistic scenario that consists in maintaining healthy and unhealthy cells in a controlled stable steady state (cancer dormancy). Mathematical modeling of cancer treatment using radiotherapy has also gained a lot of attention which includes but not limited to the work of [20] where they developed a Lokta – Volterra Competitive model that analyses the population dynamic and considers the interaction between the healthy and mutated cell as they compete for body resources. The model considers only the cancer cell during the radiotherapy. [21] have improved on [20] by adding perturbation theory in order to consider the effect of radiotherapy on the healthy cell during the radiotherapy protocol by taking four different modes of treatment. [22] have used Caputo – Fabrizio Fractional Derivative to integrate the radiotherapy model of cancer treatment which proved that fractional derivative gives important information about the process. [23] have added Hadamard Fractional Derivation to the radiotherapy cancer treatment model which proved to have a unique positive solution. [24] has improved on the previous classical work of radiotherapy cancer treatment by taking into consideration the status of the treatments and predict the outcome of the other treatment plans through incorporating Caputo Fractional Derivative in the previous cancer treatment models. Since most types of cancer disease are resistant to treatment, therefore, a combination of more than one therapeutic option has gained much attention from many researchers such as [25] that developed a mathematical model of tumor-immune interactions with chemotherapy by exploring one quadratic control and one linear control on the coupled system of ordinary differential equations toward the determination of theoretically improved approaches to treating a cancer patient. [26] used the stability theory of differential equations to propose and analyzed a nonlinear mathematical model for the study of the interaction between tumor cells and oncolytic viruses. [27] have developed a mathematical model of ordinary differential equations of an immune response to tumor growth which gets affected by treatments chemotherapy, interleukin-2, and adoptive immunotherapy. [28] propose a new mathematical model which explains the combination of immunotherapy with chemotherapy as very effective in controlling tumor growth thereby better treatment effect can be achieved. [29] has developed a new and a combined cancer treatment mathematical model with an ordinary differential equation for stem cell therapy and chemotherapy with the hope to cure cancer disease and improve patient's quality of life. However, as hence the thought to extend [29] to fractional order is a novel work to be carried out.

Overview of the Existing Model

Following the existing mathematical model by [29] that explain the relationship and the interactions between the stem cells and chemotherapy for the treatment of cancer. The model was able to explore how chemotherapy affect the stem cells, the effect or cells and the tumor cells. It also explained clearly the interactions between the effect or cells and the tumor cells as both component fights against one another. Hence the stem cell that became effect or cells fight the tumor cells by improving the immune system of the cancer patient while chemotherapy kills the infected cells and also the healthy cells. Thus, the model equations are

$$\begin{aligned}
\frac{dS}{dt} &= \gamma_1 S - k_s MS \\
\frac{dE}{dt} &= \alpha - \mu E + \frac{p_1 ES}{(S+1)} - p_2(T+M)E \\
\frac{dT}{dt} &= r(1-bT)T - (p_3 E + k_T M)T \\
\frac{dM}{dt} &= -\gamma_2 M + V(t)
\end{aligned} \tag{1a}$$

where $S(t)$ $E(t)$ $T(t)$, and $M(t)$ are the concentration of stem cells, effect or cells, tumor cells, and chemotherapy concentration drug with the initial conditions $S(0) = S_0$, $E(0) = E_0$, $T(0) = T_0$, and $M(0) = 0$ if $V_0 = 0$. $0 \le t \le \infty$

Table 1: Model Parameters and their description

Parameter	Description	Value
S	Stem Cells	1
E	Effector Cells	1
T	Tumor Cells	1
γ_1	The Decay Rate of Concentration of the Stem Cells	-0.02825
σ	Rate of Produced the Effector Cells	0.17
μ	The Natural Death Rate of the Effector Cells	0.03
b	Carrying Capacity of the Tumor Cells	10^{-9}
k_s	Fractional Stem Cells killed by Chemotherapy	1
p_1	Maximum Proliferation Rate of the Effector Cells	0.1245
r	Tumor Growth Rate	0.18
p_2	Decay Rate of the Effector Cells killed by Tumor Cells and Chemotherapy	1
k_T	Fractional Tumor Cells killed by Chemotherapy	0.9
p_3	Decay Rate of the Tumor Cells killed by the Effector Cells	0.9
γ_2	Decay Rate of Chemotherapy Drug	6.4
$V(t)$	The time dependent external influx of Chemotherapy Drug	1

The extended Model

The extended model is formulated by integrating the Caputo Fabrizio fractional derivative following the methods of [30],[31], [32] and [33] where some parameters in the system model are modified to ensure that the right- and left-hand sides of the resultant fractional equations possess the same dimensions. Consequently, (1a) becomes

$$
\begin{aligned}
{}^{CF}D^{q}S(t) &= \gamma_1^{q}S - k_s^{q}MS \\
{}^{CF}D^{q}E(t) &= \sigma^{q} - \mu^{q}E + \frac{p_1^{q}ES}{(S+1)} - p_2^{q}(T+M)E \\
{}^{CF}D^{q}T(t) &= r^{q}\left(1-b^{q}T\right)T - \left(p_3^{q}E + k_T^{q}M\right)T \\
{}^{CF}D^{q}M(t) &= -\gamma_2^{q}M + V(t)
\end{aligned}
\qquad (1b)
$$

along with the initial conditions $S(0)=S_0$, $E(0)=E_0$, $T(0)=T_0$, and $M(0)=0$ if $V_0=0$, where ${}^{CF}D^{q}$ denote the fractional derivative operator,that is, the Caputo-Fabrizio type with the fractional order q. It is worth noting that, as $q\to 1$, the fractional system (1b) tends to the classic integer model (1a).

The rationale for Caputo – Fabrizio is their advantage over the Reimann – Liouville fractional operator. The Riemann–Liouville fractional-order differential equations required to have initial conditions in terms of fractional order derivatives which, as commonly known, have no universally accepted physical interpretations and furthermore; derivative of a constant function under this fractional operator is not zero. While the operators Caputo, the Caputo–Fabrizio, and Atangana–Baleanu–Caputo which, by their very definitions, do not have issues of fractional-order initial conditions and their derivatives for a constant function is also zero [34].

The Existence and Uniqueness of solution for the Model

Consider the first order ordinary differential equation

$$\frac{dy}{dt} = f(t,y) \qquad y(t_0)=y_0 \qquad (2)$$

If $f(t,y)$ is continues near (t_0,y_0) then the solution to (2) exist, so also if $f(t,y)$ and $\frac{\partial f}{\partial y}$ are both continues near (t_0,y_0) then (2) is said to have a unique solution.

Definition: Lipschitz Condition

It is said that f satisfies a Lipschitz condition on a set D if there exists a constant $L\geq 0$ such that $|f(t,u)-f(t,v)|\leq L|u-v|$ for all $\{(t,u),(t,v)\}\in D$ and L is a Lipschitz constant. Lipschitz conditions are connected with contractive mapping which have important application to the existence, uniqueness and approximation of equation – including ordinary differential equations [35].

Definition: Fixed Point

A fixed point is kind of x_0 which satisfies $T(x_0)=x_0$, that is x_0 does not move by the transformation T

Definition: Contraction Mapping

If (x,d) be nonempty complete metric space, $T: x\to x,$ for all $x,y\in X$ $\exists\, q\in[0,1)$ such that $d(T(x),T(y))\leq qd(x,y)$. Then T is a contraction mapping.

Definition: Banach Fixed Point Theorem

Let (x,d) be nonempty metric space with $T: x\to x,$ is a contraction there exist a unique fixed point x_0 such that $T(x_0)=x_0$.

Banach contraction principle can be applied to derive the existence and uniqueness of solution to initial value problems provided that the function has satisfied Lipschitz condition.

Now let X be complete normed linear space (Banach Space) and $T: x\to x$ is called contraction if $\|Tx-Ty\|\leq\alpha\|x-y\|$ for all $x,y\in X$ for some $\alpha<1$.

[34] have found the existence and uniqueness of solution through a fixed-point theory by applying fractional operation as

$${}^{CF}I^{q}\left[{}^{CF}D^{q}f(t)\right] = f(t)-f(0) \qquad (3)$$

$$
\begin{aligned}
S(t)-S(0) &= {}^{CF}I_t^{q}\left[\gamma_1^{q}S - k_s^{q}MS\right] \\
E(t)-E(0) &= {}^{CF}I_t^{q}\left[\sigma^{q} - \mu^{q}E + \frac{p_1^{q}ES}{(S+1)} - p_2^{q}(T+M)E\right] \\
T(t)-T(0) &= {}^{CF}I_t^{q}\left[r^{q}\left(1-b^{q}T\right)T - \left(p_3^{q}E + k_T^{q}M\right)T\right] \\
M(t)-M(0) &= {}^{CF}I_t^{q}\left[-\gamma_2^{q}M + V(t)\right]
\end{aligned}
\qquad (4)
$$

Applying the ideas presented in [36] we get

Applying the ideas presented in [36] we get

$$\begin{aligned}
S(t)-S(0)&=\frac{2(1-q)}{(2-q)\omega(q)}\left[\gamma_1^q S-k_s^q MS\right]+\frac{2q}{(2-q)\omega(q)}\int_0^t\left[\gamma_1^q S-k_s^q MS\right]du\\
E(t)-E(0)&=\frac{2(1-q)}{(2-q)\omega(q)}\left[\sigma^q-\mu^q E+\frac{p_1^q ES}{(S+1)}-p_2^q(T+M)E\right]+\frac{2q}{(2-q)\omega(q)}\int_0^t\left[\sigma^q-\mu^q E+\frac{p_1^q ES}{(S+1)}-p_2^q(T+M)E\right]du\\
T(t)-T(0)&=\frac{2(1-q)}{(2-q)\omega(q)}\left[r^q\left(1-b^qT\right)T-\left(p_3^q E+k_T^q M\right)T\right]+\frac{2q}{(2-q)\omega(q)}\int_0^t\left[r^q\left(1-b^qT\right)T-\left(p_3^q E+k_T^q M\right)T\right]du\\
M(t)-M(0)&=\frac{2(1-q)}{(2-q)\omega(q)}\left[-\gamma_2^q M+V(t)\right]+\frac{2q}{(2-q)\omega(q)}\int_0^t\left[-\gamma_2^q M+V(t)\right]du
\end{aligned} \tag{5}$$

For simplicity; let

$$\begin{aligned}
b_1(t,S)&=\gamma_1^q S-k_s^q MS\\
b_2(t,E)&=\sigma^q-\mu^q E+\frac{p_1^q ES}{(S+1)}-p_2^q(T+M)E\\
b_3(t,T)&=r^q\left(1-b^qT\right)T-\left(p_3^q E+k_T^q M\right)T\\
b_4(t,M)&=-\gamma_2^q M+V
\end{aligned} \tag{6}$$

Theorem: The kernels b_1, b_2, b_3 and b_4 assures the Lipschitz condition and contraction if the following conditions respectively fulfils

$$0<\gamma_1^q S-k_s^q a_4<1 \tag{7}$$

$$0\le\mu^q+p_1^q\frac{a_1}{a_1+1}-p_2^q(a_2+a_3)<1 \tag{8}$$

$$0\le r^q+\left(-p_3^q a_2+k_T^q a_4\right)<1 \tag{9}$$

$$0\le\gamma_2^q<1 \tag{10}$$

Proof: Taking two functions S and S_1, and start from b_1 and proceeds as follows

$$b_1(t,S)-b_1(t,S_1)=\left[\left(\gamma_1^q S(t)-k_s^q M(t)S(t)\right)-\left(\gamma_1^q S_1(t)-k_s^q M(t)S_1(t)\right)\right] \tag{11}$$

$$=\gamma_1^q\left(S(t)-S_1(t)\right)-k_s^q M(t)\left(S(t)-S_1(t)\right) \tag{12}$$

Applying norm on (12), we get

$$\begin{aligned}
&\le\gamma_1^q\left\|S(t)-S_1(t)\right\|+k_s^q\left\|M(t)\left(S(t)-S_1(t)\right)\right\|\\
&\le\gamma_1^q\left\|S(t)-S_1(t)\right\|+k_s^q\left\|M(t)\right\|\left\|\left(S(t)-S_1(t)\right)\right\|\\
&\le\gamma_1^q\left\|S(t)-S_1(t)\right\|+k_s^q a_4\left\|\left(S(t)-S_1(t)\right)\right\|\\
&\le\gamma_1^q+k_s^q a_4\left\|S(t)-S_1(t)\right\|
\end{aligned} \tag{13}$$

Taking $c_1=\left(\gamma_1^q+k_s^q a_4\right)$ where $\|M\|\le a_4$ is bounded, then (13) became

$$\left\|b_1(t,S)-b_1(t,S_1)\right\|\le c_1\left\|S(t)-S_1(t)\right\| \tag{14}$$

This implies that Lipschitz condition is satisfied for b_1. Moreover (14) implies that it is also a contraction.
Similarly,

$$b_2(t,E)-b_2(t,E_1)=\left[\begin{array}{l}\left(\sigma^q-\mu^q E(t)+\frac{p_1^q E(t)S(t)}{(S(t)+1)}-p_2^q(T(t)+M(t))E(t)\right)-\\ \left(\sigma^q-\mu^q E_1(t)+\frac{p_1^q E_1(t)S(t)}{(S(t)+1)}-p_2^q(T(t)+M(t))E_1(t)\right)\end{array}\right] \tag{15}$$

Simplifying (15) we get

$$=-\mu^q\left(E(t)-E_1(t)\right)+\frac{p_1^q S(t)}{(S(t)+1)}\left(E(t)-E_1(t)\right)-p_2^q\left(T(t)+M(t)\right)\left(E(t)-E_1(t)\right) \tag{16}$$

Applying norms on (16) we then have

$$\leq \mu^q \|E(t)-E_1(t)\| + \left\| \frac{p_1^q S(t)}{(S(t)+1)} (E(t)-E_1(t)) \right\| + \left\| \left(-p_2^q T(t) - p_2^q M(t)\right)(E(t)-E_1(t)) \right\| \quad (17)$$

$$\leq \mu^q \|E(t)-E_1(t)\| + p_1^q \left\| \frac{S(t)}{(S(t)+1)} \right\| \|(E(t)-E_1(t))\| - p_2^q \|T(t)\| - p_2^q \|M(t)\| \|(E(t)-E_1(t))\| \quad (18)$$

$$\leq \mu^q \|E(t)-E_1(t)\| + p_1^q \frac{a_1}{a_1+1} \|(E(t)-E_1(t))\| - p_2^q (a_2+a_3) \|(E(t)-E_1(t))\| \quad (19)$$

$$\leq \mu^q + p_1^q \frac{a_1}{a_1+1} - p_2^q (a_2+a_3) \|(E(t)-E_1(t))\| \quad (20)$$

Taking $c_2 = \mu^q + p_1^q \frac{a_1}{a_1+1} - p_2^q (a_2+a_3)$ where $\|S(t)\| = a_1$ is bounded, then it is attained that

$$\|b_2(t,S) - b_2(t,S_1)\| \leq c_2 \|E(t) - E_1(t)\| \quad (21)$$

This implies that Lipschitz condition is satisfied for b_2 . Moreover (21) implies that it is also a contraction.

Again,

$$b_3(t,T) - b_3(t,T_1) = \begin{pmatrix} \left[\left(r^q T(t) - r^q b^q T^2(t)\right) - \left(p_3^q E(t) + k_T^q M(t)\right) T(t)\right] - \\ \left[\left(r^q T(t)_1 - r^q b^q T_1^2(t)\right) - \left(p_3^q E(t) + k_T^q M(t)\right) T_1(t)\right] \end{pmatrix} \quad (22)$$

$$= r^q \left(T(t) - T(t)_1\right) - r^q b^q \left(T^2(t) - T_1^2(t)\right) - \left(p_3^q E(t) + k_T^q M(t)\right)\left(T(t) - T_1(t)\right) \quad (23)$$

Applying norm on (23)

$$\leq r^q \|(T(t) - T(t)_1)\| - r^q b^q \left\|\left(T^2(t) - T_1^2(t)\right)\right\| - \left\|\left(p_3^q E(t) + k_T^q M(t)\right)\left(T(t) - T_1(t)\right)\right\| \quad (24)$$

$$\leq r^q \|(T(t) - T(t)_1)\| - r^q b^q \left\|\left(T^2(t) - T_1^2(t)\right)\right\| - p_3^q \|E(t)\| + k_T^q \|M(t)\| \|(T(t) - T_1(t))\| \quad (25)$$

$$\leq r^q \|(T(t) - T(t)_1)\| - r^q b^q \left\|\left(T^2(t) - T_1^2(t)\right)\right\| + \left(-p_3^q a_2 + k_T^q a_4\right) \|(T(t) - T_1(t))\| \quad (26)$$

$$\leq r^q + \left(-p_3^q a_2 + k_T^q a_4\right) \|(T(t) - T(t)_1)\| - r^q b^q \left\|\left(T^2(t) - T_1^2(t)\right)\right\| \text{ for } T^2 > T \quad (27)$$

$$\leq c_3 \|(T(t) - T(t)_1)\| \quad (28)$$

$$\|b_3(t,T) - b_3(t,T_1)\| \leq c_3 \|T(t) - T_1(t)\| \quad (29)$$

This implies that Lipschitz condition is satisfied for b_3 . Moreover (29) implies that it is also a contraction.

Finally,

$$b_4(t,M) - b_4(t,M_1) = \left(-\gamma_2^q M(t) + V\right) - \left(-\gamma_2^q M_1(t) + V\right) \quad (30)$$

$$= -\gamma_2^q M(t) + \gamma_2^q M_1(t) \quad (31)$$

$$= -\gamma_2^q \left(M(t) - M_1(t)\right) \quad (32)$$

Taking the norm on (32)

$$\leq \gamma_2^q \|M(t) - M_1(t)\| \quad (33)$$

$$\leq c_4 \|M(t) - M_1(t)\|$$

$$\|b_4(t,M) - b_4(t,M_1)\| \leq c_4 \|M(t) - M_1(t)\| \quad (34)$$

where $c_4 = \gamma_2^q$

This implies that Lipschitz condition is satisfied for b_4 . Moreover (34) implies that it is also a contraction.

Simplifying (34) further, by replacing the kernels we get

$$\begin{aligned} S(t) &= S(0) + \frac{2(1-q)}{(2-q)\omega(q)} b_1(t,S) + \frac{2q}{(2-q)\omega(q)} \int_0^t b_1(u,S)du \\ E(t) &= E(0) + \frac{2(1-q)}{(2-q)\omega(q)} b_2(t,E) + \frac{2q}{(2-q)\omega(q)} \int_0^t b_2(u,E)du \\ T(t) &= T(0) + \frac{2(1-q)}{(2-q)\omega(q)} b_3(t,T) + \frac{2q}{(2-q)\omega(q)} \int_0^t b_3(u,T)du \\ M(t) &= M(0) + \frac{2(1-q)}{(2-q)\omega(q)} b_4(t,M) + \frac{2q}{(2-q)\omega(q)} \int_0^t b_4(u,M)du \end{aligned} \quad (35)$$

Next the recursive formula is presented as

$$\begin{aligned}
S_n(t) &= \frac{2(1-q)}{(2-q)\omega(q)} b_1(t, S_{(n-1)}) + \frac{2q}{(2-q)\omega(q)} \int_0^t b_1(u, S_{(n-1)}) du \\
E_n(t) &= \frac{2(1-q)}{(2-q)\omega(q)} b_2(t, E_{(n-1)}) + \frac{2q}{(2-q)\omega(q)} \int_0^t b_2(u, E_{(n-1)}) du \\
T_n(t) &= \frac{2(1-q)}{(2-q)\omega(q)} b_3(t, T_{(n-1)}) + \frac{2q}{(2-q)\omega(q)} \int_0^t b_3(u, T_{(n-1)}) du \\
M_n(t) &= \frac{2(1-q)}{(2-q)\omega(q)} b_4(t, M_{(n-1)}) + \frac{2q}{(2-q)\omega(q)} \int_0^t b_4(u, M_{(n-1)}) du
\end{aligned} \tag{36}$$

$$\begin{aligned}
S_{(n-1)}(t) &= \frac{2(1-q)}{(2-q)\omega(q)} b_1(t, S_{(n-2)}) + \frac{2q}{(2-q)\omega(q)} \int_0^t b_1(u, S_{(n-2)}) du \\
E_{(n-1)}(t) &= \frac{2(1-q)}{(2-q)\omega(q)} b_2(t, E_{(n-2)}) + \frac{2q}{(2-q)\omega(q)} \int_0^t b_2(u, E_{(n-2)}) du \\
T_{(n-1)}(t) &= \frac{2(1-q)}{(2-q)\omega(q)} b_3(t, T_{(n-2)}) + \frac{2q}{(2-q)\omega(q)} \int_0^t b_3(u, T_{(n-2)}) du \\
M_{(n-1)}(t) &= \frac{2(1-q)}{(2-q)\omega(q)} b_4(t, M_{(n-2)}) + \frac{2q}{(2-q)\omega(q)} \int_0^t b_4(u, M_{(n-2)}) du
\end{aligned} \tag{37}$$

The succeeding terms difference is evaluated as

$$\begin{aligned}
D_{1n}(t) &= S_n(t) - S_{(n-1)}(t) = \frac{2(1-q)}{(2-q)\omega(q)} b_1(t, S_{(n-1)}) - b_1(t, S_{(n-2)}) + \frac{2q}{(2-q)\omega(q)} \int_0^t \left(b_1(u, S_{(n-1)}) - b_1(u, S_{(n-2)}) \right) du \\
D_{2n}(t) &= E_n(t) - E_{(n-1)}(t) = \frac{2(1-q)}{(2-q)\omega(q)} b_2(t, E_{(n-1)}) - b_2(t, E_{(n-2)}) + \frac{2q}{(2-q)\omega(q)} \int_0^t \left(b_2(u, E_{(n-1)}) - b_2(u, E_{(n-2)}) \right) du \\
D_{3n}(t) &= T_n(t) - T_{(n-1)}(t) = \frac{2(1-q)}{(2-q)\omega(q)} b_3(t, T_{(n-1)}) - b_3(t, T_{(n-2)}) + \frac{2q}{(2-q)\omega(q)} \int_0^t \left(b_3(u, T_{(n-1)}) - b_3(u, T_{(n-2)}) \right) du \\
D_{4n}(t) &= M_n(t) - M_{(n-1)}(t) = \frac{2(1-q)}{(2-q)\omega(q)} b_4(t, M_{(n-1)}) - b_4(t, M_{(n-2)}) + \frac{2q}{(2-q)\omega(q)} \int_0^t \left(b_4(u, M_{(n-1)}) - b_4(u, M_{(n-2)}) \right) du
\end{aligned} \tag{38}$$

Taking the norm of (38)

$$\begin{aligned}
\|D_{1n}(t)\| &= \|S_n(t) - S_{(n-1)}(t)\| = \left\| \frac{2(1-q)}{(2-q)\omega(q)} b_1(t, S_{(n-1)}) - b_1(t, S_{(n-2)}) + \frac{2q}{(2-q)\omega(q)} \int_0^t \left(b_1(u, S_{(n-1)}) - b_1(u, S_{(n-2)}) \right) du \right\| \\
\|D_{2n}(t)\| &= \|E_n(t) - E_{(n-1)}(t)\| = \left\| \frac{2(1-q)}{(2-q)\omega(q)} b_2(t, E_{(n-1)}) - b_2(t, E_{(n-2)}) + \frac{2q}{(2-q)\omega(q)} \int_0^t \left(b_2(u, E_{(n-1)}) - b_2(u, E_{(n-2)}) \right) du \right\| \\
\|D_{3n}(t)\| &= \|T_n(t) - T_{(n-1)}(t)\| = \left\| \frac{2(1-q)}{(2-q)\omega(q)} b_3(t, T_{(n-1)}) - b_3(t, T_{(n-2)}) + \frac{2q}{(2-q)\omega(q)} \int_0^t \left(b_3(u, T_{(n-1)}) - b_3(u, T_{(n-2)}) \right) du \right\| \\
\|D_{4n}(t)\| &= \|M_n(t) - M_{(n-1)}(t)\| = \left\| \frac{2(1-q)}{(2-q)\omega(q)} b_4(t, M_{(n-1)}) - b_4(t, M_{(n-2)}) + \frac{2q}{(2-q)\omega(q)} \int_0^t \left(b_4(u, M_{(n-1)}) - b_4(u, M_{(n-2)}) \right) du \right\|
\end{aligned} \tag{39}$$

Simplifying (39) further, we get

$$\begin{aligned}
\|S_n(t) - S_{(n-1)}(t)\| &\le \frac{2(1-q)}{(2-q)\omega(q)} \|b_1(t, S_{(n-1)}) - b_1(t, S_{(n-2)})\| + \frac{2q}{(2-q)\omega(q)} \left\| \int_0^t \left(b_1(u, S_{(n-1)}) - b_1(u, S_{(n-2)}) \right) du \right\| \\
\|E_n(t) - E_{(n-1)}(t)\| &\le \frac{2(1-q)}{(2-q)\omega(q)} \|b_2(t, E_{(n-1)}) - b_2(t, E_{(n-2)})\| + \frac{2q}{(2-q)\omega(q)} \left\| \int_0^t \left(b_2(u, E_{(n-2)}) - b_2(u, E_{(n-2)}) \right) du \right\| \\
\|T_n(t) - T_{(n-1)}(t)\| &\le \frac{2(1-q)}{(2-q)\omega(q)} \|b_3(t, T_{(n-1)}) - b_3(t, T_{(n-2)})\| + \frac{2q}{(2-q)\omega(q)} \left\| \int_0^t \left(b_3(u, T_{(n-1)}) - b_3(u, T_{(n-2)}) \right) du \right\| \\
\|M_n(t) - M_{(n-1)}(t)\| &\le \frac{2(1-q)}{(2-q)\omega(q)} \|b_4(t, M_{(n-1)}) - b_4(t, M_{(n-2)})\| + \frac{2q}{(2-q)\omega(q)} \left\| \int_0^t \left(b_4(u, M_{(n-2)}) - b_4(u, M_{(n-2)}) \right) du \right\|
\end{aligned} \tag{40}$$

As Lipschitz condition are satisfied by the kernels, we have

$$\begin{aligned}
\left\|S_n(t)-S_{(n-1)}(t)\right\| &\le \frac{2(1-q)}{(2-q)\omega(q)}c_1\left\|S_{(n-1)}-S_{(n-2)}\right\|+\frac{2q}{(2-q)\omega(q)}c_1\int_0^t\left\|S_{(n-1)}-S_{(n-2)}\right\|du\\
\left\|E_n(t)-E_{(n-1)}(t)\right\| &\le \frac{2(1-q)}{(2-q)\omega(q)}c_2\left\|E_{(n-1)}-E_{(n-2)}\right\|+\frac{2q}{(2-q)\omega(q)}c_2\int_0^t\left\|E_{(n-1)}-E_{(n-2)}\right\|du\\
\left\|T_n(t)-T_{(n-1)}(t)\right\| &\le \frac{2(1-q)}{(2-q)\omega(q)}c_3\left\|T_{(n-1)}-T_{(n-2)}\right\|+\frac{2q}{(2-q)\omega(q)}c_3\int_0^t\left\|\left(T_{(n-1)}-T_{(n-2)}\right)\right\|du\\
\left\|M_n(t)-M_{(n-1)}(t)\right\| &\le \frac{2(1-q)}{(2-q)\omega(q)}c_4\left\|M_{(n-1)}-M_{(n-2)}\right\|+\frac{2q}{(2-q)\omega(q)}c_4\int_0^t\left\|M_{(n-1)}-M_{(n-2)}\right\|du
\end{aligned} \tag{41}$$

Hence we have

$$\begin{aligned}
\left\|D_{1n}(t)\right\| &\le \frac{2(1-q)}{(2-q)\omega(q)}c_1\left\|D_{1(n-1)}(t)\right\|+\frac{2q}{(2-q)\omega(q)}c_1\int_0^t\left\|D_{1(n-1)}(u)\right\|du\\
\left\|D_{2n}(t)\right\| &\le \frac{2(1-q)}{(2-q)\omega(q)}c_2\left\|D_{2(n-1)}(t)\right\|+\frac{2q}{(2-q)\omega(q)}c_2\int_0^t\left\|D_{2(n-1)}(u)\right\|du\\
\left\|D_{3n}(t)\right\| &\le \frac{2(1-q)}{(2-q)\omega(q)}c_3\left\|D_{3(n-1)}(t)\right\|+\frac{2q}{(2-q)\omega(q)}c_3\int_0^t\left\|D_{3(n-1)}(u)\right\|du\\
\left\|D_{4n}(t)\right\| &\le \frac{2(1-q)}{(2-q)\omega(q)}c_4\left\|D_{4(n-1)}(t)\right\|+\frac{2q}{(2-q)\omega(q)}c_4\int_0^t\left\|D_{4(n-1)}(u)\right\|du
\end{aligned} \tag{42}$$

Hence based on the above analysis there exist and a unique solution to (1b).

Numerical Simulations

We now present the results of the simulations of the mathematical model using Caputo – Fabrizio fractional order derivative for cancer treatment by stem cells and chemotherapy. In the simulation we use the values of the parameters in table 1 above and the initial conditions, as given in the table.

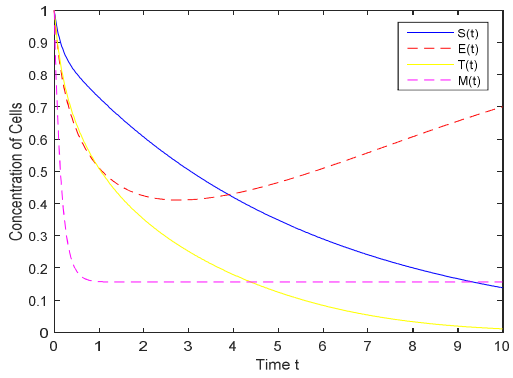

Figure 1a: Solution using FLMMs at $\alpha = 1$

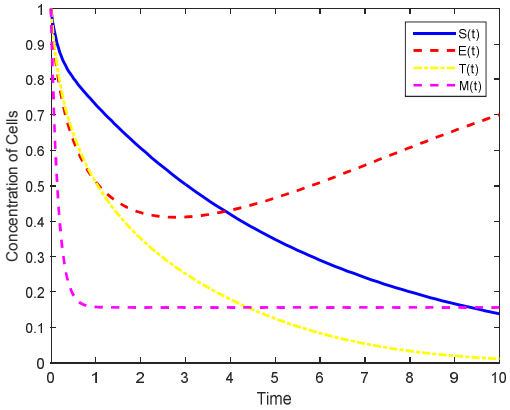

Figure 1b: Solution by RKM

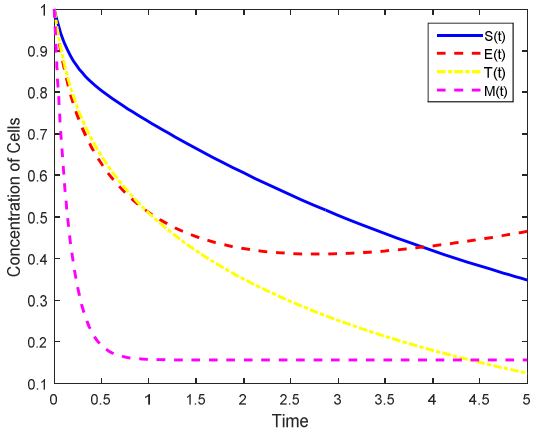

Figure 2a: Solution using RKM at t = [0, 5]

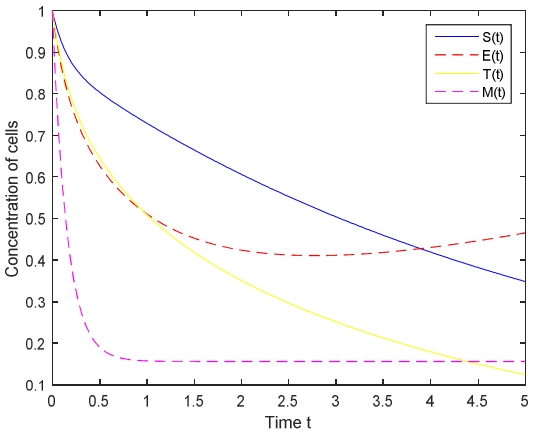

Figure 2b: Solution by FLMMs at t = [0, 5]

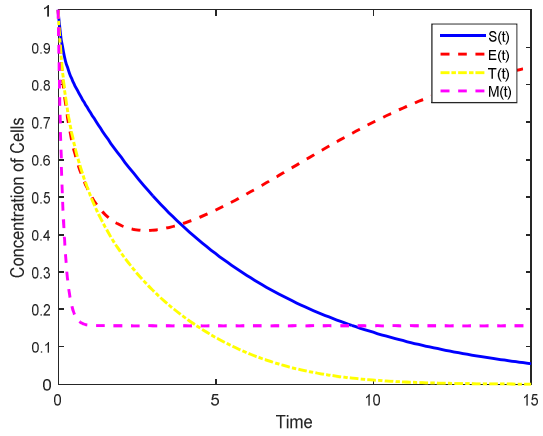

Figure 3a: Solution by RKM at t = [0, 15]

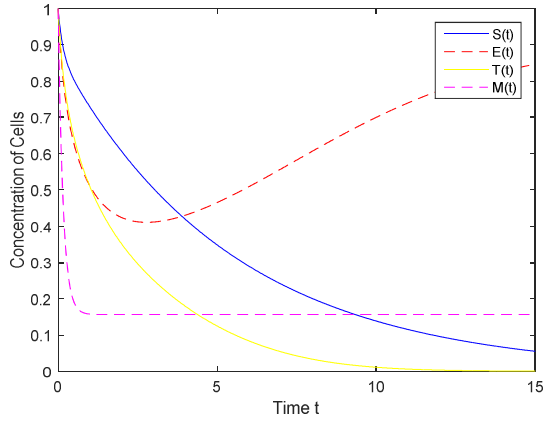

Figure 3b: Solution by FLMMs at t = [0, 15]

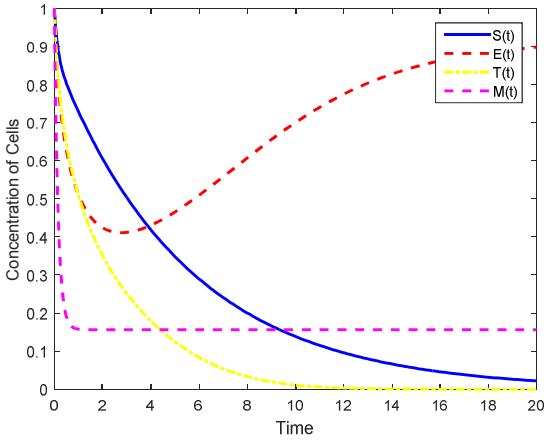

Figure 4a: Solution by RKM at t = [0, 20]

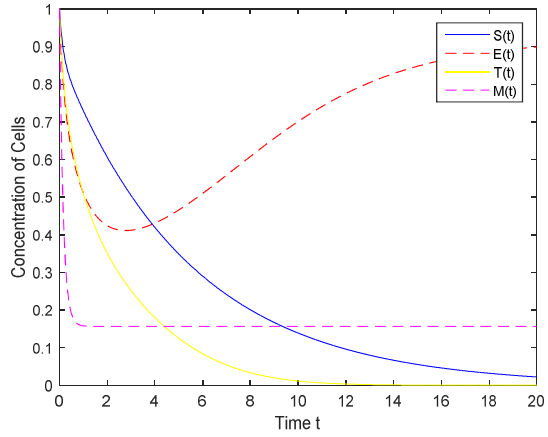

Figure 4b: Solution by FLMMs at t = [0, 20]

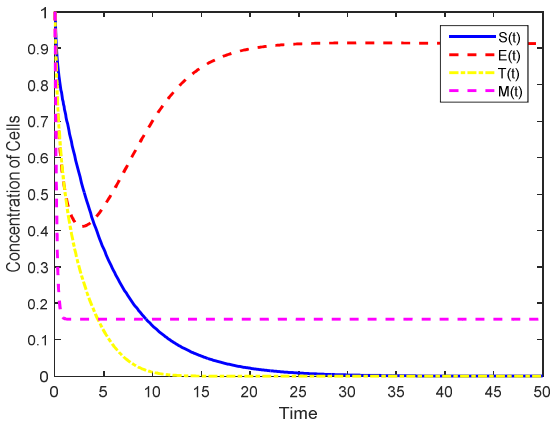

Figure 5a: Solution using RKM at t = [0, 50]

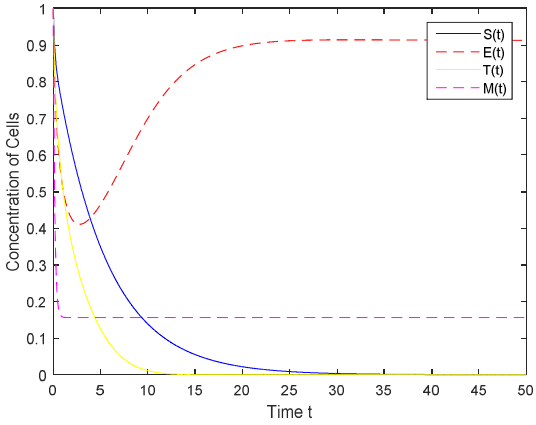

Figure 5b: Solution by FLMMs at t = [0, 50]

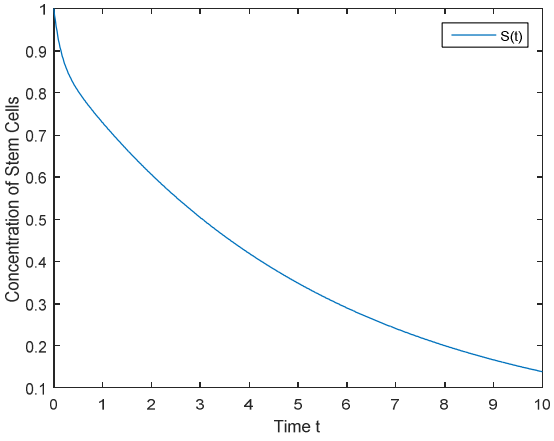

Figure 6a: Concentration of Stem Cell by RKM

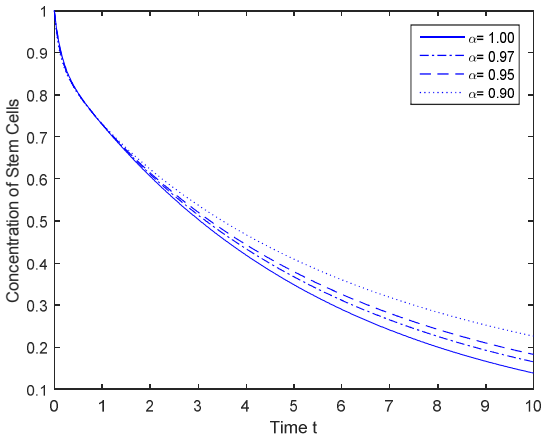

Figure 6b: Concentration of Stem Cell by FLMMs

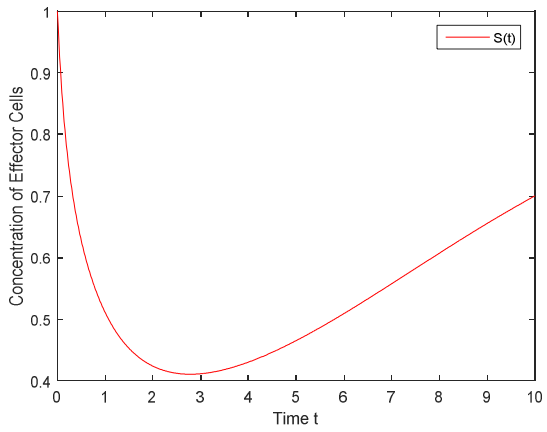

Figure 7a: Concentration of Effector Cell by RKM

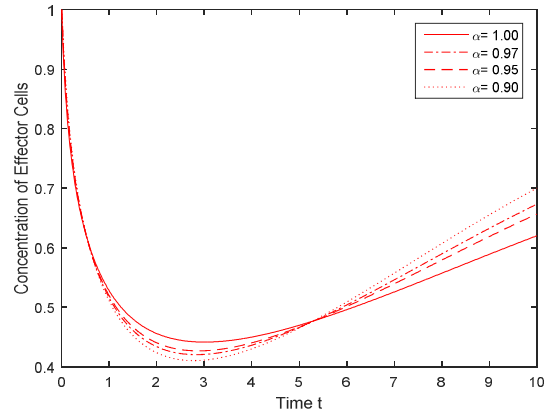

Figure 7b: Concentration Effector Cell by FLMMs

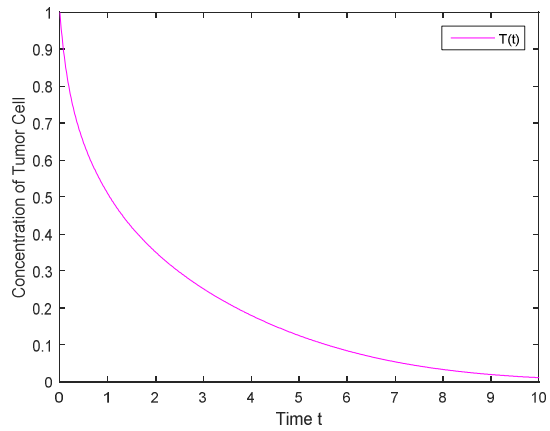

Figure 8a: Concentration of Tumor Cell by RKM

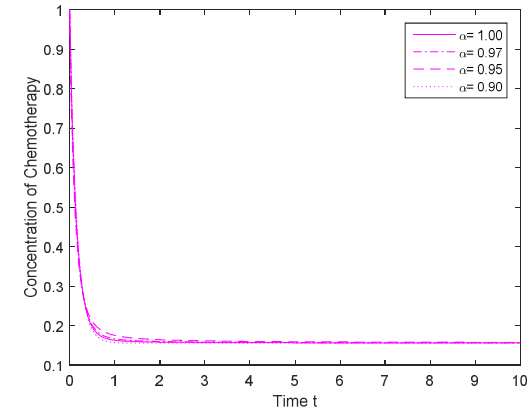

Figure 8b: Concentration of Tumor Cell by FLMMs

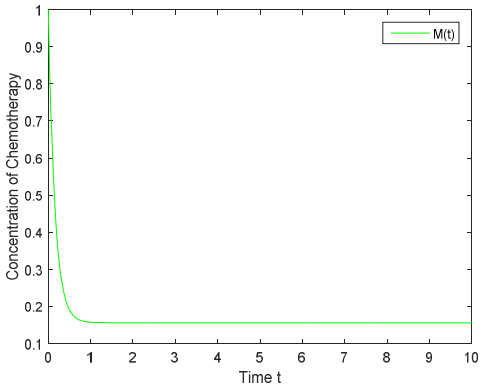

Figure 9a: Concentration of Chemotherapy Drug by RKM

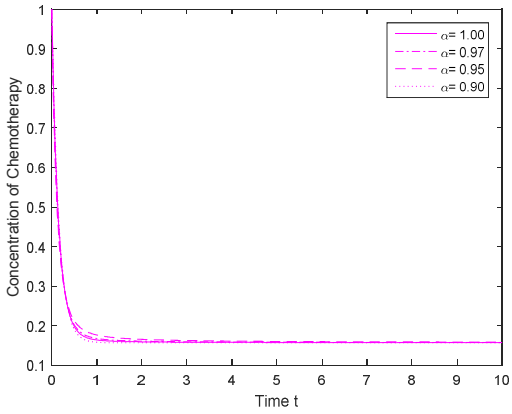

Figure 9b: Concentration of Chemotherapy drug by FLMMs

CONCLUSION

The numerical simulation of the fractional order mathematical model for cancer treatment by stem cells and chemotherapy has been carried out through a reliable and accurate numerical codes and Matlab routine that performed effectively. In this section, we compare the results obtained by FLMMs at the value of $\alpha = 1$ and results of the classical method obtained by the famous in-built Runge Kutta method of order four as presented in figure 1a and figure 1b respectively and the two results are in good agreement. Based on the results presented, we conclude that FLMMs is reliable for solving any system of equation with high level of accuracy. Based on the figures obtained in this section, there is no any significance difference in the results obtained at different time interval of the concentration of cells by both the FLMMs and the classical RKM of order four. The numerical simulation performed in this section is by varying the fractional order because fractional order model offers realistic information about the dynamic of the model. Thus, this section also highlights the effect of the memory which is the main aim of fractional derivatives, that is, keeping track of history of diseases. Based on the results obtained we conclude that our results are reliable. Hence this work has contributed to research activities in the field of cancer treatment with stem cells and chemotherapy.

Conflict of interest

The authors declare that, there are no conflicts of interest for the study.

Authors' contributions statement:

All authors contributed equally to this work. They all read and approved the final version of the manuscript.

REFERENCE

1. Mohammed A, Salihu J., Nafisatu U., Hauwa Y. K., Kwami A. M. and Okai J. O. "A Lethal and A Non-Cummunicable Disease in Nigeria: The Common Cancer Incidence and their Types," Global Scientific Journals, 2022.
2. Alexei T., Simeone M. and Demise E. K. , "A Mathematical Model of Gene Therapy for the treatment of cancer," https://www.researchgate.net/publication/267829423, 2013.
3. Abubakar I. B., Ukwuani - Kwaja A. N., Garba A. D., "Ethnobotanical Study of Medicinal Plants used for Cancer Treatment in Kebbi State, North - West Nigeria," Acta Ecologica Sinica, 2020.
4. Abubakar M. S., Musa A. M., Ahmed A., Hussaini I. M., "The Perception and Practice of Traditional Medicine in the Treatment of Cancers and Inflammations by the Hausa and Fulani tribes of Northern Nigeria.," Journal of Ethnopharmacology, vol. 111, pp. 625 - 629, 2017.
5. Abimbola S., Maryna V., Lucinda B. and Trevor K. , "Cytooxicity Evaluation of Selected Nigerian Plants used in Traditional Cancer Treatment.," Journal of Medicinal Plants Research , vol. 5, no. 11, pp. 2442 - 2444, 2011.
6. Aliyu U. M., Awosan K. J. Oche M. O., Taiwo A. O., Jimoh A. O. and Okuofo E. C., "Prevalence and Correlates of Complementary and Alternative Medicine use among Cancer Patients in Usman Danfodiyo University Teaching Hospital Sokoto Nigeria," Niger J. Chin Pract., vol. 20, pp. 1576 - 83, 2017.
7. Alison L. A., Sharon A. V., Alan B. T. and Ann F. C. , "Tumor Dormancy and Cancer Stem Cells: Implications for the Biology and Treatment of Brast Cancer Metastasis," Breast Disease, vol. 26, pp. 87 - 98, 2007.
8. Gbadamosi I. T. and Erinoso S. M. (2016), "A Review of Twenty Ethnobotanicals used in Management of Breast Cancer in Abeokuta, Ogun State Nigeria," African Journal of Pharmacy and Pharmacology, vol. 10, no. 27, pp. 546 - 564, 2016.
9. G. D. I., "Combination of Chemotherapy and Immunotherapy for Cancer; A Paradigm Revisited.," The cancer Oncology, vol. 8, no. 1, pp. 2-3, 2007.
10. Mostafa A., Fabien C., and Abderrahim E., "Discrete - Maturity Structured Model of Cell Differentiation with Applications to Acute Myelogenous Leukemia.," Journal of Biological Systems, vol. 16, no. 3, pp. 395 - 424, 2008.
11. Ozbay H., Bonnet C., Benjelloun H., and Clairambault J., "Stability Analysis ofCell Dynamics in Leukemia.," Math Model Nat. Phanom, vol. 7, no. 1, pp. 203 - 234, 2012.
12. Avila J. I., Bonnet C., Clairambault J., Ozbay H., Niculeseu S., I., Merhi F., Tang R., and Marie J. P., "A New Model of Cell Dynamics in Acute Myloid Leukemia involving Distributed Delays;," in 10th IFAC Workshop on Time Delay Systems, The International Federation of Automatic Control , Northeastern University, Boston, USA., June 22 - 24 2012.
13. Ozbay H., Bonner C., Benjelloun H., and Clairambault J., "Stability Analysis of Cell Dynamic in Leukemia.," Math. Model Nat. Phenom, vol. 7, no. 1, pp. 203 - 234, 2012.
14. Avila J. I., Bonnet C., Ozbay H., Clairmbau J., Nieuleseu S. I., HirschP. and Delhommeauz F., "A coupled Model for Healthy and Cancerous Cells Dynamics in Acute Myloid Leukemia," in 19th World Congress. The International Federation of Automatic Control , Cape Town, South Africa, 2014.
15. Mostafa A., Abdennassser C., and Tarik - Mohammed T., "Age Structured and Delay Differential - Difference Model of Hematopoietic Stem Cells Dynamics.," Discrete and Continues Dynamical Systems - Series B. American Institute of Mathematical Science, p. 27, 2015.
16. Emilia F., Catherine B., Frederic M., and Walid D., "Stability of the Cell Dynamic in Acute Myloid Leukemia.," Systems and Control Letters, Elsavier, pp. 91-100, 2016.
17. Djema W., Bonnet C., Clairambault J., Mazanc F., Hirsch P., and Delhommeau F., "Stability of a Delay System coupled to a Delay Differential - Difference System Describing the Coexistence of Ordinary and Mutated Hematopoietic Stem Cells," Journal of Theoretical Biology, 2016.
18. Djema W., Bonnet C., Clairambault J., Mazanc F., Hirsch P., and Delhommeau F., "Analysis of a Model of Dormancy in Cancer as the State of Coexistence between Tumor and Healthy Stem Cells," in American Control Conference May 24 - 26, Seattle USA, 2017.
19. Djema W. Catherine B., Frederic M., Jean C., Emilia F., Pierre H., and Francois D., "Control in Dormancy or Eradication of Cancer Stem Cells: Mathematical Modeling and Stability Issues," Journal of Theorical Biology , (2018.
20. Belostotski G., and Freedman H. I., "A Control Theory Model for Cancer Treatment by Radiotherapy.," International Journal of Pure and Applied Mathematics., pp. 447-480, 2005.
21. Freedman H. I., and Belostotski G., "Pertubed Model for Cancer Treatment by Radiotherapy.," Differential Equations and Dynamical Systems, pp. 115 - 133, 2009.
22. Mustafa A. D., Erean C., Hasan B., and Haci M. B. , "Cancer Treatment Model with the Caputo Fabrizio Fractional Derivative," The European Physical Journal Plus, vol. 133, no. 92, 2018.
23. Awadalla M., Yemeni Y. Y. and Abuassaba K., "A new Fractional Model for the Cancer Treatment by Radiotherpay using Hadamard Fractional Derivative.," Online Mathematics, pp. 14 - 18, 2019.
24. Musiliu F. F., Sharidan S., Fuaada M. S., and Ilyas Khan , "Numerical Simulation of Normal and Cancer Cells Population with Fractional Derivatives," Computer Methods and Program in Biomedicine, 2019.
25. Pillis L. G., De, Gu, W., Fister K. R., Head T. and Maplws K. , "Chemotherpy for Tumors: An Analysis of the Dynamics and a study of quadratic and Linear Controls," vol. 209, pp. 292 - 315, 2010.
26. Agarwal M., Bhadauria A., S., and Ai E. T., "Mathematical Modeling and Analysis of Tumor Therapy with Oncolytic Virus," pp. 131 - 140, 2011.
27. Baloni J., and Us R. (2013), "Mathematical Modelling of Strategic Treatments on Tumor Growth," Applied and Computational Mathematics, vol. 2, no. 4, 2013.
28. Pang L., Shen L., and Zhao Z., "Mathematical Modeling and Analysis of the Tumor Treatment Regiments with pulsed Immunogtherapy and Chemotherapy," vol. 7, no. 1, pp. 203 - 234, 2012.
29. M. A. Alqudah, "Cancer Treatment by Stem Cells and Chemotherpy as a mathemtical model with Numerical Simulations," Alexandria Engineering Hournal, 2020.
30. K. Diethelm, "AFractional Calculus Based Model for the Simulation of an Outbreak of Dengue Fever.," Nonlinear Dun, vol. 71, pp. 613 - 619, 2013.
31. Amin J., Sadia A., and Dumitru B., "A New Fractional Modeling and Control Strategy for the Outbreak of Dengue Fever," Physica A, vol. 435, p. 122524, 2019.
32. Sania Q. and Atangana A., "Mathemtical Analysis of Dengue Fever Outbreak by Novel Fractional Operators with Filed Data," Physica A, vol. 526, p. 121127, 2019.
33. Zafar I., Nauman A., Dumitru B., Waleed A., Muhammad R., Muhammad A., and Ali S. A., "Positivity and Boundedness Preserving Numerical Algorithm for the Solution of Fractional Nonlinear Model of HIV /AIDS Transmission.," Chaos, Solitons and Fractals, vol. 134, p. 109706, 2020.

34. Sania Q. and Atangana A., "Mathematical Analysis of Dengue Fever Outbreak by Novel Fractional Operators with Field Data," Physica A., vol. 526, p. 121127, 2019.
35. C. C. T., "School of Mathematics and Statistics," The University of New Saints Wales Sidney Australia.
36. Rashid J., Muhammad A. K., Poom K. and Phatiphat T., "Modeling the Transmission of Dengue Infection through Fractional Derivatives.," Chaos, Soliton and Fractals, vol. 127, pp. 189 - 216, 2019.

****