APPLICATION OF CAPUTO-FABRIZIO DERIVATIVE TO A CANCER MODEL WITH UNKNOWN PARAMETERS

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ABSTRACT. The present work explores the dynamics of a cancer model with fractional derivative. The model is formulated in fractional type of Caputo-Fabrizio derivative. We analyze the chaotic behavior of the proposed model with suggested parameters. Stability results for the fixed points are shown. A numerical scheme is implemented to obtain the graphical results in the sense of Caputo-Fabrizio derivative with various values of the fractional order parameter. Further, we show the graphical results in order to study that the model behaves the periodic and quasi periodic limit cycles as well as chaotic behavior for the given set of parameters.

1. Introduction. Cancer is considered the most killing diseases worldwide and the control of the tumor growth gotten special attentions from the researchers. It has many types, such as skin cancer, breast cancer, prostate cancer, lung cancer and many more. It is not yet possible to determine that someone develops the cancer and the other does not. But it came from the research that there are some risk factor that may increase the chances to become a cancer infected person, such as exposure to chemical or other substances, and a family history[2]. Various factors involved in tumor treatment response of the treatment of tumor diseases such as tumor severity, treatment application patient’s immune response. In the past decades, the researchers approached to study the dynamics of tumor and cancer self-remission by formulating various types of mathematical models [13, 19]. The cells of tumor are characterized by various numbers of genetic and epigenetic events that lead to the appearance of specific antigens known as neo-antigens, triggering anti-tumoral by the immune system [6, 10]. The characteristic of cancer is characterized by its ability to attack and react, showing tissue disorders similar to the immune system.

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All these observations lead to hypothesis formulation that the immune system can eliminate the tumor [16].

In mathematical models, the phenomenon of stability and chaos analysis have a key role to understand the dynamics of cancer, tumor and others epidemics models have been studied by many researchers [6, 7, 8, 20]. The author in [7], studied the chaotic behavior and the optimal control of the tumor and cancer self-remission system. Adaptive control and chaotic behavior of two prey with control and one predator with nonlinear feedback is proposed and analyzed in [8]. A stochastic prey predator model with optimal control analysis is investigated in [6]. Similarly, a mathematical model on cancer with radiovirotherapy is discussed in [4].

Fractional models play a key role in mathematical modeling of daily life problems and known as generalized models. The fractional order models are called generalized models in the sense where it can be analyzed not only for arbitrary case but also for non-integer case. The fractional order models are considered better than the integer order, due to its heredity and memory properties. Besides this, the crossover behavior in nonlinear system of epidemic models can only be studied effectively through fractional modeling. Also, for the epidemic data and their fitting to the model, the fractional order models are considered useful.

The fractional calculus is not only applied to biological models but its application can also be seen in many other areas of science and engineering [15, 23]. Various operators of fractional order are considered in literature, which belongs [0, 1]. For example, the author’s in [21, 18], presented the elementary concept related to fractional derivative and theories. A new derivative with exponential kernel is proposed in [3]. Some new recent work regarding the fractional derivative and their applications to models arising science and engineering are documented in [12, 5, 11, 17, 22]. A fractional derivative and its application to some linear and nonlinear chaotic system is considered in [12]. Application of the chaos synchronization within the scope of fractional derivative is proposed in [5]. A Zika virus model and its dynamics in fractional derivative is investigated in [11]. The oxygen diffusion equations and their application to capillary tissues with the use of fractional derivative are discussed in [17]. The impact of diabetes and resistant strains with fractional optimal control problem is formulated in [22]. These new results regarding the analysis of fractional differential equations for the solutions of Caputo-Fabrizio operators can be more helpful in our future work. We will study this work in future considering the novel analysis shown in aforementioned work.

Inspired from the above recent works on the application of fractional derivative to various models related to science and engineering, we wish to consider a mathematical model on the dynamics of cancer within the scope of fractional calculus that is formulated before in [9] for the integer case. We present the cancer model in fractional Caputo-Fabrizio derivative to investigate its behavior for different values of the fractional order parameter. We briefly discussed above the models associated to the cancer disease and the fractional related models recently published. Further, in the next section, we formulate the basic cancer model and its formulation. The basic concepts of the fractional derivative and their related results are presented in Section 3. Formulation of the cancer model with in the scope of fractional Caputo-Fabrizio derivative is presented in Section 4. In section 5, we further give a brief
details of the equilibrium points related to the cancer fractional model and their stability. A novel numerical approach for the solution of fractional cancer model is suggested in Section 6. Finally, the obtained results on the fractional cancer model are summarized in Section 7.

2. Basic model. Considering a cancer mathematical model for spontaneous tumor regression and progression, which is an interaction between the anticancer agent cell, lymphocytes and macrophages, that are natural killer cells, which destroy the malignant cells. The model is considered as a prey-predator like system. The model variables are given by \( x(t), y(t) \) and \( z(t) \) which respectively denote the densities of tumor cells, hunting predator cells, and resting cells at any time \( t \). The model can be described through the following system of nonlinear differential equations,

\[
\frac{dx(t)}{dt} = q + rx(t)\left(1 - \frac{x(t)}{K_1}\right) - \theta x(t)y(t),
\]

\[
\frac{dy(t)}{dt} = \beta y(t)z(t) - d_1 y(t),
\]

\[
\frac{dz(t)}{dt} = mz(t)\left(1 - \frac{z(t)}{K_2}\right) - \beta y(t)z(t) - d_2 z(t).
\]

Here in model (1), the conversion of normal cells to malignant ones is given by \( q \), \( \theta \) measures the conversion of tumor cells to hunting predator cells, the growth rate of tumor cells is given by \( r \), the conversion of resting cells to hunting cells is given by a rate \( \beta \), the natural death rates of hunting and resting cells is given by \( d_1 \) and \( d_2 \) respectively, \( m \) measures the growth rate of resting predator cell, \( K_1 \) and \( K_2 \) respectively measure the maximum carrying capacity of tumor and hunting cells. The given model (1) is about the cancer cells so the appropriate initial conditions be \( x(0) > 0, y(0) > 0, \) and \( z(0) > 0 \).

2.1. Reduced model. To make the model more simple, we are reducing its parameters. We then do the following set of new variables and modified time:

\[
\tilde{t} = \frac{qt}{K_1}, \quad y_1(t) = \frac{x(t)}{K_1}, \quad y_2(t) = \frac{\theta K_1 y(t)}{q}, \quad y_3(t) = \frac{z(t)}{K_2}.
\]

Using the expressions defined in (2) and applying into (1), we obtain the following reduced model,

\[
\frac{dy_1(t)}{dt} = 1 + A_1 y_1(t)(1 - y_1(t)) - y_1(t)y_2(t),
\]

\[
\frac{dy_2(t)}{dt} = A_2 y_2(t)y_3(t) - A_3 y_2(t),
\]

\[
\frac{dy_3(t)}{dt} = y_3(t)\left(A_4(1 - y_3(t)) - A_5 y_2(t) - A_6\right),
\]

where \( A_1 = rK_1/q \), \( A_2 = \beta K_1 K_2/q \), \( A_3 = K_1 d_1/q \), \( A_4 = mK_1/q \), \( A_5 = \beta/\theta \), \( A_6 = d_2 K_1/q \).

3. Basic concepts of fractional operator. Here in this subsection, we recalled the basic concepts involved in the Caputo-Fabrizio derivative.
Definition 3.1. [3]. For a function given by \( \varphi \in M^1(c,d) \) provided that \( d > a \), \( \omega \in [0,1] \), then the Caputo-Fabrizio derivative definition follows:

\[
D^\omega_t(\varphi(t)) = \frac{B(\omega)}{1-\omega} \int_a^t \varphi'(x) \exp \left[ -\omega \frac{t-x}{1-\omega} \right] dx.
\]  

(4)

In the above definition, \( B(\omega) \) represents the normalized function where \( B(0) = B(1) = 1 \) [3]. Whenever \( \varphi \notin M^1(c,d) \), then the representation of the definition above follows:

\[
D^\omega_t(\varphi(t)) = \omega B(\omega) \int_a^t (\varphi(t) - \varphi(x)) \exp \left[ -\omega \frac{t-x}{1-\omega} \right] dx.
\]  

(5)

Remark 1.

Letting \( \beta = \frac{1-\omega}{\omega} \in [0,\infty) \), \( \omega = \frac{1}{1+\beta} \in [0,1] \), so the equation (5) represented as follows:

\[
D^\beta_t(\varphi(t)) = \frac{B(\beta)}{\omega} \int_a^t \varphi'(x) \exp \left[ -\frac{t-x}{\beta} \right] dx, \quad B(0) = B(\infty) = 1.
\]  

(6)

Further,

\[
\lim_{\beta \to 0} \frac{1}{\beta} \exp \left[ -\frac{t-x}{\beta} \right] = \delta(x-t).
\]  

(7)

The associated integral to the Caputo-Fabrizio derivative is given in the following [14]:

Definition 3.2. Let \( 0 < \omega < 1 \), and the fractional derivative given by

\[
D^\omega_t(\varphi(t)) = g(t),
\]  

then the associated integral of the fractional order \( \omega \) described is as follows:

\[
I^\omega_t(\varphi(t)) = \frac{2(1-\omega)}{(2-\omega)B(\omega)}g(t) + \frac{2\omega}{(2-\omega)B(\omega)} \int_0^t g(s)ds, \quad t \geq 0.
\]  

(9)

Remark 2. Using the result

\[
\frac{2}{2B(\omega) - \omega B(\omega)} = 1,
\]  

(10)

which gives \( B(\omega) = \frac{2}{2-\omega}, \quad 0 < \omega < 1 \), the authors in [14] give the new CF fractional derivative of order \( 0 < \omega < 1 \), which is defined as below:

\[
D^\omega_t(\varphi(t)) = \frac{1}{1-\omega} \int_0^t \varphi'(x) \exp \left[ -\omega \frac{t-x}{1-\omega} \right] dx.
\]  

(11)

4. A fractional cancer model. The model proposed in (3) in integer case and its dynamics can be studied more effectively, therefore, we generalized the model (3) in Caputo-Fabrizio fractional derivative given as follows:

\[
\begin{align*}
C^\omega_0 D^\omega_t y_1(t) &= 1 + A_1 y_1(t)(1 - y_1(t)) - y_1(t) y_2(t), \\
C^\omega_0 D^\omega_t y_2(t) &= A_2 y_2(t) y_3(t) - A_3 y_2(t), \\
C^\omega_0 D^\omega_t y_3(t) &= y_3(t) \left( A_4(1 - y_3(t)) - A_5 y_2(t) - A_6 \right),
\end{align*}
\]  

(12)

with appropriate non-negative initial values.
4.1. **Equilibrium points and their analysis.** We obtain the possible equilibria for the fractional cancer growth model (12) by setting
\[
\frac{CF}{0}D_\tau^\sigma y_1 = \frac{CF}{0}D_\tau^\sigma y_2 = \frac{CF}{0}D_\tau^\sigma y_3 = 0
\]
The following possible equilibria for the cancer model (12) exists:

\[
P_1 = \left[ \frac{1}{2} \left( 1 + \sqrt{1 + \frac{4}{A_1}} \right), 0, 0 \right], \quad P_2 = \left[ \frac{1}{2} \left( 1 - \sqrt{1 + \frac{4}{A_1}} \right), 0, 0 \right],
\]

\[
P_3 = \left[ \frac{1}{2} \left( 1 + \sqrt{1 + \frac{4}{A_1}} \right), 0, \left( 1 - \frac{A_6}{A_4} \right) \right], \quad P_4 = \left[ \frac{1}{2} \left( 1 - \sqrt{1 + \frac{4}{A_1}} \right), 0, \left( 1 - \frac{A_6}{A_4} \right) \right],
\]

\[
P_5 = \left\{ \frac{1}{2A_1} \left[ (A_1 - \omega) - \sqrt{(A_1 - \omega)^2 + 4A_1} \right], \frac{A_4}{A_5} \left( 1 - \frac{A_3}{A_2} \right) - \frac{A_6}{A_5} \frac{A_3}{A_2} \right\},
\]

\[
P_6 = \left\{ \frac{1}{2A_1} \left[ (A_1 - \omega) + \sqrt{(A_1 - \omega)^2 + 4A_1} \right], \frac{A_4}{A_5} \left( 1 - \frac{A_3}{A_2} \right) - \frac{A_6}{A_5} \frac{A_3}{A_2} \right\}
\]

\[(13)\]

where \( \omega = (A_4 (A_2 - A_3) - A_2 A_6)/A_2 A_5 \). For the cancer growth model (12), we obtain multiple equilibria and we can see that the equilibrium \( P_1 \) is feasible biologically. The feasibility of the equilibrium \( P_3 \) depends on the condition \( A_4 > A_6 \). Similarly, the possibility of the last equilibrium point \( P_6 \) could be feasible biologically if \( A_3 > A_2 \) and the condition in the second component \( \frac{A_4}{A_5} \left( 1 - \frac{A_3}{A_2} \right) - \frac{A_6}{A_5} \frac{A_3}{A_2} > 0 \). The remaining equilibrium points \( P_2, P_4 \) and \( P_5 \) are not biologically feasible. The three possible equilibria for the cancer model given by (12) are \( P_1, P_3 \) and \( P_6 \) and their stability are presented in the following:

The cancer model given by (12) has the Jacobian matrix given by

\[
J = \begin{pmatrix}
-y_2 + (1 - 2y_1)A_1 & -y_1 & 0 \\
0 & y_3A_2 - A_3 & A_2y_2 \\
0 & -y_3A_5 & -A_5y_2 + A_4(1 - 2y_3) - A_6
\end{pmatrix}
\]

\[(14)\]

4.2. **Case 1.** At the equilibrium point \( P_1 \), we have

\[
J_{P_1} = \begin{pmatrix}
-\sqrt{A_1(A_1 + 4)} & -\frac{A_1 + \sqrt{A_1(A_1 + 4)}}{2A_1} & 0 \\
0 & -A_3 & 0 \\
0 & 0 & A_4 - A_6
\end{pmatrix}
\]

\[(15)\]

The eigenvalues associated to the matrix \( J_{P_1} \), are \(-\sqrt{A_1(A_1 + 4)}, -A_3, A_4 - A_6\). Here, we can see that the first two are negative while the third one with conditions imposed on equilibria \( A_4 > A_6 \) becomes positive, so this leads to instability of the system at \( P_1 \).

4.3. **Case 2.** At the equilibrium point \( P_2 \), we have

\[
J_{P_2} = \begin{pmatrix}
-\sqrt{A_1(A_1 + 4)} & -\frac{A_1 + \sqrt{A_1(A_1 + 4)}}{2A_1} & 0 \\
0 & A_2 \left( 1 - \frac{A_6}{A_4} \right) - A_3 & 0 \\
0 & -A_5 \left( 1 - \frac{A_6}{A_4} \right) & A_6 - A_4
\end{pmatrix}
\]

\[(16)\]

The associated eigenvalues of \( J_{P_2} \) are \(-\sqrt{A_1(A_1 + 4)}, A_6 - A_4, A_2 \left( 1 - \frac{A_6}{A_4} \right) - A_3\) according to the equilibrium point \( P_2 \) is clearly unstable.
5. Numerical procedure for the solution of cancer model. Here, in this section, we present an efficient numerical procedure for the solution of fractional Caputo-Fabrizio cancer model (3). The numerical procedure presented for the fractional cancer model is described in [1]. To follow the method, we have to write first the fractional cancer model (3) in fractional Volterra type and then the application of fundamental theorem of integration is used. To get the required scheme we apply it to the first equation of the fractional model (3). We have the following results:

\[
J_{P_{6}} = \begin{pmatrix}
L_1 & \frac{-\varpi+A_1+\sqrt{(A_1-\varpi)^2+4A_1}}{2A_1} & 0 \\
0 & 0 & \frac{A_2(A_4-A_6)-A_3A_4}{A_2} \\
0 & \frac{-A_3A_5}{A_2} & \frac{-A_3A_5}{A_2} - 2A_6
\end{pmatrix},
\]

where \( L_1 = \frac{A_3A_4+A_2(-A_4+\frac{\varpi-\sqrt{\varpi^2+A_1(-2\varpi+A_4+4)}A_4+A_6}{A_2A_5}) }{A_2A_5} \). The eigenvalues associated to the Jacobian matrix \( J_{P_{6}} \) are given by:

\[
\lambda_1 = \varpi - \sqrt{(A_1-\varpi)^2+4A_1},
\]

\[
\lambda_2 = \left[ -A_3A_4 + \sqrt{A_3^2A_4^2 - 4A_2^4A_3A_5\varpi/2A_2} \right],
\]

\[
\lambda_3 = \left[ -A_3A_4 - \sqrt{A_3^2A_4^2 - 4A_2^4A_3A_5\varpi} / 2A_2 \right].
\]

Obviously, \( \lambda_1 \) is clearly negative, the other two eigenvalues have negative real parts. So, at the conditions imposed on the equilibrium point \( P_6 \) and their stability clearly show the asymptotic stability of the cancer model (3).

4.4. Case 3. At the equilibrium point \( P_6 \), we have

\[
y_1(t) - y_1(0) = \frac{1 - \omega}{B(\omega)} G_1(t, y_1) + \frac{\omega}{B(\omega)} \int_0^t G_1(\vartheta, y_1) d\vartheta.
\]

We obtain by considering \( t = t_{m+1}, m = 0, 1, 2, \ldots \),

\[
y_1(t_{m+1}) - y_1(0) = \frac{1 - \omega}{B(\omega)} G_1(t_m, y_1(t_m)) + \frac{\omega}{B(\omega)} \int_0^{t_{m+1}} G_1(t, y_1) dt,
\]

and

\[
y_1(t_m) - y_1(0) = \frac{1 - \omega}{B(\omega)} G_1(t_m, y_1(t_{m-1})) + \frac{\omega}{B(\omega)} \int_0^{t_m} G_1(t, y_1) dt.
\]

Further, we obtain the difference between the successive terms as:

\[
y_{1m+1} - y_{1m} = \frac{1 - \omega}{B(\omega)} \left\{ G_1(t_m, y_1(t_m)) - G_1(t_{m-1}, y_1(t_{m-1})) \right\}
\]

\[
+ \frac{\omega}{B(\omega)} \int_{t_m}^{t_{m+1}} G_1(t, y_1) dt.
\]

We approximate the function given by \( G_1(t, y_1) \) in the interval \([t_k, t_{k+1}]\), using the interpolation polynomial

\[
P_k(t) \approx \frac{G(t_k, y_k)}{h}(t - t_{k-1}) - \frac{G(t_{k-1}, y_{k-1})}{h}(t - t_k),
\]
where $h = t_m - t_{m-1}$. The integrals given in (22) are obtained using the expressions given by $P_k(t)$, we then get the following:

$$
\int_{t_m}^{t_{m+1}} G_1(t, y_1) dt = \int_{t_m}^{t_{m+1}} \left( \frac{G_1(t_m, y_{1m})}{h} (t - t_m) - \frac{G_1(t_{m-1}, y_{1m-1})}{h} (t - t_m) \right) dt
$$

$$
= \frac{3h}{2} G_1(t_m, y_{1m}) - \frac{h}{2} G_1(t_{m-1}, y_{1m-1}). \tag{24}
$$

Using equation (24) in (22), we obtain the following after some simplifications,

$$
y_{1m+1} = y_{1m} + \left( \frac{1 - \omega}{B(\omega)} + \frac{3\omega h}{2B(\omega)} \right) G_1(t_m, y_{1m}) - \left( \frac{1 - \omega}{B(\omega)} + \frac{\omega h}{2B(\omega)} \right) G_1(t_{m-1}, y_{1m-1}). \tag{25}
$$

The procedure described above was for the first equation of the fractional cancer model (3) and follows the same procedure for the remaining equations of the fractional cancer model (3), we have the following:

$$
y_{2m+1} = y_{2m} + \left( \frac{1 - \omega}{B(\omega)} + \frac{3\omega h}{2B(\omega)} \right) G_2(t_m, y_{2m}) - \left( \frac{1 - \omega}{B(\omega)} + \frac{\omega h}{2B(\omega)} \right) G_2(t_{m-1}, y_{2m-1}),
$$

$$
y_{3m+1} = y_{3m} + \left( \frac{1 - \omega}{B(\omega)} + \frac{3\omega h}{2B(\omega)} \right) G_3(t_m, y_{3m}) - \left( \frac{1 - \omega}{B(\omega)} + \frac{\omega h}{2B(\omega)} \right) G_3(t_{m-1}, y_{3m-1}). \tag{26}
$$

We utilize the procedure presented above and obtain the graphical results for the fractional cancer model (12) with various values of the fractional order parameter $\omega$. Model variables and their dynamics are depicted in Figures 1-5. The time level for Figures 1-5 is considered up to 100 days. We observe in Figure 1, the model variables behavior for the integer case. For the fractional order $\omega = 0.95, 0.9, 0.85$ and 0.5, the population of tumor density, hunting cell density, and resting cell density decrease. By decreasing the fractional order parameter $\omega$, we can see the graphical results in Figures 2-5, the decrease in the population of tumor density, hunting cell density, and resting cell density. Figures 1-5 are obtained by using the step size $h = 0.002$ with the initial conditions and set of parameter values $A_1 = 0.4, A_2 = 5.9, A_3 = 0.3, A_4 = 0.5, A_5 = 0.06, A_6 = 0.05$. While Figures 6-8 show the chaotic behavior for the cancer fractional model (12) obtained by using the parameter values $A_1 = 2.5, A_2 = 4.5, A_3 = 0.6, A_4 = 3.5, A_5 = 02, A_6 = 0.1$. Further, Figures 9-11 are obtained which show the chaotic behavior by considering the set of parameters above with $h = 0.2$ and the fractional order parameter $\omega = 1, 0.9, 0.8$.

6. **Conclusion.** The dynamics of a cancer model in fractional derivative is analyzed. Initially, we presented a cancer model in integer case and then, with some set of suitable parameters scaling the model is reduced. The reduced model was considered and applied the Caputo-Fabrizio fractional operator. We found that there exists multiple equilibria for the cancer fractional model. The possible three
equilibria that is feasible biologically were used to present the model stability. We found the only equilibrium that is feasible and for which the fractional cancer model is asymptotically stable. A novel numerical scheme (Adams-Bashforth) for the solution of the fractional model is presented. Numerical solution of the fractional cancer model with various values of the fractional order parameter are obtained for different set of parameter values. The present investigations confirm that fractional order modeling of cancer dynamics can be best describe the complexities involve in the tumor growth. This fractional model will be more helpful for the real data of patients who are suffering from cancer. The real data can be fitted to the model in order to investigate the realistic parameters and then that parameters should be used to study the dynamics of the cancer in more accuracy by implementing policy for the cancer reduction in community. The dynamics of the model variables and the chaotic behavior for various values of the fractional order parameter reveal
the importance of the fractional derivative. In future, we will extend this work by using the novel techniques available in literature to obtain their solutions and make comparison.

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Figure 3. The plot shows the dynamics of the model (1), when $\omega = 0.9$. 
Figure 4. The plot shows the dynamics of the model (1), when $\omega = 0.85$. 
Figure 5. The plot shows the dynamics of the model (1), when $\omega = 0.5$. 
Figure 6. The plot shows the dynamics of the model (1), when $\omega = 1$. 
Figure 7. The plot shows the dynamics of the model (1), when $\omega = 0.9$. 
Figure 8. The plot shows the dynamics of the model (1), when $\omega = 0.8$. 
Figure 9. The plot shows the dynamics of the model (1), when $\omega = 1$. 
Figure 10. The plot shows the dynamics of the model (1), when $\omega = 0.9$. 
Figure 11. The plot shows the dynamics of the model (1), when $h = 0.2$ and $\omega = 0.8$. 
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