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FRACTIONAL MATHEMATICAL MODEL UNDERLYING MIXED TREATMENTS USING ENDOCRINE DIET THERAPY AND IMMUNOTHERAPY FOR BREAST CANCER

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Abstract. To understand cancer as a biomathematical process, we establish our model to give an analytical and a numerical examination of the fractional derivative impact on developing breast cancer with endocrine diet therapy and immunotherapy. So, we try, in this paper, to formulate the cancer dynamics involving the normal cells, tumor cells, immune cells, estrogen (endocrine parameter) and immunotherapy. We show the wellposedness of the breast cancer model and we analyze the existence and the stability of the equilibria, then, we discuss the numerical results in order to conclude that the use of fractional derivatives provides more useful information about the stability of the breast cancer dynamics with mixed treatments model.

Keywords: cancer modeling; breast cancer; hormonal therapy; immunotherapy; oncolytic treatement; fractional order derivative equation.

2020 AMS Subject Classification: 92B05, 26A33, 34A08, 34A12, 37M05.

1. INTRODUCTION

Cancer is a significant factor of death, the second cause of mortality worldwide after cardiovascular diseases [1], it can be caused by a variety of factors [2, 3], like smoking, poor eating,

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genetic factors that can be transmitted from parents and others under research. Cancer can attack in any organ of the body like lung, breast, prostate, colon and others, which can be brought on by genetic changes that make healthy cells grow and divide uncontrollably with abnormal manners and form a masses or tissues called tumors. The treatments of cancer are vulnerable include surgery, chemotherapy, radiation therapy, immunotherapy, virotherapy and many others new cures that doctors and health scientists continue to develop and optimize to achieve a good results. The most frequent cancer diagnosis among female is breast cancer [4], according to "Global Cancer Statistics 2020," a collaborative report from the American Cancer Society (ACS) and the International Agency for Research on Cancer (IARC), it is estimated about 2.3 million new cases per year in the world. The reseach is permanently actif about this subject to recognize the main elements involved in the behavior, dynamics and evolution of cancer in order to highlight the aspect of healing, it describes the cell cycle control in breast cancer as potential oncogenes or tumor suppressor genes [5, 6]. To better understand the cancer behavior and how to overcome this pathology, many researcher use theoretical and empirical tools as main manner to study the phenomenon biomathematically [7]. The development of epidemiology methods for tracking dynamics diseases could reap advantages from the use of modeling and simulation, which are crucial decision-making tools. In order to handle actual conditions, the models must be customized for each individual case because every disease has unique biological properties. Several recent studies have produced some intriguing findings, such as those demonstrating theorically how appropriate treatment might limit cells proliferation [8], the estimation of cancer velocity as a hybrid PDE-ODE model [9], many mathematical and analytical techniques have been developed to examine the link between tumor cells and the immune system throughout the therapeutic phase, most of them are based on ordinery differential equations (ODEs) [10, 11], stochastic processes in modeling [12–15] can measure time courses of cells cancer growth, using several mathematical models of diffusion imaging. In [16], prognostic factors and genotypes among patients with breast cancer are predicted to opting for an appropriate therapeutic techniques and treatments, the dataset of cellular images is also used in the diagnosis and treatment processes of various diseases as an artificial intelligence-based technologies [17]. The model named Normal-Tumor-Immune-UnHealthy Diet Model (NTIUNHDM) [10, 11] is

studied to show that boosting of the immune system can contribute to reduce the risk of cancer. In a comparable direction, we have noticed that among the most recent models, the model investigating the effects of estrogen combined with immunotherapy describe cancer in a realistic way by the following equations system.

$$
(1) \qquad \begin{cases} \dfrac{dN}{dt} &= N(a_1 - b_1 N) - \frac{d_1 NT}{1+c_1 T} - l_1 NE, \\ \dfrac{dT}{dt} &= T(a_2 - b_2 T) - g_1 IT - m_1 T + l_1 NE, \\ \dfrac{dI}{dt} &= s + \frac{d_2 IT}{1+c_2 T} - g_2 IT - m_2 I - \frac{p_E IE}{j_E+E} + \frac{p_M IM}{j_M+M}, \\ \dfrac{dE}{dt} &= p - \theta E, \\ \dfrac{dM}{dt} &= v - nM + \frac{p_I MI}{j_I+I}. \end{cases}
$$

This model describe the interactions between normal cells N, tumor cells T , immune cells I, estrogen E and immunotherapy M. In the first equation, the variation of normal cells N is displayed by logistic function $N(a_1 - b_1 N)$, where a_1 is the logistic growth rate and b_1 is the natural death of the normal cells; saturated term $\frac{d_1 NT}{1+c_1 T}$,where d_1 describes the inhibition rate of normal cells and ε expresses the saturation effect due to the DNA damage; bilinear fonction $l_1 NE$ which means the reduction effect of excess estrogen leads to DNA mutation and thus normal cells population. In the second equation, the tumor cells variate with logistic growth, $T(a_2 - b_2 T)$, where a_2 is the logistic growth rate and b_2 is the natural death of the tumor cells; the immune response and tumor cells effect bilinearly tumor cells $g_1 IT$ where , g_1 is the inactivation rate of tumor cells due immune cells ; $m_1 T$ natural degradation of tumor cells is linear,where m_1 is the death rate of tumor cells and the bilinear mutation of normal cells is transformed to tumor cells $l_1 NE$. In the third equation, s is the constant source rate of immune response; tumor cells and the immune response effect bilinearly the immune response $g_2 IT$, where , g_2 is the inactivation of immune cells due tumour cells; $m_2 I$ the immune response naturally degrades in a linear fonction, where m is the natural death rate of immune cells; $\frac{d_2 IT}{1+c_2 T}$,

where r is the immune response rate, and o is the immune threshold rate; $\frac{p_E IE}{j_E+E}$ saturated term the immune response of due to the estrogen; $\frac{p_M IM}{j_M+M}$ saturated term the immune response due to the immunotherapy. In the fourth equation, the s, this hormonal variable estrogen exist with p, where p is the source rate of estrogen, and θE is linear fonction decreasing the estrogen, where θ is the decay rate from the body. In the fifth equation, the production of immunotherapy from activated immune cells is injected with the fonction v, dissipate lineary nM and be saturated by $\frac{p_I MI}{j_I+I}$.

To study this research in our situation, we formulate the dynamic of breast cancer with fractional derivatives approach to investigate these studies. We cite as examples to illustrate how the application of fractional calculations can be used to study the behavior of various dynamics [18–22]. This approach is regarded as the generalization of the standard theory of calculus to derivatives and integrals, and its success stems from its demonstrated efficacy in accurately.

$$
\left\{
\begin{array}{rcl}
D^{\alpha}N &=& N(a_1 - b_1 N) - \frac{d_1 NT}{1+c_1 T} - l_1 NE, \\
D^{\alpha}T &=& T(a_2 - b_2 T) - g_1 IT - m_1 T + l_1 NE, \\
D^{\alpha}I &=& s + \frac{d_2 IT}{1+c_2 T} - g_2 IT - m_2 I - \frac{p_E IE}{j_E+E} + \frac{p_M IM}{j_M+M}, \\
D^{\alpha}E &=& p - \theta E, \\
D^{\alpha}M &=& v - nM + \frac{p_I MI}{j_I+I}.
\end{array}
\right. \tag{2}
$$

Where D^{α} is the fractional differentiation operator and α is fractional derivative order.

Every characterisation of the equation's system of model (2) is translated using the schematization of a compartmental diagram at Fig. 1 of breast cancer dynamic as follow.

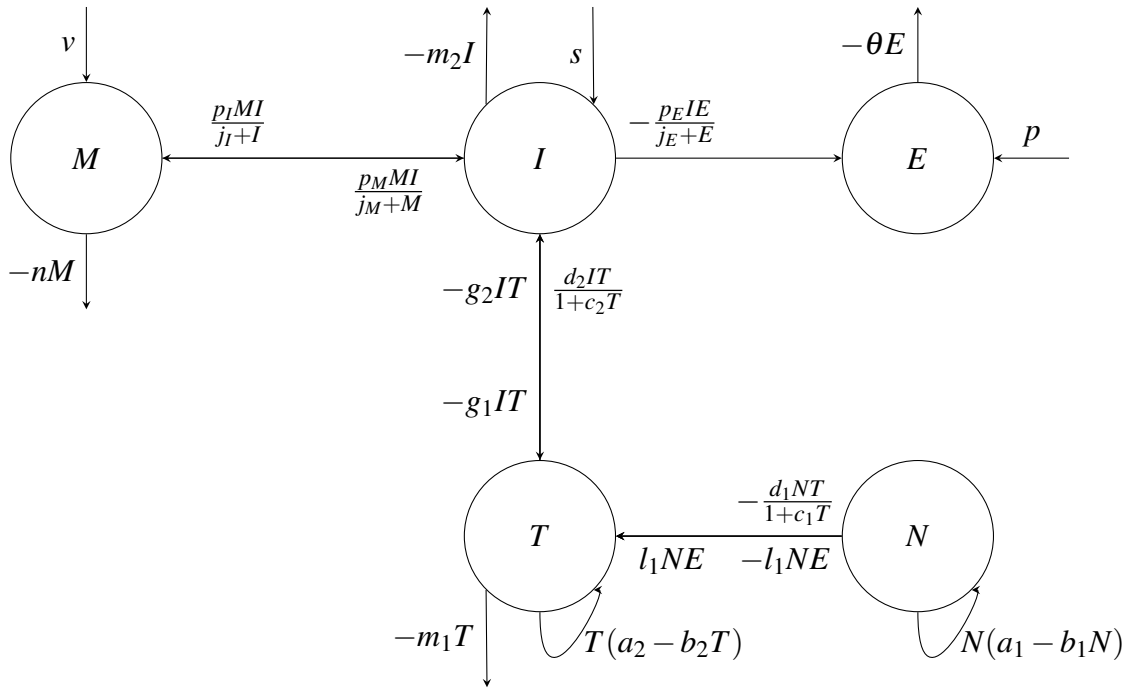

FIGURE 1. Schematic diagram of breast cancer behavior of the formulation (2)

This paper is organized into sections: The next one will provide some mathematical resources regarding fractional derivative, section 3 will establish the solutions and analyze the outcomes of the fractional system model (2), section 4 will provide numerical interpretations, and section 5 will conclude all sets.

2. MATHEMATICAL TOOLS

The fractional order integral and derivative are briefly defined in this section. We provide some preliminary definitions as follow:

Definition 1. *The α-order fractional integral of the function f is defined by:*

$$I^{\alpha}f = \frac{1}{\Gamma(\alpha)}\int_0^t (t-s)^{\alpha-1}f(s)ds$$

With $\alpha > 0$ and $f : \mathbb{R} \to \mathbb{R}$.

Where $\Gamma(.)$ is the known function Gamma ($\Gamma : z \mapsto \int_0^{+\infty} t^{z-1}\mathrm{e}^{-t}\,\mathrm{d}t$).

Definition 2. *The Caputo fractional derivative of the function f is given by:*

$$D^{\alpha} f = \frac{1}{\Gamma(1-\alpha)} \int_0^t \frac{f'(s)}{(t-s)^{\alpha}} ds$$

With $0 < \alpha < 1$ and $f : \mathbb{R} \to \mathbb{R}$.

$$D^{\alpha} f = \frac{1}{\Gamma(n-\alpha)} \int_0^t \frac{f^{(n)}(y)}{(t-y)^{\alpha-n+1}} dy, \quad n-1 < \alpha < n$$

In general case.

Remark 1. *The Caputo fractional derivative can be defined as an inverse operation of fractional integration. It can be presented as follow by the next definition:*

$$D^{\alpha} f = I^{n-\alpha} D^n f$$

With $D = d/dt$ and $n-1 < \alpha < n, \quad n \in \mathbb{N}^*$.

Definition 3. *[23] The Mittag-Leffler function is defined by:*

$$E_{\alpha} = \sum_{i=0}^{+\infty} \frac{z^i}{\Gamma(\alpha i + 1)}$$

With $\alpha > 0$.

The Mittag-Leffler function, which may be thought of as a generalization of the role of the exponential function for ordinary differential equations, plays a significant role in case of fractional differential equations.

Theorem 1. *[24] The fractional differential equation $D^{\alpha} y = g(t,y), y(t_0) = y_0$, with $0 < \alpha \leq 1$, D^{α} is the time fractional order derivative in the Caputo sense and $g(t,y) : R^+ \times R^m \to R^m$ is a vector field. Jac is considered as Jacobian matrix of $g(t,y)$ at the equilibruim point.*
So, the equilibrium point is local asymptotically stable if only if $\forall \lambda \in spc(Jac)$, $|arg(\lambda)| > \frac{\alpha\pi}{2}$(See Fig. 2).

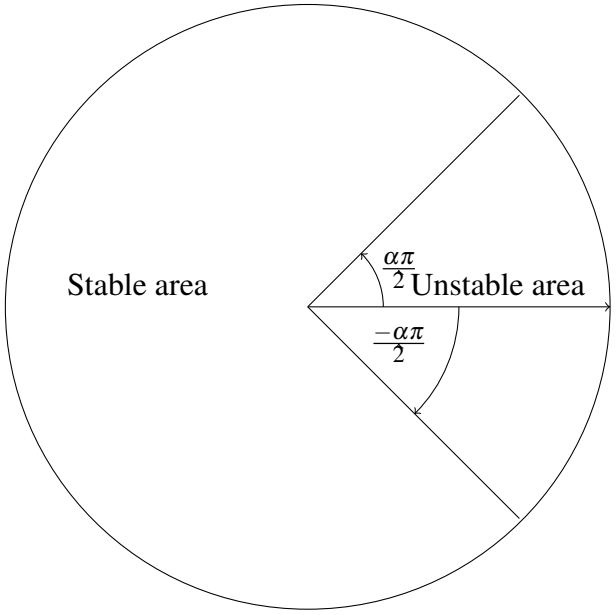

FIGURE 2. Fractional derivative stability diagram

3. ANALYSIS OF FRACTIONAL-ORDER MATHEMATICAL MODEL FOR BREAST CANCER

To demonstrate how well-posed the formulation is, we will establish the positivity and boundedness of solutions in this section. We will also discuss about the local stability and analyze the equilibrium states.

3.1. Well-posedness of breast cancer dynamic. We will concede that the initial conditions of the solutions N_0, T_0, I_0, E_0 and M_0 are positive for biological reasons.

Proposition 1. *The solution of the problem* (2) *is non-negative.*

Proof. Now, Let's show that the $\Omega = \{(N,T,I,E,M) \in \mathbb{R}^5_+ / \text{ for all time } t\}$ that express the variable regions is a positively invariant.
Indeed, for $(N,T,T,E,M) \in \Omega$, we have:

$$D^\alpha N\big|_{N=0} = 0 \geq 0,$$

$$D^\alpha T\big|_{T=0} = 0 \geq 0,$$

$$D^\alpha I\big|_{I=0} = s \geq 0,$$

$$D^{\alpha}E\big|_{E=0} = p \geq 0,$$

$$D^{\alpha}M\big|_{M=0} = v(0) \geq 0.$$

Due to biological limitations, all initial conditions of the solutions are therefore positive and logically constrained. So, we deduce the result of non-negativity of the solusions. □

Proposition 2. *The solution of the problem* (2) *is bounded.*

Proof. For the boundness, we have from (2):

$$D^{\alpha}N \leq N(a_1 - b_1 N)$$

We assume that λ_N and C_N two positive constants, to the effect that:

$$D^{\alpha}N + \lambda_N N \leq C_N$$

So, we deduce that N is bounded because: $N \leq N(0)E_{\alpha}(-\lambda_N t^{\alpha}) + C_N(1 - E_{\alpha}(-\lambda_N t^{\alpha}))$.
We have also, with $a = Max(a_1, a_2)$ and $b = Min(b_1, b_2)$:

$$D^{\alpha}(N+T) \leq (N+T)(a - b(N+T))$$

Then, we pose λ_T and C_T two positive constants, to the effect that:

$$D^{\alpha}(N+T) + \lambda_T(N+T) \leq C_T$$

Since N is bounded, T is also.

$$D^{\alpha}I \leq s + (\frac{d_2}{c_2} - m_2 - p_E + p_M)I$$

We pose λ_I and C_I two positive constants, to the effect that:

$$D^{\alpha}I + \lambda_I I \leq C_I$$

So, we deduce that I is bounded.
From the model (2) we get the next equality.

$$D^{\alpha}E + \theta E = p$$

$$E = E(0)E_{\alpha}(-\theta t^{\alpha}) + p(1 - E_{\alpha}(-\theta t^{\alpha}))$$

That give the bounded solution for E.

The last equation of model (2) give:

$$D^{\alpha}M \leq v - nM + p_I M$$

We pose λ_T and C_T two positive constants, to the effect that:

$$D^{\alpha}M + \lambda_M M \leq C_M$$

We deduce the boundedness of M.

As a final result, the solution of the problem (2) is bounded. □

3.2. Breast cancer equilibria. The steady states of the model (2), the equilibrium instance verify the following equation's system:

$$\left\{\begin{array}{rcl} 0 & = & N(a_1 - b_1 N) - \frac{d_1 NT}{1+c_1 T} - l_1 NE, \\ 0 & = & T(a_2 - b_2 T) - g_1 IT - m_1 T + l_1 NE, \\ 0 & = & s + \frac{d_2 IT}{1+c_2 T} - g_2 IT - m_2 I - \frac{p_E IE}{j_E+E} + \frac{p_M IM}{j_M+M}, \\ 0 & = & p - \theta E, \\ 0 & = & v - nM + \frac{p_I MI}{j_I+I}. \end{array}\right. \tag{3}$$

With simple calculation, we notice the equilibrium points as follow:

• Free tumor equilibrium point $P_f(N_f, 0, I_f, E_f, M_f)$.

With:

$$N_f = \frac{a_1}{b_1 + \frac{l_1 p}{\theta}}$$

$$I_f = \frac{s}{m_2 + \frac{p_E p}{\theta j_E + p} - \frac{p_M M_f}{j_M + M_f}}$$

$$E_f = \frac{p}{\theta}$$

$$M_f = \frac{v}{n - \frac{p_I I_f}{j_I + I_f}}$$

It exist if $n \geq \frac{p_I I_f}{j_I + I_f}$ and $m_2 + \frac{p_E p}{\theta j_E + p} \geq \frac{p_M M_f}{j_M + M_f}$.

• Death free tumor equilibrium points $P_{df}(0,0,I_{df},E_{df},M_{df})$.

With:

$$I_{df} = Roots(P_{I_{df}})$$

$$E_{df} = \frac{p}{\theta}$$

$$M_{df} = \frac{v}{n - \frac{p_I I_{df}}{j_I + I_{df}}}$$

We pose:

$$P_{I_{df}} = A_{df}X^2 + B_{df}X + C_{df}$$

With:

$A_{df} = vp_M - (m_2 + \frac{p_E p}{\theta j_E + p})(v + j_M(n - p_I))$,

$B_{df} = vp_M j_I - (m_2 + \frac{p_E p}{\theta j_E + p})(j_I(v + j_M n)) + s(v + j_M(n - p_I))$,

$C_{df} = s j_I(v + j_M n)$.

It exist if $n \geq \frac{p_I I_{df}}{j_I + I_{df}}$.

• Death with tumor equilibrium points $P_d(0,T_d,I_d,E_d,M_d)$.

With:

$$T_d = Roots(P_{I_d})$$

$$I_d = \frac{a_2 - m_1 - b_2 T_d}{g_1}$$

$$E_d = \frac{p}{\theta}$$

$$M_d = \frac{v}{n - \frac{p_I I_d}{j_I + I_d}}$$

We pose:

$$P_{I_d} = A_d X^3 + B_d X^2 + C_d X + D_d$$

With:

$A_d = b_2 g_2$,

$B_d = b_2 m_2 + \frac{b_2 g_2}{c_2} - b_2 \frac{d_2}{c_2} + (b_2 - a_2)(\frac{p_E E_d}{j_E + E_d} - \frac{p_M M_d}{j_M + M_d}) - a_2 g_2 + m_1 g_2$,

$C_d = b_2 m_2 \frac{1}{c_2} - a_2 m_2 - a_2 d g_2 \frac{1}{c_2} + \frac{d_2}{c_2} a_2 + (b_2 - a_2)\frac{1}{c_2}(\frac{p_E E_d}{j_E + E_d} - \frac{p_M M_d}{j_M + M_d}) + g_1 s + m_1 m_2 + m_1 g_2 \theta - \frac{d_2}{c_2} m_1 + m_1(\frac{p_E E_d}{j_E + E_d} - \frac{p_M M_d}{j_M + M_d})$,

$D_d = \frac{m_1}{c_2}(\frac{p_E E_d}{j_E+E_d} - \frac{p_M M_d}{j_M+M_d}) + \frac{m_1 m_2}{c_2} + \frac{g_1 s}{c_2} - \frac{a_2 m_2}{c_2}$.

It exist if $n \geq \frac{p_I I_d}{j_I+I_d}$ and $a_2 \geq m_1 + b_2 T_d$.

• Co-existing point $P_c(N_c, T_c, I_c, E_c, M_c)$.

With:

$$N_c = \frac{1}{b_1}\left(a_1 - \frac{d_1 T_c}{1+c_1 T_c} - l_1 \frac{p}{\theta}\right)$$

$$T_c = Roots(P_{I_c})$$

$$I_c = \frac{s}{g_2 T_c + m_2 + \frac{p_E p}{\theta j_E + p} - \frac{d_2 T_c}{1+c_2 T_c} - \frac{p_M M_c}{j_M+M_c}}$$

$$E_c = \frac{p}{\theta}$$

$$M_c = \frac{v}{n - \frac{p_I I_c}{j_I+I_c}}$$

We pose:

$$P_{I_c} = A_c X^2 + B_c X + C_c$$

With:

$A_c = b_2$,

$B_c = g_1 I_c + m_1 - a_2$,

$C_c = l_1 N_c E_c$,

It exist if $n \geq \frac{p_I I_c}{j_I+I_c}$, $\quad g_2 T_c + m_2 + \frac{p_E p}{\theta j_E+p} \geq \frac{d_2 T_c}{1+c_2 T_c} + \frac{p_M M_c}{j_M+M_c}$ and $a_1 \geq \frac{d_1 T_c}{1+c_1 T_c} + l_1 \frac{p}{\theta}$.

3.3. Local stability of the equilibria. In this part, we give the stability resultats as the following theorems.

Theorem 2. *At free tumor state $P_f(N_f, 0, I_f, E_f, M_f)$.*

The equilibrium point P_f is stable if $|Arg(Roots(Q_f))| > \frac{\alpha\pi}{2}$.

Proof. The Jacobian matrix at P_f is:

$$J_{P_f} = \begin{pmatrix} a_1 - 2b_1N_f - l_1E_f & -d_1N_f & 0 & -l_1N_f & 0 \\ l_1E_f & a_2 - g_1I_f - m_1 & 0 & l_1N_f & 0 \\ 0 & d_2I_f - g_2I_f & -m_2 - \frac{p_E E_f}{j_E+E_f} + \frac{p_M M_f}{j_M+M_f} & -\frac{p_E j_E I_f}{(j_E+E_f)^2} & \frac{p_M j_M I_f}{(j_M+M_f)^2} \\ 0 & 0 & 0 & -\theta & 0 \\ 0 & 0 & \frac{p_I j_I M_f}{(j_I+I_f)^2} & 0 & -n + \frac{p_I I_f}{j_I+I_f} \end{pmatrix}$$

The characteristic polynomial of J_{P_f} is:

$$Q_f = (X+\theta)[X^4 + A_3X^3 + A_2X^2 + A_1X + A_0]$$

With:

$A_0 = (-n + \frac{p_I I_f}{j_I+I_f})((a_1 - 2b_1N_f - l_1E_f)(-m_2 - \frac{p_E E_f}{j_E+E_f} + \frac{p_M M_f}{j_M+M_f})(-m_2 - \frac{p_E E_f}{j_E+E_f} + \frac{p_M M_f}{j_M+M_f}) - (-d_1N_f)(l_1E_f)(-m_2 - \frac{p_E E_f}{j_E+E_f} + \frac{p_M M_f}{j_M+M_f}) - (-g_1T_f)(\frac{d_2I_f}{(1+c_1T_f)^2} - g_2I_f)(a_1 - 2b_1N_f - l_1E_f)) - (a_1 - 2b_1N_f - l_1E_f)(-m_2 - \frac{p_E E_f}{j_E+E_f} + \frac{p_M M_f}{j_M+M_f})(\frac{p_I j_I M_f}{(j_I+I_f)^2})(\frac{p_M j_M I_f}{(j_M+M_f)^2})$,

$A_1 = (\frac{p_I j_I M_f}{(j_I+I_f)^2})(\frac{p_M j_M I_f}{(j_M+M_f)^2})((a_1 - 2b_1N_f - l_1E_f) + (-m_2 - \frac{p_E E_f}{j_E+E_f} + \frac{p_M M_f}{j_M+M_f})) + (-n + \frac{(}{a}1 - 2b_1N_f - l_1E_f)cp_I I_f j_I + I_f)((-d_1N_f)(l_1E_f) + (-g_1T_f)(\frac{d_2I_f}{(1+c_1T_f)^2} - g_2I_f) - (a_1 - 2b_1N_f - l_1E_f)(-m_2 - \frac{p_E E_f}{j_E+E_f} + \frac{p_M M_f}{j_M+M_f}) - (a_1 - 2b_1N_f - l_1E_f)(a_2 - g_1I_f - m_1) - (-m_2 - \frac{p_E E_f}{j_E+E_f} + \frac{p_M M_f}{j_M+M_f})(-m_2 - \frac{p_E E_f}{j_E+E_f} + \frac{p_M M_f}{j_M+M_f})) - (a_1 - 2b_1N_f - l_1E_f)(-m_2 - \frac{p_E E_f}{j_E+E_f} + \frac{p_M M_f}{j_M+M_f})(-m_2 - \frac{p_E E_f}{j_E+E_f} + \frac{p_M M_f}{j_M+M_f}) + (-d_1N_f)(l_1E_f)(-m_2 - \frac{p_E E_f}{j_E+E_f} + \frac{p_M M_f}{j_M+M_f}) + (-g_1T_f)(\frac{d_2I_f}{(1+c_1T_f)^2} - g_2I_f)(a_1 - 2b_1N_f - l_1E_f)$,

$A_2 = (-n + \frac{p_I I_f}{j_I+I_f})((a_1 - 2b_1N_f - l_1E_f) + (-m_2 - \frac{p_E E_f}{j_E+E_f} + \frac{p_M M_f}{j_M+M_f}) + (-m_2 - \frac{p_E E_f}{j_E+E_f} + \frac{p_M M_f}{j_M+M_f})) + (a_1 - 2b_1N_f - l_1E_f)(-m_2 - \frac{p_E E_f}{j_E+E_f} + \frac{p_M M_f}{j_M+M_f}) + (a_1 - 2b_1N_f - l_1E_f)(-m_2 - \frac{p_E E_f}{j_E+E_f} + \frac{p_M M_f}{j_M+M_f}) + (-m_2 - \frac{p_E E_f}{j_E+E_f} + \frac{p_M M_f}{j_M+M_f})(-m_2 - \frac{p_E E_f}{j_E+E_f} + \frac{p_M M_f}{j_M+M_f}) - (-d_1N_f)(l_1E_f) - (-g_1T_f)(\frac{d_2I_f}{(1+c_1T_f)^2} - g_2I_f) - (\frac{p_I j_I M_f}{(j_I+I_f)^2})(\frac{p_M j_M I_f}{(j_M+M_f)^2})$,

$$A_3 = n - \frac{p_I I_f}{j_I + I_f} - (a_1 - 2b_1 N_f - l_1 E_f) - (a_2 - g_1 I_f - m_1) - (-m_2 - \frac{p_E E_f}{j_E + E_f} + \frac{p_M M_f}{j_M + M_f}).$$

So, we get the stability, since $|arg(Roots(Q_f))| > \frac{\alpha\pi}{2}$, according to the theorem 1, . □

Theorem 3. *At death free tumor stages* $P_{df}(0,0,I_{df},E_{df},M_{df})$.

The equilibrium point P_{df} *is stable if* $l_1 E_{df} \geq a_1$, $m_1 + g_1 I_{df} \geq a_2$ *and* $|arg(Roots(Q_{df}))| > \frac{\alpha\pi}{2}$.

Proof. The Jacobian matrix at P_{df} is:

$$J_{P_{df}} = \begin{pmatrix} a_1 - l_1 E_{df} & 0 & 0 & 0 & 0 \\ l_1 E_f & a_2 - g_1 I_{df} - m_1 & 0 & 0 & 0 \\ 0 & d_2 I_{df} - g_2 I_{df} & -m_2 - \frac{p_E E_{df}}{j_E + E_{df}} + \frac{p_M M_{df}}{j_M + M_{df}} & -\frac{p_E j_E I_{df}}{(j_E + E_{df})^2} & \frac{p_M j_M I_{df}}{(j_M + M_{df})^2} \\ 0 & 0 & 0 & -\theta & 0 \\ 0 & 0 & \frac{p_I j_I M_{df}}{(j_I + I_{df})^2} & 0 & -n + \frac{p_I I_{df}}{j_I + I_{df}} \end{pmatrix}$$

The characteristic polynomial of $J_{P_{df}}$ is:

$$Q_{df} = (X + \theta)(X + l_1 E_{df} - a_1)(X + m_1 + g_1 I_{df} - a_2)[X^2 + B_1 X + B_0]$$

With:

$$B_0 = (n - \frac{p_I I_{df}}{j_I + I_{df}})(m_2 + \frac{p_E E_{df}}{j_E + E_{df}} - \frac{p_M M_{df}}{j_M + M_{df}}) - \frac{p_M j_M I_{df} p_I j_I M_{df}}{(j_I + I_{df})^2 (j_M + M_{df})^2},$$

$$B_1 = (n + m_2 + \frac{p_E E_{df}}{j_E + E_{df}} - \frac{p_M M_{df}}{j_M + M_{df}} - \frac{p_I I_{df}}{j_I + I_{df}}).$$

So, we have the stability, since, $l_1 E_{df} \geq a_1$, $m_1 + g_1 I_{df} \geq a_2$ and $|arg(Roots(Q_{df}))| > \frac{\alpha\pi}{2}$. □

Theorem 4. *At death with tumor stages* $P_d(0,T_d,I_d,E_d,M_d)$

The equilibrium point P_d *is stable if* $|Arg(Roots(Q_d))| > \frac{\alpha\pi}{2}$.

Proof. The Jacobian matrix at P_d is:

$$J_{P_d} = \begin{pmatrix} a_1 - \frac{d_1 T_d}{1+c_1 T_d} - l_1 E_d & 0 & 0 & 0 & 0 \\ l_1 E_d & a_2 - 2b_2 T_d - g_1 I_d - m_1 & -g_1 T_d & 0 & 0 \\ 0 & \frac{d_2 I_d}{(1+c_1 T_d)^2} - g_2 I_d & \frac{d_2 T_d}{1+c_2 T_d} - m_2 - \frac{p_E E_d}{j_E+E_d} + \frac{p_M M_d}{j_M+M_d} & -\frac{p_E j_E I_d}{(j_E+E_d)^2} & \frac{p_M j_M I_d}{(j_M+M_d)^2} \\ 0 & 0 & 0 & -\theta & 0 \\ 0 & 0 & \frac{p_I j_I M_d}{(j_I+I_d)^2} & 0 & -n + \frac{p_I I_d}{j_I+I_d} \end{pmatrix}$$

The characteristic polynomial of J_{P_d} is:

$$Q_d = (X+\theta)[X^4 + C_3 X^3 + C_2 X^2 + C_1 X + C_0]$$

With:

$C_0 = (-n + \frac{p_I I_d}{j_I+I_d})((a_1 - \frac{d_1 T_d}{1+c_1 T_d} - l_1 E_d)(\frac{d_2 T_d}{1+c_2 T_d} - m_2 - \frac{p_E E_d}{j_E+E_d} + \frac{p_M M_d}{j_M+M_d})(\frac{d_2 T_d}{1+c_2 T_d} - m_2 - \frac{p_E E_d}{j_E+E_d} + \frac{p_M M_d}{j_M+M_d}) + (g_1 T_d)(\frac{d_2 I_d}{(1+c_1 T_d)^2} - g_2 I_d)(a_1 - \frac{d_1 T_d}{1+c_1 T_d} - l_1 E_d)) - (a_1 - \frac{d_1 T_d}{1+c_1 T_d} - l_1 E_d)(\frac{d_2 T_d}{1+c_2 T_d} - m_2 - \frac{p_E E_d}{j_E+E_d} + \frac{p_M M_d}{j_M+M_d})(\frac{p_I j_I M_d}{(j_I+I_d)^2})(\frac{p_M j_M I_d}{(j_M+M_d)^2})$,

$C_1 = (\frac{p_I j_I M_d}{(j_I+I_d)^2})(\frac{p_M j_M I_d}{(j_M+M_d)^2})((a_1 - \frac{d_1 T_d}{1+c_1 T_d} - l_1 E_d) + (\frac{d_2 T_d}{1+c_2 T_d} - m_2 - \frac{p_E E_d}{j_E+E_d} + \frac{p_M M_d}{j_M+M_d})) + (-n + (a_1 - \frac{d_1 T_d}{1+c_1 T_d} - l_1 E_d) c p_I I_d j_I + I_d)((-g_1 T_d)(\frac{d_2 I_d}{(1+c_1 T_d)^2} - g_2 I_d) - (a_1 - \frac{d_1 T_d}{1+c_1 T_d} - l_1 E_d)(\frac{d_2 T_d}{1+c_2 T_d} - m_2 - \frac{p_E E_d}{j_E+E_d} + \frac{p_M M_d}{j_M+M_d}) - (a_1 - \frac{d_1 T_d}{1+c_1 T_d} - l_1 E_d)(\frac{d_2 T_d}{1+c_2 T_d} - m_2 - \frac{p_E E_d}{j_E+E_d} + \frac{p_M M_d}{j_M+M_d}) - (\frac{d_2 T_d}{1+c_2 T_d} - m_2 - \frac{p_E E_d}{j_E+E_d} + \frac{p_M M_d}{j_M+M_d})(\frac{d_2 T_d}{1+c_2 T_d} - m_2 - \frac{p_E E_d}{j_E+E_d} + \frac{p_M M_d}{j_M+M_d})) - (a_1 - \frac{d_1 T_d}{1+c_1 T_d} - l_1 E_d)(\frac{d_2 T_d}{1+c_2 T_d} - m_2 - \frac{p_E E_d}{j_E+E_d} + \frac{p_M M_d}{j_M+M_d})(\frac{d_2 T_d}{1+c_2 T_d} - m_2 - \frac{p_E E_d}{j_E+E_d} + \frac{p_M M_d}{j_M+M_d}) + (-g_1 T_d)(\frac{d_2 I_d}{(1+c_1 T_d)^2} - g_2 I_d)(a_1 - \frac{d_1 T_d}{1+c_1 T_d} - l_1 E_d)$,

$C_2 = (-n + \frac{p_I I_d}{j_I+I_d})((a_1 - \frac{d_1 T_d}{1+c_1 T_d} - l_1 E_d) + (\frac{d_2 T_d}{1+c_2 T_d} - m_2 - \frac{p_E E_d}{j_E+E_d} + \frac{p_M M_d}{j_M+M_d}) + (\frac{d_2 T_d}{1+c_2 T_d} - m_2 - \frac{p_E E_d}{j_E+E_d} + \frac{p_M M_d}{j_M+M_d})) + (a_1 - \frac{d_1 T_d}{1+c_1 T_d} - l_1 E_d)(\frac{d_2 T_d}{1+c_2 T_d} - m_2 - \frac{p_E E_d}{j_E+E_d} + \frac{p_M M_d}{j_M+M_d}) + (a_1 - \frac{d_1 T_d}{1+c_1 T_d} - l_1 E_d)(\frac{d_2 T_d}{1+c_2 T_d} - m_2 - \frac{p_E E_d}{j_E+E_d} + \frac{p_M M_d}{j_M+M_d}) + (\frac{d_2 T_d}{1+c_2 T_d} - m_2 - \frac{p_E E_d}{j_E+E_d} + \frac{p_M M_d}{j_M+M_d})(\frac{d_2 T_d}{1+c_2 T_d} - m_2 - \frac{p_E E_d}{j_E+E_d} + \frac{p_M M_d}{j_M+M_d}) + (g_1 T_d)(\frac{d_2 I_d}{(1+c_1 T_d)^2} - g_2 I_d) - (\frac{p_I j_I M_d}{(j_I+I_d)^2})(\frac{p_M j_M I_d}{(j_M+M_d)^2})$,

$C_3 = n - \frac{p_I I_d}{j_I+I_d} - (a_1 - \frac{d_1 T_d}{1+c_1 T_d} - l_1 E_d) - (\frac{d_2 T_d}{1+c_2 T_d} - m_2 - \frac{p_E E_d}{j_E+E_d} + \frac{p_M M_d}{j_M+M_d}) - (\frac{d_2 T_d}{1+c_2 T_d} - m_2 - \frac{p_E E_d}{j_E+E_d} + \frac{p_M M_d}{j_M+M_d})$.

We get the stability, since $|arg(Roots(Q_d))| > \frac{\alpha\pi}{2}$, according to the theorem 1. □

Theorem 5. *At Co-existing stages $P_c(N_c, T_c, I_c, E_c, M_c)$.*

The equilibrium point P_c is stable if $|Arg(Roots(Q_c))| > \frac{\alpha\pi}{2}$.

Proof. The Jacobian matrix at P_c is:

$$J_{P_c} = \begin{pmatrix} a_1 - 2b_1N_c - \frac{d_1T_c}{1+c_1T_c} - l_1E_c & -\frac{d_1N_c}{(1+c1T_c)^2} & 0 & -l_1N_c & 0 \\ l_1E_c & a_2 - 2b_2T_c - g_1I_c - m_1 & -g_1T_c & l_1N_c & 0 \\ 0 & \frac{d_2I_c}{(1+c_1T_c)^2} - g_2I_c & \frac{d_2T_c}{1+c_2T_c} - m_2 - \frac{p_EE_c}{j_E+E_c} + \frac{p_MM_c}{j_M+M_c} & -\frac{p_Ej_EI_c}{(j_E+E_c)^2} & \frac{p_Mj_MI_c}{(j_M+M_c)^2} \\ 0 & 0 & 0 & -\theta & 0 \\ 0 & 0 & \frac{p_Ij_IM_c}{(j_I+I_c)^2} & 0 & -n + \frac{p_II_c}{j_I+I_c} \end{pmatrix}$$

The characteristic polynomial of J_{P_c} is:

$$Q_c = (X+\theta)[X^4 + D_3X^3 + D_2X^2 + D_1X + D_0]$$

With:

$$D_0 = (-n + \frac{p_II_c}{j_I+I_c})((a_1 - 2b_1N_c - \frac{d_1T_c}{1+c_1T_c} - l_1E_c)(\frac{d_2T_c}{1+c_2T_c} - m_2 - \frac{p_EE_c}{j_E+E_c} + \frac{p_MM_c}{j_M+M_c})(\frac{d_2T_c}{1+c_2T_c} - m_2 - \frac{p_EE_c}{j_E+E_c} + \frac{p_MM_c}{j_M+M_c}) - (-\frac{d_1N_c}{(1+c1T_c)^2})(l_1E_c)(\frac{d_2T_c}{1+c_2T_c} - m_2 - \frac{p_EE_c}{j_E+E_c} + \frac{p_MM_c}{j_M+M_c}) - (-g_1T_c)(\frac{d_2I_c}{(1+c_1T_c)^2} - g_2I_c)(a_1 - 2b_1N_c - \frac{d_1T_c}{1+c_1T_c} - l_1E_c)) - (a_1 - 2b_1N_c - \frac{d_1T_c}{1+c_1T_c} - l_1E_c)(\frac{d_2T_c}{1+c_2T_c} - m_2 - \frac{p_EE_c}{j_E+E_c} + \frac{p_MM_c}{j_M+M_c})(\frac{p_Ij_IM_c}{(j_I+I_c)^2})(\frac{p_Mj_MI_c}{(j_M+M_c)^2}),$$

$$D_1 = (\frac{p_Ij_IM_c}{(j_I+I_c)^2})(\frac{p_Mj_MI_c}{(j_M+M_c)^2})((a_1 - 2b_1N_c - \frac{d_1T_c}{1+c_1T_c} - l_1E_c) + (\frac{d_2T_c}{1+c_2T_c} - m_2 - \frac{p_EE_c}{j_E+E_c} + \frac{p_MM_c}{j_M+M_c})) + (-n + \frac{(}{a}1 - 2b_1N_c - \frac{d_1T_c}{1+c_1T_c} - l_1E_c)cp_II_cj_I + I_c)((-\frac{d_1N_c}{(1+c1T_c)^2})(l_1E_c) + (-g_1T_c)(\frac{d_2I_c}{(1+c_1T_c)^2} - g_2I_c) - (a_1 - 2b_1N_c - \frac{d_1T_c}{1+c_1T_c} - l_1E_c)(\frac{d_2T_c}{1+c_2T_c} - m_2 - \frac{p_EE_c}{j_E+E_c} + \frac{p_MM_c}{j_M+M_c}) - (a_1 - 2b_1N_c - \frac{d_1T_c}{1+c_1T_c} - l_1E_c)(a_2 - 2b_2T_c - g_1I_c - m_1) - (\frac{d_2T_c}{1+c_2T_c} - m_2 - \frac{p_EE_c}{j_E+E_c} + \frac{p_MM_c}{j_M+M_c})(\frac{d_2T_c}{1+c_2T_c} - m_2 - \frac{p_EE_c}{j_E+E_c} + \frac{p_MM_c}{j_M+M_c})) - (a_1 - 2b_1N_c - \frac{d_1T_c}{1+c_1T_c} - l_1E_c)(\frac{d_2T_c}{1+c_2T_c} - m_2 - \frac{p_EE_c}{j_E+E_c} + \frac{p_MM_c}{j_M+M_c})(\frac{d_2T_c}{1+c_2T_c} - m_2 - \frac{p_EE_c}{j_E+E_c} + \frac{p_MM_c}{j_M+M_c}) + (-\frac{d_1N_c}{(1+c1T_c)^2})(l_1E_c)(\frac{d_2T_c}{1+c_2T_c} - m_2 - \frac{p_EE_c}{j_E+E_c} + \frac{p_MM_c}{j_M+M_c}) + (-g_1T_c)(\frac{d_2I_c}{(1+c_1T_c)^2} - g_2I_c)(a_1 - 2b_1N_c - \frac{d_1T_c}{1+c_1T_c} - l_1E_c),$$

$$D_2 = (-n + \frac{p_II_c}{j_I+I_c})((a_1 - 2b_1N_c - \frac{d_1T_c}{1+c_1T_c} - l_1E_c) + (\frac{d_2T_c}{1+c_2T_c} - m_2 - \frac{p_EE_c}{j_E+E_c} + \frac{p_MM_c}{j_M+M_c}) + (\frac{d_2T_c}{1+c_2T_c} - m_2 - \frac{p_EE_c}{j_E+E_c} + \frac{p_MM_c}{j_M+M_c})) + (a_1 - 2b_1N_c - \frac{d_1T_c}{1+c_1T_c} - l_1E_c)(\frac{d_2T_c}{1+c_2T_c} - m_2 - \frac{p_EE_c}{j_E+E_c} + \frac{p_MM_c}{j_M+M_c}) + (a_1 - 2b_1N_c - \frac{d_1T_c}{1+c_1T_c} - l_1E_c)(\frac{d_2T_c}{1+c_2T_c} - m_2 - \frac{p_EE_c}{j_E+E_c} + \frac{p_MM_c}{j_M+M_c}) + (\frac{d_2T_c}{1+c_2T_c} - m_2 - \frac{p_EE_c}{j_E+E_c} + \frac{p_MM_c}{j_M+M_c})(\frac{d_2T_c}{1+c_2T_c} - m_2 - \frac{p_EE_c}{j_E+E_c} + \frac{p_MM_c}{j_M+M_c}) - (-\frac{d_1N_c}{(1+c1T_c)^2})(l_1E_c) - (-g_1T_c)(\frac{d_2I_c}{(1+c_1T_c)^2} - g_2I_c) - (\frac{p_Ij_IM_c}{(j_I+I_c)^2})(\frac{p_Mj_MI_c}{(j_M+M_c)^2}),$$

$D_3 = n - \frac{p_I I_c}{j_I + I_c} - (a_1 - 2b_1 N_c - \frac{d_1 T_c}{1+c_1 T_c} - l_1 E_c) - (a_2 - 2b_2 T_c - g_1 I_c - m_1) - (\frac{d_2 T_c}{1+c_2 T_c} - m_2 - \frac{p_E E_c}{j_E + E_c} + \frac{p_M M_c}{j_M + M_c})$.

According to the theorem 1, we get the stability since $|arg(Roots(Q_c))| > \frac{\alpha\pi}{2}$. □

4. NUMERICAL SIMULATION

In order to validate theoretical findings, in this part, we attempt to numerically represent the solution to the problem (2). We employ the numerical method for fractional differential equations based on the approximation of Lagrange interpolation. The general guidelines of this method is given by the next equation:

$$X - X(0) = \frac{1}{\Gamma(\alpha)} \int_0^t F(s, X(s))(t-s)^{\alpha-1} ds$$

By discretizing the integral, we set h is the subdivision step, we pose $t_n = nh$ for $n = 0, 1, 2, \ldots$ considering uniform subdivision of a time line.

$$X(t_{n+1}) - X(t_n) = \frac{1}{\Gamma(\alpha)} \left(\int_0^{t_{n+1}} F(s, X(s))(t_{n+1} - s)^{\alpha-1} ds - \int_0^{t_n} F(s, X(s))(t_n - s)^{\alpha-1} ds \right)$$

The Lagrange interpolation approximation of $F(s, X(s))$ function as polynomial P is:

$$P(s) \simeq \frac{s - t_{n-1}}{t_n - t_{n-1}} F(t_n, X(t_n)) + \frac{s - t_n}{t_{n-1} - t_n} F(t_{n-1}, X(t_{n-1}))$$

In accordance with the Adams technique, we simulate numerically the fractional system (2) to obtain graphical observations of the outcomes. The parameters listed in the Table 1 are used for our numerical simulations.

Parameter	Description	Value
a_1	Logistic growth rate of the normal cells	0.7 or 1.5
a_2	Logistic growth rate of the tumor cells	0.3 or 1.3
b_1	Natural death of normal cells	0.98
b_2	Natural death of tumor cells	0.4
c_1	Saturation effect of normal by tumor	5.55
c_2	Saturation effect of immune response by tumor	0.33
d_1	Inhibition rate of normal cells due to tumor cells	6.86
d_2	Inhibition rate of immune response due to tumor cells	0.66
g_1	Inactivation rate of tumor by immune response	3×10^{-6}
g_2	Inactivation rate of immune response by tumor	10^{-7}
m_1	Death rate of tumor cells as a result of starvation	0.1
m_2	Death rate of immune response as a result of starvation	0.29
l_1	Mutation rate by estrogen	0.2
s	Source rate of immune response	0.4
p	Source rate of estrogen	3
θ	Source rate of estrogen	0.97
v	Drug injection	1.3×10^2
n	Mitigation rate of immunotherapy as a result of starvation	0.29
p_E	Suppression rate of immune cells by estrogen	0.2
p_M	Production rate of immune cells by immunotherapy	0.18
p_I	Production rate of immunotherapy by immune cells	0.18
j_E	Threshold rate of estrogen	400
j_M	Threshold rate of immunotherapy	12
j_I	Threshold rate of immune response	12

TABLE 1. Parameters for the model (2), their descriptions and values

We analyze numerically the behavior of cancer by presenting the plots of normal cells, tumor cells, immune cells, estrogen and immunotherapy at fractional derivative order values $\alpha \in \{1, 0.9, 0.8, 0.7\}$ for a period of 300 days as we explain the dynamic of breast cancer as depicted by system (2).

In figures 3, 4, 5, 6 and 7, we obtain a numerical results of free tumor equilibrium stability for logistic growth rates of normal and tumor cells values $a_1 = 1.5$ and $a_2 = 1.3$ respectively. We also show that the curves of the solutions quickly converge for an ordinary time variation ($\alpha = 1$). We should notice that for higher values of α, we gain a substantial result and an interpretation that describes the long memory behavior and the solutions converge more quickly to the regular state. The fractional derivative order α impact is shown efficiently for high values.

In figures 8, 9, 10, 11 and 12, we get a numerical results of death free tumor equilibrium state stability for logistic growth rates of normal and tumor cells values respectively $a_1 = 0.7$ and $a_2 = 0.3$. We also notice the same impact of fractional derivative.

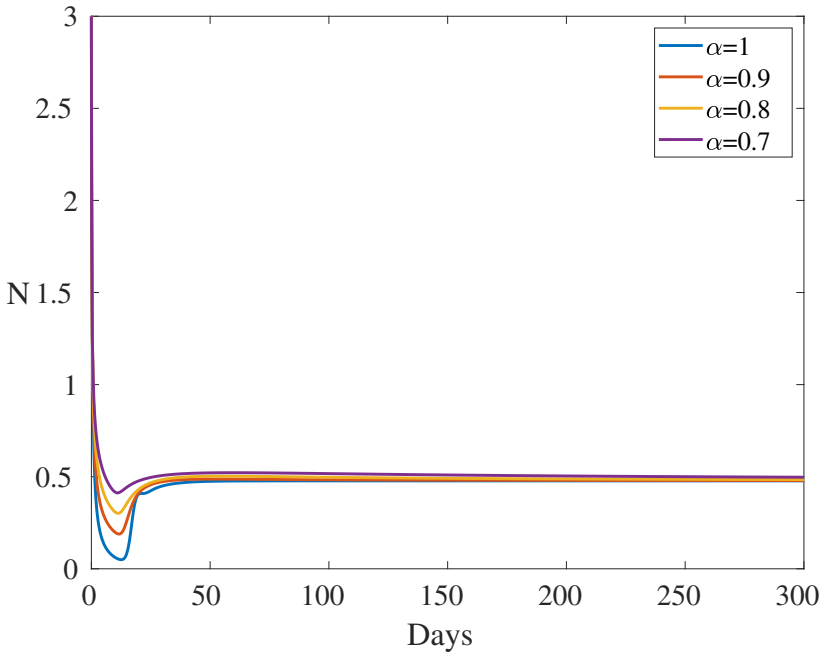

FIGURE 3. Numerical simulation results of normal cells at free tumor equilibrium

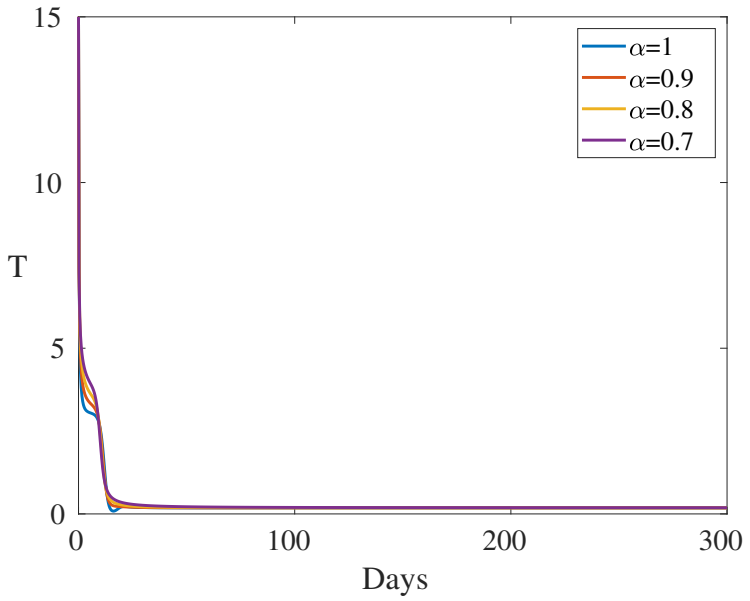

FIGURE 4. Numerical simulation results of tumor cells at free tumor equilibrium

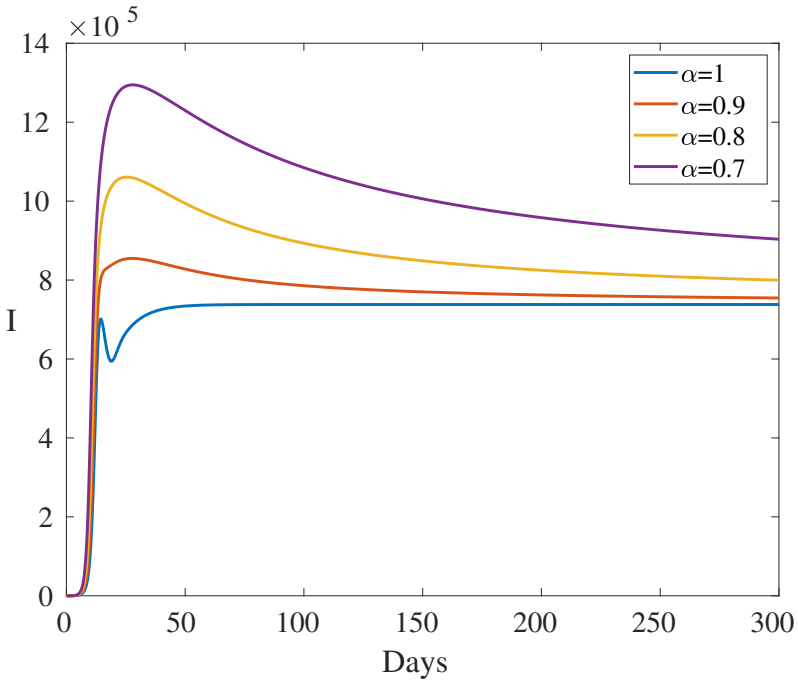

FIGURE 5. Numerical simulation results of immune cells at free tumor equilibrium

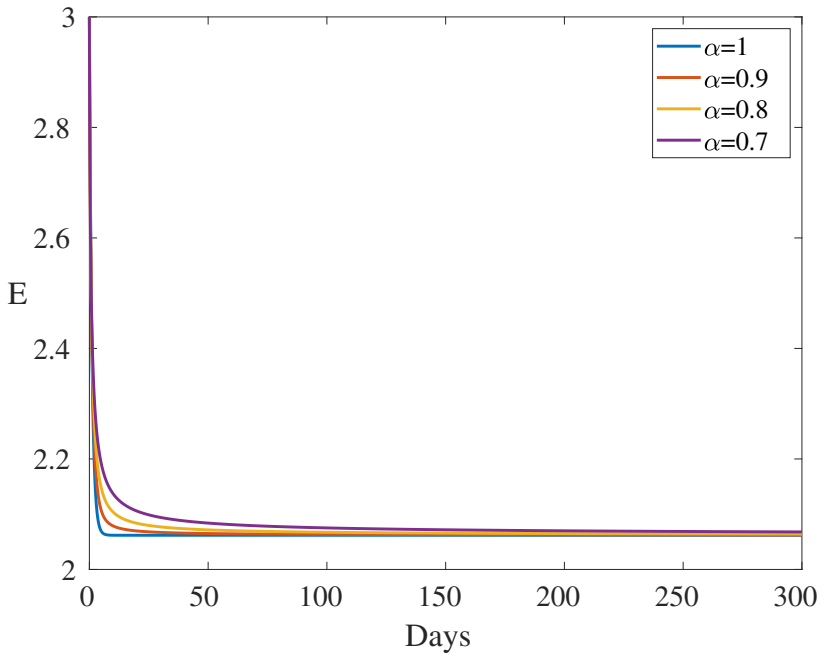

FIGURE 6. Numerical simulation results of estrogen at free tumor equilibrium

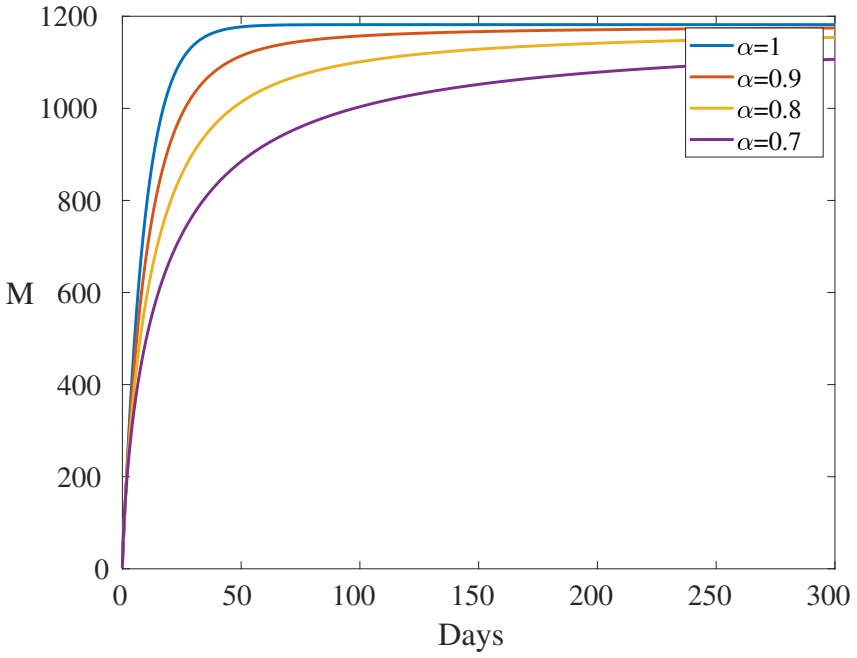

FIGURE 7. Numerical simulation results of immunotherapy at free tumor equilibrium

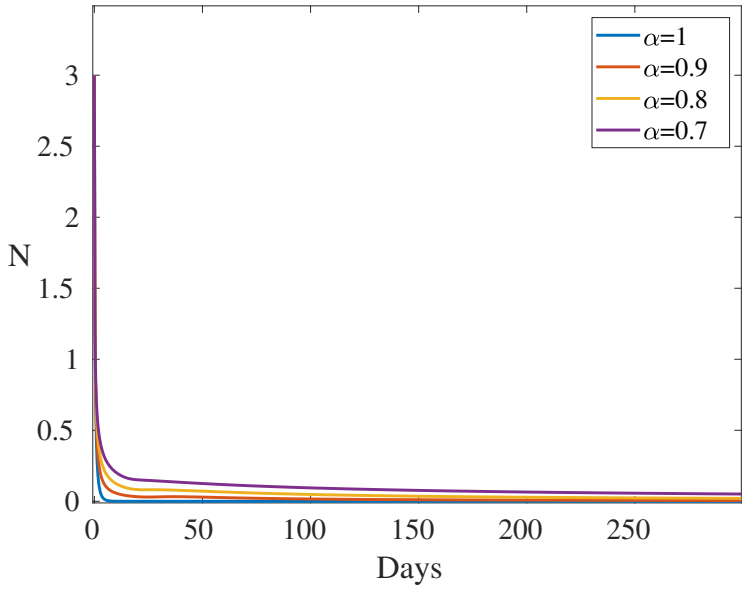

FIGURE 8. Numerical simulation results of normal cells at death free tumor equilibrium

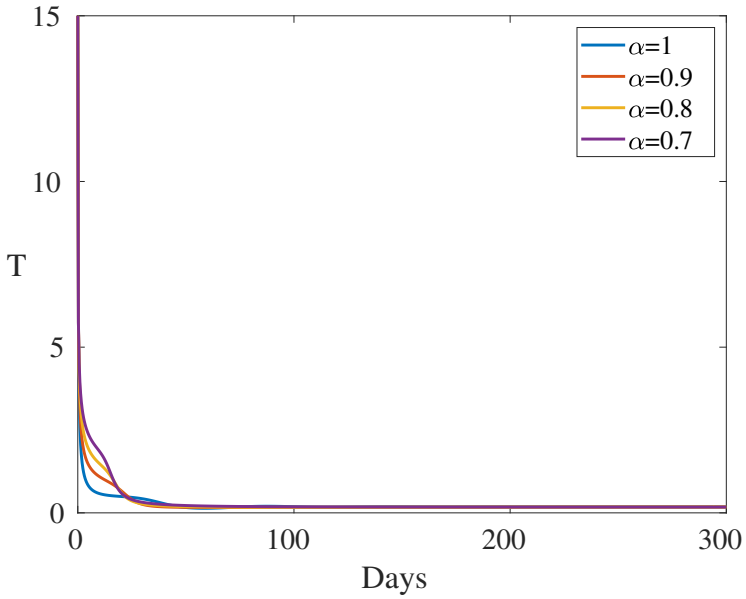

FIGURE 9. Numerical simulation results of tumor cells at death free tumor equilibrium

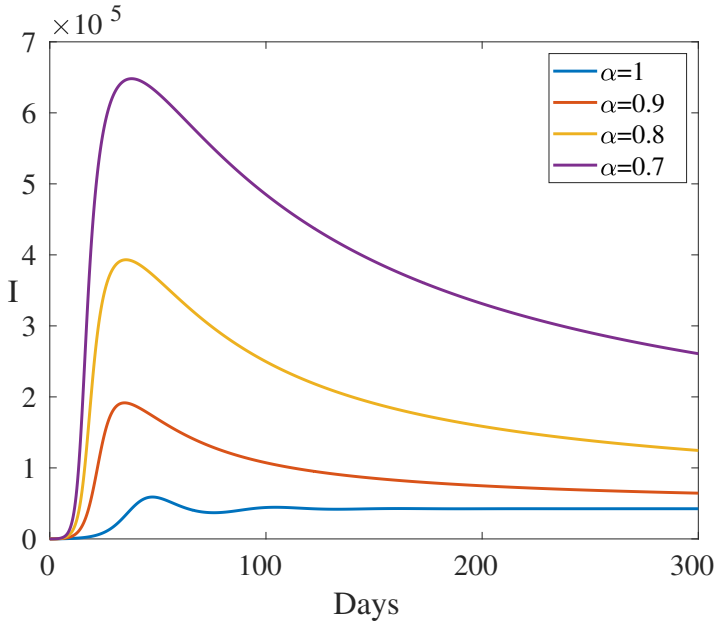

FIGURE 10. Numerical simulation results of immune cells at death free tumor equilibrium

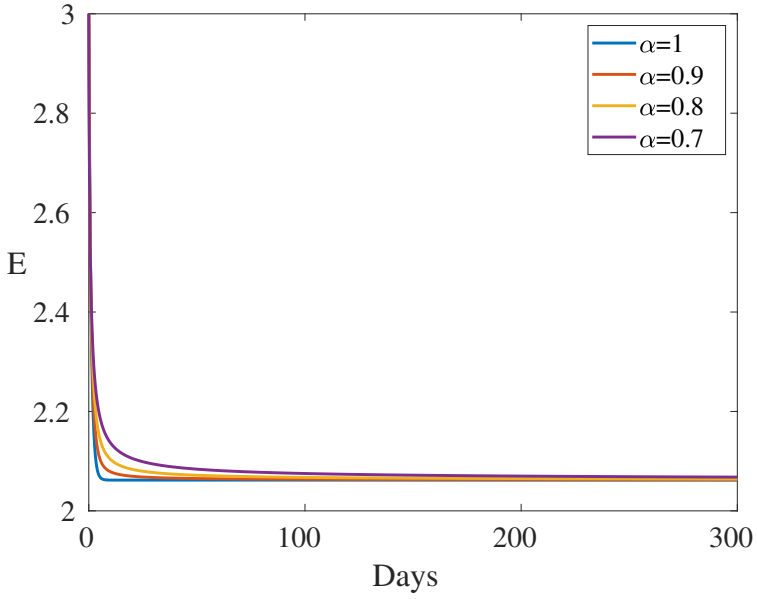

FIGURE 11. Numerical simulation results of estrogen at death free tumor equilibrium

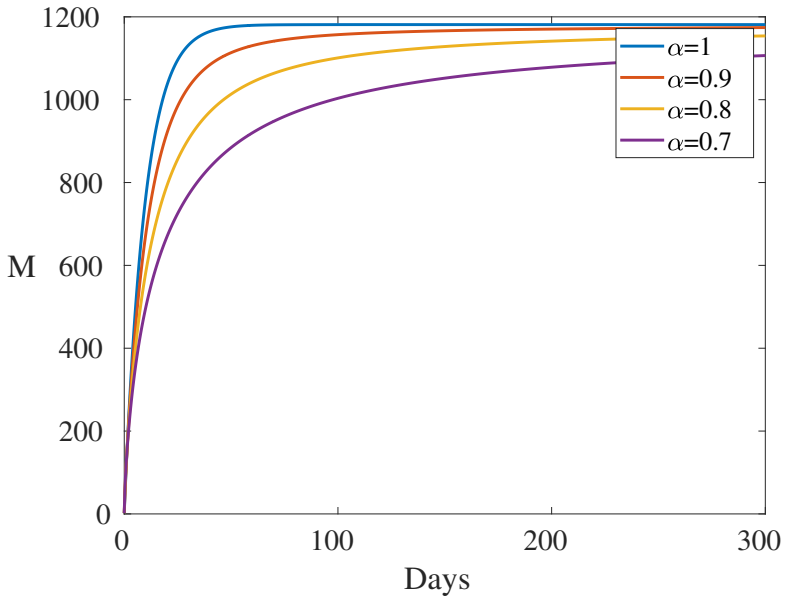

FIGURE 12. Numerical simulation results of immunotherapy at death free tumor equilibrium

5. CONCLUSION

In this work, we realize the existence and well-posedness of the solutions for the proposed fractional system (2). Specifically, our mathematical study can explain and show the evolution of breast cancer. Then, we analyze the stability of the equilibrium points known as free tumor, death free tumor, death free tumor and co-existing equilibruim, respectively. In order to analyze our results numerically, we also demonstrate how the stability of the steady states is influenced by the α-order of the fractional derivative for α values near to unit, which represents the long memory behavior of breast cancer.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interests.

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