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Fractional derivative model for tumor cells and immune system competition

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Modeling a dynamics of complex biologic disease such as cancer still present a complex dealing. So, we try in our case to study it by considering the system of normal cells, tumor cells and immune response as mathematical variables structured in fractional-order derivatives equations which express the dynamics of cancer's evolution under immunity of the body. We will analyze the stability of the formulated system at different equilibrium points. Numerical simulations are carried out to get more helpful and specific outcome about the variations of the cancer's dynamics.

Keywords: *cancer modeling; immune response; fractional-order; stability; numerical solution.*

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1. Introduction

Cancer is a disease that can start in any organ of the body when abnormal cells (tumor cells) grow uncontrollably, it is a major killer throughout human history, the second cause leading to death globally, one in six deaths accounting for an estimated studies according to World Health Organization (WHO) [1]. Cancer affects almost 18 million around the world in 2018, of these 9.5 million cases were in men and 8.5 million in women [2]. There are many varieties of cancers which are considered as biological process with predisposing factor describing at [3], cancers of the lung, breast, prostate and colon and rectum have all become more frequent in countries where risk factors such as cigarette smoking, unhealthful dietary habits and exposure to dangerous chemicals work. However, the most causes of many different type cancers still remain unknown. In case, many treatment and solution can be used in order to help the patients by one or combined specific care such as surgery, radiation, chemotherapy, immunotherapy, hormone therapy, and psychological support is also needed.

From a mathematical point of view, biological phenomena are carefully designed as mathematical models [4–7]. Particularly with fractional order derivatives [8–11], using fractional calculus as an empirical method of describing the properties of several characteristics studied, this field of mathematical analysis is considered an old and yet novel topic. Fractional differential equations can be considered as one of the extensions of classical ordinary differential equations. In reality, a biological phenomenon may depend not only on the time of treatment or time of stating the illness but also on the previous time history, which can be successfully modeled by using the theory of derivatives and integrals of fractional order [12]. The practice of fractional calculations, can also cover the behavior of different dynamics, we cite as an example [13] the drinking behavior leading to road accidents and violence.

Several recent works give an interesting results as showing that optimal therapy can control proliferation to reduce specially cervical cancer [14], the formulating of a hybrid PDE-ODE Model test the feasibility and well- posedness [15] of the cancer velocity, in a stochastic approach to show colorectal cancer prediction [16], SEIR epidemic model with fractional order [17] estimating mutation rates tumor, and with fractional approach [18], eliminating cancer cells with immune system less, an

new model is also studied [19] to present and analysis fractional-order tumor virotherapy model with two time delays. In the same sense, we can note that among the recent models, we find the model named the Normal Tumor Immune UNHealthy Diet Model (NTIUNHDM) [20] that describes well the dynamic of cancer with immunity and proposes the system of ordinary differential equations as follow:

$$\begin{cases} \dfrac{dN}{dt} = rN(1-\beta N) - \nu NI - \gamma NT, \\ \dfrac{dT}{dt} = r_1 T(1-\beta_1 T) + \beta_2 NT - \beta_3 TI, \\ \dfrac{dI}{dt} = \sigma - \delta I + \dfrac{\rho NI}{m+N} + \dfrac{\rho_1 TI}{m_1+T} - \mu NI - \mu_1 TI, \end{cases} \tag{1}$$

where the variables N, T and I correspond to normal cells, tumor cell and immune system response, respectively. The parameters of the first equation are: r marks the grown-up normal cells, β refers to the division rate of normal cells to their abnormal ones, ν denotes immune cells that inhibit abnormal cells, whereas σ denotes the rate at which tumor cells attack normal cells. For the second equation, the parameters are: r_1 denotes the limited growth of tumor cells, β_1 means that tumor cells are confronting a decline caused by the body's ingrown tumor during the process of dietary metabolism, β_2 denotes the pace at which abnormal cells become converted into their tumors counterparts and β_3 signifies the rate of inhibition or the eradication of tumor cells caused by the immune cells' response. For the third equation the parameter σ denotes a constant source of the immune system response, which is generated in the body on a daily basis, δ signifies the natural rate at which immune cells die, ρ, ρ_1 denote this response rate by normal cells respectively by tumor cells, while the immune system's threshold rate is given by m for the normal cells and m_1 for the tumor cells and μ, μ_1 signify reduced immune cells due to the manner in which they interact with normal cells, respectively with tumor cells.

In our case, to explore these studies further we will build our formulation on NTIUNHDM and to well know about the analysis of the structured dynamical model previously cited, we study it with fractional derivatives approach reputed as the generalization of the standard theory of calculus to derivatives and integrals, its success derives from its proven effectiveness in accurately describing innumerable the biological phenomenon of cancer, we formulate our model by fractional order derivatives equation with the next system as follow:

$$\begin{cases} D^\alpha N = rN(1-\beta N) - \nu NI - \gamma NT, \\ D^\alpha T = r_1 T(1-\beta_1 T) + \beta_2 NT - \beta_3 TI, \\ D^\alpha I = \sigma - \delta I + \dfrac{\rho NI}{m+N} + \dfrac{\rho_1 TI}{m_1+T} - \mu NI - \mu_1 TI, \end{cases} \tag{2}$$

where D^α is the fractional differentiation operator and α is fractional derivative order.

To get more details about the model (2), we can describe the equations of the system. The first equation express the variation of normal cells, it is formulated in three parts the first one main the natural grow up, the rests express the eliminations of the normal cells due to immune response and tumor, respectively. The second equation is the variation of tumor cells, expressing also in three parts, the first one in logistic growth, the second part describing the pace of transformation from normal cells to their tumors counterparts and the third equation is divided to five expressions, first one describes the natural existence of immunity, the second term is the normal death, the two next represent the saturated rate of immune response due to normal cells and tumor, respectively, the two last express the inhibitions of the immune response due to normal cells and tumor, respectively. To visualize better the interaction between normal cells, tumor cells and immune response formulated previously, Fig. 1 illustrates this in the following schematic diagram.

This paper will be organized in Sections: The next one will give some mathematical tools about fractional derivative, Section 3 establishes the solutions and analyze the results of fractional system modeled, Section 4 give numerical interpretations to conclude in the last section all sets.

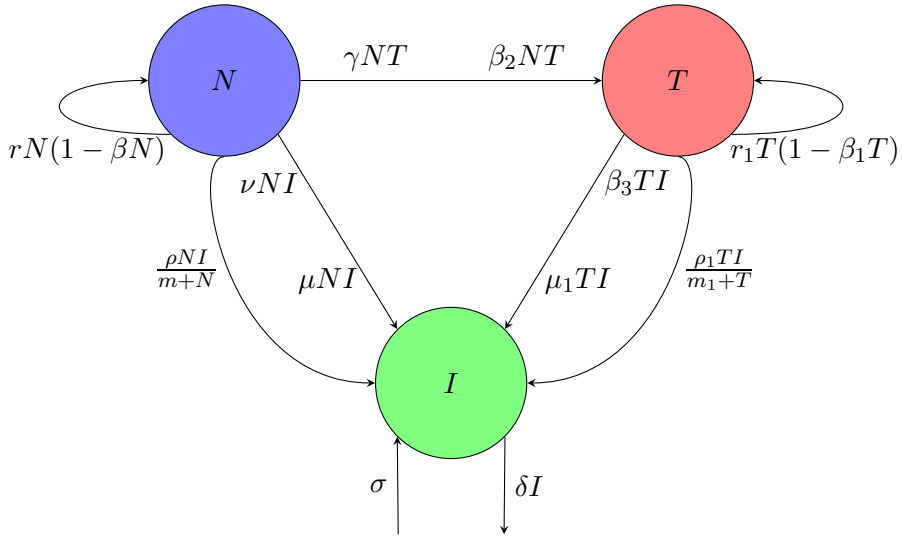

Fig. 1. Schematic diagram of NTIUNHDM.

2. Mathematical tools

In this section, we present some preliminary definitions of the fractional order integral and derivative which are the principal tools of the analysis in this study.

Definition 1. *The α-order fractional integral of the function f, with $\alpha > 0$ and $f\colon \mathbb{R} \to \mathbb{R}$ defined by*

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

where $\Gamma(\cdot)$ is the known function Gamma.

The fractional derivative is introduced as an inverse operation to fractional integration. It is defined as follow and the next Definition:

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

where $D = d/dt$ and $n - 1 < \alpha \leqslant n$, $n \in \mathbb{N}$.

Definition 2. *The Caputo fractional derivative of the function f, with $0 < \alpha < 1$ and $f\colon \mathbb{R} \to \mathbb{R}$ is given by*

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

Definition 3. *The Mittag–Leffler function is defined by, with $\alpha > 0$:*

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

Lemma 1 (Ref. [21]). *Let $F\colon \mathbb{R}^n \to \mathbb{R}^n$ verified such that fractional equation*

$$\begin{cases} D^{\alpha} X = F(X), \\ X(0) = X_0 \end{cases}$$

and satisfies both following conditions:

1) *F and $\frac{\partial F}{\partial X}$ are continuous on $\mathbb{R}^n$;*
2) *$\|F(X)\| \leqslant c_1 + c_2 \|X\|$ for all $X \in \mathbb{R}^n$, with c_1 and c_2 two positive constants.*

Then, the solution exists and uniquely defined on $[0, +\infty)$.

Lemma 2 (Ref. [22]). *The fractional differential equation $D^\alpha X = PX$, with $P \in \mathbb{R}^{n\times n}$, $X(0) = X_0$, $0 < \alpha < 1$, $X \in \mathbb{R}^n$ and $\mathrm{spc}(P)$ is considered as the spectrum of the matrix P.*

The equilibrium point is local asymptotically stable if only if $\forall\lambda \in \mathrm{spc}(P)$, $|\arg(\lambda)| > \frac{\alpha\pi}{2}$ (see Fig. 2).

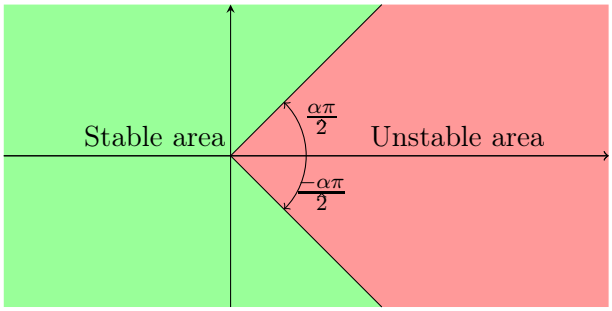

Fig. 2. Stability and non-stability areas in case of fractional derivative model.

3. Mathematical analysis of the model

In this section, we will establish the positivity and boundedness of solutions to show the well posedness of the formulation and we will discuss the local stability also to analyze the different equilibrium points.

3.1. Positivity and boundedness

For biological reasons, we will admit that the initial conditions of the solutions are positive.

Proposition 1. The solutions of the problem (2) exist, are non-negative and bounded.

Proof. The model (2) can be written as:

$$\begin{cases} D^\alpha X = F(X), \\ X(0) = X_0, \end{cases}$$

with $X = \begin{pmatrix} N \\ T \\ I \end{pmatrix}$.

We pose $C_1 = \begin{pmatrix} 0 \\ 0 \\ \sigma \end{pmatrix}$, $c_1 = \|C_1\|$,

$$A_1 = \begin{pmatrix} r & 0 & 0 \\ 0 & r_1 & 0 \\ 0 & 0 & -\delta \end{pmatrix}, \qquad a_1 = \|A_1\|,$$

$$A_2 = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & \frac{\rho N}{m+N} + \frac{\rho_1 T}{m_1+T} \end{pmatrix}, \qquad A_{22} = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & \rho+\rho_1 \end{pmatrix}, \qquad a_2 = \|A_{22}\|,$$

$$A_3 = \begin{pmatrix} -r\beta & \delta & \nu \\ \beta_2 & r_1\beta_1 & -\beta_3 \\ -\mu & -\mu_1 & 0 \end{pmatrix}, \qquad a_3 = \|A_3\|,$$

and

$$V = \begin{pmatrix} N & 0 & 0 \\ 0 & T & 0 \\ 0 & 0 & I \end{pmatrix}, \qquad \|V\| = \|X\|.$$

We involve that $F(X) = C_1 + A_1X + A_2X + VA_3X$.

So, we get $\|F(X)\| \leqslant c_1 + (a_1 + a_2)\|X\| + a_3\|X\|^2$.

Therefore, we involve having a unique solution on $[0, +\infty)$.

Now, let us show that the $\Omega = \{(N(t), T(t), I(t)) \in \mathbb{R}^3_+ : \text{ for all time } t\}$ which express the variable regions is a positively invariant.

Indeed, for $(N(t), T(t), T(t)) \in \Omega$, we have:

$$D^\alpha N\big|_{N=0} = 0 \geqslant 0, \quad D^\alpha T\big|_{T=0} = 0 \geqslant 0, \quad \text{and} \quad D^\alpha I\big|_{I=0} = \rho \geqslant 0.$$

Therefore, all solutions initiating are positive and they logical constraint due to biological qualifications.

$$N(0) \geqslant 0, \quad T(0) \geqslant 0, \quad \text{and} \quad I(0) \geqslant 0.$$

Which make the Proof of the non-negativity results.

For the boundness, we have from (2):

$$D^\alpha N \leqslant rN(1 - \beta N).$$

Let λ_N be a positive constant, we have the following relationship:

$$\begin{aligned} D^\alpha N + \lambda_N N &\leqslant -r\beta N^2 + rN + \lambda_N N \\ &\leqslant -r\beta \left(N^2 - \frac{r + \lambda_N}{r\beta} N + \left(\frac{r + \lambda_N}{2r\beta} \right)^2 - \left(\frac{r + \lambda_N}{2r\beta} \right)^2 \right) \\ &\leqslant -r\beta \left(N - \frac{r + \lambda_N}{2r\beta} \right)^2 + \frac{(r + \lambda_N)^2}{4r\beta} \\ &\leqslant \frac{(r + \lambda_N)^2}{4r\beta}. \end{aligned}$$

We pose $C_N = \frac{(r+\lambda_N)^2}{4r\beta}$.

So, we deduce: $N(t) \leqslant N(0)E_\alpha(-\lambda_N t^\alpha) + C_N(1 - E_\alpha(-\lambda_N t^\alpha))$.

Since, $0 < E_\alpha(-\lambda_N t^\alpha) \leqslant 1$ and $1 - E_\alpha(-\lambda_N t^\alpha) \leqslant 1$.

Then, we obtain the boundness of N.

From (2):

$$D^\alpha T \leqslant r_1 T(1 - \beta_1 T).$$

Let λ_T be a positive constant, we have the following relationship:

$$\begin{aligned} D^\alpha T + \lambda_T T &\leqslant -r_1\beta_1 T^2 + r_1 T + \lambda_T T \\ &\leqslant -r_1\beta_1 \left(T^2 - \frac{r_1 + \lambda_T}{r_1\beta_1} T + \left(\frac{r_1 + \lambda_T}{2r_1\beta_1} \right)^2 - \left(\frac{r_1 + \lambda_T}{2r_1\beta_1} \right)^2 \right) \\ &\leqslant -r_1\beta_1 \left(T - \frac{r_1 + \lambda_T}{2r_1\beta_1} \right)^2 + \frac{(r_1 + \lambda_T)^2}{4r_1\beta_1} \\ &\leqslant \frac{(r_1 + \lambda_T)^2}{4r_1\beta_1}. \end{aligned}$$

We pose $C_T = \frac{(r_1+\lambda_T)^2}{4r_1\beta_1}$.

So, we deduce: $T(t) \leqslant T(0)E_\alpha(-\lambda_T t^\alpha) + C_T\big(1 - E_\alpha(-\lambda_T t^\alpha)\big)$.

Since, $0 < E_\alpha(-\lambda_T t^\alpha) \leqslant 1$ and $1 - E_\alpha(-\lambda_T t^\alpha) \leqslant 1$.

Then, we obtain the boundness of T.

From (2) we have:

$$D^\alpha I + \delta I \leqslant \sigma.$$

We pose $C_I = \sigma/\delta$.

So, we deduce: $I(t) \leqslant I(0)E_\alpha(-\delta t^\alpha) + C_I\big(1 - E_\alpha(-\delta t^\alpha)\big)$.

Since, $0 < E_\alpha(-\delta t^\alpha) \leqslant 1$ and $1 - E_\alpha(-\delta t^\alpha) \leqslant 1$.

Then, we obtain the boundness of I. ∎

3.2. Stability of equilibrium

At the equilibrium instance, the steady states of the viral infection, the variation over time of the system (2) are nulls. So, we notice the equilibrium point $E^*(N^*, T^*, I^*)$ should verify the following system:

$$\begin{cases} 0 = rN^*(1-\beta N^*) - \nu N^* I^* - \gamma N^* T^*, \\ 0 = r_1 T^*(1-\beta_1 T^*) + \beta_2 N^* T^* - \beta_3 T^* I^*, \\ 0 = \sigma - \delta I^* + \dfrac{\rho N^* I^*}{m+N^*} + \dfrac{\rho_1 T^* I^*}{m_1+T^*} - \mu N^* I^* - \mu_1 T^* I^*. \end{cases} \tag{3}$$

With simple calculation, we get tree equilibrium points, that can be named as follow.

The disease free equilibrium point $E_0(0,0,I_0)$ as response stage. With

$$I_0 = \frac{\sigma}{\delta}.$$

The first endemic equilibrium point $E_1(N_1,0,I_1)$ as coexisting stage. With

$$N_1 = \frac{1}{\beta}, \qquad I_1 = \frac{\beta(1+m\beta)\sigma}{(1+m\beta)(\beta\delta+\mu)-\beta\rho}.$$

The second endemic equilibrium point $E_2(0,T_2,I_2)$ as resisting stage. With

$$T_2 = \frac{1}{6\beta_1}\left[6 - \frac{2^{\frac{2}{3}}\left(C_3+\sqrt{C_3^2+4C_4}\right)^{\frac{1}{3}} + 2r_1\beta_3 C_1}{r_1\beta_3\mu} + \frac{2^{\frac{4}{3}}\beta_3\left(-r_1C_1^2+C_2\right)}{\mu\left(C_3+\sqrt{C_3^2+4C_4}\right)^{\frac{1}{3}}}\right],$$

$$I_2 = \frac{1}{6\beta_3^2\mu}\left[2\beta_1\beta_3 C_1 + \frac{2^{\frac{4}{3}}r_1\beta_3^2\left(-r_1C_1^2+C_2\right)}{\left(C_3+\sqrt{C_3^2+4C_4}\right)^{\frac{1}{3}}} + 2^{\frac{2}{3}}\left(C_3+\sqrt{C_3^2+4C_4}\right)^{\frac{1}{3}}\right].$$

Where:

$$\begin{aligned} C_1 &= 2\mu_1 + \beta_1\left(\delta + m_1\mu_1 - \rho_1\right), \\ C_2 &= 3\mu_1\left(r_1\left(1+m_1\beta_1\right)\left(\beta_1\delta+\mu_1\right) - r_1\beta_1\rho_1 + \beta_1\beta_3\sigma\right), \\ C_3 &= r_1^2\beta_3^3\left(r_1C_1\left(-\mu\left(C_1-\mu\right) + \beta_1^2\left(2\delta^2 + 2\left(-m_1\mu_1+\rho_1\right)^2 - \delta\left(5m_1\mu_1+4\rho_1\right)\right)\right)\right) \\ &\quad + 9\left(\mu_1+\beta_1\left(\delta+2m_1\mu_1+\rho_1\right)\right)r_1^2\beta_1\beta_3^4\mu_1\sigma, \\ C_4 &= -r_1^3\beta_3^6\left(\alpha_1\left(\mu_1\left(C_1-\mu_1\right) + \beta_1^2\left(\delta^2 + \left(-m_1\mu_1+\rho_1\right)^2 - \delta\left(m_1\mu_1+2\rho_1\right)\right)\right) - 3\beta_1\beta_3\mu_1\sigma\right)^3. \end{aligned}$$

Proposition 2. At response stage $E_0(0,0,I_0)$. The equilibrium point E_0 is stable when $I_0 > \mathrm{Max}(\frac{r}{\nu}, \frac{r_1}{\beta_1})$.

Proof. The Jacobian matrix at E_0 is

$$J_{E_0} = \begin{pmatrix} r-\nu I_0 & 0 & 0 \\ 0 & r_1-\beta_1 I_0 & 0 \\ \frac{\rho I_0}{m}-\mu I_0 & \frac{\rho_1 I_0}{m_1}-\mu_1 I_0 & -\delta \end{pmatrix}$$

And the $\mathrm{spc}(J_{E_0}) = \{r-\nu I_0, r_1-\beta_1 I_0, -\delta\}$.

So, when $r < \nu I_0$ and $r_1 < \beta_1 I_0$ the E_0 is stable, else it is not.

Therefore, we can argue that the immunity must be as strong to have the stability. Otherwise, the infection will diverge from the state of stability E_0.

At this stage, only the immunity operates in normal way. ∎

Proposition 3. At coexisting stage $E_1(N_1, 0, I_1)$. The equilibrium point E_1 is stable when the following conditions are verified:

1) $\frac{r_1\beta+\beta_2}{\beta_3\beta} < I_1$;
2) $\begin{cases} \Delta_{P_1} \geqslant 0, \\ a_0 > 0, \\ a_1 > 0, \end{cases}$ or $\begin{cases} \Delta_{P_1} < 0, \\ \alpha < \frac{2}{\pi} \operatorname{Arctan} \frac{\sqrt{-\Delta_{P_1}}}{a_1}. \end{cases}$

Proof. The Jacobian matrix at E_1 is

$$J_{E_1} = \begin{pmatrix} r - 2r\beta N_1 - \nu I_1 & -\nu N_1 & -\gamma N_1 \\ 0 & r_1 + \beta_2 N_1 - \beta_3 I_1 & 0 \\ \frac{\rho m I_1}{(m+N_1)^2} - \mu I_1 & \frac{\rho_1 m_1 I_1}{(m_1+N_1)^2} - \mu_1 I_1 & -\delta + \frac{\rho N_1}{m+N_1} - \mu N_1 \end{pmatrix}.$$

And the $\operatorname{spc}(J_{E_1}) = \{\lambda_0, \lambda_1, \lambda_2\}$, when $\lambda_0 = r_1 + \beta_2 N_1 - \beta_3 I_1$ and $\lambda_1, \lambda_2 \in S_1$, when S_1 is the roots set of the following polynomial P_1:

$$P_1 = X^2 + a_1 X + a_0.$$

With: $a_1 = -(r - 2r\beta N_1 - \nu I_1 - \delta + \frac{\rho N_1}{m+N_1} - \mu N_1)$ and $a_0 = \big(-\delta + \frac{\rho N_1}{m+N_1} - \mu N_1\big)(r - 2r\beta N_1 - \nu I_1) + \gamma N_1 \big(\frac{\rho m I_1}{(m+N_1)^2} - \mu I_1\big)$.

We pose $\Delta_{P_1} = a_1^2 - 4a_0$. As $\frac{r_1\beta+\beta_2}{\beta_3\beta} < I_1$ we get $\lambda_0 \in \mathbb{R}^-$.

Furthermore, if $\Delta_{P_1} \geqslant 0$ naturally λ_1, λ_2 are real, and if more $a_i > 0$, $\forall i \in \{1, 0\}$, we get the negativity. So, $\lambda_1, \lambda_2 \in \mathbb{R}^-$. Moreover, if $\Delta_{P_1} < 0$ it is obvious that λ_1, λ_2 are complex, $\lambda_1 = \overline{\lambda_2}$ and $\tan(\operatorname{Arg}(\lambda_i)) = \pm\frac{\sqrt{-\Delta_{P_1}}}{a_1}$, $\forall i \in \{1, 2\}$. So, $|\operatorname{Arg}(\lambda_i)| = \operatorname{Arctan} \frac{\sqrt{-\Delta_{P_1}}}{a_1}$.

Therefore, we can say that the immunity have to be so robust to ensure the stability. Or else, the infection will deviate from the stable state E_1. ∎

Proposition 4. At resisting stage $E_2(0, T_2, I_2)$. The equilibrium point E_2 is stable when one of the following conditions is verified:

1) $r < \nu I_2 + \gamma T_2$,
2) $\begin{cases} \Delta_{P_2} \geqslant 0, \\ b_0 > 0, \\ b_1 > 0, \end{cases}$ or $\begin{cases} \Delta_{P_2} < 0, \\ \alpha < \frac{2}{\pi} \operatorname{Arctan} \frac{\sqrt{-\Delta_{P_2}}}{b_1}. \end{cases}$

Proof. The Jacobian matrix at E_2 is

$$J_{E_2} = \begin{pmatrix} r - \nu I_2 - \gamma T_2 & 0 & 0 \\ \beta_2 T_2 & r_1 - 2r_1\beta_1 T_2 - \beta_3 I_2 & -\beta_3 T_2 \\ \frac{\rho I_2}{m} - \mu I_2 & \frac{\rho_1 I_2}{m_1} - \mu_1 I_2 & -\delta + \frac{\rho_1 T_2}{m_1+T_2} - \mu_1 T_2 \end{pmatrix}.$$

And the $\operatorname{spc}(J_{E_2}) = \{r - \nu I_2 - \gamma T_2\} \cup S_2$ when S_2 is the roots set of the following polynomial:

$$P_2 = X^2 + b_1 X + b_0.$$

With: $b_1 = -\big(r_1 - 2r_1\beta_1 T_2 - \beta_3 I_2 - \delta + \frac{\rho_1 T_2}{m_1+T_2} - \mu_1 T_2\big)$ and $b_0 = (r_1 - 2r_1\beta_1 T_2 - \beta_3 I_2)\big(-\delta + \frac{\rho_1 T_2}{m_1+T_2} - \mu_1 T_2\big) + \beta_3 T_2 \big(\frac{\rho_1 I_2}{m_1} - \mu_1 I_2\big)$.

We pose $\Delta_{P_2} = b_1^2 - 4b_0$. So, when $\Delta_{P_2} \geqslant 0$ and $b_i > 0$, $\forall i \in \{1, 0\}$ the roots of P_2 are real negative. And when $\Delta_{P_2} < 0$, $b_1 > 0$ and $\alpha < \frac{2}{\pi} \operatorname{Arctan} \frac{\sqrt{-\Delta_{P_2}}}{b_1}$, we get the stability criterion.

At this stage, the normal cells disappear completely, letting the growth proliferation parameter r deciding for the stability of E_2, we can summarize from the theorem that for small values of r are favored for stability. ∎

4. Numerical simulations

In this section, we try to see numerically the solution of the problem (2) in order to verify theoretical results. For this purpose, we use the numerical approach for fractional differential equation [23] based on the Lagrange interpolation approximation.

For our numerical simulations, we will use the parameters given at the Table 1.

Table 1. Parameters for the model, their descriptions, values and units.

Parameter	Description	Value	Reference
r	Logistic grown-up rate of normal cells	0.4312	[20]
β_1	Multiplicative inverse of normal cells	2.99×10^{-6}	[20]
ν	Inhibition rate of normal cells by immune response	0.1379	[20]
γ	Inhibition rate by tumor	0.9314	[20]
r_1	Logistic grown-up rate of tumor	0.4426	[20]
β_1	Multiplicative inverse of tumor	0.4	[20]
β_2	Pace of change from normal to tumor cells	1.189	[20]
β_3	Inhibition rate of tumor by immune response	0.1469	[20]
σ	Source of the immune system response	0.7	[20]
δ	Natural death rate of immune response	0.57	[20]
ρ	Proliferation rate of immune response by normal cells	0.2710	[20]
μ	Inhibition rate of immune response by normal cells	0.813	[20]
m	Threshold rate by normal cells	0.813	[20]
ρ_1	Proliferation rate of immune response by tumor	0.7829	[20]
μ_1	Inhibition rate of immune response by tumor	0.3634	[20]
m_1	Threshold rate by tumor	0.8620	[20]
α	Fractionnel derivative order	$\in [0, 1]$	

In what follows, we give the guidelines of the principle of this method, since our problem can be formulated as the fractional differential equation:

$$\begin{cases} D^{\alpha} X(t) = F(t, X(t)), \\ X(0) = X_0. \end{cases} \tag{4}$$

The fundamental theorem of calculus on equation (4) give the next equation,

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

With uniform subdivision of a time line, for $n = 0, 1, 2, \ldots$ we pose $t_n = nh$ where h is the subdivision step, of $t \in \{t_n, t_{n+1}\}$

$$X(t_{n+1}) - X(t_n) = \frac{1}{\Gamma(\alpha)} (A_1 - A_0),$$

with $A_1 = \int_0^{t_{n+1}} F(s, X(s))(t_{n+1} - s)^{\alpha-1} ds$, and $A_0 = \int_0^{t_n} F(s, X(s))(t_n - s)^{\alpha-1} ds$.

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

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

Corresponding to Adams method [24], we program numerically the solution of fractional system (2) to get the graphical observations over the results.

First, we discuss the dynamic of cancer modeled by system (2), we analyzed the plots at fractional order values $\alpha \in \{1, 0.9, 0.8, 0.7\}$ during 100 days. In Figures 3–5, we demonstrate the general dynamic behavior of the normal cells, tumor cells and the immune system response when the abnormal cells established themselves in the tissue and the cancer disease propagate as tumor cells. We can also

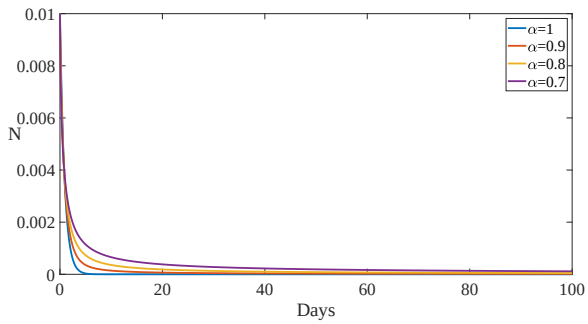

Fig. 3. Numerical simulation results of the normal cells for different fractional order values.

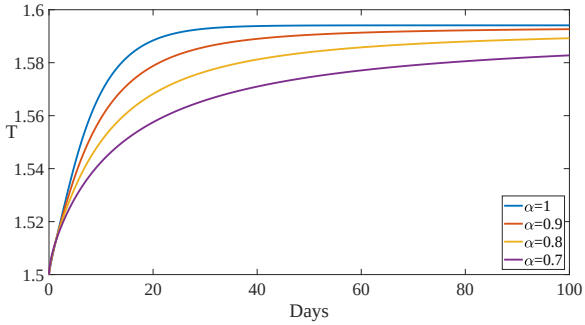

Fig. 4. Numerical simulation results of the tumor cells for different fractional order values.

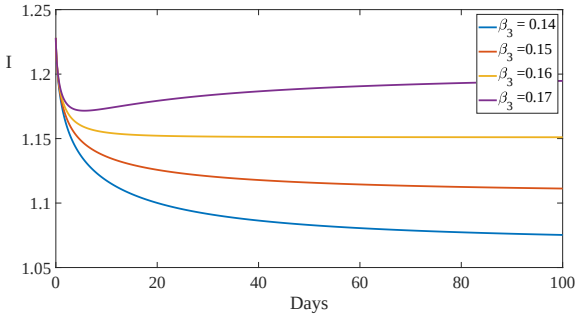

Fig. 5. Numerical simulation results of the immune system response for different fractional order values.

observe from the numerical outcomes in Figure 3 the curves of normal cells solution converge to zero, it is done speedy with higher α values, in Figure 4 tumor cells proliferate also with the same manner, for an ordinary time variation (α=1), the evolution's velocity of tumor cells is optimal. In Figure 5 the description of the immune system response is regressing naturally with the fractional order α in a decreasing way.

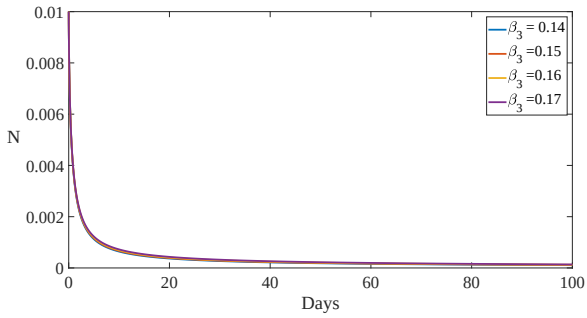

Fig. 6. Numerical simulation results of the normal cells for different values of inhibition rate of tumor by immune response, when $\alpha = 0.7$.

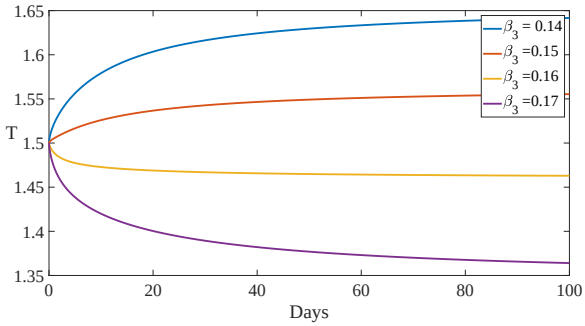

Fig. 7. Numerical simulation results of the tumor cells for different values of inhibition rate of tumor by immune response, when $\alpha = 0.7$.

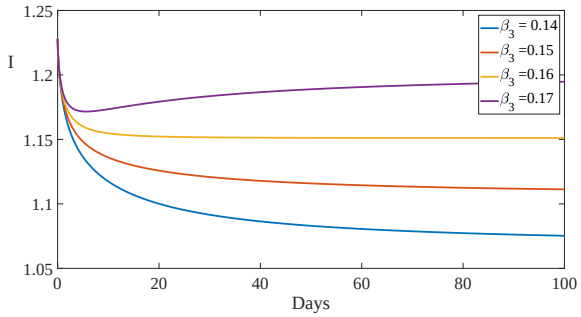

Fig. 8. Numerical simulation results of the immune system response for different values of inhibition rate of tumor by immune response, when $\alpha = 0.7$.

The fractional derivative order α effect is showing efficiently for high values, we should note that for higher values of α, we get significant results and interpretations, which describe the long memory behavior and the solutions converge more quickly to the regular state. Besides this we can say that the behavior of the system is slow when the fractional order values decreases, so the normal cells, tumor cells and the immune system response reactions take a long time to converge.

In Figures 6–8, we study the sensitivity of tumor's inhibition rate by immune response, the sensitivity analysis allows us to measure the relative change in a state variable when a parameter changes. In our case, the positive effect of increasing β_3 is well visualized at Figure 7 where tumor cells converge

towards lower values for higher values of β_3, the curve expresses for $\beta_3 = 14$ that the tumor cells attend 1.64 at day 100 and at the same time the tumor cells can get off to 1.56 for $\beta_3 = 15$, to 1.46 for $\beta_3 = 16$ and to 1.37 for $\beta_3 = 17$, on the other side about the immune system response at Figure 8, the effect is reverse, the immunity cells increase in time when the inhibition of tumor rate by immune response increase, for $\beta_3 = 14$ the immunity cells decrease to converge towards 1.075 and for $\beta_3 = 17$ immunity cells converge around higher value next to 1.2, we can say that the progression of the immune system response is relative to the inhibition rate of tumor β_3 and that also help to reduce the tumor. However, Figure 6 expresses that the normal cells do not undergo much change with the variation of β_3 value.

5. Conclusion

Oncolytic disease remains one of the most biologic phenomena under research, specially our mathematical study can explain and show the evolution of cancer formulated with the model (2) by α-order fractional derivatives equations which are used to have the long memory behavior of the cancer dynamics, we realize the existence, uniqueness and the well posedness of the solutions of the proposed fractional system have been examined. Then we analyze the steady states named response, coexisting and resisting stage respectively to add the numerical results in order to show that the α-order of the fractional derivative has an effect on the steady states stability. Moreover, we performed higher α values next to unit to analyze our results practically, which describe the long memory behavior thus the solutions go more quickly to the converged terms.

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Модель конкуренції пухлинних клітин та імунної системи з дробовими похідними

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Моделювання динаміки складних біологічних захворювань, таких як рак, все ще є складною задачею. Отже, у нашому випадку намагаємося вивчити це, розглядаючи систему нормальних клітин, пухлинних клітин та імунну відповідь як математичні змінні, які є в структурі диференціальних рівнянь дробового порядку та виражають динаміку еволюції раку в умовах імунітету організму. Проаналізовано стійкість сформульованої системи в різних точках рівноваги. Чисельне моделювання виконується для отримання більш корисних і конкретних результатів щодо варіацій динаміки раку.

Ключові слова: *моделювання раку; імунна відповідь; дробовий порядок; стійкість; числовий розв'язок.*