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Mathematical Modeling of Skin Cancer with the Effect of Stress

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Abstract: This paper introduces a mathematical model for skin cancer, formulated by fractional order differential equations (FODE). Considering the importance of the stress factor, it is included in the model and its effect on tumor cells is scrutinized. The study examines the local stability of equilibrium points and evaluates the impact of fractional derivatives on the dynamic behavior of the system. In addition, numerical simulations are conducted to analyze the influence of fractional order derivatives and distinct parameters on population dynamics. The presentation of graphs based on various fractional orders and parameter values aids in the visualization of the findings. The study further investigates the impact of stress on tumor cells. The outcomes are expected to provide valuable insights to medical researchers in developing appropriate measures for screening and treating skin cancer.

Cilt Kanserinin Stres Etkisiyle Matematiksel Modellenmesi

Anahtar Kelimeler
Kesirli Mertebeden Diferansiyel Denklemler,
Cilt Kanseri,
Nümerik Simülasyonlar,
Varlık ve Teklik

Öz: Bu çalışmada cilt kanseri için kesirli mertebeli diferansiyel denklemler (FODE) ile formüle edilen matematiksel bir model sunulmuştur. Stres faktörünün önemi dikkate alınarak modele dahil edilmiş ve tümör hücreleri üzerindeki etkisi araştırılmıştır. Denge noktalarının yerel kararlılığı incelenmiştir ve kesirli türevlerin sistemin dinamik davranışı üzerindeki etkisi değerlendirilmiştir. Ek olarak, kesirli mertebeli türevlerin ve farklı parametrelerin popülasyon dinamikleri üzerindeki etkisini analiz etmek için sayısal simülasyonlar yapılmıştır. Çeşitli kesirli mertebe ve parametre değerlerine dayalı grafiklerin sunulması, bulguların görselleştirilmesine yardımcı olmaktadır. Ayrıca stresin tümör hücreleri üzerindeki etkisi de araştırılmıştır. Sonuçların, tıbbi araştırmacılara cilt kanserinin taranması ve tedavisi için uygun önlemlerin geliştirilmesinde değerli bilgiler sağlaması beklenmektedir.

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1. Introduction

Basal cell and squamous cell carcinomas are two examples of non-melanoma skin malignancies. Despite the rarity of death, surgical treatment is both uncomfortable and disfiguring. It is hard to identify the temporal trends in the occurrence of these malignancies since the proper recording of them has not been accomplished. But particular studies from Australia, Canada, and the US show that the prevalence of non-melanoma skin cancers grew by a factor of more than two between the 1960s and the 1980s. Despite being far less common than non-melanoma skin cancers, malignant melanoma is the most common kind of skin cancer fatality and is more frequently reported and appropriately diagnosed than non-melanoma skin cancers. Malignant melanoma incidence has considerably grown in the US since the early 1970s, rising by an average of 4% yearly. A person's UV exposure habits, genetic make-up, and attitude all have an impact on their risk of getting malignant melanoma, according to several research. The incidence of skin malignancies, including melanoma and nonmelanoma, has gone up recently. Every year, there are 2 to 3 million occurrences of non-melanoma skin cancer and 132.000 cases of melanoma skin cancer globally. Data released by the Skin Cancer Foundation

indicates that one in three cancer diagnoses are related to skin cancer, and one in five Americans will have skin cancer at some time in their life. The atmosphere's ability to prevent dangerous solar UV radiation from penetrating the Earth's surface declines as ozone levels drop. It is anticipated that there would be 4.500 more incidences of melanoma skin cancer and 300.000 more cases of non-melanoma skin cancer for every 10% drop in ozone levels (https://www.who.int/news-room/questions-and-answers/item/radiation-ultraviolet-(uv)radiation-and-skin-cancer).

Skin cancer arises from the skin cells, which are the fundamental building blocks of the skin tissue. Normally, these cells undergo a process of growth and division to produce new cells, while old and damaged cells are naturally eliminated. However, in certain cases, this intricate balance is disrupted, resulting in an uncontrolled proliferation of cells that form a tumor mass [1, 2]. Melanoma, the deadliest type of skin cancer, originates from melanocytes and undergoes a distinct clinical course marked by two stages. Melanomas can specifically advance to the malignant vertical growth phase (VGP) following an initial phase of radial development in the epidermis [3]. The cells called melanocytes, which produce the pigment melanin that gives skin its color, give birth to melanoma, a highly aggressive tumor. Melanoma continues to be one of the most aggressive types of cancer even after much study [4]. Melanoma is a very aggressive form of skin cancer with a high death rate and an incidence that is rising quickly. Melanoma is a desirable target for the development of therapeutic vaccinations since it is a solid tumor. T-cell resistance to tumor-associated antigens (TAAs), however, may limit the spectrum of functional tumor-reactive T-cells and so reduce the efficacy of such vaccinations. This may make it more difficult for vaccinations to produce robust antitumor immunity [5]. Tumors can effectively evade the host's natural defences through a multi-step process known as cancer immune editing. Changing from immunosurveillance to immunotolerance of the tumor is the key stage in immunoediting, which greatly lowers the immune system's capacity to combat cancer. As a result of this process, CD4+ T cells adopt a Type-2" T helper 2 (Th2) phenotype rather than a Type-1" T helper 1 (Th1) phenotype, which favours humoral responses and inhibits cytotoxic effector activities [6, 7, 8]. Tumor cells exploit host defence mechanisms to promote their progression, invasion, and metastasis. One of these mechanisms involves the production of TGF-β cytokine, which exerts an immunosuppressive effect by interfering with antigen presentation to lymph nodes and suppressing the effector functions of CD4+ and CD8+ T cells, such as proliferation, differentiation, and acquisition of effector molecules [9,10]. Although there is a wide range of medications under investigation for use in tumor immunotherapy clinical trials, their primary therapeutic objectives involve the disruption or reversal of tumor-induced immunosuppression [11, 12]. The potential of oncolytic viral therapies as a cancer treatment has been widely recognized, primarily because certain viruses (known as oncolytic viruses) can reproduce within tumor cells without causing harm to normal tissue cells [13]. Models represent a complex network of biological components, incorporating a structure derived from existing knowledge and parameters based on available data [14]. Although many life scientists continue to rely on simple cause-and-effect relationships to expand their understanding, leading researchers have observed that the direct connection between observation and insight is becoming less clear [15]. Effective computer models can be important resources for cancer researchers; systems biologists provide biochemical models of cancer, while physical oncologists provide tissue models. By using systems biology, researchers may learn how the network structure and dynamic behavior of melanoma cells influence the biochemical pathways involved in drug resistance, invasiveness, proliferation, and survival [16].

Researchers have studied various skin cancer system interactions. For example, partial differential equations (PDEs) were used by Eikenberry et al. [17] to create a spatially explicit model that captured the dynamics of melanoma invasion in the skin. In [18], presented a mathematical simulation of the immune response brought on by the simultaneous administration of activated OT1 cytotoxic T cells (CTLs) and anti-CD137 monoclonal antibodies. The treatment targets melanoma in B16 OVA mouse models treated with a particular immunotherapy approach. Nikolov and Menov [19] studied how vaccinations, particularly those based on antigens and dendritic cells, affect the control of melanoma micrometastasis. A mathematical model of tumor cell interactions with M1 and M2 macrophages was presented by Shu et al. [20]. In [21], Özköse et al. presented a mathematical model of stem cells and chemotherapy for cancer treatment using fractional order differential equations. Lai and Friedman [22], developed a mathematical model to address the question of how BRAF/MEK inhibitors and PD-1 inhibitors interact in the treatment of melanoma. Özköse et al. [23], a novel fractional-order mathematical model was investigated that incorporates the Caputo fractional derivative and accounts for the population dynamics of tumor cells, macrophage cells, active macrophage cells, and host cells.

The purpose of this work is to construct a fractional-order mathematical model and analyze the effects of stress on cancer cell proliferation, which is motivated by the preceding explanation. We have presented a model motivated by Öztürk and Özköse's [24] work. A fractional differential equations model research that examines the relationship between the immune system and the tumor was offered by [24]. In this model, we added the stress effect in the model and analyzed it. Considering the importance of the stress factor, its effect on tumor cells has been scrutinized. Consistent systems with coherent units of measurement on both sides of the equations are

crucial tools in fractional systems. Modifying the variables on the right side of the equations, such as elevating them to the power of α, is necessary to achieve dimensional consistency. This approach helps ensure dimensional compatibility, providing a clearer demonstration of how the fractional order influences the developed system. And from this point of view, we take into consideration this in terms of mathematical perspective [25].

2. Preliminaries

Definition 1. [26] The fractional integral of order $\alpha > 0$, of the function $f(t),\ t > 0$ is given by

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

and the fractional derivative of order $\alpha \in (n-1, n),\ t > 0$ is given by

$$D^{\alpha} f(t) = I^{n-\alpha} D^{\alpha} f(t) \left(D = \frac{d}{dt}\right),$$

where $\alpha > 0$ and $\Gamma(.)$ is the Gamma function.

Definition 2. [26] The Caputo fractional derivative of order $\alpha > 0$ of a function $f: (0, \infty) \to \mathcal{R}$ is given by

$${}_0^C D_t^{\alpha} f(t) = \begin{cases} \frac{1}{\Gamma(n-\alpha)} \int_0^t \frac{\left(\frac{d}{d\tau)^n f(\tau)}\right)}{(t-\tau)^{\alpha-n+1}} d\tau, & 0 \le n-1 < \alpha < n, n = [\alpha], n \in N, \\ \left(\frac{d}{dt}\right)^n f(t), & \alpha = n, n \in N. \end{cases} \tag{1}$$

Definition 3. [26] The Laplace transform (LT) of the function $f(t)$ of order $\alpha > 0$ is defined by

$$L[\,{}_0^C D_t^{\alpha} f(t)] = s^{\alpha} F(s) - \sum_{v=0}^{n-1} f^{(v)}(0) s^{\alpha-v-1}\,. \tag{2}$$

Definition 4. [26] The Laplace transform (LT) of the function $f(t) = t^{\vartheta_1 - 1} E_{\vartheta, \vartheta_1}\left(\pm \omega t^{\vartheta}\right)$ is defined as

$$L\left[t^{\vartheta_1 - 1} E_{\vartheta, \vartheta_1}\left(\pm \omega t^{\vartheta}\right)\right] = \frac{s^{\vartheta - \vartheta_1}}{s^{\vartheta} \pm \omega}\,. \tag{3}$$

Theorem 1. [27, 28, 29] Consider the following fractional-order system:

$$\frac{d^{\alpha} x}{dt^{\alpha}} = f(x),\ x(0) = x_0, \tag{4}$$

with $\alpha \in (0,1]$ and $x \in R^n$. The zeros of the function $f(X^*) = 0$ are the equilibrium points of the system (5) and these equilibrium points:

(1) Asymptomatically stable $\Leftrightarrow$ the eigenvalues λ_i of the Jacobian matrix $J(X^*)$ satisfy that $|\arg(\lambda_i)| > \frac{\alpha\pi}{2}$, $\forall i, i = 1,2, \dots, n$.

(2) Unstable $\Leftrightarrow \exists i$, such that the corresponding eigenvalue λ_i of $J(X^*)$ satisfy

$$|\arg(\lambda_i)| < \frac{\alpha\pi}{2}, i = 1,2, \dots, n.$$

Theorem 2. [30] Take into account the polynomial equation

$$P(\lambda) = \lambda^n + a_1\lambda^{n-1} + \cdots + a_{n-1}\lambda + a_n.$$

(1) For $n = 1$, the condition for $|\arg(\lambda_i)| > \frac{\alpha\pi}{2}$ is $\alpha_1 > 0$,

(2) For $n = 2$, the condition for $|\arg(\lambda_i)| > \frac{\alpha\pi}{2}$ are either Routh-Hurwitz conditions [31] ($a_1 > 0, a_2 > 0$) or $a_1 < 0, 4a_2 > a_1^2, |\tan^{-1}(4a_2 > a_1^2)| > \frac{\alpha\pi}{2}$.

3. Mathematical Modelling

The use of mathematical models in predicting the severity and progression of skin cancers, as well as forecasting their future manifestations, has proven notably effective. Such models also hold promise in developing treatments for a wide array of ailments. Several mathematical representations have been devised to elucidate the nature of skin cancer and its detrimental influence on various chronic conditions. This study's objective is to explore the association between stress and skin cancer using a distinct model. The evaluation of skin cancer incorporates the consideration of three cell types: macrophage cells (M_1), active macrophage cells (M_2), and tumor cells (T).

Consistent systems with coherent units of measurement on both sides of the equations are crucial tools in fractional systems. Modifying the variables on the right side of the equations, such as elevating them to the power of α, is necessary to achieve dimensional consistency. This approach helps ensure dimensional compatibility, providing a clearer demonstration of how the fractional order influences the developed system. The proposed fractional-order model can be represented as follows:

$$\begin{aligned}
{}_0^cD_t^\alpha M_1(t) &= M_1(t)\varphi_1^\alpha\left(1 - \frac{M_1(t)}{\theta_1^\alpha}\right) - \delta^\alpha M_1(t)M_2(t) - \gamma_1^\alpha M_1(t) + \eta_1^\alpha M_2(t) - s_1^\alpha M_1(t),\\
{}_0^cD_t^\alpha M_2(t) &= M_2(t)(\delta^\alpha M_1(t) - \gamma_2^\alpha) - s_2^\alpha M_2(t),\\
{}_0^cD_t^\alpha T(t) &= T(t)\varphi_2^\alpha\left(1 - \frac{T(t)}{\theta_2^\alpha}\right) - \sigma^\alpha T(t)M_2(t) + c^\alpha,
\end{aligned} \tag{5}$$

with the initial conditions: $M_1(0) = M_{1_0} \geq 0$, $M_2(0) = M_{2_0} \geq 0$, $T(0) = T_0 \geq 0$, where $t \geq 0$ and α $(0 < \alpha \leq 1)$ is order of model.

4. Existence and Uniqueness (E&U)

With the initial conditions $M_1(0) = M_{1_0}, M_2(0) = M_{2_0}, T(0) = T_0$, let's consider the system (5). It is possible to express system (5) as follows:

$${}_0^cD_t^\alpha X(t) = \begin{cases} B_1X(t) + M_1(t)B_2X(t) + M_2(t)B_3X(t) + T(t)B_4X(t) + V \\ X(t_0) = X_0 \end{cases} \tag{6}$$

Table 1. The biological meanings of the parameters and numerical values

Par.	Description	Values	Reference
θ_1	The macrophages' carrying capacity	20	[24]
θ_2	The tumor cells' carrying capacity	10	[24]
φ_1	Macrophage cells' growth rate	0.5	[24]
φ_2	Tumor cells' growth rate	0.4	[24]
γ_1	The natural death rate of the macrophage cells	0.07	[24]
γ_2	The active-macrophages cells' natural mortality rate	0.7	[24]
σ	The proportion of tumor cells being destroyed	0.3	[24]
δ	The proportion of inactive macrophages that become	0.201	[24]
c	The transformation rate of normal cells to malignant ones	9.8	[24]
η_1	The rate at which activated macrophages transform into	0.05	[24]
s_1	Stress-related macrophage cell degeneration	0.02	Estimated
s_2	Stress-related active-macrophage cell degeneration	0.02	Estimated

Where

$$X(t)=\begin{pmatrix}M_1(t)\\M_2(t)\\T(t)\end{pmatrix},\qquad X(0)=\begin{pmatrix}M_1(0)\\M_2(0)\\T(0)\end{pmatrix},\ B_1=\begin{pmatrix}\varphi_1^{\alpha}-\gamma_1^{\alpha}-s_1^{\alpha} & \eta_1^{\alpha} & 0\\ 0 & -\gamma_1^{\alpha}-s_2^{\alpha} & 0\\ 0 & 0 & \varphi_2^{\alpha}\end{pmatrix},$$

$$B_2=\begin{pmatrix}\frac{-\varphi_1^{\alpha}}{\theta_1^{\alpha}} & -\delta^{\alpha} & 0\\ 0 & 0 & 0\\ 0 & 0 & 0\end{pmatrix},\ B_3=\begin{pmatrix}0 & 0 & 0\\ \delta^{\alpha} & 0 & 0\\ 0 & 0 & 0\end{pmatrix},\ B_4=\begin{pmatrix}0 & 0 & 0\\ 0 & 0 & 0\\ 0 & -\sigma^{\alpha} & \frac{-\varphi_2^{\alpha}}{\theta_2^{\alpha}}\end{pmatrix},\ V=\begin{pmatrix}0\\0\\c^{\alpha}\end{pmatrix}.$$

In view of [32, 33, 34, 35], the definitions required for E&U are given following:

Definition 5. Assume that $C^*[0,\tau]$ represents the class of continuous column vector $X(t)$. The continuous functions on the interval $[0,\tau]$ are represented by the components $M_1, M_2, T \in C^*[0,\tau]$. The norm of $X \in C^*[0,\tau]$ is

$$\| X \| = \sup_t |e^{-Nt}M_1(t)| + \sup_t |e^{-Nt}M_2(t)| + \sup_t |e^{-Nt}T(t)|$$

when $t > \psi \geq m$, we write $C_{\psi}^*[0,\tau]$ and $C_{\psi}[0,\tau]$.

Definition 6. $X \in C^*[0,\tau]$ is a solution of the initial value problem *(IVP)* (6) if

(1) $(t, X(t)) \in D, t \in [0,\tau]$ where $D = [0,\tau] \times K, K = \{(M_1, M_2, T) \in R_+^3 : |M_1| \leq p, |M| \leq r, |T| \leq w\}; p, r, w$ are positive constants.

(2) $X(t)$ satisfy (6).

Theorem 3. The initial value problem (6) has a unique solution $X \in C^*[0,\tau]$.

Proof. The FODE in (6) can be represented based on the characteristics of fractional calculus:

$$I^{1-\alpha}\frac{d}{dt}X(t) = B_1X(t) + M_1(t)B_2X(t) + M_2(t)B_3X(t) + T(t)B_4X(t) + V.$$

Operating with I^{α} we get

$$X(t) = X(0) + I^{\alpha}(B_1X(t) + M_1(t)B_2X(t) + M_2(t)B_3X(t) + T(t)B_4X(t) + V). \quad (7)$$

Now let $F: C^*[0,\tau] \to C^*[0,\tau]$ be defined by

$$FX(t) = X(0) + I^{\alpha}(B_1X(t) + M_1(t)B_2X(t) + M_2(t)B_3X(t) + T(t)B_4X(t) + V). \quad (8)$$

Then

$$\begin{aligned} e^{-Nt}(FX - FY) = \; & e^{-Nt}I^{\alpha}(B_1(X(t) - Y(t)) + M_1(t)B_2(X(t) - Y(t)) \\ & + M_2(t)B_3(X(t) - Y(t)) + T(t)B_4(X(t) - Y(t))) \\ & \leq \frac{1}{\Gamma(\alpha)}\int_0^t (t-s)^{\alpha-1}e^{-N(t-s)}(X(s) - Y(s)) \\ & \times e^{-Ns}(B_1 + pB_2 + rB_3 + wB_4)ds \\ & \leq \frac{(B_1 + pB_2 + rB_3 + wB_4)}{N^{\alpha}} \parallel X - Y \parallel \int_0^t \frac{s^{\alpha-1}}{\Gamma(\alpha)}ds \end{aligned}$$

This implies that

$$\parallel FX - FY \parallel \leq \frac{(B_1 + pB_2 + rB_3 + wB_4)}{N^{\alpha}} \parallel X - Y \parallel$$

If N is chosen such that:

$$N^{\alpha} > B_1 + pB_2 + rB_3 + wB_4,$$

then we obtain

$$\parallel FX - FY \parallel \leq \parallel X - Y \parallel$$

And the operator F has a fixed point. As a result, (7) has a unique solution $X \in C^*[0,\tau]$. From (7), it has been concluded that:

$$X(t) = X(0) + \frac{t^{\alpha}}{\Gamma(\alpha+I)}(B_1X(0) + M_1(0)B_2X(0) + M_2(0)B_3X(0) + T(0)B_4X(0) + V) + I^{\alpha-1}(B_1X'(t) + M_1'(t)B_2X(t) + M_1(t)B_2X'(t) + M_2'(t)B_3X(t) + M_2(t)B_3X'(t) + T'(t)B_4X(t) + T(t)B_4X'(t))$$

and

$$\frac{dX(t)}{dt} = \frac{t^{\alpha-1}}{\Gamma(\alpha)}(B_1X(0) + M_1(0)B_2X(0) + M_2(0)B_3X(0) + T(0)B_4X(0) + V) + I^{\alpha}(B_1X'(t) + M_1'(t)B_2X(t) + M_1(t)B_2X'(t) + M_2'(t)B_3X(t) + M_2(t)B_3X'(t) + T'(t)B_4X(t) + T(t)B_4X'(t))$$

$$e^{-Nt}X'(t) = e^{-Nt}\left[\frac{t^{\alpha-1}}{\Gamma(\alpha)}(B_1X(0) + M_1(0)B_2X(0) + M_2(0)B_3X(0) + T(0)B_4X(0) + V) + I^{\alpha}(B_1X'(t) + M_1'(t)B_2X(t) + M_1(t)B_2X'(t) + M_2'(t)B_3X(t) + M_2(t)B_3X'(t) + T'(t)B_4X(t) + T(t)B_4X'(t))\right]$$

from here, the conclusion $X' \in C_{\sigma}^{*}[0,\tau]$ is reached. Then, from (7), we have

$$\frac{dX(t)}{dt} = \frac{d}{dt}I^{\alpha}(B_1X(t) + M_1(t)B_2X(t) + M_2(t)B_3X(t) + T(t)B_4X(t) + V),$$

$$I^{1-\alpha}\frac{dX(t)}{dt} = I^{1-\alpha}\frac{d}{dt}I^{\alpha}(B_1X(t) + M_1(t)B_2X(t) + M_2(t)B_3X(t) + T(t)B_4X(t) + V),$$

$$D^{\alpha}X(t) = B_1X(t) + M_1(t)B_2X(t) + M_2(t)B_3X(t) + T(t)B_4X(t) + V$$

and

$$X(0) = X_0 + I^{\alpha}(B_1X(t) + M_1(t)B_2X(t) + M_2(t)B_3X(t) + T(t)B_4X(t) + V),$$

therefore (7) is equivalent to the initial value problem (6).

5. Equilibrium Points and Their Stability (E&S)

To calculate the equilibria of system (5), let

$$\begin{aligned} &{}_0^C D_t^{\alpha} M_1(t) = 0,\\ &{}_0^C D_t^{\alpha} M_2(t) = 0,\\ &{}_0^C D_t^{\alpha} T(t) = 0. \end{aligned}$$

Thus

$$\begin{aligned} &M_1\varphi_1^{\alpha}\left(1 - \frac{M_1}{\theta_1^{\alpha}}\right) - \delta^{\alpha}M_1M_2 - \gamma_1^{\alpha}M_1 + \eta_1^{\alpha}M_2 - s_1^{\alpha}M_1 = 0,\\ &M_2(\delta^{\alpha}M_1 - \gamma_2^{\alpha}) - s_2^{\alpha}M_2 = 0,\\ &T\varphi_2^{\alpha}\left(1 - \frac{T}{\theta_2^{\alpha}}\right) - \sigma^{\alpha}TM_2 + c^{\alpha} = 0. \end{aligned} \tag{9}$$

Then the equilibrium points are:

$$E_1 = \left(0,0,\frac{\theta_2^\alpha}{2} - \frac{1}{2}\theta_2^{\frac{\alpha}{2}}\varphi_2^{-\frac{\alpha}{2}}(4c^\alpha + \theta_2^\alpha\varphi_2^\alpha)^{\frac{1}{2}}\right)$$

$$E_2 = \left(0,0,\frac{\theta_2^\alpha}{2} + \frac{1}{2}\theta_2^{\frac{\alpha}{2}}\varphi_2^{-\frac{\alpha}{2}}(4c^\alpha + \theta_2^\alpha\varphi_2^\alpha)^{\frac{1}{2}}\right)$$

$$E_3 = \left(\theta_1^\alpha\varphi_1^\alpha(-s_1^\alpha - \gamma_1^\alpha + \varphi_1^\alpha), 0, \frac{\theta_2^\alpha}{2} - \frac{1}{2}\theta_2^{\frac{\alpha}{2}}\varphi_2^{-\frac{\alpha}{2}}(4c^\alpha + \theta_2^\alpha\varphi_2^\alpha)^{\frac{1}{2}}\right)$$

$$E_4 = \left(\theta_1^\alpha\varphi_1^\alpha(-s_1^\alpha - \gamma_1^\alpha + \varphi_1^\alpha), 0, \frac{\theta_2^\alpha}{2} + \frac{1}{2}\theta_2^{\frac{\alpha}{2}}\varphi_2^{-\frac{\alpha}{2}}(4c^\alpha + \theta_2^\alpha\varphi_2^\alpha)^{\frac{1}{2}}\right)$$

$$\begin{aligned} E_5 = \Bigg(&\delta^{-\alpha}(s_2^\alpha + \gamma_2^\alpha), \frac{\delta^{-2\alpha}(s_2^\alpha + \gamma_2^\alpha)\theta_1^{-\alpha}\left(-(s_2^\alpha + \gamma_2^\alpha)\varphi_1^\alpha - \delta^\alpha\theta_1^\alpha(s_1^\alpha + \gamma_1^\alpha - \varphi_1^\alpha)\right)}{s_2^\alpha + \gamma_2^\alpha - \eta_1^\alpha} \\ &\frac{\delta^{-2\alpha}\theta_1^{-\alpha}\varphi_2^{-\alpha}}{2(s_2^\alpha + \gamma_2^\alpha - \eta_1^\alpha)}(\sigma^\alpha(s_2^\alpha + \gamma_2^\alpha)^2\theta_2^\alpha\varphi_1^\alpha + \delta^\alpha\sigma^\alpha(s_2^\alpha + \gamma_2^\alpha)\theta_1^\alpha\theta_2^\alpha(s_1^\alpha + \gamma_1^\alpha - \varphi_1^\alpha) \\ &+\delta^{2\alpha}(s_2^\alpha + \gamma_2^\alpha - \eta_1^\alpha)\theta_1^\alpha\theta_2^\alpha\varphi_2^\alpha - \delta^{2\alpha}(\theta_2^\alpha(4c^\alpha(s_2^\alpha + \gamma_2^\alpha - \eta_1^\alpha)^2\theta_1^{2\alpha}\varphi_2^\alpha + \delta^{-4\alpha}\theta_2^\alpha(\delta^{2\alpha}\eta_1^\alpha\theta_1^\alpha\varphi_2^\alpha \\ &-(s_2^\alpha + \gamma_2^\alpha)\left(\sigma^\alpha\left((s_2^\alpha + \gamma_2^\alpha)\varphi_1^\alpha + \delta^\alpha\theta_1^\alpha(s_1^\alpha + \gamma_1^\alpha - \varphi_1^\alpha)\right) + \delta^{2\alpha}\theta_1^\alpha\varphi_2^\alpha\right)^2\right)\Big)^{\frac{1}{2}}\Bigg)\Bigg) \end{aligned}$$

$$\begin{aligned} E_6 = \Bigg(&\delta^{-\alpha}(s_2^\alpha + \gamma_2^\alpha), \frac{\delta^{-2\alpha}(s_2^\alpha + \gamma_2^\alpha)\theta_1^{-\alpha}\left(-(s_2^\alpha + \gamma_2^\alpha)\varphi_1^\alpha - \delta^\alpha\theta_1^\alpha(s_1^\alpha + \gamma_1^\alpha - \varphi_1^\alpha)\right)}{s_2^\alpha + \gamma_2^\alpha - \eta_1^\alpha} \\ &\frac{\delta^{-2\alpha}\theta_1^{-\alpha}\varphi_2^{-\alpha}}{2(s_2^\alpha + \gamma_2^\alpha - \eta_1^\alpha)}(\sigma^\alpha(s_2^\alpha + \gamma_2^\alpha)^2\theta_2^\alpha\varphi_1^\alpha + \delta^\alpha\sigma^\alpha(s_2^\alpha + \gamma_2^\alpha)\theta_1^\alpha\theta_2^\alpha(s_1^\alpha + \gamma_1^\alpha - \varphi_1^\alpha) \\ &+\delta^{2\alpha}(s_2^\alpha + \gamma_2^\alpha - \eta_1^\alpha)\theta_1^\alpha\theta_2^\alpha\varphi_2^\alpha + \delta^{2\alpha}(\theta_2^\alpha(4c^\alpha(s_2^\alpha + \gamma_2^\alpha - \eta_1^\alpha)^2\theta_1^{2\alpha}\varphi_2^\alpha + \delta^{-4\alpha}\theta_2^\alpha(\delta^{2\alpha}\eta_1^\alpha\theta_1^\alpha\varphi_2^\alpha \\ &-(s_2^\alpha + \gamma_2^\alpha)\left(\sigma^\alpha\left((s_2^\alpha + \gamma_2^\alpha)\varphi_1^\alpha + \delta^\alpha\theta_1^\alpha(s_1^\alpha + \gamma_1^\alpha - \varphi_1^\alpha)\right) + \delta^{2\alpha}\theta_1^\alpha\varphi_2^\alpha\right)^2\right)\Big)^{\frac{1}{2}}\Bigg)\Bigg) \end{aligned}$$

5.1. Positivity and boundedness

The positivity and boundedness of the model (5) solution have been analyzed in this section. Let $R_+^3 = \zeta(t) \in R^3 : \zeta(t) \geq 0$ and $\zeta(t) = [M_1(t), M_2(t), T(t)]^T$. Let us reviewthe lemma that will be utilized to prove that the solution to model (5) is non-negative.

Lemma 1. (Generalized Mean Value Theorem) [26] Assume that $w(t) \in C[a,b]$ and ${}_0^C D_t^\alpha w(t) \in C[a,b]$ for $0 < \alpha \leq 1$, then $w(t) = w(a) + \frac{1}{\Gamma(\alpha)}\,{}_0^C D_t^\alpha w(\tau)(t-\alpha)^\alpha$, where $0 \leq \tau \leq t, \forall t \in (a,b]$.

Remark 1. If $w \in C[a,b]$ and ${}_0^C D_t^\alpha w(t) \geq 0, \forall t \in (a,b]$, then the function $w(t)$ is non-increasing for all $t \in (a,b]$.

Theorem 4. The solution of model (5) along with initial conditions is bounded in R_+^3.

Proof.

$$\begin{aligned} &{}_0^C D_t^\alpha M_1(t)|_{M_1(t)=0} = \eta_1^\alpha M_2(t) \geq 0, \\ &{}_0^C D_t^\alpha M_2(t)|_{M_2(t)=0} = 0 \geq 0, \\ &{}_0^C D_t^\alpha T(t)|_{T(t)=0} = c^\alpha \geq 0. \end{aligned} \tag{10}$$

If $(M_1(t), M_2(t), T(t)) \in R_+^3$, then from system (10) and Remark 1, the solution of model (5) can only be of high hyperplanes $M_1(t) = 0, M_2(t) = 0$ and $T(t) = 0$. This concludes that the area R_+^3 is a positive invariant set.

Theorem 5. The region $Q = \{M_1(t), M_2(t), T(t) \in R_+^3,\ 0 < M_1(t), M_2(t), T(t) \leq c^\alpha p_1 + N(0)p_2\}$ is a positive invariant set for the system (5).

Proof. (5) yields the following:

$$\begin{aligned} {}_0^C D_t^\alpha N(t) = \quad & M_1(t)\varphi_1^\alpha - \frac{\varphi_1^\alpha}{\theta_1^\alpha} M_1^2(t) - \gamma_1^\alpha M_1(t) + \eta_1^\alpha M_2(t) - s_1^\alpha M_1(t) \\ & -\gamma_2^\alpha M_2(t) - s_2^\alpha M_2(t) + T(t)\varphi_2^\alpha - \frac{\varphi_2^\alpha}{\theta_2^\alpha} T^2(t) - \sigma^\alpha T(t) M_2(t) + c^\alpha \end{aligned}$$

This gives ${}_0^C D_t^\alpha N(t) \leq c^\alpha + M_1(t)\varphi_1^\alpha + \eta_1^\alpha M_2(t) + T(t)\varphi_2^\alpha \leq c^\alpha + N(t)$.

When LT is applied to the previous equation, the outcome is:

$$s^v w(N) - s^{v-1} N(0) \leq c^\alpha + w(N)$$

which further gives $w(N) \leq \frac{c^\alpha}{s^{v-1}-1} + \frac{s^{v-1}}{s^v - 1} N(0)$, from the definitions 3 and 4, we get that if $(M_1(t), M_2(t), T(t)) \in R_+^3$, then

$$N(t) \leq c^\alpha t^v E_{v,v+1}(t^v) + t^{v-1} E_{v,1}(t^v) N(0) \leq c^\alpha p_1 + N(0) p_2$$

where p_1 and p_2 are constants.
Thus $N(t)$ (the total cell) is bounded and $M_1(t), M_2(t), T(t)$ are bounded.

5.2. Stability of the equilibria

Here, we outline the prerequisites for equilibria's stability.

Theorem 6. Let E_1 be the equilibrium points system (5). Then E_1 is unstable.

Proof. The Jacobian matrix of model (5) evaluated at equilibrium point E_1 is given by

$$J(E_1) = \begin{pmatrix} \varphi_1^\alpha - s_1^\alpha - \gamma_1^\alpha & \eta_1^\alpha & 0 \\ 0 & -\gamma_2^\alpha - s_2^\alpha & 0 \\ 0 & -\sigma^\alpha \left(\frac{\theta_2^\alpha}{2} - \frac{1}{2} \theta_2^{\frac{\alpha}{2}} \varphi_2^{-\frac{\alpha}{2}} (4c^\alpha + \theta_2^\alpha \varphi_2^\alpha)^{\frac{1}{2}} \right) & \theta_2^{-\frac{\alpha}{2}} \varphi_2^{\frac{\alpha}{2}} (4c^\alpha + \theta_2^\alpha \varphi_2^\alpha)^{\frac{1}{2}} \end{pmatrix}$$

The characteristic equation is $|J(E_1) - \lambda I| = 0$. Hence the eigenvalues of $J(E_1)$ are written as

$$\lambda_1 = -s_2^{\alpha} - \gamma_2^{\alpha},$$
$$\lambda_2 = \theta_2^{-\frac{\alpha}{2}} \varphi_2^{\frac{\alpha}{2}} (4c^{\alpha} + \theta_2^{\alpha} \varphi_2^{\alpha})^{\frac{1}{2}},$$
$$\lambda_3 = -s_1^{\alpha} - \gamma_1^{\alpha} + \varphi_1^{\alpha}.$$

We know that $\varphi_1, \varphi_2, \theta_1, \theta_2, \delta, \gamma_1, \gamma_2, \eta_1, \sigma, c$ are positive. Since $\lambda_1 < 0$ and $|\arg(\lambda_1)| > \frac{\alpha\pi}{2}, \lambda_2 > 0$ and $|\arg(\lambda_2)| < \frac{\alpha\pi}{2}$. According to the Theorem (1), equilibrium point E_1 is unstable.

Theorem 7. Let E_2 be the equilibrium points system (5). Assume that $\varphi_1^{\alpha} < s_1^{\alpha} + \gamma_1^{\alpha}$. Then E_2 is locally asymptotically stable (LAS).

Proof. The Jacobian matrix of model (5) obtained at E_2 equilibrium point is given by

$$J(E_2) = \begin{pmatrix} \varphi_1^{\alpha} - \gamma_1^{\alpha} - s_1^{\alpha} & \eta_1^{\alpha} & 0 \\ 0 & -\gamma_2^{\alpha} - s_2^{\alpha} & 0 \\ 0 & -\sigma^{\alpha}\left(\frac{\theta_2^{\alpha}}{2} + \frac{1}{2}\theta_2^{\frac{\alpha}{2}} \varphi_2^{-\frac{\alpha}{2}} (4c^{\alpha} + \theta_2^{\alpha}\varphi_2^{\alpha})^{\frac{1}{2}}\right) & -\theta_2^{-\frac{\alpha}{2}} \varphi_2^{\frac{\alpha}{2}} (4c^{\alpha} + \theta_2^{\alpha}\varphi_2^{\alpha})^{\frac{1}{2}} \end{pmatrix}$$

The characteristic equation is $|J(E_2) - \lambda I| = 0$. Hence the eigenvalues of $J(E_2)$ are written as

$$\lambda_1 = -s_2^{\alpha} - \gamma_2^{\alpha},$$
$$\lambda_2 = -\theta_2^{-\frac{\alpha}{2}} \varphi_2^{\frac{\alpha}{2}} (4c^{\alpha} + \theta_2^{\alpha} \varphi_2^{\alpha})^{\frac{1}{2}},$$
$$\lambda_3 = -s_1^{\alpha} - \gamma_1^{\alpha} + \varphi_1^{\alpha}.$$

We know that $\varphi_1, \varphi_2, \theta_1, \theta_2, \delta, \gamma_1, \gamma_2, \eta_1, \sigma, c$ are positive. Since $\lambda_1 < 0$ and $|\arg(\lambda_1)| > \frac{\alpha\pi}{2}$, $\lambda_2 < 0$ and $|\arg(\lambda_2)| > \frac{\alpha\pi}{2}$, We assume that $\varphi_1^{\alpha} < s_1^{\alpha} + \gamma_1^{\alpha}$ then $\lambda_3 < 0$ and $|\arg(\lambda_3)| > \frac{\alpha\pi}{2}$. Therefore, all eigenvalues satisfy $|\arg(\lambda_i)| > \frac{\alpha\pi}{2}$. Hence by Theorem (1), E_2 is locally asymptotic stable.

Theorem 8. Let E_3 be the equilibrium points system (5). Then E_3 is unstable.

Proof. The Jacobian matrix of model (5) evaluated at equilibrium point E_3 is given by

$$J(E_3) = \begin{pmatrix} s_1^{\alpha} + \gamma_1^{\alpha} - \varphi_1^{\alpha} & \eta_1^{\alpha} + \theta_1^{\alpha}\varphi_1^{-\alpha}\delta^{\alpha}(s_1^{\alpha} + \gamma_1^{\alpha} - \varphi_1^{\alpha}) & 0 \\ 0 & -s_2^{\alpha} - \gamma_2^{\alpha} - \theta_1^{\alpha}\varphi_1^{-\alpha}\delta^{\alpha}(s_1^{\alpha} + \gamma_1^{\alpha} - \varphi_1^{\alpha}) & 0 \\ 0 & -\sigma^{\alpha}\left(\frac{\theta_2^{\alpha}}{2} - \frac{1}{2}\theta_2^{\frac{\alpha}{2}} \varphi_2^{-\frac{\alpha}{2}} (4c^{\alpha} + \theta_2^{\alpha}\varphi_2^{\alpha})^{\frac{1}{2}}\right) & \theta_2^{-\frac{\alpha}{2}} \varphi_2^{\frac{\alpha}{2}} (4c^{\alpha} + \theta_2^{\alpha}\varphi_2^{\alpha})^{\frac{1}{2}} \end{pmatrix}$$

The characteristic equation is $|J(E_3) - \lambda I| = 0$. Hence the eigenvalues of $J(E_3)$ are written as

$$\lambda_1 = \theta_2^{-\frac{\alpha}{2}} \varphi_2^{\frac{\alpha}{2}} (4c^{\alpha} + \theta_2^{\alpha} \varphi_2^{\alpha})^{\frac{1}{2}},$$
$$\lambda_2 = s_1^{\alpha} + \gamma_1^{\alpha} - \varphi_1^{\alpha},$$
$$\lambda_3 = -s_2^{\alpha} - \gamma_2^{\alpha} - \theta_1^{\alpha}\varphi_1^{-\alpha}\delta^{\alpha}(s_1^{\alpha} + \gamma_1^{\alpha} - \varphi_1^{\alpha}).$$

We know that $\varphi_1, \varphi_2, \theta_1, \theta_2, \delta, \gamma_1, \gamma_2, \eta_1, \sigma, c$ are positive. $\lambda_1 > 0$ and $|\arg(\lambda_1)| < \frac{\alpha\pi}{2}$. According to the Theorem (1), equilibrium point E_3 is unstable.

Theorem 9. Let E_4 be the equilibrium points system (5). Assume that $s_1^\alpha + \gamma_1^\alpha < \varphi_1^\alpha$ and $-\theta_1^\alpha \varphi_1^{-\alpha} \delta^\alpha (s_1^\alpha + \gamma_1^\alpha - \varphi_1^\alpha) < s_2^\alpha + \gamma_2^\alpha$. Then E_4 is LAS.

Proof. The Jacobian matrix of model (5) evaluated at equilibrium point E_4 is given by

$$J(E_4) = \begin{pmatrix} s_1^\alpha + \gamma_1^\alpha - \varphi_1^\alpha & \eta_1^\alpha + \theta_1^\alpha \varphi_1^{-\alpha} \delta^\alpha (s_1^\alpha + \gamma_1^\alpha - \varphi_1^\alpha) & 0 \\ 0 & -s_2^\alpha - \gamma_2^\alpha - \theta_1^\alpha \varphi_1^{-\alpha} \delta^\alpha (s_1^\alpha + \gamma_1^\alpha - \varphi_1^\alpha) & 0 \\ 0 & -\sigma^\alpha \left(\frac{\theta_2^\alpha}{2} + \frac{1}{2} \theta_2^{\frac{\alpha}{2}} \varphi_2^{-\frac{\alpha}{2}} (4c^\alpha + \theta_2^\alpha \varphi_2^\alpha)^{\frac{1}{2}} \right) & -\theta_2^{-\frac{\alpha}{2}} \varphi_2^{\frac{\alpha}{2}} (4c^\alpha + \theta_2^\alpha \varphi_2^\alpha)^{\frac{1}{2}} \end{pmatrix}$$

The characteristic equation is $|J(E_4) - \lambda I| = 0$. Hence the eigenvalues of $J(E_4)$ are written as

$\lambda_1 = -\theta_2^{-\frac{\alpha}{2}} \varphi_2^{\frac{\alpha}{2}} (4c^\alpha + \theta_2^\alpha \varphi_2^\alpha)^{\frac{1}{2}}$,
$\lambda_2 = s_1^\alpha + \gamma_1^\alpha - \varphi_1^\alpha$.
$\lambda_3 = -S_2^\alpha - \gamma_2^\alpha - \theta_1^\alpha \varphi_1^{-\alpha} \delta^\alpha (s_1^\alpha + \gamma_1^\alpha - \varphi_1^\alpha)$.

We know that $\varphi_1, \varphi_2, \theta_1, \theta_2, \delta, \gamma_1, \gamma_2, \eta_1, \sigma, c$ are positive. Since $\lambda_1 < 0$ and $|\arg(\lambda_1)| > \frac{\alpha\pi}{2}$. We assume that $s_1^\alpha + \gamma_1^\alpha < \varphi_1^\alpha$ and $-\theta_1^\alpha \varphi_1^{-\alpha} \delta^\alpha (s_1^\alpha + \gamma_1^\alpha - \varphi_1^\alpha) < s_2^\alpha + \gamma_2^\alpha$ then $\lambda_2 < 0$ and $|\arg(\lambda_2)| > \frac{\alpha\pi}{2}$, $\lambda_3 < 0$ and $|\arg(\lambda_3)| > \frac{\alpha\pi}{2}$. Therefore, all eigenvalues satisfy $|\arg(\lambda_i)| > \frac{\alpha\pi}{2}$. Hence by Theorem (1), E_4 is locally asymptotic stable.

Theorem 10. Let E_5 be the equilibrium points system (5). Assume that

$s_2^\alpha + \gamma_2^\alpha < \eta_1^\alpha, s_2^\alpha + \gamma_2^\alpha < -\delta^\alpha \theta_1^\alpha \varphi_1^{-\alpha} (s_1^\alpha + \gamma_1^\alpha - \varphi_1^\alpha)$ and
$(s_2^\alpha + \gamma_2^\alpha)^2 \varphi_1^\alpha < \eta_1^\alpha \left(2(s_2^\alpha + \gamma_2^\alpha) \varphi_1^\alpha + \delta^\alpha \theta_1^\alpha (s_1^\alpha + \gamma_1^\alpha - \varphi_1^\alpha) \right)$

Then the E_5 is locally asymptotically stable.

Proof.

$$J(E_5) = \begin{pmatrix} j_{11} & \eta_1^\alpha - (s_2^\alpha + \gamma_2^\alpha) & 0 \\ j_{21} & 0 & 0 \\ 0 & j_{32} & j_{33} \end{pmatrix}$$

Where

$$j_{11} = -s_1^\alpha - \gamma_1^\alpha + \varphi_1^\alpha - 2\delta^{-\alpha} (s_2^\alpha + \gamma_2^\alpha) \theta_1^{-\alpha} \varphi_1^\alpha + \left(\frac{\delta^{-\alpha} \theta_1^{-\alpha} (s_2^\alpha + \gamma_2^\alpha) \left(\delta^\alpha s_1^\alpha \theta_1^\alpha + \delta^\alpha \gamma_1^\alpha \theta_1^\alpha + \varphi_1^\alpha (s_2^\alpha + \gamma_2^\alpha - \delta^\alpha \theta_1^\alpha) \right)}{s_2^\alpha + \gamma_2^\alpha - \eta_1^\alpha} \right),$$

$$j_{21} = \frac{\delta^{-\alpha} \theta_1^{-\alpha} (s_2^\alpha + \gamma_2^\alpha) \left(-\varphi_1^\alpha (s_2^\alpha + \gamma_2^\alpha) - \delta^\alpha \theta_1^\alpha (s_1^\alpha + \gamma_1^\alpha - \varphi_1^\alpha) \right)}{s_2^\alpha + \gamma_2^\alpha - \eta_1^\alpha},$$

$$j_{32} = \frac{-\sigma^{\alpha}\delta^{-2\alpha}\theta_1^{-\alpha}\varphi_2^{-\alpha}}{2(s_2^{\alpha}+\gamma_2^{\alpha}-\eta_1^{\alpha})}(\sigma^{\alpha}(s_2^{\alpha}+\gamma_2^{\alpha})^2\theta_2^{\alpha}\varphi_1^{\alpha}+\delta^{\alpha}\sigma^{\alpha}(s_2^{\alpha}+\gamma_2^{\alpha})\theta_1^{\alpha}\theta_2^{\alpha}(s_1^{\alpha}+\gamma_1^{\alpha}-\varphi_1^{\alpha})$$
$$+\delta^{2\alpha}(s_2^{\alpha}+\gamma_2^{\alpha}-\eta_1^{\alpha})\theta_1^{\alpha}\theta_2^{\alpha}\varphi_2^{\alpha}-\delta^{2\alpha}(\theta_2^{\alpha}(4c^{\alpha}(s_2^{\alpha}+\gamma_2^{\alpha}-\eta_1^{\alpha})^2\theta_1^{2\alpha}\varphi_2^{\alpha}+\delta^{-4\alpha}\theta_2^{\alpha}(\delta^{2\alpha}\eta_1^{\alpha}\theta_1^{\alpha}\varphi_2^{\alpha}$$
$$-(s_2^{\alpha}+\gamma_2^{\alpha})\left(\sigma^{\alpha}\left((s_2^{\alpha}+\gamma_2^{\alpha})\varphi_1^{\alpha}+\delta^{\alpha}\theta_1^{\alpha}(s_1^{\alpha}+\gamma_1^{\alpha}-\varphi_1^{\alpha})\right)+\delta^{2\alpha}\theta_1^{\alpha}\varphi_2^{\alpha}\right)\Big)^2\Big)\Big)^{\frac{1}{2}}\Bigg),$$

$$j_{33} = \theta_1^{-\alpha}\theta_2^{-\alpha}(s_2^{\alpha}+\gamma_2^{\alpha}-\eta_1^{\alpha})^{-1}(\theta_2^{\alpha}(4c^{\alpha}(s_2^{\alpha}+\gamma_2^{\alpha}-\eta_1^{\alpha})^2\theta_1^{2\alpha}\varphi_2^{\alpha}+\delta^{-4\alpha}\theta_2^{\alpha}(\delta^{2\alpha}\eta_1^{\alpha}\theta_1^{\alpha}\varphi_2^{\alpha}$$
$$-(s_2^{\alpha}+\gamma_2^{\alpha})\left(\sigma^{\alpha}\left((s_2^{\alpha}+\gamma_2^{\alpha})\varphi_1^{\alpha}+\delta^{\alpha}\theta_1^{\alpha}(s_1^{\alpha}+\gamma_1^{\alpha}-\varphi_1^{\alpha})\right)+\delta^{2\alpha}\theta_1^{\alpha}\varphi_2^{\alpha}\right)\Big)^2\Big)\Big)^{\frac{1}{2}}.$$

The characteristic equation is $|J(E_5)-\lambda I|=0$. Hence

$$(\lambda+Z)(\lambda^2+G\lambda+R)=0 \tag{11}$$

where

$$G=\delta^{-\alpha}\theta_1^{-\alpha}\left((s_2^{\alpha}+\gamma_2^{\alpha})^2\varphi_1^{\alpha}-\eta_1^{\alpha}\left(2(s_2^{\alpha}+\gamma_2^{\alpha})\varphi_1^{\alpha}+\delta^{\alpha}\theta_1^{\alpha}(s_1^{\alpha}+\gamma_1^{\alpha}-\varphi_1^{\alpha})\right)\right)(s_2^{\alpha}+\gamma_2^{\alpha}-\eta_1^{\alpha})^{-1},$$

$$R=\delta^{-\alpha}(s_2^{\alpha}+\gamma_2^{\alpha})\theta_1^{-\alpha}\left(-(s_2^{\omega}+\gamma_2^{\alpha})\varphi_1^{\alpha}-\delta^{\alpha}\theta_1^{\alpha}(s_1^{\omega}+\gamma_1^{\sigma}-\varphi_1^{\omega})\right),$$

$$Z = -\theta_1^{-\alpha}\theta_2^{-\alpha}(s_2^{\alpha}+\gamma_2^{\alpha}-\eta_1^{\alpha})^{-1}(\theta_2^{\alpha}(4c^{\alpha}(s_2^{\alpha}+\gamma_2^{\alpha}-\eta_1^{\alpha})^2\theta_1^{2\alpha}\varphi_2^{\alpha}+\delta^{-4\alpha}\theta_2^{\alpha}(\delta^{2\alpha}\eta_1^{\alpha}\theta_1^{\alpha}\varphi_2^{\alpha}$$
$$-(s_2^{\alpha}+\gamma_2^{\alpha})\left(\sigma^{\alpha}\left((s_2^{\alpha}+\gamma_2^{\alpha})\varphi_1^{\alpha}+\delta^{\alpha}\theta_1^{\alpha}(s_1^{\alpha}+\gamma_1^{\alpha}-\varphi_1^{\alpha})\right)+\delta^{2\alpha}\theta_1^{\alpha}\varphi_2^{\alpha}\right)\Big)^2\Big)\Big)^{\frac{1}{2}}.$$

Let λ_1,λ_2 and λ_3 be the roots of (11). Given the presumptions, we may say that $\varphi_1,\varphi_2,\theta_1,\theta_2,\delta,\gamma_1,\gamma_2,\eta_1,\sigma,c$ are positive. Therefore $\lambda_1=-Z<0, G>0, R>0$. Thus, from Routh-Hurwitz Criteria if $G>0, R>0$ then λ_2 and λ_3 are negative or have negative real parts. Due to this, all eigenvalues ensure $|\arg(\lambda_i)|>\frac{\alpha\pi}{2}$ and E_5 is local asymptotically stable.

Eigenvalues of $J(E_5)$ are:

$$\lambda_1 = \theta_1^{-\alpha}\theta_2^{-\alpha}(s_2^{\alpha}+\gamma_2^{\alpha}-\eta_1^{\alpha})^{-1}(\theta_2^{\alpha}(4c^{\alpha}(s_2^{\alpha}+\gamma_2^{\alpha}-\eta_1^{\alpha})^2\theta_1^{2\alpha}\varphi_2^{\alpha}+\delta^{-4\alpha}\theta_2^{\alpha}(\delta^{2\alpha}\eta_1^{\alpha}\theta_1^{\alpha}\varphi_2^{\alpha}$$
$$-(s_2^{\alpha}+\gamma_2^{\alpha})\left(\sigma^{\alpha}\left((s_2^{\alpha}+\gamma_2^{\alpha})\varphi_1^{\alpha}+\delta^{\alpha}\theta_1^{\alpha}(s_1^{\alpha}+\gamma_1^{\alpha}-\varphi_1^{\alpha})\right)+\delta^{2\alpha}\theta_1^{\alpha}\varphi_2^{\alpha}\right)\Big)^2\Big)\Big)^{\frac{1}{2}},$$

$$\lambda_2 = -\frac{1}{2(s_2^{\alpha}+\gamma_2^{\alpha}-\eta_1^{\alpha})}(\delta^{-\alpha}(s_2^{\alpha}+\gamma_2^{\alpha})(s_2^{\alpha}+\gamma_2^{\alpha}-2\eta_1^{\alpha})\theta_1^{-\alpha}\varphi_1^{\alpha}-\eta_1^{\alpha}(s_1^{\alpha}+\gamma_1^{\alpha}-\varphi_1^{\alpha})$$
$$+(s_2^{\alpha}+\gamma_2^{\alpha}-\eta_1^{\alpha})\left(\delta^{-2\alpha}\theta_1^{-2\alpha}\left(4\delta^{\alpha}(s_2^{\alpha}+\gamma_2^{\alpha})\theta_1^{\alpha}\left((s_2^{\alpha}+\gamma_2^{\alpha})\varphi_1^{\alpha}+\delta^{\alpha}\theta_1^{\alpha}(s_1^{\alpha}+\gamma_1^{\alpha}-\varphi_1^{\alpha})\right)\right.\right.$$
$$\left.\left.+\left((s_2^{\alpha}+\gamma_2^{\alpha})^2\varphi_1^{\alpha}-\eta_1^{\alpha}\left(2(s_2^{\alpha}+\gamma_2^{\alpha})\varphi_1^{\alpha}+\delta^{\alpha}\theta_1^{\alpha}(s_1^{\alpha}+\gamma_1^{\alpha}-\varphi_1^{\alpha})\right)\right)^2(s_2^{\alpha}+\gamma_2^{\alpha}-\eta_1^{\alpha})^{-2}\right)\Big)^{\frac{1}{2}}\Bigg),$$

$$\lambda_3 = \frac{1}{2(s_2^\alpha+\gamma_2^\alpha-\eta_1^\alpha)}(-\delta^{-\alpha}(s_2^\alpha+\gamma_2^\alpha)(s_2^\alpha+\gamma_2^\alpha-2\eta_1^\alpha)\theta_1^{-\alpha}\varphi_1^\alpha+\eta_1^\alpha(s_1^\alpha+\gamma_1^\alpha-\varphi_1^\alpha)$$
$$+(s_2^\alpha+\gamma_2^\alpha-\eta_1^\alpha)\big(\delta^{-2\alpha}\theta_1^{-2\alpha}\big(4\delta^\alpha(s_2^\alpha+\gamma_2^\alpha)\theta_1^\alpha\big((s_2^\alpha+\gamma_2^\alpha)\varphi_1^\alpha+\delta^\alpha\theta_1^\alpha(s_1^\alpha+\gamma_1^\alpha-\varphi_1^\alpha)\big)$$
$$+\Big((s_2^\alpha+\gamma_2^\alpha)^2\varphi_1^\alpha-\eta_1^\alpha\big(2(s_2^\alpha+\gamma_2^\alpha)\varphi_1^\alpha+\delta^\alpha\theta_1^\alpha(s_1^\alpha+\gamma_1^\alpha-\varphi_1^\alpha)\big)\Big)^2(s_2^\alpha+\gamma_2^\alpha-\eta_1^\alpha)^{-2}\Big)\Big)^{\frac{1}{2}}\Bigg).$$

Theorem 11. Let E_6 be the equilibrium points system (5). Assume that

$s_2^\alpha+\gamma_2^\alpha>\eta_1^\alpha, s_2^\alpha+\gamma_2^\alpha<-\delta^\alpha\theta_1^\alpha\varphi_1^{-\alpha}(s_1^\alpha+\gamma_1^\alpha-\varphi_1^\alpha)$ and
$(s_2^\alpha+\gamma_2^\alpha)^2\varphi_1^\alpha>\eta_1^\alpha\big(2(s_2^\alpha+\gamma_2^\alpha)\varphi_1^\alpha+\delta^\alpha\theta_1^\alpha(s_1^\alpha+\gamma_1^\alpha-\varphi_1^\alpha)\big)$

Then the E_6 is locally asymptotically stable.

Proof.

$$J(E_6)=\begin{pmatrix} j_{11} & \eta_1^\alpha-(s_2^\alpha+\gamma_2^\alpha) & 0\\ j_{21} & 0 & 0\\ 0 & j_{32} & j_{33}\end{pmatrix}$$

where

$$j_{11}=-s_1^\alpha-\gamma_1^\alpha+(1-2\delta^{-\alpha}(s_2^\alpha+\gamma_2^\alpha)\theta_1^{-\alpha})\varphi_1^\alpha-\left(\frac{\delta^{-\alpha}(s_2^\alpha+\gamma_2^\alpha)\theta_1^{-\alpha}\big(-(s_2^\alpha+\gamma_2^\alpha)\varphi_1^\alpha-\delta^\alpha\theta_1^\alpha(s_1^\alpha+\gamma_1^\alpha-\varphi_1^\alpha)\big)}{s_2^\alpha+\gamma_2^\alpha-\eta_1^\alpha}\right),$$
$$j_{21}=\frac{\delta^{-\alpha}(s_2^\alpha+\gamma_2^\alpha)\theta_1^{-\alpha}\big(-(s_2^\alpha+\gamma_2^\alpha)\varphi_1^\alpha-\delta^\alpha\theta_1^\alpha(s_1^\alpha+\gamma_1^\alpha-\varphi_1^\alpha)\big)}{s_2^\alpha+\gamma_2^\alpha-\eta_1^\alpha},$$

$$j_{32}=\frac{-\sigma^\alpha\delta^{-2\alpha}\theta_1^{-\alpha}\varphi_2^{-\alpha}}{2(s_2^\alpha+\gamma_2^\alpha-\eta_1^\alpha)}(\sigma^\alpha(s_2^\alpha+\gamma_2^\alpha)^2\theta_2^\alpha\varphi_1^\alpha+\delta^\alpha\sigma^\alpha(s_2^\alpha+\gamma_2^\alpha)\theta_1^\alpha\theta_2^\alpha(s_1^\alpha+\gamma_1^\alpha-\varphi_1^\alpha)$$
$$+\delta^{2\alpha}(s_2^\alpha+\gamma_2^\alpha-\eta_1^\alpha)\theta_1^\alpha\theta_2^\alpha\varphi_2^\alpha+\delta^{2\alpha}(\theta_2^\alpha(4c^\alpha(s_2^\alpha+\gamma_2^\alpha-\eta_1^\alpha)^2\theta_1^{2\alpha}\varphi_2^\alpha+\delta^{-4\alpha}\theta_2^\alpha(\delta^{2\alpha}\eta_1^\alpha\theta_1^\alpha\varphi_2^\alpha$$
$$-(s_2^\alpha+\gamma_2^\alpha)\big(\sigma^\alpha\big((s_2^\alpha+\gamma_2^\alpha)\varphi_1^\alpha+\delta^\alpha\theta_1^\alpha(s_1^\alpha+\gamma_1^\alpha-\varphi_1^\alpha)\big)+\delta^{2\alpha}\theta_1^\alpha\varphi_2^\alpha\big)\big)^2\big)\big)^{\frac{1}{2}}\Bigg),$$

$$j_{33}=-\theta_1^{-\alpha}\theta_2^{-\alpha}(s_2^\alpha+\gamma_2^\alpha-\eta_1^\alpha)^{-1}(\theta_2^\alpha(4c^\alpha(s_2^\alpha+\gamma_2^\alpha-\eta_1^\alpha)^2\theta_1^{2\alpha}\varphi_2^\alpha+\delta^{-4\alpha}\theta_2^\alpha(\delta^{2\alpha}\eta_1^\alpha\theta_1^\alpha\varphi_2^\alpha$$
$$-(s_2^\alpha+\gamma_2^\alpha)\big(\sigma^\alpha\big((s_2^\alpha+\gamma_2^\alpha)\varphi_1^\alpha+\delta^\alpha\theta_1^\alpha(s_1^\alpha+\gamma_1^\alpha-\varphi_1^\alpha)\big)+\delta^{2\alpha}\theta_1^\alpha\varphi_2^\alpha\big)\big)^2\big)\big)^{\frac{1}{2}}.$$

The characteristic equation is $|J(E_6)-\lambda I|=0$. Hence

$$(\lambda+K)(\lambda^2+G\lambda+R)=0 \tag{12}$$

where

$$G=\delta^{-\alpha}\theta_1^{-\alpha}\Big((s_2^\alpha+\gamma_2^\alpha)^2\varphi_1^\alpha-\eta_1^\alpha\big(2(s_2^\alpha+\gamma_2^\alpha)\varphi_1^\alpha+\delta^\alpha\theta_1^\alpha(s_1^\alpha+\gamma_1^\alpha-\varphi_1^\alpha)\big)\Big)(s_2^\alpha+\gamma_2^\alpha-\eta_1^\alpha)^{-1},$$

$$R=\delta^{-\alpha}(s_2^\alpha+\gamma_2^\alpha)\theta_1^{-\alpha}\big(-(s_2^\alpha+\gamma_2^\alpha)\varphi_1^\alpha-\delta^\alpha\theta_1^\alpha(s_1^\alpha+\gamma_1^\alpha-\varphi_1^\alpha)\big),$$

$$K = \theta_1^{-\alpha}\theta_2^{-\alpha}(s_2^\alpha+\gamma_2^\alpha-\eta_1^\alpha)^{-1}(\theta_2^\alpha(4c^\alpha(s_2^\alpha+\gamma_2^\alpha-\eta_1^\alpha)^2\theta_1^{2\alpha}\varphi_2^\alpha+\delta^{-4\alpha}\theta_2^\alpha(\delta^{2\alpha}\eta_1^\alpha\theta_1^\alpha\varphi_2^\alpha$$
$$-(s_2^\alpha+\gamma_2^\alpha)\left(\sigma^\alpha\left((s_2^\alpha+\gamma_2^\alpha)\varphi_1^\alpha+\delta^\alpha\theta_1^\alpha(s_1^\alpha+\gamma_1^\alpha-\varphi_1^\alpha)\right)+\delta^{2\alpha}\theta_1^\alpha\varphi_2^\alpha\right)\right)^2\Big)^{\frac{1}{2}}.$$

Let λ_1, λ_2 and λ_3 be the roots of (12). By the assumptions, we know that $\varphi_1, \varphi_2, \theta_1, \theta_2, \delta, \gamma_1, \gamma_2, \eta_1, \sigma, c$ are pozitive. Therefore $\lambda_1 = -K < 0, G > 0, R > 0$. From Routh-Hurwitz Criteria if $G > 0, R > 0$ then λ_2 and λ_3 are negative or have negative real parts. Due to this, all eigenvalues ensure $|\arg(\lambda_i)| > \frac{\alpha\pi}{2}$ by Theorem (1) and E_6 is local asymptotically stable.

Eigenvalues of $J(E_6)$ are:

$$\lambda_1 = -\theta_1^{-\alpha}\theta_2^{-\alpha}(s_2^\alpha+\gamma_2^\alpha-\eta_1^\alpha)^{-1}(\theta_2^\alpha(4c^\alpha(s_2^\alpha+\gamma_2^\alpha-\eta_1^\alpha)^2\theta_1^{2\alpha}\varphi_2^\alpha+\delta^{-4\alpha}\theta_2^\alpha(\delta^{2\alpha}\eta_1^\alpha\theta_1^\alpha\varphi_2^\alpha$$
$$-(s_2^\alpha+\gamma_2^\alpha)\left(\sigma^\alpha\left((s_2^\alpha+\gamma_2^\alpha)\varphi_1^\alpha+\delta^\alpha\theta_1^\alpha(s_1^\alpha+\gamma_1^\alpha-\varphi_1^\alpha)\right)+\delta^{2\alpha}\theta_1^\alpha\varphi_2^\alpha\right)\right)^2\Big)^{\frac{1}{2}},$$

$$\lambda_2 = -\frac{1}{2(s_2^\alpha+\gamma_2^\alpha-\eta_1^\alpha)}(\delta^{-\alpha}(s_2^\alpha+\gamma_2^\alpha)(s_2^\alpha+\gamma_2^\alpha-2\eta_1^\alpha)\theta_1^{-\alpha}\varphi_1^\alpha-\eta_1^\alpha(s_1^\alpha+\gamma_1^\alpha-\varphi_1^\alpha)$$
$$+(s_2^\alpha+\gamma_2^\alpha-\eta_1^\alpha)\left(\delta^{-2\alpha}\theta_1^{-2\alpha}\left(4\delta^\alpha(s_2^\alpha+\gamma_2^\alpha)\theta_1^\alpha\left((s_2^\alpha+\gamma_2^\alpha)\varphi_1^\alpha+\delta^\alpha\theta_1^\alpha(s_1^\alpha+\gamma_1^\alpha-\varphi_1^\alpha)\right)\right.\right.$$
$$\left.\left.+\left((s_2^\alpha+\gamma_2^\alpha)^2\varphi_1^\alpha-\eta_1^\alpha\left(2(s_2^\alpha+\gamma_2^\alpha)\varphi_1^\alpha+\delta^\alpha\theta_1^\alpha(s_1^\alpha+\gamma_1^\alpha-\varphi_1^\alpha)\right)\right)^2(s_2^\alpha+\gamma_2^\alpha-\eta_1^\alpha)^{-2}\right)^{\frac{1}{2}}\right),$$

$$\lambda_3 = \frac{1}{2(s_2^\alpha+\gamma_2^\alpha-\eta_1^\alpha)}(-\delta^{-\alpha}(s_2^\alpha+\gamma_2^\alpha)(s_2^\alpha+\gamma_2^\alpha-2\eta_1^\alpha)\theta_1^{-\alpha}\varphi_1^\alpha+\eta_1^\alpha(s_1^\alpha+\gamma_1^\alpha-\varphi_1^\alpha)$$
$$+(s_2^\alpha+\gamma_2^\alpha-\eta_1^\alpha)\left(\delta^{-2\alpha}\theta_1^{-2\alpha}\left(4\delta^\alpha(s_2^\alpha+\gamma_2^\alpha)\theta_1^\alpha\left((s_2^\alpha+\gamma_2^\alpha)\varphi_1^\alpha+\delta^\alpha\theta_1^\alpha(s_1^\alpha+\gamma_1^\alpha-\varphi_1^\alpha)\right)\right.\right.$$
$$\left.\left.+\left((s_2^\alpha+\gamma_2^\alpha)^2\varphi_1^\alpha-\eta_1^\alpha\left(2(s_2^\alpha+\gamma_2^\alpha)\varphi_1^\alpha+\delta^\alpha\theta_1^\alpha(s_1^\alpha+\gamma_1^\alpha-\varphi_1^\alpha)\right)^2(s_2^\alpha+\gamma_2^\alpha-\eta_1^\alpha)^{-2}\right)^{\frac{1}{2}}\right).$$

6. Numerical Scheme for the Provided Skin Cancer Model in the Caputo Fractional (CF) Derivative Sense

Using the CF operator, the dynamics of the proposed fractional-order model (5) are investigated. Using the Adams-type estimator-corrector approach, we carry out numerical simulations for the suggested nonlinear fractional-order system [36, 37, 38, 39]. We examine the subsequent Cauchy-type ordinary differential equation within the context of the α-order Caputo operator:

$$_0^C D_t^\alpha \Phi(t) = f\left(t, \Phi(t)\right),\ \Phi^{(b)}(0) = \Phi_0^b,\ 0 < a \le 1, 0 < t \le \tau \tag{13}$$

where $b = 0,1,\dots,n-1$, and $n = \lceil\alpha\rceil$ Equation (13) can be turned to the Voltera equation:

$$\Phi(t) = \sum_{b=0}^{n-1}\Phi_0^{(b)}\frac{t^b}{b!} + \frac{1}{\Gamma(a)}\int_0^t (t-s)^{\alpha-1}\Phi(s,\Phi(s))ds \tag{14}$$

Considering the Adam-Bashforth-Moulton algorithm [37] along with the proposed predictor-corrector scheme to provide numerical solutions for the model, we adopt $h = \frac{\tau}{N}, t_z = zh$, and $z = 0,1,\dots,N \in Z^+$, allowing $\Phi_z \approx \Phi(t_z)$ for discretization. The associated corrector formula is derived as per the reference [40].

$$M_{1_{q+1}} = \sum_{z=0}^{q-1} M_{1_0}^{(z)} \frac{t_{q+1}^z}{z!} + \frac{h^\alpha}{\Gamma(\alpha+2)} \sum_{z=0}^{q} (p_{z,q+1}) \left(M_{1_z} \varphi_1^\alpha \left(1 - \frac{M_{1_z}}{\theta_1} \right) \right.$$
$$\left. -\delta^\alpha M_{1_z} M_{2_z} - \gamma_1^\alpha M_{1_z} + \eta_1^\alpha M_{2_z} - s_1^\alpha M_{1_z} \right)$$
$$+ \frac{h^\alpha}{\Gamma(\alpha+2)} \sum_{z=0}^{q} (p_{q+1,q+1}) \left(M_{1_{q+1}}^{PF} \varphi_1^\alpha \left(1 - \frac{M_{1q+1}^{PF}}{\theta_1} \right) \right.$$
$$\left. -\delta^\alpha M_{1_{q+1}}^{PF} M_{2_{q+1}}^{PF} - \gamma_1^\alpha M_{1_{q+1}}^{PF} + \eta_1^\alpha M_{2_{q+1}}^{PF} - s_1^\alpha M_{1_{q+1}}^{PF} \right),$$

$$M_{2_{q+1}} = \sum_{z=0}^{q-1} M_{2_0}^{(z)} \frac{t_{q+1}^z}{z!} + \frac{h^\alpha}{\Gamma(\alpha+2)} \sum_{z=0}^{q} (p_{z,q+1}) \left(M_{2_z} \left(\delta^\alpha M_{1_z} - \gamma_2^\alpha \right) - s_2^\alpha M_{2_z} \right)$$
$$+ \frac{h^\alpha}{\Gamma(\alpha+2)} \sum_{z=0}^{q} (p_{q+1,q+1}) \left(M_{2_{q+1}}^{PF} \left(\delta^\alpha M_{1_{q+1}}^{PF} - \gamma_2^\alpha \right) - s_2^\alpha M_{2_{q+1}}^{PF} \right),$$

$$T_{q+1} = \sum_{z=0}^{q-1} T_0^{(z)} \frac{t_{q+1}^z}{z!} + \frac{h^\alpha}{\Gamma(\alpha+2)} \sum_{z=0}^{q} (p_{z,q+1}) \left(T_z \varphi_2^\alpha \left(1 - \frac{T_z}{\theta_2^\alpha} \right) - \sigma^\alpha T_z M_{2_z} + c^\alpha \right)$$
$$+ \frac{h^\alpha}{\Gamma(\alpha+2)} \sum_{z=0}^{q} (p_{q+1,q+1}) \left(T_{q+1}^{PF} \varphi_2^\alpha \left(1 - \frac{T_{q+1}^{PF}}{\theta_2^\alpha} \right) - \sigma^\alpha T_{q+1}^{PF} M_{2_{q+1}}^{PF} + c^\alpha \right),$$

Where

$$p_{z,q+1} = \begin{cases} q^{\alpha+1} - (q-\alpha)(q+1)^\alpha, \text{ifz } = 0, \\ (q-z+2)^{\alpha+1} + (q-z)^{\alpha+1} - 2(q-z+1)^{\alpha+1}, \text{if } 1 \le z \le q, \\ 1, \text{ifz } = q+z. \end{cases} \tag{15}$$

The next step is to build the coincident predictor formula. Φ_{q+1}^{PF}. The following formula can be used to compute the predictor:

$$\begin{aligned} M_{1_{q+1}}^{PF} = \; & \sum_{z=0}^{q-1} M_{1_0}^{(z)} \frac{t_{q+1}^z}{z!} + \frac{h^\alpha}{\Gamma(\alpha+1)} \sum_{z=0}^{q} (j_{z,q+1}) \left(M_{1_z} \varphi_1^\alpha \left(1 - \frac{M_{1_z}}{\theta_1} \right) \right. \\ & \left. -\delta^\alpha M_{1_z} M_{2_z} - \gamma_1^\alpha M_{1_z} + \eta_1^\alpha M_{2_z} - s_1^\alpha M_{1_z} \right), \\ M_{2_{q+1}}^{PF} = \; & \sum_{z=0}^{q-1} M_{2_0}^{(z)} \frac{t_{q+1}^z}{z!} + \frac{h^\alpha}{\Gamma(\alpha+1)} \sum_{z=0}^{q} (j_{z,q+1}) \left(M_{2_z} \left(\delta^\alpha M_{1_z} - \gamma_2^\alpha \right) - s_2^\alpha M_{2_z} \right), \\ T_{q+1}^{PF} = \; & \sum_{z=0}^{q-1} T_0^{(z)} \frac{t_{q+1}^z}{z!} + \frac{h^\alpha}{\Gamma(\alpha+1)} \sum_{z=0}^{q} (j_{z,q+1}) \left(T_z \varphi_2^\alpha \left(1 - \frac{T_z}{\theta_2^\alpha} \right) - \sigma^\alpha T_z M_{2_z} + c^\alpha \right). \end{aligned} \tag{16}$$

where

$$j_{z,q+1} = (q+1-z)^\alpha - (q-z)^\alpha.$$

7. Numerical Simulations and Discussion

We have used the Adams-Bashforth Moulton Predictor-Corrector technique to generate numerical solutions for system (5) with initial conditions $(M_{1_0}, M_{2_0}, T_0) = (33, 22, 50)$ and parameters given in Table (1). The goal of the numerical simulations is to investigate the effects of changing α values and parameter values on the dynamic behavior of model (5). Table (1) provides specific information on the parameter values used in the numerical simulations. We have performed numerical simulations using the parameter values from Table (1) to investigate the temporal dynamics of each sub-population at various fractional parameter α values. And we have calculated the equilibrium points as $E_6 = (M_1, M_2, T) = (3.58209, 1.71324, 14.2925)$ Additionally, graphics are produced to emphasize how changes in particular parameter values can have a significant impact on cell behavior. Considering different parameter values and fractional-order values, the dynamic patterns of the suggested skin cancer model are shown in Figures (1), (2), (3), (4), and (5). In particular, Figure (1) illustrates how the

fractional scenario affects tumor cells by showing how they behave at various α values. The tumor cells exhibit a decreasing trend as α values rise.

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Fig. (1) examines the evolution of the active tumor cells throughout time. As can be seen in the illustration, the memory effect of the tumor cells increases when the fractional-order α lowers from the unit. In non-integer settings, these cells therefore take longer to stabilize. Furthermore, the tumor cells behave in an unstable way when α is a unit, but the system remains stable over the long run when α is not an integer, indicating one of the essential properties of the fractional-order derivatives.

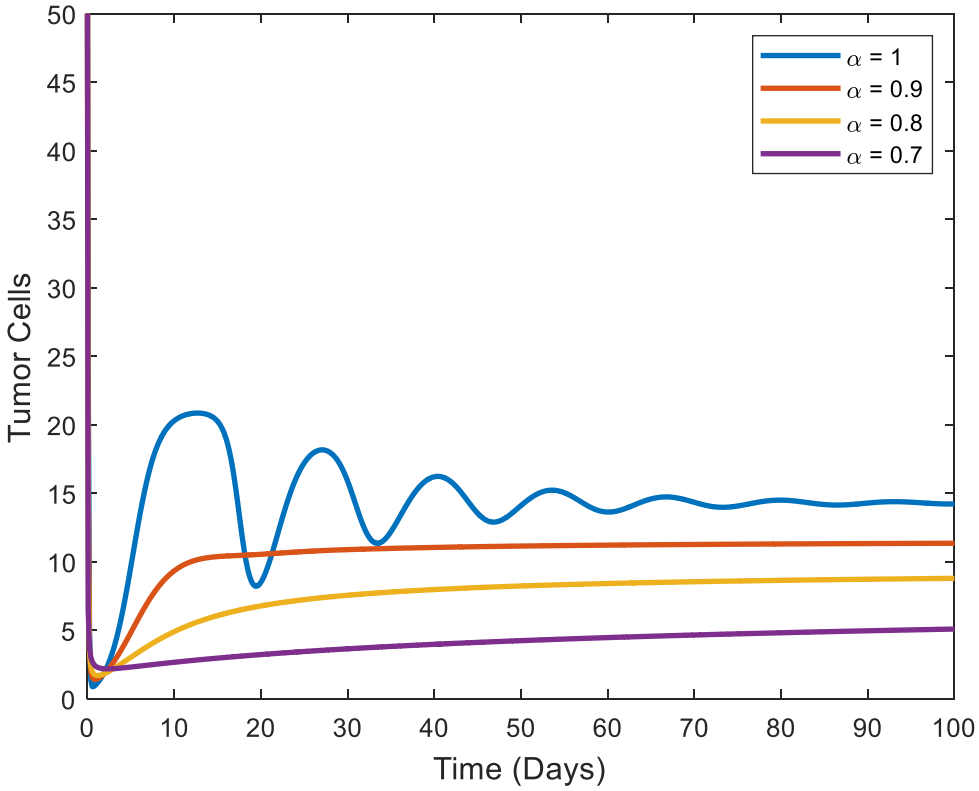

Figure 1. Change of the tumor cells over time of the varying fractional-order derivative

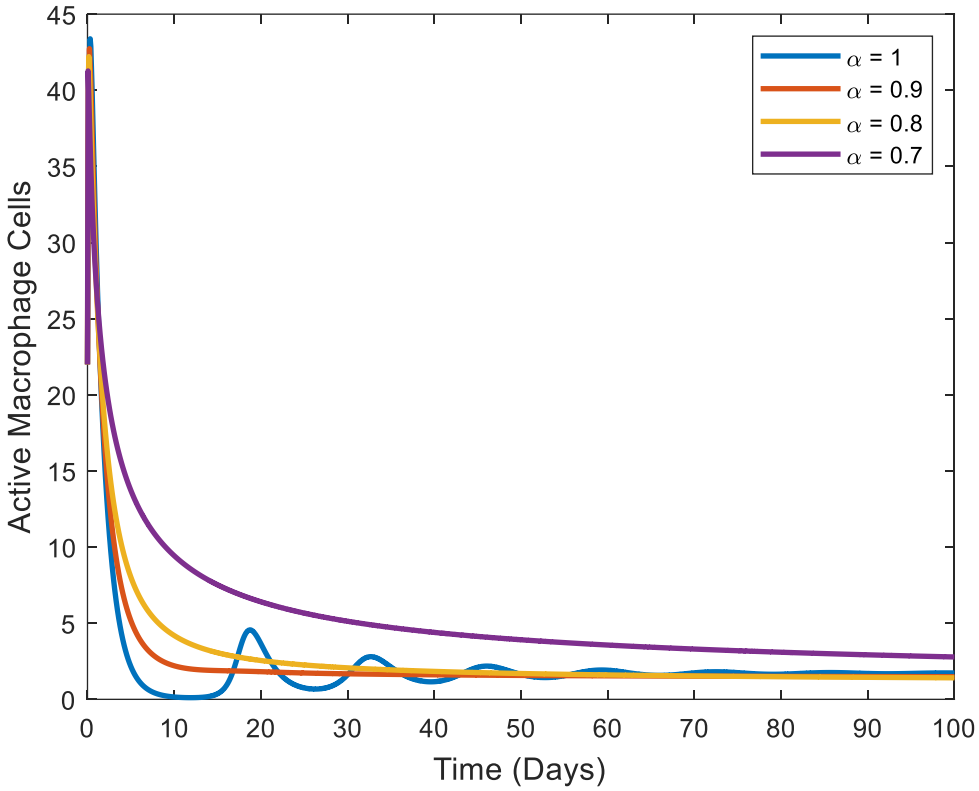

Figure 2. Change of the active macrophages cells over time of the varying fractional-order derivative

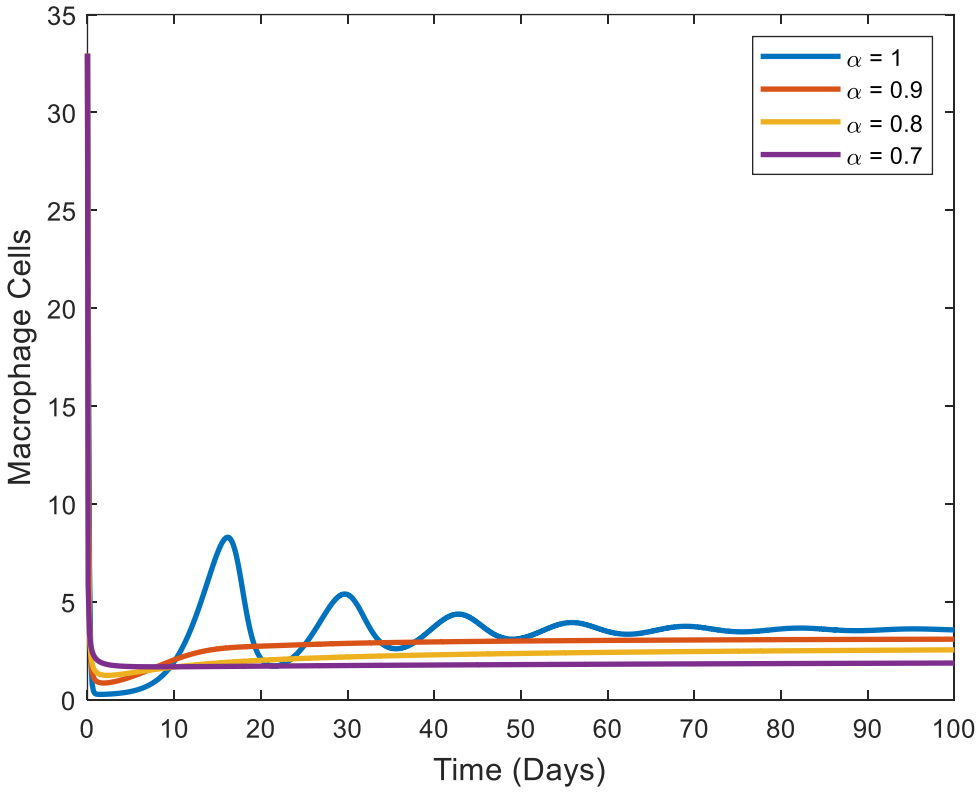

Figure 3. Change of the macrophages cells over time with the varying fractional-order derivative

Additionally, Fig. (2) shows that there are generally more active macrophage cells when $\alpha = 0.7$ than when $\alpha = 1$. As a result, the fractional order predicts a higher number of active macrophage cells than the estimate obtained in the integer-order scenario. Moreover, after 100 days, it is seen that the body still has active macrophage cells when $\alpha = 0.7$. On the eleventh day, however, it can be seen that they begin to disappear in an integer-order scenario.

The agreement between the distribution of active macrophage cells and the behavior of fractional derivatives is evident from the effect of $\alpha = 0.7$. The wider stability region of fractional differential equations compared to integer-order equations, which implies that they are at least as stable as integer-order equations, is one of the main reasons for employing FODEs. Moreover, all the necessary conditions for the existence of solutions to fractional-order equations, as stated in [24, 41], must be met. Hence, Fig. (1) provides empirical evidence supporting this theoretical finding, indicating that the stability zone of the proposed model increases as α decreases from unity.

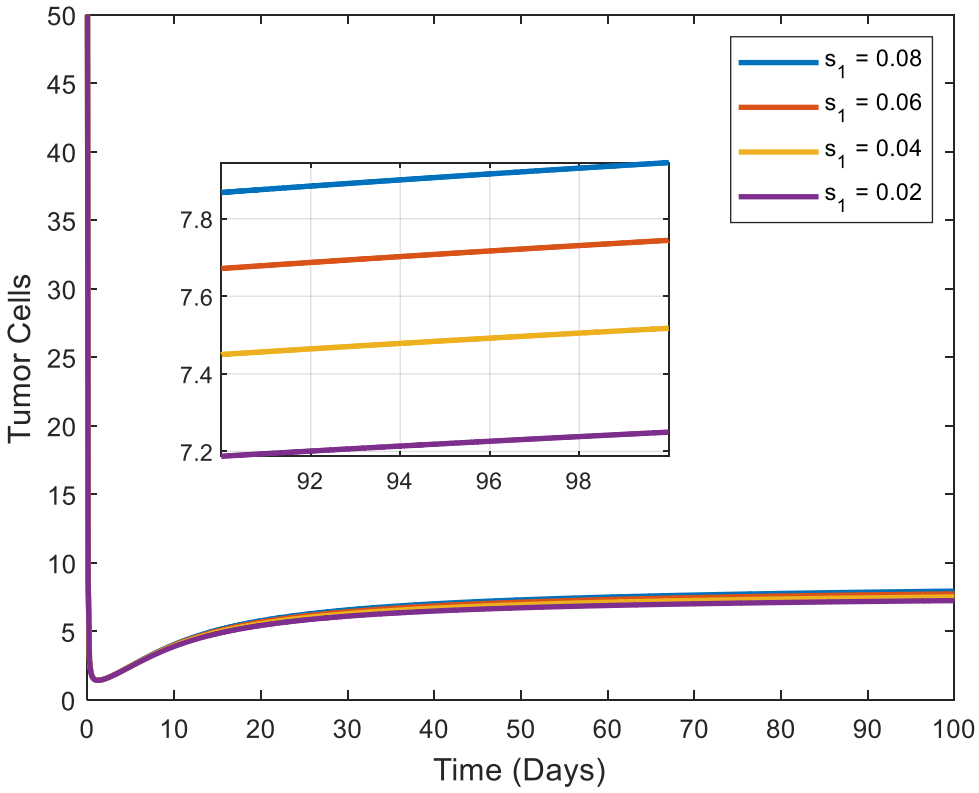

Figure 4. Change of the tumor cells over time of the different s_1 values and $\alpha = 0.8$

Figure (3) showcases a trend akin to the one witnessed in active macrophage cells. With deviations of the fractional-order parameter α from unity, there is a noticeable rise in the memory effect exhibited by macrophagecells. In the context of fractional circumstances, this rise implies a decrease in the peak count of macrophage cells, aiming towards stability over time. This behavior demonstrates how α affects the dynamics of the proposed system model for skin cancer.

Figure (4) depicts an increase in tumor cells under the fractional-order case $\alpha = 0.8$ as s_1 values increase. Similarly, in Figure (5), it can be observed that s_2 has a substantial effect on the regression of tumor cells, with an increase in s_2 resulting in an increase in the number of cancer cells.

The fractional-order derivative attenuates the oscillation behavior close to the positive equilibrium point, as seen in Figure (1). The occurrence of periodic solutions is related to cancer models. It implies that tumor levels may vary around an equilibrium point even in the absence of treatment. Clinical observations of the "Jeff's Phenomenon" have been made [42], and it has been documented in several cancer model organisms [24, 43]. As

seen in Fig. (4), the number of tumor cells grows with an increase in s_1, and the number of tumor cells increases with an increase in s_2 in Fig. (5).

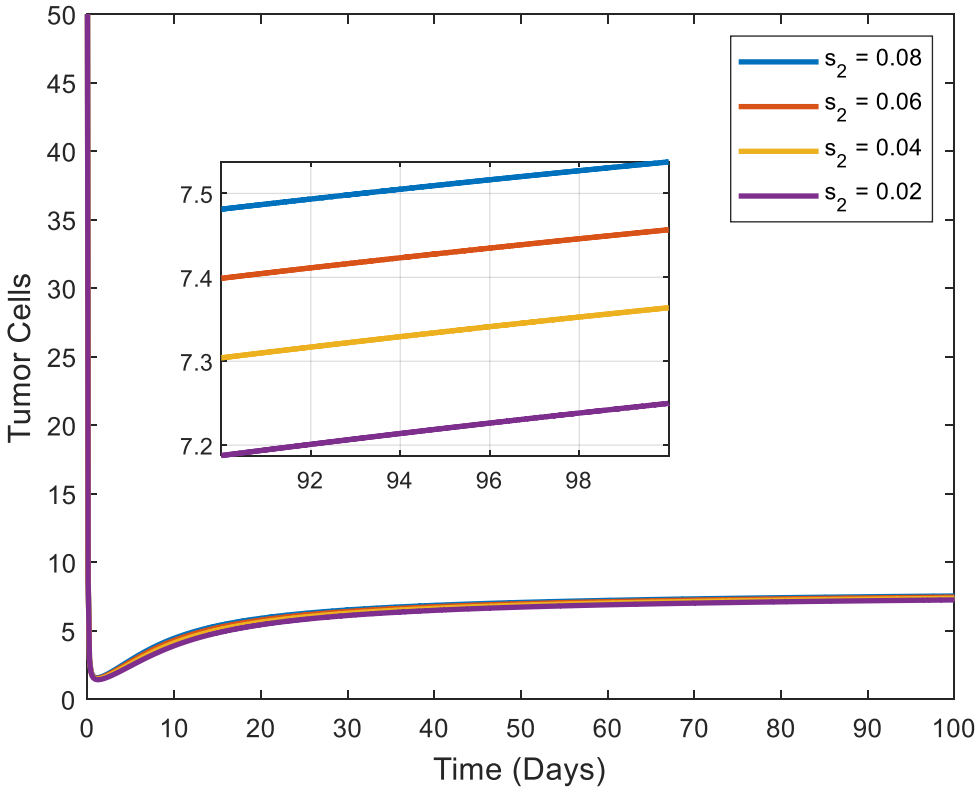

Figure 5. Change of the tumor cells over time of the different s_2 values and $\alpha = 0.8$

8. Conclusions

This paper focuses on the Caputo fractional order cancer-immune system model, which is a system of fractional differential equations (5) with Caputo fractional derivatives. We investigate the local asymptotic stability of the tumor-free and tumor-infection fixed points of the system and demonstrate that under certain conditions, the equilibrium points of the model (5) are asymptotically stable. We then examine the existence and uniqueness of the solution and provide numerical simulations to validate the theoretical results. To explore the effects of varying the fractional order derivative and to analyze the behaviour of the system, we generate figures for different α values. Our results show that as α decreases from 1, the cells reach equilibrium points more quickly, and we conclude that the Caputo fractional derivative yields more realistic results than integer order derivatives. It is observed that the density of tumor cells increases as stress increases. It is seen that the system is stable as the fractional derivative value decreases from 1, which shows that the stability region of fractional derivatives is wider than full-order derivatives. Our model differs from other studies in the literature on skin cancer by examining the relationship between stress and skin cancer. Additionally, it differs from other models in terms of the mathematical analysis presented here. Stress plays a significant role in cancer development, and our results indicate that reducing stress leads to a decrease in the number of tumors. We also observe significant changes in the number of macrophage cells, the number of active macrophage cells, and the number of tumor cells as α varies. We anticipate that this study will make valuable contributions to the fields of mathematics and medicine.

Declaration of Competing interest

The authors declared that they have no competing interests.

References

[1] O'Sullivan, D. E., Brenner, D. R., Demers, P. A., Villeneuve, P. J., Friedenreich, C. M., King, W. D., & ComPARe Study Group. (2019). Indoor tanning and skin cancer in Canada: A meta-analysis and attributable burden estimation. Cancer epidemiology, 59, 1-7.

[2] Hylands P. Skin cancer: types, diagnosis and prevention. Heart Fail 2019;10. p. 00.

[3] Gray-Schopfer, V., Wellbrock, C., & Marais, R. (2007). Melanoma biology and new targeted therapy. Nature, 445(7130),851-857.

[4] Morgan, R. A., Dudley, M. E., Wunderlich, J. R., Hughes, M. S., Yang, J. C., Sherry, R. M., ... & Rosenberg, S. A. (2006). Cancer regression in patients after transfer of genetically engineered lymphocytes. Science, 314(5796),126-129.

[5] Nuzzo, C., Pino, M. S., & Cognetti, F. (2014). Systemic therapy in melanoma. Skin Cancer: A Practical Approach, 461-474.

[6] Kirkwood, J. M., Tarhini, A. A., Panelli, M. C., Moschos, S. J., Zarour, H. M., Butterfield, L. H., & Gogas, H. J. (2008). Next generation of immunotherapy for melanoma. Journal of Clinical Oncology, 26(20), 3445-3455.

[7] Dunn, G. P., Bruce, A. T., Ikeda, H., Old, L. J., & Schreiber, R. D. (2002). Cancer immunoediting: from immunosurveillance to tumor escape. Nature immunology, 3(11), 991-998.

[8] Fridman, W. H., Pagès, F., Sautès-Fridman, C., & Galon, J. (2012). The immune contexture in human tumours: impact on clinical outcome. Nature Reviews Cancer, 12(4), 298-306.

[9] Thomas, D. A., & Massagué, J. (2005). TGF- β directly targets cytotoxic T cell functions during tumor evasion of immune surveillance. Cancer cell, 8(5), 369-380.

[10] Moutsopoulos, N. M., Wen, J., & Wahl, S. M. (2008). TGF- β and tumors-an ill-fated alliance. Current opinion in immunology, 20(2), 234-240.

[11] Sun, H., Cao, D., Shen, K., Yang, J., Xiang, Y., Feng, F., ... & Song, L. (2018). Piver Type II vs. Type III hysterectomy in the treatment of early-stage cervical cancer: midterm follow-up results of a randomized controlled trial. Frontiers in Oncology, 8, 568.

[12] Dougan M, Dranoff G, Dougan SK. Cancer immunotherapy: beyond checkpoint blockade. Annu Rev Cancer Biol. (2018) 3:55-75. doi: 10.1146/ annurev-cancerbio-030518-055552

[13] Marelli, G., Howells, A., Lemoine, N. R., & Wang, Y. (2018). Oncolytic viral therapy and the immune system: a double-edged sword against cancer. Frontiers in immunology, 9, 866.

[14] Sabbar, Y., Yavuz, M., & Özköse, F. (2022). Infection Eradication Criterion in a General Epidemic Model with Logistic Growth, Quarantine Strategy, Media Intrusion, and Quadratic Perturbation. Mathematics, 10(22),4213.

[15] Weinberg, R. A. (2014). Coming full circle-from endless complexity to simplicity and back again. Cell, 157(1), 267-271.

[16] Kolch, W., Halasz, M., Granovskaya, M., & Kholodenko, B. N. (2015). The dynamic control of signal transduction networks in cancer cells. Nature Reviews Cancer, 15(9), 515-527.

[17] Eikenberry, S., Thalhauser, C., & Kuang, Y. (2009). Tumor-immune interaction, surgical treatment, and cancer recurrence in a mathematical model of melanoma. PLoS computational biology, 5(4), e1000362.

[18] Pennisi, M. (2012). A mathematical model of immune-system-melanoma competition. Computational and mathematical methods in medicine, 2012.

[19] Nikolov, S., & Nenov, M. (2019). Modelling vaccine quantity in mathematical models of melanoma treatment. Series on Biomechanics.

[20] Shu, Y., Huang, J., Dong, Y., & Takeuchi, Y. (2020). Mathematical modeling and bifurcation analysis of pro- and anti-tumor macrophages. Applied Mathematical Modelling, 88, 758-773.

[21] Özköse, F., ŞENEL, M. T., & Habbireeh, R. (2021). Fractional-order mathematical modelling of cancer cells-cancer stem cells-immune system interaction with chemotherapy. Mathematical Modelling and Numerical Simulation with Applications, 1(2), 67-83.

[22] Lai, X., & Friedman, A. (2017). Combination therapy for melanoma with BRAF/MEK inhibitor and immune checkpoint inhibitor: a mathematical model. BMC Systems Biology, 11(1), 1-18.

[23] Özköse, F., Yılmaz, S., Yavuz, M., Öztürk, İ., Şenel, M. T., Bağcı, B. Ş., ... & Önal, Ö. (2022). A fractional modeling of tumor-immune system interaction related to lung cancer with real data. The European Physical Journal Plus, 137, 1-28.

[24] Öztürk, I., & Özköse, F. (2020). Stability analysis of fractional order mathematical model of tumor-immune system interaction. Chaos, Solitons & Fractals, 133, 109614.

[25] Carvalho, A. R., Pinto, C., & Baleanu, D. (2018). HIV/HCV coinfection model: a fractional-order perspective for the effect of the HIV viral load. Advances in Difference Equations, 2018(1), 1-22.

[26] Podlubny I . Fractional differential equations. Academic Press, New York; 1999.

[27] Ghaziani, R. K., Alidousti, J., & Eshkaftaki, A. B. (2016). Stability and dynamics of a fractional order Leslie-Gower prey-predator model. Applied Mathematical Modelling, 40(3), 2075-2086.

[28] Petras I . Fractional -order nonlinear systems: modeling, analysis and simulation. London, Beijing: Springer; 2011.

[29] Baisad, K., & Moonchai, S. (2018). Analysis of stability and Hopf bifurcation in a fractional Gauss-type predator-prey model with Allee effect and Holling type-III functional response. Advances in difference equations, 2018, 1-20.

[30] Ahmed, E., El-Sayed, A. M. A., & El-Saka, H. A. (2007). Equilibrium points, stability and numerical solutions of fractional-order predator-prey and rabies models. Journal of Mathematical Analysis and Applications, 325(1), 542-553.

[31] Allen, L. J. An introduction to mathematical biology., 2007. ISBN, 10, 0-13.

[32] Özköse, F., Yavuz, M., Şenel, M. T., & Habbireeh, R. (2022). Fractional order modelling of omicron SARS-CoV-2 variant containing heart attack effect using real data from the United Kingdom. Chaos, Solitons & Fractals, 157,111954 .

[33] Özköse, F. (2023). Modeling of psoriasis by considering drug influence: A mathematical approach with memory trace. Computers in Biology and Medicine, 107791.

[34] Özköse, F. (2023). Long-Term Side Effects: A Mathematical Modeling of COVID-19 and Stroke with Real Data. Fractal and Fractional, 7(10),719.

[35] Özköse, F., Habbireeh, R., & Şenel, M. T. (2023). A novel fractional order model of SARS-CoV-2 and Cholera disease with real data. Journal of Computational and Applied Mathematics, 423, 114969.

[36] Diethelm, K., & Freed, A. D. (1998). The FracPECE subroutine for the numerical solution of differential equations of fractional order. Forschung und wissenschaftliches Rechnen, 1999, 57-71.

[37] Diethelm, K. (1997). An algorithm for the numerical solution of differential equations of fractional order. Electronic transactions on numerical analysis, 5(1), 1-6.

[38] Garrappa, R. (2010). On linear stability of predictor-corrector algorithms for fractional differential equations. International Journal of Computer Mathematics, 87(10), 2281-2290.

[39] Garrappa, R. (2018). Numerical solution of fractional differential equations: A survey and a software tutorial. Mathematics, 6(2), 16.

[40] Li, C., & Tao, C. (2009). On the fractional Adams method. Computers & Mathematics with Applications, 58(8),1573-1588.

[41] Rihan, F. A., & Velmurugan, G. (2020). Dynamics of fractional-order delay differential model for tumorimmune system. Chaos, Solitons & Fractals, 132, 109592.

[42] R.H. Thomlinson, Measurement and management of carcinoma of the breast. Clin.Radiol. 33(5), 481–493 (1982).

[43] Sarkar, R. R., & Banerjee, S. (2005). Cancer self remission and tumor stability–a stochastic approach. Mathematical Biosciences, 196(1), 65-81.