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ANALYSIS OF TUMOR-IMMUNE RESPONSE MODEL BY USING CONFORMABLE FRACTIONAL ORDER DERIVATIVE

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Abstract: In this research paper, the authors propose a generalized three-dimensional fractional order tumor-immune response model. The generalization of the model is made by introducing interleukin-2 (IL_2) cell population as the third variable in the proposed system. The study of the proposed model is performed by using a new concept of fractional-order derivatives called as conformable fractional-order derivative. The authors aim to study, analyze, and compare the dynamical behavior of both the three-dimensional fractional order model and the conformable fractional order version of the proposed model. The stability analysis is done for both versions of the model at the biologically feasible equilibrium points. To validate the theoretical results numerically, numerical simulation is performed by using a piecewise constant approximation process.

Keywords and Phrases: Tumor-Immune Response System, Fractional Derivatives, Stability Analysis, Numerical Simulation.

2020 Mathematics Subject Classification: 92C37, 26A33, 65P40.

1. Introduction

Tumors are considered among the families of soaring mortality diseases, revealing an insanity of cellular augmentation which often induces uncontrolled growth of cells [8, 29]. Researchers are working for understanding the dynamics of interaction between tumor cells and the immune system. In terms of biology and mathematics, the Immune system is regarded as one of the most interesting schemes. The immune system can do multiple functions with various metabolic pathways. Therefore, almost all effector cells perform more than one function and each function of the immune system is typically done by more than one effector cell. Hence, this makes it a more complex system [2]. Integer-order differential equations are being used for modelling tumor phenomena for a long time [23, 9, 24, 25, 14, 21, 26], on the other hand, differential equations with fractional order have a short history in modeling such phenomena with memory [30]. Research on fractional calculus has gained much interest over the past few decades and differential equations with fractional order have been used in different research areas like medicine [13], finance [10], engineering [33], physics [19, 35], and chemistry [37]. Fractional order differential equations are widely used to model biological systems and there are valuable applications and good results in this field [3, 20- 22, 34, 36, 38]. It is also expressed that models of biological systems developed by differential equations with fractional order display more realistic results compared to models developed by integer order differential equations [5, 8, 28]. This is only because of the fact that fractional order derivatives involve memory concepts and that is quite favorable to work on biological processes.

In this research paper, we study the tumor-immune interaction model by applying the newly introduced definition called "conformable fractional order derivative", which was introduced in the year 2014 by Khalil et al. [17]. According to this definition, if we consider a function $f : [a, \infty) \to \infty$ and let $0 < \alpha \leq 1$ be the order of the function. Then:

1. The left fractional derivative of a function beginning from a, in limit form is defined by:

$$(T_\alpha^a f)(t) = \lim_{\epsilon \to 0} \frac{f(t + \epsilon(t-a)^{1-\alpha}) - f(t)}{\epsilon}, \tag{1}$$

   if the limit exists.

2. The right fractional derivative of a function ending at b, in limit form is

defined by:

$$({}^{b}_{\alpha}Tf)(t) = -\lim_{\epsilon \to 0} \frac{f(t + \epsilon(b-t)^{1-\alpha}) - f(t)}{\epsilon}, \tag{2}$$

if the limit exists.

3. The Caputo type fractional order derivative of the function is defined by:

$$D^{a}_{\alpha} f(t) = \frac{1}{\Gamma(1-\alpha)} \int_{a}^{t} \frac{f^{n}x}{(t-x)^{\alpha-n+1}} dx. \tag{3}$$

4. If the function $f(t)$ is differentiable at $t \in [a, \infty)$. Then, we have the following results:

$$(T^{a}_{\alpha} f)(t) = (t-a)^{1-\alpha} f'(t) \quad \textit{and} \quad ({}^{b}_{\alpha}Tf)(t) = (t-b)^{1-\alpha} f'(t). \tag{4}$$

Integer-order derivatives and conformable fractional-order derivatives have a few common basic properties also. In [1] Abdeljawad introduced a conformable fractional order version of Taylor series expansion, exponential functions, integration by parts, Gronwall's inequality, and Laplace transforms. Physical and biological applications of conformable fractional-order derivatives can be found in [4, 11, 27, 32]. In [16] Kartal and Gurcan considered the conformable fractional-order logistic equation with piecewise constant arguments by adopting the method presented by Gopalsamy in [15].

2. Fractional Order Tumor-Immune Interaction Systems

Consider a fractional-order tumor-immune interaction model given by FA Rihan et al. [31], which includes an external source of effector cells and immune stimulation effects by treatment of interleukin-2 (IL_2) cells. In the paper, the author's assumed three populations of the activated immune-system cells ($E(t)$), the tumor cells ($T(t)$), and the concentration of IL_2 cells in the tumor-site compartment. The mathematical model in [32], governed by the fractional-order differential equations is given by:

$$\begin{aligned} D^{\alpha_1} E(t) &= s_1 + p_1 E(t)T(t) - p_2 E(t) + p_3 E(t) I_L(t), \\ D^{\alpha_2} T(t) &= p_4 T(t)(1 - p_5 T(t)) - p_6 E(t) T(t), \\ D^{\alpha_3} I_L(t) &= s_2 + p_7 E(t) T(t) - p_8 I_L(t), \qquad 0 \le \alpha_i \le 1, \qquad i = 1,2,3. \end{aligned} \tag{5}$$

In research work [12], E. Balci, applied conformable fractional-order derivative on model (5) in absence of concentration of IL_2 in the tumor site compartment.

In this paper, we will study the dynamical behavior of model (5) in presence of immunotherapy (Interleukin-2) cells by using a conformable fractional order derivative.
Now, in order to reduce the sensitivity of system (5), we use the following re-scaling for non-dimensionalization of model (5):

$$x(t) = E(t)/E_0,\ y(t) = T(t)/T_0,\ z(t) = (I_L(t))/I_L0,\ \sigma = s_1/(E_0t_0),$$
$$\omega = (p_1T_0)/t_0,\ \delta = p_2/t_0,\ \theta = (p_3I_L0)/t_0,\ \gamma = p_4/t_0,\ \beta = p_5T_0,$$
$$1 = (p_0E_0)/t_0,\ \sigma' = s_2/(I_L0t_0),\ \omega' = (p_7E_0T_0)/(I_L0t_0), \quad \delta' = p_8/t_0.$$

Therefore, by applying these substitutions on model (5), we obtain the required non-dimentionlized Caputo-type fractional-order tumor-immune interaction model in presence of immunotherapy:

$$\begin{aligned} D^\alpha x(t) &= \sigma + \omega x(t)y(t) - \delta x(t) + \theta x(t)z(t), \\ D^\alpha y(t) &= \gamma y(t)(1 - \beta y(t)) - x(t)y(t), \\ D^\alpha z(t) &= \sigma' + \omega' x(t)y(t) - \delta' z(t). \end{aligned} \tag{6}$$

Where, $x(0) = x_0 \geq 0, \quad y(0) = y_0 \geq 0, \quad z(0) = z_0 \geq 0$ are the given initial conditions and the parameters are defined in [31]. Some of the parameters used in this model with their biological meaning are; σ, which is an external source of effector cells with δ as the death rate of effector cells. ω is the rate of antigenicity of tumor (response of the immune system to the tumor), θ is the cooperation rate of effector cells to interleukin-2 parameter, γ is the growth rate of tumor cells, β^{-1} is the maximal carrying capacity of the biological environment. σ' is the external source of input for interleukin-2 cells, ω' is the rate of competition between tumor cells and effector cells, and δ' is the loss rate parameter of interleukin-2 cells.
Now, the conformable fractional-order form of system (6) is given by:

$$\begin{aligned} T_\alpha E(t) &= \sigma + \omega ET - \delta E + \theta EIL_2, \\ T_\alpha T(t) &= \gamma T(1 - \beta T) - ET, \\ T_\alpha IL_2(t) &= \sigma' + \omega' ET - \delta' IL_2, \end{aligned} \tag{7}$$

where, T_α represents the conformable fractional-order derivative of the functions $E(t)$, $T(t)$, and $IL_2(t)$ with respect to time t, which is already defined in equation (4).

3. Stability analysis of model (6)

The stability analysis of the model (6) can be done by using the following equilibrium points: $E_0(x,0,0)$, $E_1(x,y,0)$, $E_2(0,y,z)$, and $E_3(x,y,z)$. These equilibrium points can be obtained by solving the following system of equations:

$$\begin{aligned} \sigma+\omega x(t)y(t)-\delta x(t)+\theta x(t)z(t) &= 0, \\ \gamma y(t)(1-\beta y(t))-x(t)y(t) &= 0, \\ \sigma'+\omega' x(t)y(t)-\delta' z(t) &= 0. \end{aligned} \tag{8}$$

The required equilibrium points obtained from system (8) are given by:

1. $E_0\left(\frac{\sigma}{\delta},0,0\right)$, the tumor-free equilibrium point.
2. $E_1\left(\frac{\sigma\omega'-\omega\sigma'}{\delta\omega'},\frac{1+\sqrt{\Delta}}{2\beta},0\right)$, the IL_2 free equilibrium point. Where $\Delta = \frac{1+4\sigma'\beta}{\gamma\omega'}$.
3. $E_2\left(0,\frac{1}{\beta},\frac{\sigma'}{\delta'}\right)$, the tumor-dominant equilibrium point.
4. $E_3(\bar{x},\bar{y},\bar{z})$, the positive interior equilibrium point given by.

The stability analysis at these equilibrium points of system (6) can be done by using following theorems [12]:

Theorem 1. *At the tumor-free equilibrium point $E_0(\sigma/\delta,0,0)$ of the model (6), the following results hold:*
1. if $\sigma > \delta\gamma$, the tumor-free equilibrium point is locally asymptotically stable.
2. if $\sigma < \delta\gamma$,, the tumor-free equilibrium point is unstable and it is a saddle point.

Proof. The Jacobian matrix of system (6) at the equilibrium point $E_0(\sigma/\delta,0,0)$ is given by:

$$J_{E_0} = \begin{pmatrix} -\delta & \sigma\omega/\delta & \sigma\theta/\delta \\ 0 & \gamma-\sigma/\delta & 0 \\ 0 & \omega'\sigma/\delta & -\delta' \end{pmatrix},$$

which gives the eigenvalues as: $\lambda_1=-\delta$, $\lambda_2=\gamma-\sigma/\delta$, $\lambda_3=-\delta'$.
Here $\lambda_1,\ \lambda_3$ satisfies the condition $|arg(\lambda)| > \alpha\pi/2$. λ_2 will satisfy these conditions conditionally, i.e. if $\sigma > \delta\gamma \Rightarrow \lambda_2 < 0$, implies that $|arg(\lambda_2)| > \alpha\pi/2$, therefore the equilibrium point is locally asymptotically stable and if $\sigma < \delta\gamma \Rightarrow \lambda_2 > 0$, implies that $arg(\lambda_2) = 0$. Which always satisfies $|arg(\lambda)| < \alpha\pi/2$. Therefore, by the

theorem stated in [12], the equilibrium point E_0 is a saddle point, so it is unstable.

Theorem 2. *The equilibrium point* $E_1\left(\frac{\sigma\omega' - \omega\sigma'}{\delta\omega'}, \frac{1+\sqrt{\Delta}}{2\beta}, 0\right)$, *of the system (6) is conditionally locally asymptotically stable.*

Proof. At the equilibrium point $E_1(x, y, 0)$ of the system (6), the Jacobian matrix is given by:

$$J_{E_1} = \begin{pmatrix} \omega y - \delta & \omega x & \theta x \\ -y & \gamma - 2\beta\gamma y - x & 0 \\ \omega' y & \omega' x & -\delta' \end{pmatrix}.$$

The eigenvalues of the above matrix are given by the roots of the characteristic equation:

$$\lambda^3 + P_1\lambda^2 + P_2\lambda + P_3 = 0 \tag{9}$$

Where,

$$\begin{aligned} P_1 &= 2\beta\gamma y - \omega y - \gamma + \delta + \delta' + x, \\ P_2 &= \omega y\delta' - \delta\delta' + \omega'\theta xy - (2\beta\gamma y - \gamma + x)(\delta + \delta' - \omega y - \omega xy), \\ P_3 &= (2\beta\gamma y - \gamma + x)(\omega y\delta' - \delta\delta' + \omega'\theta xy) - \omega\delta xy - \omega'\theta x^2 y, \quad \textit{and} \\ x &= (\sigma\omega' - \omega\sigma')/(\delta\omega'), \qquad y = (1+\sqrt{\Delta})/2\beta. \end{aligned}$$

To discuss the stability conditions of the equilibrium point, we first evaluate the discriminant of the characteristic equation by using the stability conditions defined in (3).

$$\textit{Discriminant}: \qquad D = 18P_1P_2P_3 + (P_1P_2)^2 - 4P_1^2P_3 - 4P_2^2 - 27P_3^3.$$

The equilibrium point is locally asymptotically stable if any one of the following conditions are satisfied:

1, $D > 0, P_1 > 0, P_3 > 0$ and $P_1P_2 > P_3$,

2, $D < 0, P_1 \geqslant 0, P_2 \geqslant 0, P_3 > 0$ and $\alpha < 2/3$,

3, $D < 0, P_1 > 0, P_2 > 0, P_1P_2 = P_3$ and $\alpha \in (0, 1)$.

Theorem 3. *For the equilibrium point,* $E_2(0, y, z)$, *if* $y \neq 0$ *and* $\omega/\beta + (\sigma\theta')/\delta' < \delta$, *then the equilibrium point is locally asymptotically stable (LAS).*

Proof. The Jacobian matrix of the system (6) at the equilibrium point $E_2(0, 1/\beta, \sigma'/\delta')$ is given by:

$$J_{E_2} = \begin{pmatrix} \omega y - \delta + \theta z & 0 & 0 \\ -y & \gamma - 2\beta\gamma y & 0 \\ \omega' y & 0 & -\delta' \end{pmatrix}$$

It's eigenvalues are given by: $\lambda_1 = \omega/\beta + (\theta\sigma')/\delta' - \delta$, $\lambda_2 = -\gamma$, $\lambda_3 = -\delta'$. For λ_2 and λ_3, the equilibrium point is locally asymptotically stable. For λ_1, if $\omega/\beta + (\theta\sigma')/\delta' < \delta$, the equilibrium point is asymptotically stable. If $\omega/\beta + (\theta\sigma')/\delta' < \delta$, then $\lambda_1 > 0$, so the equilibrium point is unstable. Hence, the system is conditionally locally asymptotically stable.

Theorem 4. *The positive interior equilibrium point $E_3(x, y, z)$ is conditionally locally asymptotically stable.*

Proof. The Jacobian matrix of system (6) at the positive interior equilibrium point $E_3(x, y, z)$ is given by:

$$J_{E_3} = \begin{pmatrix} \omega y - \delta + \theta z & \omega x & \theta x \\ -y & \gamma - 2\beta\gamma y - x & 0 \\ \omega' y & \omega' x & -\delta' \end{pmatrix}.$$

Its characteristic equation is given by: $\lambda^3 + R_1\lambda^2 + R_2\lambda + R_3 = 0$.
Where, $R_1 = (2\beta\gamma - \omega)y + x + \delta - \theta z - \gamma + x + \delta'$,
$R_2 = (\gamma - 2\beta\gamma y - x)((\omega y - \delta + \theta z) - \delta') - \delta(\omega y - \delta + \theta z) - (\omega'\theta - \omega)xy$ and
$R_3 = (\gamma - 2\beta\gamma y - x)(-\delta'(\omega y - \delta + \theta z) - \omega'\theta xy)) - \delta'\omega xy - \omega'\theta x^2 y.$
To determine the stability conditions for the positive interior equilibrium point, we will make use of the same criteria defined in theorem 2.

Table 1: Parameter values to be used for numerical simulations

Model Parameters	Biological interpretation of the parameters	Parameter values	References
σ	External source of effector cells	(0, 1)	
ω	Antigenicity rate of tumor (immune response to the tumor)	0.04	
δ	Death rate of effector cells	0.3743	
θ	Cooperation rate of effector cells to interleukin-2 parameter	1	
γ	Growth rate of tumor cells	1.636	[11,13,18]
β^{-1}	Maximal carrying capacity of the Biological Environment	2×10^{-3}	
σ'	External source of input for Interleukin-2 cells	1	
ω'	Competition rate between tumor cells and effector cells	1	
δ'	loss rate parameter of interleukin-2	0.02	

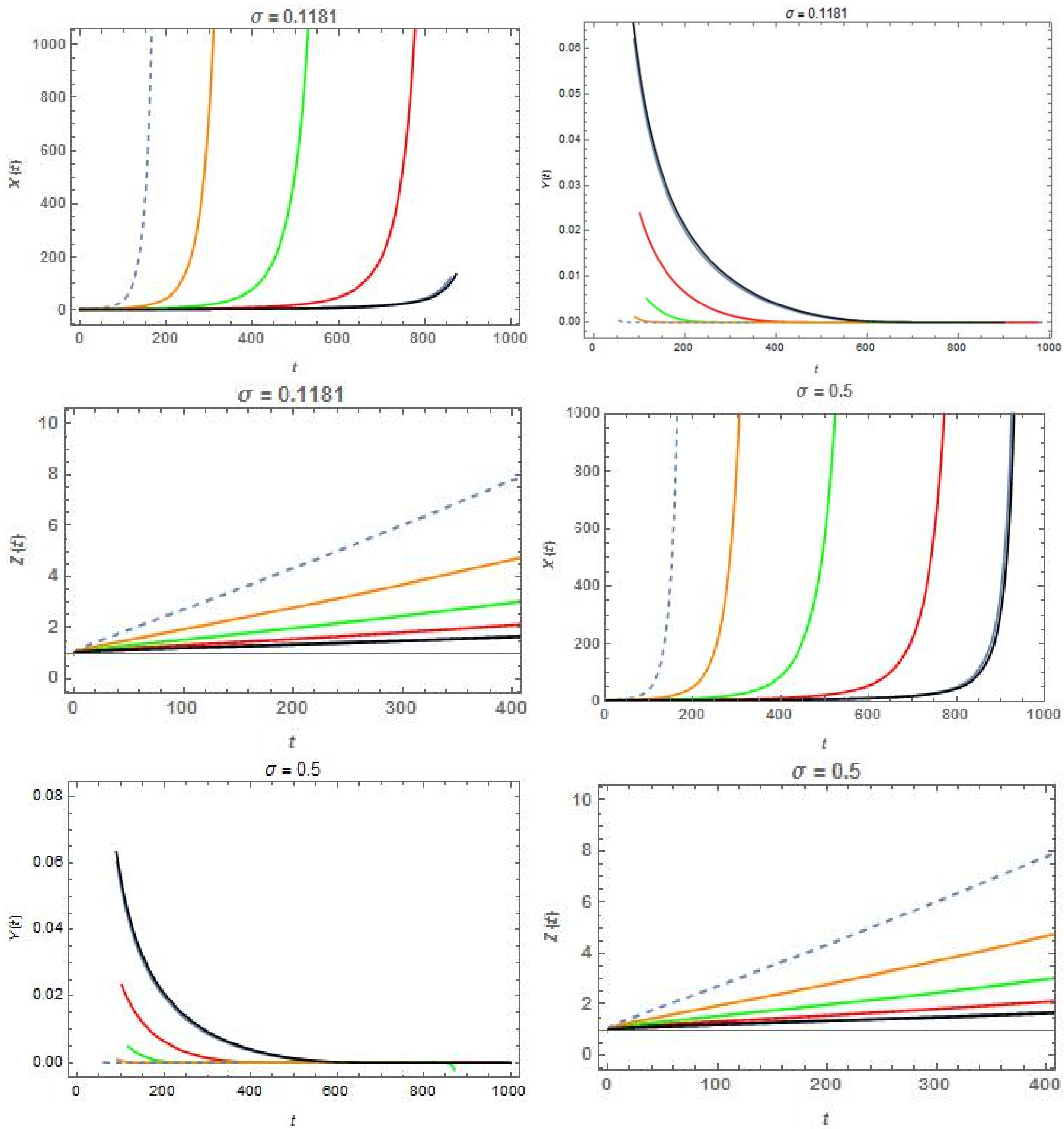

Figure 1: Graphical time series analysis of the model (6) by varying the parameter α. Here, black line denotes $\alpha = 0.005$, blue line denotes $\alpha = 0.01$, red line denotes $\alpha = 0.1$, green line denotes $\alpha = 0.2$, orange line denotes $\alpha = 0.3$, and dashed line denotes $\alpha = 0.4$. The initial conditions are chosen as: $(x, y, z) = (1.5, 1, 10)$ for $\sigma = 0.1181$ in upper three plots and $\sigma = 0.5$ in lower three plots. The population growth of effector cells ($x(t)$) is shown on the left, tumor cells ($y(t)$) at the center, and IL_2 (Immunotherapy) ($z(t)$) on the right.

4. Dynamical Behavior of the Proposed Model (7)

4.1. Discretization Process

The discretization of the proposed tumor-immune interaction model (7) can be done by using a piecewise constant approximation process [16]. Therefore, from the proposed model (7), we obtain:

$$\begin{aligned} T_\alpha E(t) &= \sigma + \omega E(t) T\left(\left[\frac{t}{h}\right] h\right) - \delta E(t) + \theta E(t) IL_2\left(\left[\frac{t}{h}\right] h\right), \\ T_\alpha T(t) &= \gamma T(t)(1-\beta T(t)) - E\left(\left[\frac{t}{h}\right] h\right) T(t), \\ T_\alpha IL_2(t) &= \sigma' + \omega' E\left(\left[\frac{t}{h}\right] h\right) T\left(\left[\frac{t}{h}\right] h\right) - \delta' IL_2(t). \end{aligned} \tag{10}$$

Where, $E(0) = E_0$, $T(0) = T_0$, $IL_2(0) = IL_{2(0)}$, $[t]$ is the integral value of $t \in [0, \infty)$, and $h > 0$ is the discretization parameter. Now we use the following definition of conformable fractional-order derivative:

$$(T_\alpha^a f)(t) = (t-a)^{1-\alpha} f'(t). \;\; For \;\; t \in [nh, (n+1)h) \;\; or \;\; t \in [(n-1)h, nh).$$

By applying this definition to the first equation of model (10), we get

$$E'(t) + E(t)[(\delta - \omega T(nh) - \theta IL_2(nh))/(t-nh)^{1-\alpha}] = \sigma/(t-nh)^{1-\alpha)}.$$

This is a first-order linear differential equation and its solution is given by:

$$E(t) = \frac{(\delta - \omega T(nh) - \theta IL_2(nh))\, E(nh) + \sigma \left(\exp(\delta - \omega T(nh) - \theta IL_2(nh)) \dfrac{(t-nh)^\alpha}{\alpha}\right)}{(\delta - \omega T(nh) - \theta IL_2(nh)) \left(\exp(\delta - \omega T(nh) - \theta IL_2(nh)) \frac{h^\alpha}{\alpha}\right)}.$$

Letting $t \to (n+1)h$, then we obtain the required difference equation given by:

$$E((n+1)h) = \frac{(\delta - \omega T(nh) - \theta IL_2(nh)) E(nh) + \sigma \left(\exp(\delta - \omega T(nh) - \theta IL_2(nh)) \frac{h^\alpha}{\alpha}\right)}{(\delta - \omega T(nh) - \theta IL_2(nh)) \left(\exp(\delta - \omega T(nh) - \theta IL_2(nh)) \frac{h^\alpha}{\alpha}\right)}.$$

By adjusting the notations of the difference equation and by replacing $nh \to n$, we get the required equation given by:

$$E(n+1) = \frac{\sigma + ((\delta - \omega T(n) - \theta IL_2(n)) E(n) - \sigma) \exp\left(\omega T(n) + \theta IL_2(n) - \delta\right) \frac{h^\alpha}{\alpha}}{\delta - \omega T(n) - \theta IL_2(n)}.$$

Now by applying the same definition to the second equation of system (10), we have

$$\begin{aligned} (t-nh)^{1-\alpha}T'(t) &= \gamma T(t)[1-\beta T(t)] - E(nh)T(t) \\ \Rightarrow \qquad \frac{T'(t)}{T^2(t)} - \frac{(\gamma - E(nh))}{(t-nh)^{1-\alpha}}\frac{1}{T(t)} &= \frac{-\beta\gamma}{(t-nh)^{1-\alpha}}. \end{aligned}$$

Multiplying both sides by $\exp\left((\gamma - E(nh))\dfrac{(t-nh)^{\alpha}}{\alpha}\right)$ and solving the equation, we obtain the required solution given by:

$$T(t) = \frac{T(nh)(\gamma - E(nh))}{(\gamma - E(nh) - \gamma\beta T(nh))\left(\exp(E(nh)-\gamma)\frac{(t-nh)^{\alpha}}{\alpha}\right) + \beta\gamma T(nh)}.$$

Letting $t \to (n+1)h$ and again by adjusting the notations of difference equation and also by replacing $nh \to n$, we obtain the required difference equation given by:

$$T(n+1) = \frac{T(n)(\gamma - E(n))}{(\gamma - E(n) - \gamma\beta T(n))\left(\exp(E(n)-\gamma)\frac{h^{\alpha}}{\alpha}\right) + \beta\gamma T(n)}.$$

Finally applying the same definition to the third equation of system (10), we have

$$\begin{aligned} (t-nh)^{1-\alpha}IL_2'(t) &= \sigma' + \omega' E(nh)T(nh) - \delta' I_L(t) \\ \Rightarrow \qquad IL_2'(t) + \frac{\delta'}{(t-nh)^{1-\alpha}}IL_2(t) &= \frac{(\sigma' + \omega' E(nh)T(nh))}{(t-nh)^{1-\alpha}}. \end{aligned}$$

Multiplying both sides by $\exp\left(\delta'\dfrac{(t-nh)^{\alpha}}{\alpha}\right)$, and solving the equation, we obtain the required solution of the equation given by:

$$IL_2(t) = \frac{(\sigma' + \omega' E(nh)T(nh) + (\delta' IL_2(nh) - (\sigma' + \omega' E(nh)T(nh)))\exp\left(-\delta'\dfrac{(t-nh)^{\alpha}}{\alpha}\right)}{\delta'}.$$

Letting $t \to (n+1)h$ and by adjusting the difference equation notation again and also by replacing $nh \to n$, we get the required difference equation, given by:

$$IL_2(n+1) = \frac{(\sigma' + \omega' E(n)T(n))\left(1 - \exp(-\delta'(\dfrac{h^{\alpha}}{\alpha}))\right) + \delta' IL_2(n)\exp\left(-\delta'(\dfrac{h^{\alpha}}{\alpha})\right)}{\delta'}.$$

Hence, the required three-dimensional conformable fractional-order derivative model in discrete form is given by:

$$\begin{aligned} E(n+1) &= \frac{\sigma + ((\delta - \omega T(n) - \theta IL_2(n))E(n) - \sigma)\exp\left(\omega T(n) + \theta IL_2(n) - \delta\right)\frac{h^\alpha}{\alpha}}{\delta - \omega T(n) - \theta IL_2(n)}, \\ T(n+1) &= \frac{T(n)(\gamma - E(n))}{(\gamma - E(n) - \gamma\beta T(n))\left(\exp(E(n)-\gamma)\frac{h^\alpha}{\alpha}\right) + \beta\gamma T(n)}, \\ IL_2(n+1) &= \frac{(\sigma' + \omega' E(n)T(n))\left(1 - \exp(-\delta'(\frac{h^\alpha}{\alpha}))\right) + \delta' IL_2(n)\exp\left(-\delta'(\frac{h^\alpha}{\alpha})\right)}{\delta'}. \end{aligned} \tag{11}$$

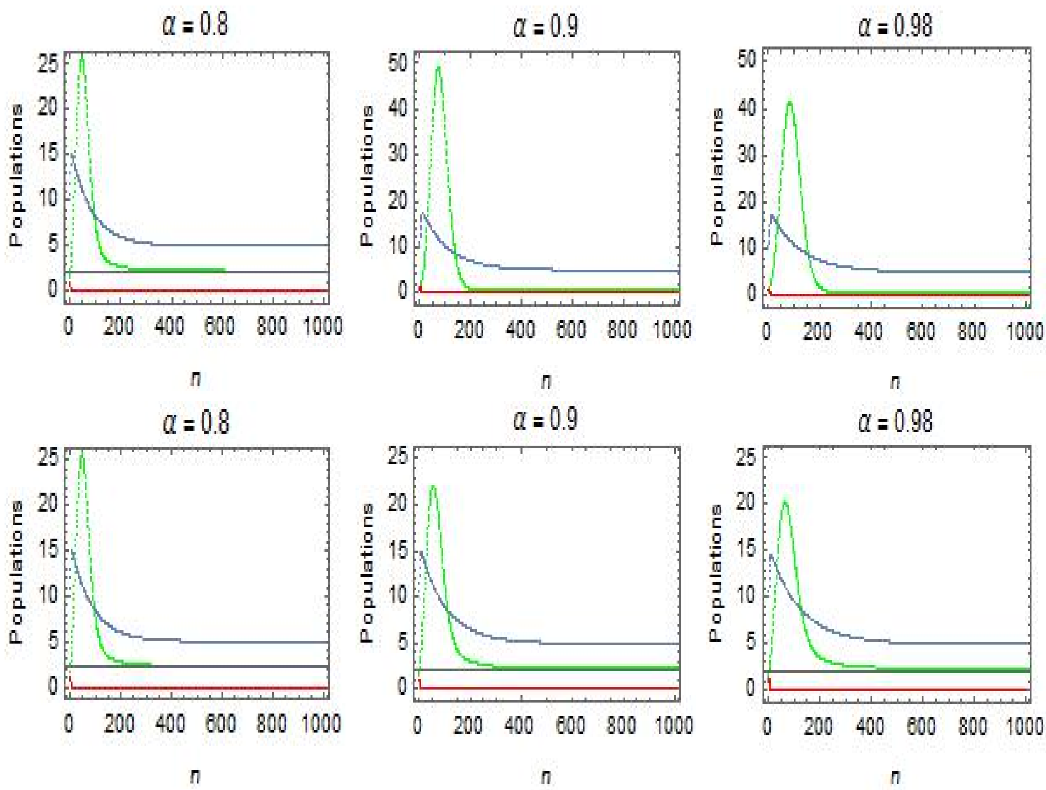

Figure 2: Stable dynamical behaviour of model (11) for the parameter values given in Table 1 with initial conditions $(E, T, IL_2) = (1.5, 1, 10)$ and with $\sigma = 0.1181$ in first row and $\sigma = 0.5$ in second row. The population growth of effector cells $(E(n))$, tumor cells $(T(n))$, and interleukin-2 (IL_2) cells is shown by green line, red line, and blue line respectively.

4.2. Stability analysis of discrete system (11)

The local asymptotic stability analysis of system (11) can be done at the following three equilibrium points: $E_0\left(\frac{\sigma}{\delta},0,0\right)$, $E_1\left(\frac{(\sigma\omega'-\omega\sigma')}{\delta\omega'},\frac{(\omega'(\gamma\delta-\sigma)+\omega\sigma')}{\beta\gamma\delta\omega'},0\right)$, $E_2\left(0,\frac{1}{\beta},\frac{\sigma'}{\delta'}\right)$.

Theorem 5. *For the equilibrium point* $E_0\left(\frac{\sigma}{\delta},0,0\right)$, *we have the following results:*
1 if $\delta\gamma<\sigma$ *, the system is locally asymptotically stable.*
2 if $\delta\gamma>\sigma$*, the system is unstable.*

Proof. The Jacobian matrix of the discrete system (11) at the equilibrium point $E_0\left(\frac{\sigma}{\delta},0,0\right)$ is given by:

$$J_{E_0}=\begin{pmatrix}\exp(-\delta\frac{h^\alpha}{\alpha}) & \frac{\omega\sigma(1-\exp(-\delta\frac{h^\alpha}{\alpha}))}{\delta^2} & \frac{\theta\sigma(1-\exp(-\delta\frac{h^\alpha}{\alpha}))}{\delta^2}\\ 0 & \exp[(\gamma-\frac{\sigma}{\delta})\frac{h^\alpha}{\alpha}] & 0\\ 0 & \frac{\omega'\sigma(1-\exp(-\delta'\frac{h^\alpha}{\alpha}))}{\delta\delta'} & \exp(-\delta'\frac{h^\alpha}{\alpha})\end{pmatrix}.$$

The eigenvalues of the matrix are given by: $\lambda_1=\exp(-\delta\frac{h^\alpha}{\alpha})$, $\lambda_2=\exp[(\gamma-\frac{\sigma}{\delta})\frac{h^\alpha}{\alpha}]$, $\lambda_3=\exp(-\delta'\frac{h^\alpha}{\alpha})$.
From the eigenvalues, it is easy to show that the equilibrium point is locally asymptotically stable if $\delta\gamma<\sigma$ and unstable if $\delta\gamma>\sigma$.

Theorem 6. *For the equilibrium point* $E_1(x',y',0)$*, the discrete system (11) is conditionally locally asymptotically stable. Where* $x'=\frac{(\sigma\omega'-\omega\sigma')}{\delta\omega'}$*, and* $y'=\frac{(\omega'(\gamma\delta-\sigma)+\omega\sigma')}{\beta\gamma\delta\omega'}$.

Proof. The Jacobian matrix of the discrete system (11) at the equilibrium point $E_1(x',y',0)$ is given by:

$$J_{E_1}=\begin{pmatrix}a_{11} & a_{12} & a_{13}\\ a_{21} & a_{22} & 0\\ a_{31} & a_{32} & a_{33}\end{pmatrix}.$$

Where, $a_{11}=\exp\left(-(\delta-\omega y')\frac{h^\alpha}{\alpha}\right)$,

$$a_{12}=\frac{\omega(\delta-\omega y')\exp\left(-(\delta-\omega y')\frac{h^\alpha}{\alpha}\right)((\delta-\omega y')x'-\sigma)\frac{h^\alpha}{\alpha}+\omega\sigma\left(1-\exp\left(-(\delta-\omega y')\frac{h^\alpha}{\alpha}\right)\right)}{(\delta-\omega y')^2},$$

$$a_{13}=\frac{\theta(\delta-\omega y')\exp\left(-(\delta-\omega y')\frac{h^\alpha}{\alpha}\right)((\delta-\omega y')x'-\sigma)\frac{h^\alpha}{\alpha}+\theta\sigma\left(1-\exp\left(-(\delta-\omega y')\frac{h^\alpha}{\alpha}\right)\right)}{(\delta-\omega y')^2},$$

$$a_{21} = \frac{\beta\gamma y'^2\left(1-\exp\left(-(\gamma-x')\frac{h^\alpha}{\alpha}\right)\right) - y'\exp\left(-(\gamma-x')\frac{h^\alpha}{\alpha}\right)(\gamma-x'-\gamma\beta y')(\gamma-x')\frac{h^\alpha}{\alpha}}{\left((\gamma-x'-\gamma\beta y')\exp\left(-(\gamma-x')\frac{h^\alpha}{\alpha}\right)+\beta\gamma y'\right)^2},$$

$$a_{22} = \frac{(\gamma-x')^2\exp\left(-(\gamma-x')\frac{h^\alpha}{\alpha}\right)}{\left((\gamma-x'-\gamma\beta y')\exp\left(-(\gamma-x')\frac{h^\alpha}{\alpha}\right)+\beta\gamma y'\right)^2}, \quad a_{31} = \frac{\omega' y'}{\delta'}\left(1-\exp\left(-\delta\frac{h^\alpha}{\alpha}\right)\right),$$

$$a_{32} = \frac{\omega' x'}{\delta'}\left(1-\exp\left(-\delta\frac{h^\alpha}{\alpha}\right)\right), \quad \text{and} \quad a_{33} = \exp\left(-\delta\frac{h^\alpha}{\alpha}\right).$$

Its characteristic equation is given by:

$$\lambda^3 + A_1\lambda^2 + A_2\lambda + A_3 = 0. \tag{12}$$

Where, $A_1 = -(a_{11}+a_{22}+a_{33})$, $A_2 = a_{22}a_{33}+a_{11}a_{33}-a_{13}a_{31}+a_{11}a_{22}-a_{12}a_{21}$, $A_3 = a_{11}a_{22}a_{33} - a_{12}a_{21}a_{33} + a_{13}a_{21}a_{32} - a_{13}a_{31}a_{22}$.
The stability conditions of the discrete system (11) at the equilibrium point $E_1(x', y', 0)$ are defined by using the following lemma:

Lemma 1. [10] *Consider a cubic polynomial of the type:*

$$\lambda^3 + \beta_1\lambda^2 + \beta_2\lambda + \beta_3 = 0. \tag{13}$$

Where, β_1, β_2, and β_3 are real constants. Furthermore, all the roots of the polynomial (13) lie within the open unit disk if and only if the following conditions are satisfied:

$$|\beta_1 + \beta_3| < 1 + \beta_2, \quad |\beta_1 - 3\beta_3| < 3 - \beta_2, \quad \beta_3^2 + \beta_2 - \beta_1\beta_3 < 1. \tag{14}$$

Therefore, the equilibrium point $E_1(x', y', 0)$ is locally asymptotically stable if and only if the following conditions are satisfied:

$$|A_1 + A_3| < 1 + A_2, \quad |A_1 - 3A_3| < 3 - A_2, \quad A_3^2 + A_2 - A_1A_3 < 1. \tag{15}$$

Where A_1, A_2 and A_3 are defined above.

Theorem 7. *For the equilibrium point $E_2\left(0, \frac{1}{\beta}, \frac{\sigma'}{\delta'}\right)$, the discrete system (11) is conditionally locally asymptotically stable.*

Proof. The Jacobian matrix of the system (11) at the equilibrium point $E_2\left(0, \frac{1}{\beta}, \frac{\sigma'}{\delta'}\right)$ is given by:

$$J_{E_2} = \begin{pmatrix} b_{11} & b_{12} & b_{13} \\ b_{21} & b_{22} & 0 \\ b_{31} & 0 & b_{33} \end{pmatrix}.$$

Where, $b_{11} = \exp\left(-a_1 \frac{h^\alpha}{\alpha}\right) = \exp\left(-\left(\frac{\beta(\delta\delta' - \theta\sigma') - \delta'\omega}{\beta\delta'}\right)\frac{h^\alpha}{\alpha}\right)$,

$$b_{12} = \frac{\omega\sigma\left(1 - \left(\exp\left(-a_1\frac{h^\alpha}{\alpha}\right)\left(a_1\frac{h^\alpha}{\alpha} + 1\right)\right)\right)}{a_1^2}, \quad b_{13} = \frac{\theta\sigma\left(1 - \left(\exp\left(-a_1\frac{h^\alpha}{\alpha}\right)\left(a_1\frac{h^\alpha}{\alpha} + 1\right)\right)\right)}{a_1^2},$$

$$b_{21} = \frac{1 - \exp\left(-\gamma\frac{h^\alpha}{\alpha}\right)\left(1 + \gamma\frac{h^\alpha}{\alpha}\left(\frac{\delta' - \beta\sigma'}{\delta'}\right)\right)}{\beta\left(1 + \left(\frac{\delta' - \beta\sigma'}{\delta'}\right)\exp\left(-\gamma\frac{h^\alpha}{\alpha}\right)\right)^2}, \quad b_{22} = \frac{\exp\left(-\gamma\frac{h^\alpha}{\alpha}\right)}{\left(1 + \left(\frac{\delta' - \beta\sigma'}{\delta'}\right)\exp\left(-\gamma\frac{h^\alpha}{\alpha}\right)\right)^2},$$

$$b_{31} = \frac{\omega'\left(1 - \exp\left(-\delta'\frac{h^\alpha}{\alpha}\right)\right)}{\beta\delta'}, \quad b_{33} = \exp\left(-\delta'\frac{h^\alpha}{\alpha}\right).$$

Its characteristic equation is given by:

$$\lambda^3 + R_1\lambda^2 + R_2\lambda + R_3 = 0, \tag{16}$$

where, $R_1 = -(b_{11} + b_{22} + b_{33})$, $R_2 = b_{22}b_{33} + b_{11}b_{33} - b_{13}b_{31} + b_{11}b_{22} - b_{12}b_{21}$, $R_3 = b_{11}b_{22}b_{33} - b_{12}b_{21}b_{33} - b_{13}b_{31}b_{22}$.

Again, the stability conditions for system (11) at the equilibrium point $E_2\left(0, \frac{1}{\beta}, \frac{\sigma'}{\delta'}\right)$ are defined by using lemma 1. Which states that, the equilibrium point $E_2\left(0, \frac{1}{\beta}, \frac{\sigma'}{\delta'}\right)$ is locally asymptotically stable if and only if the following conditions are satisfied:

$$|R_1 + R_3| < 1 + R_2, \quad |R_1 - 3R_3| < 3 - R_2, \quad R_3^2 + R_2 - R_1R_3 < 1, \tag{17}$$

where, R_1, R_2, and R_3 are defined above.

Now the system (11) has a positive interior equilibrium point under the following positivity conditions:

1. $\theta\sigma' \geq \delta\delta'$
2. $\gamma > \frac{\left(\delta'\omega + \sqrt{\Delta'}\right)}{\theta\omega'}$, where $\Delta' = (\theta\omega'\gamma + \delta'\omega)^2 + 4\theta\omega'\gamma\beta(\theta\sigma' - \delta\delta')$, and
3. $\delta > \frac{\omega\left(\theta\omega'\gamma + \delta'\omega + \sqrt{\Delta'}\right)}{2\theta\omega'\gamma\beta}$.

Therefore, the positive interior equilibrium point of the system (11) under these positivity conditions is given by: $E^*(\overline{x}, \overline{y}, \overline{z})$. Where,

$$\overline{x} = \frac{1}{2}\left(\gamma - \frac{\delta'\omega + \sqrt{\Delta'}}{\theta\omega'}\right), \quad \overline{y} = \frac{\theta\omega'\gamma + \delta'\omega + \sqrt{\Delta'}}{2\theta\omega'\gamma\beta}, \quad \overline{z} = \frac{1}{\theta}\left(\delta - \frac{\omega(\theta\omega'\gamma + \delta'\omega + \sqrt{\Delta'})}{2\theta\omega'\gamma\beta}\right).$$

Theorem 8. *The positive interior equilibrium point $E^*(\overline{x}, \overline{y}, \overline{z})$ of the model (11)*

under the above mentioned positivity conditions is locally asymptotically stable.
Proof. The Jacobian matrix of the system (8) at the positive interior equilibrium point $E^*(\overline{x},\overline{y},\overline{z})$ is given by:

$$J_{E_3} = \begin{pmatrix} c_{11} & c_{12} & c_{13} \\ c_{21} & c_{22} & 0 \\ c_{31} & c_{32} & c_{33} \end{pmatrix}.$$

Where,

$$c_{11} = \exp\left(-a_1\frac{h^\alpha}{\alpha}\right),\ c_{12} = \frac{\omega a_1 \exp\left(-a_1\frac{h^\alpha}{\alpha}\right)(a_1\overline{x}-\sigma)\frac{h^\alpha}{\alpha} + \omega\sigma\left(1-\exp\left(-a_1\frac{h^\alpha}{\alpha}\right)\right)}{a_1^2},$$

$$c_{13} = \frac{\theta a_1 \exp\left(-a_1\frac{h^\alpha}{\alpha}\right)(a_1\overline{x}-\sigma)\frac{h^\alpha}{\alpha} + \theta\sigma\left(1-\exp\left(-a_1\frac{h^\alpha}{\alpha}\right)\right)}{a_1^2},$$

$$c_{21} = \frac{\beta\gamma\overline{y}^2\left(1-\exp(-b_1)\right) - \overline{y}b_1c_1\exp(-b_1)}{\left(c_1\exp(-b_1)+\beta\gamma\overline{y}\right)^2}, \quad c_{22} = \frac{(\gamma-\overline{x})^2\exp(-b_1)}{\left(c_1\exp(-b_1)+\beta\gamma\overline{y}\right)^2},$$

$$c_{31} = \frac{\omega'\overline{y}\left(1-\exp\left(-\delta'\frac{h^\alpha}{\alpha}\right)\right)}{\delta'}, \quad c_{32} = \frac{\omega'\overline{x}\left(1-\exp\left(-\delta'\frac{h^\alpha}{\alpha}\right)\right)}{\delta'},$$

$$c_{33} = \exp\left(-\delta'\frac{h^\alpha}{\alpha}\right),\ a_1 = \delta-\omega\overline{y}-\theta\overline{z}, \quad b_1 = (\gamma-\overline{x})\,\tfrac{h^\alpha}{\alpha}, \quad c_1 = \gamma-\overline{x}-\gamma\beta\overline{y}.$$

Its characteristic equation is given by:

$$\lambda^3 + r_1\lambda^2 + r_2\lambda + r_3 = 0. \tag{18}$$

Where, $r_1 = -\left(\exp\left(-a_1\frac{h^\alpha}{\alpha}\right) + \frac{(\gamma-\overline{x})^2\exp(-b_1)}{\left(c_1\exp(-b_1)+\beta\gamma\overline{y}\right)^2} + \exp\left(-\delta'\frac{h^\alpha}{\alpha}\right)\right)$,

$$r_2 = \exp\left(-\delta'\frac{h^\alpha}{\alpha}\right)\left(\frac{(\gamma-\overline{x})^2\exp(-b_1)}{(c_1\exp(-b_1)+\beta\gamma\overline{y})^2} + \exp\left(-a_1\frac{h^\alpha}{\alpha}\right)\right) - \left(\frac{\omega'\overline{y}\left(1-\exp\left(-\delta'\frac{h^\alpha}{\alpha}\right)\right)}{\delta'}\right)$$

$$\left(\frac{\theta a_1\exp\left(-a_1\frac{h^\alpha}{\alpha}\right)(a_1\overline{x}-\sigma)\frac{h^\alpha}{\alpha} + \theta\sigma\left(1-\exp\left(-a_1\frac{h^\alpha}{\alpha}\right)\right)}{a_1^2}\right)$$

$$+\left(\exp\left(-a_1\frac{h^\alpha}{\alpha}\right)\left(\frac{(\gamma-\overline{x})^2\exp(-b_1)}{(c_1\exp(-b_1)+\beta\gamma\overline{y})^2}\right)\right)$$

$$-\left(\frac{\omega a_1\exp\left(-a_1\frac{h^\alpha}{\alpha}\right)(a_1\overline{x}-\sigma)\frac{h^\alpha}{\alpha} + \omega\sigma\left(1-\exp\left(-a_1\frac{h^\alpha}{\alpha}\right)\right)}{a_1^2}\right)$$

$$\left(\frac{\beta\gamma\overline{y}^2(1-\exp(-b_1)-\overline{y}b_1c_1\exp(-b_1)}{(c_1\exp(-b_1)+\beta\gamma\overline{y})^2}\right),$$

$$r_3=\left(\exp\left(-\delta'\frac{h^\alpha}{\alpha}\right)\right)\left(\exp(-a_1\frac{h^\alpha}{\alpha}\right)\left(\frac{(\gamma-\overline{x})^2\exp(-b_1)}{(c_1\exp(-b_1)+\beta\gamma\overline{y})^2}\right)$$

$$-\left(\frac{\omega a_1\exp\left(-a_1\frac{h^\alpha}{\alpha}\right)(a_1\overline{x}-\sigma)\frac{h^\alpha}{\alpha}+\omega\sigma\left(1-\exp\left(-a_1\frac{h^\alpha}{\alpha}\right)\right)}{a_1^2}\right)$$

$$\left(\frac{\beta\gamma\overline{y}^2(1-\exp(-b_1)-\overline{y}b_1c_1\exp(-b_1)}{(c_1\exp(-b_1)+\beta\gamma\overline{y}]^2}\right)\left(\exp\left(-\delta'\frac{h^\alpha}{\alpha}\right)\right)$$

$$+\left(\frac{\theta a_1\exp\left(-a_1\frac{h^\alpha}{\alpha}\right)(a_1\overline{x}-\sigma)\frac{h^\alpha}{\alpha}+\theta\sigma\left(1-\exp\left(-a_1\frac{h^\alpha}{\alpha}\right)\right)}{a_1^2}\right)$$

$$\left(\frac{\omega'\overline{x}\left(1-\exp\left(-\delta'\frac{h^\alpha}{\alpha}\right)\right)}{\delta'}\right)\left(\frac{\beta\gamma\overline{y}^2(1-\exp(-b_1))-\overline{y}b_1c_1\exp(-b_1)}{(c_1\exp(-b_1)+\beta\gamma\overline{y})^2}\right)$$

$$-\left(\frac{\theta a_1\exp\left(-a_1\frac{h^\alpha}{\alpha}\right)(a_1\overline{x}-\sigma)\frac{h^\alpha}{\alpha}+\theta\sigma\left(1-\exp\left(-a_1\frac{h^\alpha}{\alpha}\right)\right)}{a_1^2}\right)\left(\frac{\omega'\overline{y}\left(1-\exp\left(-\delta'\frac{h^\alpha}{\alpha}\right)\right)}{\delta'}\right)$$

$$\left(\frac{(\gamma-\overline{x})^2\exp(-b_1)}{(c_1\exp(-b_1)+\beta\gamma\overline{y})^2}\right).$$

Therefore, under the positivity conditions defined above, the positive interior equilibrium point $E^*(\overline{x},\overline{y},\overline{z})$ is locally asymptotically stable if and only if the following conditions are satisfied:

$$|r_1+r_3|<1+r_2,\qquad |r_1-3r_3|<3-r_2,\qquad r_3^2+r_2-r_1r_3<1, \tag{19}$$

where r_1,r_2 and r_3 given above are the coefficients of the characteristic equation (18).

5. Result Discussion

The stability analysis at the tumor free equilibrium point for the system (6) and the system (11) shows that both the systems are stable if and only if $\sigma>\delta\gamma$. The positive interior equilibrium point is always stable under the positivity conditions defined for both the systems. To explore the effects of constant source rate of effector cells, we choose two different values of parameter σ and kept other parameters fixed for both the systems. The effects of σ for these two values on both the systems is shown graphically in Figure 1 and Figure 2, for five different values of α. For smaller values of α and larger values of σ, the growth rate of tumor cells increases slowly as compared to the growth rate of effector cells and IL_2 cells, which is shown in Figure 1. As the value of α increases and value of σ decreases the growth rate of tumor cells increases and the system exhibits oscillatory behaviour with higher peaks. But, after some time intervals the growth rate of tumor cells starts slowing down and then population growth of tumor cells remains constant. This analysis shows that there is great role of fractional order parameter α and the parameter σ on the behaviour of model.

Analysis of Figure 1: We fix the value of σ at 0.1181, and increase α through the values 0.005, 0.01, 0.1, 0.2, 0.3, 0.4, 0.5. Effector cells show growth spurts at decreasing values of time as α is increased. Tumor cell population, for all values of alpha tend to vanish as time increases. We observe that, as α increases, the slope increases and tumor cells tend to vanish quickly. Hence, the growth rate of the tumor cells can be effectively reduced by increasing α. On the other hand, growth rate of interleukin-2 cells increases with increase in α. Next, we fix the value of σ at 0.5 and α is increased through the same values. We observe similar dynamics for all the three population cells. So, it follows that even with change in the external source of effector cells, the populations exhibit stable dynamics for different values of fractional order parameter.

Analysis of Figure 2: Here the discretized model (11) is simulated. Firstly, σ is fixed at 0.1181, and α is increased through values 0.8, 0.9 and 0.98. All the three cell populations show similar dynamics with peaks of the effector cells being slightly different. Next, we change σ to 0.5 and we again observe similar dynamics which indicates that the cell populations show stable dynamics even with change in the external source parameter of effector cells and change in α. We observe that change in slopes of the growth curve of the cell populations does not vary much in any cases. Hence discretization leads to more stable dynamics than the original fractional-order model (6).

Analysis of Figure 3: Once again, we simulate the discretized model (11). Firstly, we fix the value of σ at 0.01, and obtain dynamics for different values of $n = 500,\ 1000,\ 2000$. We observe same dynamics for all three cell populations. Next, we vary the value of σ to 0.1181 and observe the same dynamics for all the three values of n. However, comparing these graphs with the previous graphs, we observe variation in the peak values of effector cell population. Next, we change the value of σ to 0.25, then to 0.5 and lastly to 0.75. We observe that the populations of tumor cells and interleukin-2 cells show no change in their dynamics while the peak values attained by the effector cells shows decline as σ increases. Hence, we conclude that after discretization, variation in the external source of effector cells has no effect on the dynamics of tumor cells and interleukin-2 cells, but only on effector cells. We also observe that the tumor cells are vanishing with the same

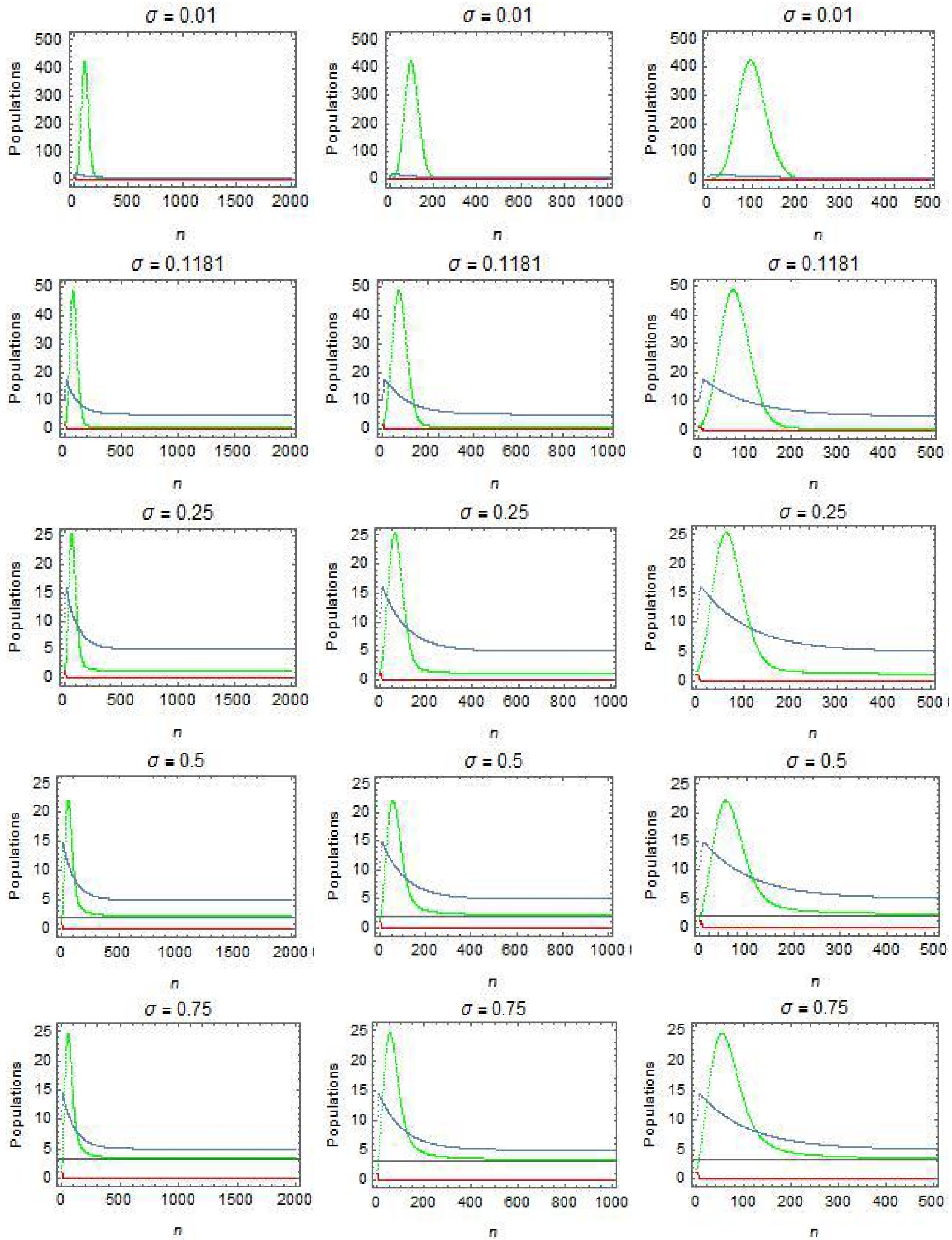

Figure 3: Dynamical behaviour of discrete model (11) for discretized-time parameter $n = 2000,\ 1000$, and 500, by varying the parameter σ. The other parameter values are given in Table 1 with initial conditions $(E, T, IL_2) = (1.5, 1, 10)$. The population growth of effector cells $(E(n))$, tumor cells $(T(n))$ and Imterleukin-2 (IL_2) cells is shown by green line, red line and blue line respectively.

decay rate for all values of σ and this establishes the effectiveness of the proposed system to limit the growth rate of tumor cells in all types of systems.

6. Conclusion

In this paper, we have studied three dimensional tumor-immune interaction model defined by the system of fractional-order differential equations (6) and (7) developed by using Caputo and conformable fractional order derivatives respectively. On system (7), the discretization process is applied to find the discrete version of the system (6) by using piecewise constant approximation method, which is represented by system (11).

In this paper, we have applied conformable fractional-order derivative in order to study the behaviour of tumor-immune interaction system without facing any difficulties which the other fractional-order derivatives are facing while dealing with biological systems. The conformable fractional order derivative involves the concept of long run memory, which is best suitable for understanding the behaviour of tumor-immune interaction models. Graphical time series analysis for both the systems is done, which shows that both system exhibit different dynamical behaviours. The time series analysis shows that there is sudden increase in the population growth of tumor cells initially, but as the time increases, the population growth of tumor cells starts decreasing and then after some time becomes constant. Furthermore, the conformable fractional derivative can be applied to other tumor-immune interaction models with some more complex behaviours. We can also study the behaviour of tumor-immune interaction system by considering the population growth of other effector cells especially macrophages by using conformable fractional derivative.

The observations of the stable dynamics for all the cell populations of fractional order tumor model where effector cells increase, tumor cells decay to zero while interleukin-2 cells stay within a fixed range for all values of fractional order parameter establishes effectiveness of interleukin-2 cells in the model. Further, discretization leads to more stable dynamics as we observe that along with tumor cells and interleukin-2 cells, effector cells population too shows same dynamics even after varying sigma and fractional order parameter. Hence, our numerical simulations confirm with our analytical findings.

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