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Stability and Dynamical Analysis of Generalized Tumor-Immune Interaction Model with Conformable Fractional Derivative

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1 Abstract

Fractional order tumor-immune interaction models are being frequently used for understanding the complex behaviour of immune system and tumor growth. In this paper, a generalized fractional order tumor-immune interaction model has been developed by introducing immunotherapy (IL_2 cells) as a third variable in the model. The study of generalized model is done by using conformable fractional order derivative. The stability analysis is done for both fractional order tumor model and its conformable fractional order version. By considering some biological equilibrium points for both versions of the model, the stability analysis around these fixed points shows that both the systems are stable at some fixed points under some stability conditions, which are defined in the model analysis.The numerical and graphical analysis is also done for both the systems by varying two parameters and keeping other parameters fixed for better understanding the dynamics of proposed model.

keywords : Tumor growth, immune system, fractional derivative, stability, fixed points, tumor-immune interaction, discretization.

2 Introduction

Tumors are considered among the families of soaring mortality diseases, revealing an insanity of cellular augmentation which often induce uncontrolled growth of cells [6,25]. Researchers are working for understanding the dynamics of interaction between tumor cells and immune system. In terms of biology and mathematics, Immune system is regarded as one of the most interesting schemes. Immune system can do multiple functions with various metabolic pathways. Therefore, almost all the 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 more complex system [2]. Integer order differential equations are being used for modelling tumor phenomena since long time [7,16,20], on the other hand differential equations with fractional order have short

history in modelling such phenomena with memory [26]. Research on fractional calculus has gained much interest over the past few decades and differential equations with fractional order has been used in different research areas like medicine [14], finance [10], engineering [29], physics [22,30] and chemistry [31]. Fractional order differential equations are widely used to model biological systems and there are valuable applications and good results in this field. It is also expressed that models of biological systems developed by differential equations with fractional order display more realistic results as compered to models developed by integer order differential equations [5,8,24]. This is only because of the fact that fractional order derivatives involve memory concept and that is quite favourable to work on biological processes. In this research paper, we will study the tumor-immune interaction model by applying newly introduced definition called "conformable fractional order derivative", which was introduced in year 2014 by Khalil et al. [19]. According to this definition, if we consider a function $f : [a, \infty) \to \infty$ and let $0 \leq a \leq 1$ be the order of the function. Then
1, Left hand derivative of fractional order 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, Right hand derivative of fractional order ending at b, in limit form is defined by :

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

if the limit exists.

3, Capito fractional derivative is defined by :

$$D_\alpha^a f(t) = \int_a^t \frac{f^n x}{(t-x)^{\alpha-n+1}} dx \tag{3}$$

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

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

Integer order derivatives and conformable fractional order derivatives have few common basic properties also. In [1] Abdeljawad introduced 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 derivative can be found in [4,11,18,,23,28]. In [18] Kartal and Gurcan considered the conformable fractional order logistic equation with piecewise constant arguments with adopting the method presented by Gopalsamy in [17].

3 Fractional Order Models of Tumor-Immune Interaction System

Consider a fractional order tumor-immune interaction model given by FA Rihan et al.[27], which include external sources of effector cells and immune stimulation effects by treatment interleukin-2 (IL-2). They assumed three populations of the activated immune-system cells, E(t) ; the tumor cells, T(t) ; and the concentration of IL-2 in the

tumor-site compartment. The mathematical model [27], governed by the fractional order differential equations is given by

$$\begin{aligned} D^{\alpha_1}E(t) &= s_1 + p_1E(t)T(t) - p_2E(t) + p_3E(t)I_L(t) \\ D^{\alpha_2}T(t) &= p_4T(t)(1 - p_5T(t)) - p_6E(t)T(t) \\ D^{\alpha_3}I_L(t) &= s_2 + p_7E(t)T(t) - p_8I_L(t), \quad 0 \leq \alpha_i \leq 1, i = 1, 2, 3. \end{aligned} \tag{5}$$

In study [13], E. Balci, applied conformable fractional derivative on model (5) in absence of concentration of IL-2 in the tumor site compartment. In this paper, we will study the dynamical behaviour of model (5) in presence of immune therapy by using conformable fractional order derivative.
Now, in order to reduce the sensitivity of system (5), we will use the following re-scalling for non-dimensionalization of model (5) :

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

Therefore, by applying these substitutions in model (5), we get the required fractional order tumor-immune interaction model in presence of immunotherapy with capito sense as follows :

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

Where, $x(0) = x_0 \geq 0, y(0) = y_0 \geq 0, z(0) = z_0 \geq 0$ are the given initial conditions and the parameters are defined in [27]. 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 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 :

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

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

4 Stability analysis of fractional order tumor-immune interaction 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 $E_3(x, y, z)$. which can be obtained

by solving the following system of equations.

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

These equillibrium points are given by $E_0(\sigma/\delta, 0, 0)$, the tumor free equilibrium point, $E_1((\sigma\omega' - \omega\sigma')/(\delta\omega'), (1 + \sqrt{\Delta})/2\beta, 0)$, where $\Delta = 1 + 4\sigma'\beta/\gamma\omega'$, $E_2(0, 1/\beta, \sigma'/\delta')$ and the coexistence endemic equilibrium point given by $E_3(\bar{x}, \bar{y}, \bar{z})$.
The stability analysis at these equilibrium points of the system can be done by following theorems [13]

Theorem 1 : By considering the equilibrium point $E_0(\sigma/\delta, 0, 0)$ of model (6), the following results holds true ;
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 : At the equilibrium point $E_0(\sigma/\delta, 0, 0)$ of system (6), The jacobian matrix is given by ;

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

Which gives the eigen values as $\lambda_1 = -\delta$, $\lambda_2 = \gamma - \sigma/\delta$, $\lambda_3 = -\delta'$. Here λ_1, λ_3 satisfy the condition $|arg(\lambda)| > \alpha\pi/2$ and λ_2 will satisfy the condition conditionally, i.e. if $\sigma > \delta\gamma \Rightarrow \lambda_2 < 0$, therefore $|arg(\lambda_2)| > \alpha\pi/2$, the equilibrium point is locally asymptotically stable and if $\sigma < \delta\gamma \Rightarrow \lambda_2 > 0$. Hence $arg(\lambda_2) = 0$. Which always satisfies $|arg(\lambda)| < \alpha\pi/2$. Therefore, by theorem stated in [13], the equilibrium point E_0 is a saddle point, so it is unstable.

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

Proof : At the equillibrium 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 eigen values of the above matrix are given by the roots of characteristic equation

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

Where, $P_1 = 2\beta\gamma y - \omega y - \gamma + \delta + \delta + x$, $P_2 = \omega y\delta' - \delta\delta' + \omega'\theta xy - (2\beta\gamma y - \gamma + x)(\delta + \delta' - \omega y - \omega xy)$, $P_3 = (2\beta\gamma y - \gamma + x)(\omega y\delta' - \delta\delta' + \omega'\theta xy) - \omega\delta xy - \omega'\theta x^2 y$ and $x = (\sigma\omega' - \omega\sigma')/(\delta\omega')$, $y = (1 + \sqrt{\Delta})/2\beta$.

To determine the stability analysis of the equilibrium point, we first evaluate the discriminant of the characteristic equation by using stability conditions defined in [3].

$$Discriminant : D = 18P_1P_2P_3 + (P_1P_2)^2 - 4P_1^2P_3 - 4P_2^2 - 27P_3^3$$

The equilibrium point is locally asymptotically stable if any one of the following conditions is 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 $\alpha \Subset (0, 1)$

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.

Proof : The jacobian matrix of the system (6) at 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 eigen values 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 coexistence equilibrium point $E_3(x, y, z)$ is conditionally locally asymptotically stable.

Proof : The jacobian matrix of system (6) at the endemic 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 of the endemic equilibrium point, we will use the same criteria as defined in theorem 2.

TABLE 1 – Parameter values to be used for numerical simulations

Parameters	Biological meanings	Parameter values	Refrence
σ	External source of effector cells	(0, 1)	[21,15]
ω	Antigenicity rate of tumor (immune response to the tumor)	0.04	[15]
δ	Death rate of effector cells	0.3743	[21,15]
θ	Cooperation rate of effector cells to interleukin-2 parameter	1	
γ	Growth rate of tumor cells	1.636	[21,15]
β^{-1}	Maximal carrying capacity of the Biological Environment	2×10^{-3}	[21,15]
σ'	External source of input for Interleukin-2 cells	1	[12]
ω'	Competition rate between tumor cells and effector cells	1	[12]
δ'	loss rate parameter of interleukin-2	0.02	[12]

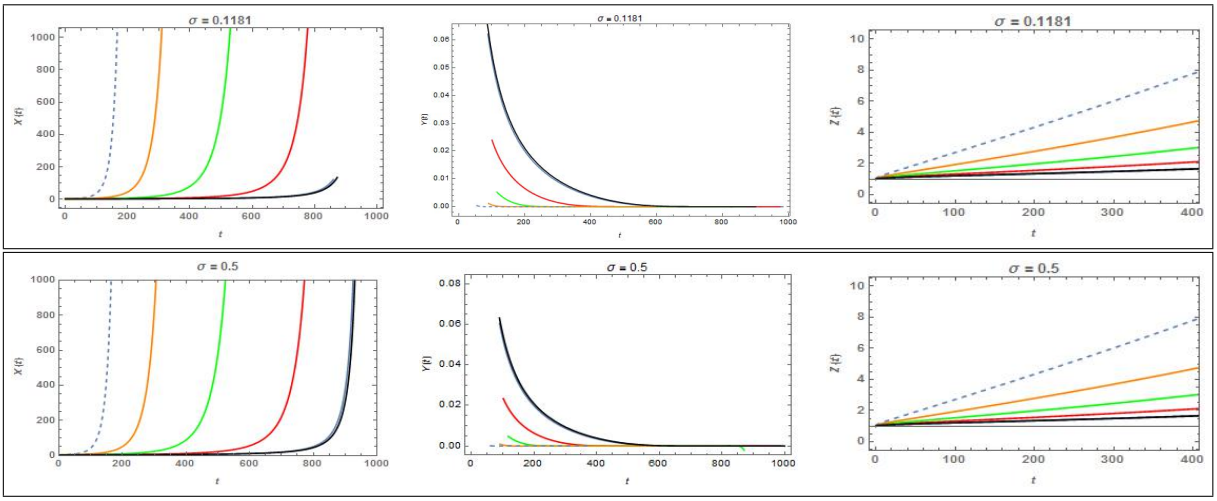

FIGURE 1 – Graphical time series analysis of model (6) by varying the parameter α. Where black line denotes $\alpha = 0.005$, Blue line denotes $\alpha = 0.01$, Red line denotes $\alpha = 0.1$, Green line denotes $\alpha = 0.2$, Orange line denotes $\alpha = 0.3$ and Dashed line denotes $\alpha = 0.4$ with initial conditions $(x, y, z) = (1.5, 1, 10)$ for $\sigma = 0.1181$ in upper box and $\sigma = 0.5$ in lower box with population growth of Effector cells (x(t)) on left, Tumor cells (y(t)) at center and Immunotherapy (z(t)) on right.

5 Dynamical behaviour of conformable fractional order tumor model (7)

5.1 Discretization process

The discretization process of tumor-immune model (7) can be done by using piecewise constant approximation process [18]. Then the model (7) will become

$$T_\alpha E(t) = \sigma + \omega E(t)T([t/h]h) - \delta E(t) + \theta E(t)I_L([t/h]h)$$
$$T_\alpha T(t) = \gamma T(t)(1 - \beta T(t)) - E([t/h]h)T(t)$$
$$T_\alpha I_L(t) = \sigma' + \omega' E([t/h]h)T([t/h]h) - \delta' I_L(t) \quad (10)$$

Where $E(0) = E_0$, $T(0) = T_0$, $I_L(0) = I_L(0)$, $[t]$ is the integral value of $t \Subset [0, \infty)$ and $h > 0$ is the discretization parameter. Now we will apply the following definition of conformable fractional derivative defined as

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

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

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

This is a first order linear differential equation. Therefore, its solution is given by

$$E(t) = \frac{[\delta - \omega T(nh) - \theta I_L(nh)]E(nh) + \sigma[\exp[\delta - \omega T(nh) - \theta I_L(nh)]\frac{(t-nh)^\alpha}{\alpha}]}{[\delta - \omega T(nh) - \theta I_L(nh)][\exp[\delta - \omega T(nh) - \theta I_L(nh)]\frac{h^\alpha}{\alpha}]}$$

Let $t \to (n + 1)h$. Then we get the required difference equation given by

$$E((n + 1)h) = \frac{[\delta - \omega T(nh) - \theta I_L(nh)]E(nh) + \sigma[\exp[\delta - \omega T(nh) - \theta I_L(nh)]\frac{h^\alpha}{\alpha}]}{[\delta - \omega T(nh) - \theta I_L(nh)][\exp[\delta - \omega T(nh) - \theta I_L(nh)]\frac{h^\alpha}{\alpha}]}$$

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

$$E(n + 1) = \frac{\sigma + [[\delta - \omega T(n) - \theta I_L(n)]E(n) - \sigma]\exp[\omega T(n) + \theta I_L(n) - \delta]\frac{h^\alpha}{\alpha}]}{\delta - \omega T(n) - \theta I_L(n)}$$

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

$$(t-nh)^{1-\alpha}T'(t) = \gamma T(t)[1-\beta T(t)]-E(nh)T(t) \Rightarrow \frac{T'(t)}{T^2(t)}-\frac{(\gamma - E(nh))}{(t - nh)^{1-\alpha}}\frac{1}{T(t)} = \frac{-\beta\gamma}{(t - nh)^{1-\alpha}}$$

Multiplying both sides by $\exp[(\gamma - E(nh))\frac{(t-nh)^\alpha}{\alpha}]$ and solving the equation, we get the required solution given by

$$T(t) = \frac{T(nh)(\gamma - E(nh))}{[\gamma - E(nh) - \gamma\beta T(nh)][\exp(E(nh) - \gamma)\frac{(t-nh)^\alpha}{\alpha}] + \beta\gamma T(nh)}$$

Let $t \to (n + 1)h$. Then again by adjusting the notations of difference equation and by replacing $nh \to n$, we get the required difference equation given by

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

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

$$(t-nh)^{1-\alpha}I'_L(t) = \sigma'+\omega' E(nh)T(nh)-\delta' I_L(t) \Rightarrow I'_L(t)+\frac{\delta'}{(t - nh)^{1-\alpha}}I_L(t) = \frac{(\sigma' + \omega' E(nh)T(nh))}{(t - nh)^{1-\alpha}}$$

Multiplying both sides by $\exp[\delta' \frac{(t-nh)^\alpha}{\alpha}]$, and solving the equation, we get required solution of the equation given by

$$I_L(t) = \frac{(\sigma' + \omega' E(nh)T(nh) + [\delta' I_L(nh) - (\sigma' + \omega' E(nh)T(nh))] \exp[-\delta' \frac{(t-nh)^\alpha)}{\alpha}]}{\delta'}$$

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

$$I_L(n+1) = \frac{[\sigma' + \omega' E(n)T(n)](1 - \exp(-\delta'(\frac{h^\alpha}{\alpha})) + \delta' I_L(n) \exp(-\delta'(\frac{h^\alpha}{\alpha})}{\delta'}$$

Hence the required three-dimensional conformable fractional model in discrete form is given by

$$\begin{aligned} E(n+1) &= \frac{\sigma + [[\delta - \omega T(n) - \theta I_L(n)]E(n) - \sigma] \exp[\omega T(n) + \theta I_L(n) - \delta] \frac{h^\alpha}{\alpha}]}{\delta - \omega T(n) - \theta I_L(n)} \\ T(n+1) &= \frac{T(n)(\gamma - E(n))}{[\gamma - E(n) - \gamma\beta T(n)][\exp(E(n) - \gamma) \frac{h^\alpha}{\alpha}] + \beta\gamma T(n)} \\ I_L(n+1) &= \frac{[\sigma' + \omega' E(n)T(n)](1 - \exp(-\delta'(\frac{h^\alpha}{\alpha})) + \delta' I_L(n) \exp(-\delta'(\frac{h^\alpha}{\alpha})}{\delta'} \end{aligned} \quad (11)$$

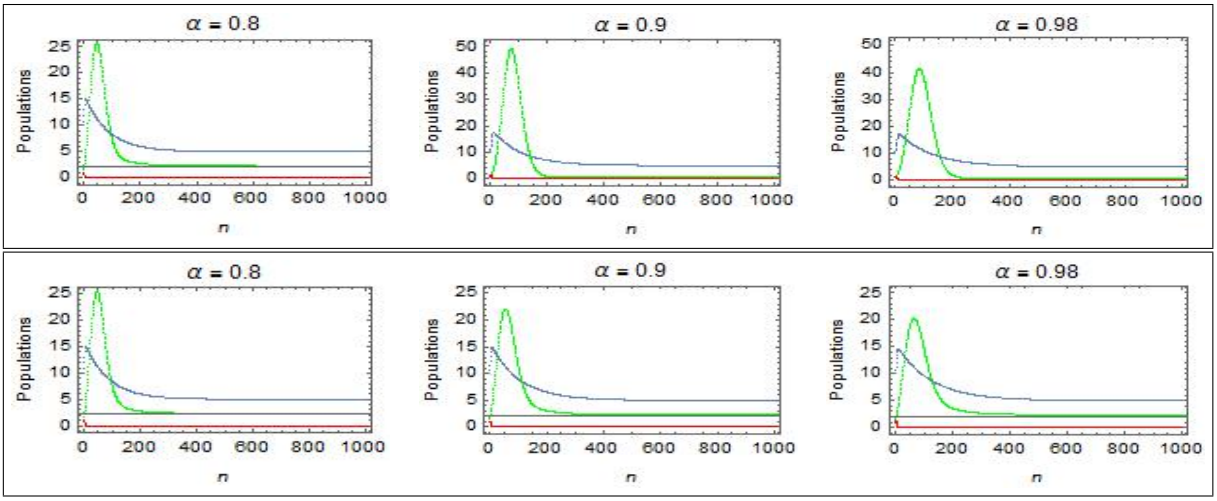

FIGURE 2 – Stable dynamical behaviour of model (11) for the parameter values given in table 1 with initial conditions $(E, T, IL_2) = (1.5, 1, 10)$ and with $\sigma = 0.1181$ in upper box and $\sigma = 0.5$ in lower box. The population growth of Effector cells (E(n)), Tumor cells (T(n)) and Imterleukin-2 (I_{L2}) cells is shown by green line, red line and blue line respectively

5.2 Stability analysis of model (11)

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

Theorem 5.2.1 : For the equilibrium point $E_0(\frac{\sigma}{\delta}, 0, 0)$, 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 system (11) at the equilibrium point $E_0(\frac{\sigma}{\delta}, 0, 0)$ 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 eigen values 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 eigen values, it is easy to show that the equilibrium point is locally asymptotically stable if $\delta\gamma < \sigma$ and unstable if $\delta\gamma > \sigma$.

Theorem 5.2.2 : For the equilibrium point $E_1(x', y', 0)$, the system is conditionally locally asymptotically stable. Where $x' = \frac{(\sigma\omega' - \omega\sigma')}{\delta\omega'}$, $y' = \frac{(\omega'(\gamma\delta - \sigma) + \omega\sigma')}{\beta\gamma\delta\omega'}$

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

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

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

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

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

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

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

$a_{32} = \frac{\omega' x'}{\delta'}[1 - \exp(-\delta\frac{h^\alpha}{\alpha})]$, $a_{33} = \exp(-\delta\frac{h^\alpha}{\alpha})$

Its characteristic equation is given by $\lambda^3 + A_1\lambda^2 + A_2\lambda + A_3 = 0$
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 system (11) at the equilibrium point $E_1(x', y', 0)$ are defined by using the following lemma.

Lemma 5.2.2.1 : [9] Consider a cubic polynomial of the type

$$\lambda^3 + \beta_1\lambda^2 + \beta_2\lambda + \beta_3 = 0$$

Where β_1, β_2 and β_3 are real constants. Furthermore, all the roots of polynomial lie within the open unit disk if and only if the following conditions are satisfied
$|\beta_1 + \beta_3| < 1 + \beta_2$, $|\beta_1 - 3\beta_3| < 3 - \beta_2$, $\beta_3^2 + \beta_2 - \beta_1\beta_3 < 1$.
Therefore, the equilibrium point $E_1(x', y', 0)$ is locally asymptotically stable if and only

if the following conditions are satisfied

$$|A_1 + A_3| < 1 + A_2 \ , \ |A_1 - 3A_3| < 3 - A_2 \ , \ A_3^2 + A_2 - A_1A_3 < 1$$

Where A_1, A_2 and A_3 are defined above.

Theorem 5.2.3 : For the equilibrium point $E_2(0, \frac{1}{\beta}, \frac{\sigma'}{\delta'})$, the system is conditionally locally asymptotically stable.

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

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

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

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

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

$b_{31} = \dfrac{\omega'[1 - \exp(-\delta'\frac{h^\alpha}{\alpha})]}{\beta\delta'}$, $b_{33} = \exp(-\delta'\frac{h^\alpha}{\alpha})$

Its characteristic equation is given by

$$\lambda^3 + R_1\lambda^2 + R_2\lambda + R_3 = 0$$

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 of the system (11) at the equilibrium point $E_2(0, \frac{1}{\beta}, \frac{\sigma'}{\delta'})$ are defined by using lemma 5.2.2.1. which says that, the equilibrium point $E_2(0, \frac{1}{\beta}, \frac{\sigma'}{\delta'})$ is locally asymptotically stable if and only if the following conditions are satisfied

$$|R_1 + R_3| < 1 + R_2 \ , \ |R_1 - 3R_3| < 3 - R_2 \ , \ R_3^2 + R_2 - R_1R_3 < 1$$

Where R_1, R_2 and R_3 are defined above.

Now the system (11) has a positive endemic equilibrium state under the following positivity conditions.

1, $\theta\sigma' \geqslant \delta\delta'$

2, $\gamma > \frac{[\delta'\omega + \sqrt{\Delta'}]}{\theta\omega'}$, where $\Delta' = [\theta\omega'\gamma + \delta'\omega]^2 + 4\theta\omega'\gamma\beta[\theta\sigma' - \delta\delta']$ and

3, $\delta > \frac{\omega(\theta\omega'\gamma + \delta'\omega + \sqrt{\Delta'})}{2\theta\omega'\gamma\beta}$

Therefore, the positive endimic equilibrium point of the system (11) under these positivity conditions is given by $E^*(\overline{x}, \overline{y}, \overline{z})$, where $\overline{x} = \frac{1}{2}[\gamma - \dfrac{\delta'\omega + \sqrt{\Delta'}}{\theta\omega'}]$, $\overline{y} = \dfrac{\theta\omega'\gamma + \delta'\omega + \sqrt{\Delta'}}{2\theta\omega'\gamma\beta}$,

$\overline{z} = \frac{1}{\theta}[\delta - \dfrac{\omega(\theta\omega'\gamma + \delta'\omega + \sqrt{\Delta'})}{2\theta\omega'\gamma\beta}]$

Theorem 5.2.4 : The coexistence equilibrium point $E^*(\overline{x}, \overline{y}, \overline{z})$ of the model (11) under the positivity conditions is locally asymptotically stable.

Proof : The jacobian matrix of the system (11) at the positive 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, $c_{11}=\exp(-a_1\frac{h^\alpha}{\alpha})$, $c_{12}=\dfrac{\omega a_1\exp(-a_1\frac{h^\alpha}{\alpha})(a_1\overline{x}-\sigma)\frac{h^\alpha}{\alpha}+\omega\sigma[1-\exp(-a_1\frac{h^\alpha}{\alpha})]}{a_1^2}$

$c_{13}=\dfrac{\theta a_1\exp(-a_1\frac{h^\alpha}{\alpha})(a_1\overline{x}-\sigma)\frac{h^\alpha}{\alpha}+\theta\sigma[1-\exp(-a_1\frac{h^\alpha}{\alpha})]}{a_1^2}$, $c_{21}=\dfrac{\beta\gamma\overline{y}^2(1-\exp(-b_1))-\overline{y}b_1c_1\exp(-b_1)}{[c_1\exp(-b_1)+\beta\gamma\overline{y}]^2}$

$c_{22}=\dfrac{[\gamma-\overline{x}]^2\exp(-b_1)}{[c_1\exp(-b_1)+\beta\gamma\overline{y}]^2}$, $c_{31}=\dfrac{\omega'\overline{y}(1-\exp(-\delta'\frac{h^\alpha}{\alpha}))}{\delta'}$, $c_{32}=\dfrac{\omega'\overline{x}(1-\exp(-\delta'\frac{h^\alpha}{\alpha}))}{\delta'}$,

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

Its characteristic equation is given by

$$\lambda^3+r_1\lambda^2+r_2\lambda+r_3=0$$

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

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

$(\dfrac{\theta a_1\exp(-a_1\frac{h^\alpha}{\alpha})(a_1\overline{x}-\sigma)\frac{h^\alpha}{\alpha}+\theta\sigma[1-\exp(-a_1\frac{h^\alpha}{\alpha})]}{a_1^2})+[\exp(-a_1\frac{h^\alpha}{\alpha})(\dfrac{[\gamma-\overline{x}]^2\exp(-b_1)}{[c_1\exp(-b_1)+\beta\gamma\overline{y}]^2})]$

$-[\dfrac{\omega a_1\exp(-a_1\frac{h^\alpha}{\alpha})(a_1\overline{x}-\sigma)\frac{h^\alpha}{\alpha}+\omega\sigma[1-\exp(-a_1\frac{h^\alpha}{\alpha})]}{a_1^2}][\dfrac{\beta\gamma\overline{y}^2(1-\exp(-b_1)-\overline{y}b_1c_1\exp(-b_1)}{[c_1\exp(-b_1)+\beta\gamma\overline{y}]^2}]$

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

$-[\dfrac{\omega a_1\exp(-a_1\frac{h^\alpha}{\alpha})(a_1\overline{x}-\sigma)\frac{h^\alpha}{\alpha}+\omega\sigma[1-\exp(-a_1\frac{h^\alpha}{\alpha})]}{a_1^2}][\dfrac{\beta\gamma\overline{y}^2(1-\exp(-b_1)-\overline{y}b_1c_1\exp(-b_1)}{[c_1\exp(-b_1)+\beta\gamma\overline{y}]^2}]$

$(\exp(-\delta'\frac{h^\alpha}{\alpha}))+[\dfrac{\theta a_1\exp(-a_1\frac{h^\alpha}{\alpha})(a_1\overline{x}-\sigma)\frac{h^\alpha}{\alpha}+\theta\sigma[1-\exp(-a_1\frac{h^\alpha}{\alpha})]}{a_1^2}][\dfrac{\omega'\overline{x}(1-\exp(-\delta'\frac{h^\alpha}{\alpha}))}{\delta'}]$

$(\dfrac{\beta\gamma\overline{y}^2(1-\exp(-b_1))-\overline{y}b_1c_1\exp(-b_1)}{[c_1\exp(-b_1)+\beta\gamma\overline{y}]^2})-[\dfrac{\theta a_1\exp(-a_1\frac{h^\alpha}{\alpha})(a_1\overline{x}-\sigma)\frac{h^\alpha}{\alpha}+\theta\sigma[1-\exp(-a_1\frac{h^\alpha}{\alpha})]}{a_1^2}]$

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

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

$|r_1+r_3|<1+r_2$, $|r_1-3r_3|<3-r_2$, $r_3^2+r_2-r_1r_3<1$

Where r_1, r_2 and r_3 are defined above.

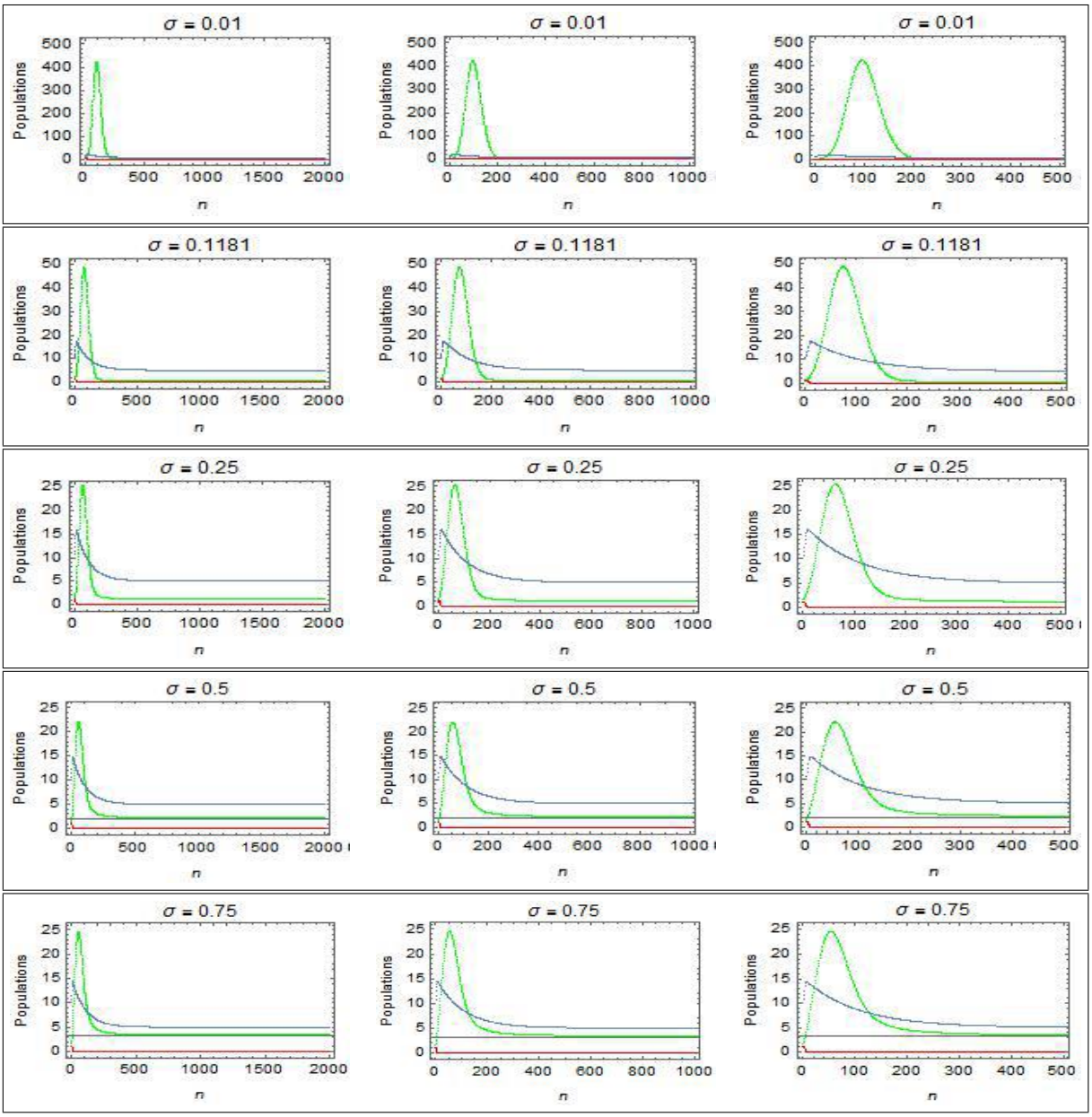

FIGURE 3 – Dynamical behaviour of model (11) for discretized-time parameter n = 2000, 1000 and 500, by varying the parameter σ.The other parameter values are given in table 1 with initial conditions $(E, T, IL_2) = (1.5, 1, 10)$. The population growth of Effector cells (E(n)), Tumor cells (T(n)) and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

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6 Conclusion

In this paper, we have studied three dimensional tumor-immune interaction model that is given by the system of fractional order differential equations (6) and (7) which have caputo and conformable fractional order derivative respectively. On system (7), the discretization process is applied, in order to find the discrete version of the system by using piecewise constant approximation process, which is represented by system (11).
The stability analysis at tumor free equilibrium point for system (6) and system (11) shows that both the systems are stable if and only if $\sigma > \delta\gamma$. The coexistence equilibrium point is always stable under the positivity conditions defined for both the systems. In order to explore the effects of constant source rate of effectors cells, we have chosen two different values of parameter σ and kept other parameters fixed for both systems. The effect of σ for these two values on both the systems is shown graphically by 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.
In this paper, we have applied conformable fractional 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 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. Further, the conformable fractional derivative can be applied to other tumor models with 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 stable dynamics of all the cell populations of fractional order tumor model where effector cells increase, tumor cells decay to zero while immunotherapy cells stay within a fixed range for all values of fractional order parameter establishes effectiveness of immunotherapy in the model. Further, discretization leads to more stable dynamics as we observe that along with tumor cells and immunotherapy 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.

Analysis of figure 1 : We fix the value of sigma at 0.1181, and increase alpha through 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 alpha is increased. Tumor cells population, for all values of alpha, tend to vanish as time increases, we observe that as alpha 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 alpha. On the other hand, growth rate of immunotherapy cells increases with increase in alpha. Next, we fix the value of sigma at

0.5, and alpha is increased through the same values. We observe similar dynamics for all the three populations. So, it follows that even with change in the external source of Effector cells, the populations exhibit stable dynamics for different fractional orders.

Analysis of figure 2 : Here the discretized model is simulated. Firstly, sigma is fixed at 0.1181, and alpha is increased through values 0.8, 0.9 and 0.98, all the three populations show similar dynamics, with peaks of the effector cells being slightly different. Next, we change sigma to 0.5, and we again observe similar dynamics which indicates that the populations show stable dynamics even with change in source of effector cells and change in alpha.
We observe that change in slopes of the growth curve of the populations does not vary much in any cases, hence discretization leads to more stable dynamics than the original fractional order model.

Analysis of figure 3 : We once again simulate the discretized model. Here we firstly fix the value of sigma at 0.01, and obtain dynamics for different values of n= 500, 1000, 2000. We observe same dynamics for all three populations Next, we vary the value of sigma to 0.1181 and observe same dynamics for all 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 sigma to 0.25, then to 0.5 and lastly to 0.75. We found that the populations of tumor cells and that of immunotherapy cells show no change in their dynamics while the peak values attained by the effector cells shows decline as sigma 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 immunotherapy cells, but only on effector cells. We observe tumor cells vanishing with the same decay rate for all values of sigma and this establishes the effectiveness of the proposed system to stop the growth of tumor cells in all types of systems.

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Figures

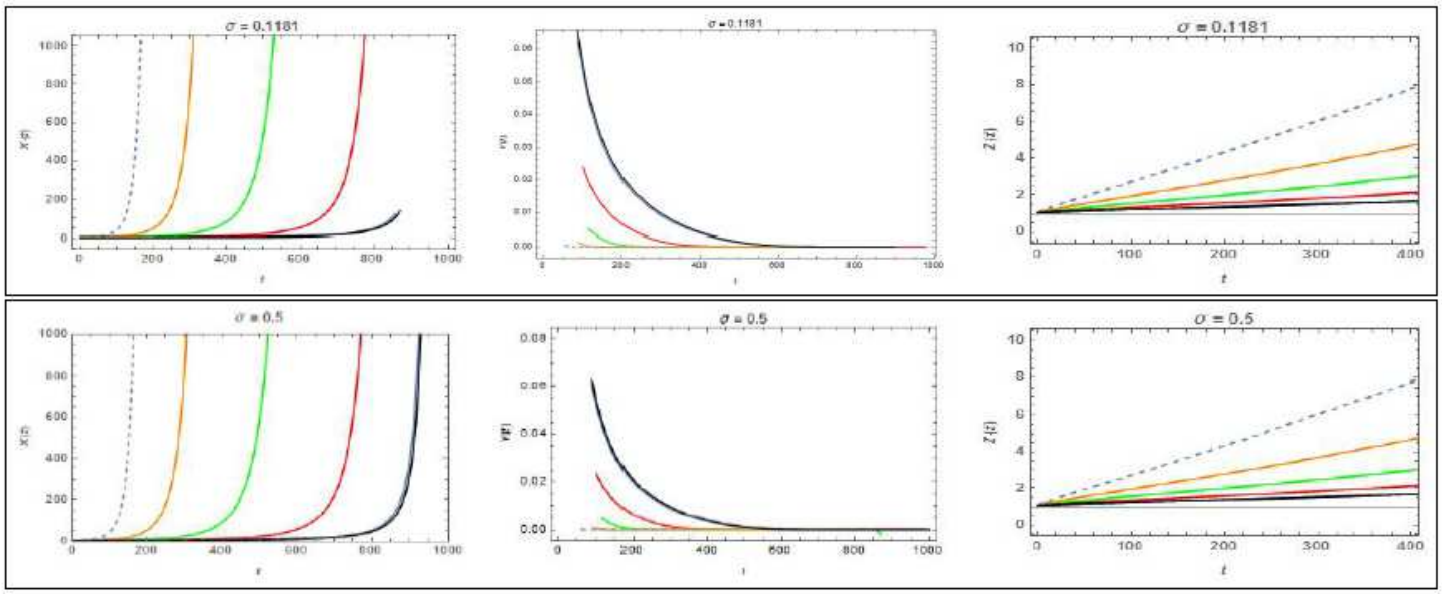

Figure 1

Graphical time series analysis of model (6) by varying the parameter α. Where black line denotes α = 0.005, Blue line denotes α = 0.01, Red line denotes α = 0.1, Green line denotes α = 0.2, Orange line denotes α = 0.3 and Dashed line denotes α = 0.4 with initial conditions (x; y; z) = (1:5; 1; 10) for σ = 0:1181 in upper box and σ = 0:5 in lower box with population growth of Effector cells (x(t)) on left, Tumor cells (y(t)) at center and Immunotherapy (z(t)) on right.

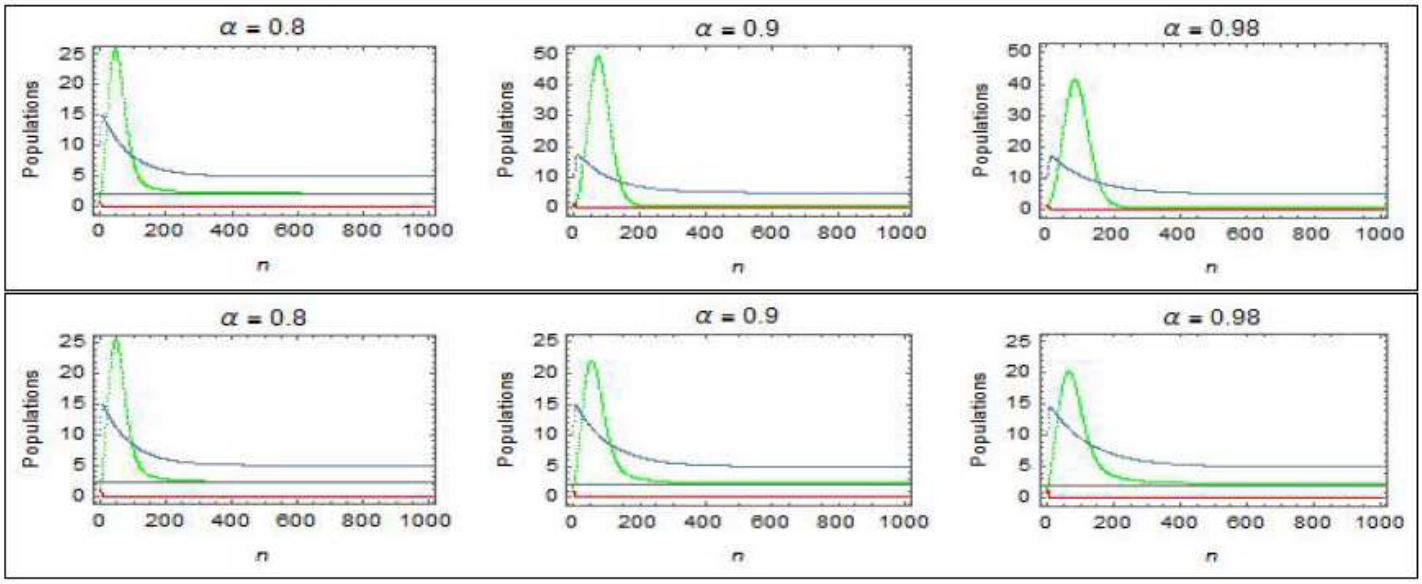

Figure 2

Stable dynamical behaviour of model (11) for the parameter values given in table 1 with initial conditions (E; T; IL2) = (1:5; 1; 10) and with σ = 0:1181 in upper box and σ = 0:5 in lower box. The population growth of Effector cells (E(n)), Tumor cells (T(n)) and Imterleukin-2 (IL2) cells is shown by green line, red line and blue line respectively

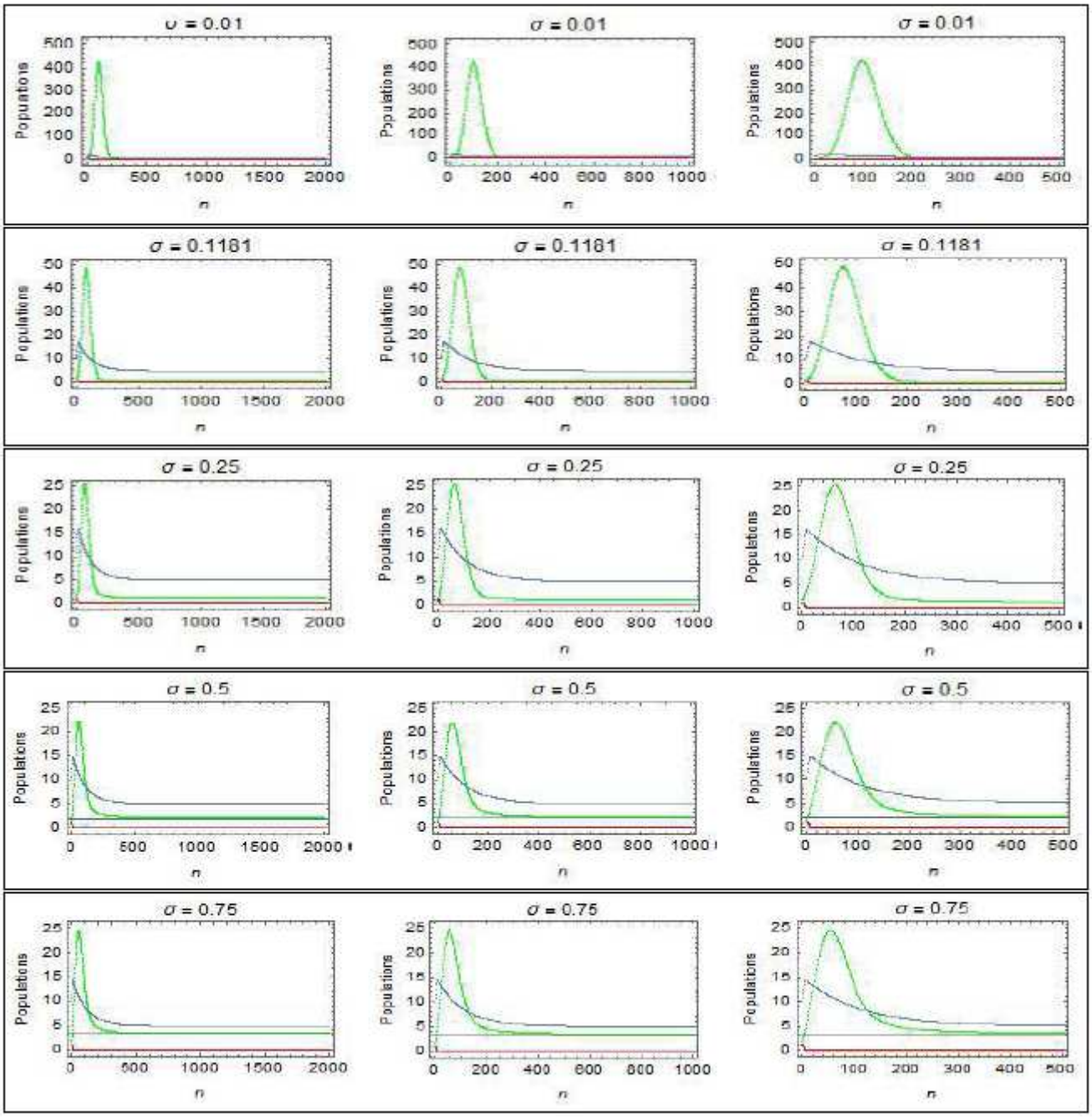

Figure 3

Dynamical behaviour of 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; IL2) = (1:5; 1; 10). The population growth of Effector cells (E(n)), Tumor cells (T(n)) and Imterleukin-2 (IL2) cells is shown by green line, red line and blue line respectively.