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Dynamical Analysis of Tumor-Immune Interaction Model with Nonlinear Activation Rate

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Abstract In this research work, we study the dynamical behavior of the proposed model representing three cell populations (tumor cells and two types of macrophage cells) and the nonlinear activation rate (Michaelis-Menten dynamics) of tumor-immune interaction. The proposed model is described by the system of three ordinary differential equations. To understand the dynamic behavior of the proposed model, stability and bifurcation analysis are performed. Stability analysis is done at the biologically feasible equilibrium points obtained from the model. For bifurcation analysis first, the proposed model is converted into its discrete version by implementing Euler's forward scheme, then the explicit criteria of Hopf-bifurcation analysis are applied. Which demonstrates the long-term survival of M1-type of macrophages, M2-type of macrophages, and tumor cells. Furthermore, with the help of numerical simulation, sensitivity analysis is done for both dependence on initial conditions as well as dependence on parameters by using MATLAB software.

1 Introduction

The tumor-immune interaction system is considered one of the most fascinating schemes in the mathematical modeling of the biological system. The immune system is the most complex system in our body, in which the effector cells can play a dual role and do multiple functions with several metabolic pathways. Over the last few decades, the pro-tumor and anti-tumor activities of effector cells especially macrophages gained much interest in tumor immunotherapy [4, 18, 30, 36]. Macrophages are developed by the body's defense system and released from the bone marrow as immature monocytes. These types of cells are engaged by chemokines into the tissue and go through differentiation into macrophages after circulating in the blood [12]. Depending on the pathologic position to which macrophages are recruited, they can show a collection of phenotypes and functions. Macrophages are the white blood cells in the tissues, which help in crunching bacteria invaders and healing injured tissues. Some macrophages are genetically engineered effector cells that have great potential to kill tumor cells. Some macrophages can also immigrate to tumors from the surrounding tissues [23]. Based on the macrophages' activation position, M1-type and M2-type of macrophages are the two different sub-types of these cells. [5, 7]. Numerous types of research have been conducted and have permitted categorizing M1-type as cells capable of generating a huge amount of pro-inflammatory cytokines, showing soaring levels of major histocompatibility complex molecules and implicated in the killing of tumor cells and pathogens. In the meantime, the body's immune system develops other activated M2-type cells, which can decrease the pro-inflammatory response, eliminate cell wastes and stimulate tissue repair [10, 24, 34, 37]. The immune system develops activated M2 cells because the anti-tumor properties of M1 cells develop a long-lasting immunological reaction. This may result in harm to tissues and DNA. The macrophages mainly belonging to the M2 population are present in neoplastic tissues and are called tumor-associated macrophages [25].

In a recent study, it has been observed that tumor growth can lead to M1→M2 polarization [3]. Another recent study has recommended a re-polarization of macrophage cells with regard to the classically activated M1 macrophage cells as a successful treatment proposal to guarantee tumor elimination [2]. A huge study has been done to help understand the tumor-macrophage interaction system [13, 14, 15, 16, 17]. During the 1980s, De Boer et al. published a research

paper on the mathematical model of interaction between T lymphocytes and macrophages that induce an immunological response against tumors [29]. In 1998, Owen and Sherrate used a five-dimensional ODE-based model to understand the roles of macrophages' existence, invasion, and capacity to destroy tumor cells specifically in avascular tumors [22]. They looked at how macrophages responded to chemoattractants and the rate at which mutant cells produced regulatory substances. To assess the capacity of the modified macrophages to reverse tumor alterations as model parameters are changed, In 2004, Byrne et al. [11] and Owen et al. [21] proposed two mathematical models, depicting the dynamics among healthy cells, tumor cells, and invading macrophages. Both investigations demonstrated the non-initiative sensitivity of such methods to the tumor and therapeutic parameters. Additionally, Web et al. extended the research work done in [21] to demonstrate how medicines with restricted diffusion rates or those that are not cell cycle sensitive enable macrophages to efficiently target hypoxic tumor cells [33]. In order to determine whether the variation in the M2/M1 ratio and the re-polarization of macrophages records for the distinction in tumor formation or tumor decline, Den Breems and Eftimie developed a new non-spatial mathematical framework. This framework refers to the relationships between tumor cells, M1 type of macrophages and M2 type of macrophages, and Th1 and Th2 cells. [27].

The remaining part of the research article is organized in the following manner: In section 2, we present the proposed model and explain how it is created. Next, non-dimensionalization, linearization, and stability analysis of the proposed model are done. In section 3, Euler's forward method is implemented for the discretization of the model. Bifurcation analysis is done by using explicit criteria of Hopf-bifurcation at the critical value of the bifurcation parameter. In section 4, numerical simulation and sensitivity analysis for the parameters and initial condition is done, to support and prove analytical results. Finally, in section 5, concluding remarks are given.

2 Tumor-Macrophage Interaction Model

Consider an ODE-based tumor-macrophages interaction model proposed by S Yaqin et al. [32].

$$\begin{aligned}
\frac{dx(t)}{dt} &= ax(t)(1-bx(t)) - fx(t)y(t) + gx(t)z(t),\\
\frac{dy(t)}{dt} &= x(t)y(t) - d_1y(t) - r_1y(t) + r_2z(t),\\
\frac{dz(t)}{dt} &= e_2x(t)z(t) - d_2z(t) + r_1y(t) - r_2z(t).
\end{aligned} \tag{2.1}$$

Inspired by the mathematical model (2.1), we have extended the work of S Yaqin et al. [32] by applying the nonlinear activation rate or recruitment rate of macrophages by tumor cells in the model. This positive nonlinear or heterogenetic activation rate is called Michaelis-Menten Kinetics (MMK) based dynamics of the tumor-immune response system.

Mathematically, Michaelis-Menten Kinetics is defined by $\frac{\eta\varphi(t)\psi(t)}{\epsilon+\psi(t)}$, where $\varphi(t)$ denotes the no. of tumor cells at time t, $\psi(t)$ denotes the no. of effector cells (macrophages) at time t. η and ϵ are positive constants. Michaelis-Menten type of response rate is the same as the term used by Kuznotsev et al. [35], Kieschner and Panetta [8] and Owen and Sherrat [20]. This research work divides the effector cells into type-1 (M1) and type-2 (M2) macrophages. Where M1 macrophage cells play anti-tumor activities and help in controlling the growth of tumor cells and M2 macrophage cells play pro-tumor activities.

Now, to study the effects of type-1 macrophages (anti-tumor) and type-2 macrophages (pro-tumor) on the growth and development of tumors, We take a look at a basic mathematical model given by S Yaqin et al. [32]. Then, by applying Michaelis-Menten Kinetics-based activation rate

to the model (2.1), we have

$$\begin{aligned}\frac{dT}{dt} &= aT(1-bT) - \frac{fTM1}{a_1+T} + \frac{gTM2}{a_2+T},\\ \frac{dM1}{dt} &= \frac{e_1TM1}{a_1+T} - d_1M1 - r_1M1 + r_2M2,\\ \frac{dM2}{dt} &= \frac{e_2TM2}{a_2+T} - d_2M2 + r_1M1 - r_2M2.\end{aligned} \tag{2.2}$$

In this mathematical model, there are three variables or cell populations; the tumor cells (T), the type-1 macrophages (M1), and the type-2 macrophages (M2). The following biological presumptions have been used to develop the proposed model (2.2).

In the first equation, the logistic growth term is being used because the growth of the tumor cells starts declining after reaching environmental carrying capacity due to a lack of nutrients in the environment [1, 19]. Therefore, tumor cells multiply logistically at a rate a, till environmental carrying capacity b^{-1}. f is the rate at which tumor cells are killed by $M1$ macrophage cells [6]. In the meantime, augmentation of tumor cells increases by the presence of $M1$ cells [7]. In the second equation, e_1 is the activation rate of $M1$ macrophages due to pro-inflammatory cytokines secreted by the tumor cells [2]. r_1 is the rate at which re-polarization of $M1 \to M2$ macrophage cells occurs by different types of immune cells. $M1$ cells have half-life span of $\frac{1}{d_1}$. In the third equation, e_2 is the rate at which $M2$ macrophages are activated with the help of cytokines, which are connected with tumor-promoting environment [2]. r_2 is the rate at which re-polarization of $M2 \to M1$ macrophage cells occurs by different types of immune cells present in the surrounding environment. $M2$ cells have half-life span of $\frac{1}{d_2}$. We will choose $d_1 = d_2$ in the model analysis.

Now, we nondimensionalize the generalized model (2.2) by using the following substitutions:

$$x = \frac{T}{T(0)}, \quad y = \frac{M_1}{M_2(0)}, \quad z = \frac{M_2}{M_2(0)}, \quad \tau = e_1T(0)t, \quad \alpha = \frac{a}{e_1T(0)}, \quad \beta = bT(0), \quad \gamma_1 = \frac{f}{e_1T(0)}, \quad \gamma_2 = \frac{g}{e_1T(0)}, \quad \alpha_1 = \frac{a_1}{T(0)}, \quad \alpha_2 = \frac{a_2}{T(0)}, \quad \delta_1 = \frac{1}{T(0)}, \quad \omega_1 = \frac{d_1}{e_1T(0)}, \quad \theta_1 = \frac{r_1}{e_1T(0)}, \quad \delta_2 = \frac{e_2}{e_1T(0)}, \quad \omega_2 = \frac{d_2}{e_1T(0)}, \quad \theta_2 = \frac{r_2}{e_1T(0)}.$$

Therefore, the required dimensionless form of the proposed model (2.2) is given by

$$\begin{aligned}\frac{dx}{dt} &= \alpha x(1-\beta x) - \frac{\gamma_1 xy}{\alpha_1+x} + \frac{\gamma_2 xz}{\alpha_2+x},\\ \frac{dy}{dt} &= \frac{\delta_1 xy}{\alpha_1+x} - \omega_1 y - \theta_1 y + \theta_2 z,\\ \frac{dz}{dt} &= \frac{\delta_2 xz}{\alpha_2+x} - \omega_2 z + \theta_1 y - \theta_2 z.\end{aligned} \tag{2.3}$$

2.1 Stability analysis of system (2.3)

System (2.3)'s equilibrium points can be used to conduct the stability analysis. The equilibrium points can be obtained as follows:

$$\begin{aligned}\frac{dx}{dt} &= 0 \Rightarrow \quad \alpha x(1-\beta x) - \frac{\gamma_1 xy}{\alpha_1+x} + \frac{\gamma_2 xz}{\alpha_2+x} = 0,\\ \frac{dy}{dt} &= 0 \Rightarrow \quad \frac{\delta_1 xy}{\alpha_1+x} - \omega_1 y - \theta_1 y + \theta_2 z = 0,\\ \frac{dz}{dt} &= 0 \Rightarrow \quad \frac{\delta_2 xz}{\alpha_2+x} - \omega_2 z + \theta_1 y - \theta_2 z = 0.\end{aligned}$$

By solving these three equations simultaneously, we obtain two solution points given by $E_1(0,0,0)$, $E_2(\frac{1}{\beta},0,0)$ and a quadratic equation in x given by:

$$R(x) = Ax^2 - Bx + C = 0. \tag{2.4}$$

Where,

$A = \delta_1\delta_2 - \delta_1(\omega_2 + \theta_2) - \delta_2(\omega_1 + \theta_1) + \omega_2(\omega_1 + \theta_1) + \omega_1\theta_2,$

$B = \delta_1\alpha_2(\omega_2 + \theta_2) + \delta_2\alpha_1(\omega_1 + \theta_1) - (\alpha_1 + \alpha_2)[\omega_2(\omega_1 + \theta_1) + \omega_1\theta_2],$

$C = \alpha_1\alpha_2[\omega_1(\omega_2 + \theta_2) + \omega_2\theta_1].$

Its discriminant is given by: $\Delta = B^2 - 4AC.$
By some calculations and substitutions, we get:

$$\Delta = [(\alpha_2 - \alpha_1)l + \alpha_2 m + \alpha_1 n]^2 + 4\alpha_1\alpha_2 l(m - \delta_1\delta_2).$$

Where,

$l = \omega_2(\omega_1 + \theta_1) + \omega_1\theta_2$, $m = \delta_1(\omega_2 + \theta_2)$, $n = \delta_2(\omega_1 + \theta_1)$.
Therefore, $\Delta \geqslant 0$, if $m \geqslant \delta_1\delta_2$. i.e., if $\omega_2 + \theta_2 \geqslant \delta_2$.
Which implies there exist real roots for the quadratic equation (2.4).

Now, there exists at least one positive root for the quadratic equation (2.4), if the following positivity condition is satisfied:

$$\delta_1\alpha_2(\omega_2 + \theta_2) + \delta_2\alpha_1(\omega_1 + \theta_1) > (\alpha_1 + \alpha_2)[\omega_2(\omega_1 + \theta_1) + \omega_1\theta_2].$$

Again, if there exists an interior equilibrium point $E_3(\bar{x}, \bar{y}, \bar{z})$. Then the equilibrium point E_3 needs to satisfy the system (2.3).

Let's take $\bar{x} = x^*$, then from system (2.3), we obtain:

$$\begin{aligned}
&\alpha x^*(1 - \beta x^*) - \tfrac{\gamma_1 x^*\bar{y}}{\alpha_1 + x^*} + \tfrac{\gamma_2 x^*\bar{z}}{\alpha_2 + x^*} = 0,\\
&\frac{\delta_1 x^*\bar{y}}{\alpha_1 + x^*} - \omega_1\bar{y} - \theta_1\bar{y} + \theta_2\bar{z} = 0,\\
&\frac{\delta_2 x^*\bar{z}}{\alpha_2 + x^*} - \omega_2\bar{z} + \theta_1\bar{y} - \theta_2\bar{z} = 0.
\end{aligned}$$

Now, by solving the system of these three equations simultaneously for $\bar{y}$ and $\bar{z}$, we obtain:

$$\bar{y} = \frac{\alpha(1 - \beta x^*)(\alpha_1 + x^*)[\delta_2 x^* - \omega_2(\alpha_2 + x^*)]}{\gamma_1[\delta_2 x^* - \omega_2(\alpha_2 + x^*)] + \gamma_2[\delta_1 x^* - \omega_1(\alpha_1 + x^*)]} \quad \text{and}$$
$$\bar{z} = -\frac{\alpha(1 - \beta x^*)(\alpha_2 + x^*)[\delta_1 x^* - \omega_1(\alpha_1 + x^*)]}{\gamma_1[\delta_2 x^* - \omega_2(\alpha_2 + x^*)] + \gamma_2[\delta_1 x^* - \omega_1(\alpha_1 + x^*)]}.$$

Therefore, the equilibrium point $E_3(\bar{x}, \bar{y}, \bar{z})$ of system (2.3) is given by:

$$E_3(\bar{x}, \bar{y}, \bar{z}) = (x^*, \frac{\alpha(1 - \beta x^*)(\alpha_1 + x^*)[\delta_2 x^* - \omega_2(\alpha_2 + x^*)]}{\gamma_1[\delta_2 x^* - \omega_2(\alpha_2 + x^*)] + \gamma_2[\delta_1 x^* - \omega_1(\alpha_1 + x^*)]},$$
$$- \frac{\alpha(1 - \beta x^*)(\alpha_2 + x^*)[\delta_1 x^* - \omega_1(\alpha_1 + x^*)]}{\gamma_1[\delta_2 x^* - \omega_2(\alpha_2 + x^*)] + \gamma_2[\delta_1 x^* - \omega_1(\alpha_1 + x^*)]}).$$

For interior equilibrium point $E_3(\bar{x}, \bar{y}, \bar{z})$ to be positive, we need to define positivity conditions for $E_3(\bar{x}, \bar{y}, \bar{z})$. So, we have obtained the following conditions on x^*, which needs to be satisfied for positive interior equilibrium $E_3(\bar{x}, \bar{y}, \bar{z})$ and the conditions are given by:

$$\frac{\gamma_1\omega_2\alpha_2 + \gamma_2\omega_1\alpha_1}{\gamma_1\delta_2 + \gamma_2\delta_1 - \omega_2 - \omega_1} < \frac{\omega_2\alpha_2}{\delta_2 - \omega_2} < x^* < \frac{\omega_1\alpha_1}{\delta_1 - \omega_1} < \frac{1}{\beta}. \tag{2.5}$$

Table 1. System parameters and variables with numerical values used for Numerical Simulation

Dimensional Parameters	Parameter Values and Units	Parameter Biological Meaning	Dimensionless Parameters	Parameter Source
$T(0)$	10^6 cells(c)	No. of initial T cells	x_0	
$M1(0)$	10^6 cells	No. of initial M1 cells	y_0	
$M2(0)$	10^6 cells	No. of initial M2 cells	z_0	
a	0.565 /day	Growth rate of T cells	α	
b^{-1}	$2 \times 10^9/cells$	Environmental carrying Capacity	β^{-1}	
d_1	0.2 /day(d)	Mortality rate of M1 cells	ω_1	
d_2	0.2 /day(d)	Mortality rate of M2 cells	ω_2	
f	$2 \times 10^{-6}/cd$	Death rate of T cells by M1 cells	γ_1	[27, 32]
g	$10^{-7}/cd$	Death rate of T cells by M2 cells	γ_1	
e_1	$10^{-6}/cd$	Enabling rate of M1 by T cells	δ_1	
e_2	$9 \times 10^{-7}/cd$	Enabling rate of M2 by T cells	δ_2	
r_1	0.05/day	M1 to M2 conversion rate	θ_1	
r_2	0.04/day	M2 to M1 conversion rate	θ_2	
a_1	0.002/day	Half saturation constant	α_1	
a_2	0.004/day	Half saturation constant	α_2	

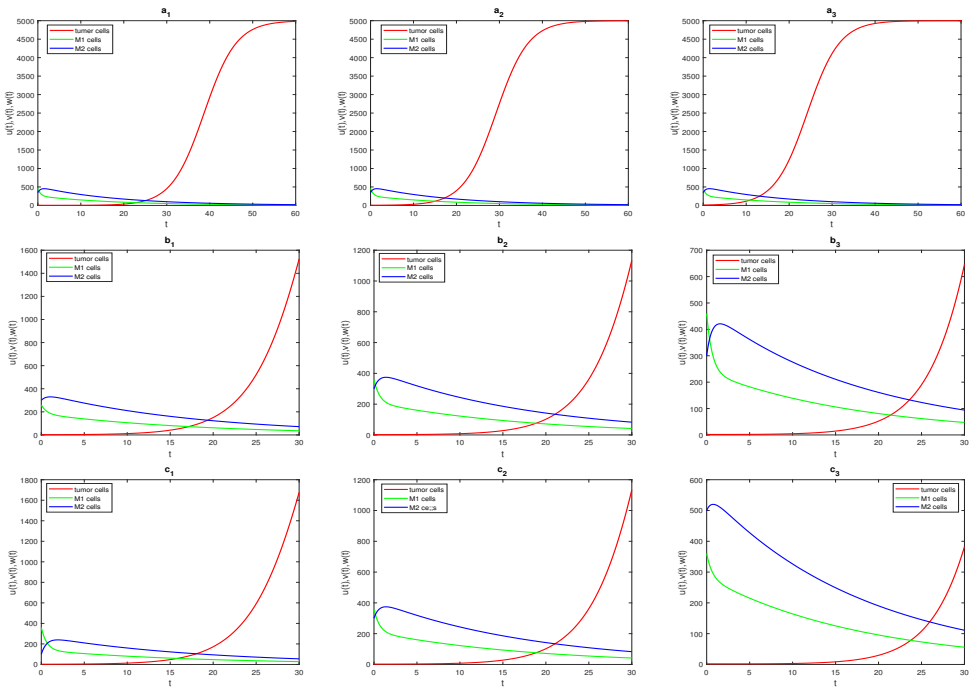

Figure 1. Graphical time series analysis of the model (2.3) with respect to the initial conditions. In a_1, a_2, and a_3, the three different initial values of the tumor cells are taken respectively as (x_0, y_0, z_0)= (2, 460, 346), (4, 460, 346), (10, 460, 346). In b_1, b_2, and b_3, the three different initial values of the M1 cells are taken respectively as (2, 260, 300), (2, 360, 300), (2, 460, 300). In c_1, c_2, and c_3, the three different initial values of the M2 cells are taken respectively as (2, 360, 100), (2, 360, 300), (2, 360, 500).

2.2 Linearization Process

To perform the stability analysis of the system (2.3), we first linearize the system at the general equilibrium point $E_3(\bar{x},\bar{y},\bar{z})$. For linearization of the system, we approximate the equations of the system at $E_3(\bar{x},\bar{y},\bar{z})$. This can be done by finding the tangent to these functions at $E_3(\bar{x},\bar{y},\bar{z})$, as follows:

$$\begin{aligned}
\frac{dx}{dt} &= [\alpha - 2\alpha\beta\bar{x} - \frac{\alpha_1\gamma_1\bar{y}}{(\alpha_1+\bar{x})^2} + \frac{\alpha_2\gamma_2\bar{z}}{(\alpha_2+\bar{x})^2}](x-\bar{x}) - [\frac{\gamma_1\bar{x}}{\alpha_1+\bar{x}}](y-\bar{y}) + [\frac{\gamma_2\bar{x}}{\alpha_2+\bar{x}}](z-\bar{z}),\\
\frac{dy}{dt} &= [\frac{\alpha_1\delta_1\bar{y}}{(\alpha_1+\bar{x})^2}](x-\bar{x}) + [\frac{\delta 1\bar{x}}{\alpha_1+\bar{x}} - \omega_1 - \theta_1](y-\bar{y}) + \theta_2(z-\bar{z}),\\
\frac{dz}{dt} &= [\frac{\alpha_2\delta_2\bar{z}}{(\alpha_2+\bar{x})^2}](x-\bar{x}) + \theta_1(y-\bar{y}) + [\frac{\delta_2\bar{x}}{\alpha_2+\bar{x}} - \omega_2 - \theta_2](z-\bar{z}).
\end{aligned} \tag{2.6}$$

This is the required linearized form of the system (2.3). The matrix representation of the linearized system (2.6) is given by:

$$\begin{pmatrix} \frac{dx}{dt} \\ \frac{dy}{dt} \\ \frac{dz}{dt} \end{pmatrix} = \begin{pmatrix} r_{11} & r_{12} & r_{13} \\ r_{21} & r_{22} & \theta_2 \\ r_{31} & \theta_1 & r_{33} \end{pmatrix} \begin{pmatrix} x-\bar{x} \\ y-\bar{y} \\ z-\bar{z} \end{pmatrix}.$$

Where,

$r_{11} = \alpha(1-2\beta\bar{x}) - \frac{\alpha_1\gamma_1\bar{y}}{(\alpha_1+\bar{x})^2} + \frac{\alpha_2\gamma_2\bar{z}}{(\alpha_2+\bar{x})^2}$, $r_{12} = -\frac{\gamma_1\bar{x}}{\alpha_1+\bar{x}}$, $r_{13} = \frac{\gamma_2\bar{x}}{\alpha_2+\bar{x}}$,

$r_{21} = \frac{\alpha_1\delta_1\bar{y}}{(\alpha_1+\bar{x})^2}$, $r_{22} = \frac{\delta_1\bar{x}}{\alpha_1+\bar{x}} - \omega_1 - \theta_1$, $r_{31} = \frac{\alpha_2\delta_2\bar{z}}{(\alpha_2+\bar{x})^2}$, $r_{33} = \frac{\delta_2\bar{x}}{\alpha_2+\bar{x}} - \omega_2 - \theta_2$.

The stability analysis of system (2.3) at equilibrium points $E_1(0,0,0)$ and $E_2(\frac{1}{\beta},0,0)$ by considering its linearized form (2.6) can be done by using the following results:

Theorem 1: The tumor-free equilibrium point $E_1(0,0,0)$ of system (2.3) is always unstable.
Proof: Consider the linearized form of system (2.3). The Jacobean matrix of linearized system (2.6) at the equilibrium point $E_1(0,0,0)$ is given by:

$$\begin{pmatrix} \alpha & 0 & 0 \\ 0 & -\omega_1-\theta_1 & \theta_2 \\ 0 & \theta_1 & -\omega_2-\theta_2 \end{pmatrix}.$$

Its characteristic equation is: $(\alpha-\lambda)[(-\omega_1-\theta_1-\lambda)(-\omega_2-\theta_2-\lambda)-\theta_1\theta_2] = 0$

or, $\qquad (\alpha-\lambda)[(\omega_1+\lambda)(\omega_2+\lambda)+\theta_1(\omega_2+\lambda)+\theta_2(\omega_1+\lambda)] = 0.$

From the characteristic equation, it can be observed that one of the eigenvalues is positive. So, we conclude that system (2.3) is unstable at the tumor-free equilibrium point $E_1(0,0,0)$.

Theorem 2: The tumor-dominant equilibrium point $E_2(\frac{1}{\beta},0,0)$ of the system (2.3) is locally asymptotically stable if the following two conditions are satisfied:

1. $\dfrac{\delta_1}{\beta\alpha_1+1} + \dfrac{\delta_2}{\beta\alpha_2+1} < (\omega_1+\omega_2+\theta_1+\theta_2).$
2. $\dfrac{\delta_2-\omega_2(\beta\alpha_2+1)}{\beta\alpha_2+1} > \theta_2(\dfrac{\delta_1-\omega_1(\beta\alpha_1+1)}{\delta_1-(\omega_1+\theta_1)(\beta\alpha_1+1)}).$

Proof: Consider the system (2.3) with equilibrium point $E_2(\frac{1}{\beta},0,0)$. The Jacobian matrix of the system of equations is given by:

$$\begin{pmatrix} -\alpha & -\frac{\gamma_1}{\beta\alpha_1+1} & \frac{\gamma_2}{\beta\alpha_2+1} \\ 0 & \frac{\delta 1}{\beta\alpha_1+1}-\omega_1-\theta_1 & \theta_2 \\ 0 & \theta_1 & \frac{\delta_2}{\beta\alpha_2+1}-\omega_2-\theta_2 \end{pmatrix}.$$

The characteristic equation of the matrix is given by:

$$(\alpha+\lambda)[(\lambda+\omega_1-\frac{\delta 1}{\beta\alpha_1+1}+\theta_1)(\lambda+\omega_2-\frac{\delta_2}{\beta\alpha_2+1}+\theta_2)-\theta_1\theta_2]=0.$$

Either $\lambda=-\alpha$ or

$$\lambda^2-\lambda(r+a-\theta_2-\theta_1)+ar-a\theta_2-r\theta_1=0. \tag{2.7}$$

Where, $a=\frac{\delta 1}{\beta\alpha_1+1}-\omega_1$, $r=\frac{\delta_2}{\beta\alpha_2+1}-\omega_2$.

Solving equation (2.7) for λ we get:

$$\lambda=\frac{(r+a-\theta_2-\theta_1)\pm\sqrt{(\theta_2-\theta_1-r+a)^2+4\theta_1\theta_2}}{2}.$$

Here, the discriminant of the above quadratic equation which is actually a characteristic equation of the Jacobian matrix is always positive. i.e.,

$$(\theta_2-\theta_1-r+a)^2+4\theta_1\theta_2>0.$$

Now from the above analysis, it can be observed that the roots of a quadratic equation (2.7) are negative if they will satisfy the following conditions, which are given by:

$$r+a-\theta_2-\theta_1>0 \text{ and } ar-a\theta_2-r\theta_1>0.$$

i.e., if,

$$\delta_2>\frac{(\beta\alpha_2+1)[(\beta\alpha_1+1)(\omega_1+\omega_2+\theta_1+\theta_2)-\delta_1]}{(\beta\alpha_1+1)}=\varepsilon_0. \tag{2.8}$$

and

$$\delta_2<(\beta\alpha_2+1)[\frac{\theta_2(\delta_1-\omega_1(\beta\alpha_1+1))+\omega_2(\delta_1-(\omega_1+\theta_1)(\beta\alpha_1+1))}{\delta_1-(\omega_1+\theta_1)(\beta\alpha_1+1)}]=\varepsilon_1. \tag{2.9}$$

The eigenvalues of the above matrix are negative reals if $\varepsilon_0<\delta_2<\varepsilon_1$. These are the local asymptotic stability conditions for the equilibrium point $E_2(\frac{1}{\beta},0,0)$. Hence system (2.3) is conditionally locally asymptotically stable for the tumor dominant equilibrium point.

From the above analysis, it can be observed there exists at most one positive interior equilibrium point for the system (2.3), if and only if (2.5) holds. Let us consider $E_3(\bar{x},\bar{y},\bar{z})$, the unique positive interior equilibrium point. Then, we have the following results for $E_3(\bar{x},\bar{y},\bar{z})$ of system (2.3).

Theorem 3: The positive interior equilibrium point $E_3(\bar{x},\bar{y},\bar{z})$ of the system (2.3) is conditionally locally asymptotically stable.

Proof: Here we will consider the coefficient matrix from the linearized system (2.6), which is the required Jacobian matrix of system (2.3) and is given by:

$$\begin{pmatrix} \alpha(1-2\beta\bar{x})-\frac{\alpha_1\gamma_1\bar{y}}{(\alpha_1+\bar{x})^2}+\frac{\alpha_2\gamma_2\bar{z}}{(\alpha_2+\bar{x})^2} & -\frac{\gamma_1\bar{x}}{\alpha_1+\bar{x}} & \frac{\gamma_2\bar{x}}{\alpha_2+\bar{x}} \\ \frac{\alpha_1\delta_1\bar{y}}{(\alpha_1+\bar{x})^2} & \frac{\delta_1\bar{x}}{\alpha_1+\bar{x}}-\omega_1-\theta_1 & \theta_2 \\ \frac{\alpha_2\delta_2\bar{z}}{(\alpha_2+\bar{x})^2} & \theta_1 & \frac{\delta_2\bar{x}}{\alpha_2+\bar{x}}-\omega_2-\theta_2 \end{pmatrix}.$$

To do a stability analysis of system (2.3) at the positive interior equilibrium point. We need to find out the nature of the eigenvalues of the above matrix. Now the characteristic equation of the above Jacobian matrix is given by:

$$\lambda^3 + X_1\lambda^2 + X_2\lambda + X_3 = 0. \tag{2.10}$$

Where,

$$X_1 = -\alpha(1-2\beta\bar{x}) + \frac{\alpha_1\gamma_1\bar{y}}{(\alpha_1+\bar{x})^2} - \frac{\alpha_2\gamma_2\bar{z}}{(\alpha_2+\bar{x})^2} - \frac{\delta_1\bar{x}}{\alpha_1+\bar{x}} - \frac{\delta_2\bar{x}}{\alpha_2+\bar{x}} + \omega_1 + \omega_2 + \theta_1 + \theta_2,$$

$$X_2 = [\alpha(1-2\beta\bar{x}) - \frac{\alpha_1\gamma_1\bar{y}}{(\alpha_1+\bar{x})^2} + \frac{\alpha_2\gamma_2\bar{z}}{(\alpha_2+\bar{x})^2}][\frac{\delta_1\bar{x}}{\alpha_1+\bar{x}} - \omega_1 - \theta_1 + \frac{\delta_2\bar{x}}{\alpha_2+\bar{x}} - \omega_2 - \theta_2] + (\frac{\delta_1\bar{x}}{\alpha_1+\bar{x}} - \omega_1 - \theta_1)(\frac{\delta_2\bar{x}}{\alpha_2+\bar{x}} - \omega_2 - \theta_2) + (\frac{\alpha_1\delta_1\bar{y}}{(\alpha_1+\bar{x})^2})(\frac{\gamma_1\bar{x}}{\alpha_1+\bar{x}}) + (\frac{\alpha_2\delta_2\bar{z}}{(\alpha_2+\bar{x})^2})(\frac{\gamma_2\bar{x}}{\alpha_2+\bar{x}}) - \theta_1\theta_2,$$

$$X_3 = (\frac{\delta_1\bar{x}}{\alpha_1+\bar{x}} - \omega_1 - \theta_1)[(\frac{\alpha_2\delta_2\bar{z}}{(\alpha_2+\bar{x})^2})(\frac{\gamma_2\bar{x}}{\alpha_2+\bar{x}}) - (\frac{\alpha_1\delta_1\bar{y}}{(\alpha_1+\bar{x})^2})(\frac{\gamma_1\bar{x}}{\alpha_1+\bar{x}})] + (\alpha(1-2\beta\bar{x}) - \frac{\alpha_1\gamma_1\bar{y}}{(\alpha_1+\bar{x})^2} + \frac{\alpha_2\gamma_2\bar{z}}{(\alpha_2+\bar{x})^2})[\theta_1\theta_2 - (\frac{\delta_1\bar{x}}{\alpha_1+\bar{x}} - \omega_1 - \theta_1)(\frac{\delta_2\bar{x}}{\alpha_2+\bar{x}} - \omega_2 - \theta_2)] - \theta_1(\frac{\alpha_1\delta_1\bar{y}}{(\alpha_1+\bar{x})^2})(\frac{\gamma_2\bar{x}}{\alpha_2+\bar{x}}) + \theta_2(\frac{\alpha_2\delta_2\bar{z}}{(\alpha_2+\bar{x})^2})(\frac{\gamma_1\bar{x}}{\alpha_1+\bar{x}}), \quad \text{and}$$

$$\bar{x} = x^*, \qquad \bar{y} = \frac{\alpha(1-\beta x^*)(\alpha_1+x^*)[\delta_2 x^* - \omega_2(\alpha_2+x^*)]}{\gamma_1[\delta_2 x^* - \omega_2(\alpha_2+x^*)] + \gamma_2[\delta_1 x^* - \omega_1(\alpha_1+x^*)]},$$

$$\bar{z} = -\frac{\alpha(1-\beta x^*)(\alpha_2+x^*)[\delta_1 x^* - \omega_1(\alpha_1+x^*)]}{\gamma_1[\delta_2 x^* - \omega_2(\alpha_2+x^*)] + \gamma_2[\delta_1 x^* - \omega_1(\alpha_1+x^*)]}.$$

Now we will discuss the nature of roots of equation (2.10) by using the following lemma:

Lemma 1: Consider a cubic equation of the form:

$$u^3 + r_1u^2 + r_2u + r_3 = 0\,,$$

where, r_1, r_2, and r_3 are the real coefficients (constants) with u as a variable. The system is locally asymptotically stable at the positive interior equilibrium point, if and only if the following conditions are satisfied:

$$r_1 > 0\,, \qquad r_3 > 0 \quad \text{and} \quad r_1r_2 - r_3 > 0.$$

These conditions are called the Routh-Hurwitz stability conditions, which guarantee: $Re(u) < 0$.

Now we will apply the same lemma to the cubic equation (2.10), which has been obtained from the system (2.3) at the equilibrium point $E_3(\bar{x}, \bar{y}, \bar{z})$.

Consider the cubic equation (2.10): $\lambda^3 + X_1\lambda^2 + X_2\lambda + X_3 = 0.$

Suppose that the positivity conditions defined by (2.5) are satisfied, then the interior equilibrium point $E_3(\bar{x}, \bar{y}, \bar{z})$ of the system (2.3) is locally asymptotically stable if and only if the following conditions are satisfied:

$$X_1 > 0, \qquad X_3 > 0, \qquad X_1X_2 - X_3 > 0. \tag{2.11}$$

Where, X_1, X_2 and X_3 are the coefficients of cubic equation (2.10).

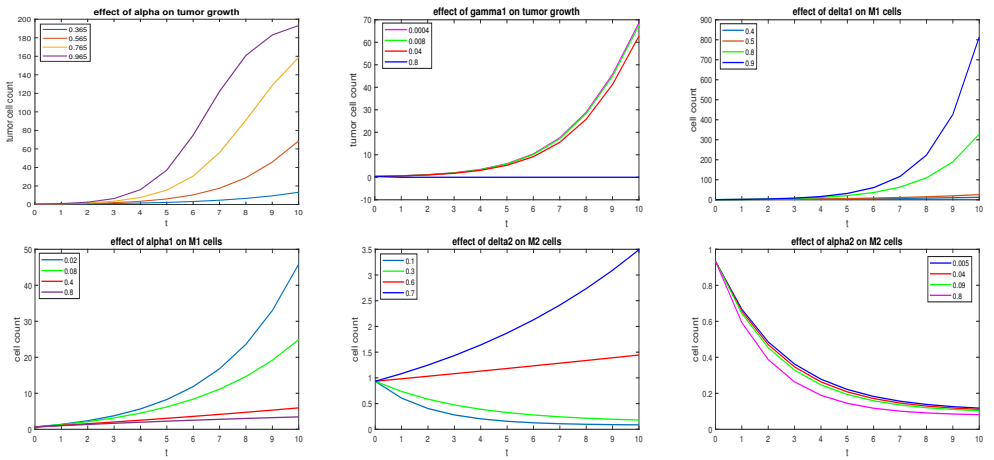

Figure 2. Sensitivity analysis of model (2.3) when parameters α, γ_1, δ_1, α_1, δ_2 and α_2 are varied in 1st, 2nd, 3rd, 4th, 5th and 6th graph respectively. All four parameters are given four different values as shown in their respective figures. The initial conditions are chosen as $(x_0, y_0, z_0) = (0.367, 0.643, 0.934)$ and the other parameter values are the same as in Table 1.

3 Bifurcation Analysis

3.1 Hopf-Bifurcation:

In this section, we analyze and study the existence of Hopf-bifurcation for system (2.3) at the equilibrium point $E_3(\bar{x}, \bar{y}, \bar{z})$. In order to find out the parametric conditions for the existence of Hopf-bifurcation of the system (2.3), we use an explicit criterion of Hopf-bifurcation without calculating the eigenvalues of the matrix obtained from the system (2.3) at the positive interior equilibrium point [9, 26, 38]. The explicit criteria of Hopf bifurcation can be found in [39].

To discuss the bifurcation dynamics of the tumor-immune interaction model (2.3), we convert it into its discrete counterpart by implementing Euler's forward scheme (method) and obtain the following discrete system:

$$\begin{aligned} x(n+1) &= x(n) + h[\alpha x(n)(1-\beta x(n)) - \frac{\gamma_1 x(n) y(n)}{\alpha_1 + x(n)} + \frac{\gamma_2 x(n) z(n)}{\alpha_2 + x(n)}], \\ y(n+1) &= y(n) + h[\frac{\delta_1 x(n) y(n)}{\alpha_1 + x(n)} - \omega_1 y(n) - \theta_1 y(n) + \theta_2 z(n)], \\ z(n+1) &= z(n) + h[\frac{\delta_2 x(n) z(n)}{\alpha_2 + x(n)} - \omega_2 z(n) + \theta_1 y(n) - \theta_2 z(n)]. \end{aligned} \tag{3.1}$$

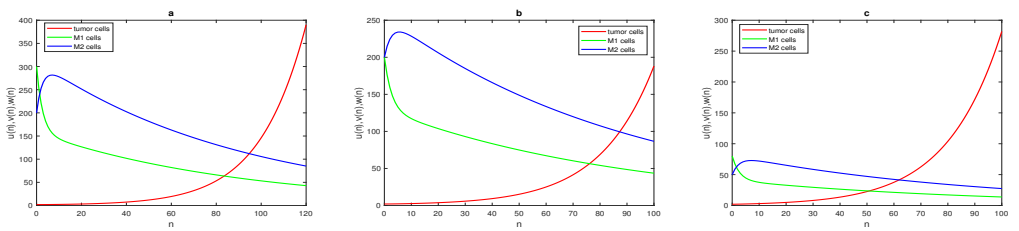

Figure 3. Graphical time series analysis of Discrete model (3.1). In graph a, the initial cell population is chosen as (2, 300, 200). In graph b, the initial population is chosen as (2, 200, 200). In c, the initial condition is chosen as (1, 80, 50).

Now, applying Taylor series expansion on each equation of system (3.1) separately, we obtain the required linearized version of the system (3.1) in matrix form given by:

$$\begin{pmatrix} F_1 \\ F_2 \\ F_3 \end{pmatrix} = \begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & h\theta_2 \\ a_{31} & h\theta_1 & a_{33} \end{pmatrix} \begin{pmatrix} u-\bar{x} \\ v-\bar{y} \\ w-\bar{z} \end{pmatrix}. \tag{3.2}$$

Where, F_1, F_2, and F_3 represent the first, second, and third equations respectively of the system (3.2). Also,

$a_{11} = 1 + h[\alpha(1-2\beta x) - \frac{\gamma_1 y}{\alpha_1+x} + \frac{\gamma_2 z}{\alpha_2+x}]$, $a_{12} = -\frac{h\gamma_1 x}{\alpha_1+x}$, $a_{13} = \frac{h\gamma_2 x}{\alpha_2+x}$,

$a_{21} = \frac{h\alpha_1\delta_1 y}{(\alpha_1+x)^2}$, $a_{22} = 1 + h[\frac{\delta_1 x - (\alpha_1+x)(\omega_1\theta_1)}{\alpha_1+x}]$, $a_{31} = \frac{h\alpha_2\delta_2 z}{(\alpha_2+x)^2}$,

$a_{33} = 1 + h[\frac{\delta_2 x - (\alpha_2+x)(\omega_2\theta_2)}{\alpha_2+x}]$.

The characteristic equation of the Jacobian matrix of linearized discrete system (3.1) at the interior equilibrium point $E_3(\bar{x},\bar{y},\bar{z})$ is given by:

$$\lambda^3 + c_2\lambda^2 + c_1\lambda + c_0 = 0. \tag{3.3}$$

Where,

$c_2 = -(a_{11}+a_{22}+a_{33})$,

$c_1 = a_{11}(a_{22}+a_{33}) + a_{22}a_{33} - h^2\theta_1\theta_2 - a_{12}a_{21} - a_{13}a_{31}$,

$c_0 = -a_{11}a_{22}a_{33} + a_{11}h^2\theta_1\theta_2 + a_{12}a_{21}a_{33} - a_{12}a_{31}h\theta_2 - a_{13}a_{21}h\theta_1 + -a_{13}a_{31}a_{22}$.

Let us take $n = 3$, then the lemma given in [39], gives us the conditions on parameters under which model (3.1) experiences Hopf-bifurcation. We will choose h as the bifurcation parameter for analyzing the existence of Hoph- bifurcation of system (2.3) at the interior equilibrium point $E_3(\bar{x},\bar{y},\bar{z})$.

Theorem 4: [39] The coexistence positive equilibria $E_3(\bar{x},\bar{y},\bar{z})$ of the discrete system (3.1) experiences a Hopf bifurcation at the crucial value of the bifurcation parameter $h = h_0$ if the following conditions are satisfied:

1 *Eigenvalue Criteria:* $D_2^+(h_0) > 0$, $D_2^-(h_0) = 0$, $c_{h_0}(1) > 0$, $(-1)^3 c_{h_0}(-1) > 0$.

2 *Transversality Condition:* $(\frac{d}{dh}(D_2^-(h)))_{h=h_0} \neq 0$.

3 *Resonance or non-resonance criteria:* $cos(\frac{2\pi}{k}) = 1 - \frac{0.5c_{h_0}(1)D_0^-(h_0)}{D_1^+(h_0)}$ or $cos(\frac{2\pi}{k}) \neq 1 - \frac{0.5c_{h_0}(1)D_0^-(h_0)}{D_1^+(h_0)}$, $k = 3,4,5,...$

Where c_2, c_1, c_0 are the coefficients of the characteristic equation (3.3) and h_0 is the possible real root of:

$$1 - c_1(h) + c_0(h)(c_2(h) - c_0(h)) = 0. \tag{3.4}$$

Proof: Taking $n = 3$ and h as the bifurcation parameter, then from equation (3.3) we obtain:

$D_2^{\pm}(h_0) = det(R_1 \pm R_2)$. Where, $R_1 = \begin{pmatrix} 1 & c_2 \\ 0 & 1 \end{pmatrix}$ and $R_2 = \begin{pmatrix} c_1 & c_0 \\ c_0 & 0 \end{pmatrix}$.

Therefore, $D_2^-(h_0) = det(R_1 - R_2) = \begin{pmatrix} 1-c_1 & c_2-c_0 \\ -c_0 & 1 \end{pmatrix} = 1 - c_1 + c_0(c_2 - c_0) = 0$

$\Longrightarrow \quad D_2^-(h_0) = 0,$

$$D_2^+(h_0) = det(R_1 + R_2) = \begin{pmatrix} 1+c_1 & c_2+c_0 \\ c_0 & 1 \end{pmatrix} = 1 + c_1 - c_0(c_2 + c_0) > 0$$
$$\Longrightarrow \quad D_2^+(h_0) > 0.$$

Also, $C_{h_0}(1) = 1 + c_2 + c_1 + c_0 > 0, \quad \Longrightarrow \quad C_{h_0}(1) > 0,$

$$(-1)^3 C_{h_0}(-1) = 1 - c_2 + c_1 - c_0 > 0 \quad \Longrightarrow \quad (-1)^3 C_{h_0}(-1) > 0,$$

$$(\tfrac{d}{dh}(D_2^-(h)))_{h=h_0} = \tfrac{d}{dh}(\begin{pmatrix} 1-c_1 & c_2-c_0 \\ -c_0 & 1 \end{pmatrix})_{h=h_0} = \tfrac{d}{dh}(1 - c_1 + c_0(c_2 - c_0))_{h=h_0} \neq 0$$
$$\Longrightarrow \quad (\tfrac{d}{dh}(D_2^-(h)))_{h=h_0} \neq 0,$$

and $\quad 1 - \dfrac{0.5c_{h_0}(1)D_0^-(h_0)}{D_1^+(h_0)} = 1 - \dfrac{0.5(1 + c_2 + c_1 + c_0)}{1 + c_0} \neq cos(\dfrac{2\pi}{k})$

$$\Longrightarrow \quad 1 - \frac{0.5c_{h_0}(1)D_0^-(h_0)}{D_1^+(h_0)}, \qquad k = 3, 4, 5, ...$$

All these conditions are verified for the set of parameter values chosen in the numerical simulation section below. The critical value of the bifurcation parameter is $h = h_0 = 0.4137$.

4 Numerical Simulation and Result Discussion

In this section, we discuss the dynamics of our proposed model (2.2), by using biologically suitable numerical values of parameters. The dimensionless form of model (2.2) vanishes the dependence of variables and parameters on units. Therefore, the numerical values of non-dimensional parameters have been used and are mentioned in table 1 with their respective numerical values. Let us take:

$\alpha = 0.565$, $\beta = 0.0005$, $\gamma_1 = 0.000002$, $\gamma_2 = 0.0000001$, $\alpha_1 = 0.002$, $\alpha_2 = 0.004$, $\delta_1 = 0.6$, $\delta_2 = 0.2$, $\omega_1 = 0.2$, $\omega_2 = 0.022$, $\theta_1 = 0.05$, $\theta_2 = 0.444$.

By using these numerical values of parameters in the analytic findings of the proposed model (2.3), we obtain $0.0004 < x^* < 0.001$, $\varepsilon_0 = 0.1160$, $\varepsilon_1 = 0.5294$ and $0.1160 < \delta_2 < 0.5294$ is also satisfied. By using these conditions, it can be observed that the equilibrium point E_1 is unstable, and E_2 is locally asymptotically stable. This shows that our analytical results agree with numerical simulation.

Again, the interior equilibrium points E_3 exist only if $0.0004 < x^* < 0.001$ under the set of values of parameters mentioned above. From equation (2.4), we obtain one positive root, which satisfies the positivity conditions for interior equilibrium point E_3. We take this positive root of a quadratic equation (2.4) as the value of x^* for calculating the interior equilibrium point. Therefore, we have:

$$\bar{x} = x^* = 0.000984, \quad \bar{y} = 842.5901, \quad \bar{z} = 788.7461.$$

By substituting the above-mentioned numerical values of parameters and the interior equilibrium point $E_3(0.000984, 842.5901, 788.7461)$ in expression (2.11). We observe that all three conditions for stability of the positive interior equilibrium point are satisfied. Hence it is numerically also found that the interior equilibrium point E_3 is locally asymptotically stable.

Furthermore, the roots of the characteristic equation (2.10) at $E_3(0.000984, 842.5901, 788.7461)$ are given by $\lambda_1 = 0.3131$ and two complex conjugate roots $\lambda_{2,3} = -0.0679 \pm 0.1738i$.

For the numerical simulation of bifurcation analysis, the following numerical values of parameters are chosen for the analysis of the discrete model (3.1) [27, 32]:

$\alpha = 0.565$, $\beta = 0.0005$, $\gamma_1 = 0.000002$, $\gamma_2 = 0.0000001$, $\alpha_1 = 0.002$, $\alpha_2 = 0.004$, $\delta_1 = 0.6$, $\delta_2 = 0.2$, $\omega_1 = 0.2$, $\omega_2 = 0.022$, $\theta_1 = 0.05$, $\theta_2 = 0.444$, and $h \in [0.1, 0.9]$.

Initially, we choose $h = 0.1$ and the initial conditions as $(u(0), v(0), w(0)) = (4.2, 0.2, 2.6)$ [40, 41].
Also, the characteristic equation (3.3), is given by:

$$\lambda^3 - 2.0534\lambda^2 + 0.9886\lambda + 0.000122 = 0.$$

Its roots are given by: $\lambda = -0.00012, 0.7711, 0.9825$.

Now, for the numerical simulation of bifurcation analysis, first, we must calculate the critical value of the bifurcation parameter, which is obtained from equation (3.4). While solving equation (3.4), we obtain four different values of the bifurcation parameter. The suitable critical value of the bifurcation parameter is chosen as $h = h_0 = 0.4134$. With the help of the critical value, all three conditions for the existence of Hopf bifurcation analysis are verified by using MATLAB.

The existence of Hopf bifurcation is shown by defining the three conditions (see theorem 4) at the coexistence equilibrium point. It is confirmed at the critical value of the bifurcation parameter obtained from equation (3.4). The graphical analysis shows that the bifurcation parameter plays an important role in controlling the growth of tumor cells. With the help of Michael's-Menten Kinetics, it is easy to understand and control the growth of tumor cells in the long run. The limited response of macrophages to the tumor is the main function of Michael's-Menten Kinetics, which helps in controlling the growth of tumor cells.

The sensitivity analysis of our proposed model (2.3) is done in two ways. First, we choose different initial conditions for plotting the growth curves, which shows that there is a great response of tumor cells, M1, and M2 macrophages to initial conditions (see figure 1). Second, we varied some important parameters within the small range and kept other parameters fixed to understand the role of these important parameters on tumor growth and activation response rate of macrophages (see figure 2).

Further, to check and analyse the effect of Michaelis-Menten kinetics on the population growth of the proposed model (2.3), we vary the parameters involved in Michael-Menten kinetics. Firstly, we varied the parameters $\delta_1 = [0.9, 0.8, 0.5, 0.4]$ and $\alpha_1 = [0.02, 0.08, 0.4, 0.8]$, separately for second equation of model (2.3). The effect of these two parameters on the population growth of M1 macrophages is shown graphically in figure 2. For M2 macrophages, we vary the parameters $\delta_2 = [0.1, 0.3, 0.5, 0.7]$ and $\alpha_2 = [0.006, 0.04, 0.9, 0.8]$, separately in order to analyse the effect of these two parameters on population growth of third equation in the system (2.3). Which is again shown graphically in figure 2. Finally, we vary the parameters $\gamma_1 = [0.0004, 0.008, 0.04, 0.8]$ and $\alpha = [0.365, 0.565, 0.765, 0.965]$, separately in the first equation of model (2.3) to check and analyse the effect of these two parameters on population growth of tumor cells. Which is again shown graphically in figure 2. The initial conditions for all three equations are chosen as $(x_0, y_0, z_0) = (0.367, 0.643, 0.934)$ for the above analysis of the model (2.3).

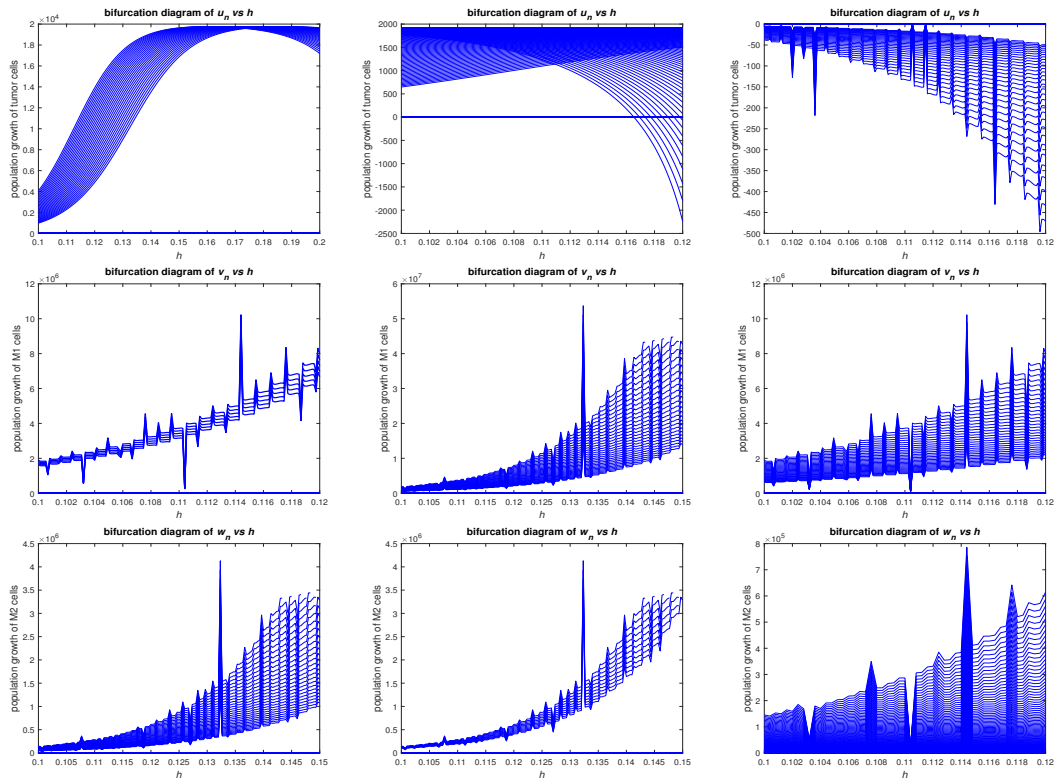

Figure 4. Bifurcation diagrams of the discrete model (3.1) with respect to the bifurcation parameter h. The diagram shows the effect of bifurcation parameter h separately on each variable (cell population).

5 Conclusion

In this paper, we have studied the proposed model (2.2) by introducing the concept of Michael's Menten-based dynamics of tumor-immune interaction among three cell populations of M1-type of macrophages, M2-type of macrophages, and tumor cells. The stability and dynamical analysis of the proposed model is done by using the equilibrium points of the system (2.3). In order to study and prove the existence of all three equilibrium points, we linearized system (2.3) to obtain its Jacobian matrix. Then we used the same Jacobian matrix for the stability analysis of the model (2.3). First, we studied the stability and existence of tumor-free equilibrium point E_1. It has been proved in theorem 1, that the tumor-free equilibrium point is always unstable. Secondly, we studied the existence of tumor dominant equilibrium point E_2. The stability analysis of E_2 in proof of theorem 2 shows that the tumor dominant equilibrium point is locally asymptotically stable if the activation rate of M2 macrophages by tumor cells is limited, i.e., $(\varepsilon_0 < \delta_2 < \varepsilon_1)$. So, we can say that Michael's-Menten kinetics has a great role in limiting the activation rate of M2 macrophages to tumor cells. Then thirdly, we studied the stability and existence of positive interior equilibrium point E_3 by using stability criteria defined by lemma 1. This shows that the interior equilibrium is locally asymptotically stable (LAS) if the conditions defined by lemma 1 are satisfied. The LAS conditions are satisfied numerically as well.

Finally, we declare that our proposed model (2.2) with three cell populations (variables) and the nonlinear activation rate of type-1 (M1) macrophages and type-2 (M2) macrophages by tumor cells is an important feature for controlling and understanding the heterogenic and dual character of immune cells and their role in tumor development. So, we suggest our readers use this nonlinear activation (recruitment) concept of immune cells by tumor cells in other models too, for a better understanding of the complex dynamics of the tumor-immune interaction systems. Further, in the future, we can use the time delay concept and fractional order derivatives as well in such types of biological models.

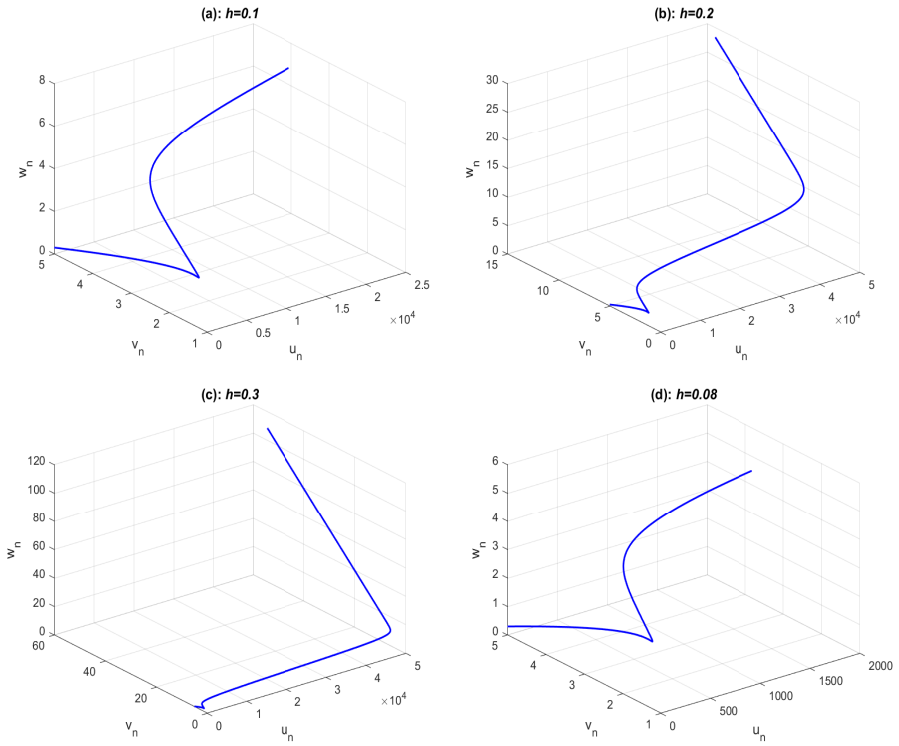

Figure 5. 3D phase portraits of population growth competition between all the three cell types (tumor cells, M1 cells, and M2 cells) of the discrete system (3.1) for four different values of the parameter h. The initial populations are chosen as $(u(n), v(n), w(n)) = (0.0029, 5, 0.3)$.

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Availability of data and material: Data availability is not applicable to this research work.

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