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Discretization and bifurcation analysis of tumor immune interaction in fractional form

Muhammad Taj [1], Mohamed A. Khadimallah [2,3], Muzamal Hussain*[4], Yahya Rashid [2],
Waqas Ishaque [1,5], S.R. Mahmoud [6], Qamar Din [5], Afaf S. Alwabli [7] and Abdelouahed Tounsi [8,9]

[1] *Department of Mathematics, University of Azad Jammu and Kashmir, Muzaffarabad, 1300, Azad Kashmir, Pakistan*
[2] *Prince Sattam Bin Abdulaziz University, College of Engineering, Civil Engineering Department, BP 655, Al-Kharj, 16273, Saudi Arabia*
[3] *Laboratory of Systems and Applied Mechanics, Polytechnic School of Tunisia, University of Carthage, Tunis, Tunisia*
[4] *Department of Mathematics, Govt. College University Faisalabad, 38000, Faisalabad, Pakistan*
[5] *Department of Mathematics University of Poonch Rawalakot 12350, Azad Kashmir, Pakistan*
[6] *GRC Department, Faculty of Applied studies, King Abdulaziz University, Jeddah, Saudi Arabia*
[7] *Department of Biological Sciences, Rabigh-Faculty of Science & Arts, King Abdulaziz University, Jeddah, Saudi Arabia*
[8] *YFL (Yonsei Frontier Lab), Yonsei University, Seoul, Korea*
[9] *Department of Civil and Environmental Engineering, King Fahd University of Petroleum & Minerals,*
31261 Dhahran, Eastern Province, Saudi Arabia

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Abstract. A tumor immune interaction is a main topic of interest in the last couple of decades because majority of human population suffered by tumor, formed by the abnormal growth of cells and is continuously interacted with the immune system. Because of its wide range of applications, many researchers have modeled this tumor immune interaction in the form of ordinary, delay and fractional order differential equations as the majority of biological models have a long range temporal memory. So in the present work, tumor immune interaction in fractional form provides an excellent tool for the description of memory and hereditary properties of inter and intra cells. So the interaction between effector-cells, tumor cells and interleukin-2 (IL-2) are modeled by using the definition of Caputo fractional order derivative that provides the system with long-time memory and gives extra degree of freedom. Moreover, in order to achieve more efficient computational results of fractional-order system, a discretization process is performed to obtain its discrete counterpart. Furthermore, existence and local stability of fixed points are investigated for discrete model. Moreover, it is proved that two types of bifurcations such as Neimark-Sacker and flip bifurcations are studied. Finally, numerical examples are presented to support our analytical results.

Keywords: tumor immune interaction; stability; Neimark-Sacker bifurcation; period-doubling bifurcation

1. Introduction

Cancer is a group of diseases caused by the abnormal growth of cells characterized by DNA has a potential to spread in other parts of body. In all types of cancer some of the body cells grow in an abnormal way and damage the surrounding tissues.

The healthy body has a strong immune system to defend it against cancer caused by the failure of immune system and the other mechanism within the body (Ucar *et al.* 2019). The cancer cases have been arising very quickly since the last few decades and it has estimated that about 18.1 millions people suffered from this disease every year and out of which 9.6 millions people died (Rowlands and Gunnell 2009). The new cases of cancer have been arising continuously and it is estimated that these numbers may reach to 22.2 millions till 2030 (Bray *et al.* 2012).

Hence, it is the need of time to develop new, advanced and cost effective methods in order to deal with such cases. Currently, the most common cancer treatments are immunotherapy (Curti *et al.* 1996, Banerjee 2008), chemotherapy (Chabner and Roberts 2005), radiotherapy (Thariat *et al.* 2013) and surgery (Wyld *et al.* 2015). Inspite of all these treatments it relapses, therefore it is the need for a more effective treatment is obvious. Mehar *et al.* (2019) investigated the buckling load parameters of the graded nanotube sandwich structure under the influence of uniform thermal loading. The corresponding properties of the graded nanotube sandwich evaluated via the extended rule of mixture including temperature dependent properties of each constituent. The nanotube structural model derived mathematically using a higher-order polynomial displacement to maintain the required shear stress continuity and thermal distortion via Green-Lagrange strain. Kar *et al.* (2017) investigated the numerically the postbuckling load parameter of the functionally graded shell panels under uniform and non-uniform thermal environment using nonlinear finite element method. The shell structure is assumed to be under three different thermal fields (uniform, linear and nonlinear temperature) across the panel thickness

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*Corresponding author, Ph.D., Research Scholar,
E-mail: muzamal45@gmail.com;
muzamalhussain@gcuf.edu.pk

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including the temperature dependent properties of each constituent. Modeling of tumor-immune interaction has attracted much attention and this interaction is very complex and mathematical models which are in the form of ordinary differential equations are studied by De Boer *et al.* (1985), Kuznetsov *et al.* (1994), Kirschner and Panetta (1998), De Pillis and Radunskaya (2003), De Pillis *et al.* (2006), Eladdadi *et al.* (2018), delay differential equations are studied by Villasana and Radunskaya (2003), Gałach (2003), Banerjee and Sarkar (2008) and fractional order differential equations are investigated by Podlubny (1999), Rihan *et al.* (2016), Ucar *et al.* (2019) that can help to improve our understanding on the dynamics of this biological phenomenon. Kar and Panda (2016) studied the post-buckling behaviour of functionally graded curved shell panels of different shell geometries (spherical, elliptical, cylindrical and hyperbolic) are investigated under the uniaxial and the biaxial edge compression. The inhomogeneity of the functionally graded material along the thickness direction is achieved using power-law distribution through Voigt's micromechanical model to obtain the effective material properties. Most of the models consist of two main populations, tumor and effector cells, the first one is hunting predator (cytotoxic T lymphocytes) and the later is resting predator cells (T-Helper cells) which are main disturbance of immune system. Cytotoxic T lymphocytes (CTLs) are responsible to kill the tumor cells and resting predator cells, account for the activity of native cytotoxic T lymphocytes. Katariya and Panda (2020) evaluated the computational post-buckling strength of the tilted sandwich composite shell structure. The computational responses are obtained using a mathematical model derived using the higher-order type of polynomial kinematic in association with the through-thickness stretching effect. Duan *et al.* (2019) studied the stability of tumor-immune responses to chemotherapy system. In this system, there are several steady states. In order to explore the stability of these steady states, the upper Lyapunov exponents of linearized system in these steady states are computed by means of second-order algorithm for stochastic simulation Gaussian white noises. The results show that, one steady state is globally asymptotical stable if and only if the noises are weak, but another steady state is always unstable whether the noise is strong or weak. Moreover, the trajectory of system evolution initiating from anywhere is simulated by same algorithm, which proves preceding conclusions and exhibits the globally asymptotical stable steady state is a sink when noises are weak. Katariya and Panda (2020) investigated a general mathematical model for laminated curved structure of different geometries using higher-order shear deformation theory to evaluate in-plane and out of plane shear stress and strains correctly. Subsequently, the model has to be validated by comparing the responses with developed simulation model (ANSYS) as well as available published literature. Duan *et al.* (2019) investigated the influence of Gaussian colored noises on the stability of tumor-immune responses to chemotherapy system. By means of the unified colored noise approximation of multidimensional stochastic dynamic system, the system is changed into the stochastic system with Gaussian white noises. I derive the analytic formula of the maximum Lyapunov exponent of system as a function of intensities and correlation times of Gaussian colored noises, then I find the noise-enhanced stability phenomenon, which is detected by the maximum Lyapunov exponent. Moreover, the correlation time τ_1 of $\xi_1(t)$ influences the stability of steady state becomes unstable if $\tau_1 \to 0.15$, which also increases as the correlation time τ_2 of $\xi_2(t)$ increases. Katariya and Panda (2020) studied the computational post-buckling strength of the tilted sandwich composite shell structure is evaluated. The computational responses are obtained using a mathematical model derived using the higher-order type of polynomial kinematic in association with the through-thickness stretching effect.

In order to describe tumor and effector cells interaction, many researchers have used different parameters such as vaccine (Marincola *et al.* 1995), drug concentrations (Arafa *et al.* 2013), therapies (Itik *et al.* 2009), Lotka-Volterra terms (Elsadany and Matouk 2015), logistic terms (Abbas *et al.* 2011) and many more like these to treat this hazard disease and they also have investigated the various dynamical properties such as stability analysis, bifurcation and chaos control (Huang *et al.* 2016, Wen 2005, Ahmed *et al.* 2007, Wen *et al.* 2008, Din 2017, Din and Ishaque 2020). Kar *et al.* (2016) explored the buckling responses of functionally graded curved (spherical, cylindrical, hyperbolic and elliptical) shell panels under elevated temperature load are investigated numerically using finite element steps. The effective material properties of the functionally graded shell panel are evaluated using Voigt's micromechanical model through the power-law distribution with and without temperature dependent properties. Now a days, fractional order differential equations is an active area of research. As the theory of fractional order differential equations is not fully developed yet but it has a wide range of applications that are used in many scientific fields such as population dynamics (Matouk and Elsadany 2016), fluid mechanics (Tarasov 2008, Thamareerat *et al.* 2017), mechanics (Laskin 2002, Gorenflo and Mainardi 1997), physics (Yuste *et al.* 2004, Hilfer 2000), chemistry (Oldham 2010), finance (Chen 2008), epidemiology (Arenas *et al.* 2016, Ahmed *et al.* 2012, González-Parra *et al.* 2014), medicine (Rutter and Kuang 2017) and engineering (El-Sayed *et al.* 2016, Tenreiro Machado *et al.* 2010). Recently some researcher used different methods for nonlinear modeling (Avcar 2019, Karami *et al.* 2017, 2018, Madani *et al.* 2016, Simsek, 2011). Panda and Katariya (2015) studied the free vibration and the buckling (mechanical and/or thermal) behaviour of laminated composite flat and curved panels. Simulation model has been developed using ANSYS Parametric design language code in the ANSYS environment. Katariya *et al.* (2017) reported the thermal buckling strength of the sandwich shell panel structure and subsequent improvement of the same by embedding shape memory alloy (SMA) fibre via a general higher-order mathematical model in conjunction with finite element method.

Researchers have shown that many population models that are established in the form of fractional-order differential equations give better results than those which are in the form of classical integer-order (Monje *et al.* 2010, Jun *et al.* 2014, Matouk *et al.* 2015, Zhang *et al.* 2016). Also, many biological phenomena such as system memory and hereditary characteristics can be defined by means of these equations, therefore the fractional-order systems give us the information not only about the current state of the system but also about its past (evolutionary) state.

2. Theoretical formation

In Kirschner and Panetta (1998) author proposed a mathematical model which is in the form of ordinary differential equations constituted as the effector cells (E), tumor cells (T) and the cytokine (IL-2).

$$\begin{cases} \dfrac{dE}{dt} & = cT - \mu_2 E + \dfrac{p_1 E I_l}{g_1 + I_l} + s_1, \\ \dfrac{dT}{dt} & = r_2(T)T - \dfrac{aET}{g_2 + T}, \\ \dfrac{dI_L}{dt} & = \dfrac{p_2 ET}{g_3 + T} - \mu_3 I_l + s_2 \end{cases} \tag{1}$$

with initial conditions

$$\{E(0) = E_0, \qquad T(0) = T_0, \qquad I_L(0) = I_{L_0}. \tag{2}$$

In order to obtain efficient computational results, we are interchanging Eq. (1) into fractional ordered by using caputo fractional ordered derivative which is defined as

$$D^{\alpha} f(t) = I^{m-\alpha} f^{m}(t), \alpha > 0, \tag{3}$$

when m is the positive integer satisfying $m \geq \alpha$, and I^{θ} represents fractional integral operator of ordered θ that are defined by

$$I^{\theta} g(t) = \frac{1}{\Gamma(\theta)} \int_0^t (t-s)^{\theta-1} g(s) ds, \quad \theta > 0, \tag{4}$$

where $\Gamma(\cdot)$ represents Euler's Gamma function. Moreover, the fractional order counter part of Eq. (1) is stated as

$$\begin{cases} \dfrac{d^{\alpha}E}{dt^{\alpha}} & = cT - \mu_2 E + \dfrac{p_1 E I_l}{g_1 + I_l} + s_1, \\ \dfrac{d^{\alpha}T}{dt^{\alpha}} & = r_2(T)T - \dfrac{aET}{g_2 + T}, \\ \dfrac{d^{\alpha}I_L}{dt^{\alpha}} & = \dfrac{p_2 ET}{g_3 + T} - \mu_3 I_l + s_2, \end{cases} \tag{5}$$

with initial conditions

$$\{E(0) = E_0, \qquad T(0) = T_0, \qquad I_L(0) = I_{L_0}. \tag{6}$$

Where $0 < \alpha \leq 1$, $\frac{d^{\alpha}}{dt^{\alpha}}$ is in the sense of Caputo fractional derivative is defined in Eq. (3) The model in Eq. (5) consist of three set of fractional order differential equations, first one is used to represent the rate of change for the effector-cell population. The First term in the equation is for recruitment due to the direct presence of tumor. The parameter c exhibits the immunogenicity of tumor which is the ability of a particular substance to stimulate an immune response in the body. The term 3 is a proliferation term, also known as Michaelis-Menten form in which effector cells are stimulated by glycoprotein (IL-2). Eventually, s_1 is the treatment term that represents an external source of LAK cells is a white blood cells that has used to kill the tumor cells. The second equation describes rate of change of the tumor cells, constituted by logistic growth function which has been chosen as

$$\{r_2(T) = r_2(1 - bT) \tag{7}$$

Michaelis-Menten Kinetics modeled the second term that represents the limited immune response for tumor DeLisi and Rescigno (1977) in which the rate constant a shows the strength of the immune response. Finally, third equation gives the rate of change for concentration of interleukin-2 (IL-2) a type of protein that regulates the activity of white blood cells that provides strength to the immune system. The main resources of interleukin-2 are activated $CD4^{+}$ T cells and activated $\mathrm{CD8}^{+}$ T cells (Liao 2011). The next term μ_3 gives the loss rate of IL-2. Finally, s_2 is a treatment term constitute an external input of IL-2 into the system.

For the complete development in Eqs. (5)-(7), we must choose values of parameters which are most appropriate for the model and for initial conditions. As the terms in our model Eq. (5) are analogous with the terms of first two equations of the models (De Boer *et al.* 1985) and (Kuznetsov 1994). In model Eq. (5) values of the treatment terms s_1 and s_2 were first defined where no previous study was done. We choose the most appropriate and short range values for this model Eq. (5) and explore these numerical values in the bifurcation analysis in next section. For mathematical analysis, one can non-dimensionalize the above system to reduce the number of parameters by using the following transformations

$$\begin{array}{llll} x = \dfrac{E}{E_0}, & y = \dfrac{T}{T_0}, & z = \dfrac{I_l}{I_{L_0}}, & \\ \tau = t_s t, & \overline{c} = \dfrac{cT_0}{t_s E_0}, & \overline{p_1} = \dfrac{p_1}{t_s}, & \overline{g_1} = \dfrac{g_1}{I_{L_0}}, \\ \overline{\mu_2} = \dfrac{\mu_2}{t_s}, & \overline{g_2} = \dfrac{g_2}{T_0}, & \overline{b} = bT_0, & \\ \overline{r_2} = \dfrac{r_2}{t_s}, & \overline{a} = \dfrac{aE_0}{t_s T_0}, & \overline{p_1} = \dfrac{p_1}{t_s}, & \overline{\mu_3} = \dfrac{\mu_3}{t_s}, \\ \overline{p_2} = \dfrac{p_2 E_0}{t_s I_{L_0}}, & \overline{g_3} = \dfrac{g_3}{T_0}, & s_1 = \dfrac{s_1}{t_s E_0}, & \overline{s_2} = \dfrac{s_2}{t_s I_{L_0}}. \end{array}$$

Then removing the over bar notation, we obtained the following fractional-order system

$$\begin{cases} \dfrac{d^{\alpha}x}{d\tau^{\alpha}} & = cy - \mu_2 x + \dfrac{p_1 xz}{g_1 + z} + s_1, \\ \dfrac{d^{\alpha}y}{d\tau^{\alpha}} & = r_2 y(1 - by) - \dfrac{axy}{g_2 + y}, \\ \dfrac{d^{\alpha}z}{d\tau^{\alpha}} & = \dfrac{p_2 xy}{g_3 + y} - \mu_3 z + s_2. \end{cases} \tag{8}$$

One possible for scaling is to define: $E_0 = T_0 = I_{L_0} = \frac{1}{b}$ and $t_s = r_2$. These appropriate scaling need to be chosen for solving this system. Latest study shows that discrete dynamical system gives better computational results than related to continuous system Agarwal and Karahanna (2000). Now by the method of discretization Eq. (8), proposed as follows

$$\begin{cases} \frac{d^\alpha x}{d\tau^\alpha} & = cy([\frac{t}{k}]k) - \mu_2 x([\frac{t}{k}]k) + \frac{p_1 x([\frac{t}{k}]k) z([\frac{t}{k}]k)}{g_1 + z([\frac{t}{k}]k)} + s_1, \\ \frac{d^\alpha y}{d\tau^\alpha} & = r_2 y([\frac{t}{k}]k)(1 - by([\frac{t}{k}]k) - \frac{ax([\frac{t}{k}]k) y([\frac{t}{k}]k)}{g_2 + y([\frac{t}{k}]k)}, \\ \frac{d^\alpha z}{d\tau^\alpha} & = \frac{p_2 x([\frac{t}{k}])k y([\frac{t}{k}]k)}{g_3 + y([\frac{t}{k}]k)} - \mu_3 z([\frac{t}{k}]k) + s_2, \end{cases} \tag{9}$$

with initial conditions

$$\{x(0) = x_0 \geq 0, y(0) = y_0 \geq 0, z(0) = z_0 \geq 0 \tag{10}$$

Moreover, suppose $t \in [0, h] \Rightarrow \frac{t}{h} \in [0,1)$ so that system Eq. (9) gives

$$\begin{cases} \frac{d^\alpha x}{d\tau^\alpha} & = cy_0 - \mu_2 x_0 + \frac{p_1 x_0 z_0}{g_1 + z_0} + s_1, \\ \frac{d^\alpha y}{d\tau^\alpha} & = r_2 y_0(1 - by_0) - \frac{a x_0 y_0}{g_2 + y_0}, \\ \frac{d^\alpha z}{d\tau^\alpha} & = \frac{p_2 x_0 y_0}{g_3 + y_0} - \mu_3 z_0 + s_2, \end{cases} \tag{11}$$

The solution of Eq. (9) is given by

$$\begin{cases} x_1(t) & = x_0 + I^\alpha[cy_0 - \mu_2 x_0 + \frac{p_1 x_0 z_0}{g_1 + z_0} + s_1], \\ y_1(t) & = y_0 + I^\alpha[r_2 y_0(1 - by_0) - \frac{a x_0 y_0}{g_2 + y_0}], \\ z_1(t) & = z_0 + I^\alpha[\frac{p_2 x_0 y_0}{g_3 + y_0} - \mu_3 z_0 + s_2], \end{cases} \tag{12}$$

where I^α is the Riemann-Liouville integeral operator of order α which is defined in Eq. (4). From Eqs. (4) and (12), it takes the form

$$\begin{cases} x_1(t) & = x_0 + \frac{t^\alpha}{\Gamma(\alpha+1)}[cy_0 - \mu_2 x_0 + \frac{p_1 x_0 z_0}{g_1 + z_0} + s_1], \\ y_1(t) & = y_0 + \frac{t^\alpha}{\Gamma(\alpha+1)}[r_2 y_0(1 - by_0) - \frac{a x_0 y_0}{g_2 + y_0}], \\ z_1(t) & = z_0 + \frac{t^\alpha}{\Gamma(\alpha+1)}[\frac{p_2 x_0 y_0}{g_3 + y_0} - \mu_3 z_0 + s_2], \end{cases} \tag{13}$$

Likewise, $t \in [k, 2k) \Rightarrow t/k \in [1,2)$, we found

$$\begin{cases} \frac{d^\alpha x}{d\tau^\alpha} & = cy_1 - \mu_2 x_1 + \frac{p_1 x_1 z_1}{g_1 + z_1} + s_1, \\ \frac{d^\alpha y}{d\tau^\alpha} & = r_2 y_1(1 - by_1) - \frac{a x_1 y_1}{g_2 + y_1}, \\ \frac{d^\alpha z}{d\tau^\alpha} & = \frac{p_2 x_1 y_1}{g_3 + y_1} - \mu_3 z_1 + s_2, \end{cases} \tag{14}$$

The solution of Eq. (14) is given by

$$\begin{aligned} x_2(t) &= x_1(k) + \frac{(t-k)^\alpha}{\Gamma(\alpha+1)} \begin{bmatrix} cy_1(k) - \mu_2 x_1(k) \\ + \frac{p_1 x_1(k) z_1(k)}{g_1 + z_1(k)} + s_1 \end{bmatrix} \\ y_2(t) &= y_1(k) + \frac{(t-k)^\alpha}{\Gamma(\alpha+1)} \begin{bmatrix} r_2 y_1(k)\big(1 - by_1(k)\big) \\ - \frac{a x_1(k) y_1(k)}{g_2 + y_1(k)} \end{bmatrix} \\ z_2(t) &= z_1(k) + \frac{(t-k)^\alpha}{\Gamma(\alpha+1)} \begin{bmatrix} \frac{p_2 x_1(k) y_1(k)}{g_3 + y_1(k)} \\ -\mu_3 z_1(k) + s_2 \end{bmatrix} \end{aligned} \tag{15}$$

Continuing in this way for n number of iterations, one can find solution of Eq. (15) for $t \in [nk, (n+1)k)$ as follows

$$\begin{cases} x_{n+1}(t) & = x_n(nk) + \frac{(t-nk)^\alpha}{\Gamma(\alpha+1)}[cy_n(nk) - \mu_2 x_n(nk) + \frac{p_1 x_n(nk) z_n(nk)}{g_1 + z_n(nk)} + s_1], \\ y_{n+1}(t) & = y_n(nk) + \frac{(t-nk)^\alpha}{\Gamma(\alpha+1)}[r_2 y_n(nk)(1 - by_n(nk)) - \frac{a x_n(nk) y_n(nk)}{g_2 + y_n(nk)}], \\ z_{n+1}(t) & = z_n(nk) + \frac{(t-nk)^\alpha}{\Gamma(\alpha+1)}[\frac{p_2 x_n(nk) y_n(nk)}{g_3 + y_n(nk)} - \mu_3 z_n(nk) + s_2]. \end{cases} \tag{16}$$

Next, considering $t \longrightarrow (n+1)h$ and taking into account the notation of difference equations, system Eq. (16) takes the following form

$$\begin{cases} x_{n+1} & = x_n + \dfrac{k^\alpha}{\Gamma(\alpha+1)}[cy_n - \mu_2 x_n + \dfrac{p_1 x_n z_n}{g_1 + z_n} + s_1], \\ y_{n+1} & = y_n + \dfrac{k^\alpha}{\Gamma(\alpha+1)}[r_2 y_n(1 - by_n) - \dfrac{a x_n y_n}{g_2 + y_n}], \\ z_{n+1} & = z_n + \dfrac{k^\alpha}{\Gamma(\alpha+1)}[\dfrac{p_2 x_n y_n}{g_3 + y_n} - \mu_3 z_n + s_2], \end{cases} \tag{17}$$

with initial conditions

$$\begin{cases} x(0) = x_0 \geq 0, \quad y(0) = y_0 \geq 0, \\ z(0) = z_0 \geq 0 \end{cases} \tag{18}$$

The key findings of this article are summarized as follows:

- Taking into account the above system Eq. (17) is a good representative of tumor immune interaction, and here we discuss the stability of positive equilibrium points.
- Fluctuating behavior is observed in system Eq. (17) with the variation in source term parameter and the discretization parameter. Therefore, g_1 and k is taken as bifurcation parameter in order to study Neimark-Sacker bifurcation and period doubling bifurcation in system Eq. (17). Furthermore, the first Lyapunov exponent is calculated in closed form in order to discuss direction of Neimark-Sacker bifurcation and period doubling bifurcation.

In the forthcoming investigation, we explore existence of positive steady-state for system Eq. (17) and taking into account the method of linearisation, local dynamics for system Eq. (17) is carried out. Furthermore, normal forms theory of bifurcation is implemented for the investigation related to existence and direction of Neimark-Sacker bifurcation at positive fixed point of system Eq. (17).

3. Methodology

In this section, first we investigate existence of equilibria for system Eq. (17). For this, any equilibrium of model Eq. (17) solves the following algebraic system

$$\begin{cases} cy - \mu_2 x + \dfrac{p_1 xz}{g_1 + z} + s_1 = 0, \\ r_2 y(1 - by) - \dfrac{axy}{g_2 + y} = 0, \\ \dfrac{p_2 xy}{g_3 + y} - \mu_3 z + s_2 = 0. \end{cases} \tag{19}$$

Then, it is easy to see that system Eq. (19) has following solutions

$$E_1 = \left(0,0,\frac{s_2}{\mu_3}\right), \quad E_2 = \left(0,\frac{1}{b},\frac{s_2}{\mu_3}\right),$$
$$\text{and} \quad E_3 = \left(\frac{s_1(\mu_3 g_1 + s_2)}{\mu_2\mu_3 g_1 + s_2(\mu_2 - p_1)},0,\frac{s_2}{\mu_3}\right).$$

Consequently, E_1, E_2 and E_3 are three biologically feasible boundary equilibrium points of system Eq. (17). Beside these three boundary equilibria, system Eq. (17) also has some interior equilibrium. This interior equilibrium cannot be found in closed form. Furthermore, the interior equilibrium point for system Eq. (17) may not be unique. In our case, we are interested in unique positive equilibrium point of system Eq. (17) due to biological relevance. Assume that $P = (x^*, y^*, z^*)$ an interior equilibrium point of system Eq. (17), then it follows that

$$\begin{aligned} x^* &= \frac{r_2}{a}(g_2 + y^*)(1 - by^*), \\ z^* &= \frac{1}{a\mu_3(g_3 + y^*)}\left(\begin{array}{c} -p_2 r_2 b y^{*3} \\ +(p_2 r_2 - p_2 r_2 - p_2 r_2 g_2 b)y^{*2} \end{array}\right) \\ &\quad + \frac{1}{a\mu_3(g_3 + y^*)}(y^*(p_2 r_2 g_2 + s_2 a) + s_2 a g_3), \end{aligned}$$

where y^* is one of the real root of the following quintic polynomial

$$A_1 y^{*5} + A_2 y^{*4} + A_3 y^{*3} + A_4 y^{*2} + A_5 y^* + A_6 = 0,$$

where

$$A_1 = p_2 r_2^2 b^2 p_1 - \mu_2 r_2^2 p_2 b^2,$$

$$\begin{aligned} A_2 = {} & -p_2 c b r_2 a - 2p_2 g_2 \mu_2 r_2^2 b^2 + 2p_2 r_2^2 b \mu_2 \\ & +2p_2 r_2^2 b^2 g_2 p_1 - 2p_2 r_2^2 b p_1, \end{aligned}$$

$$\begin{aligned} A_3 = {} & a p_2 c r_2 - a p_2 c r_2 g_2 b + a r_2 \mu_2 g_1^2 \mu_3 b - p_2 r_2^2 b^2 g_2^2 \mu_2 \\ & +4p_2 r_2^2 b g_2 \mu_2 - p_2 r_2^2 \mu_2 + s_2 a b r_2 \mu_2 + p_2 r_2^2 b^2 g_2^2 p_1 \\ & -4p_2 r_2^2 g_2 b p_1 + p_2 r_2^2 p_1 - s_2 a b p_1 r_2, \end{aligned}$$

$$\begin{aligned} A_4 = {} & c g_1 \mu_3 a^2 + a p_2 c r_2 g_2 + s_2 c a^2 - a r_2 \mu_2 \mu_3 g_1 \\ & -a r_2 \mu_2 \mu_3 g_1 g_3 b + a r_2 \mu_2 \mu_3 g_1 g_2 b - 2p_2 r_2^2 g_2 \mu_2 \\ & +2p_2 r_2^2 b g_2^2 \mu_2 + s_2 a g_2 b r_2 \mu_2 + s_2 a g_3 b r_2 \mu_2 \\ & -s_2 a \mu_2 r_2 + 2p_2 r_2^2 g_2 p_1 - 2p_2 r_2^2 g_2^2 b p_1 - s_2 a g_2 b p_1 r_2 \\ & +s_2 a p_1 r_2 + p_2 r_2 s_1 a - p_2 r_2 g_2 b s_1 a \end{aligned}$$

$$\begin{aligned} A_5 = {} & c g_1 a^2 \mu_3 g_3 + s_2 c a_2^2 g_3 - a r_2 \mu_2 \mu_3 g_1 g_3 \\ & +a r_2 \mu_2 \mu_3 g_1 g_2 g_3 b - a r_2 \mu_2 \mu_3 g_1 g_2 - g_2^2 p_2 r_2^2 \mu_2 \\ & -s_2 a g_2 \mu_2 r_2 + s_2 a g_3 g_2 b \mu_2 r_2 - s_2 a g_3 r_2 \mu_2 \\ & +g_2^2 p_2 r_2^2 p_1 + s_2 a r_2 g_2 p_1 - s_2 a g_2 g_3 b p_1 r_2 \\ & +s_2 a g_3 p_1 r_2 + s_1 a p_2 r_2 g_2 + s_2 a^2 s_1 + s_1 g_1 a^2 \mu_3 \end{aligned}$$

and

$$\begin{aligned} A_6 = {} & -a r_2 \mu_2 \mu_3 g_1 g_2 g_3 - s_2 a g_3 g_2 p_1 r_2 \\ & +s_1 s_2 a^2 g_3 + s_1 a^2 \mu_3 g_1. \end{aligned}$$

The existence of unique positive fixed point of system Eq. (17) as shown in Fig. 1. Moreover, in Fig. 1, red, brown and green portions represent first, second and third equations of system Eq. (17), respectively. Consequently, intersection of three planes clearly depicted in Fig. 1.

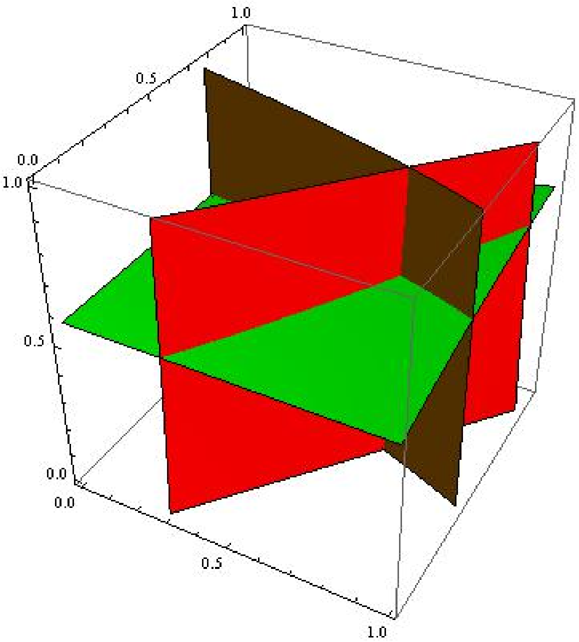


Fig. 1 Existence of unique positive fixed point of system Eq. (17) in xyz-space

Next, we discuss local stability analysis for fixed points of system Eq. (17). For this, first we consider three boundary equilibria E_1, E_2 and E_3. The following results examined the dynamics of system Eq. (17) about these three fixed points.

Theorem 2.1 The following results hold true for equilibria E_1, E_2 and E_3 of system Eq. (17).

(i) Equilibrium point E_1 is unstable.

(ii) Equilibrium E_2 is a sink if and only if the following conditions are satisfied

$$\frac{\mathrm{k}^{\alpha}\mu_3}{\Gamma(\alpha+1)} < 2, \qquad \mathrm{p}_1\mathrm{s}_2 < \mu_2(\mathrm{s}_2+\mathrm{g}_1\mu_3),$$
$$\frac{\mathrm{k}^{\alpha}\mu_2}{\Gamma(\alpha+1)} - 2 < \frac{\mathrm{k}^{\alpha}\mathrm{p}_1\mathrm{s}_2}{\Gamma(\alpha+1)(\mathrm{s}_2+\mathrm{s}_1\mu_3)} < \frac{\mathrm{k}^{\alpha}\mu_2}{\Gamma(\alpha+1)},$$

and

$$\frac{as_1(s_2+g_1\mu_3)}{g_2(\mu_2(s_2+g_1\mu_3)-p_1s_2)} - 2 < \frac{k^{\alpha}r_2}{\Gamma(\alpha+1)} < \frac{as_1(s_2+g_1\mu_3)}{g_2(\mu_2(s_2+g_1\mu_3)-p_1s_2)}.$$

(iii) Equilibrium point E_3 is a sink if and only if the following conditions are satisfied

$$\frac{\mu_3k^{\alpha}}{\Gamma(\alpha+1)} < 2,$$

and

$$|A| < 1 + B < 2,$$

where

$$A = -\frac{k^{\alpha}\big(p_1s_2-(\mu_2+r_2)(g_1\mu_3+s_2)\big)}{\Gamma(\alpha+1)(g_1\mu_3+s_2)} - 2,$$

and

$$B = \frac{k^{2\alpha}\begin{pmatrix} s_2\big(ac+r_2(bg_2+1)(\mu_2-p_1)\big) \\ +g_1\mu_3\big(ac+\mu_2r_2(bg_2+1)\big) \end{pmatrix}}{\Gamma(\alpha+1)^2(bg_2+1)(g_1\mu_3+s_2)} + 1 + \frac{k^{\alpha}\big(p_1s_2-(\mu_2+r_2)(g_1\mu_3+s_2)\big)}{\Gamma(\alpha+1)(g_1\mu_3+s_2)}.$$

Proof. (i) First, we see that Jacobian matrix of system Eq. (17) at equilibrium E_1 is computed as follows

$$J(E_1) = \begin{pmatrix} \frac{k^{\alpha}\left(\frac{p_1s_2}{s_2+g_1\mu_3}-\mu_2\right)}{\Gamma(\alpha+1)} & \frac{ck^{\alpha}}{\Gamma(\alpha+1)} & 0 \\ 0 & \frac{r_2k^{\alpha}}{\Gamma(\alpha+1)}+1 & 0 \\ 0 & 0 & 1-\frac{k^{\alpha}\mu_3}{\Gamma(\alpha+1)} \end{pmatrix}$$

Obviously, eigenvalues of $J(E_1)$ are $\lambda_1 = 1 + \frac{k^{\alpha}r_2}{\Gamma(1+\alpha)} > 1$, $\lambda_2 = 1 - \frac{k^{\alpha}\mu_3}{\Gamma(1+\alpha)}$ and $\lambda_3 = \frac{k^{\alpha}\left(-\mu_2+\frac{p_1s_2}{s_2+g_1\mu_3}\right)}{\Gamma(1+\alpha)}$. Hence, E_1 is unstable. (ii) Similarly, Jacobian matrix of system Eq. (17) at equilibrium E_2 is computed as follows

$$J(E_2) = \begin{pmatrix} a_{11} & \frac{ck^{\alpha}}{\Gamma(\alpha+1)} & a_{13} \\ 0 & \frac{\left(r_2+\frac{as_1(s_2+g_1\mu_3)}{g_2(p_1s_2-\mu_2(s_2+g_1\mu_3))}\right)k^{\alpha}}{\Gamma(\alpha+1)}+1 & 0 \\ 0 & \frac{k^{\alpha}p_2s_1(s_2+g_1\mu_3)}{\Gamma(\alpha+1)g_3(\mu_2(s_2+g_1\mu_3)-p_1s_2)} & 1-\frac{k^{\alpha}\mu_3}{\Gamma(\alpha+1)} \end{pmatrix}$$

where

$$a_{11} = \frac{\left(\frac{p_1s_2}{s_2+g_1\mu_3}-\mu_2\right)k^{\alpha}}{\Gamma(\alpha+1)} + 1,$$

and

$$a_{13} = \frac{k^{\alpha}g_1p_1s_1\mu_3^2}{\Gamma(\alpha+1)(s_2+g_1\mu_3)(\mu_2(s_2+g_1\mu_3)-p_1s_2)}.$$

Due to some simple computation, it follows that $\lambda_1 = 1 - \frac{\mu_3k^{\alpha}}{\Gamma(\alpha+1)}$, $\lambda_2 = \frac{k^{\alpha}\left(\frac{p_1s_2}{g_1\mu_3+s_2}-\mu_2\right)}{\Gamma(\alpha+1)} + 1$ and $\lambda_3 = \frac{k^{\alpha}\left(\frac{as_1(g_1\mu_3+s_2)}{g_2(p_1s_2-\mu_2(g_1\mu_3+s_2))}+r_2\right)}{\Gamma(\alpha+1)} + 1$ are eigenvalues of $J(E_2)$.

Assume that $p_1 s_2 < \mu_2(s_2 + g_1\mu_3)$, then each λ_i for all $i = 1,2,3$ lies inside the open unit disk if and only if the following inequalities hold true

$$\frac{k^\alpha \mu_3}{\Gamma(\alpha+1)} < 2,$$

$$\frac{k^\alpha \mu_2}{\Gamma(\alpha+1)} - 2 < \frac{k^\alpha p_1 s_2}{\Gamma(\alpha+1)(s_2 + s_1\mu_3)} < \frac{k^\alpha \mu_2}{\Gamma(\alpha+1)},$$

and

$$\frac{a s_1(s_2 + g_1\mu_3)}{g_2(\mu_2(s_2 + g_1\mu_3) - p_1 s_2)} - 2 < \frac{k^\alpha r_2}{\Gamma(\alpha+1)} < \frac{a s_1(s_2 + g_1\mu_3)}{g_2(\mu_2(s_2 + g_1\mu_3) - p_1 s_2)}.$$

(iii) Finally, we see that Jacobian matrix of system Eq. (17) at equilibrium E_3 is computed as follows

$$J(E_3) = \begin{pmatrix} \frac{\left(\frac{p_1 s_2}{s_2 + g_1\mu_3} - \mu_2\right)k^\alpha}{\Gamma(\alpha+1)} + 1 & \frac{c k^\alpha}{\Gamma(\alpha+1)} & 0 \\ -\frac{a k^\alpha}{b g_2 \Gamma(\alpha+1) + \Gamma(\alpha+1)} & 1 - \frac{k^\alpha r_2}{\Gamma(\alpha+1)} & 0 \\ \frac{k^\alpha p_2}{b g_3 \Gamma(\alpha+1) + \Gamma(\alpha+1)} & 0 & 1 - \frac{k^\alpha \mu_3}{\Gamma(\alpha+1)} \end{pmatrix}$$

Furthermore, the characteristic polynomial of $J(E_3)$ is given by

$$P(\lambda) = \left(\lambda - 1 + \frac{k^\alpha \mu_3}{\Gamma(\alpha+1)}\right)(\lambda^2 + A\lambda + B), \qquad (20)$$

where

$$A = -\frac{k^\alpha\big(p_1 s_2 - (\mu_2 + r_2)(g_1\mu_3 + s_2)\big)}{\Gamma(\alpha+1)(g_1\mu_3 + s_2)} - 2,$$

and

$$B = \frac{k^{2\alpha}\begin{pmatrix} s_2\big(ac + r_2(b g_2 + 1)(\mu_2 - p_1)\big) \\ + g_1\mu_3\big(ac + \mu_2 r_2(b g_2 + 1)\big) \end{pmatrix}}{\Gamma(\alpha+1)^2(b g_2 + 1)(g_1\mu_3 + s_2)} + 1 + \frac{k^\alpha\big(p_1 s_2 - (\mu_2 + r_2)(g_1\mu_3 + s_2)\big)}{\Gamma(\alpha+1)(g_1\mu_3 + s_2)}.$$

Then, an application of Jury condition yields that E_3 is a sink if and only if the following conditions are satisfied

$$\frac{\mu_3 k^\alpha}{\Gamma(\alpha+1)} < 2,$$

and

$$|A| < 1 + B < 2.$$

Theorem 2.2 The system Eq. (17) has a unique positive fixed point (x^*, y^*, z^*) is locally asymptotically stable if

$$|\xi_2 + \xi_0| < 1 + \xi_1,$$
$$|\xi_2 - 3\xi_0| < 3 - \xi_1,$$

and

$$\xi_0^2 + \xi_1 - \xi_2\xi_0 < 1.$$

Proof: The jacobian matrix for the system Eq. (17) at a unique and positive equilibrium point (x^*, y^*, z^*) is calculated as

$$J(x^*, y^*, z^*) = \begin{pmatrix} s_{11} & s_{12} & s_{13} \\ s_{21} & s_{22} & s_{23} \\ s_{31} & s_{32} & s_{33} \end{pmatrix}.$$

where

$$s_{11} = \frac{k^\alpha\left(\frac{p_1 z}{g_1 + z} - \mu_2\right)}{\Gamma(\alpha+1)} + 1,$$
$$s_{12} = \frac{c k^\alpha}{\Gamma(\alpha+1)},$$
$$s_{13} = \frac{g_1 p_1 x k^\alpha}{\Gamma(\alpha+1)(g_1 + z)^2},$$
$$s_{21} = -\frac{a y k^\alpha}{\Gamma(\alpha+1)(g_2 + y)},$$
$$s_{22} = \frac{k^\alpha\left(r_2(1 - 2by) - \frac{a g_2 x}{(g_2 + y)^2}\right)}{\Gamma(\alpha+1)} + 1,$$
$$s_{23} = 0,$$
$$s_{31} = \frac{p_2 y k^\alpha}{\Gamma(\alpha+1)(g_3 + y)},$$
$$s_{32} = \frac{g_3 p_2 x k^\alpha}{\Gamma(\alpha+1)(g_3 + y)^2},$$

and

$$s_{33} = 1 - \frac{\mu_3 k^\alpha}{\Gamma(\alpha+1)}.$$

The characteristic equation of the Jacobian matrix at positive steady state (x^*, y^*, z^*) is given by

$$P(T) = T^3 + \beta_2 T^2 + \beta_1 T + \beta_0 = 0,$$

where

$$\begin{cases} \xi_2 = -s_{11} - s_{22} - s_{33}, \\ \xi_1 = s_{11}s_{22} - s_{12}s_{21} - s_{13}s_{31} + s_{11}s_{33} + s_{22}s_{33}, \\ \xi_0 = s_{13}s_{22}s_{31} - s_{13}s_{21}s_{32} + s_{12}s_{21}s_{33} - s_{11}s_{22}s_{33}. \end{cases} \qquad (21)$$

Now applying condition Edelstein-Keshet (2005), the positive steady state is asymptotically stable if the following conditions hold

$$
\begin{gathered}
|\xi_2 + \xi_0| < 1 + \xi_1, \\
|\xi_2 - 3\beta_0| < 3 - \xi_1,
\end{gathered}
$$

and

$$\xi_0^2 + \xi_1 - \xi_2\xi_0 < 1.$$

In order to study the Hopf bifurcation of system Eq. (17) for this an explicit criterion of Hopf bifurcation is stated in

Lemma 2.1 onsider an n-dimension non linear discrete time map: (Wen 2005)

$$M_{l+1} = f_\zeta(M_l),$$

where $M_{l+1}, M_l \in R^n$, are the state vectors, l is the iterative index, and $\zeta \in \mathbb{R}$ represents bifurcation parameter. Let $M^* \in \mathbb{R}^n$ be a fixed point of f_ζ and the characteristic polynomial for the Jacobian matrix $J(M^*) = (a_{ij})_{n\times n}$ of n dimensional map f_ζ is given by

$$P_\zeta(\lambda) = \lambda^n + c_1\lambda^{n-1} + \cdots + c_{n-1}\lambda + c_n, \tag{22}$$

where $c_i = c_i(\zeta, u)$, $i = 1, 2, \cdots, n$. Consider a series of determinants: $(\tau_i^\pm(\zeta, u))_{i=0}^n$ $\tau_0^\pm(\zeta, u) = 1$ defined as follows

$$\tau_i^\pm(\zeta, u) = \det(M_1 \pm M_2), \tag{23}$$

where

$$
\begin{gathered}
M_1 = \begin{bmatrix} 1 & c_1 & c_2 & \cdots & c_{i-1} \\ 0 & 1 & c_1 & \cdots & c_{i-2} \\ 0 & 0 & 1 & \cdots & c_{i-3} \\ \cdots & \cdots & \cdots & \cdots & \cdots \\ 0 & 0 & 0 & \cdots & 1 \end{bmatrix}, \\
M_2 = \begin{bmatrix} c_{n-i+1} & c_{n-i+2} & \cdots & c_{n-1} & c_n \\ c_{n-i+2} & c_{n-i+3} & \cdots & c_n & 0 \\ \cdots & \cdots & \cdots & \cdots & \cdots \\ c_{n-1} & c_n & \cdots & 0 & 0 \\ c_n & 0 & \cdots & 0 & 0 \end{bmatrix}.
\end{gathered}
\tag{24}
$$

Furthermore, if the following condition are satisfied

- $(C1)$ Eigenvalue assignment: $\tau_{n-1}^-(\zeta_0, u) = 0, \tau_{n-1}^+(\zeta_0, u) > 0, P_{\zeta_0}(1) > 0, (-1)^n P_{\zeta_0}(-1) > 0, \tau_i^\pm(\zeta_0, u) > 0.$ for $i = n-3,\ n-5,\ \cdots$, 2(or 1), when n is odd (or even, respectively).
- $(C2)$ Transversality condition: $\left(\frac{d}{d\zeta}(\tau_{n-1}^-(\zeta, u))\right)_{\zeta=\zeta_0} \neq 0.$
- $(C3)$ Non-resonance condition: $\cos\left(\frac{2\pi}{l}\right) \neq \varphi$, or resonance condition $\cos\left(\frac{2\pi}{r}\right) = \varphi$. where, $r = 3,4,5,\cdots$, and $\varphi = 1 - 0.5P_{\zeta_0}(1)\tau_{n-3}^-(\zeta_0, u)/\tau_{n-2}^+(\zeta_0, u)$. then Neimark-Sacker bifurcation occurs at critical value ζ_0.

The above axioms indicates that system Eq. (17) undergoes Neimark-Sacker bifurcations for $n = 3$ when k is taken as bifurcation parameter.

Lemma 2.2 The unique positive equilibrium point $(\mathrm{x}^*, \mathrm{y}^*, \mathrm{z}^*)$ of system Eq. (17) undergoes Neimark-Sacker bifurcation at $k = k_0$ if the following conditions hold

$$
\begin{gathered}
1 - \xi_1 + \xi_0(\xi_2 - \xi_0) = 0, \\
1 + \xi_1 - \xi_0(\xi_2 + \xi_0) > 0, \\
1 + \xi_2 + \xi_1 + \xi_0 > 0, \\
1 - \xi_2 + \xi_1 - \xi_0 > 0, \\
\frac{d}{dk}(1 - \xi_1 + \xi_0(\xi_2 - \xi_0))_{k=k_0} \neq o,
\end{gathered}
$$

and

$$\cos\left(\frac{2\pi}{r}\right) \neq 1 - \frac{1 + \xi_2 + \xi_1 + \xi_0}{2(1 + \xi_0)}\ r = 3,4,5,\cdots,$$

where ξ_2, ξ_1 and ξ_0 are given in Eq. (21), and k_0 be any possible real root of

$$1 - \xi_1(k) + \xi_0(k)(\xi_2(k) - \xi_0(k)) = 0.$$

Proof: Taking $n = 3$ and k as bifurcation parameter, then it follows from Lemma Eq. (21) such that

$$
\begin{aligned}
&\tau_2^-(k) = 1 - \xi_1 + \xi_0(\xi_2 - \xi_0) = 0, \\
&\tau_2^+(k) = 1 + \xi_1 - \xi_0(\xi_2 + \xi_0) > 0, \\
&P_k(1) = 1 + \xi_2 + \xi_1 + \xi_0 > 0, \\
&(-1)^3 P_k(-1) = 1 - \xi_2 + \xi_1 - \xi_0 > 0, \\
&\left(\frac{d}{dk}(\tau_2^-(k))\right)_{k=k_0} = \frac{d}{dk}(1 - \xi_1 + \xi_0(\xi_2 - \xi_0))_{k=k_0} \neq o,
\end{aligned}
$$

and

$$-0.5P_k(1)\tau_0^-(k)/\tau_1^+(k) = 1 - \frac{1 + \xi_2 + \xi_1 + \xi_0}{2(1 + \xi_0)}.$$

In this section, we studied an explicit criterion of flip bifurcation under which the unique positive steady state of system Eq. (17) undergoes period doubling bifurcation without finding the eigenvalues for system Eq. (17) it is stated as:

Lemma 2.3 Consider a general n-dimensional map (Wen *et al.* 2008)

$$\mathrm{X}_{\mathrm{l}+1} = \mathrm{f}_\mathrm{v}(\mathrm{X}_\mathrm{k})$$

where $X_{l+1}, X_l \in R^n$, are the state vectors, l is the iterative index, and $\nu \in \mathbb{R}$ represents bifurcation parameter with same conditions Eqs. (22), (23) and (24) as discussed in above Lemma. Moreover, if the following axioms are fulfilled:

- $(H1)$ Eigenvalues assignment: $P_{\nu_o}(-1) = 0,\ \tau_{n-1}^\pm(\nu_o, u) > 0, P_{\nu_o}(1) > 0, \tau_i^\pm(\nu_o, u) > 0.$ $i = n-2,\ n-4, \cdots$, 1(or 2), when n is even (or odd, respectively).
- $(H2)$ Transversality condition:

$\frac{\sum_{i=1}^{n}(-1)^{n-i}a'_i}{\sum_{i=1}^{n}(-1)^{n-i}(n-i+1)a_{i-1}}v_o$, where a'_i denotes derivative of $a(v)$ at $v = v_o$, then period-doubling bifurcation occurs at critical value v_o.

The following Lemma provides the parametric conditions under which the system Eq. (17) undergoes flip bifurcation for $n = 3$ and when g_1 is taken as a bifurcation parameter.

Lemma 2.4 The system Eq. (17) has a unique positive equilibrium point (x^*, y^*, z^*) undergoes flip bifurcation at $g_1 = g_0$ if

$$\begin{aligned}
&1 - \xi_1 + \xi_0(\xi_2 - \xi_0) > 0,\\
&1 + \xi_1 - \xi_0(\xi_2 + \xi_0) > 0,\\
&1 + \xi_2 + \xi_1 + \xi_0 > 0,\\
&1 - \xi_2 + \xi_1 - \xi_0 = 0,\\
&1 \pm (\xi_0) > 0,
\end{aligned}$$

and

$$\frac{\xi_2' - \xi_1' + \xi_0'}{3 - 2\xi_2 + \xi_1} g_o \neq 0.$$

where ξ_2, ξ_1 and ξ_0 are given in Eq. (21), ξ_i' is derivative of $\xi(g_1)$ at $g_1 = g_0$ and g_0 be any possible real root of

$$1 - \xi_2(g_1) + \xi_1(g_1) - \xi_0(g_1) = 0.$$

4. Results and discussions

Example 3.1 In order to approve our theoretical discussion, first we take $\alpha = 0.9$, $c = 1.6$, $\mu_2 = 0.90$, $p_1 = 0.8$, $g_1 = 1.2$, $s_1 = 1.39$, $r_2 = 1.9$, $b = 0.2$, $a = 0.61$, $g_2 = 2$, $p_2 = 0.4$, $g_3 = 3.5$, $\mu_3 = 1.60$, $s_2 = 0.80$. and $k \in [0.1,1]$ with initial conditions $(x_0, y_0, z_0) = (7.507238394,\ 1.945989670,\ 0.7203886005)$, then system Eq. (17) undergoes Hopf bifurcation at $k = 0.714828$. At $\alpha = 0.9$, $c = 1.6$, $\mu_2 = 0.90$, $p_1 = 0.8$, $g_1 = 1.2$, $s_1 = 1.39$, $r_2 = 1.9$, $b = 0.2$, $a = 0.61$, $g_2 = 2$, $p_2 = 0.4$, $g_3 = 3.5$, $\mu_3 = 1.60$, $s_2 = 0.80$ and $k = 0.714828$, the characteristic polynomial of Eq. (17) is calculated at positive fixed point is given as

$$\lambda^3 - 1.34655\lambda^2 + 0.377755\lambda + 0.363809 = 0. \quad (25)$$

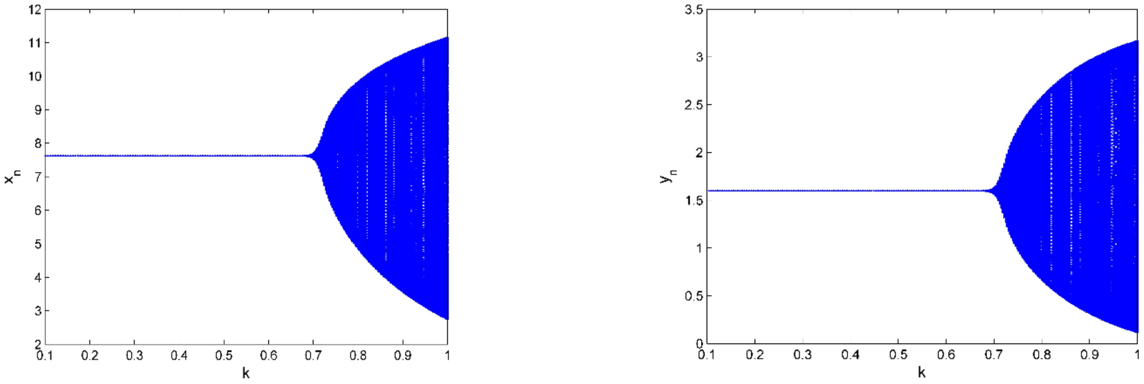
The roots of Eq. (25) are $\lambda_1 = -0.363809$ and $\lambda_{1,2} = 0.85518 \pm 0.518332i$ with $|\lambda_{1,2}| = 1$. Thus, criterion for existence of Hopf bifurcation is satisfied. Next, we verify conditions of Lemma 2.3 as follows

$$\mathbb{D}_2^-(0.714828) = 1 - \beta_1 + \beta_0(\beta_2 - \beta_0) = 0,$$

$$\mathbb{D}_2^+(0.714828) = 1 + \beta_1 - \beta_0(\beta_2 + \beta_0) = 1.73529 > 0,$$

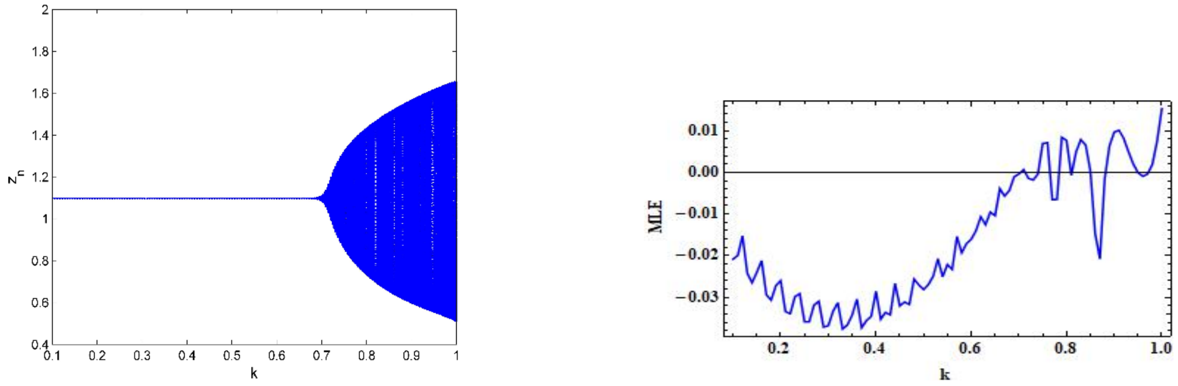
$$P_{0.714828}(1) = 1 + \beta_2 + \beta_1 + \beta_0 = 0.395014 > 0,$$

$$(-1)^3 P_{0.714828}(-1) = 1 - \beta_2 + \beta_1 - \beta_0 = 2.3605 > 0,$$



(a) Bifurcation diagram for x_n

(b) Bifurcation diagram for y_n



(c) Bifurcation diagram for z_n

(d) Maximum Lyapunov exponents

Fig. 2 Bifurcation diagrams and MLE for system Eq. (17) with $\alpha = 0.9$, $c = 1.6$, $\mu_2 = 0.90$, $p_1 = 0.8$, $g_1 = 1.2$, $s_1 = 1.39$, $r_2 = 1.9$, $b = 0.2$, $a = 0.61$, $g_2 = 2$, $p_2 = 0.4$, $g_3 = 3.5$, $\mu_3 = 1.60$, $s_2 = 0.80$. and $k \in [0.1,1]$ with initial conditions $(x_0, y_0, z_0) = (7.507238394,\ 1.945989670,\ 0.7203886005)$

$$\left(\frac{\mathrm{d}}{\mathrm{dh}}(\mathbb{D}_2^-(\mathrm{h}))\right)_{\mathrm{k}=0.714828}$$
$$=\frac{\mathrm{d}}{\mathrm{dh}}\left(1-\beta_1+\beta_0(\beta_2-\beta_0)\right)_{\mathrm{k}=0.714828}$$
$$=-0.639851\neq 0,$$

and

$$1-\frac{0.5\mathrm{P}_{0.714828}(1)\mathbb{D}_0^-(0.714828)}{\mathbb{D}_1^+(0.714828)}$$
$$=1-\frac{1+\beta_2+\beta_1+\beta_0}{2(1+\beta_0)}=0.85518.$$

Solving $\cos\left(\frac{2\pi}{\mathrm{l}}\right)=0.85518$, we have $\mathrm{l}=\pm 11.5309$. Shows that non-resonance condition is satisfied. Bifurcation diagrams and maximum Lyapunov exponents (MLE) are shown in Fig. 2.

Hence, the condition of above lemma 2.3 near the positive equilibrium point $(x^*, y^*, z^*) = (7.507238394, 1.945989670, 0.7203886005)$ are satisfied at critical value of bifurcation parameter, $k = 0.714828$.

Moreover, Fig. 2 shows that all three population undergoes Hopf bifurcation see Figs. 2(a)-(c) and the corresponding maximum Lyapunov exponents $(MLEs)$ are shown in Fig. 2(d).

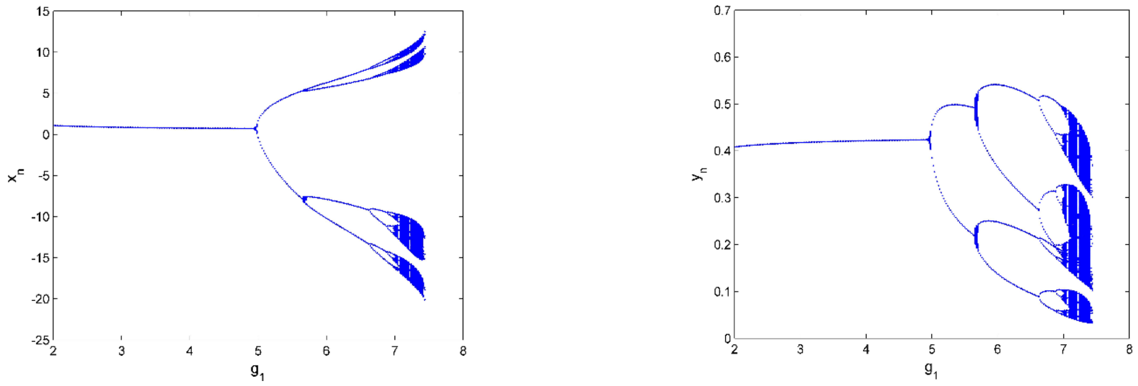
Example 3.2 For period doubling bifurcation, we take $\mathrm{k}=0.4550, \alpha=0.84, \mathrm{c}=1.2,\ \mu_2=4.90,\ \mathrm{p}_1=5.69,\ \mathrm{s}_1=2.01,\ \mathrm{r}_2=1.84,\ \mathrm{b}=2.211,\ \mathrm{a}=0.9,\ \mathrm{g}_2=5.11,\ \mathrm{p}_2=4.9,\ \mathrm{g}_3=2.9,\ \mu_3=1.8,\ \mathrm{s}_2=2.4,$ and $\mathrm{g}_1\in[2,8]$ with initial conditions $(\mathrm{x}_0,\mathrm{y}_0,\mathrm{z}_0)=(1.580743476807648,\ 0.4237874682205479,\ 0.7128186635233262)$, then system Eq. (17) undergoes period doubling bifurcation at $\mathrm{g}_1=4.980043990029326$. At $\mathrm{k}=0.4550,\ \alpha=0.84,\ \mathrm{c}=1.2,\ \mu_2=4.90,\ \mathrm{p}_1=5.69,\ \mathrm{s}_1=2.01,\ \mathrm{r}_2=1.84,\ \mathrm{b}=2.211,\ \mathrm{a}=0.9,\ \mathrm{g}_2=5.11,\ \mathrm{p}_2=4.9,\ \mathrm{g}_3=2.9,\ \mu_3=1.8,\ \mathrm{s}_2=2.4$ and $\mathrm{g}_1=4.980043990029326$, the characteristic polynomial of Eq. (17) is computed as follows

$$\lambda^3+0.856838\lambda^2-0.132479\lambda+0.0106828=0. \quad (26)$$

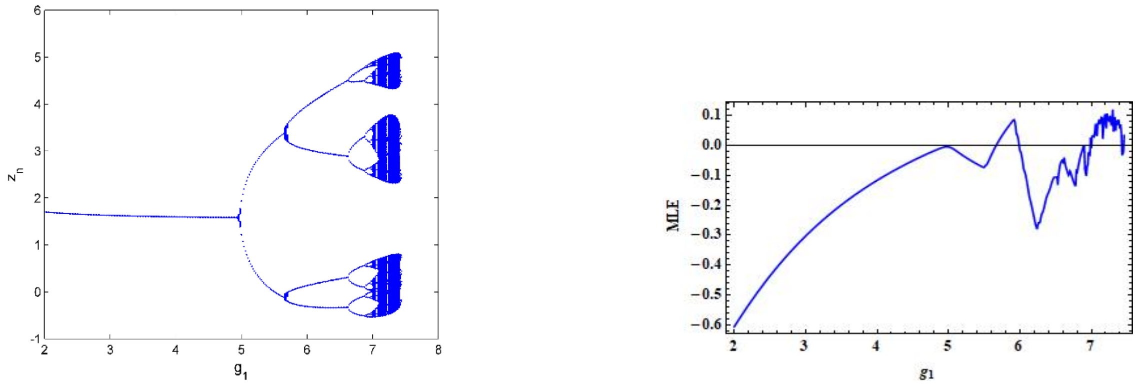
The solutions of Eq. (26) are $\lambda_1=-1$ and $\lambda_{1,2}=0.071581\pm 0.0745586i$ with $|\lambda_{1,2}|=1$. Hence, eigenvalues assignment for existence of PDB is satisfied. Next, we prove the conditions of Lemma 2.4 as follows

$$\mathbb{D}_2^-(4.980043990029326)$$
$$=1-\beta_1+\beta_0(\beta_2-\beta_0)=1.14152>0,$$

$$\mathbb{D}_2^+(4.980043990029326)$$
$$=1+\beta_1-\beta_0(\beta_2+\beta_0)=0.858253>0,$$



(a) Bifurcation diagram for x_n (b) Bifurcation diagram for y_n



(c) Bifurcation diagram for z_n (d) Maximum Lyapunov exponents

Fig. 3 Bifurcation diagrams and MLE for system Eq. (17) with $k=0.4550,\ \alpha=0.84,\ c=1.2,\ \mu_2=4.90,\ p_1=5.69,\ s_1=2.01,\ r_2=1.84,\ b=2.211,\ a=0.9,\ g_2=5.11,\ p_2=4.9,\ g_3=2.9,\ \mu_3=1.8, s_2=2.4$ and $g_1=4.980043990029326$ with initial conditions $(x_0,y_0,z_0)=(1.580743476807648,\ 0.4237874682205479,\ 0.7128186635233262)$

$$\mathbb{D}_1^+(4.980043990029326) = 1 + \beta_0 = 1.01068 > 0,$$

$$\mathbb{D}_1^-(4.980043990029326) = 1 - \beta_0 = 0.989317 > 0,$$

$$P_{4.980043990029326}(1) = 1 + \beta_2 + \beta_1 + \beta_0 = 1.73504 > 0,$$

$$P_{4.980043990029326}(-1) = 1 - \beta_2 + \beta_1 - \beta_0 = 0,$$

and

$$T_{4.980043990029326} = \frac{\beta_2' - \beta_1' + \beta_0'}{3 - 2\beta_2 + \beta_1} = 0.0978696 \neq 0.$$

Hence, all the conditions of period doubling bifurcation near the unique positive fixed point $(1.580743476807648,\ 0.4237874682205479,\ 0.7128186635233262)$ at the critical value of the bifurcation parameter $g_1 = 4.980043990029326$ are satisfied. The bifurcation diagrams and maximum Lyapunov exponents (MLE) are depicted in Fig. 3.

Hence, by 2.4 the conditions near the unique positive fixed point $(x^*, y^*, z^*) = (1.580743476807648, 0.4237874682205479, 0.7128186635233262)$ at critical value of Flip bifurcation $g_1 = 4.980043990029326$ are satisfied. Moreover, Fig. 3.2 depicted that all three population undergo Flip bifurcation see Figs. 3(a)-(c) and the corresponding $(MLEs)$ are shown in Fig. 3(d).

5. Conclusions

Tumor immune interaction model is modified by using the definition of caputo fractional order derivative that provides an excellent description of memory and hereditary properties of inter and intra cells. Also, the treatment terms are included where s_1 and s_2 denote respectively injection rate of effectors cells for adoptive cellular immunotherapy and an injection rate of IL-2 for immunotherapy. The parametric conditions are obtained and under these conditions a positive equilibrium point is asymptotically stable. On the other hand, by considering k and g_1 as bifurcation parameters, the modified model experiences Neimark-Sacker bifurcation and Period doubling bifurcation at its positive steady state. Finally, the Lyapunov exponent is computed in closed form for the justification of direction of Neimark-Sacker and period doubling bifurcation.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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