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Bifurcation analysis of a discrete-time tumor-immune system

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Abstract. The tumor-immune interaction plays a key role in tumor growth and its progression. Tumor is a group of diseases in which some of the human body cells start unchecked, uncontrolled and abnormal proliferation or division. Now a days, tumor-immune interaction is a great topic of interest from last few decades because immune cells interact in different ways, such as by releasing cytokines that activate other immune cells, directly killing the tumor cells, absorbing and presenting tumor antigen. The antitumor activity of helper T lymphocytes in providing help in generation and maintenance of CD8+ cytotoixc T cells and memory T cells are necessary for tumor control. So, in this work, we explore dynamics and bifurcation analysis of the discrete-time tumor-immune system in the interior of $\mathbb{R}_+^3$. More precisely, it is proved that the discrete tumor-immune system has tumor-free equilibrium solution, tumor-dominant equilibrium solution and immune-control equilibrium solution under certain restrictions to the involved parameters. Then by linear stability theory, local dynamics with different topological classifications are investigated about tumor-free equilibrium solution, tumor-dominant equilibrium solution and immune-control equilibrium solution of the discrete tumor-immune system. Further, for the discrete tumor-immune system, existence of periodic points and convergence rate are also investigated. It is also investigated that the existence of possible bifurcations about tumor-free equilibrium solution and immune-control equilibrium solution, and proved that there exists no flip bifurcation about tumor-free equilibrium solution. Moreover, it is proved that about immune-control equilibrium solution there exist hopf and flip bifurcations, and we have studied these bifurcations by utilizing explicit criterion. Finally, numerically verified theoretical results.

Keywords: bifurcation; discrete tumor-immune system; explicit criterion; numerical simulation

1. Introduction

A tumor is an abnormal development of tissue which may be a fluid filled vesicle or solid mass of cells. Tumor may be benign or malignant. Malignant tumor has the ability to spread out in another parts of the body from the primary site of invasion. In all types of malignancy some of the body cells grow abnormally, proliferate in an unregulated fashion and also damage the surrounding tissues or cells. Many risk factors are involved in the development of tumor such as heredity, ionizing radiations, chemical substances, diet, stress, age, sun exposure and virus. The immune system has the ability to protect and monitor the onset of tumor. The human immune response normally works with two components, the innate and the adaptive component. The innate component response quickly and protect the body from pathogens by macrophages, neutrophil leukocytes and Natural Killer (NK) cells. NK cells circulate in blood and have the ability to target cancerous cells. The adaptive response work specifically against particular pathogen and also maintains a memory of pathogen encountered, for quick reactivation of the defense if required in the future. Dendritic cells (DCs), B lymphocytes and T lymphocytes are the main cells of adaptive immune response. DCs are antigen-presenting cells while B-cells produce antibodies against specific pathogen. T lymphocytes develop into different types like T regulatory cells, cytotoxic T lymphocytes, T memory and T helper cells. Cytotoxic T lymphocytes (CTLs, also called CD8+T cells or killer T cells) kill any foreign cells entered in the body. Their activity is regulated by CD+4 T cells are commonly classified into T helper (Th) cells and T regulatory cells. T helper cells mainly control adaptive immune response against cancer or tumor by activating other immune cells. These cells activate macrophages to engulf pathogen, B cells to produce antibodies and CTLs to kill target cells and cancerous cells. Tumor development results due to escape from immunosurveillance and immune deficiencies (Mahlbacher *et al*. 2019).

Cancer is still a leading cause of deaths in the world. Radiotherapy, chemotherapy and surgery are the main treatment of tumors. Now a days, adaptive cellular immunotherapy (ACI) by the use of cytokines is used for the treatment of tumor. Cytokines are proteins that stimulate both humoral and cell mediated immune response. These are produced by activated T cells during cell-mediate immune response. Interleukin-2 is the main cytokine, causes growth, activation and differentiation of T cells. It is produced by CD+4 cells and CD+8 cells (CTLs or cytotoxic T cells). ACI refer to the injection of cultured immune cells that have anti-tumor activity into tumor bearing host (Lee and Margolin 2011). Similarly, Koutu *et al*. (2019) studied the effect of nanoparticles on human epithelial cancer cell and suggested that nanoparticles can inhibit the stimulation of tumor cells. At present, so, there is a need to develop

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most effective method for controlling this devastated disease.

In previous year, extensive work has been done to develop mathematical models for understanding the tumor growth and immune system interaction (Arciero *et al.* 2004, Lejeune *et al.* 2008, Liu *et al.* 2009, de Pillis *et al.* 2005, Kirschner and Panetta 1998, Galach 2003, Kuznetsov *et al.* 1994, Liu *et al.* 2012). Since, early 1990s tumor-immune interactions are developed by Adam and Bellomo (1997). A detailed summary of pervious work of tumor-immune dynamics can be found in published article of Eftimie *et al.* (2011) provide a framework for models to describe tumor-immune system interaction. The simplest model consists of two components immune cells and tumor cells. Kuznetsov *et al.* (1994) proposed a simple but classical mathematics model of a cell mediated response to a growing tumor cell. Kuznetsov *et al.* (1994) model can repress tumor sneaking and dormancy. Galach (2003) firstly simplified Kuznetsov-Taylor model by Michaelis-Menten form with a Lotka-Volterra form for the immune system reactions. Galach (2003) also developed time-delay model for a state of the “returning” tumor. The mechanism of dynamics between ECs, TSs and IL-2 was illustrated by Kirschner and Panetta (1998). Kirschner and Panetta (1998) introduced ACI treatment to describe short term and long term tumor oscillations. The global dynamics of the Kirschner and Panetta (1998) model, by generalized lypunov method, was done by Kirschner and Tsygvintsev (2009). To explore effect of CTLs and NKs in tumor surveillance, de Pillis *et al.* (2005) proposed numerous mathematical models. Szymanska (2003) developed two models for the detection of cancer antigen by helper T cells to compare the two types of immunotherapy treatment. The interaction between tumors and Th1 and Th2 cells, by producing cytokines upon stimulation, was studied by Eftimie *et al.* (2010). Moreover, in the past decades, many mathematical models for cancer have been presented which may be classified as discrete, continuous or combination of both (Anderson *et al.* 2018, Byrne 2010, Chaplain 2011, Cristini *et al.* 2008, Deisboeck *et al.* 2011, Alfonso *et al.* 2017, Kreeger and Lauffenburger 2010, Edelman *et al.* 2010, Enderling and Chaplain 2014, Michor *et al.* 2011, Frieboes *et al.* 2011, Baldock *et al.* 2013, Hatzikirou *et al.* 2012, Szymañska *et al.* 2018). The ability of macrophages kill tumor cells in avascular tumor presented by Owen and Sherratt (1999). Recently, den Breems and Eftimie (2016) evaluated the effect of macrophages repolarization on tumor growth. In the field of onco-immunology, the role of cytotoxic T lymphocytes (CTLs) has been a leadings focus due to their antitumor activity (Maher and Davies, 2004). Kirschner and Panetta (1998) first time investigated the role of CTLs on tumor growth and regression. Robertson-Tessi *et al.* (2015) presented a model in which CTLs, dendritic cells, T regulatory cells and T helper cells along with interaction and their effects of tumor cells are modeled with immuno- and chemotherapy. Li *et al.* (2021) investigated the separation of tumor cells from the peripheral blood by using hydrodynamics model. On the other hand, in recent years, many scientists studied the dynamical behavior of different substances in several disciplines of applied science. For instance, Ahmed *et al.* (2020) studied the dynamic behavior of multi-phase crystalline porous shells. Ebrahimi *et al.* (2019) have investigated dynamic behavior of MEE curved nanobeams. Moreover, dynamic behavior of hygro-magneto-thermo-electrical nanobeam was studied by Ebrahimi *et al.* (2020).

2. Mathematical formation of discrete-time tumor-immune system

Dong *et al.* (2014) purposed continuous-time tumor-immune system represented by the following system of first-order ordinary differential equations:

$$\begin{aligned}\frac{dT}{dt} &= aT(1-bT)-nET,\\ \frac{dE}{dt} &= k_1TE-d_1E+pEH,\\ \frac{dH}{dt} &= s_2+k_2TH-d_2H.\end{aligned} \tag{1}$$

It is noted here that 1st, 2nd and 3rd equation of tumor-immune system Eq. (1) respectively denote rate of change of TCs, ECs and HTCs populations. Moreover, interpretation of T, E, H and involved parameters are presented in the Table 1.

Now continuous-time tumor-immune system Eq. (1) takes the form:

$$\begin{aligned}\frac{dP}{dt} &= \alpha P(1-\beta P)-PQ,\\ \frac{dQ}{dt} &= \omega_1PQ-\delta_1Q+\rho QR,\\ \frac{dR}{dt} &= \sigma_2+\omega_2PR-\delta_2R,\end{aligned} \tag{2}$$

by using following non-dimensionalize transformations:

$$\begin{aligned}&P=\frac{T}{T_0}, \quad Q=\frac{E}{E_0}, \quad R=\frac{H}{H_0}, \quad \tau=nT_0t,\\ &\alpha=\frac{a}{nT_0}, \quad \beta=bT_0, \quad \omega_1=\frac{k_1}{n}, \quad \delta_1=\frac{d_1}{nT_0},\\ &\rho=\frac{p}{n}, \quad \sigma_2=\frac{s_2}{nT_0H_0}, \quad \omega_2=\frac{k_2}{n}, \quad \delta_2=\frac{d_2}{nT_0}\end{aligned} \tag{3}$$

where P, Q and R respectively denote dimensionless densities of TCs, ECs and HTCs populations. It is important here to mention that the discrete-time models governed by difference equations are more appropriate than the continuous ones in the case where populations have non-overlapping generations, and discrete models can also provide efficient computational results for numerical simulations. For instance, tumor-immune system Eq. (1) after discretization, by Euler-forward formula, takes the following form:

$$\begin{aligned}\mathrm{P}_{t+1} &= (1+\alpha\,\mathrm{h})\mathrm{P}_t-\alpha\mathrm{h}\beta\,\mathrm{P}_t^2-\mathrm{hP}_t\mathrm{Q}_t,\\ \mathrm{Q}_{t+1} &= (1-\mathrm{h}\delta_1)\mathrm{Q}_t+\mathrm{h}\omega_1\mathrm{P}_t\,\mathrm{Q}_t+\mathrm{h}\rho\mathrm{Q}_t\mathrm{R}_t,\\ \mathrm{R}_{t+1} &= h\sigma_2+(1-\mathrm{h}\delta_2)\mathrm{R}_t+\mathrm{h}\omega_2\mathrm{P}_t\mathrm{R}_t,\end{aligned} \tag{4}$$

with h is step size and τ is replaced by t.

Table 1 Patient demographics and lesion features

Parameters	Interpretation
T	Population of TCs
E	Population of ECs
H	Population of HTCs
a	TCs maximal growth rate
b	Carrying capacity of the biological environment for TCs
n	Loss rate of TCs by ECs interaction
k_1	ECs simulation rate by ECs-lysed TCs debris
p	Activation rate of ECs by HTCs
s_2	Birth rate of HTCs produced in the bone marrow
k_2	HTCs stimulation rate

3. Theoretical findings

In this section, we will study existence of equilibrium solutions along with linearized form, local dynamical classification with topological classifications, existence of periodic points of period-l and bifurcation analysis of the discrete-time tumor-immune system Eq. (4). In order to find equilibrium solutions, one needs to solve following algebraic system:

$$\begin{gathered} \mathrm{P} = (1+\alpha\,\mathrm{h})\mathrm{P} - \alpha\mathrm{h}\beta\mathrm{P}^2 - \mathrm{hPQ}, \\ \mathrm{Q} = (1-\ \mathrm{h}\delta_1)\mathrm{Q} + \mathrm{h}\omega_1\mathrm{PQ} + \mathrm{h}\rho\mathrm{QR}, \\ \mathrm{R} = h\sigma_2 + (1-\ \mathrm{h}\delta_2)\mathrm{R} + \mathrm{h}\omega_2\mathrm{PR}. \end{gathered} \tag{5}$$

It is easy to verify that $S_0 = \left(0,0,\frac{\sigma_2}{\delta_2}\right)$, $S_1 = \left(\frac{1}{\beta},0,\frac{\beta\sigma_2}{\beta\delta_2-\omega_2}\right)$ satisfied Eq. (5) obviously. Thus, for all h, α, β, δ_1, ω_1, ρ, δ_2, ω_2, the system Eq. (4) has tumor-free equilibrium solution S_0 and tumor-dominant equilibrium solution S_1 if $\beta > \frac{\omega_2}{\delta_2}$. In order to find interior equilibrium solution, i.e., immune-control equilibrium solution, of the system Eq. (4), one needs to solve following system:

$$\begin{gathered} \alpha - \alpha\beta\mathrm{P}\ - \mathrm{Q} = 0, \\ \delta_1 -\ \omega_1\mathrm{P} -\ \rho\mathrm{R} = 0, \\ \sigma_2 - \delta_2\mathrm{R} +\ \omega_2\mathrm{PR} = 0. \end{gathered} \tag{6}$$

From 1st and 3rd equations of Eq. (6), one gets:

$$\mathrm{Q} = \alpha - \alpha\beta\mathrm{P}, \tag{7}$$

and

$$\mathrm{R} = \frac{\sigma_2}{\delta_2 - \omega_2\mathrm{P}}. \tag{8}$$

Using Eq. (7) and Eq. (8) in 2nd equation of system Eq. (6), one gets:

$$F(P) = \omega_1\omega_2P^2 - (\delta_1\omega_2 + \omega_1\delta_2)P + \delta_1\delta_2 - \rho\sigma_2. \tag{9}$$

From Eq. (9), the calculation yields: $\Delta = (\delta_1\omega_2 - \omega_1\delta_2)^2 + 4\omega_1\omega_2\rho\sigma_2 > 0$. For this, it is noted that if immune-control equilibrium solution $S_2(P^*,Q^*,R^*) = S_2\left(P^*,\alpha-\alpha\,\beta\mathrm{P}^*,\frac{\sigma_2}{\delta_2-\omega_2\mathrm{P}^*}\right)$ exists then P^* is real root of Eq. (9) and moreover, it should satisfied the following condition:

$$\mathrm{P}^* < \frac{1}{\beta},\frac{\delta_2}{\omega_2}. \tag{10}$$

From Eq. (10), one can conclude that both Q^* and R^* are positive. Additionally, there exists immune-control equilibrium solution of the system Eq. (4) if

$$\rho < \frac{\delta_1\delta_2}{\sigma_2}, \tag{11}$$

and

$$\mathrm{P}^* < \frac{\delta_1}{\omega_1}, \tag{12}$$

where $\mathrm{P}^* = \frac{\delta_1\omega_2+\omega_1\delta_2-\sqrt{\Delta}}{2\omega_1\omega_2}$.

Now, the linearized form of the system Eq. (4) about equilibrium solution $S(P,Q,R)$ under the map

$$(f_1,f_2,f_3) \longmapsto (P_{t+1},Q_{t+1},R_{t+1}\,), \tag{13}$$

is

$$\Psi_{t+1} = \mathrm{J}|_{S(P,Q,R)}\Psi_t, \tag{14}$$

where

$$\mathrm{J}|_{S(P,Q,R)} = \begin{pmatrix} \begin{Bmatrix} 1+\alpha\,\mathrm{h}- \\ 2\,\mathrm{h}\alpha\,\beta\mathrm{P}-\mathrm{hQ} \end{Bmatrix} & -hP & 0 \\ \mathrm{h}\omega_1\mathrm{Q} & \begin{Bmatrix} 1-\ \mathrm{h}\delta_1+ \\ \mathrm{h}\omega_1\mathrm{P}+\mathrm{h}\rho\mathrm{R} \end{Bmatrix} & \mathrm{h}\,\rho\,\mathrm{Q} \\ \mathrm{h}\,\omega_2\,\mathrm{R} & 0 & \begin{Bmatrix} 1-\mathrm{h}\delta_2+ \\ \mathrm{h}\omega_2\mathrm{P} \end{Bmatrix} \end{pmatrix} \tag{15}$$

and

$$\begin{gathered} f_1 = (1+\alpha\,\mathrm{h})\mathrm{P} - \alpha\mathrm{h}\beta\,\mathrm{P}^2 - \mathrm{hPQ}, \\ f_2 = (1-\ \mathrm{h}\delta_1)\mathrm{Q} + \mathrm{h}\omega_1\mathrm{PQ} + \mathrm{h}\rho\mathrm{QR}, \\ f_3 = h\sigma_2 + (1-\ \mathrm{h}\delta_2)\mathrm{R} + \mathrm{h}\omega_2\mathrm{PR}. \end{gathered} \tag{16}$$

Next, local dynamic behavior of the system Eq. (4) about S_0, S_1 and S_2 are explored. It is noted that about S_0, Eq. (15) becomes

$$\mathrm{J}|_{S_0} = \begin{pmatrix} 1+\ \mathrm{h}\alpha & 0 & 0 \\ 0 & 1-\ \mathrm{h}\delta_1 + \dfrac{h\rho\sigma_2}{\delta_2} & 0 \\ \dfrac{h\sigma_2\omega_2}{\delta_2} & 0 & 1-\mathrm{h}\delta_2 \end{pmatrix} \tag{17}$$

with characteristic roots are

$$\lambda_1 = 1+\ \mathrm{h}\alpha, \lambda_2 = 1-\mathrm{h}\delta_2, \lambda_3 = 1-\ \mathrm{h}\delta_1 + \frac{h\rho\sigma_2}{\delta_2} \tag{18}$$

From Eq. (18), and by stability theory Grove *et al.* (2004), Wikan (2013), Elaydi (1996), Kulenovic and Ladas (2001), Camouzis and Ladas (2007), one can conclude local dynamic behavior of system Eq. (4) about S_0 as follows.

Lemma 3.1. About S_0, following statements hold:

(i) For all allowed parametric values h, α, β, δ_1, ω_1, ρ, δ_2 and ω_2, S_0 is never sink,

(ii) S_0 is a source if

$$h > max\left\{\frac{2}{\delta_2},\frac{2\,\delta_2}{\delta_1\delta_2-\rho\sigma_2}\right\} \tag{19}$$

with

$$\delta_1 > \frac{\rho\sigma_2}{\delta_2} \tag{20}$$

(iii) S_0 is a saddle if (20) holds and additionally

$$0 < h < min\left\{\frac{2}{\delta_2}, \frac{2\,\delta_2}{\delta_1\delta_2 - \rho\sigma_2}\right\} \tag{21}$$

(iv) S_0 is non-hyperbolic if

$$h = \frac{2}{\delta_2}, \tag{22}$$

or

$$h = \frac{2\,\delta_2}{\delta_1\delta_2 - \rho\sigma_2}. \tag{23}$$

Now, for S_1, Eq. (15) becomes

$$J|_{S_1} = \begin{pmatrix} 1 - h\alpha & -\frac{h}{\beta} & 0 \\ 0 & 1 - h\delta_1 + \frac{h\omega_1}{\beta} + \frac{h\beta\rho\sigma_2}{\beta\delta_2 - \omega_2} & 0 \\ \frac{h\beta\sigma_2\,\omega_2}{\beta\delta_2 - \omega_2} & 0 & 1 - h\delta_2 + \frac{h\omega_2}{\beta} \end{pmatrix} \tag{24}$$

with characteristic roots are

$$\begin{aligned} \lambda_1 &= 1 - h\alpha, \\ \lambda_2 &= 1 - h\delta_1 + \frac{h\omega_1}{\beta} + \frac{h\beta\rho\sigma_2}{\beta\delta_2 - \omega_2}, \\ \lambda_3 &= 1 - h\delta_2 + \frac{h\omega_2}{\beta}. \end{aligned} \tag{25}$$

Lemma 3.2. About S_1, following statements hold:

(i) S_1 is a sink if

$$0 < h < min\left\{\frac{2}{\alpha}, \frac{2\beta}{\beta\delta_2 - \omega_2}, \frac{2\beta(\beta\delta_2 - \omega_2)}{(\beta\delta_1 - \omega_1)(\beta\delta_2 - \omega_2) - \beta^2\rho\sigma_2}\right\} \tag{26}$$

with

$$\rho < \frac{(\beta\delta_1 - \omega_1)(\beta\delta_2 - \omega_2)}{\beta^2\sigma_2} \tag{27}$$

and

$$\beta > max\left\{\frac{\omega_1}{\delta_1}, \frac{\omega_2}{\delta_2}\right\}, \tag{28}$$

(ii) S_1 is a source if (27) along with (28) hold and additionally

$$h > max\left\{\frac{2}{\alpha}, \frac{2\beta}{\beta\delta_2 - \omega_2}, \frac{2\beta(\beta\delta_2 - \omega_2)}{(\beta\delta_1 - \omega_1)(\beta\delta_2 - \omega_2) - \beta^2\rho\sigma_2}\right\} \tag{29}$$

(iii) S_1 is a saddle if (27) along with (28) hold and additionally

$$h > \frac{2}{\alpha} \tag{30}$$

and

$$0 < h < min\left\{\frac{2\beta}{\beta\delta_2 - \omega_2}, \frac{2\beta(\beta\delta_2 - \omega_2)}{(\beta\delta_1 - \omega_1)(\beta\delta_2 - \omega_2) - \beta^2\rho\sigma_2}\right\} \tag{31}$$

or

$$h > \frac{2\beta(\beta\delta_2 - \omega_2)}{(\beta\delta_1 - \omega_1)(\beta\delta_2 - \omega_2) - \beta^2\rho\sigma_2} \tag{32}$$

and

$$0 < h < min\left\{\frac{2}{\alpha}, \frac{2\beta}{\beta\delta_2 - \omega_2}\right\} \tag{33}$$

or

$$h > \frac{2\beta}{\beta\delta_2 - \omega_2} \tag{34}$$

and

$$0 < h < min\left\{\frac{2}{\alpha}, \frac{2\beta(\beta\delta_2 - \omega_2)}{(\beta\delta_1 - \omega_1)(\beta\delta_2 - \omega_2) - \beta^2\rho\sigma_2}\right\} \tag{35}$$

(iv) S_1 is nonhyperbolic if

$$h = \frac{2}{\alpha} \tag{36}$$

or

$$h = \frac{2\beta(\beta\delta_2 - \omega_2)}{(\beta\delta_1 - \omega_1)(\beta\delta_2 - \omega_2) - \beta^2\rho\sigma_2} \tag{37}$$

or

$$h = \frac{2\beta}{\beta\delta_2 - \omega_2} \tag{38}$$

In order to find local dynamic behavior about S_2 of system Eq. (4) following theorem is utilized which shows the fact that all roots of characteristic equation of $J|_{S_2}$ whose absolute value less than one (see Theorem 1.2.3 of Camouzis and Ladas, 2007).

Theorem 3.3. The necessary and sufficient conditions for roots of following polynomial

$$P(\lambda) = \lambda^3 + \mathcal{G}_1\lambda^2 + \mathcal{G}_2\lambda + \mathcal{G}_3 \tag{39}$$

satisfying $|\lambda_{1,2,3}| < 1$ are

$$\begin{gathered} |\mathcal{G}_1 + \mathcal{G}_3| < 1 + \mathcal{G}_2, |\mathcal{G}_1 - 3\mathcal{G}_3| < 3 - \mathcal{G}_2, \\ \mathcal{G}_3^2 + \mathcal{G}_2 - \mathcal{G}_3\mathcal{G}_1 < 1. \end{gathered} \tag{40}$$

Lemma 3.4. S_2 is a stable if

$$\begin{gathered} |\mathcal{G}_1 + \mathcal{G}_3| < 1 + \mathcal{G}_2, |\mathcal{G}_1 - 3\mathcal{G}_3| < 3 - \mathcal{G}_2, \\ \mathcal{G}_3^2 + \mathcal{G}_2 - \mathcal{G}_3\mathcal{G}_1 < 1. \end{gathered} \tag{41}$$

where

$$\begin{gathered} \mathcal{G}_1 = -3 + hQ^* - h\alpha + 2h\alpha\beta P^* + h\delta_1 + \\ h\delta_2 - h\rho R^* - h\omega_1 P^* - h\omega_2 P^*, \end{gathered} \tag{42}$$

$$\begin{gathered} \mathcal{G}_2 = 3 - 2hQ^* + 2h\alpha - 4h\alpha\beta P^* - 2h\delta_1 + h^2\delta_1 Q^* \\ -h^2\alpha\delta_1 + 2h^2\alpha\beta\delta_1 P^* - 2h\delta_2 + h^2\delta_2 Q^* - \\ h^2\alpha\delta_2 + 2h^2\alpha\beta\delta_2 P^* + h^2\delta_1\delta_2 + 2h\rho R^* - \\ h^2\rho Q^* R^* + h^2\alpha\rho R^* - 2h^2\alpha\beta\rho P^* R^* - h^2\delta_2\rho R^* + \\ 2h\omega_1 P^* + h^2\alpha\omega_1 P^* - 2h^2\alpha\beta\omega_1 P^{*2} - h^2\delta_2\omega_1 P^* + \\ 2h\omega_2 P^* - h^2\omega_2 P^* Q^* + h^2\alpha\omega_2 P^* - 2h^2\alpha\beta\omega_2 P^{*2} \\ -h^2\delta_1\omega_2 P^* + h^2\rho\omega_2 P^* R^* + h^2\omega_1\omega_2 P^{*2}, \end{gathered} \tag{43}$$

$$\begin{gathered}\mathcal{G}_3 = -1 + \mathcal{Q}, \\ \mathcal{Q} = h\,Q^* - h\alpha + 2h\alpha\beta P^* + h\,\delta_1 - h^2\delta_1 Q^* + \\ h^2\alpha\delta_1 - 2\,h^2\alpha\beta\delta_1 P^* + h\,\delta_2 - h^2\delta_2 Q^* + h^2\alpha\delta_2 - \\ 2h^2\alpha\beta\delta_2 P^* - h^2\delta_1\delta_2 + h^3\delta_1\delta_2 Q^* - h^3\alpha\delta_1\delta_2 + \\ 2h^3\alpha\beta\delta_1\delta_2 P^* - h\rho R^* + h^2\rho Q^* R^* - h^2\alpha\rho R^* + \\ 2h^2\alpha\beta\rho P^* R^* + h^2\delta_2\rho R^* - h^3\delta_2\rho Q^* R^* + h^3\alpha\delta_2\rho R^* - \\ 2h^3\alpha\beta\delta_2\rho P^* R^* - h\omega_1 P^* - h^2\alpha\omega_1 P^* + \\ 2h^2\alpha\beta\omega_1 {P^*}^2 + h^2\delta_2\omega_1 P^* + h^3\alpha\delta_2\omega_1 P^* - \\ 2h^3\alpha\beta\delta_2\omega_1 {P^*}^2 - h\omega_2 P^* + h^2\omega_2 P^* Q^* - h^2\alpha\omega_2 P^* + \\ 2h^2\alpha\beta\omega_2 {P^*}^2 + h^2\delta_1\omega_2 P^* - h^3\delta_1\omega_2 P^* Q^* - \\ h^3\alpha\delta_1\omega_2 {P^*}^2 h^3\alpha\beta\delta_1\omega_2 {P^*}^2 - h^2\rho\omega_2 P^* R^* + \\ 2h^3\rho\omega_2 P^* Q^* R^* - h^3\alpha\rho\omega_2 P^* R^* - 2h^3 {P^*}^2 R^*\alpha\beta\rho\omega_2 + \\ h^2 {P^*}^2\omega_1\omega_2 + h^3 {P^*}^2\alpha\omega_1\omega_2 - 2h^3 {P^*}^3\alpha \times \beta\omega_1\omega_2.\end{gathered} \tag{44}$$

Proof. About S_2, Eq. (15) becomes

$$\mathrm{J}|_{S_2} = \begin{pmatrix} \begin{Bmatrix} 1+\ \mathrm{h}\alpha - \\ 2\ \mathrm{h}\alpha\beta P^* - \mathrm{h}Q^* \end{Bmatrix} & -hP^* & 0 \\ \mathrm{h}\omega_1 Q^* & \begin{Bmatrix} 1-\ \mathrm{h}\delta_1 + \\ \mathrm{h}\omega_1 P^* + \mathrm{h}\rho R^* \end{Bmatrix} & \mathrm{h}\rho Q^* \\ \mathrm{h}\omega_2 R^* & 0 & \begin{Bmatrix} 1 - \mathrm{h}\delta_2 + \\ \mathrm{h}\omega_2 P^* \end{Bmatrix} \end{pmatrix} \tag{45}$$

The characteristic equation of $\mathrm{J}|_{S_2}$ about S_2 is

$$P(\lambda) = \lambda^3 + \mathcal{G}_1\lambda^2 + \mathcal{G}_2\lambda + \mathcal{G}_3 = 0 \tag{46}$$

where $\mathcal{G}_1$, $\mathcal{G}_2$ and $\mathcal{G}_3$ are depicted in Eqs. (42), (43) and (44). Now, Theorem 3.3 implies that S_2 is a sink if $|\mathcal{G}_1 + \mathcal{G}_3| < 1 + \mathcal{G}_2, |\mathcal{G}_1 - 3\mathcal{G}_3| < 3 - \mathcal{G}_2$ and $\mathcal{G}_3^2 + \mathcal{G}_2 - \mathcal{G}_3\mathcal{G}_1 < 1$.

Motivated from the work of Wikan (2013), hereafter, it is explored that S_0 and S_1 are periodic points with period-1.

Theorem 3.5. S_0 and S_1 are periodic points of prime period-1.

Proof. From Eq. (4), one denotes

$$\mathcal{P} := (f_1, f_2, f_3) \tag{47}$$

where $f_1(P,Q,R), f_2(P,Q,R)$ and $f_3(P,Q,R)$ are depicted in Eq. (16). From Eq. (47), the computation yields

$$\mathcal{P}|_{S_0} = S_0\left(0,0,\tfrac{\sigma_2}{\delta_2}\right), \mathcal{P}|_{S_1} = S_1\left(\tfrac{1}{\beta}, 0, \tfrac{\beta\sigma_2}{\beta\delta_2 - \omega_2}\right). \tag{48}$$

So, Eq. (48) implies that S_0 and S_1 are periodic points of prime period-1

Theorem 3.6. S_0 is a periodic point of period-l.

Proof. From Eq. (47), we have

$$\mathcal{P}^2 = \begin{pmatrix} (1+\alpha\,\mathrm{h})f_1 - \alpha\mathrm{h}\beta\, {f_1}^2 - \mathrm{h}f_1 f_2, \\ (1-\ \mathrm{h}\delta_1)f_2 + \mathrm{h}\omega_1 f_1 f_2 + \mathrm{h}\rho f_2 f_3, \\ h\sigma_2 + (1-\ \mathrm{h}\delta_2)f_3 + \mathrm{h}\omega_2 f_1 f_3 \end{pmatrix} \tag{49}$$
$$\Rightarrow \mathcal{P}^2|_{S_0} = S_0\left(0,0,\frac{\sigma_2}{\delta_2}\right),$$

$$\mathcal{P}^3 = \begin{pmatrix} (1+\alpha\,\mathrm{h}){f_1}^2 - \alpha\mathrm{h}\beta\, {f_1}^3 - \mathrm{h}{f_1}^2{f_2}^2, \\ (1-\ \mathrm{h}\delta_1){f_2}^2 + \mathrm{h}\omega_1 {f_1}^2{f_2}^2 + \mathrm{h}\rho {f_2}^2{f_3}^2, \\ h\sigma_2 + (1-\ \mathrm{h}\delta_2){f_3}^2 + \mathrm{h}\omega_2 {f_1}^2{f_3}^2 \end{pmatrix} \tag{50}$$
$$\Rightarrow \mathcal{P}^3|_{S_0} = S_0\left(0,0,\frac{\sigma_2}{\delta_2}\right),$$

$$\mathcal{P}^l = \begin{pmatrix} (1+\alpha\,\mathrm{h}){f_1}^{l-1} - \alpha\mathrm{h}\beta\, {f_1}^l - \mathrm{h}{f_1}^{l-1}{f_2}^{l-1}, \\ (1-\ \mathrm{h}\delta_1){f_2}^{l-1} + \mathrm{h}\omega_1 {f_1}^{l-1}{f_2}^{l-1} + \mathrm{h}\rho {f_2}^{l-1}{f_3}^{l-1}, \\ h\sigma_2 + (1-\ \mathrm{h}\delta_2){f_3}^{l-1} + \mathrm{h}\omega_2 {f_1}^{l-1}{f_3}^{l-1} \end{pmatrix} \tag{51}$$
$$\Rightarrow \mathcal{P}^l|_{S_0} = S_0\left(0,0,\frac{\sigma_2}{\delta_2}\right).$$

Eqs. (49), (50) and (51) implies that S_0 is a periodic point of period-l.

Theorem 3.7. S_1 is a periodic point of period-l.

Proof. From Eqs. (49), (50) and (51), the computation $\mathcal{P}^2|_{S_1} = S_1, \mathcal{P}^3|_{S_1} = S_1, \cdots, \mathcal{P}^l\big|_{S_1} = S_1$ yields the required statement.

Now, convergence rate of the system Eq. (4) is studied in the following theorem:

Theorem 3.8. If $\{(P_t, Q_t, R_t)\}$ is a positive solution of the system Eq. (4) such that $\lim\limits_{t\to\infty}\{(P_t, Q_t, R_t)\} = S(P,Q,R)$ then

$$\varphi_t = \begin{pmatrix} \varphi_t^1 \\ \varphi_t^2 \\ \varphi_t^3 \end{pmatrix} \tag{52}$$

satisfying the following mathematical relation:

$$\lim_{t\to\infty} \sqrt[t]{\|\varphi_t\|} = |\lambda\mathrm{J}|_S|, \lim_{t\to\infty} \frac{\|\varphi_{t+1}\|}{\|\varphi_t\|} = |\lambda\mathrm{J}|_S| \tag{53}$$

Proof. It is recall that if $\{(P_t, Q_t, R_t)\}$ is a positive solution of the system Eq. (4) such that $\lim\limits_{t\to\infty}\{(P_t, Q_t, R_t)\} = S(P,Q,R)$ then in order for error terms, one has

$$\begin{aligned} P_{t+1} - P &= \begin{gathered}(1 + \alpha\mathrm{h} - \alpha\mathrm{h}\beta(\mathrm{P}_t + \mathrm{P}) - \mathrm{h}\ \mathrm{Q})(\mathrm{P}_t - \mathrm{P}) \\ -h\mathrm{P}_t(\mathrm{Q}_t - \mathrm{Q}),\end{gathered} \\ Q_{t+1} - Q &= \begin{gathered}\mathrm{h}\omega_1\mathrm{Q}_t(\mathrm{P}_t - \mathrm{P}) + \begin{pmatrix} 1 - \mathrm{h}\delta_1 + \\ \mathrm{h}\omega_1 P + \mathrm{h}\rho\mathrm{R}_t \end{pmatrix}(\mathrm{Q}_t - \mathrm{Q}) \\ +h\rho\mathrm{Q}(\mathrm{R}_t - \mathrm{R}),\end{gathered} \\ R_{t+1} - R &= \mathrm{h}\omega_2\mathrm{R}_t(\mathrm{P}_t - \mathrm{P}) + (1 - \mathrm{h}\delta_2 + \mathrm{h}\omega_2 P)(\mathrm{R}_t - \mathrm{R}). \end{aligned} \tag{54}$$

Set

$$\varphi_t^1 = P_t - P, \varphi_t^2 = Q_t - Q, \varphi_t^3 = R_t - R \tag{55}$$

In view of Eq. (55), Eq. (54) becomes:

$$\begin{aligned} \varphi_{t+1}^1 &= \alpha_{11}\varphi_t^1 + \alpha_{12}\varphi_t^2, \\ \varphi_{t+1}^2 &= \alpha_{21}\varphi_t^1 + \alpha_{22}\varphi_t^2 + \alpha_{23}\varphi_t^3 \\ \varphi_{t+1}^3 &= \alpha_{31}\varphi_t^1 + \alpha_{33}\varphi_t^3, \end{aligned} \tag{56}$$

where

$$\begin{gathered} \alpha_{11} = 1 + \alpha\mathrm{h} - \alpha\mathrm{h}\beta(\mathrm{P}_t + \mathrm{P}) - \mathrm{h}\ \mathrm{Q}, \alpha_{12} = -h\mathrm{P}_t, \\ \alpha_{21} = \mathrm{h}\omega_1\mathrm{Q}_t, \alpha_{22} = 1 - \mathrm{h}\delta_1 + \mathrm{h}\omega_1 P + \mathrm{h}\rho\mathrm{R}_t, \\ \alpha_{23} = h\rho\mathrm{Q}, \alpha_{31} = \mathrm{h}\omega_2\mathrm{R}_t, \alpha_{33} = 1 - \mathrm{h}\delta_2 + \mathrm{h}\ \omega_2 P. \end{gathered} \tag{57}$$

From Eq. (57), one has

$$\begin{aligned} &\lim_{t\to\infty}\alpha_{11} = 1 + \alpha\mathrm{h} - 2\alpha\mathrm{h}\beta P - \mathrm{h}\ \mathrm{Q}, \\ &\lim_{t\to\infty}\alpha_{12} = -h\mathrm{P}, \qquad \lim_{t\to\infty}\alpha_{21} = \mathrm{h}\omega_1\mathrm{Q}, \\ &\lim_{t\to\infty}\alpha_{22} = 1 - \mathrm{h}\delta_1 + \mathrm{h}\omega_1 P + \mathrm{h}\rho\mathrm{R}, \\ &\lim_{t\to\infty}\alpha_{23} = h\rho\mathrm{Q}, \qquad \lim_{t\to\infty}\alpha_{31} = \mathrm{h}\omega_2\mathrm{R}, \\ &\lim_{t\to\infty}\alpha_{33} = 1 - \mathrm{h}\delta_2 + \mathrm{h}\ \omega_2 P, \end{aligned} \tag{58}$$

that is

$$\begin{aligned}&\alpha_{11}=1+\alpha\mathrm{h}-2\alpha\mathrm{h}\beta P-\mathrm{h}\,\mathrm{Q}+\sigma_{11},\\&\alpha_{12}=-h\mathrm{P}+\sigma_{12},\qquad \alpha_{21}=\mathrm{h}\omega_1\mathrm{Q}+\sigma_{21},\\&\alpha_{22}=1-\mathrm{h}\delta_1+\mathrm{h}\omega_1 P+\mathrm{h}\rho\mathrm{R}+\sigma_{22},\\&\alpha_{23}=h\rho\mathrm{Q}+\sigma_{23},\qquad \alpha_{31}=\mathrm{h}\omega_2\mathrm{R}+\sigma_{31},\\&\alpha_{33}=1-\mathrm{h}\delta_2+\mathrm{h}\,\omega_2 P+\sigma_{33,}\end{aligned}\tag{59}$$

where $\sigma_{11},\ \sigma_{12},\ \sigma_{21},\ \sigma_{22},\ \sigma_{23},\ \sigma_{31},\ \sigma_{33}\to 0$ as $t\to\infty$. From the existing work of Pituk (2002), one has following error system:

$$\varphi_{t+1}=(A+B_t)\varphi_t,\tag{60}$$

where $A=\mathrm{J}|_{S(P,Q,R)}$ and $B_t=\begin{pmatrix}\sigma_{11}&\sigma_{12}&0\\\sigma_{21}&\sigma_{22}&\sigma_{23}\\\sigma_{31}&0&\sigma_{33}\end{pmatrix}$. Therefore, one has the following limiting system of error terms

$$\begin{pmatrix}\varphi^1_{t+1}\\\varphi^2_{t+1}\\\varphi^3_{t+1}\end{pmatrix}=\mathrm{J}|_{S(P,Q,R)}\begin{pmatrix}\varphi^1_t\\\varphi^2_t\\\varphi^3_t\end{pmatrix},\tag{61}$$

which is same as linearized system of the system Eq. (4) about $S(P,Q,R)$. Particularly, Eq. (61) implies that $\begin{pmatrix}\varphi^1_{t+1}\\\varphi^2_{t+1}\\\varphi^3_{t+1}\end{pmatrix}=\mathrm{J}|_{S_0}\begin{pmatrix}\varphi^1_t\\\varphi^2_t\\\varphi^3_t\end{pmatrix}$ and $\begin{pmatrix}\varphi^1_{t+1}\\\varphi^2_{t+1}\\\varphi^3_{t+1}\end{pmatrix}=\mathrm{J}|_{S_1}\begin{pmatrix}\varphi^1_t\\\varphi^2_t\\\varphi^3_t\end{pmatrix}$ which are same as respective linearized system obtained at S_0 and S_1 of the system Eq. (4).

Now, bifurcation analysis about S_0, S_1 and $S_2(P^*,Q^*,R^*)$ of the system Eq. (4) is explored deeply by bifurcation theory (Guckenheimer and Holmes 1983, Kuznetsov 2004, Sohel Rana 2017, Al-Basyouni and Khan 2020, Mehrjooee *et al*. 2020, Chakraborty *et al*. 2020, Liu and Cai 2019, Beddington *et al*. 1975, Chen 2006, Fang *et al*. 2012, Agiza and Elabbssy 2009, Liu and Xiao 2007, Khan *et al*. 2016, 2017).

From Eq. (18), the computation yields $\lambda_2|_{(22)}=-1$ but $\lambda_{1,3}|_{(22)}=1+\frac{2\alpha}{\delta_2},1-\frac{2\delta_1}{\delta_2}+\frac{2\rho\sigma_2}{\delta_2^2}\neq 1$ or -1, which implies that the system Eq. (4) may undergo flip bifurcation if $(h,\alpha,\beta,\delta_1,\omega_1,\rho,\sigma_2,\delta_2,\omega_2)$ located in the set:

$$\mathcal{F}|_{S_0}=\left\{(h,\alpha,\beta,\delta_1,\omega_1,\rho,\sigma_2,\delta_2,\omega_2):h=\frac{2}{\delta_2}\right\}\tag{62}$$

The following Theorem guarantees the fact that if $(h,\ \alpha,\ \beta,\ \delta_1,\ \omega_1,\ \rho,\ \sigma_2,\ \delta_2,\ \omega_2)\in\mathcal{F}|_{S_0}$ then the system Eq. (4) does not undergo flip bifurcation.

Theorem 3.9. If $(h,\alpha,\beta,\delta_1,\omega_1,\rho,\sigma_2,\delta_2,\omega_2)\in\mathcal{F}|_{S_0}$ then system Eq. (4) does not undergo flip bifurcation.

Proof. Since system Eq. (4) is invariant with respect to $P=Q=0$. Therefore, in order to determine bifurcation, system Eq. (4) is restricted on $P=Q=0$, where it becomes

$$\mathrm{R}_{t+1}=h\sigma_2+(1-\mathrm{h}\delta_2)\mathrm{R}_t\tag{63}$$

From Eq. (63), one denotes the map

$$\mathrm{f(R)}:=h\sigma_2+(1-\mathrm{h}\delta_2)\mathrm{R}\tag{64}$$

Now, if $h=h^*=\frac{2}{\delta_2}$ and $R=R^*=\frac{\sigma_2}{\delta_2}$ then from Eq. (64), one gets

$$\left.\frac{\partial\mathrm{f}}{\partial R}\right|_{h=h^*=\frac{2}{\delta_2},\ R=R^*=\frac{\sigma_2}{\delta_2},}=-1\tag{65}$$

$$\left.\frac{\partial\mathrm{f}}{\partial h}\right|_{h=h^*=\frac{2}{\delta_2},\ R=R^*=\frac{\sigma_2}{\delta_2},}=0\tag{66}$$

and

$$\left.\frac{\partial^2\mathrm{f}}{\partial R^2}\right|_{h=h^*=\frac{2}{\delta_2},\ R=R^*=\frac{\sigma_2}{\delta_2},}=0\tag{67}$$

It is noted that the condition obtained in Eq. (66) and Eq. (67) violates the non-degenerate condition for the existence of flip bifurcation and hence, one can say that the system Eq. (4) does not undergo flip bifurcation if $(h,\alpha,\beta,\delta_1,\omega_1,\rho,\sigma_2,\delta_2,\omega_2)\in\mathcal{F}|_{S_0}$.

Hereafter, by utilizing explicit criterion, we will explore hopf and flip bifurcations by choosing h as a bifurcation parameter about S_2 of the system Eq. (4). For this, first we quote following explicit criterion for exploring hopf bifurcation for system Eq. (4) about S_2 motivated from the work of Wen (2005).

Lemma 3.10. Consider the following n-dimensional discrete dynamical system:

$$P_{n+1}=f_h(P_n)\tag{68}$$

where $h\in\mathbb{R}$ is considered as a bifurcation parameter. Moreover, characteristic polynomial of $\mathrm{J}|_P$ about P of n-dimensional discrete dynamical system, which is depicted in Eq. (68), is

$$\Gamma(\lambda)=\lambda^n+\mathcal{G}_1\lambda^{n-1}+\mathcal{G}_2\lambda^{n-2}+\cdots+\mathcal{G}_n\tag{69}$$

Now, considering the determinants: $\Delta_0^{\pm}(h)=1$, $\Delta_1^{\pm}(h)$, $\cdots$, $\Delta_n^{\pm}(h)$, which can be expressed as

$$\Delta_j^{\pm}(h)=\left|\begin{pmatrix}1&\mathcal{G}_1&\mathcal{G}_2&\cdots&\mathcal{G}_{j-1}\\0&1&\mathcal{G}_1&\cdots&\mathcal{G}_{j-2}\\0&0&1&\cdots&\mathcal{G}_{j-3}\\\cdots&\cdots&\cdots&\cdots&\cdots\\0&0&0&0&1\end{pmatrix}\pm\begin{pmatrix}\mathcal{G}_{n-j+1}&\mathcal{G}_{n-j+2}&\cdots&\mathcal{G}_{n-1}&\mathcal{G}_n\\\mathcal{G}_{n-j+2}&\mathcal{G}_{n-j+3}&\cdots&\mathcal{G}_n&0\\\cdots&\cdots&\cdots&\cdots&\cdots\\\mathcal{G}_{n-1}&\mathcal{G}_n&\cdots&0&0\\\mathcal{G}_n&0&\cdots&0&0\end{pmatrix}\right|\tag{70}$$

where $j=1,\cdots n$. Furthermore, hopf bifurcation occurs at critical value $h=h_0$ if following parametric conditions hold:

Γ_1: Eigenvalue assignment: $P_{h_0}(1)>0,\ (-1)^nP_{h_0}(-1)>0,\ \Delta^-_{n-1}(h_0)=0,\ \Delta^+_{n-1}(h_0)>0,\Delta^{\pm}_j(h_0)>0$ where $j=n-3,\ n-5,\cdots,1$ (or 2) when n is even (or odd, respectively).

Γ_2: Transversality condition: $\frac{d}{dh}\left(\Delta^-_{n-1}(h_0)\right)\pm 0$.

Γ_3 : Nonresonance condition: $\cos\left(\frac{2\pi}{l}\right)\neq 1-0.5P_h(1)\frac{\Delta^-_{n-3}(h_0)}{\Delta^+_{n-2}(h_0)}$ or resonance condition $\cos\left(\frac{2\pi}{l}\right)=1-0.5P_h(1)\frac{\Delta^-_{n-3}(h_0)}{\Delta^+_{n-2}(h_0)}$, where $l=3,4,\cdots$.

Theorem 3.11. If

$$\begin{gathered}
1-\mathcal{G}_2+\mathcal{G}_3(\mathcal{G}_1-\mathcal{G}_3)=0,\\
1+\mathcal{G}_2-\mathcal{G}_3(\mathcal{G}_1+\mathcal{G}_3)>0,\\
1+\mathcal{G}_1+\mathcal{G}_2+\mathcal{G}_3>0,\\
1-\mathcal{G}_1+\mathcal{G}_2-\mathcal{G}_3>0,\\
\frac{d}{dh}\left(1-\mathcal{G}_2+\mathcal{G}_3(\mathcal{G}_1-\mathcal{G}_3)\right)\Big|_{h=h_0}\neq 0,\\
\cos\left(\frac{2\pi}{l}\right)\neq 1-\frac{1+\mathcal{G}_1+\mathcal{G}_2+\mathcal{G}_3}{2(1+\mathcal{G}_3)}, l=3,4,\cdots,
\end{gathered} \tag{71}$$

then about S_2, system Eq. (4) undergoes a hopf bifurcation at a critical value h_0 where $\mathcal{G}_1$, $\mathcal{G}_2$ and $\mathcal{G}_3$ are depicted in Eqs. (42), (43) and (44), and h_0 is the real root of $1-\mathcal{G}_2(h_0)+\mathcal{G}_3(h_0)\left(\mathcal{G}_1(h_0)-\mathcal{G}_3(h_0)\right)=0$.

Proof: By utilizing Lemma 3.10 for $n=3$, one gets:

$$\begin{gathered}
\Delta_2^-(h)=1-\mathcal{G}_2+\mathcal{G}_3(\mathcal{G}_1-\mathcal{G}_3)=0,\\
\Delta_2^+(h)=1+\mathcal{G}_2-\mathcal{G}_3(\mathcal{G}_1+\mathcal{G}_3)>0,\\
P_h(1)=1+\mathcal{G}_1+\mathcal{G}_2+\mathcal{G}_3>0,\\
(-1)^3P_h(-1)=1-\mathcal{G}_1+\mathcal{G}_2-\mathcal{G}_3>0,\\
\frac{d}{dh}\left(\Delta_2^-(h)\right)\Big|_{h=h_0}=\frac{d}{dh}\left(\begin{matrix}1-\mathcal{G}_2+\\ \mathcal{G}_3(\mathcal{G}_1-\mathcal{G}_3)\end{matrix}\right)\Bigg|_{h=h_0}\neq 0.
\end{gathered} \tag{72}$$

Finally,

$$1-0.5P_h(1)\frac{\Delta_0^-(h_0)}{\Delta_1^+(h_0)}=1-\frac{1+\mathcal{G}_1+\mathcal{G}_2+\mathcal{G}_3}{2(1+\mathcal{G}_3)}$$

Hereafter, we will also quote following explicit criterion for exploring flip bifurcation about S_2 of the system Eq. (4) by choosing h as a bifurcation parameter motivated from the work of Wen (2005) and Yao (2012).

Lemma 3.12. Consider the system Eq. (68) with $h\in\mathbb{R}$ is a bifurcation parameter. Moreover, characteristic polynomial of $\mathrm{J}|_P$ about P of Eq. (68) is of the form, which is depicted in Eq. (69). Now, considering the determinants: $\Delta_0^{\pm}(h)=1,\Delta_1^{\pm}(h),\cdots,\Delta_n^{\pm}(h)$, which are depicted in Eq. (70) and $j=1,\cdots,n$. Furthermore, flip bifurcation occur at critical value $h=h_0$ if following parametric conditions hold:

Γ_1: Eigenvalue assignment: $P_{h_0}(-1)=0$, $P_{h_0}(1)>0$, $\Delta_{n-1}^{\pm}(h_0)>0$, $\Delta_j^{\pm}(h_0)>0$ where $j=n-3,n-5,\cdots,1$ (or 2) when n is even (or odd, respectively).

Γ_2: Transversality condition: $\frac{\sum_{i=1}^{n}(-1)^{n-i}\acute{\mathcal{G}}_i}{\sum_{i=1}^{n}(-1)^{n-i}(n-i+1)\mathcal{G}_{i-1}}\neq 0$, where $\acute{\mathcal{G}}_i$ represent the derivative w.r.t h at $h=h_0$.

Theorem 3.13. If

$$\begin{gathered}
1-\mathcal{G}_2+\mathcal{G}_3(\mathcal{G}_1-\mathcal{G}_3)>0,\\
1+\mathcal{G}_2-\mathcal{G}_3(\mathcal{G}_1+\mathcal{G}_3)>0,\\
1+\mathcal{G}_1+\mathcal{G}_2+\mathcal{G}_3>0,\\
1-\mathcal{G}_1+\mathcal{G}_2-\mathcal{G}_3=0,\\
1\pm\mathcal{G}_3>0,\\
\frac{\acute{\mathcal{G}}_1-\acute{\mathcal{G}}_2+\acute{\mathcal{G}}_3}{3-2\mathcal{G}_1+\mathcal{G}_2}\neq 0,
\end{gathered} \tag{73}$$

then about S_2, system Eq. (4) undergoes a flip bifurcation at a critical value h_0 where h_0 is the real root $1-\mathcal{G}_1(h_0)+\mathcal{G}_2(h_0)-\mathcal{G}_3(h_0)=0$.

Proof. For $n=3$, Lemma 3.12 gives

$$\begin{gathered}
\Delta_2^-(h)=1-\mathcal{G}_2+\mathcal{G}_3(\mathcal{G}_1-\mathcal{G}_3)>0,\\
\Delta_2^+(h)=1+\mathcal{G}_2-\mathcal{G}_3(\mathcal{G}_1+\mathcal{G}_3)>0,\\
P_h(1)=1+\mathcal{G}_1+\mathcal{G}_2+\mathcal{G}_3>0,\\
P_h(-1)=1-\mathcal{G}_1+\mathcal{G}_2-\mathcal{G}_3=0,\\
\Delta_j^{\pm}=1\pm\mathcal{G}_3>0,\\
\frac{\sum_{i=1}^{3}(-1)^{3-i}\acute{\mathcal{G}}_i}{\sum_{i=1}^{3}(-1)^{3-i}(3-i+1)\mathcal{G}_{i-1}}=\frac{\acute{\mathcal{G}}_1-\acute{\mathcal{G}}_2+\acute{\mathcal{G}}_3}{3-2\mathcal{G}_1+\mathcal{G}_2}\neq 0.
\end{gathered} \tag{74}$$

4. Numerical simulations

Theoretical results are illustrated numerically by presenting following cases in this section:

Case I: If $\delta_1=0.6,\omega_1=1.15$, $\rho=0.3743$, $\sigma_2=0.38$, $\delta_2=0.6$, $\omega_2=0.02$ then from Eq. (9) the calculation yields: $0.023\,P^2-0.702\,P+0.217766=0$where $P^*=0.3134265420760517$ is one of its positive solution. Additionally, if $\beta=0.6$ then from Eq. (10), (11) and Eq. (12), one gets:

$$\begin{gathered}
P^*=0.3134265420760517\\
<\frac{1}{\beta}=1.6666666666666667,\qquad \frac{\delta_2}{\omega_2}=30,
\end{gathered} \tag{75}$$

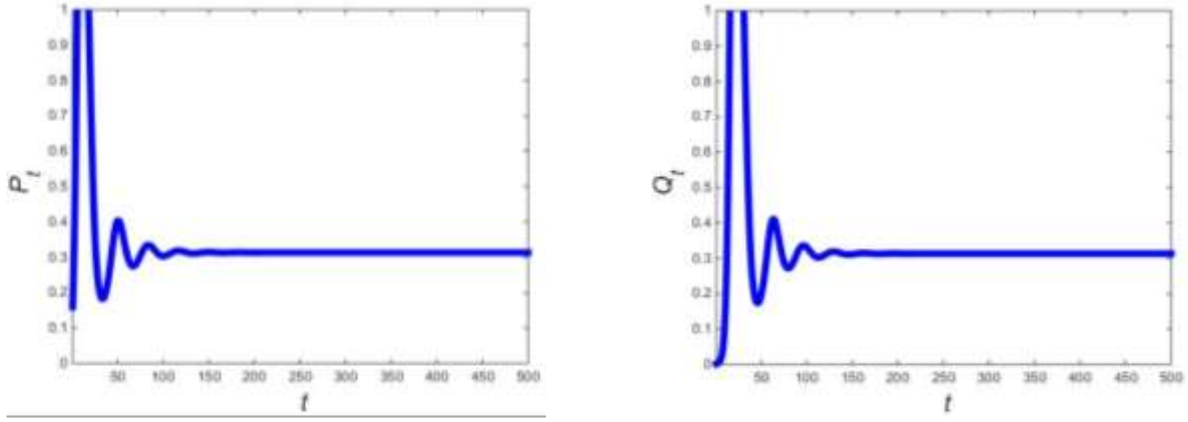
$$\rho=0.3743<\frac{\delta_1\delta_2}{\sigma_2}=0.9473684210526316 \tag{76}$$

and

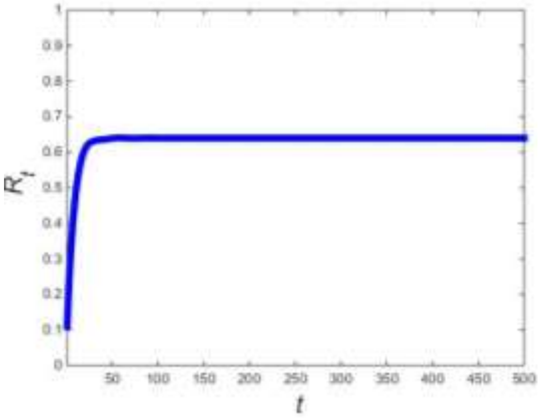
$$\begin{gathered}
\mathrm{P}^*=0.3134265420760517\\
<\frac{\delta_1}{\omega_1}=0.5217391304347826.
\end{gathered} \tag{77}$$

From Eq. (75), (76) and Eq. (77), it can be concluded that all conditions for the existence of positive root of Eq. (9) hold. Therefore, $P^*=0.3134265420760517$ is the candidate for P-coordinate of interior equilibrium solution. Moreover, if $\alpha=3.1$ then from Eq. (7) and Eq. (8) one gets: $Q^*=2.517026631738544, R^*=0.6400199749199588.$ Hence, in this case the immune-control equilibrium solution of system Eq. (4) is $S_2(0.3134265420760517, 2.517026631738544, 0.6400199749199588)$. Finally, if $h=0.4$ then from Eq. (41) computation yields $|\mathcal{G}_1+\mathcal{G}_3|=3.2244591257592488<1+\mathcal{G}_2=3.2591750150147965$, $|\mathcal{G}_1-3\mathcal{G}_3|=0.4438948828503597<3-\mathcal{G}_2=0.7408249849852035$ and $\mathcal{G}_3^2+\mathcal{G}_2-\mathcal{G}_3\mathcal{G}_1=0.9841632666808762<1$, which implies that the immune-control equilibrium solution $S_2(0.3134265420760517, 2.517026631738544, 0.6400199749199588)$ of the system Eq. (4) is a sink. In this case plots for system Eq. (4) with initial values $(P_0,Q_0,R_0)=(0.16,0.15,0.11)$ are drawn in Fig. 1 which shows the fact that the immune-control equilibrium solution $S_2(0.3134265420760517, 2.517026631738544, 0.6400199749199588)$ is a sink. Finally, periodic oscillations can see in the time evolution curves of TCs and ECs of the system Eq. (4) about $S_2(0.3134265420760517, 2.517026631738544,0.6400199749199588)$ in Fig. 2.

Case II: Now, in this case, it is proved that at h

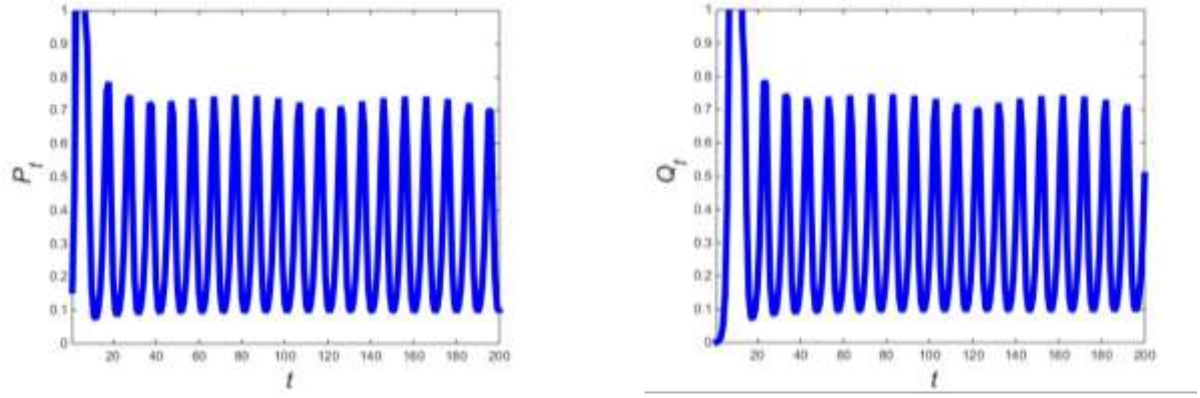


(a) Plot for TCs (b) Plot fo ECs



(c) Plot for HTCs

Fig. 1 Plots for the discrete tumor-immune system (4)



(a) Plot for TCs (b) Plot fo ECs

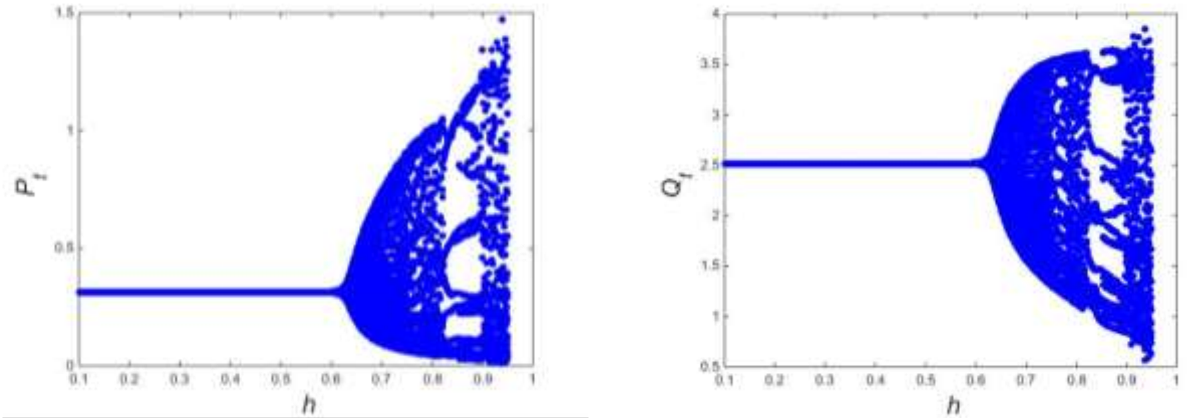
Fig. 2 Plots for the discrete tumor-immune system (4)

$= 0.6379893179787479$, system Eq. (4) undergoes a hopf bifurcation if $\delta_1 = 0.6, \omega_1 = 1.15,\ \rho = 0.3743,\ \sigma_2 = 0.38,\ \delta_2 = 0.6,\ \omega_2 = 0.02,\ \alpha = 3.1,\ \beta = 0.6$ and $h \in [0.1,0.95]$ with value $(P_0, Q_0, R_0) = (0.16,0.15,0.11)$. If $\delta_1 = 0.6,\ \omega_1 = 1.15,\ \rho = 0.3743,\ \sigma_2 = 0.38,\ \delta_2 = 0.6,\ \omega_2 = 0.02,\ \alpha = 3.1,\ \beta = 0.6$ and $h = 0.6379893179787479$ then from Eq. (46) one gets:

$$\begin{aligned}&\lambda^3 - 2.2492748833121623\lambda^2\\&+2.008708619823128\lambda\\&-0.6185734581998303 = 0\end{aligned} \tag{78}$$

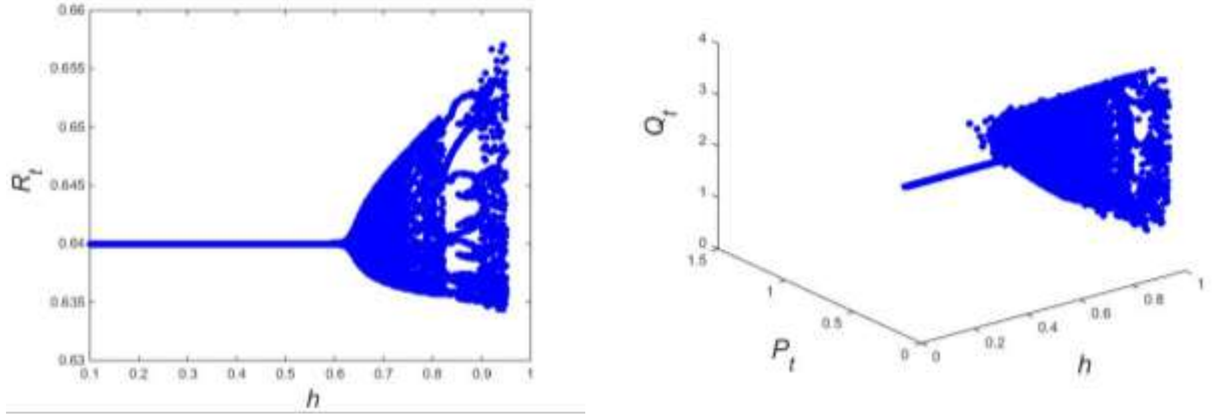
whose roots are $\lambda_{1,2} = 0.8153507125561669 \pm 0.57896737000815\iota,\ \lambda_3 = 0.6185734581998287$ where $|\lambda_{1,2}| = |0.8153507125561669 \pm 0.57896737000815\iota| = 1.$

This implies that for said parametric values the eigenvalues criterion for the existence of hopf bifurcation holds, and hence, the system Eq. (4) may undergo hopf bifurcation. In the rest of simulation, it is proved that system Eq. (4) must undergo hopf bifurcation. For instance, if $\delta_1 = 0.6,\ \omega_1 = 1.15,\ \rho = 0.3743,\ \sigma_2 = 0.38,\ \delta_2 = 0.6,\ \omega_2 = 0.02,\ \alpha = 3.1,\ \beta = 0.6$ and $h = 0.63798931$



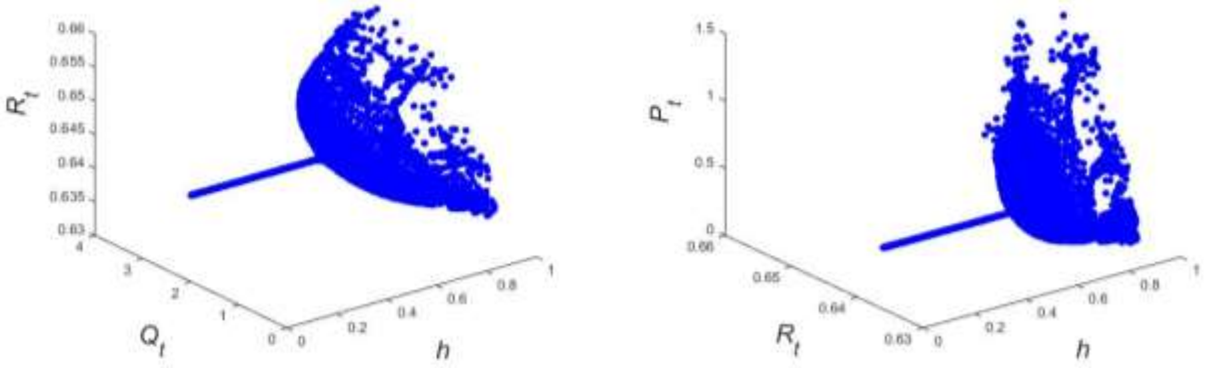
(a) Bifurcation diagram for TCs

(b) Bifurcation diagram for ECs



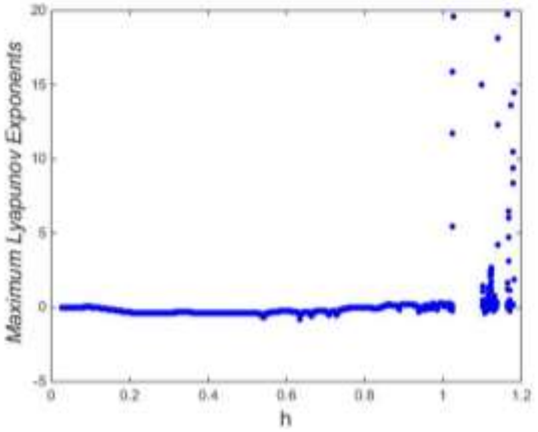
(c) Bifurcation diagram for HTCs

(d) Bifurcation diagram for TCs and ECs



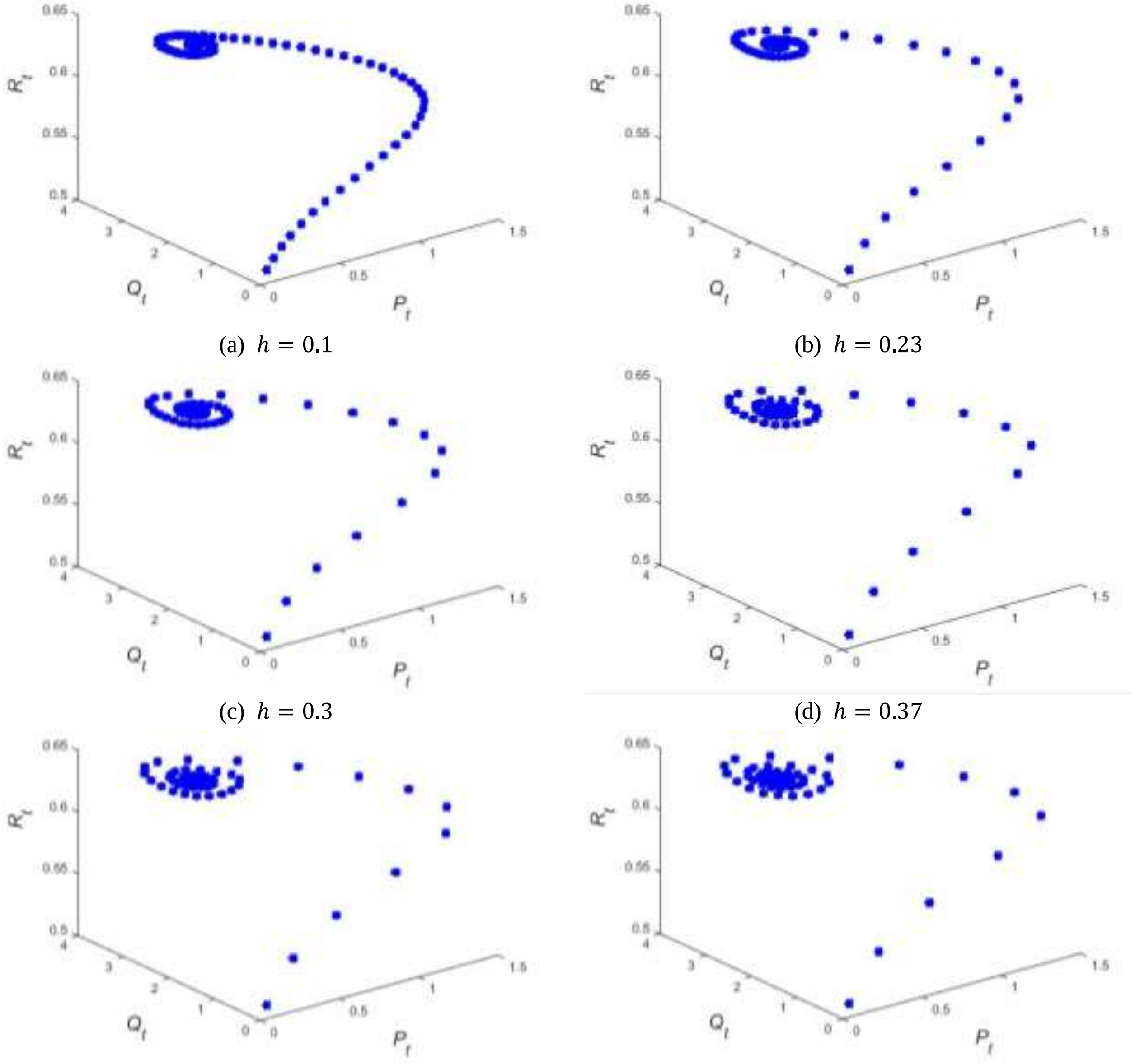
(e) Bifurcation diagram for ECs and HTCs

(f) Bifurcation diagram for HTCs and TCs



(g) Maximum Lyapunov Exponent

Fig. 3 Bifurcation diagrams and Maximum Lyapunov Exponents for the discrete tumor-immune system (4) if $\delta_1 = 0.6$, $\omega_1 = 1.15$, $\rho = 0.3743, \sigma_2 = 0.38, \delta_2 = 0.6, \omega_2 = 0.02, \alpha = 3.1, \beta = 0.6$ and $h \in [0.1, 0.95]$ with initial value $(P_0, Q_0, R_0) = (0.16, 0.15, 0.11)$



(a) $h = 0.1$ (b) $h = 0.23$

(c) $h = 0.3$ (d) $h = 0.37$

(e) $h = 0.4$ (f) $h = 0.45$

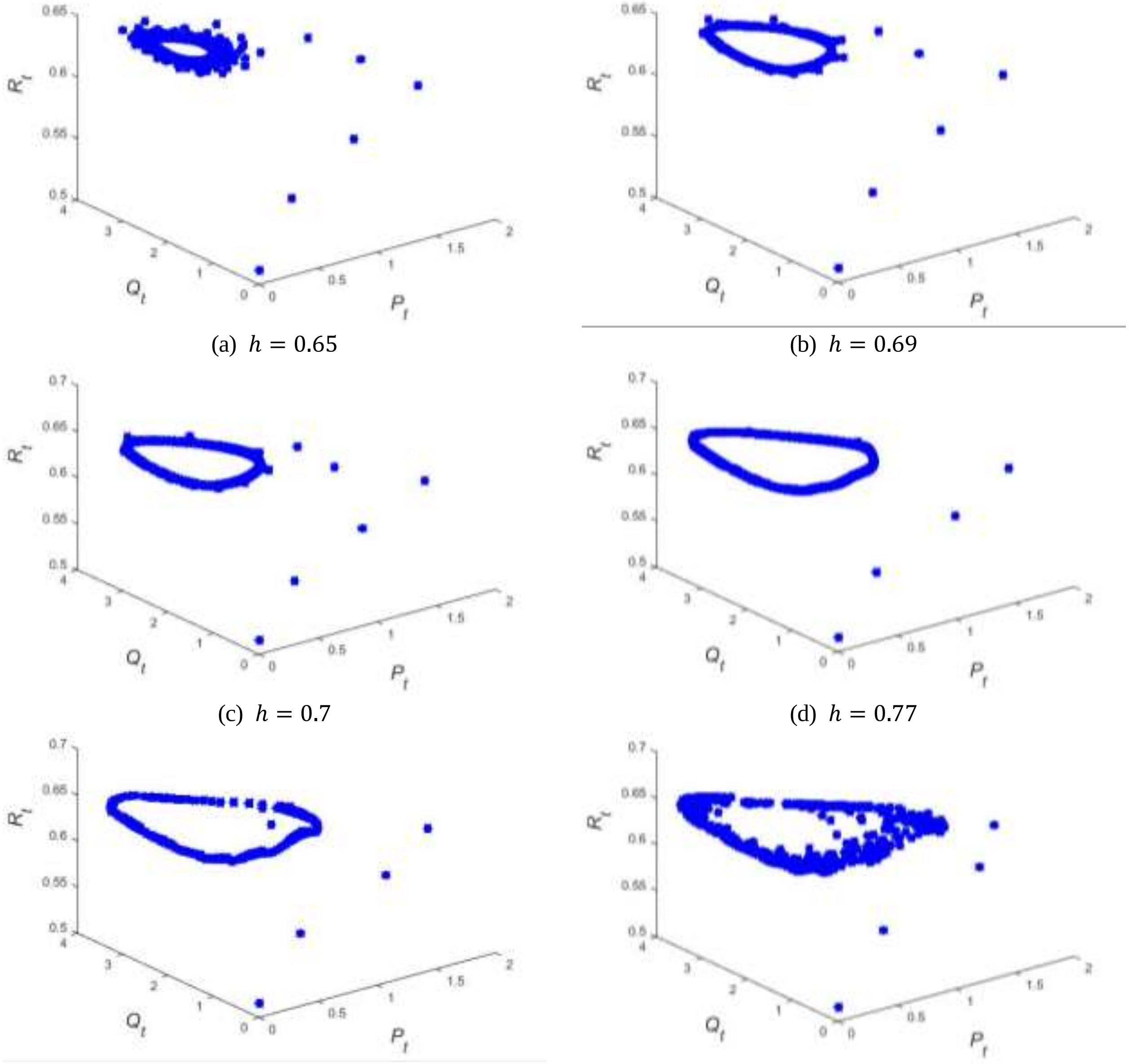
Fig. 4 Stable focus for the discrete tumor-immune system (4) if $\delta_1 = 0.6, \omega_1 = 1.15,\ \rho = 0.3743, \sigma_2 = 0.38, \delta_2 = 0.6,$ $\omega_2 = 0.02, \alpha = 3.1, \beta = 0.6$ and $h = 0.1, 0.23, 0.3, 0.37, 0.4, 0.45$with initial value $(P_0, Q_0, R_0) = (0.16,0.4,0.5)$

79787479 then from Eq. (71) the computation yields

$$\begin{aligned}
&1 - \mathcal{G}_2 + \mathcal{G}_3(\mathcal{G}_1 - \mathcal{G}_3) = 0,\\
&1 + \mathcal{G}_2 - \mathcal{G}_3(\mathcal{G}_1 + \mathcal{G}_3)\\
&= 1.2347337536214067 > 0,\\
&1 + \mathcal{G}_1 + \mathcal{G}_2 + \mathcal{G}_3 = 0.14086027831113523 > 0,\\
&1 - \mathcal{G}_1 + \mathcal{G}_2 - \mathcal{G}_3 = 5.876556961335121 > 0,\\
&\frac{d}{dh}\left(1 - \mathcal{G}_2 + \mathcal{G}_3(\mathcal{G}_1 - \mathcal{G}_3)\right)\Big|_{h=0.6379893179787479}\\
&= 1.1102230246251565 \times 10^{-15} \pm 0,\\
&1 - \frac{1 + \mathcal{G}_1 + \mathcal{G}_2 + \mathcal{G}_3}{2(1 + \mathcal{G}_3)} = 0.8153507125561646.
\end{aligned} \tag{79}$$

Moreover, $\cos\left(\frac{2\pi}{l}\right) = 0.8153507125561646$ implies $l = \pm 10.175831103316161$. Thus, from Eq. (79) all conditions of Theorem 3.11 hold and hence, it can be concluded that system Eq. (4) undergoes hopf bifurcation. So, hopf bifurcation diagram and maximum Lypunov exponents are drawn in Fig. 3. Moreover, for certain values of h, Fig. 4 shows that immune-control equilibrium $S_2(0.3134265420760517,\ 2.517026631738544,$ $0.6400199749199588)$ of system Eq. (4) with initial value $(P_0, Q_0, R_0) = (0.16,0.4,0.5)$ is a stable focus. Finally, Fig. 5 shows that interior equilibrium solution $S_2(0.3134265420760517,\ 2.517026631738544,$ $0.6400199749199588)$ of the system Eq. (4) with initial values $(P_0, Q_0, R_0) = (0.16,0.4,0.5)$ is an unstable focus.

Case III: If $\delta_1 = 0.3, \omega_1 = 0.15,\ \rho = 0.05,\ \sigma_2 = 0.2,$ $\delta_2 = 0.34,\ \omega_2 = 0.27$then from Eq. (9) the calculation yields: $0.0405\,P^2 - 0.132P + 0.092 = 0$, where $P^* =$



(a) $h = 0.65$ (b) $h = 0.69$

(c) $h = 0.7$ (d) $h = 0.77$

(e) $h = 0.82$ (f) $h = 0.9$

Fig. 5 Unstable focus for the discrete tumor-immune system (4) if $\delta_1 = 0.6, \omega_1 = 1.15,\ \rho = 0.3743, \sigma_2 = 0.38, \delta_2 = 0.6,$ $\omega_2 = 0.02,\ \alpha = 3.1,\ \beta = 0.6$ and $h = 0.65, 0.69, 0.7, 0.77, 0.82, 0.9$ initial value $(P_0, Q_0, R_0) = (0.16,0.4,0.5)$

1.0098814618266105 is one of its positive solution. Additionally, if $\beta = 0.89$ then from Eq. (10), (11) and Eq. (12), one gets:

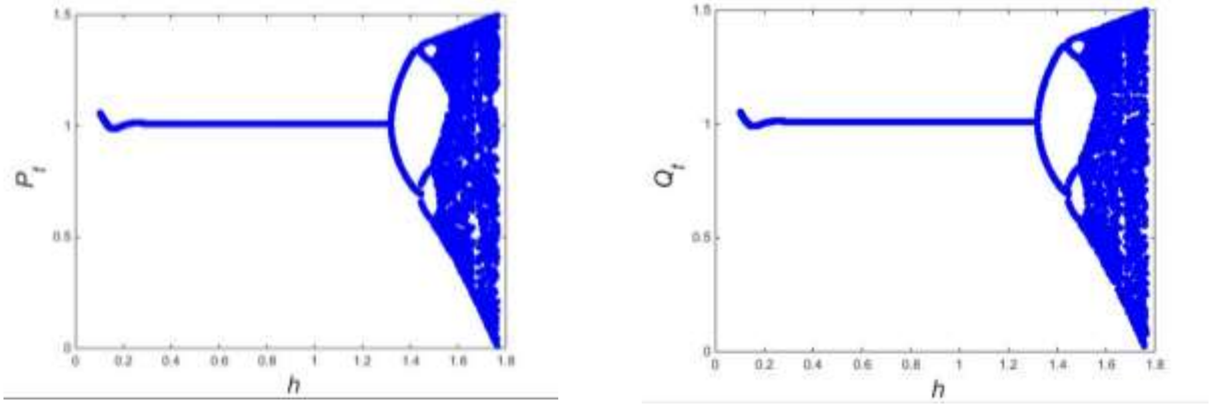
$$\begin{aligned} \mathrm{P}^* &= 1.0098814618266105 \\ &< \frac{1}{\beta} = 1.1235955056179776, \\ \frac{\delta_2}{\omega_2} &= 1.2592592592592593 \end{aligned} \tag{80}$$

$$\rho = 0.05 < \frac{\delta_1 \delta_2}{\sigma_2} = 0.51 \tag{81}$$

and

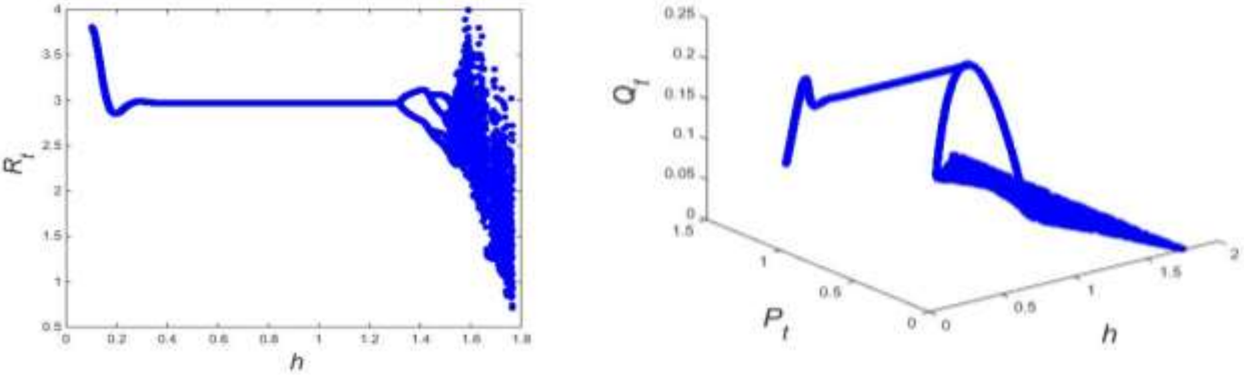
$$\mathrm{P}^* = 1.0098814618266105 < \frac{\delta_1}{\omega_1} = 2 \tag{82}$$

From Eq. (80), (81) and Eq. (82), it can be concluded that all conditions for the existence of positive root of Eq. (9) hold. Therefore, $\mathrm{P}^* = 1.0098814618266105$ is the candidate for P-coordinate of interior equilibrium solution. Moreover, if $\alpha = 1.7$ then from Eq. (7) and Eq. (8), one gets:$\mathrm{Q}^* = 0.17204934825633833$ and $\mathrm{R}^* = 2.970355614520166$. Hence, in this case the immune-control equilibrium solution of the system Eq. (4) is $S_2(1.0098814618266105,$ $0.17204934825633833,\ 2.970355614520166)$. Finally, if $h = 0.4$ then from Eq. (41) computation yields $|\mathcal{G}_1 + \mathcal{G}_3| = 2.7438464403239835 <\ 1 + \mathcal{G}_2 = 2.7444046581180617, |\mathcal{G}_1 - 3\mathcal{G}_3| = 1.216008427747287 <\ 3 - \mathcal{G}_2 = 1.2555953418819383$ and $\mathcal{G}_3^2 + \mathcal{G}_2 - \mathcal{G}_3\mathcal{G}_1 = 0.9881525591522907 <\ 1$, which implies that the immune-control equilibrium solution $S_2(1.0098814618266105, 0.17204934825633833,$



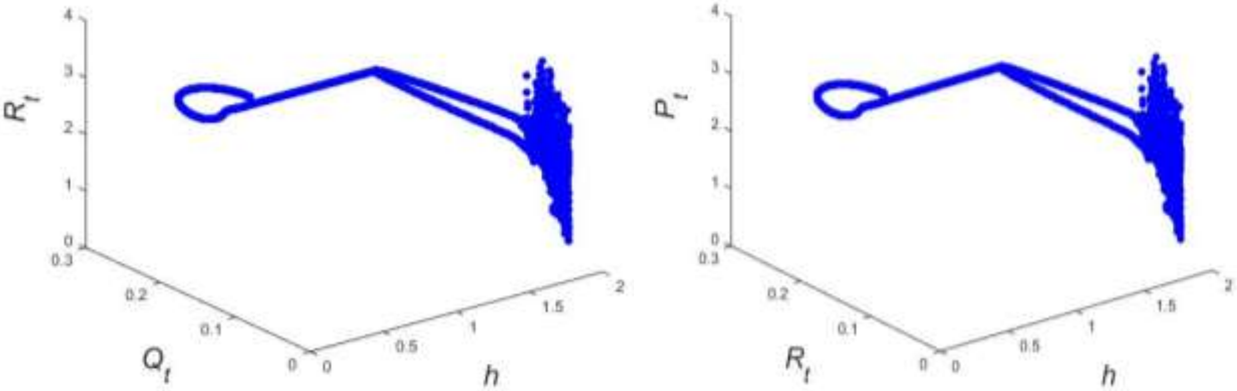
(a) Bifurcation diagram for TCs

(b) Bifurcation diagram for ECs



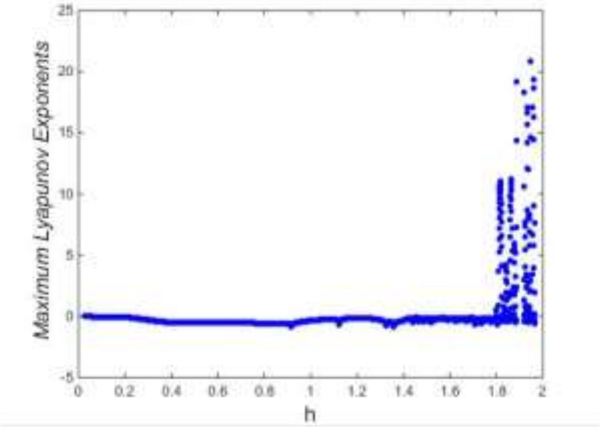
(c) Bifurcation diagram for HTCs

(d) Bifurcation diagram for TCs and ECs



(e) Bifurcation diagram for ECs and HTCs

(f) Bifurcation diagram for HTCs and TCs



(g) Maximum Lyapunov Exponent

Fig. 6 Bifurcation diagrams and Maximum Lyapunov Exponents for the discrete tumor-immune system (4) if $\delta_1 = 0.3$, $\omega_1 = 0.15$, $\rho = 0.05, \sigma_2 = 0.2, \delta_2 = 0.34, \omega_2 = 0.27, \alpha = 1.7, \beta = 0.89$ and $h \in [0.1, 2.2]$ with $(P_0, Q_0, R_0) = (0.16, 0.15, 0.11)$

$2.970355614520166)$ is a sink. Hereafter, it is proved that at $h = 1.3210765274785776$, the system Eq. (4) undergoes a flip bifurcation if $\delta_1 = 0.3, \omega_1 = 0.15,\ \rho = 0.05,\ \sigma_2 = 0.2,\ \delta_2 = 0.34,\ \omega_2 = 0.27, \alpha = 1.7, \beta = 0.89$ and $h \in [0.1,2.2]$ with initial value $(P_0, Q_0, R_0) = (0.16,\ 0.15,\ 0.11)$. If $\delta_1 = 0.3,\ \omega_1 = 0.15,\ \rho = 0.05,\ \sigma_2 = 0.2,\ \delta_2 = 0.34,\ \omega_2 = 0.27,\ \alpha = 1.7,\ \beta = 0.89,\ h = 1.3210765274785776$ then from Eq. (46) , one gets:

$$\begin{aligned}&\lambda^3 - 2.2492748833121623\lambda^2\\&+2.008708619823128\lambda\\&-0.6185734581998303 = 0\end{aligned} \tag{83}$$

whose roots are $\lambda_1 = -1$ but $\lambda_{2,3} = 0.7264286135915285, 0.822347409340407 \neq 1$ or -1. This implies that for said parametric values the eigenvalues criterion for the existence of flip bifurcation holds, and hence, the system Eq. (4) may undergo flip bifurcation. In the rest of simulation, it is proved that the system Eq. (4) must undergo flip bifurcation. For instance, if $\delta_1 = 0.3,\ \omega_1 = 0.15,\ \rho = 0.05,\ \sigma_2 = 0.2,\ \delta_2 = 0.34,\ \omega_2 = 0.27,\ \alpha = 1.7,\ \beta = 0.89,\ h = 1.3210765274785776$ then from Eq. (73) the computation yields

$$\begin{aligned}&1 - \mathcal{G}_2 + \mathcal{G}_3(\mathcal{G}_1 - \mathcal{G}_3) = 0.36977521532871305 > 0,\\&1 + \mathcal{G}_2 - \mathcal{G}_3(\mathcal{G}_1 + \mathcal{G}_3)\\&= 0.0009797046982977144 > 0,\\&1 + \mathcal{G}_1 + \mathcal{G}_2 + \mathcal{G}_3 = 0.020109794417836557 > 0,\\&1 - \mathcal{G}_1 + \mathcal{G}_2 - \mathcal{G}_3 = 0,\\&1 + \mathcal{G}_3 = 1.902564424285876 > 0\\&1 - \mathcal{G}_3 = 0.09743557571412409 > 0\\&\frac{\acute{\mathcal{G}}_1 - \acute{\mathcal{G}}_2 + \acute{\mathcal{G}}_3}{3 - 2\mathcal{G}_1 + \mathcal{G}_2} = -1.8896662214842446 \neq 0\end{aligned} \tag{84}$$

Thus, from Eq. (84) all conditions of Theorem 3.13 hold and hence, it can be concluded that the system Eq. (4) undergoes flip bifurcation. So, flip bifurcation diagram and maximum Lypunov exponents are drawn in Fig. 6.

5. Conclusions

This works is about the local dynamical properties, existence of period-points and bifurcation analysis of the discrete tumor-immune system in $\mathbb{R}_+^3$. Algebraically, it is proved that for all $h,\ \alpha,\ \beta,\ \delta_1,\ \omega_1,\ \rho,\ \sigma_2,\ \delta_2,\ \omega_2,$, the discrete tumor-immune system Eq. (4) has tumor-free equilibrium solution S_0 and tumor-dominant equilibrium solution S_1. Moreover, if Eq. (10), (11) and Eq. (12) hold then $S_2(P^*, Q^*, R^*) = S_2\left(P^*, \alpha - \alpha\,\beta P^*, \frac{\sigma_2}{\delta_2 - \omega_2 P^*}\right)$ is immune-control equilibrium solution of the system Eq. (4), where P^* in the positive solution of $F(P) = \omega_1\omega_2 P^2 - (\delta_1\omega_2 + \omega_1\delta_2)P + \delta_1\delta_2 - \rho\sigma_2 = 0$. Further, local dynamical characteristics with topological classifications about S_0, S_1 and S_2 are explored simultaneously. It is shown that S_0, S_1 of the system Eq. (4) are periodic points of period-l. We have also studied convergence rate for the system Eq. (4). Further, in order to understand dynamics of the system Eq. (4) deeply, we have studied the possible bifurcation scenarios. It is proved that about S_0 there exist no flip bifurcation if $(h,\ \alpha,\ \beta,\ \delta_1,\ \omega_1,\ \rho,\ \sigma_2,\ \delta_2,\ \omega_2) \in \mathcal{F}|_{S_0} = \left\{(h,\ \alpha,\ \beta,\ \delta_1,\ \omega_1,\ \rho,\ \sigma_2,\ \delta_2,\ \omega_2): h = \frac{2}{\delta_2}\right\}$ but system Eq. (4) undergoes both hopf and flip bifurcations about S_2 by choosing h as bifurcation parameter. We have studied hopf and flip bifurcations about S_2 of the system Eq. (4) by utilizing explicit criterion. Finally, theoretical results are verified numerically.

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