Advances in Applied Mathematics and Mechanics
Adv. Appl. Math. Mech., Vol. **5**, No. 2, pp. 146-162

DOI: 10.4208/aamm.12-m1224
April 2013

Numerical Approximation of Hopf Bifurcation for Tumor-Immune System Competition Model with Two Delays

Jing-Jun Zhao*, Jing-Yu Xiao and Yang Xu

Department of Mathematics, Harbin Institute of Technology, Harbin 150001, Heilongjiang, China

Received 20 March 2012; Accepted (in revised version) 20 July 2012

Available online 28 January 2013

Abstract. This paper is concerned with the Hopf bifurcation analysis of tumor-immune system competition model with two delays. First, we discuss the stability of state points with different kinds of delays. Then, a sufficient condition to the existence of the Hopf bifurcation is derived with parameters at different points. Furthermore, under this condition, the stability and direction of bifurcation are determined by applying the normal form method and the center manifold theory. Finally, a kind of Runge-Kutta methods is given out to simulate the periodic solutions numerically. At last, some numerical experiments are given to match well with the main conclusion of this paper.

AMS subject classifications: 34K18, 37G10, 37G15, 37N25

Key words: Hopf bifurcation, delay, tumor-immune, dynamical system, periodic solution.

1 Introduction

At present, cancer is still a leading cause of death in the world, even if that is still not known about its mechanisms of establishment and destruction. In many cases, surgery is not represent a cure. Many patients can not find the tumor in time, then later degeneration can occur. The theoretical study of tumor-immune dynamics has a long history [1]. A detailed description of virus, antivirus, and body dynamics can be found in [2–4].

Immune system plays a key role in the initial stage when tumor occurs. The immune system responses consist of two different interacting responses: the cellular response and the humoral response. The cellular response is carried by T lymphocytes. The humoral response is related to the other class of cells, called B lymphocytes. A dynamics of the

*Corresponding author.
Email: hit_zjj@hit.edu.cn (J.-J. Zhao)

antitumor immune response in vivo is complicated and not well understood. A number of mathematical models of the interactions between the immune system and a growing tumor have been developed [5, 6]et al. The kinetics of cell mediated cytotoxicity in vitro have also been described by mathematical models [7, 8]et al.

The mathematical model with which we are dealing, was proposed in papers by Galach [9] and Yafia [10]. In the former paper, the author developed a simple model of tumor immune system competition without delay, whose idea was inspired from [11]. It is shown that this model had a nonnegative periodic solution when the parameters changed. In the latter paper, the author published a series of papers to analyze the Hopf bifurcation problem which predict the occurrence of a limit cycle bifurcation.

The aim of this paper is to show that the tumor-immune dynamics with two delays has a Hopf bifurcation as the time delays changed. The existence of critical values of the delays are investigated, in which stability of the nontrivial steady states changed. Main result of this paper is given in Section 3. Based on the Hopf bifurcation theorem, we show the occurrence of Hopf bifurcation when the delay crosses some critical value. In Section 4, we determine the direction and stability of the branch of periodic solutions bifurcating from the nontrivial steady state by using the theory presented in Hassard et al. [12]. In Section 5, we construct Runge-Kutta methods with the interpolation procedure for the system with two delays. Finally in Section 6, we give some numerical examples to show that the Hopf bifurcation can occur at some critical values. Moreover, numerical comparisons are made between our Runge-Kutta methods and dde23 function in matlab.

2 Mathematical model

The Kuznetsov and Taylor's model describes the response of effector (ECs) to the growth of tumor cells (TCs). This model differs from others because it takes into account the penetration of TCs by ECs, which simultaneously causes the inactivation of ECs. It is assumed that there exist interactions between ECs and TCs in vitro, which can be described by the kinetic scheme shown in Fig. 1, where E, T, C, E^*, and T^* are the local concentrations of ECs, TCs, EC-TC complexes, inactivated ECs, and "lethally hit" TCs, respectively. Here, k_1 and k_{-1} denote the rates of bindings of ECs to TCs and the detachment of ECs

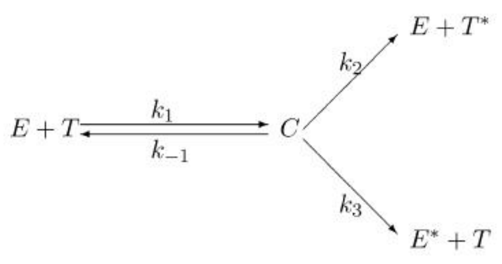

Figure 1: Kinetic scheme describing interactions between ECs and TCs.

from TCs without damaging them, k_2 is the rate at which EC-TC interactions program TCs for lysis, and k_3 is the rate at which EC-TC interactions inactivate ECs.

The model is as follows

$$\begin{cases} \dfrac{dE}{dt}=s+F(C,T)-d_1E-k_1ET+(k_{-1}+k_2)C, \\ \dfrac{dT}{dt}=aT(1-bT)-k_1ET+(k_{-1}+k_3)C, \\ \dfrac{dC}{dt}=k_1ET-(k_{-1}+k_2+k_3)C, \\ \dfrac{dE^*}{dt}=k_3C-d_2E^*, \\ \dfrac{dT^*}{dt}=k_2C-d_3T^*, \end{cases}$$

where s is normal rate of the flow of adult ECs into the tumor site. $F(C,T)=fC/(g+T)$ describes the accumulation of ECs in the tumor site; d_1, d_2 and d_3 are the coefficients of the processes of destruction and migration for E, E^* and T^*, respectively; a is the coefficients of the maximal growth of tumor; b is the environment capacity.

It is claimed in [11] that experiment observations motivate the approximation $dC/dt\approx 0$. Therefore, it is assumed that $C\approx KET$, where $K=k_1/(k_2+k_3+k_{-1})$, and the model can be reduced to two equations which describe the behavior of ECs and TCs only, i.e.,

$$\begin{cases} \dfrac{dx}{dt}=\sigma+\dfrac{\rho xy}{\eta+y}-\mu xy-\delta x, \\ \dfrac{dy}{dt}=\alpha y(1-\beta y)-xy, \end{cases} \tag{2.1}$$

where $x(t)$, $y(t)$ denote the dimensionless density of ECs and TCs, respectively. Here,

$$\sigma=\frac{s}{k_2KE_0T_0}, \qquad \rho=\frac{f}{k_2T_0}, \qquad \eta=\frac{g}{T_0}, \\ \mu=\frac{k_3}{k_2}, \qquad \delta=\frac{d_1}{Kk_2T_0}, \qquad \alpha=\frac{a}{Kk_2T_0}, \qquad \beta=bT_0.$$

Replace the Michaelis-Menten form of the function $F(C,T)$ with a Lotka-Volterra form as [9]. The function $F(C,T)$ should be in the form $F(C,T)=F(E,T)=\theta ET$ as the analysis in [9]. Then the model takes the form

$$\begin{cases} \dfrac{dx}{dt}=\sigma+\omega xy-\delta x, \\ \dfrac{dy}{dt}=\alpha y(1-\beta y)-xy, \end{cases} \tag{2.2}$$

where $\omega=k_2(\theta-m)/K$ and the other parameters have the same meaning as in Eq. (2.1).

Immune system needs some time to develop a suitable response after the recognition of non-self cells, therefore we introduce time delay denoted by τ_1 into the model. For the reproduction of the TCs, we consider the time delay denoted by τ_2. Then, from the original model (2.2), we obtain a new model with two delays

$$\begin{cases} \dfrac{dx}{dt} = \sigma + \omega x(t-\tau_1)y(t-\tau_1) - \delta x, \\ \dfrac{dy}{dt} = \alpha y(1-\beta y(t-\tau_2)) - xy, \end{cases} \tag{2.3}$$

where the parameters α, β, δ, ω and σ have the same meaning introduced in Eq. (2.2). τ_1 and τ_2 are constant time delays.

The existence and uniqueness of solution of system (2.2) for every $t>0$ are established in [9], and in the same paper it is shown that if $\omega \geq 0$, these solutions are nonnegative for any nonnegative initial conditions (biologically realistic case). In this paper, we consider the case when the immune response is positive (i.e., $\omega > 0$).

3 Existence of local Hopf bifurcation

Considering system (2.3) and supposing that $\omega > 0$, we consider two cases $\alpha\delta < \sigma$ and $\alpha\delta > \sigma$.

Assumption 3.1 $\omega > 0, \quad \alpha\delta < \sigma.$

Eq. (2.3) has a unique equilibrium $P_0 = (\sigma/\delta, 0)$. The linearized system around P_0 takes the form

$$\begin{cases} \dfrac{dx}{dt} = \dfrac{\omega\sigma}{\delta} y(t-\tau_1) - \delta x, \\ \dfrac{dy}{dt} = \Big(\alpha - \dfrac{\sigma}{\delta}\Big) y, \end{cases}$$

which leads to the characteristic equation

$$(\lambda+\delta)\Big(\lambda - \alpha + \frac{\sigma}{\delta}\Big) = 0, \tag{3.1}$$

where λ is the characteristic value. The following lemma therefore is apparent.

Lemma 3.1. *Under the condition* 3.1 *the equilibrium* P_0 *is asymptotically stable for all* $\tau_1, \tau_2 \geq 0$.

Assumption 3.2 $\omega > 0, \quad \alpha\delta > \sigma.$

Under hypothesis 3.2, system (2.3) have two equilibriums $P_0 = (\sigma/\delta, 0)$ and $P_2 = (x_2, y_2)$, where

$$x_2 = \frac{-\alpha(\beta\delta-\omega)+\sqrt{\Delta}}{2\omega}, \qquad y_2 = \frac{\alpha(\beta\delta+\omega)-\sqrt{\Delta}}{2\alpha\beta\omega},$$

with $\Delta = \alpha^2(\beta\delta-\omega)^2 + 4\alpha\beta\sigma\omega$.

Lemma 3.2. *Assumption* 3.2, *the steady state* P_0 *of* (2.3) *is unstable for all* $\tau_1 \geq 0$, $\tau_2 \geq 0$.

Proof. The Eq. (3.1) has two roots $\lambda_1 = \alpha - \sigma/\delta$ and $\lambda_2 = -\delta$. As $\alpha\delta > \sigma$, λ_1 is positive, then P_0 is unstable. $\square$

For P_2, the characteristic equation is

$$\lambda^2 + A\lambda + (C_1\lambda + D_1)e^{-\lambda\tau_1} + (C_2\lambda + D_2)e^{-\lambda\tau_2} + Ee^{-\lambda(\tau_1+\tau_2)} = 0, \tag{3.2}$$

where $A = \delta$, $C_1 = -\omega y_2$, $D_1 = \omega x_2 y_2$, $C_2 = \alpha\beta y_2$, $D_2 = \alpha\beta\delta y_2$, $E = -\omega\alpha\beta y_2^2$.

We consider the stability of P_2 in three cases.

Case 1: $\tau_1 = 0$, $\tau_2 = 0$.

In this case, Eq. (3.2) becomes

$$\lambda^2 - (\omega y_2 - \delta + \alpha - 2\alpha\beta y_2 - x_2)\lambda + \omega x_2 y_2 = 0. \tag{3.3}$$

Lemma 3.3. *Assumption* 3.2, *the equilibrium* P_2 *of* (2.2) *is asymptotically stable.*

Proof. Assumption 3.2, $x_2 > 0$, $y_2 > 0$, we can easily obtain that $\omega x_2 y_2 > 0$, $\omega y_2 - \delta + \alpha - 2\alpha\beta y_2 - x_2 < 0$, then the roots of (3.3) have no positive real part. $\square$

Case 2: $\tau_1 > 0$, $\tau_2 = 0$.

In this case, Eq. (3.2) becomes

$$\lambda^2 + p\lambda + r + (s\lambda + q)e^{-\lambda\tau_1} = 0, \tag{3.4}$$

where $p = \delta + \alpha\beta y_2$, $r = \delta\alpha\beta y_2$, $s = -\omega y_2$, $q = \alpha\omega y_2(1 - 2\beta y_2)$.

The stability of equilibrium P_2 is a result of the localization of the roots of (3.4). Following the main result of [10], the Hopf bifurcation may occur by using the delay τ_1 as a parameter of bifurcation.

Lemma 3.4. *For* $\tau_2 = 0$, *Assumption* 3.2 *and*

$$\alpha > \sup\Big\{\frac{\omega}{\beta}, \frac{\sigma}{\delta}\Big\}, \quad 0 < \beta < \frac{2\omega(2\sigma - \alpha\delta) - \sqrt{\Delta_1}}{2\alpha^2\delta^2}, \tag{H1}$$

then the nontrivial steady state P_2 *is asymptotically stable for* $\tau_1 < \tau_1^0$ *and unstable for* $\tau_1 > \tau_1^0$, *where*

$$\tau_1^0 = \frac{1}{\zeta}\arccos\Big\{\frac{q(\zeta^2 - r) - ps\zeta^2}{s^2\zeta^2 + q^2}\Big\}$$

and

$$\zeta = \frac{1}{2}(s^2 - p^2 + 2r) + \frac{1}{2}\big[(s^2 - p^2 + 2r)^2 - 4(r^2 - q^2)\big]^{\frac{1}{2}}.$$

Case 3: $\tau_1>0$, $\tau_2>0$

We consider Eq. (3.2) with τ_1 in its stable interval $[0,\tau_1^0)$. Under the Assumptions 3.2 and (H1), we regard τ_2 as a parameter. Let is is a root of Eq. (3.2), where $i^2=-1$, then we can get the equation

$$s^4+\overline{A}s^2+\overline{B}+2\overline{C}\sin(s\tau_1)+2\overline{D}\cos(s\tau_1)=0, \tag{3.5}$$

where

$$\begin{aligned}
&\overline{A}=A^2+C_2^2-C_1^2, &&\overline{B}=D_2^2-D_1^2-E^2,\\
&\overline{C}=sC_1E-s^3C_2-sAD_2, &&\overline{D}=-D_1E-s^2D_2+s^2AC_2.
\end{aligned}$$

Define $F(s)=s^4+\overline{A}s^2+\overline{B}+2\overline{C}\sin(s\tau_1)+2\overline{D}\cos(s\tau_1)$. It is easy to check that

$$\begin{aligned}
F(0)=&D_2^2-(D_1+E)^2=(\alpha\beta\delta y_2)^2-(\omega x_2y_2-\omega\alpha\beta y_2^2)^2\\
=&y_2^2[(\alpha\beta\delta)^2-(\alpha\beta\delta+\sqrt{\Delta})^2]<0,
\end{aligned}$$

and $F(+\infty)=+\infty$, then there are finite positive roots s_1, s_2, $\cdots$, s_k in $[0,+\infty)$. For every fixed s_i, there exists a sequence $\{\tau_{2i}^j|j=1,2,3,\cdots,\}$ such that (3.5) holds. Let

$$\tau_2^0=\min\{\tau_{2i}^j|i=1,2,\cdots,\ j=1,2,3,\cdots,\}.$$

When $\tau_2=\tau_2^0$, (3.2) has a pair of purely imaginary roots $\pm is_0$ for $\tau_1\in[0,\tau_1^0)$.

In the following, we assume

$$\Big[\frac{d}{dt}(Re\lambda)\Big]\Big|_{\lambda=is}\neq 0. \tag{H2}$$

Therefore, by the general Hopf bifurcation theorem for functional differential equations in [13], we have the following result on stability and bifurcation in system (2.3).

Theorem 3.1. *For system* (2.3)*, suppose Assumption* 3.2, (H1), (H2) *are satisfied and* $\tau_1\in[0,\tau_1^0)$*. Then the equilibrium* $P_2(x_2,y_2)$ *is asymptotically stable when* $\tau_2\in[0,\tau_2^0)$ *and unstable when* $\tau_2>\tau_2^0$*. System* (2.3) *undergoes a Hopf bifurcation at* P_2 *when* $\tau_2=\tau_2^0$*.*

4 Direction and stability of the Hopf bifurcation

The method we used is based on the normal form method and the center manifold theory presented in Hassard et al. [12]. Without lose of generality, we assume that $\tau_1^*\in[0,\tau_1^0)$. Let $x_1(t)=x(t)-x_2$, $y_1(t)=y(t)-y_2$ and $t\mapsto t/\tau_2$, then (2.3) can be rewritten as

$$\begin{aligned}
\begin{pmatrix}\dot{x}_1(t)\\ \dot{y}_1(t)\end{pmatrix}=&\tau_2\begin{pmatrix}-\delta & 0\\ -y_2 & \alpha-\alpha\beta y_2-x_2\end{pmatrix}\begin{pmatrix}x_1(t)\\ y_1(t)\end{pmatrix}+\tau_2\begin{pmatrix}\omega y_2 & \omega x_2\\ 0 & 0\end{pmatrix}\begin{pmatrix}x_1(t-\frac{\tau_1^*}{\tau_2})\\ y_1(t-\frac{\tau_1^*}{\tau_2})\end{pmatrix}\\
&+\tau_2\begin{pmatrix}0 & 0\\ 0 & -\alpha\beta y_2\end{pmatrix}\begin{pmatrix}x_1(t-1)\\ y_1(t-1)\end{pmatrix}+\tau_2\begin{pmatrix}g_1(x_1,y_1)\\ g_2(x_1,y_1)\end{pmatrix},
\end{aligned} \tag{4.1}$$

where

$$g_1(x_1,y_1)=\omega x_1\Big(t-\frac{\tau_1^*}{\tau_2}\Big)y_1\Big(t-\frac{\tau_1^*}{\tau_2}\Big), \tag{4.2a}$$

$$g_2(x_1,y_1)=-\alpha\beta y_1(t)y_1(t-1)-x_1(t)y_1(t). \tag{4.2b}$$

Let $u(t)=(x_1,y_1)$, then

$$\dot{u}(t)=Mu(t)+Nu\Big(t-\frac{\tau_1^*}{\tau_2}\Big)+Pu(t-1)+G(t,u), \tag{4.3}$$

where $G(t,u,\tau_2)=\tau_2(g_1,g_2)^T$ and

$$M(\tau_2)=\tau_2\begin{pmatrix}-\delta & 0\\ -y_2 & \alpha-\alpha\beta y_2-x_2\end{pmatrix},\quad N(\tau_2)=\tau_2\begin{pmatrix}\omega y_2 & \omega x_2\\ 0 & 0\end{pmatrix},\quad P(\tau_2)=\tau_2\begin{pmatrix}0 & 0\\ 0 & -\alpha\beta y_2\end{pmatrix}.$$

For $\phi\in C([-1,0],\mathbb{R}^2)$, let $\phi=(\phi_1,\phi_2)$ and $\mu\in\mathbb{R}$. Define

$$L_\mu(\phi)=(\tau_2^0+\mu)M\phi(0)+(\tau_2^0+\mu)N\phi\Big(-\frac{\tau_1^*}{\tau_2^0+\mu}\Big)+(\tau_2^0+\mu)P\phi(-1).$$

By the Riesz representation theorem, there exists a matrix $\eta(\theta,\mu)$ in $\mathbb{R}^{2\times 2}$, whose elements are of bounded variation functions such that

$$L_\mu(\phi)=\int_{-1}^0[d\eta(\theta,\mu)]\phi(\theta).$$

In fact, we can choose

$$\eta(\theta,\mu)=\begin{cases}(\tau_2^0+\mu)(M+N+P), & \theta=0,\\ (\tau_2^0+\mu)(N+P), & \theta\in\Big[-\frac{\tau_1^*}{\tau_2^0+\mu},0\Big),\\ (\tau_2^0+\mu)P, & \theta\in\Big(-1,-\frac{\tau_1^*}{\tau_2^0+\mu}\Big),\\ 0, & \theta=-1.\end{cases}$$

For $\phi\in C^1([-1,0],\mathbb{R}^2)$, define the operator $A(\mu)$ as

$$A(\mu)\phi(\theta)=\begin{cases}\int_{-1}^0[d\eta(\xi,\mu)]\phi(\xi), & \theta=0,\\ \dfrac{d\phi(\theta)}{d\theta}, & \theta\in[-1,0).\end{cases}$$

Let $h(\mu,\phi)=(\tau_2^0+\mu)(h_1,h_2)^T$, with

$$\begin{pmatrix}h_1\\ h_2\end{pmatrix}=\begin{pmatrix}\omega\phi_1\big(-\frac{\tau_1^*}{\tau_2^0+\mu}\big)\phi_2\big(-\frac{\tau_1^*}{\tau_2^0+\mu}\big)\\ -\alpha\beta\phi_2(0)\phi_2(-1)-\phi_1(0)\phi_2(0)\end{pmatrix}. \tag{4.4}$$

If we further define the operator $R(\mu)$ as

$$R(\mu)=\begin{cases} h(\mu,\phi), & \theta=0,\\ 0, & \theta\in[-1,0),\end{cases}$$

then system (4.1) is equivalent to the following operator equation

$$\dot{u}_t=A(\mu)u_t+R(\mu)u_t, \tag{4.5}$$

where $u_t=u(t+\theta)$, $\theta\in[-1,0]$.

For $\psi\in C^1([0,1],(\mathbb{R}^2)^*)$, we define

$$A^*\psi(\zeta)=\begin{cases} \displaystyle\int_{-1}^{0}[d\eta(\xi,\mu)]\psi(-\xi), & \zeta=0,\\ \displaystyle -\frac{d\psi(\zeta)}{d\zeta}, & \zeta\in(0,1],\end{cases}$$

and a bilinear form

$$\langle\psi(\zeta),\phi(\theta)\rangle=\bar{\psi}(0)^T\phi(0)-\int_{-1}^{0}\int_{0}^{\theta}\bar{\psi}(\xi-\theta)^T d\eta(\theta)\phi(\xi)d\xi,$$

where $\eta(\theta)=\eta(\theta,0)$. $A(0)$ and A^* are adjoint operators. By the discussion before, we know $\pm is_0\tau_2^0$ are eigenvectors of $A(0)$ and A^*. We need to compute the eigenvector of $A(0)$ and A^* corresponding to $is_0\tau_2^0$.

Suppose $q(\theta)$ is the eigenvector of $A(0)$ corresponding to $is_0\tau_2^0$, then we can gain it from solving the equation $A(0)q(\theta)=is_0\tau_2^0q(\theta)$ with

$$q(\theta)=(1,r)^Te^{is_0\tau_2^0\theta},$$

where

$$r=\frac{\delta e^{is_0\tau_1^*}-\omega y_2+is_0\tau_2^0e^{is_0\tau_1^*}}{\omega x_2}.$$

Suppose $q^*(\theta)$ is the eigenvectors of A^* corresponding to $-is_0\tau_2^0$, we can obtain

$$q^*(\theta)=D(1,r^*)^Te^{is_0\tau_2^0\theta},$$

where

$$r^*=\frac{-\delta+\omega y_2e^{is_0\tau_1^*}+is_0}{y_2}.$$

Then from $\langle q^*(\zeta),q(\theta)\rangle=1$, $\langle q^*(\zeta),\bar{q}(\theta)\rangle=0\rangle$, we can get

$$\begin{aligned}\bar{D}=&\frac{1}{\langle(1,r^*)^Te^{is_0\tau_2^0\zeta},(1,r)^Te^{is_0\tau_2^0\theta}\rangle}\\ =&\frac{1}{1+\bar{r^*}r+\tau_1^*e^{-is_0\tau_1^*}(\omega y_2+r\omega x_2)+\tau_2^0e^{-is_0\tau_2^0}(-\alpha\beta y_2r^*r)}.\end{aligned}$$

Define

$$\begin{cases} z(t)=\langle q^*,u_t\rangle, \\ w(t,\theta)=w(z(t),\bar{z}(t),\theta)=u_t-Re(zq), \end{cases} \tag{4.6}$$

where

$$w(z,\bar{z},\theta)=\frac{1}{2}w_{20}(\theta)z^2+w_{11}(\theta)z\bar{z}+\frac{1}{2}w_{02}(\theta)\bar{z}^2+\cdots.$$

z and $\bar{z}$ are local coordinates for center manifold C_0 in the direction of q^* and $\bar{q^*}$. Note that w is real when u_t is real. For the solution $u_t\in C_0$ at $\mu=0$, we obtain

$$\dot{z}=\langle q^*,A(\mu)u_t+R(\mu)u_t\rangle=is_0\tau_2^0z(t)+\bar{q^*}(0)h_0(z,\bar{z}), \tag{4.7}$$

where $h_0=h|_{\mu=0}$.

Let

$$g(z,\bar{z})=\bar{q^*}(0)h_0(z,\bar{z})=g_{20}\frac{z^2}{2}+g_{11}z\bar{z}+g_{02}\frac{\bar{z}^2}{2}+g_{21}\frac{z^2\bar{z}}{2}+\cdots, \tag{4.8}$$

then using the computation process similar to that in [12], we obtain the coefficients used in determining the important quantities.

From (4.6), we have $u_t=w(z,\bar{z})+zq+\overline{zq}$, then

$$\begin{aligned} g(z,\bar{z})=&\bar{q^*}(0)h_0(z,\bar{z})=\bar{D}\begin{pmatrix}1 & \bar{r^*}\end{pmatrix}\tau_2^0\begin{pmatrix}h_1\\h_2\end{pmatrix} \\ =&\bar{D}\begin{pmatrix}1 & \bar{r^*}\end{pmatrix}\tau_2^0\begin{pmatrix}\omega x_t(-\frac{\tau_1^*}{\tau_2^0})y_t(-\frac{\tau_1^*}{\tau_2^0}) \\ -\alpha\beta y_t(0)y_t(-1)-x_t(0)y_t(0)\end{pmatrix}. \end{aligned} \tag{4.9}$$

Comparing the coefficients between (4.8) and (4.9), then

$$\begin{aligned} g_{20}=&2\bar{D}\tau_2^0\big[\omega re^{-2is_0\tau_1^*}-\alpha\beta\bar{r^*}r^2e^{-is_0\tau_2^0}-\bar{r*}r\big], \\ g_{11}=&\bar{D}\tau_2^0\big[(\omega-\bar{r^*})(r+\bar{r})-\alpha\beta\bar{r^*}r\bar{r}(e^{is_0\tau_2^0}+e^{-is_0\tau_2^0})\big], \\ g_{02}=&2\bar{D}\tau_2^0\big[\omega\bar{r},e^{2is_0\tau_1^*}-\alpha\beta\bar{r^*}\bar{r}^2e^{is_0\tau_2^0}-\bar{r*}\bar{r}\big], \\ g_{21}=&\bar{D}\tau_2^0\Big[\omega(w_{20}^{(1)}\Big(-\frac{\tau_1^*}{\tau_2^0}\Big)\bar{r}e^{is_0\tau^*}+2w_{11}^{(1)}\Big(-\frac{\tau_1^*}{\tau_2^0}\Big)re^{-is_0\tau_1^*}+w_{20}^{(2)}\Big(-\frac{\tau_1^*}{\tau_2^0}\Big)e^{is_0\tau_1^*} \\ &+2w_{11}^{(2)}\Big(-\frac{\tau_1^*}{\tau_2^0})e^{-is_0\tau_1^*}\Big)-\alpha\beta\bar{r^*}(2rw_{11}^{(2)}(-1)+\bar{r}w_{20}^{(2)}(-1)+w_{20}^2(0)\bar{r}e^{-is_0\tau_2^0} \\ &+2w_{11}^{(2)}(0)re^{-is_0\tau_2^0})-\bar{r^*}(2w_{11}^{(2)}(0)+w_{20}^{(2)}(0)+w_{20}^{(1)}(0)\bar{r}+2w_{11}^{(1)}(0)r)\Big], \end{aligned}$$

where $w=(w^{(1)},w^{(2)})$.

As far as we concerned above, we still need to compute $w_{20}(\theta)$, $w_{11}(\theta)$, $w_{02}(\theta)$ to determine the value of g_{21}. Consider the derivative

$$\begin{aligned} \dot{w} =& \dot{u}_t - \dot{z}q - \dot{\bar{z}}q \\ =& \begin{cases} Aw - 2Re(\overline{q^*(0)}h_0(z,\bar{z})q(\theta)), & \theta\in[-1,0) \\ Aw - 2Re(\overline{q^*(0)}h_0(z,\bar{z})q(0)) + h_0, & \theta = 0 \end{cases} \\ =& Aw + H(z,\bar{z},\theta) \\ =& Aw + H_{20}\frac{z^2}{2} + H_{11}z\bar{z} + H_{02}\frac{\bar{z}^2}{2} + \cdots. \end{aligned} \tag{4.10}$$

At the same time, $\dot{w}$ also can be expressed as

$$\dot{w} = w_z\dot{z} + w_{\bar{z}}\dot{\bar{z}} = \frac{\partial w}{\partial z}\dot{z} + \frac{\partial w}{\partial \bar{z}}\dot{\bar{z}}, \tag{4.11}$$

then we can obtain

$$\begin{cases} (A - 2is_0\tau_2^0)w_{20}(\theta) = -H_{20}(\theta), \\ Aw_{11}(\theta) = -H_{11}(\theta), \\ w_{20} = \overline{w_{02}}. \end{cases} \tag{4.12}$$

When $\theta\in[-1,0)$, we have

$$\begin{aligned} H(z,\bar{z},\theta) =& -\overline{q^*(0)}h_0(z,\bar{z})q(\theta) - q^*(0)\overline{h_0(z,\bar{z})q(\theta)} \\ =& -g(z,\bar{z})q(\theta) - \overline{g(z,\bar{z})q(\theta)}, \end{aligned} \tag{4.13}$$

comparing the coefficients, we have

$$H_{11} = -g_{11}q(\theta) - \overline{g_{11}q(\theta)}, \qquad H_{20} = -g_{20}q(\theta) - \overline{g_{02}q(\theta)}. \tag{4.14}$$

From the equation

$$\begin{aligned} Aw_{20}(\theta) =& \dot{w}_{20}(\theta) = 2is_0\tau_2^0 w_{20}(\theta) - H_{20}(\theta) \\ =& 2is_0\tau_2^0 w_{20}(\theta) + g_{20}q(\theta) + \overline{g_{02}q(\theta)}, \end{aligned} \tag{4.15}$$

we can obtain

$$w_{20}(\theta) = -\frac{ig_{20}}{\tau_2^0 s_0}q(\theta) + \frac{i\overline{g_{02}}}{3\tau_2^0 s_0}\overline{q(\theta)} + E_1 e^{2is_0\tau_2^0\theta}, \tag{4.16}$$

where $E_1 = (E_1^{(1)}, E_1^{(2)}) \in \mathbb{R}$ is a constant vector. Similarly, we have

$$w_{11}(\theta) = -\frac{ig_{11}}{\tau_2^0 s_0}q(\theta) + \frac{i\overline{g_{11}}}{\tau_2^0 s_0}\overline{q(\theta)} + E_2. \tag{4.17}$$

When $\theta=0$, we can solve out the value of E_1 and E_2 from

$$\int_{-1}^{0} d\eta(\theta)w_{20}(\theta)=2is_0\tau_2^0 w_{20}(0)-H_{20}(0), \tag{4.18a}$$

$$\int_{-1}^{0} d\eta(\theta)w_{11}(\theta)=-H_{11}(0), \tag{4.18b}$$

where

$$H_{20}=-g_{20}q(\theta)-\overline{g_{02}q(\theta)}+2\tau_2^0\begin{pmatrix}\omega r e^{-2is_0\tau_1^*}\\ -\alpha\beta r^2 e^{-is_0\tau_2^0}-r\end{pmatrix}, \tag{4.19a}$$

$$H_{11}=-g_{11}q(\theta)-\overline{g_{11}q(\theta)}+2\tau_2^0\begin{pmatrix}Re(r)\\ -\alpha\beta Re(r\bar{r}e^{is_0\tau_2^0})-Re(r)\end{pmatrix}. \tag{4.19b}$$

Substituting (4.19a), (4.19b) into (4.16), (4.17), we then obtain

$$(2is_0\tau_2^0 I-\int_{-1}^{0} e^{2is_0\tau_2^0\theta}d\eta(\theta))E_1=2\tau_2^0\begin{pmatrix}\omega r e^{-2is_0\tau_1^*}\\ -\alpha\beta r^2 e^{-is_0\tau_2^0}-r\end{pmatrix}. \tag{4.20}$$

Solving the equation, we get

$$E_1^{(1)}=\frac{2}{D}\begin{vmatrix}\omega r e^{-2is_0\tau_1^*} & -\omega x_2 e^{-2is_0\tau_1^*}\\ -\alpha\beta r^2 e^{-is_0\tau_2^0}-r & 2is_0+\alpha\beta y_2 e^{-2is_0\tau_2^0}\end{vmatrix}, \tag{4.21a}$$

$$E_1^{(2)}=\frac{2}{D}\begin{vmatrix}2is_0+\delta-\omega y_2 e^{-2is_0\tau_1^*} & \omega r e^{-2is_0\tau_1^*}\\ y_2 & -\alpha\beta r^2 e^{-is_0\tau_2^0}-r\end{vmatrix}, \tag{4.21b}$$

with

$$D=\begin{vmatrix}2is_0+\delta-\omega y_2 e^{-2is_0\tau_1^*} & -\omega x_2 e^{-2is_0\tau_1^*}\\ y_2 & 2is_0+\alpha\beta y_2 e^{-2is_0\tau_2^0}\end{vmatrix}. \tag{4.22}$$

Similarly, we have

$$\int_{-1}^{0} d\eta(\theta)E_2=2\tau_2^0\begin{pmatrix}Re(r)\\ -\alpha\beta Re(r\bar{r}e^{is_0\tau_2^0})-Re(r)\end{pmatrix}, \tag{4.23a}$$

$$E_2^{(1)}=\frac{2}{R}\begin{vmatrix}Re(r) & \omega x_2 e^{-is_0\tau_1^*}\\ -\alpha\beta Re(r\bar{r}e^{is_0\tau_2^0})-Re(r) & -\alpha\beta y_2 e^{-is_0\tau_2^0}\end{vmatrix}, \tag{4.23b}$$

$$E_2^{(2)}=\frac{2}{R}\begin{vmatrix}-\delta+\omega y_2 e^{-is_0\tau_1^*} & Re(r)\\ -y_2 & -\alpha\beta Re(r\bar{r}e^{is_0\tau_2^0})-Re(r)\end{vmatrix}, \tag{4.23c}$$

with

$$R=\begin{vmatrix}-\delta+\omega y_2 e^{-is_0\tau_1^*} & \omega x_2 e^{-is_0\tau_1^*}\\ -y_2 & -\alpha\beta y_2 e^{-is_0\tau_2^0}\end{vmatrix}. \tag{4.24}$$

Therefore, we can compute the following values

$$c_1(0)=\frac{i}{2\tau_2^0 s_0}\Big(g_{11}g_{20}-2|g_{11}|^2-\frac{|g_{02}|^2}{3}\Big)+\frac{g_{21}}{2},\qquad \mu_2=-\frac{Re(c_1(0))}{Re(\lambda'(\tau_2^0))}, \tag{4.25a}$$

$$T_2=-\frac{Im(c_1(0))+\mu_2 Im(\lambda'(\tau_2^0))}{\tau_2^0 s_0},\qquad \beta_2=2Re(c_1(0)). \tag{4.25b}$$

Hence, μ_2 determines the direction of the Hopf bifurcation, β_2 determines the stability of the bifurcation periodic solutions, T_2 determines the period of the bifurcating solutions.

Theorem 4.1. *For system* (2.3), *suppose Assumption* 3.2, (H1), (H2) *are satisfied and* $\tau_1=\tau_1^*\in[0,\tau_1^0)$, *then* $\tau_2=\tau_2^0$ *is a Hopf bifurcation value of system* (2.3).

(1) *If* $\mu_2>0$ $(\mu_2<0)$, *then the Hopf bifurcation is supercritical (subcritical).*

(2) *If* $\beta_2<0$ $(\beta_2>0)$, *the periodic solutions are stable (unstable).*

5 Runge-Kutta methods for differential equations of two delays

In this section, we represent a kind of Runge-Kutta methods with interpolation procedure that was proposed in In't Hout [14] for the delay differential equations (DDEs) with two delays

$$X'(t)=f(t,X(t),X(t-\tau_1),X(t-\tau_2)),$$

where $X(t)\in\mathbb{R}^d$.

The Runge-Kutta method (A,b,c) can be written as

$$\begin{cases} X_{n+1}=X_n+h\sum_{i=1}^s b_i f(t_n+c_ih,X_{n+1}^i,Y_{n+1-m_1}^i,Z_{n+1-m_2}^i),\\ X_{n+1}^j=X_n+h\sum_{i=1}^s a_{ji} f(t_n+c_ih,X_{n+1}^i,Y_{n+1-m_2}^i,Z_{n+1-m_2}^i),\end{cases} \tag{5.1}$$

where h is the step size. X_{n+1},X_{n+1}^i denote the given approximations to $X(t_{n+1})=(x(t_{n+1}),y(t_{n+1}))^T$, $X^i(t_n+c_ih)=(x(t_n+c_ih),y(t_n+c_ih))^T$.

Let $m_1=\lfloor\tau_1\rfloor$, $m_2=\lfloor\tau_2\rfloor$, where $\lfloor x\rfloor$ means the largest integer less than x. For any arbitrary real step size h, then $\tau_1=hm_1+\delta_1$, $\tau_2=hm_2+\delta_2$, where $0<\delta_i<1,i=1,2$.

Let $r,\tilde{s}\geq 0$ be integers. We consider the following interpolation formula for $Y_{n+1-m_1}^i$, $Z_{n+1-m_2}^i$, i.e.,

$$Y_{n+1-m_1}^i=X_i^h(t_n+c_ih-\tau_1),\qquad Z_{n+1-m_2}^i=X_i^h(t_n+c_ih-\tau_2), \tag{5.2}$$

where

$$X_i^h(t_j+c_ih-\varepsilon h)=\sum_{k=-r}^{\tilde{s}}L_k(\varepsilon)X_{j+1+k}^i,$$

with

$$L_j(\varepsilon)=\sum_{k=-r,k\neq j}^{\tilde{s}}\Big(\frac{\varepsilon-k}{j-k}\Big).$$

Here, h is a arbitrary real number less then τ_1 and τ_2, which is very convenient for the numerical approximation to the differential equation with multiple delays. From [15], the Runge-Kutta method (5.1) satisfies simplifying assumptions $A(p_1)$, $B(p_1)$ and if the interpolation procedure for $Y^i_{n+1-m_1}$, $Z^i_{n+1-m_2}$ is exact for polynomials of degree $\le p_2$, then it can be easily seen that process (5.1) is of an order $p \ge \min(p_1,p_2)$. Therefore, we can choose appropriate $r,\tilde{s}$ to get the high enough convergence order.

The numerical Hopf bifurcation of Runge-Kutta method for DDEs with one delay has been proved in [16]. It is shown that if the delay differential equation undergoes a Hopf bifurcation at $\tau=\tau^*$, then the discrete scheme undergoes a Hopf bifurcation at $\tau(h)=\tau^*+\mathcal{O}(h^*)$ for sufficiently small step size h, where $p\ge 1$ is the order of the Runge-Kutta method. The direction of numerical Hopf bifurcation and stability of bifurcating invariant curve are the same as that of delay differential equation. For the system of two delays, the similar result can be easily verified from [16].

Theorem 5.1. *Let the conditions in Theorem* 3.1 *hold, then the discrete scheme Eq.* (4.3) *has a Hopf bifurcation point* $\tau(h)=\tau^*+\mathcal{O}(h^p)$ *when the step size* h *is small enough.*

6 The numerical simulation to this model

In this section, using the 4-stage explicit Runge-Kutta method with Lagrange interpolation polynomials (5.1), we obtain the numerical simulations to system (4.3), which consist three cases of the analysis in the Section 3.

Let

$$f(t,u,v,w)=Mu+Nv+Pw+G(t,u,v,w), \quad u,v,w\in\mathbb{R}^2,$$

where

$$G(t,u,v,w)=\begin{pmatrix}\omega v_1v_2\\ -\alpha\beta u_2w_2-u_1u_2\end{pmatrix}.$$

We choose the similar coefficients as in [9]:

$$\alpha=1.636,\quad \beta=0.002,\quad \sigma=0.073,\quad \delta=0.545,\quad \omega=0.015. \tag{C}$$

Then positive equilibrium points are $P_2=(1.5275,33.1474)$, $P_0=(0.1339,0)$. When the Assumptions 3.2 and (H1) are satisfied, we can use the Runge-Kutta method to simulate Eq. (4.3).

Case 6.1. In [11], Kuznetsov and Taylor gave out the model (2.1) and an explicit bifurcation analysis without delay. Local and global bifurcations were calculated for realistic values of the parameters.

Then, Galach gave out a simplified model (2.2) in [9] and compared the behavior of solutions to the models in [11]. The main results can be found in these two references.

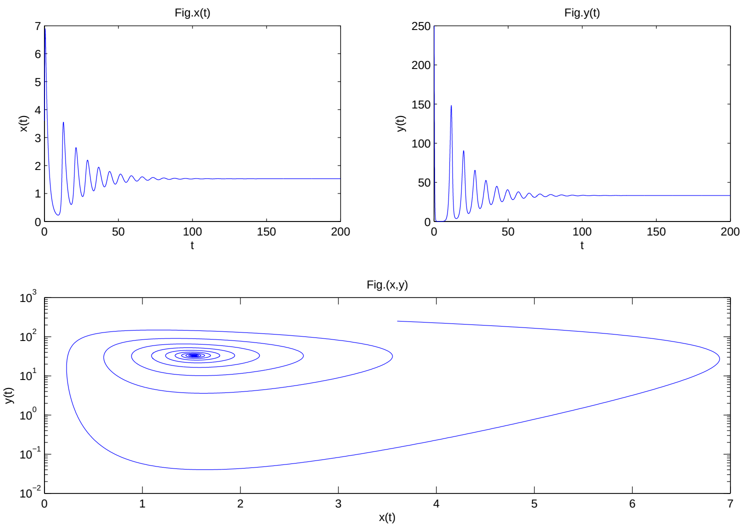

Figure 2: $\tau_1 = 0.05$, $\tau_2 = 0$, the P_2 is asymptotically stable.

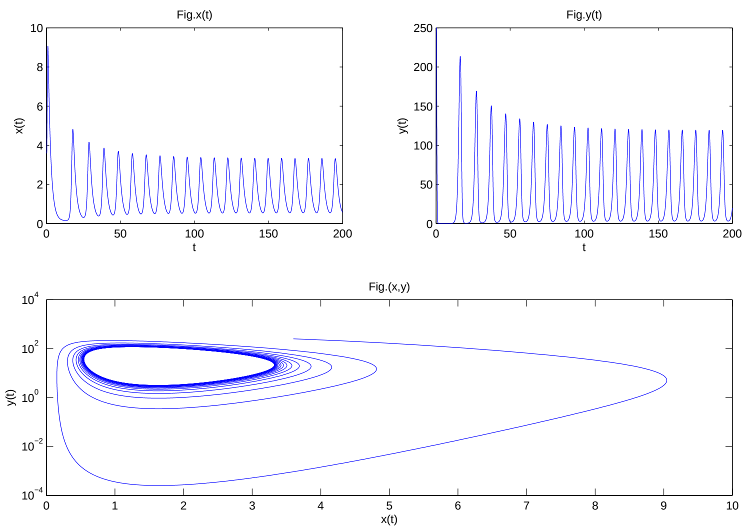

Figure 3: $\tau_1 = 0.3$, $\tau_2 = 0$, there is an asymptotically stable periodic solution around P_2.

Case 6.2. In this case, we assume $\tau_2 = 0$ and get a model with one delay about the suitable response after the recognition of non-self cells. This model was first presented in [9] and then Yafia [10] proved the Hopf bifurcation existence for $\omega > 0$.

For the coefficients satisfy condition (C), we can obtain the bifurcation point $\tau_1^0 = 0.2021$ for the eigenvalue is_0 $(s_0 = 0.8856)$. Then from Lemma 3.4, the $P_2 = (x_2, y_2)$ is asymptotically stable for $\tau_1 < \tau_1^0$ and unstable for $\tau_1 > \tau_1^0$. The stability of equilibrium P_2 and the periodic solution can be found in the Fig. 2 and Fig. 3.

The stability and direction of the Hopf bifurcation can be obtained by the similar method in [12].

Case 6.3. In this case, there are two delays. Regard τ_2 as a parameter and let $\tau_1 = 0.05 \in [0, \tau_1^0)$, we can obtain a unique root $s_0 = 0.8230$ of (3.5). Then, the Hopf bifurcation point is $\tau_2^0 = 0.9417$. Therefore, the positive equilibrium P_2 is stable when $\tau_2 < \tau_2^0$ and unstable when $\tau_2 > \tau_2^0$. It is shown that the Hopf bifurcation is supercritical in Figs. 4 and 5.

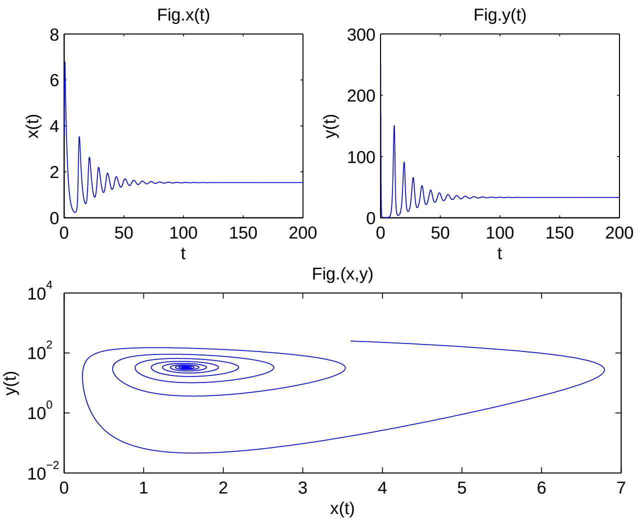

Figure 4: $\tau_1 = 0.05$, $\tau_2 = 0.1$, P_2 is asymptotically stable.

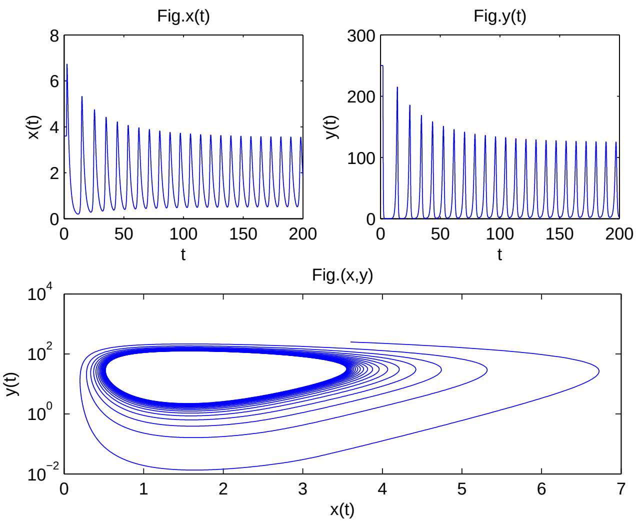

Figure 5: $\tau_1 = 0.05$, $\tau_2 = 2$, a stable periodic solution occurs.

Remark 6.1. From Figs. 2-5 the Runge-Kutta method (5.1) shows the same stability of nontrivial steady state as the exact solutions, which supports the result of Theorem 5.1.

Remark 6.2. This Runge-Kutta method and dde23 function in matlab get the similar results, in Figs. 6 and 7. We can not see which one is better directly. However, this Runge-Kutta method (5.1) is effective for solving the DDEs with multiple delays, and can get higher convergence order.

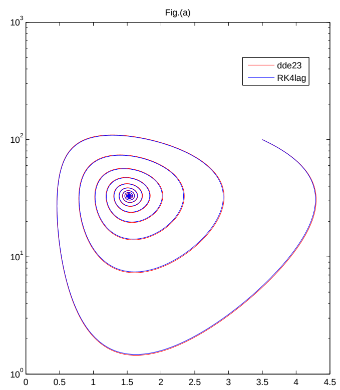

Figure 6: $\tau_1 = 0.05$, $\tau_2 = 0.1$, a stable periodic solution occurs. $h = 0.015$ (left), $h = 0.0012$ (right).

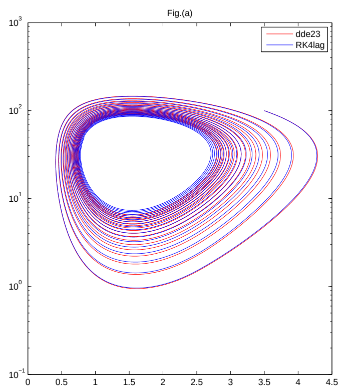

Figure 7: $\tau_1 = 0.05$, $\tau_2 = 2$, a stable periodic solution occurs. $h = 0.01$ (left), $h = 0.0012$ (right).

Acknowledgments

The authors wish to thank the anonymous referees for their valuable comments which helped us to improve the present paper. This work was supported by the National Natural Science Foundation of China (11101109, 11271102), the Natural Science Foundation of Heilongjiang Province of China (A201107) and SRF for ROCS, SEM.

References

[1] J. ADAM AND N. BELLOMO, A Survey of Models on Tumor Immune Systems Dynamics, Birkhäuser, Boston, 1996.

[2] R. BÜRGER, The Mathematical Theory of Selection, Recombination and Mutation, John Wiley, New York, 2000.

[3] O. DIECKMANN AND J. P. HEESTERBEEK, Mathematical Epidemiology of Infectious Diseases, John Wiley, New York, 2000.

[4] R. M. MAY AND M. A. NOWAK, Virus Dynamics (Mathematical Principles of Immunology and Virology), Oxford University Press, Oxford, 2000.

[5] A. ALBERT, M. FREEDMAN AND A. S. PERELSON, *Tumors and the immune system: the effects of a tumor growth modulator*, Math. Biosci., 50 (1980), pp. 25–58.

[6] R. M. THORN AND C. S. HENNEY, *Kinetic analysis of target cell destruction by effector T cell*, J. Immunol., 117 (1976), pp. 2213–2219.

[7] J. A. THOMA, G. J. THOMA AND W. CLARK, *The efficiency and linearity of the radiochromium release assay for cell-mediated cytotoxicity*, Cell. Immunol., 40 (1978), pp. 404–418.

[8] R. LEFEVER, J. HIERNAUX, J. URBAIN AND P. MEYERS, *On the kinetics and optimal specificity of cytotoxic reactions mediated by T-lymphocyte clones*, Bull. Math. Biol., 54 (1992), pp. 839–873.

[9] M. GALACH, *Dynamics of the tumor-immune system competition the effect of time delay*, Int. J. Appl. Comput. Sci., 13 (2003), pp. 395–406.

[10] R. YAFIA, *Hopf bifurcation in differential equation with delay for tumor-immune system competition model*, SIAM J. Appl. Math., 67 (2007), pp. 1693–1703.

[11] V. A. KUZNETSOV AND M. A. TAYLOR, *Nolinear dynamics of immunogenic tumors: parameter estimation and global bifurcation analysis*, Math. Biol., 56 (1994), pp. 295–321.

[12] B. HASSARD, N. KAZARINOFF AND Y. WAN, Theory and Applications of Hopf Bifurcation, Cambridge University Press, Cambridge, 1981.

[13] J. HALE, Theory of Functional Differential Equations, Springer, New York, 1977.

[14] K. J. IN'T HOUT, *A new interpolation procedure for adapting Runge-Kutta methods to delay differential equations*, BIT, 32 (1992), pp. 634–649.

[15] J. C. BUTCHER, The Numerical Analysis of Ordinary Differential Equations, John Wiley, Chichester, 1987.

[16] Q. WANG, D. S. LI AND M. Z. LIU, *Numerical Hopf bifurcation of Runge-Kutta methods for a class of delay differential equations*, Chaos Soliton Fract., 42 (2009), pp. 3087–3099.