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HOPF BIFURCATION ANALYSIS IN A SYSTEM FOR CANCER VIROTHERAPY WITH EFFECT OF THE IMMUNE SYSTEM

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Abstract. We consider a system of differential equations which is motivated biologically and simulates a cancer virotherapy. The existence of equilibrium points and their local stability are studied using the characteristic equation. We investigate Hopf bifurcation around the interior equilibrium point.

1. Introduction

Cancer is usually known by an unnatural growth in cell numbers which is called tumor and sometimes causes to death. Hence, Finding an effective method for controlling the growth rate of tumor always considered as a very important issue in medical science. Many efforts have been done to promote therapeutic ways for cancer. Surgery is the oldest one but it also contains collateral effects so that it is preferable that tumor is treated or controlled without surgery.

Cancer virotherapy is the new way which is used recently and it is effective in treatment and it uses virus to damage tumor cells. This method of therapy has been known in the early twentieth century. However, until 1949, serious experiments about it can not be found [6, 8, 4]. In the first experiments, virus found in the nature were used, but it failed because the immune system response damped the infection. Thus, prevented the virus from destroying the cancer [6, 3, 9]. The next step was done

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by genetic researchers. They produced a new generation of viruses in the laboratory which were capable for cancer virotherapy. The most important fact in the cancer treatment is the fewer non-tumor cells destroyed, the better treatment it could be. The best choice to achieve this goal is cancer virotherapy. These days, such viruses are categorized as oncolytic viruses.

There is a kind of killer cells in body which is known as cytotoxic T lymphocytes (CTL). It destroy foreign cells by knowing their special signals that have been sent to immune system. Recognizing cancer cells by immune system tumor-specific CTL starts to destroy them. Although, it may not damage all cancer cells, the cancer virotherapy after injection virus-specific CTL starts to know viruses and try to kill them. Therefore, both viruses and infected cells will be attacked by CTL. On the other hand, it helps to immune system for knowing more tumor cells which have not been recognized before. Then, tumor-specific CTL affects on both infected and non-infected cells to kill them [2, 5].

Experimental observations show that the interaction between the oncolytic virus and tumor might be too complicated. For this reason, it is almost impossible to figure out a complete theory, for finding all relations and analyzing them using the biological observations only. These convince researches to construct mathematical models simulating the virotherapy for studying unknown aspects of the phenomenon. Many of these effective models which are previously developed, based on system of differential equations [13, 12, 11, 7].

In 2001 Wodarz proposed the following system [13, 12]:

$$\dot{x} = rx(1 - \frac{x+y}{k}) - dx - \beta xy, \quad \dot{y} = \beta xy + sy(1 - \frac{x+y}{k}) - ay \tag{1.1}$$

where $y(t)$ and $x(t)$ are the number of infected and non-infected cells, respectively. Parameters s and r are the growth rate of infected and non-infected cells in a logistic model, respectively. Size of tumor of infected and non-infected tumor cells are considered to be limited by the carrying capacity k. If the total number of infected and non-infected tumor cells becomes more than k, the patient will die. Because of this fact we should have $x + y < k$. Parameter a is the death rate of infected cells by virus, and d is the death rate of non-infected cells by the immune system. Finally, β is the rate of viral infection spread in tumor cells. In the same article, Wodarz presented the following system:

$$
\begin{aligned}
\dot{x} &= rx(1 - \frac{x+y}{k}) - dx - \beta xy - P_t x Z_t, \\
\dot{y} &= \beta xy + sy(1 - \frac{x+y}{k}) - ay - P_v y Z_v - P_t y Z_t, \\
\dot{Z}_v &= C_v y Z_v - bZ_v, \\
\dot{Z}_t &= C_t y Z_t (x + y) - bZ_t.
\end{aligned}
\tag{1.2}
$$

This system contains four variables. Here, the number of virus-specific CTL and tumor-specific CTL are denoted by Z_v and Z_t, respectively. The rate of virus-specific CTL proliferate is $C_v y Z_v$ and the rate of killing the infected cells is $P_v y Z_v$. Virus-specific CTL will die at a rate bZ_v in the absence of infection. Tumor-specific CTL propagates at a rate C_t on infected and non-infected cells $(x + y)$. However, The warning signal, which is led to knowing tumor, has been recognized to be more useful in the presence of y virus. Finally, Tumor-specific CTL kills infected and non-infected cells at a rate $P_t Z_t$.

Wodarz introduced the System (1.2), but he did not present further mathematical analysis or simulation for it. In 2014, we analyzed System (1.1) [1]. Although, we know immune system response is an important factor which effect on virus therapy. Thus, we want to improve System (1.1) by considering immune system response with separate variable, which helped us to provide results that is closer than biology happening. We consider both CTL responses in one variable because some structure of responses for virus-specific CTL and tumor-specific CTL are similar. In addition, this assumption does not change the system and make its analysis easier by restricting the system into a third dimensional model.

In this paper, we introduce the system for interaction between non-infected cells, infected cells and CTL response as

$$\dot{x} = rx(1 - \frac{x+y}{k}) - \beta xy - p_1 xz, \tag{1.3}$$

$$\dot{y} = sy(1 - \frac{x+y}{k}) + \beta xy - p_2 yz - ay, \tag{1.4}$$

$$\dot{z} = c_1 xz + c_2 yz - bz. \tag{1.5}$$

The non-infected cells death with response of the immune system is presented by the term p_1xz. Infected tumor cells die with two process. They die with infection at a rate a and they die with response immune system which is given by the term p_2yz. On the other hand, CTL for tumor grows is presented by the term c_1xz and CTL for virus grows by the term c_2yz. Moreover, in the absence of any infection, the cells will die at a rate b. All the parameters of the system are non negative with initial population conditions $x(0) \geq 0$, $y(0) \geq 0$, $z(0) \geq 0$. This paper is organized as follows.

Section 2 contains the positivity and the boundedness of the model. In Section 3, we investigate the conditions for existence at positive equilibrium points and stability of important equilibrium points. We demonstrate the occurrence of Hopf bifurcation in Section 4.In Section 5, we present the numerical results. Finally, we draw some conclusion in Section 6.

2. Positively and boundedness of the solutions

The positivity and boundedness of the system (1.3-1.5) are necessary to make the system has biologically meaningful. Therefore, we study them first.

Theorem 2.1. *All the solutions of system (1.3-1.5) which starting in the $\mathbb{R}^3_+$ remain positive. Also, they remain bounded in the region $\Omega \subset \mathbb{R}^3_+$ defined by*

$$\Omega = \{(x, y, z) \in \mathbb{R}^3_+ | x \leq k, x + y \leq k, x + y + \frac{p}{c} z \leq \frac{(r + s)k}{m}\}.$$

Proof. Equation (1.3) can be written as $dx/x = \phi_1(x, y, z)dt$, where $\phi_1(x, y, z) = r(1 - \frac{x+y}{k}) - \beta y - p_1 z$. Then $x(t) = x(0)e^{\int_0^t \phi_1(x,y,z)dt} \geq 0$ for all $t \geq 0$ as $x(0) \geq 0$. Equation (1.4) gives $dy/y = \phi_2(x, y, z)dt$, where $\phi_2(x, y, z) = s(1 - \frac{x+y}{k}) + \beta x - p_2 z - a$. Then $y(t) = y(0)e^{\int_0^t \phi_2(x,y,z)dt} \geq 0$ for all $t \geq 0$ as $y(0) \geq 0$. Similarly, $z(t) \geq 0$ for all $t \geq 0$.
On the other hand, $\frac{dx}{dt} \leq rx(1 - \frac{x+y}{k}) \leq rx(1 - \frac{x}{k})$. Hence, we consider $dU/dt = rU(1 - \frac{U}{k})$, with solving this differential equation we have $U(t) = (\frac{k}{1-e^{kt_0 - rt}})$, which gives $\limsup_{t\to\infty} U(t) = k$. We know $dx/dt \leq dU/dt$, so $\limsup_{t\to\infty} x(t) \leq \limsup_{t\to\infty} U(t)$. Then, $\limsup_{t\to\infty} x(t) \leq k$. Simple calculations yield to

$$\begin{aligned} \frac{d}{dt}(x + y) &= rx(1 - \frac{x + y}{k}) - p_1 xz + sy(1 - \frac{x + y}{k}) - p_2 yz - ay \\ &\leq rx(1 - \frac{x + y}{k}) + sy(1 - \frac{x + y}{k}) \leq \delta(x + y)(1 - \frac{x + y}{k}) \end{aligned}$$

where $\delta = \max(r, s)$. Hence, similarly $\limsup_{t\to\infty}(x(t) + y(t)) \leq k$ for all $t \geq 0$.
Let $W(t) = x(t) + y(t) + \frac{p}{c} z(t)$ where $p = \min(p_1, p_2)$ and $c = \max(c_1, c_2)$. Then,

$$\begin{aligned} \frac{dW}{dt} &= \frac{dx}{dt} + \frac{dy}{dt} + \frac{p}{c}\frac{dz}{dt} = rx(1 - \frac{x + y}{k}) - p_1 xz + sy(1 - \frac{x + y}{k}) - p_2 yz - ay \\ &+ \frac{p}{c} c_1 xz + \frac{p}{c} c_2 yz - \frac{p}{c} bz \leq rx(1 - \frac{x + y}{k}) + sy(1 - \frac{x + y}{k}) - \frac{p}{c} bz \\ &\leq rx - \frac{r}{k} x^2 + sy - \frac{s}{k} y^2 - \frac{p}{c} bz = rk - (\sqrt{\frac{r}{k}} x - \sqrt{rk})^2 + sk \\ &- (\sqrt{\frac{s}{k}} y - \sqrt{sk})^2 - \frac{p}{c} bz - rx - sy \leq (r + s)k - mW \end{aligned}$$

where $m = \min(r, s, b)$. Therefore, $\limsup_{t\to\infty}(W(t)) \leq (r+s)k/m$. Thus, z is bounded above and all the solutions of the system (1.3-1.5) that started in $\mathbb{R}^3_+$ either approaches, enter or remain in the subset of

$$\Omega = \{(x, y, z) \in \mathbb{R}^3_+ | x \leq k, x + y \leq k, x + y + \frac{p}{c} z \leq \frac{(r+s)k}{m}\}.$$

Since the solutions of the system (1.3-1.5) remain bounded in the positively invariant region Ω, the model is well posed in the epidemiologically and mathematically senses.

□

3. Existence of equilibrium points and stability analysis

In this section, we study the stability of the equilibrium points.

3.1. **Equilibrium points.** System (1.3-1.5) always has two equilibrium points $E_0 = (0, 0, 0)$ and $E_1 = (k, 0, 0)$. Other equilibrium points are given by

$$\begin{aligned}
E_2 &= (0, \frac{k(s-a)}{s}, 0), \qquad E_3 = (0, \frac{b}{c_2}, \frac{-bs + c_2 k(s-a)}{c_2 k p_2}), \\
E_4 &= (\frac{b}{c_1}, 0, \frac{(c_1 k - b) r}{c_1 k p_1}), \quad E_5 = (\frac{ar + \beta k(a-s)}{\beta(\beta k + r - s)}, \frac{r(\beta k - a)}{\beta(\beta k + r - s)}, 0), \\
E_6 &= (\frac{-(a c_2 k p_1 - (b - c_2 k)(p_2 r - p_1 s) - b k p_2 \beta)}{(c_1 - c_2)(p_2 r - p_1 s) + k\beta(c_1 p_2 - c_2 p_1)} \\
&, \frac{a c_1 k p_1 - (b - c_1 k)(p_2 r - p_1 s) - b k p_1 \beta}{(c_1 - c_2)(p_2 r - p_1 s) + k\beta(c_1 p_2 - c_2 p_1)} \\
&, \frac{a(c_2 r - c_1(r + k\beta)) + \beta(-c_2 k r + c_1 k s + b(r - s + k\beta))}{(c_1 - c_2)(p_2 r - p_1 s) + k\beta(c_1 p_2 - c_2 p_1)}) := E^* = (x^*, y^*, z^*).
\end{aligned}$$

Equilibrium point E_0 means that the immune system cells, non-infected and infected tumor cells do not exist. Hence, in biology it means that both non-infected and infected cells damaged in the absence of immune system. Equilibrium point E_1 means that only non-infected tumor cells remain and the tumor grows to its carrying capacity, which shows the inefficiency of virotherapy. This equilibrium has been known as infection-free equilibrium.

The equilibrium points are biologically admissible if and only if all components are positive. If $s > a$, E_2 exists. Equilibrium point E_3 exists if $c_2k(s-a) > bs$. Furthermore, E_4 is meaningful if $c_k > b$. For existence of equilibrium point E_5 we have the following.

Case1 If $\beta k + r - s > 0$, then the denominator of components of equilibrium point E_5 is positive. Thus, for positivity of components of E_5, the numerators should be positive. Therefore, $ar + \beta k(a-s) > 0 \ and \ \beta k - a > 0$.

Case2 If $\beta k + r - s < 0$, then the denominator of components of equilibrium point E_5 is negative. Thus, we want that numerators are negative. For this we have $ar + \beta k(a-s) < 0 \ and \ \beta k - a < 0$.

Equilibrium E_6 is called interior equilibrium point. It means that immune system cells, non-infected and infected cells exist. This is compatible with what exactly can be seen in reality. Hence, E_6 is the most interesting equilibrium point from the biological point of view. For existence of E_6 we have:

Case1 If $(c_1-c_2)(p_2r-p_1s)+k\beta(c_1p_2-c_2p_1) > 0$, then the denominator of components of equilibrium point E_6 is positive. For existence of E_6, all components of E_6 should be positive. Therefore, all the numerators should be positive. Hence, we gain

$$-(ac_2kp_1 - (b - c_2k)(p_2r - p_1s) - bkp_2\beta) > 0,$$

$$ac_1kp_1 - (b - c_1k)(p_2r - p_1s) - bkp_1\beta > 0,$$

$$a(c_2r - c_1(r + k\beta)) + \beta(-c_2kr + c_1ks + b(r - s + k\beta)) > 0.$$

Case2 If $(c_1-c_2)(p_2r-p_1s)+k\beta(c_1p_2-c_2p_1) < 0$, then the denominator of components of equilibrium point E_6 is negative. Thus, all the numerators should be negative.

Hence, we get

$$-(ac_2kp_1 - (b - c_2k)(p_2r - p_1s) - bkp_2\beta) < 0,$$

$$ac_1kp_1 - (b - c_1k)(p_2r - p_1s) - bkp_1\beta < 0,$$

$$a(c_2r - c_1(r + k\beta)) + \beta(-c_2kr + c_1ks + b(r - s + k\beta)) < 0.$$

3.2. **Stability analysis.** We compute the variational matrix of the system (1.3-1.5) at any point (x, y, z). Real part of eigenvalues of this matrix at any point determine the local stability of equilibrium points. Variational matrix is given by $J = (J_{ij})_{3\times3}$, where

$$\begin{aligned} J_{11} &= r(1 - (x + y)/k) - (rx)/k - p_1z - y\beta, \quad J_{12} = -(rx)/k - x\beta, \quad J_{13} = -p_1x, \\ J_{21} &= -(sy)/k + y\beta, \quad J_{22} = s(1 - (x + y)/k) - (sy)/k - a - p_2z + x\beta, \\ J_{23} &= -p_2y, \quad J_{31} = c_1z, \quad J_{32} = c_2z, \quad J_{33} = c_1x + c_2y - b. \end{aligned}$$

At the equilibrium point E_0, the eigenvalues of J are r , $-b$ and $s - a$. Since r is positive, equilibrium point E_0 is always unstable. As a result, tumor will grow and therapy is failed in the absence of immune response and virus. In the following theorem, we study the local stability of the infection-free equilibrium.

Theorem 3.1. *The infection-free equilibrium of the system (1.3-1.5) is unstable for $k > (a/\beta)$ or $k > (b/c_1)$ and locally asymptotically stable for $k < (a/\beta)$ and $k < (b/c_1)$.*

Proof. The variational matrix of the system (1.3-1.5) at equilibrium point E_1 is given by

$$J(E_1) = \begin{bmatrix} -r & -r - k\beta & -kp_1 \\ 0 & k\beta - a & 0 \\ 0 & 0 & c_1k - b \end{bmatrix}.$$

Therefore, the eigenvalues are $-r$, $k\beta - a$, and $kc_1 - b$. Because $-r$ is negative, stability of E_1 depends on the signs of $k\beta - a$ and $kc_1 - b$. When $k > (a/\beta)$ or $k > (b/c_1)$, equilibrium point E_1 is unstable while it is asymptotically stable for $k < (a/\beta)$ and $k < (b/c_1)$. □

For local stability of interior equilibrium point we know that the characteristic equation of the variational matrix J at E_6 can be written as

$$Det(J - \lambda I_3) = \lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 = 0 \tag{3.1}$$

where

$$\begin{aligned} a_0 &= A_3A_5A_7 - A_2A_6A_7 - A_3A_4A_8 + A_1A_6A_8, \\ a_1 &= -(A_2A_4 - A_1A_5 + A_3A_7 + A_6A_8), \;\; a_2 = -(A_1 + A_5), \end{aligned} \tag{3.2}$$

where $(A_1 - A_8)$ are introduced below.

$$\begin{aligned} A_1 &= \frac{r(ac_2kp_1 - (b - c_2k)(p_2r - p_1s) - bkp_2\beta)}{k((c_1 - c_2)(p_2r - p_1s) + k(-c_2p_1 + c_1p_2)\beta)}, \\ A_2 &= \frac{(r + k\beta)(ac_2kp_1 - (b - c_2k)(p_2r - p_1s) - bkp_2\beta)}{k((c_1 - c_2)(p_2r - p_1s) + k(-c_2p_1 + c_1p_2)\beta)}, \\ A_3 &= \frac{p_1(-ac_2kp_1 + (b - c_2k)(p_2r - p_1s) + bkp_2\beta)}{(-c_1 + c_2)(p_2r - p_1s) + k(c_2p_1 - c_1p_2)\beta}, \\ A_4 &= \frac{(s - k\beta)(-ac_1kp_1 + (b - c_1k)(p_2r - p_1s) + bkp_1\beta)}{k((c_1 - c_2)(p_2r - p_1s) + k(-c_2p_1 + c_1p_2)\beta)}, \\ A_5 &= \frac{s(-ac_1kp_1 + (b - c_1k)(p_2r - p_1s) + bkp_1\beta)}{k((c_1 - c_2)(p_2r - p_1s) + k(-c_2p_1 + c_1p_2)\beta)}, \\ A_6 &= \frac{p_2(-ac_1kp_1 + (b - c_1k)(p_2r - p_1s) + bkp_1\beta)}{(c_1 - c_2)(p_2r - p_1s) + k(-c_2p_1 + c_1p_2)\beta}, \\ A_7 &= \frac{c_1(a(c_2r - c_1(r + k\beta)) + \beta(-c_2kr + c_1ks + b(r - s + k\beta)))}{(c_1 - c_2)(p_2r - p_1s) + k(-c_2p_1 + c_1p_2)\beta}, \\ A_8 &= \frac{c_2(a(c_2r - c_1(r + k\beta)) + \beta(-c_2kr + c_1ks + b(r - s + k\beta)))}{(c_1 - c_2)(p_2r - p_1s) + k(-c_2p_1 + c_1p_2)\beta}. \end{aligned} \tag{3.3}$$

Hence, in the following theorem we present some conditions for local stability of interior equilibrium point $E_6 = (x^*, y^*, z^*)$.

Theorem 3.2. *Let a_0, a_1 and a_2 be defined in (3.2). The interior equilibrium point of the system (1.3-1.5) is locally asymptotically stable if $a_0 > 0$ and $a_2a_1 - a_0 > 0$.*

Proof. According to Routh-Herwitz criterion of stability, the necessary and the sufficient conditions to all roots of characteristic equation (3.1) to be negative real parts are $a_2 > 0$, $a_0 > 0$, and $a_2a_1 - a_0 > 0$. It is clear that $a_2 > 0$. Thus, the interior equilibrium point E_6 is locally asymptotically stable if $a_0 > 0$ and $a_2a_1 - a_0 > 0$. □

4. Hopf bifurcation

In this section, we find the conditions for existence of Hopf bifurcation at the interior equilibrium point E_6. First we linearized equation (1.3-1.5) in E_6. Let $u_1(t) = x(t) - x^*$, $u_2(t) = y(t) - y^*$, and $u_3(t) = z(t) - z^*$. It leads us to E_6 to be the origin. Then (1.3-1.5) can be written as

$$\begin{aligned} \dot{u}_1 &= A_1u_1 + A_2u_2 + A_3u_3 - \frac{u_1}{k}(r(u_1+u_2) + kp_1u_3 + ku_2\beta), \\ \dot{u}_2 &= A_4u_1 + A_5u_2 + A_6u_3 - \frac{u_2}{k}(s(u_1+u_2) + kp_2u_3 - ku_1\beta), \\ \dot{u}_3 &= A_7u_1 + A_8u_2 + (c_1u_1 + c_2u_2)u_3 \end{aligned} \tag{4.1}$$

where $(A_1 - A_8)$ are introduced in (3.3). The linearization of (4.1) at (0, 0) is

$$\dot{u}_1 = A_1u_1 + A_2u_2 + A_3u_3, \;\; \dot{u}_2 = A_4u_1 + A_5u_2 + A_6u_3, \;\; \dot{u}_3 = A_7u_1 + A_8u_2$$

with the characteristic equation $\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 = 0$, where $a_2 = -(A_1 + A_5)$, $a_1 = -(A_2A_4 - A_1A_5 + A_3A_7 + A_6A_8)$, and $a_0 = A_3A_5A_7 - A_2A_6A_7 - A_3A_4A_8 + A_1A_6A_8$. If $a_0 = a_1a_2$, we have a pair of imaginary eigenvalues $\lambda_{1,2} = \pm i\sqrt{a_1}$. In this case, $\lambda_3 = -a_2$ is the real eigenvalue. Thus let $\epsilon = a_0 - a_1a_2$ and using the Implicit Function Theorem, we have $\lambda_{1,2} = \frac{-\epsilon}{2(a_1+a_2{}^2)} \pm i(\sqrt{a_1} + \epsilon\frac{\sqrt{a_1}a_2}{2a_1(a_1+a_2{}^2)}) + o(\epsilon^2)$ and

$\lambda_3 = -a_2 - \frac{\epsilon}{a_1 + a_2{}^2} + o(\epsilon^2)$. Furthermore, if $\epsilon = 0$, we may have Hopf bifurcation. On the other hand, solving a_2, a_1 and a_0 with respect to A_1, A_2 and A_3 respectively, we get

$$\begin{aligned}
A_1 &= -A_5 - a_2, \quad A_2 = -\frac{A_5{}^2 + A_3A_7 + A_6A_8 + a_1 + A_5a_2}{A_4}, \text{and} \\
A_3 &= -\frac{A_5{}^2A_6A_7 - A_4A_5A_6A_8 + A_6{}^2A_7A_8 - A_4a_0 + A_6A_7a_1 + A_5A_6A_7a_2}{A_4A_5A_7 + A_6A_7{}^2 - A_4{}^2A_8} \\
&+ \frac{A_4A_6A_8a_2}{A_4A_5A_7 + A_6A_7{}^2 - A_4{}^2A_8}.
\end{aligned}$$

In this case, we have 2-dimensional center manifold and afterwards by projecting this system on the center manifold we gain 2-dimensional system. First, we use the below transformation to get the standard system;

$$\begin{pmatrix} U_1 \\ U_2 \\ U_3 \end{pmatrix} = P^{-1} \begin{pmatrix} u_1 \\ u_2 \\ u_3 \end{pmatrix}, \text{and } P = \begin{bmatrix} P_1 & P_2 & P_3 \\ P_4 & P_5 & P_6 \\ 1 & 0 & 1 \end{bmatrix}$$

where

$$\begin{aligned}
P_1 &= \frac{A_5A_6A_7A_8 - A_4A_6A_8^2 - A_4A_8a_1}{(-A_5A_7 + A_4A_8)^2 + A_7^2a_1}, \; P_4 = -\frac{A_5A_6A_7^2 - A_4A_6A_7A_8 - A_4A_7a_1}{(-A_5A_7 + A_4A_8)^2 + A_7^2a_1}, \\
P_3 &= -\frac{-A_6A_8 + A_5a_2 + a_2^2}{A_5A_7 - A_4A_8 + A_7a_2}, \quad P_2 = -\frac{\sqrt{a_1}(A_5^2A_7 - A_4A_5A_8 + A_6A_7A_8 + A_7a_1)}{(-A_5A_7 + A_4A_8)^2 + A_7^2a_1}, \\
P_5 &= -\frac{\sqrt{a_1}(-A_4A_5A_7 - A_6A_7^2 + A_4^2A_8)}{(-A_5A_7 + A_4A_8)^2 + A_7^2a_1}, \; P_6 = -\frac{A_6A_7 - A_4a_2}{A_5A_7 - A_4A_8 + A_7a_2}.
\end{aligned}$$

Therefore, system (4.1) transforms into the following standard form;

$$\begin{aligned}
\dot{U}_1 &= -\sqrt{a_1}U_2 + G_1(U_1, U_2, U_3), \\
\dot{U}_2 &= \sqrt{a_1}U_1 + G_2(U_1, U_2, U_3), \qquad (4.2) \\
\dot{U}_3 &= -a_2U_3 + G_3(U_1, U_2, U_3)
\end{aligned}$$

where

$$
\begin{aligned}
G_1(U_1,U_2,U_3) &= \frac{1}{k\big((P_1-P_3)P_5+P_2(P_6-P_4)\big)}\Big(k\big((P_2P_6-P_3P_5)(U_1+U_3)\\
&\times (c_1(P_1U_1+P_2U_2+P_3U_3)+c_2(P_4U_1+P_5U_2+P_6U_3))\big)\\
&+ P_2(P_4U_1+P_5U_2+P_6U_3)(kp_2(U_1+U_3)+s((P_1+P_4)U_1\\
&+ (P_2+P_5)U_2+(P_3+P_6)U_3)-k(P_1U_1+P_2U_2+P_3U_3)\beta)\\
&- P_5(P_1U_1+P_2U_2+P_3U_3)(kp_1(U_1+U_3)+r((P_1+P_4)U_1\\
&+ (P_2+P_5)U_2+(P_3+P_6)U_3)+k(P_4U_1+P_5U_2+P_6U_3)\beta)\Big),\\
G_2(U_1,U_2,U_3) &= \frac{1}{k\big((P_1-P_3)P_5+P_2(P_6-P_4)\big)}\Big(k\big((P_3P_4-P_1P_6)(U_1+U_3)\\
&\times (c_1(P_1U_1+P_2U_2+P_3U_3)+c_2(P_4U_1+P_5U_2+P_6U_3))\big)
\end{aligned}
$$

$$
\begin{aligned}
&+ (P_1-P_3)(P_4U_1+P_5U_2+P_6U_3)(-kp_2(U_1+U_3)\\
&- s((P_1+P_4)U_1+(P_2+P_5)U_2+(P_3+P_6)U_3)\\
&+ k(P_1U_1+P_2U_2+P_3U_3)\beta)+(P_4-P_6)(P_1U_1+P_2U_2+P_3U_3)\\
&\times (kp_1(U_1+U_3)+r((P_1+P_4)U_1\\
&+ (P_2+P_5)U_2+(P_3+P_6)U_3)+k(P_4U_1+P_5U_2+P_6U_3)\beta)\Big),\\
G_3(U_1,U_2,U_3) &= \frac{1}{k\big((P_1-P_3)P_5+P_2(P_6-P_4)\big)}\Big(k\big((P_1P_5-P_2P_4)(U_1+U_3)\\
&\times (c_1(P_1U_1+P_2U_2+P_3U_3)+c_2(P_4U_1+P_5U_2+P_6U_3))\big)\\
&+ P_5(P_1U_1+P_2U_2+P_3U_3)(kp_1(U_1+U_3)+r((P_1+P_4)U_1\\
&+ (P_2+P_5)U_2+(P_3+P_6)U_3)+k(P_4U_1+P_5U_2+P_6U_3)\beta)\\
&- P_2(P_4U_1+P_5U_2+P_6U_3)(kp_2(U_1+U_3)+s((P_1+P_4)U_1\\
&+ (P_2+P_5)U_2+(P_3+P_6)U_3)-k(P_1U_1+P_2U_2+P_3U_3)\beta)\Big).
\end{aligned}
$$

By the existence theorem in the center manifold theory [10], there exists a center manifold which can be expressed locally as

$$W^c(0) = \{(U_1, U_2, U_3) \in R^3 | U_3 = h(U_1, U_2), |U_3| < \delta, h(0,0) = 0, Dh(0,0) = 0\}$$

for δ sufficiently small. We now compute $W^c(0)$. Assume that $h(U_1, U_2)$ have the following form:

$$U_3 = h(U_1, U_2) = b_1 U_1^2 + b_2 U_2^2 + b_3 U_1 U_2 + o(U_1, U_2). \tag{4.3}$$

Based on the invariance of $W^c(0)$ under the dynamics of (4.2), the center manifold must satisfy

$$\begin{aligned} \mathcal{N}(U_1, U_2) &= -a_2 h(U_1, U_2) + G_3(U_1, U_2, h(U_1, U_2)) \\ &- \frac{\partial h}{\partial U_1}(U_1, U_2)\big(-\sqrt{a_1} U_2 + G_1(U_1, U_2, h(U_1, U_2))\big) \end{aligned} \tag{4.4}$$

$$- \frac{\partial h}{\partial U_2}(U_1, U_2)\big(\sqrt{a_1} U_1 + G_2(U_1, U_2, h(U_1, U_2))\big).$$

Substituting (4.3) into (4.4) and equating terms of like powers to zero, we obtain

$$
\begin{aligned}
b_1 &= -\frac{1}{2a_2}\Big(2b_3\sqrt{a_1} + \big(2((-A_8c_1 + A_7c_2)(A_5^2A_7^2 - 2A_4A_5A_7A_8 + A_4^2A_8^2 + A_7^2a_1) \\
&\times (A_5A_6A_7 - A_4(A_6A_8 + a_1))^2 + (1/k)A_8(-A_4A_5A_7 - A_6A_7^2 + A_4^2A_8) \\
&\times (-A_5A_6A_7 + A_4(A_6A_8 + a + 1))(A_5^2A_7^2kp_1 + A_4^2A_8^2kp_1 - A_5A_7(2A_4A_8kp_1 \\
&+ A_6(A_7r - A_8r + A_7k\beta)) + A_7^2kp_1a_1 + A_4(A_7r - A_8r + A_7k\beta)(A_6A_8 + a_1)) \\
&- (1/k)A_7(A_5A_6A_7 - A_4(A_6A_8 + a_1))(A_5^2A_7 - A_4A_5A_8 + A_7(A_6A_8 + a_1)) \\
&\times (A_5^2A_7^2kp_2 + A_4^2A_8^2kp_2 - A_5A_7(2A_4A_8kp_2 + A_6(A_7s - A_8s + A_8k\beta)) \\
&+ A_7^2kp_2a_1 + A_4(A_7s - A_8s + A_8k\beta)(A_6A_8 + a_1)))(A_5A_7 - A_4A_8 + A_7a_2)\big)\Big/ \\
&\quad ((-A_4A_5A_7 - A_6A_7^2 + A_4^2A_8)(A_5^2A_7^2 - 2A_4A_5A_7A_8 + A_4^2A_8^2 \\
&+ A_7^2a_1)^2(a_1 + a_2^2))\Big), \\
b_2 &= -(1/(2\sqrt{a_1}))\Big(b_3a_2 + \big(\sqrt{a_1}(-A_4A_8 + A_7(A_5 + a_2))((((A_5A_7 - A_4A_8)^2 + A_7^2a_1) \\
&\times (A_5^2A_7c_1 + A_4^2A_8c_2 + A_6A_7(A_8c_1 - A_7c_2) - A_4A_5(A_8c_1 + A_7c_2) + A_7c_1a_1) \\
&\times (A_5A_6A_7 - A_4(A_6A_8 + a_1)) - (A_7(A_5A_6A_7 - A_4(A_6A_8 + a_1))(A_5^2A_7 \\
&- A_4A_5A_8 + A_7(A_6A_8 + a_1))(-(A_4^2A_8 - A_4A_5(A_7 + A_8) + A_7(A_5^2 - A_6A_7 \\
&+ A_6A_8 + a_1))s + (A_5^2A_7 - A_4A_5A_8 + A_7(A_6A_8 + a_1))k\beta))/k - (A_8(-A_7(A_4A_5 \\
&+ A_6A_7) + A_4^2A_8)(-A_5A_6A_7 + A_4(A_6A_8 + a_1))(A_4^2A_8(r + k\beta) - A_4A_5((A_7 \\
&+ A_8)r + A_7k\beta) + A_7((A_5^2 - A_6A_7 + A_6A_8 + a_1)r - A_6A_7k\beta)))/k - ((A_4A_5A_7 \\
&+ A_6A_7^2 - A_4^2A_8)(A_5^2A_7 - A_4A_5A_8 + A_7(A_6A_8 + a_1))(A_5^2A_7^2kp_1 + A_4^2A_8^2kp_1 \\
&+ A_7^2a_1kp_1 + A_4(A_6A_8 + a_1)(A_7r - A_8r + A_7k\beta) - A_5A_7(2A_4A_8kp_1 + A_6(A_7r \\
&- A_8r + A_7k\beta))))/k + ((A_4A_5A_7 + A_6A_7^2 - A_4^2A_8)(A_5^2A_7 - A_4A_5A_8 + A_7(A_6A_8
\end{aligned}
$$

$$
\begin{aligned}
&+ \quad a_1))(A_5^2A_7^2kp_2 + A_4^2A_8^2kp_2 + A_7^2a_1kp_2 + A_4(A_6A_8 + a_1)(A_7s - A_8s + A_8k\beta)\\
&- \quad A_5A_7(2A_4A_8kp_2 + A_6(A_7s - A_8s + A_8k\beta)))))/k)\Big/((-A_7(A_4A_5 + A_6A_7)\\
&+ \quad A_4^2A_8)((A_5A_7 - A_4A_8)^2 + A_7^2a_1)^2(a_1 + a_2^2)) + 1/a_2\sqrt{a_1}\big(2b_3\sqrt{a_1} + (2(-A_4A_8\\
&+ \quad A_7(A_5 + a_2))((-A_8c_1 + A_7c_2)((A_5A_7 - A_4A_8)^2 + A_7^2a_1)(A_5A_6A_7 - A_4(A_6A_8\\
&+ \quad a_1))^2 + (A_8(-A_7(A_4A_5 + A_6A_7) + A_4^2A_8)(-A_5A_6A_7 + A_4(A_6A_8 + a_1))\\
&\times \quad (A_5^2A_7^2kp_1 + A_4^2A_8^2kp_1 + A_7^2a_1kp_1 + A_4(A_6A_8 + a_1)(A_7r - A_8r + A_7k\beta)\\
&- \quad A_5A_7(2A_4A_8kp_1 + A_6(A_7r - A_8r + A_7k\beta)))))/k - 1/kA7(A_5A_6A_7 - A_4(A_6A_8\\
&+ \quad a_1))(A_5^2A_7 - A_4A_5A_8 + A_7(A_6A_8 + a_1))(A_5^2A_7^2kp_2 + A_4^2A_8^2kp_2 + A_7^2a_1kp_2\\
&+ \quad A_4(A_6A_8 + a_1)(A_7s - A_8s + A_8k\beta) - A_5A_7(2A_4A_8kp_2 + A_6(A_7s - A_8s\\
&+ \quad A_8k\beta)))))\Big/((-A_7(A_4A_5 + A_6A_7) + A_4^2A_8)((A_5A_7\\
&- \quad A_4A_8)^2 + A_7^2a_1)^2(a_1 + a_2^2)))\Big),\\
b_3 \quad &= \quad \Big(\sqrt{a_1}(A_5A_7 - A_4A_8 + A_7a_2)\big(-(2/k)(r - s + k\beta)a_1(-A_4^3A_5A_8^2 + A_7^2(A_5^2\\
&+ \quad A_6A_8 + a_1)(A_5^2 + A_6(-A_7 + A_8) + a_1) - A_4A_5A_7(2A_6A_8^2 + A_5^2(A_7 + 2A_8)\\
&+ \quad (A_7 + 2A_8)a_1) + A_4^2A_8(A_5^2(2A_7 + A_8) + A_7(A_6A_8 + a_1)))\\
&- \quad \frac{2}{-A_4A_5A_7 - A_6A_7^2 + A_4^2A_8}((-A_8c_1 + A_7c_2)(A_5^2A_7^2 - 2A_4A_5A_7A_8 + A_4^2A_8^2\\
&+ \quad A_7^2a_1)(A_5A_6A_7 - A_4(A_6A_8 + a_1))^2 + \frac{A_8}{k}(-A_4A_5A_7 - A_6A_7^2 + A_4^2A_8)\\
&\times \quad (-A_5A_6A_7 + A_4(A_6A_8 + a_1))(A_5^2A_7^2kp_1 + A_4^2A_8^2kp_1 - A_5A_7(2A_4A_8kp_1\\
&+ \quad A_6(A_7r - A_8r + A_7k\beta)) + A_7^2kp_1a_1 + A_4(A_7r - A_8r + A_7k\beta)(A_6A_8 + a_1))\\
&- \quad \frac{A_7}{k}(A_5A_6A_7 - A_4(A_6A_8 + a_1))(A_5^2A_7 - A_4A_5A_8 + A_7(A_6A_8 + a_1))(A_5^2A_7^2kp_2\\
&+ \quad A_4^2A_8^2kp_2 - A_5A_7(2A_4A_8kp_2 + A_6(A_7s - A_8s + A_8k\beta)) + A_7^2kp_2a_1 + A_4(A_7s\\
&- \quad A_8s + A_8k\beta)(A_6A_8 + a_1))) - \frac{1}{-A_4A_5A_7 - A_6A_7^2 + A_4^2A_8}((A_5^2A_7^2\\
&- \quad 2A_4A_5A_7A_8 + A_4^2A_8^2 + A_7^2a_1)(A_5^2A_7c_1 + A_4^2A_8c_2 + A_6A_7(A_8c_1 - A_7c_2)
\end{aligned}
$$

$$
\begin{aligned}
- & \quad A_4A_5(A_8c_1 + A_7c_2) + A_7c_1a_1)(A_5A_6A_7 - A_4(A_6A_8 + a_1)) \\
- & \quad \frac{-A_4A_5A_7 - A_6A_7^2 + A_4^2A_8}{k}(-A_5^2A_7 + A_4A_5A_8 - A_7(A_6A_8 + a_1))(A_5^2A_7^2kp_1 \\
+ & \quad A_4^2A_8^2kp_1 - A_5A_7(2A_4A_8kp_1 + A_6(A_7r - A_8r + A_7k\beta)) + A_7^2kp_1a_1 + A_4(A_7r \\
- & \quad A_8r + A_7k\beta)(A_6A_8 + a_1)) + \frac{-A_4A_5A_7 - A_6A_7^2 + A_4^2A_8}{k}(-A_5^2A_7 + A_4A_5A_8 \\
- & \quad A_7(A_6A_8 + a_1))(A_5^2A_7^2kp_2 + A_4^2A_8^2kp_2 - A_5A_7(2A_4A_8kp_2 + A_6(A_7s - A_8s \\
+ & \quad A_8k\beta)) + A_7^2kp_2a_1 + A_4(A_7s - A_8s + A_8k\beta)(A_6A_8 + a_1)) \\
- & \quad \frac{A_8(-A_4A_5A_7 - A_6A_7^2 + A_4^2A_8)}{k}(-A_5A_6A_7 + A_4(A_6A_8 + a_1))(A_4^2A_8(r + k\beta) \\
- & \quad A_4A_5(A_8r + A_7(r + k\beta)) + A_7(A_5^2r - A_6A_7r + A_6A_8r - A_6A_7k\beta + ra_1)) \\
- & \quad (A_7/k)(A_5A_6A_7 - A_4(A_6A_8 + a_1))(A_5^2A_7 - A_4A_5A_8 + A_7(A_6A_8 + a_1)) \\
\times & \quad (-A_4^2A_8s + A_4A_5(A_7s + A_8(s - k\beta)) + A_7(A_6A_7s - A_6A_8s + A_6A_8k\beta \\
+ & \quad A_5^2(-s + k\beta) - sa_1 + k\beta a_1)))a_2)\Big) \Big/ ((A_5^2A_7^2 - 2A_4A_5A_7A_8 + A_4^2A_8^2 + A_7^2a_1)^2 \\
\times & \quad (a_1 + a_2^2)(4a_1 + a_2^2))
\end{aligned}
$$

Finally, by substituting (4.3) into (4.2) we obtain the vector field reduced to the center manifold by

$$
\begin{aligned}
\dot{U}_1 &= -\sqrt{a_1}U_2 + \eta_1U_1U_2 + \eta_2U_1^2 + \eta_3U_2^2, \\
\dot{U}_2 &= \sqrt{a_1}U_1 + \theta_1U_1U_2 + \theta_2U_1^2 + \theta_3U_2^2
\end{aligned} \tag{4.5}
$$

where

$$
\begin{aligned}
\eta_1 &= -\Big(\sqrt{a_1}(-A_4A_8 + A_7(A_5 + a_2))\Big(\frac{-1}{-A_4A_8 + A_7(A_5 + a_2)}((A_5A_7 - A_4A_8)^2 \\
&+ \quad A_7c_1a_1) + A_7^2a_1)(A_5^2A_7c_1 + A_4^2A_8c_2 + A_6A_7(A_8c_1 - A_7c_2) - A_4A_5(A_8c_1 \\
&+ \quad A_7c_2)(A_6((A_5A_7 - A_4A_8)^2 + A_7^2a_1) + A_7(A_5A_6A_7 - A_4(A_6A_8 + a_1))a_2 \\
&+ \quad (A_4A_5A_7 + A_6A_7^2 - A_4^2A_8)a_2^2) + \frac{1}{k}\big(A_7(A_5A_6A_7 - A_4(A_6A_8 + a_1))(A_5^2A_7
\end{aligned}
$$

$$
\begin{aligned}
& - && A_4A_5A_8 + A_7(A_6A_8 + a_1))(-(A_4^2A_8 - A_4A_5(A_7 + A_8) + A_7(A_5^2 - A_6A_7 \\
& + && A_6A_8 + a_1))s + (A_5^2A_7 - A_4A_5A_8 + A_7(A_6A_8 + a_1))k\beta) + A_8(-A_7(A_4A_5 \\
& + && A_6A_7) + A_4^2A_8)(-A_5A_6A_7 + A_4(A_6A_8 + a_1))(A_4^2A_8(r + k\beta) - A_4A_5((A_7 \\
& + && A_8)r + A_7k\beta) + A_7((A_5^2 - A_6A_7 + A_6A_8 + a_1)r - A_6A_7k\beta)) + (A_4A_5A_7 \\
& + && A_6A_7^2 - A_4^2A_8)(A_5^2A_7 - A_4A_5A_8 + A_7(A_6A_8 + a_1))(A_5^2A_7^2kp_1 + A_4^2A_8^2kp_1 \\
& + && A_7^2a_1kp_1 + A_4(A_6A_8 + a_1)(A_7r - A_8r + A_7k\beta) - A_5A_7(2A_4A_8kp_1 + A_6(A_7r \\
& - && A_8r + A_7k\beta))) - (A_4A_5A_7 + A_6A_7^2 - A_4^2A_8)(A_5^2A_7 - A_4A_5A_8 + A_7(A_6A_8 \\
& + && a_1))(A_5^2A_7^2kp_2 + A_4^2A_8^2kp_2 + A_7^2a_1kp_2 + A_4(A_6A_8 + a_1)(A_7s - A_8s + A_8k\beta) \\
& - && A_5A_7(2A_4A_8kp_2 + A_6(A_7s - A_8s + A_8k\beta)))\Big)\Big)\Big/(2(-A_7(A_4A_5 + A_6A_7) \\
& + && A_4^2A_8)((A_5A_7 - A_4A_8)^2 + A_7^2a_1)^2(a_1 + a_2^2)), \\
\eta_2 & = && -\Big((-A_4A_8 + A_7(A_5 + a_2))\Big(\frac{1}{A_4A_8 - A_7(A_5 + a_2)}\big((A_8c_1 - A_7c_2)((A_5A_7 \\
& - && A_4A_8)^2 + A_7^2a_1)(-A_5A_6A_7 + A_4(A_6A_8 + a_1))(A_6((A_5A_7 - A_4A_8)^2 + A_7^2a_1) \\
& + && A_7(A_5A_6A_7 - A_4(A_6A_8 + a_1))a_2 + (A_4A_5A_7 + A_6A_7^2 - A_4^2A_8)a_2^2)\big) \\
& - && \frac{1}{k}\big(A_8(-A_7(A_4A_5 + A_6A_7) + A_4^2A_8)(-A_5A_6A_7 + A_4(A_6A_8 + a_1))(A_5^2A_7^2kp_1 \\
& + && A_4^2A_8^2kp_1 + A_7^2a_1kp_1 + A_4(A_6A_8 + a_1)(A_7r - A_8r + A_7k\beta) - A_5A_7(2A_4A_8kp_1 \\
& + && A_6(A_7r - A_8r + A_7k\beta))) + A_7(A_5A_6A_7 - A_4(A_6A_8 + a_1))(A_5^2A_7 - A_4A_5A_8 \\
& + && A_7(A_6A_8 + a_1))(A_5^2A_7^2kp_2 + A_4^2A_8^2kp_2 + A_7^2a_1kp_2 + A_4(A_6A_8 + a_1)(A_7s \\
& - && A_8s + A_8k\beta) - A_5A_7(2A_4A_8kp_2 + A_6(A_7s - A_8s + A_8k\beta))))\Big)\Big)\Big/ \\
& && ((-A_7(A_4A_5A_6A_7) + A_4^2A_8)((A_5A_7 - A_4A_8)^2 + A_7^2a_1)^2(a_1 + a_2^2)), \\
\eta_3 & = && -\Big(a_1(A_5^2A_7 - A_4A_5A_8 + A_7(A_6A_8 + a_1))(A_4^2A_8 - A_4A_5(A_7 + A_8) \\
& + && A_7(A_5^2 - A_6A_7 + A_6A_8 + a_1))(-A_4A_8 + A_7(A_5 + a_2))(r - s + k\beta)\Big)\Big/ \\
& && (((A_5A_7 - A_4A_8)^2 + A_7^2a_1)^2(a_1 + a_2^2)k),
\end{aligned}
$$

$$
\begin{aligned}
\theta_1 &= \frac{-(-A_4A_8+A_7(A_5+a_2))}{(-A_7(A_4A_5+A_6A_7)+A_4^2A_8)((A_5A_7-A_4A_8)^2+A_7^2a_1)^2(a_1+a_2^2)}\Big(((A_5A_7\\
&- A_4A_8)^2+A_7^2a_1)(A_5^2A_7c_1+A_4^2A_8c_2+A_6A_7(A_8c_1-A_7c_2)-A_4A_5(A_8c_1\\
&+ A_7c_2)+A_7c_1a_1)(-A_5A_6A_7+A_4(A_6A_8+a_1))a_2+\frac{1}{k(-A_4A_8+A_7(A_5+a_2))}\\
&\times \Big((A_7(A_5A_6A_7-A_4(A_6A_8+a_1))(-A_4A_7A_8(A_5a_1+(2A_5^2+A_6A_8+a_1)a_2\\
&+ 2A_5a_2^2)+A_4^2A_8^2(a_1+a_2(A_5+a_2))+A_7^2((A_5^2+a_1)a_2(A_5+a_2)+A_6A_8(-a_1\\
&+ A_5a_2)))(-(A_4^2A_8-A_4A_5(A_7+A_8)+A_7(A_5^2-A_6A_7+A_6A_8+a_1))s+(A_5^2A_7\\
&- A_4A_5A_8+A_7(A_6A_8+a_1))k\beta))-(A_8(-A_7(A_4A_5+A_6A_7)+A_4^2A_8)\\
&\times (-A_5A_6A_7+A_4(A_6A_8+a_1))(A_4A_8a_2+A_7(a_1-A_5a_2))(A_4^2A_8(r+k\beta)\\
&- A_4A_5((A_7+A_8)r+A_7k\beta)+A_7((A_5^2-A_6A_7+A_6A_8+a_1)r-A_6A_7k\beta)))\\
&+ ((-A_7(A_4A_5+A_6A_7)+A_4^2A_8)(A_5^2A_7-A_4A_5A_8+A_7(A_6A_8+a_1))(A_4A_8a_2\\
&+ A_7(a_1-A_5a_2))(A_5^2A_7^2kp_1+A_4^2A_8^2kp_1+A_7^2a_1kp_1+A_4(A_6A_8+a_1)(A_7r-A_8r\\
&+ A_7k\beta)-A_5A_7(2A_4A_8kp_1+A_6(A_7r-A_8r+A_7k\beta))))+(-A_7(A_4A_5+A_6A_7)\\
&+ A_4^2A_8)(-A_4A_7A_8(A_5a_1+(2A_5^2+A_6A_8+a_1)a_2+2A_5a_2^2)+A_4^2A_8^2(a_1+a_2(A_5\\
&+ a_2))+A_7^2((A_5^2+a_1)a_2(A_5+a_2)+A_6A_8(-a_1+A_5a_2)))(A_5^2A_7^2kp_2+A_4^2A_8^2kp_2\\
&+ A_7^2a_1kp_2+A_4(A_6A_8+a_1)(A_7s-A_8s+A_8k\beta)-A_5A_7(2A_4A_8kp_2+A_6(A_7s\\
&- A_8s+A_8k\beta)))\Big)\Big),\\
\theta_2 &= -\Big((-A_4A_8+A_7(A_5+a_2))\Big((A_8c_1-A_7c_2)((A_5A_7-A_4A_8)^2+A_7^2a_1)(A_5A_6A_7\\
&- A_4(A_6A_8+a_1))^2a_2+\frac{1}{(-A_4A_8+A_7(A_5+a_2))k}\Big(A_8(-A_7(A_4A_5+A_6A_7)\\
&+ A_4^2A_8)(-A_5A_6A_7+A_4(A_6A_8+a_1))(A_4A_8a_2+A_7(a_1-A_5a_2))(A_5^2A_7^2kp_1\\
&+ A_4^2A_8^2kp_1+A_7^2a_1kp_1+A_4(A_6A_8+a_1)(A_7r-A_8r+A_7k\beta)-A_5A_7(2A_4A_8kp_1\\
&+ A_6(A_7r-A_8r+A_7k\beta)))+A_7(A_5A_6A_7-A_4(A_6A_8+a_1))(-A_4A_7A_8(A_5a_1\\
&+ (2A_5^2+A_6A_8+a_1)a_2+2A_5a_2^2)+A_4^2A_8^2(a_1+a_2(A_5+a_2))+A_7^2((A_5^2+a_1)a_2
\end{aligned}
$$

$$
\begin{aligned}
\times \quad & (A_5+a_2)+A_6A_8(-a_1+A_5a_2)))(A_5^2A_7^2kp_2+A_4^2A_8^2kp_2+A_7^2a_1kp_2+A_4(A_6A_8 \\
+ \quad & a_1)(A_7s-A_8s+A_8k\beta)-A_5A_7(2A_4A_8kp_2+A_6(A_7s-A_8s+A_8k\beta)))\Big)\Big)\Big/ \\
& ((-A_7(A_4A_5+A_6A_7)+A_4^2A_8)\sqrt{a_1}((A_5A_7-A_4A_8)^2+A_7^2a_1)^2(a_1+a_2^2)), \\
\theta_3 \quad = \quad & \frac{-\sqrt{a_1}}{(((A_5A_7-A_4A_8)^2+A_7^2a_1)^2(a_1+a_2^2)k)}\Big((-A_5^2A_7+A_4A_5A_8-A_7(A_6A_8 \\
+ \quad & a_1))(A_4A_8a_2+A_7(a_1-A_5a_2))(A_4^2A_8(r+k\beta)-A_4A_5((A_7+A_8)r+A_7k\beta) \\
+ \quad & A_7((A_5^2-A_6A_7+A_6A_8+a_1)r-A_6A_7k\beta))-(-A_4A_7A_8(A_5a_1+(2A_5^2 \\
+ \quad & A_6A_8+a_1)a_2+2A_5a_2^2)+A_4^2A_8^2(a_1+a_2(A_5+a_2))+A_7^2((A_5^2+a_1)a_2(A_5+a_2) \\
+ \quad & A_6A_8(-a_1+A_5a_2)))(A_4^2A_8s+A_7(A_5^2-A_6A_7+A_6A_8+a_1)s-A_7(A_5^2+A_6A_8 \\
+ \quad & a_1)k\beta+A_4A_5(-(A_7+A_8)s+A_8k\beta))\Big).
\end{aligned}
$$

At the bifurcation point, System (4.5) becomes

$$
\begin{bmatrix} \dot{U}_1 \\ \dot{U}_2 \end{bmatrix} = \begin{bmatrix} 0 & -\sqrt{a_1} \\ \sqrt{a_1} & 0 \end{bmatrix} \begin{bmatrix} U_1 \\ U_2 \end{bmatrix} + \begin{bmatrix} f^1(U_1,U_2) \\ f^2(U_1,U_2) \end{bmatrix}
$$

where

$$
f^1(U_1,U_2)=\eta_1U_1U_2+\eta_2U_1^2+\eta_3U_2^2 \quad \text{and} \quad f^2(U_1,U_2)=\theta_1U_1U_2+\theta_2U_1^2+\theta_3U_2^2.
$$

The coefficient $a(0)\equiv a$ is given by

$$
\begin{aligned}
a \quad = \quad & \frac{1}{16}\big(f^1_{U_1U_1U_1}+f^1_{U_1U_2U_2}+f^2_{U_1U_1U_2}+f^2_{U_2U_2U_2}\big) \\
+ \quad & \frac{1}{16\sqrt{a_1}}\big(f^1_{U_1U_2}(f^1_{U_1U_1}+f^1_{U_2U_2})-f^2_{U_1U_2}(f^2_{U_1U_1}+f^2_{U_2U_2})-f^1_{U_1U_1}f^2_{U_1U_1}+f^1_{U_2U_2}f^2_{U_2U_2}\big).
\end{aligned}
$$

Therefore, $a=\frac{1}{8\sqrt{a_1}}\big(\eta_1(\eta_2+\eta_3)-\theta_1(\theta_2+\theta_3)-2\eta_2\theta_2+2\eta_3\theta_3\big)\neq 0$. Hence, from Hopf bifurcation theory in [10] we get Hopf bifurcation. Also, the periodic orbit is asymptotically stable for $a<0$ and unstable for $a>0$.

5. Numerical simulation

In this section, we carry out some numerical simulations to verify the previous results. Suppose that

$$\begin{aligned} r &= 1.1,\ \beta = 1,\ s = 1,\ k = 0.7,\ a = 0.47484, \\ b &= 0.1,\ p_1 = 1,\ p_2 = 2,\ c_1 = 2,\ c_2 = 0.1. \end{aligned} \tag{5.1}$$

In this case, $E_6 = (0.02468, 0.50642, 0.00937)$ and System (1.3-1.5) is given as

$$\begin{aligned} \dot{x} &= 1.1x(1 - \frac{x+y}{0.7}) - xy - xz, \\ \dot{y} &= y(1 - \frac{x+y}{0.7}) + xy - 2yz - 0.47484y, \\ \dot{z} &= 2xz + 0.1yz - 0.1z. \end{aligned}$$

Furthermore, restricted system to the center manifold is approximately given by

$$\begin{aligned} \dot{U}_1 &= -\sqrt{0.00675}U_2 + 0.77552U_1U_2 - 0.00471U_1^2 + 0.00471U_2^2, \\ \dot{U}_2 &= \sqrt{0.00675}U_1 + 1.87642U_1U_2 + 0.17083U_1^2 - 0.17078U_2^2. \end{aligned}$$

Thus $a_0 = a_1a_2 \approx 0.00445$, $\lambda_{1,2} \approx \pm i0.08217$ and $\lambda_3 = -0.65920$. In this case $a = -0.00013$. Therefore, we have Hopf bifurcation that bifurcating periodic orbit is stable. Thus, E_6 is unstable. These results are presented in Figures 1 and 2).

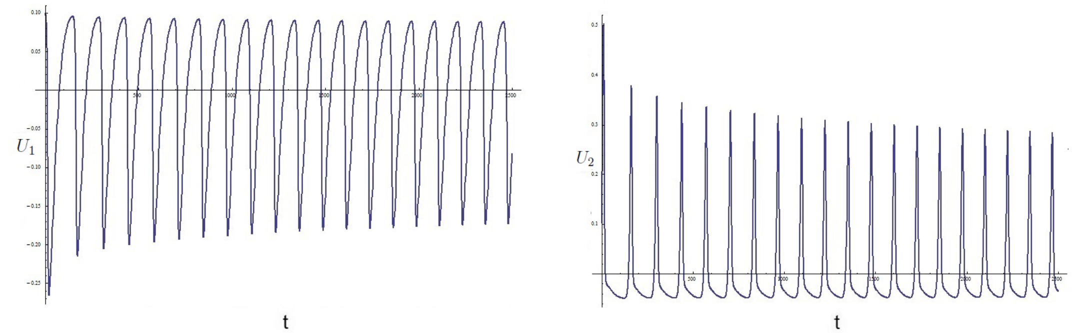

FIGURE 1. Components of the solution $U_1(t)$ and $U_2(t)$ with parameters given in (5.1).

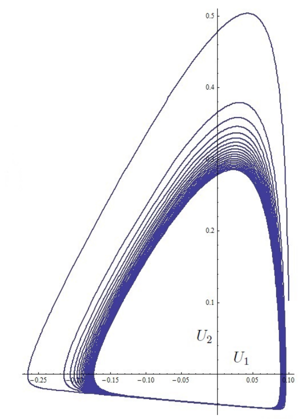

FIGURE 2. The bifurcating periodic solution.

6. Conclusion

In this paper, we consider a virus therapy for cancer and analyze stability of equilibrium points of this system. Equilibrium E_0 is unstable. It means that with this therapy, tumor does not completely destroy. Thus, we look for on other equilibrium points. Infection-free equilibrium point E_1 exists and may be stable. Stability of E_1 is not useful because it means that non-infected tumor cells exist then therapy fails.

We note that the interior equilibrium point E_6 is the most interesting equilibrium point from the biological point of view since its existence means that both of the non-infected and infected tumor cells and CTL exist. Its stability means that the tumor growth is controlled in a way that it can not reach to the carrying capacity k. Hence, under the conditions of the parameters in theorem 3.2, it means that with this therapy we could control the size of the tumor which is $x + y$, but tumor exists and not completely wasted. In addition, we noted that when $a_0 = a_1 a_2$, we have Hopf bifurcation in E_6. Moreover, theorem 3.2 means this equilibrium point is unstable. Hence, existence of Hopf bifurcation is not useful because Hopf cycle means that the size of tumor cells decreases. Exactly when we suppose that therapy is useful, tumor size increases, and this behavior repeated (See Figure 2). Although, this behavior means when we suppose that tumor treated, after some times we see that tumor grows. Thus, patient will die. Therefore, we attempted that value of parameters must be controlled in the way that we have not Hopf cycle.

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