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Transcritical bifurcation of an immunosuppressive infection model

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Abstract

In this paper, the dynamic behavior of an immunosuppressive infection model, specifically AIDS, is analyzed. We show through a simple mathematical model that a sigmoidal CTL response can lead to the occurrence of transcritical bifurcation. This condition usually occurs in immunodeficiency virus infections (such as AIDS infection) in which viruses attack immune cells $CD4^+T$. Our results imply that the dynamic interactions between the CTL immune response and HIV infection are very complex and in the CTL response, dynamics can exist the stable regions and unstable regions. At the end of the paper, numerical simulations are presented to illustrate the main results.

Keywords: CTL response; HAM/TSP; Transcritical bifurcation.

1 Introduction

One of the most complicated organs of higher organisms is the immune system. The function of the immune system is to fight off pathogenic organisms that enter and grow within the host (for example, viruses, bacteria, unicellular eukaryotic parasites such as malaria, and multicellular parasites such as worms). Immune responses can be subdivided broadly into two categories: (i) innate or nonspecific responses, and (ii) specific, adaptive responses. Innate immune mechanisms provide a first line of defense against an invading pathogen. They include physical barriers like the skin, changes in the environment of the body, such as fever, and immune cells that can fight pathogens

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in a nonspecific way. Nonspecific is the key word here and means that these responses cannot specifically recognize the physical structure of the pathogen. Instead, these nonspecifics sense that an invader is present and react. While such responses slow down the initial growth of a pathogen, they are usually insufficient to clear an infection. For removing an infection, a specific and adaptive immune response is required [14]. The adaptive immune response consists of three main branches. 1. The B cells secret antibodies that neutralize free virus particles. 2. The CTL (also known as $CD4^+$ T cells) attack infected cells. 3. The $CD4^+$ T helper cells are very important regulators that ensure that CTL and B cell responses are developed efficiently. In immunosuppressive infection models, infected cells attack to $CD4^+$ T cells and infect them; subsequently, they cannot help CTL and $CD4^+$ T cells to act efficiently. Mathematical models have been of central importance for understanding the dynamics between viral infections and immune responses, particularly in the context of a human immunodeficiency virus (HIV) infection [7]. Significant emphasis has been placed on the viral side of these dynamics, including the estimation of basic viral parameters. Subsequent work has focused on the immune side of these interactions in trying to explain a variety of experimental observations about the dynamics of immune cells in various infections. One particular part of the immune system that is very important in the fight against viral infections is the killer T cells or cytotoxic T lymphocytes (CTL). They basically fight intracellular pathogens [15]. Clinical data have shown that for some human pathogens, such as HIV, hepatitis B virus (HBV) and hepatitis C virus (HCV), drug therapy sometimes is not completely effective [7,13]. Recently, in 2015 [2,12] and 2014 [9], impaired immune responses in immunosuppressive infection models have attracted more and more attention. Mathematical models have been developed to capture the interaction *in vivo* among HIV [2,4,5,9,12,14,15].

The following model is general and satisfied the clinical data, so it was pursued by scientists; see the above references. In 2003, this model was developed and considered [5].

$$\begin{cases} \dot{y} = yg_r(y) - yz \\ \dot{z} = zf(y). \end{cases} \tag{1}$$

In this system, y is the virus population and z is the population of the immune cells. The function $g_r(y)$ should be satisfied in:

$$\begin{cases} 1. g_r(0) > 0,\ \frac{\partial g_r}{\partial y} < 0\ \forall y \\ 2. \exists\, y^* > 0\ , g_r(y^*) > 0,\ \frac{\partial g_r(y)}{\partial y} > 0 \forall r, y. \end{cases} \tag{2}$$

Also the following conditions were assumed for $f(y)$ in [5]

$$\begin{cases} 3. \exists\, y_1,\ y_2 > 0\ such\ that\ \ f(y_1) = f(y_2) = 0 \\ 4.\ \frac{\partial f}{\partial y} > 0\ for\ \ y = y_1\ and\ \ \frac{\partial f}{\partial y} < 0\ for\ \ y = y_2 \end{cases} \tag{3}$$

$g_r(y)$ is the virus growth function that depends on the viral replication rate, r, and $f(y)$ is the immune expansion function that does not depend on r. In the above case, when viral replication is high and the virus load is between y_1 and y_2, immune expansion is increasing and levels of antigen are sufficient to trigger sustained immunity [5]. In [5], a special function for $g_r(y)$ and $f(y)$ is introduced (see Model (12)). Model (12), in 2015 [2,12], was considered to investigate the stability of the CTL immune response. Shu et al [9] in 2014 obtained saddle point for system (12) which shows stable and unstable. Note that all the above investigations were on the eigenvalues with *the non-zero real part* and they didn't consider the zero eigenvalue (bifurcation theory).
In this paper, we are interested in only one zero eigenvalue of the system (12) at the fixed point, which can lead to the occurance of transcritical bifurcation [1, 6, 8]. Since our concentration is on AIDS, we change the condition (3), in order to consider a weak immune system. The difference between HIV and AIDS is: HIV is the beginning of the AIDS disease, in AIDS; virus load rises more sharply, and the $CD4^+$ T cell (which defend against ADIS cells) drops sharply [14]. From a mathematical point of view, $\frac{\partial f}{\partial y} > 0$ means that the function f is a strictly increasing function with respect to the variable y. From a biological perspective, it means that the function of immune system responses to the disease increase. In this study the conditions for $f(y)$ are as follows:

$$\begin{cases} 1.\ \exists\, y^* > 0\,;\, f(y^*) = 0 \\ 2.\ \frac{\partial f}{\partial y} = 0\ for\ y^* > 0. \end{cases} \tag{4}$$

The new conditions cause a critical situation for the function f. For this case, we try to find a zero eigenvalue to apply transcritical bifurcation. Bifurcation theory helps us to obtain conditions for the parameters to keep the disease stable. In other words, by finding a region for parameter r with respect to parameter k, we tried to keep the immune system in proper condition as long as possible. Our work is organized as follows:

In Section 2, we give some preliminary definitions of bifurcation and theorems, which are going to be used in other Sections. Section 3 is devoted to bifurcation of system (12). Section 4 illustrates our numerical results. Section 5 is the conclusion.

2 Preliminaries

Bifurcation theory is fundamental for the qualitative study of dynamical systems, and can be used to reveal complex dynamical behaviors of the biological systems under study, such as bistability, recurrence, and regular oscillation. Characterized by a controllable parameter, called the bifurcation parameter,

bifurcation occurs at a critical value of this parameter where the properties of equilibria change significantly.

We consider bifurcations of equilibria of autonomous systems which depend on one single parameter μ:

$$\dot{x} = f(x, \mu) \ , x \in \mathbb{R}^n \ , \mu \in \mathbb{R}. \tag{5}$$

The system (5) is called smooth if $f(x, \mu)$ is differentiable up to any order in both x and μ. Equilibria of (5) are solutions of the algebraic equations

$$f(x, \mu) = 0. \tag{6}$$

In order to graphically illustrate the dependence of an equilibrium x on μ, we require a scalar measure of the n-vector x. We shall use the notation $[x]$ for such a measure of x. A diagram depicting $[x]$ versus μ, where (x, μ) solves equation (1), will be called a bifurcation diagram. The continuous curves of solutions of (1) under variation of μ are called branches. The branches of smooth systems are continuous and smooth but can split into more branches. On a regular point of a branch, that is, on a point where the branch does not split or turn around, we can define the slope of the branch. We will use the following abbreviations:

$$J(x, \mu) := \frac{\partial f(x, \mu)}{\partial x}, \quad f_\mu := \frac{\partial f(x, \mu)}{\partial \mu}. \tag{7}$$

Both derivatives exist for a smooth system. Using the implicit function theorem it follows that, provided that the Jacobian matrix $J(x, \mu)$ is non-singular, locally (1) is equivalent to writing x as a function of μ, i.e, $0 = f(x(\mu), \mu)$. Then it follows from differentiating (1) with respect to μ that

$$J(x, \mu)\frac{dx}{d\mu} + f_\mu(x, \mu) = 0. \tag{8}$$

As $J(x, \mu)$ is non-singular, we can solve for $\frac{dx}{d\mu}$. A point (x, μ) is called regular if $det(J(x, \mu)) \neq 0$.

Definition 1 (Bifurcation). The appearance of a topologically nonequivalent phase portrait under a variation of parameters is called a bifurcation [1, 6, 8, 13, 25].

Definition 2. Transcritical bifurcation is a particular kind of local bifurcation, meaning that it is characterized by an equilibrium having an eigenvalue whose real part passes through zero.

A transcritical bifurcation is one in which a fixed point exists for all values of a parameter and is never destroyed. However, such a fixed point interchanges its stability region with instability region as the parameter is

varied. In other words, both before and after the bifurcation, there is one unstable and one stable fixed point [1, 6, 8, 13].

Theorem 1. *(Sotomayor Theorem) Suppose that* $f_{\mu_0}(x_0) = 0$ *and that* $n \times n$ *matrix* $A = Df(x_0, \mu_0)$ *has a simple eigenvalue* $\lambda = 0$ *with eigenvector* ν *and that* A^T *has an eigenvector* ω *corresponding to the eigenvalue* $\lambda = 0$. *Furthermore, suppose that* A *has* k *eigenvalues with a negative real part and* $(n - k - 1)$ *eigenvalues with a positive real part and that the following conditions are satisfied:*

$$\omega^T f_\mu(x_0, \mu_0) \neq 0 \ , \ \omega^T [D^2 f(x_0, \mu_0(\nu, \nu))] \neq 0 \tag{9}$$

then there is a smooth curve of equilibrium points for $\dot{x} = f(x, \mu)$ *in* $\mathbb{R}^n \times \mathbb{R}$*passing through* (x_0, μ_0) *and tangent to the hyperplane* $\mathbb{R}^n \times \mu_0$. *Depending on the signs of the expressions in (6). In this case the system experiences a saddle node bifurcation. If the conditions (9) are changed to :*

$$\begin{array}{l} \omega^T f_\mu(x_0, \mu_0) = 0, \\ \omega^T [D f_\mu(x_0, \mu_0)] \neq 0, \\ \omega^T [D^2 f(x_0, \mu_0)(\nu, \nu)] \neq 0, \end{array} \tag{10}$$

then the system (5) experiences a Pitchfork bifurcation. And if the condition (9) changed to:

$$\begin{array}{ll} \omega^T f_\mu(x_0, \mu_0) = 0, & \omega^T [D f_\mu(x_0, \mu_0)\nu] \neq 0, \\ \omega^T [D^2 f(x_0, \mu_0)(\nu, \nu)] = 0, & \omega^T [D^3 f(x_0, \mu_0)] \neq 0, \end{array} \tag{11}$$

then the system (5) experiences a Transcritical bifurcation.

Proof. For the proof, one can see [8]. □

3 Bifurcation of the system (12)

Consider the following system of differential equations:

$$\begin{cases} \dot{y} = ry(1 - \frac{y}{k}) - ay - pyz \\ \dot{z} = \frac{czy}{1+dy} - qyz - bz \end{cases} \tag{12}$$

where y and z are as before. The virus population is assumed to grow logistically: r is the viral replication rate at low viral loads, and we assume that this rate is decreased linearly with increased viral load to reach zero at a viral load k. Immune cells are assumed to be inhibited by the virus at a rate qyz and die at a rate b.
Clearly $E_0 = (0, 0)$ is a trivial equilibrium of the system. There exist an equilibrium $E_1 = (\bar{y}, 0) = (\frac{k}{r}(r - a), 0)$ provided $r > a > 0$.

The equilibrium E_1 is called the virus dominant equilibrium (VDE). Moreover, we can find another equilibrium $E^* = (y^*, z^*)$, where $y^* > 0$ and $z^* > 0$, satisfying the following equations:

$$\begin{cases} r(1 - \frac{y^*}{k}) - a - pz^* = 0 \\ \frac{cy^*}{1+dy^*} - qy^* - b = 0 \end{cases} \tag{13}$$

$E^* > 0$ means that while the virus population is growing, immune cells start to increase; therefore, our main attention will be on equilibrium E^*. It follows from the first equation of (13)

$$z^* = \frac{r(k - y^*) - ak}{pk} > 0 \tag{14}$$

By $z^* > 0$, one can find $\bar{y}$ such that

$$y^* < \bar{y} \tag{15}$$

In order to find y^* for E^*, we should solve the quadratic equation

$$h(y) = qdy^2 + (-c + q + bd)y + b = 0, \quad y^* < \bar{y} \tag{16}$$

to obtain a double root for (16), one should have

$$\Delta = 0 \Rightarrow (c - q - bd)^2 = 4bqd \Rightarrow c - q - bd = \pm 2\sqrt{bqd} \tag{17}$$

The minus sign for the root is not applicable, so

$$c - q - bd = 2\sqrt{bqd} \tag{18}$$

or equivalently $c = (\sqrt{q} + \sqrt{bd})^2$.

Conditions (17) and (18) on polynomial (16) lead to

$$g(y) = (y - \frac{c - q - bd}{2qd})^2 = (y - \frac{2\sqrt{bqd}}{2qd})^2 = (y - \sqrt{\frac{b}{qd}})^2 \tag{19}$$

Consequently,

$$y^* = \sqrt{\frac{b}{qd}} \tag{20}$$

and

$$E^* = (\sqrt{\frac{b}{qd}}, \frac{r(k - \sqrt{\frac{b}{qd}}) - ak}{pk}) \tag{21}$$

Because $y^* < \bar{y}$, we can define a threshold (see the following definition) as follow:

$$rk - ry^* > ak \Rightarrow r(k - y^*) > ak \Rightarrow r > \frac{ak}{k - y^*} \tag{22}$$

$$\Rightarrow r_t = \begin{cases} \frac{ak}{k-y^*} & \text{if } y^* < k \\ \infty & \text{if } y^* > k \end{cases} \tag{23}$$

Definition 3. In mathematical or statistical modeling, a threshold model is any model where a threshold value, or set of threshold values, is used to distinguish ranges of values where the behavior predicted by the model varies in some important way.
With the above statements, one can have the following lemma:

Lemma 1.*Suppose that (18) is satisfied.*
(a) If $r \leq a$, then the trivial equilibrium $E_0 = (0, 0)$ is the only equilibrium.
(b) If $a < r \leq r_t$ (i.e $a < r$ and $y^* \geq \bar{y}$), then there are two equilibria E_0 and $E_1 = (\bar{y}, 0)$, where $\bar{y} = \frac{k}{r}(r - a)$
(c) If $r_t < r$ (i.e $a < r$ and $y^* < \bar{y}$), then there are three equilibria, E_0, E_1 and additional equilibrium $E^* = (y^*, z^*)$ with $z^* = \frac{r(k-y^*)-ak}{pk}$.

We call E^* the immune control equilibrium(ICE).
Here we would like to determine the type of the equilibria (E_0, E_1 and E^*) for the system (12).

3.1 Global dynamics of (12)

Let (y^*, z^*) be an equilibrium of (12). The associated characteristic equation of (12) is given by

$$g_0(\lambda) = \lambda^2 + c_1\lambda + c_0 = 0 \tag{24}$$

where

$$c_1 = -(r - \frac{2r}{k}y^* - a - pz^* + \frac{cy^*}{1 + dy^*} - qy^* - b) \tag{25}$$

and

$$c_0 = (r - \frac{2r}{k}y^* - a - pz^*)(\frac{cy^*}{1+dy^*} - qy^* - b) + py^*(\frac{cz^*}{(1+dy^*)^2} - qz^*) \tag{26}$$

At $E_0 = (0, 0)$, two roots of the characteristic equation are $\lambda_1 = -b < 0$ and $\lambda_2 = -(a - r)$. Therefore, E_0 is stable if $r \leq a$. Otherwise, if $r > a$, then E_0 is a saddle point.
At E_1, $y^* = \bar{y}$, $z^* = 0$, a direct calculation implies that E_1 is stable.
At E^* we have

$$c_1 = \frac{ry^*}{k} > 0 \tag{27}$$

and

$$c_0 = py^*z^*(-q + \frac{c}{(1+dy^*)^2}) = py^*z^*g_1(y). \tag{28}$$

If $g_1(y) = 0$, then $\tilde{y} = \frac{\sqrt{c}-\sqrt{q}}{d\sqrt{q}}$. Substituting $\tilde{y}$ in $g(y)$ where

$$g(y) = (y - \frac{c - q - bd}{2qd})^2 \tag{29}$$

we have

$$\begin{aligned} g(\tilde{y}) &= (\frac{\sqrt{c} - \sqrt{q}}{d\sqrt{q}} - \frac{c - q - bd}{2qd})^2 \\ &= (\frac{\sqrt{q} + \sqrt{bd} - \sqrt{q} - \sqrt{bd}}{d\sqrt{q}})^2 = 0 \end{aligned} \tag{30}$$

$\tilde{y} = y^*$, therefore $c_0 = 0$
In this case since $\lambda_1 + \lambda_2 = -c_1 < 0$, $\lambda_1\lambda_2 = 0$ which gives us

$$\lambda_1 = 0 \tag{31}$$

and

$$\lambda_2 = -c_1 = -\frac{r}{k}\sqrt{\frac{b}{qd}} \tag{32}$$

The system (12) under condition (18) for the equilibrium E^* has one negative eigenvalue and one zero eigenvalue. Next we check the conditions for the

Transcritical bifurcation. For this purpose, we use Sotomayor theorem (see Theorem 2.3). In the following, we calculate the Jacobian matrix, second derivative of the Jacobian matrix and also eigenvector ν corresponding to eigenvalue $\lambda_1 = 0$ for A and ω,the eigenvector of $\lambda_1 = 0$, corresponding to A^T.
The Jacobian matrix of (12) is

$$A = \begin{bmatrix} r - \frac{2r}{k}y - a - pz & -py \\ \frac{cz}{(1+dy)^2} - qz & \frac{cy}{1+dy} - qy - b \end{bmatrix} \tag{33}$$

where condition (18) implies that

$$\frac{cz}{(1+dy)^2} - qz = \frac{cy}{1+dy} - qy - b = 0 \tag{34}$$

Therefore,

$$A = \begin{bmatrix} r - \frac{2r}{k}y - a - pz & -py \\ 0 & 0 \end{bmatrix} \tag{35}$$

The Jacobian matrix A at E^* will be

$$A_{E^*} = \begin{bmatrix} -\frac{r}{k}\sqrt{\frac{b}{qd}} & -p\sqrt{\frac{b}{qd}} \\ 0 & 0 \end{bmatrix} \tag{36}$$

By a direct calculation, the eigenvectors ν and ω are

$$\nu = (\nu_1, \nu_2) = (-\frac{kp}{r}, 1) \tag{37}$$

$$\omega = (\omega_1, \omega_2) = (0, 1) \tag{38}$$

$$D^2 f(E^*)(\nu,\nu) = \begin{bmatrix} \frac{\partial^2 f_1(E^*)}{\partial y^2}\nu_1\nu_1 + \frac{\partial^2 f_1(E^*)}{\partial y \partial z}\nu_1\nu_2 + \frac{\partial^2 f_1(E^*)}{\partial y \partial z}\nu_2\nu_1 + \frac{\partial^2 f_1(E^*)}{\partial z^2}\nu_2\nu_2 \\ \frac{\partial^2 f_2(E^*)}{\partial y^2}\nu_1\nu_1 + \frac{\partial^2 f_2(E^*)}{\partial y \partial z}\nu_1\nu_2 + \frac{\partial^2 f_2(E^*)}{\partial y \partial z}\nu_2\nu_1 + \frac{\partial^2 f_2(E^*)}{\partial z^2}\nu_2\nu_2 \end{bmatrix} = \begin{bmatrix} 0 \\ \sigma \end{bmatrix} \tag{39}$$

If $\sigma \neq 0$ implies that $D^2 f(E^*)(\nu,\nu) \neq 0$. Also, one should have

$$f_r(E^*) = \begin{pmatrix} \sqrt{\frac{b}{qd}}(1 - \frac{\sqrt{\frac{b}{qd}}}{k}) \\ 0 \end{pmatrix} \tag{40}$$

From (36) and (38), one can obtain

$$w^T f_r(E^*) = 0 \tag{41}$$

The above calculations and results lead to the conclusion that conditions (8) are valid. *Therefore, by the Sotomayor theorem, the system (10) undergoes transcritical bifurcation.*

4 Example (numerical simulation)

The parameters data are choosen such that the Figures 1-5 are in consistent with [2,4,5,9,12,14,15]. Since we are dealing with AIDS, the following Figures show the regions of weak immune response.

We try to find a region for parameter r with respect to parameter k. From (19), $r > \frac{ak}{k-y^*}$, but $y^* = \sqrt{\frac{b}{qd}}$, therefore

$$r > \frac{ak}{k - \sqrt{\frac{b}{qd}}} > 0 \tag{42}$$

so

$$k > \sqrt{\frac{b}{qd}} \tag{43}$$

Thus, the parameter region is obtained in Figure 1:

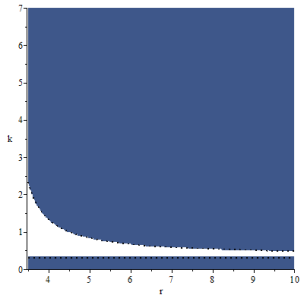

Figure 1: Parameter region r with respect to k by considering $a = 3$, $b = 2$, $q = 9$ and $d = 2$

We use numerical techniques to determine the system (12) with condition (18).

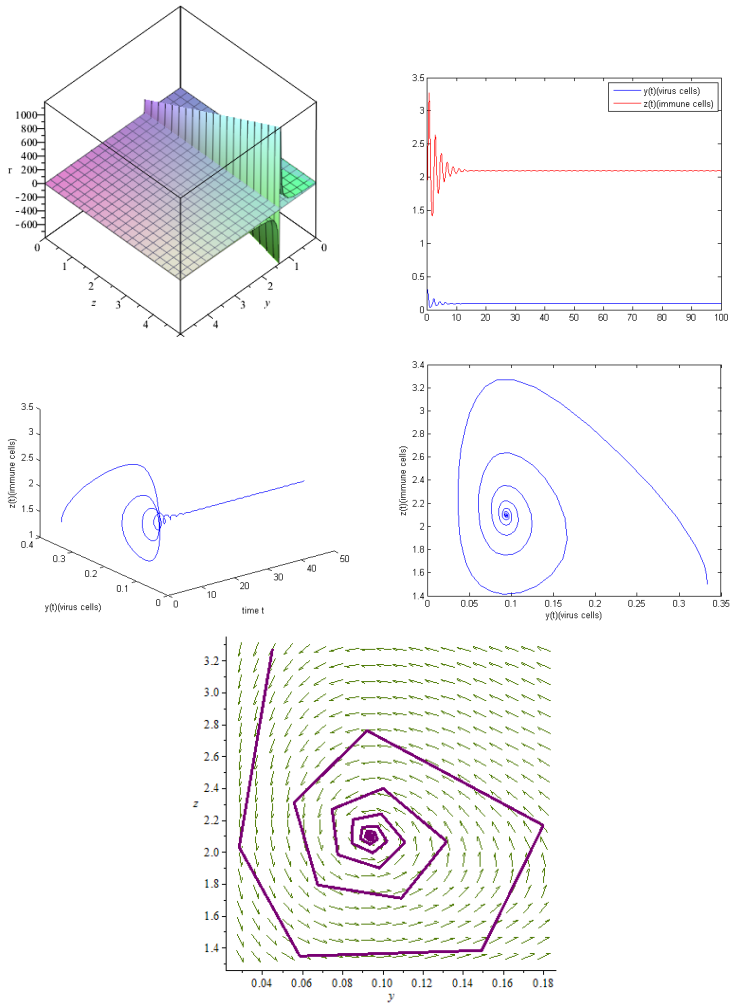

Figure 2: $a = p = 3$, $k = 4/3$, $q = 9$, $b = 2$ and $r = 10$ with initial condition $(\frac{1}{3}, \frac{3}{2})$

In Figure 2, first we obtain the parameter r with respect to y and z. Next by considering the values $a = p = 3$, $k = 4/3$, $q = 9$, $b = 2$ and $r = 10$, the stability regions of the orbits are investigated. Therefore, system (12) is in a steady state; this means that however the immune response of the body is so weak that is still can defend against the disease.
Figure 3 shows that after 100 days, immune cells could not control the growth of virus cells and so the system (12) is unstable.

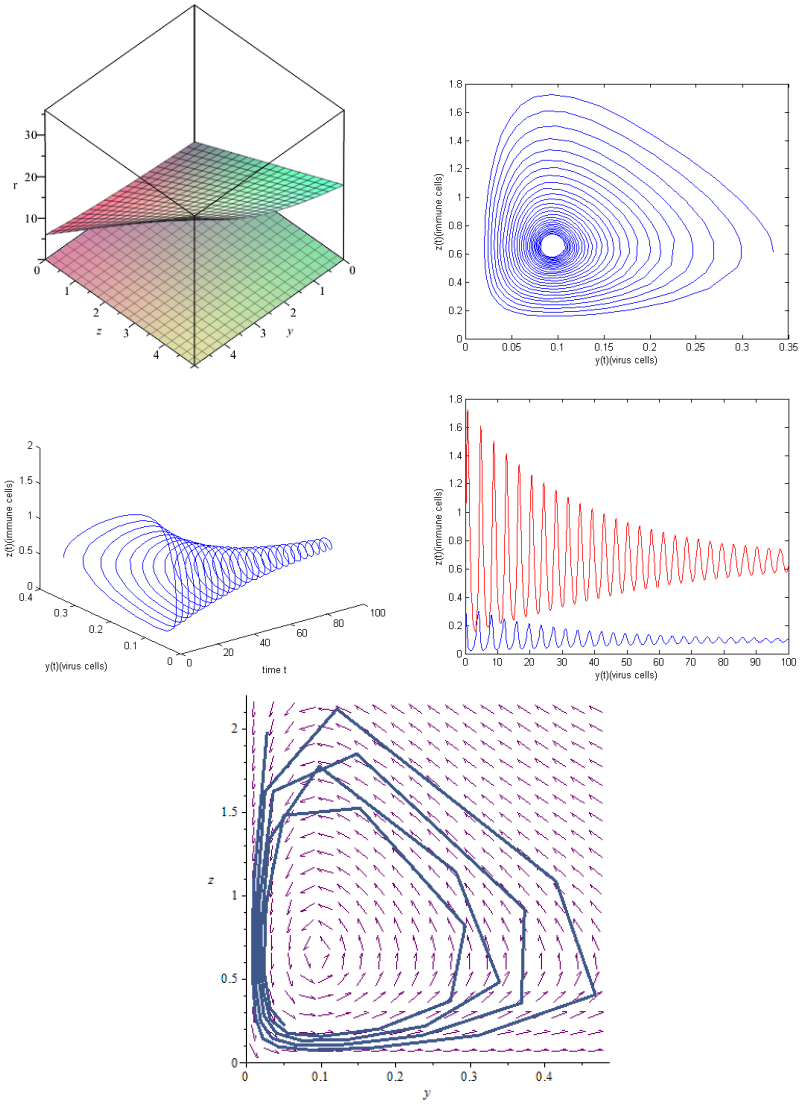

Figure 3: $a = p = 3$, $k = 10$, $q = 9$, $b = 2$ and $r = 5$ with initial condition $(\frac{1}{3}, \frac{2}{3})$

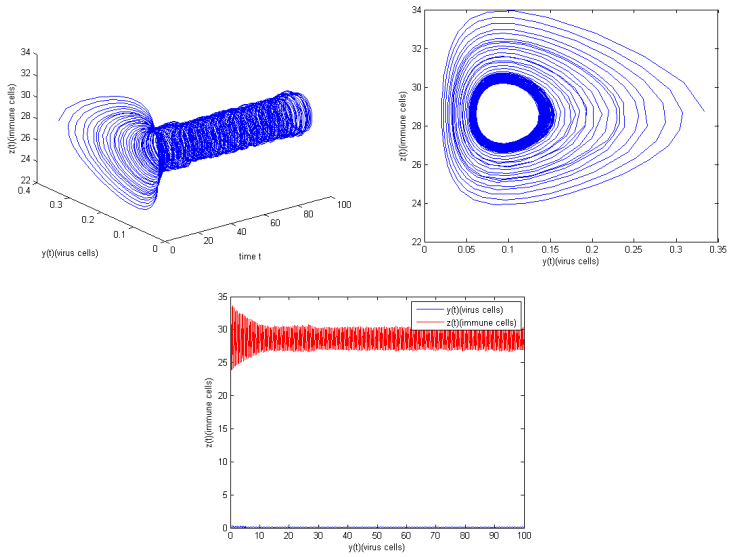

Figure 4: $a = 4$, $p = 3$, $k = 40$, $q = 9$, $b = d = 2$, $c = 36$ and $r = 5$ with initial condition $(\frac{1}{3}, \frac{115}{4})$

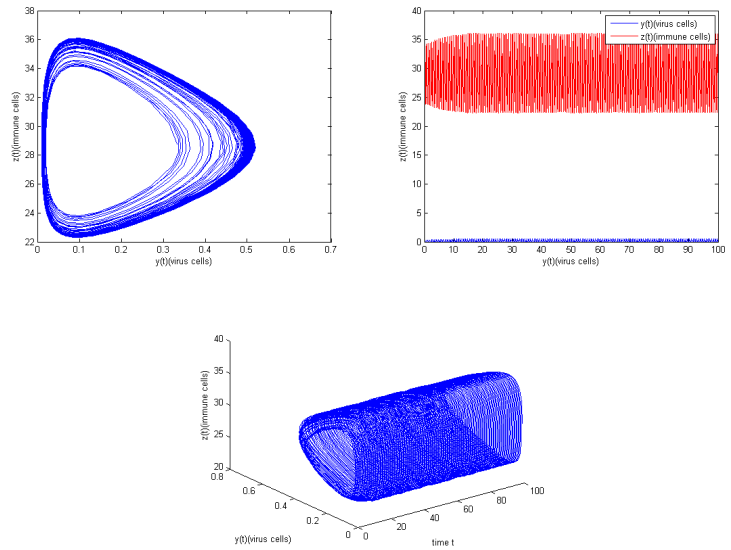

Figure 5: $a = 4$, $p = 3$, $k = 400$, $q = 9$, $b = d = 2$, $c = 36$ and $r = 5$ with initial condition $(\frac{1}{3}, \frac{115}{4})$

Results Figure 1 shows the region which one can choose r with respect to k. In Figure 2, k is small, so one can see the stable regions. Figures 3, 4 and 5 show an unstable region corresponding to an increase in the virus ($k \geq 10$). *Compares*: In this study by assuming condition (4), for system (12), we paid attention to AIDS. According to our knowledge, this condition that causes a complex dynamic is not considered in any related previous works [2, 9, 12]. The new condition was lead to an one zero eigenvalue and as a consequence, by applying Sotomayor theorem, to transcritical bifurcation. Therefore, we determined the stable and unstable regions (by different given values, small and large for k) by using transcritical bifurcation.

5 Conclusion

In this paper, we analyzed system (12), with condition (4), at the equilibrium corresponding to only one zero eigenvalue (co-dimension one bifurcation). In order to determine transcritical bifurcation, we applied condition (10) in Sotomayer theorem (see theorem 2.3). One can notice that as we mentioned in the results of our investigation, the difference between this study and others [2, 9, 12]. From the biological point of view, the stable and unstable regions correspond to the viral population load. Moreover Figures 3, 4 and 5 showed that the virus population of AIDS increases for the value of $k \geq 10$.

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انشعاب بحرانی دوسویه در مدل عفونی سرکوب کننده ی سیستم ایمنی بدن

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چکیده : در این مقاله، رفتار دینامیکی مدل عفونی سرکوب کننده ی سیستم ایمنی بدن، به ویژه ایدز، مورد تجزیه و تحلیل قرار گرفته است. ما نشان داده ایم که یک مدلسازی ساده ی ریاضی، با فرض پاسخ CTL (ایمنی بدن) به صورت تابع سیگموئید، می تواند منجر به انشعاب بحرانی دو سویه شود. معمولا این شرط، برای بیماری هایی که سیستم ایمنی بدن دچار نقص شده است (مانند ایدز) به وجود می آید و ویروس ها به سلول های ایمنی CD۴+T حمله می کنند. نتایج ما نشان می دهد که تقابل بین پاسخ ایمنی بدن و ویروس ها یHIV بسیار پیچیده است و ناحیه های دینامیکی پایدار و ناپایدار وجود دارند. در آخر با توجه به داده های کلینیکی، مثال هایی توسط شبیه سازی عددی که نشان گر نتایج اساسی است را ارائه می دهیم.

کلمات کلیدی : پاسخ CTL ؛ انشعاب بحرانی دو سویه؛ HAM/TSP .