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Dynamics of a Viral Infection Logistic Model with Delayed Nonlinear CTL Response and Periodic Immune Response

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Abstract

This paper investigates the global dynamics and bifurcation structure of a viral infection logistic model with delayed nonlinear CTL response and periodic immune response. It is proved that the basic reproduction numbers, R_0 and R_1, determine the outcome of viral infection. Besides changes in the amplititude of lytic component, we show, via numerical simulations, that , the birth rate of susceptible host cells and the maximum proliferation of target cells are crucial to the outcome of a viral infection. Time delay can alter the period of oscillation for the larger level of periodic forcing. Period doubling bifurcations of the system are observed via simulations. Our results can provide a possible explanation of the oscillation behaviors of virus population,which were observed in chronic HBV or HCV carriers.

Keywords: global stability, numerical simulation, uniform persistence, virus dynamics.

1. Introduction

The research on mathematical models has been very useful in order to understand the dynamics of immune responses. The basic viral infection model (De Boer & Perelson, 1995; De Boer & Perelson, 1998), contains three variables that depend on time, namely, $x(t)$, the population of uninfected cells, $y(t)$, the infected cells and $z(t)$, the number of cytotoxic T lymphocytes (CTLs). In (Liu,1997; Nowak & Bangham, 1996), the authors considered the dynamics of a virus population with lytic immune response, the infected cells become lysed by CTLs, $z(t)$ at a rate pyz, where the parameter p expresses the strength of the lytic component and it is a positive constant. Later on, (K. Wang, W. Wang, & Liu, 2006) considered that the strength of the lytic component was a sinusoidal function

$$p(t) = p_0 + p_1 \cos(2\pi t - \phi),$$

where p_0 is the basic strength of the lytic component, the amplitude $p_1(0 \leq p_1 < p_0)$ measures the degree of oscillation, and ϕ is the acrophase. The interaction between a population $y(t)$ and the number $z(t)$ was a linear CTL response $z' = cy - bz$. The CTL response expands in response to viral antigen derived from infected cells at a rate cy and decay in the absence of antigenic stimulation at a rate bz. Recently (Ji, Min, Zheng, & Su, 2010), considered a nonlinear CTL response $z' = cyz - bz$, with sinusoidal function $p(t) = p_0 + p_1 \cos(\frac{2\pi t}{T} - \phi)$, where T (days) represents the period of oscillation of the human immune system. The main purpose of both papers was to study the effect of oscillation of the immune system on the viral dynamic behaviors. In order to be more realistic we have considered a logistic proliferation (Hu, Zhang, Wang, Ma, & Liao, 2014; Yang, 2014; Ji, Min, & Ye, 2010) and time delays (Bai & Zhou, 2012). In (Bai & Zhou, 2012) the author considered the following mathematical model:

$$\begin{aligned} x'(t) &= s - dx(t) - \beta x(t)y(t) \\ y'(t) &= \beta x(t)y(t) - ay(t) - p(t)y(t)z(t) \\ z'(t) &= cy(t-\tau)z(t-\tau) - bz(t), \end{aligned} \tag{1}$$

where $x(t)$, $y(t)$, $z(t)$ denote the cell concentration of uninfected target cells, infected cells, and virus-specific CTLs at time t, with removal rates of d, a and b, respectively. Healthy cells are produced at a constant rate s. Infected cells are produced at rate βxy. The number of CTLs produced at time t is given by $cy(t-\tau)z(t-\tau)$, which depends on the number of CTLs and infected target cells at time $t-\tau$, for a time lag $\tau > 0$.

The authors studied the global dynamics, they showed that the basic reproduction numbers R_0 and R_1 determine the outcome of viral infection. Numerical simulations demonstrate that the changes in the amplitude of lytic component can generate a variety of dynamic patterns.

When stimulated by antigen or mitogen, T cells multiply through mitosis with a rate r, some scholars (Wang, Zhou, Wu, & Heffernan, 2009; Smith & De Leenheer, 2003; Zhou, Song, & Shi, 2008) incorporate simple logistic proliferation term $rx\left(1-\frac{x}{x_{max}}\right)$ into healthy CD4$^+$ T cells.

Motivated by the work above, we consider the following DDE model:

$$\begin{aligned} x'(t) &= s - dx(t) + rx(t)\left(1-\frac{x(t)}{k}\right) - \beta x(t)y(t) \\ y'(t) &= \beta x(t)y(t) - ay(t) - p(t)y(t)z(t) \\ z'(t) &= cy(t-\tau)z(t-\tau) - bz(t), \\ p(t) &= p_0 + p_1\cos(2\pi t - \phi), 0 \le p_1 < p_0, \end{aligned} \tag{2}$$

where the variables and parameters have the same biological meaning as in (1). r is the maximum proliferation rate of target cells and k is the maximum level of concentration of target cells in the body. The initial conditions for the system (2) are

$$\begin{aligned} x(\theta) = \phi_1(\theta),\ \ y(\theta) = \phi_2(\theta),\ \ z(\theta) = \phi_3(\theta), \\ \phi_i(\theta) \ge 0,\ \ \theta \in [-\tau, 0),\ \ \phi_i(0) > 0\ \ (i = 1, 2, 3). \end{aligned} \tag{3}$$

Here $(\phi_1(\theta), \phi_2(\theta), \phi_3(\theta)) \in C([-\tau, 0], \mathbb{R}^3_+)$ is the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into $\mathbb{R}^3_+$ with the topology of uniform convergence, where $\mathbb{R}^3_+ = \{(x_1, x_2, x_3) \mid x_i \ge 0, i = 1, 2, 3\}$

The purpose of this paper is to investigate the stability of system (2) and explore the effect the logistic growth of the healthy CD4$^+$ T cells in the dynamic of system (2).

We use a similar methodology as the one employed in Bai and Zhou (2012). Our model is more general, in particular, for $r = 0$, Bai and Zhou system is obtained. Different sufficient conditions are obtained for E_1, corresponding to the survival of free virus and the extinction of CTL response, it is called as immune-exhausted equilibrium; stability and numerical simulations are provided to illustrate our results for cases $R_1 < R_0 < 1$, $R_1 < 1 < R_0$, where R_0 and R_1 are called the basic reproduction number and the immune response reproductive number, respectively. Bai and Zhou state and prove the theorems, but they do not perform numerical simulations to illustrate their results for all the cases, they only consider the case $R_1 > 1$ in their numerical simulations. In our work, we additionally consider r as bifurcation parameter in the bifurcation diagrams. We note that for our system, multiple cyclic days appear sooner (for example, with $p_1 = 0.55$; in Bai and Zhou with $p_1 = 0.75$) than the mentioned reference. This phenomena also occurs with "r" as bifurcation parameter.

The organization of this paper is as follows: in the next section, we give some useful preliminaries result. In section 3, the stability properties of the viral free equilibrium are studied. The stability of the immune-exhausted equilibrium is investigated in the section 4. In Section 5, the uniform persistence of disease is presented. Numerical simulations are carried out to illustrate the main analytical results in section 6. In section 7,the conclusions are summarized.

2. Preliminary Results

Finding the points of equilibrium of the proposed system is equivalent to find the equilibria of the system without delay

$$\begin{aligned} s - dx + rx\left(1-\frac{x}{k}\right) - \beta xy = 0 \\ \beta xy - ay - pyz = 0 \\ cyz - bz = 0. \end{aligned} \tag{4}$$

If $y = z = 0$ and $x \neq 0$, we have that

$$s - dx + rx\left(1-\frac{x}{k}\right) = 0 \tag{5}$$

We obtain x from (5), naming it x_0:

$$x_0 = \frac{k}{2r}\left[(r-d) + \sqrt{(r-d)^2 + \frac{4rs}{k}}\right],$$

therefore a first point of equilibrium is given by

$$\left(\frac{k}{2r}\left[(r-d) + \sqrt{(r-d)^2 + \frac{4rs}{k}}\right], 0, 0\right).$$

Now, if $z = 0$ and $x, y \neq 0$, then

$$s - dx + rx\left(1 - \frac{x}{k}\right) - \beta xy = 0 \tag{6}$$

$$\beta xy - ay = 0. \tag{7}$$

From (7) we obtain x, then $x = \frac{a}{\beta}$. Replacing it in (6) we get

$$s - \frac{da}{\beta} + \frac{ra}{\beta} - \frac{ra^2}{\beta^2 k} - ay = 0. \tag{8}$$

Obtaining y from (8) we get $y = \frac{s}{a} + \frac{r}{\beta} - \frac{d}{\beta} - \frac{ra}{\beta^2 k}$. Then a second point of equilibrium is expressed by

$$\left(\frac{a}{\beta}, \frac{s}{a} + \frac{r}{\beta} - \frac{d}{\beta} - \frac{ra}{\beta^2 k}, 0\right)$$

Hence, there is only one disease-free $E_0 = \left(\frac{k}{2r}\left[(r-d) + \sqrt{(r-d)^2 + \frac{4rs}{k}}\right], 0, 0\right)$ and the system (2) also has equilibrium $E_1 = \left(\frac{a}{\beta}, \frac{s}{a} + \frac{r}{\beta} - \frac{d}{\beta} - \frac{ra}{\beta^2 k}, 0\right)$, which corresponds to the survival of free virus and the extinction of CTL. It is called an *immune-exhausted* equilibrium.

Next, we introduce the basic reproduction number for the viral infection according to the definition given in (Bacaër & Guernaoui 2006) and the theory developed in (Wang & Zhao, 2008) to the periodic case. Linearising the system (2) around E_0, we get the following equation for the infected cells y:

$$y'(t) = \beta x_0 y(t) - ay(t).$$

Let $F(t) = \beta x_0$ and $V(t) = a$. It follows from lemma 2.2 of Wang and Zhao (2008)that the basic reproduction number of system (2) is

$$R_0 = \frac{\int_0^1 F(t)dt}{\int_0^1 V(t)dt} = \frac{\beta x_0}{a} \quad \text{where} \quad x_0 = \frac{k}{2r}\left[(r-d) + \sqrt{(r-d)^2 + \frac{4rs}{k}}\right].$$

We denote

$$R_1 = \frac{k\beta}{2ar}\left[\left((r-d) - \frac{\beta b}{c}\right) + \sqrt{\left((r-d) - \frac{\beta b}{c}\right)^2 + \frac{4rs}{k}}\right].$$

It is easy to verify that $R_1 < R_0$; it also can be verified that E_1 exists if and only if $R_0 > 1$ and that

$$\hat{x} = \frac{a}{\beta} = \frac{x_0}{R_0} \quad \hat{y} = \frac{s}{a} + \frac{r}{\beta} - \frac{d}{\beta} - \frac{ra}{\beta^2 k} = (R_0 - 1)\left(\frac{s}{\beta x_0} + \frac{ar}{\beta^2 k}\right),$$

where $x_0 = \frac{k}{2r}\left[(r-d) + \sqrt{(r-d)^2 + \frac{4rs}{k}}\right]$.

The following result comes from (Xiao & Chen, 2001), lemma 2.1, will be used in our analysis.

Lemma 1. *Consider the delay differential equation*

$$x'(t) = ax(t-\tau) - bx(t),$$

where $a, b, \tau > 0$*;* $x(t) > 0$ *for all* $t \in [-\tau, 0]$*. The following holds:*

i) If $a < b$ *then* $\lim_{t\longrightarrow\infty} x(t) = 0$

ii) If $a > b$ *then* $\lim_{t\longrightarrow\infty} x(t) = +\infty$

Now we prove the following:

Lemma 2. *Under the initial conditions (3) all the solutions of system (2) are positive and ultimately uniformly bounded in* $C([-\tau, 0], \mathbb{R}^3_+)$.

Proof. Let us suppose that $x(t)$ is not always positive, and $t_1 > 0$ is the first time of t ($t > 0$) such that $x(t_1) = 0$. By the first equation of system (2), we have that $x'(t_1) = s > 0$. This means that $x(t) < 0$ for $(t_1 - \epsilon, t_1)$, where ϵ is a positive constant arbitrarily small. But this is a contradiction because $x(t)$ is always positive for $t < t_1$.

If $y(t) = 0$ is a constant solution of the system and $y(0) > 0$, the uniqueness and continuity of solutions guarantee us that, $y(t) > 0$ for all $t > 0$.

Now, we prove that $z(t)$ is positive. We realise that the third equation of system (2) can be rewritten in the following way

$$\frac{z'(t)}{z} \geq -b$$

$$\begin{aligned}
\int_0^t \frac{z'}{z} dt &\geq \int_0^t -b d\theta \\
Ln(z(t)) - Ln(z(0)) &\geq -\int_0^t b d\theta \\
Ln(z(t)) &\geq Ln(z(0)) - \int_0^t b d\theta \\
z(t) &\geq z(0)e^{-bt}.
\end{aligned}$$

Now by (3) we have that $z(t) > 0$ for all $t > 0$.

Now we show that the solutions of system (2) are uniformly bounded for all $t \geq 0$.

Let

$$L(t) = x(t) + y(t) + \frac{(p_0 - p_1)}{c} z(t + \tau),$$

then

$$\begin{aligned}
L'(t) &= x' + y' + \frac{(p_0 - p_1)}{c} z'(t + \tau) \\
&= s - dx + rx\left(1 - \frac{x}{k}\right) - ay - p(t)yz + \frac{p_0 - p_1}{c}(cyz - bz(t + \tau)).
\end{aligned}$$

Note that $-p_1 \leq p_1 \cos(2\pi t - \phi) \leq p_1$ then $p(t) = p_0 + p_1 \cos(2\pi t - \phi) \geq p_0 - p_1$, therefore $-p(t) \leq -(p_0 - p_1)$. Using the previous inequality, we obtain that,

$$\begin{aligned}
L'(t) &\leq s - dx + rx\left(1 - \frac{x}{k}\right) - ay - (p_0 - p_1)yz + \frac{p_0 - p_1}{c}(cyz - bz(t + \tau)) \\
&\leq s - dx - \frac{r}{k}\left(x - \frac{k}{2}\right)^2 + \frac{rk}{4} - ay - (p_0 - p_1)yz + \frac{p_0 - p_1}{c}(cyz - bz(t + \tau)) \\
&\leq \frac{4s + rk}{4} - dx - ay - \frac{(p_0 - p_1)b}{c} z(t + \tau) \\
&= \frac{4s + rk}{4} - mL(t),
\end{aligned}$$

where $m = \min\{d, a, b\}$. Hence $L(t) \leq \frac{4s+rk}{4m} + \epsilon$, where ϵ is an arbitrarily small constant, then $\limsup_{t \longrightarrow \infty} L(t) \leq \frac{4s+rk}{4m}$. Therefore $x(t)$, $y(t)$, and $z(t)$ are uniformly bounded in$C([-\tau, 0], \mathbb{R}^3_+)$. □

Lemma 3. *The following holds:*

$$\begin{aligned}
&If\ R_0 < 1 \Rightarrow \beta x_0 - a < 0 \\
&If\ R_0 = 1 \Rightarrow \beta x_0 - a = 0 \\
&If\ R_0 > 1 \Rightarrow \beta x_0 - a > 0
\end{aligned}$$

Proof.

$$\begin{aligned}\beta x_0 - a &= \frac{\beta k}{2r}\left[(r-d)+\sqrt{(r-d)^2+\frac{4rs}{k}}\right]-a\\ &= a\left(\frac{\beta k}{2ar}\left[(r-d)+\sqrt{(r-d)^2+\frac{4rs}{k}}\right]-1\right)\\ &= a\left(R_0-1\right).\end{aligned}$$

Therefore we have that if $R_0 < 1$, then $\beta x_0 - a < 0$; if $R_0 = 1$, then $\beta x_0 - a = 0$; if $R_0 > 1$, then $\beta x_0 - a > 0$. □

3. Stability Analysis Viral Free Equilibrium E_0

in this section, we shall consider the stability of the disease-free equilibrium E_0 of the system (2).

Theorem 4. *If $R_0 < 1$, then the disease-free equilibrium is globally asymptotically stable. It is unstable if $R_0 > 1$.*

Proof. Firstly, when $R_0 < 1$, Theorem 2.2 of Wang and Zhao (2008) implies that the disease-free equilibrium E_0 is locally asymptotically stable and is unstable if $R_0 > 1$. We now show that it attracts all nonnegative solutions of (2). If $(x(t), y(t), z(t))$ is a nonnegative solution of system (2) with initial conditions (3). From the first equation of the system, we have

$$x' < s + dx + rx\left(1-\frac{x}{k}\right).$$

Then follows from the standard comparison theorem that for any $\epsilon > 0$, there is a $\hat{t} > 0$ such that

$$x(t) < x_0 + \epsilon \ \ \forall t > \hat{t}$$

Thus, the second equation of (2) imply that

$$\begin{aligned}y' &\leq (\beta(x_0+\epsilon)-a)\,y\\ &\leq (\beta x_0 - a + \beta\epsilon)\,y\\ &\leq (\beta x_0 - a + \beta\epsilon)\,y \ \ \forall t > \hat{t}.\end{aligned}$$

Integrating the inequality from $\hat{t}$ to t ,

$$y \leq e^{(\beta x_0 - a + \beta\epsilon)(t-\hat{t})} \ \ \forall t > \hat{t}.$$

Provided that $R_0 < 1$, by lemma (3) $\beta x_0 - a < 0$ and for ϵ small enough $(\beta x_0 - a + \beta\epsilon) < 0$. This shows that $\lim_{t\longrightarrow\infty} y(t) = 0$. For any ϵ_1 sufficiently small and satisfying $\epsilon_1 < \frac{b}{c}$, there is a $T > 0$ that such for $t > T + \tau$, $z'(t) \leq c\epsilon_1 z(t-\tau) - bz(t)$. According to lemma (1) we obtain $\lim_{t\longrightarrow\infty} z(t) = 0$. If $x(0) = x_0$ then $\lim_{t\longrightarrow\infty} x(t) \leq x_0$. This implies global asymptotic stability. This completes the proof of the theorem. □

4. Stability of the Immune-exhausted Equilibrium E_1

In this section, we study the stability of the immune-exhausted equilibrium E_1.

Define

$$R_1' = \frac{4c\beta s + \beta crk + 4ca\beta x_0}{4ca\tilde{d} + 4b\beta\tilde{d}}.$$

Where $\tilde{d} = \min\{a, d\}$.

Theorem 5. *If $R_1 < 1 < R_0$, then E_1 is locally asymptotically stable. Moreover, if $R_1' < 1 < R_0$, then E_1 is globally asymptotically stable.*

Proof. Linearising the system (2) around E_1 we obtain

$$\begin{aligned}x_1' &= \left[-(d+\beta\hat{y})+r-\frac{2r\hat{x}}{k}\right]x_1 - \beta\hat{x}y_1\\ y_1' &= \beta\hat{y}x_1 - p(t)\hat{y}z_1\\ z_1' &= c\hat{y}z_1(t-\tau) - bz_1.\end{aligned} \tag{9}$$

Once this task is achieved, we just need to investigate the zero solution (or equilibrium) of system (9). Provided that $R_1 < 1 < R_0$ holds, then $c\hat{y} < b$. Therefore lemma (1) implies that $\lim_{t\to\infty} z_1(t) = 0$. Hence we get the following system:

$$\begin{aligned} x_1' &= \left[-(d+\beta\hat{y}) + r\left(1-\frac{2\hat{x}}{k}\right)\right]x_1 - \beta\hat{x}y_1 \\ y_1' &= \beta\hat{y}x_1 - p(t)\hat{y}z_1. \end{aligned}$$

The previous system can be regarded in the following way:

$$\begin{pmatrix} x_1' \\ y_1' \end{pmatrix} = \begin{pmatrix} -(d+\beta\hat{y}) + r\left(1-\frac{2\hat{x}}{k}\right) & -\beta\hat{x} \\ \beta\hat{y} & 0 \end{pmatrix}\begin{pmatrix} x_1 \\ y_1 \end{pmatrix} + \begin{pmatrix} 0 \\ -p(t)\hat{y}z_1 \end{pmatrix}.$$

It is of the form $X' = Ax + F(t)$. For $(x(0), y(0)) \in \mathbb{R}^2_+$ the solution is

$$\begin{pmatrix} x_1' \\ y_1' \end{pmatrix} = e^{At}\begin{pmatrix} x_1(0) \\ y_1(0) \end{pmatrix} + \int_0^t e^{A(t-s)}\begin{pmatrix} 0 \\ -p(s)\hat{y}z_1(s) \end{pmatrix} ds,$$

where

$$A = \begin{pmatrix} -(d+\beta\hat{y}) + r\left(1-\frac{2\hat{x}}{k}\right) & -\beta\hat{x} \\ \beta\hat{y} & 0 \end{pmatrix}.$$

Knowing that $\hat{x}$,$\hat{y}$ satisfies the first equation of system (2), we have that $-(d+\beta\hat{y}) + r\left(1-\frac{\hat{x}}{k}\right) - \frac{r\hat{x}}{k} = -\frac{s}{\hat{x}} - \frac{r\hat{x}}{k} = -\left(\frac{\beta s}{a} + \frac{ar}{k\beta}\right)$, then we can rewrite the matrix A as:

$$A = \begin{pmatrix} -\left(\frac{\beta s}{a} + \frac{ar}{k\beta}\right) & -\beta\hat{x} \\ \beta\hat{y} & 0 \end{pmatrix}.$$

Clearly the eigenvalues of A have negative real part, then there exists a constant C and μ both positive such that $\| e^{At} \| \leq Ce^{-\mu t}$ for all $t \geq 0$. Note that zero is a solution of the third equation of (9) and it is asymptotically stable when $c\hat{y} < b$. Therefore for $\epsilon > 0$ there exists $\delta_1 = \delta(\epsilon)$ such that if $\| \phi \| < \delta_1$ with $\phi \in C^+$, $\phi(0) > 0$, then $z_1(t) < \epsilon$.

Let

$$\| z_1(t,\phi) \| < \min\left\{\frac{\mu\epsilon}{2\sqrt{2}C(p_0+p_1)\hat{y}}, \frac{\epsilon}{2\sqrt{2}C}\right\} \; t \in (0,\infty).$$

Then choose $\delta_2 = \frac{\epsilon}{2\sqrt{2}C}$ such that $\| (x_1(0), y_1(0))^T \| < \delta_2$ and

$$\begin{aligned} \| (x_1(t), y_1(t))^T \| &\leq Ce^{-\mu t} \| (x_1(0), y_1(0))^T \| + \| \int_0^t e^{A(t-s)}(0, -p(s)\hat{y}z_1(s))^T \| ds \\ &\leq Ce^{-\mu t} \| (x_0, y_0)^T \| + C(p_0+p_1)\hat{y}\int_0^t e^{-\mu(t-s)} \| z_1(s) \| ds \\ &\leq C\frac{\epsilon}{2\sqrt{2}C} + \frac{C(p_0+p_1)\hat{y}}{\mu} \cdot \min\left\{\frac{\mu\epsilon}{2\sqrt{2}(p_0+p_1)\hat{y}}, \frac{\epsilon}{2\sqrt{2}}\right\} \\ &= \frac{\epsilon}{2\sqrt{2}} + \frac{\epsilon}{2\sqrt{2}} = \frac{\epsilon}{\sqrt{2}}. \end{aligned}$$

If we choose $\delta = \min\{\delta_1, \delta_2\}$ and $\| \psi \| = \| (x_1(0), y_1(0), \phi) \| < \delta$, then $\| x_1(t,\psi), y_1(t,\psi), z_1(t,\psi) \| < \epsilon$, this implies the stability of the zero solution of (9).

The next step is to show that each nonnegative solution of (2) converges to E_1 when $R_1' < 1 < R_0$ holds. Taking the two first equations of system (2) we have:

$$\begin{aligned} x' + y' &= s - dx + rx\left(1-\frac{x}{k}\right) - ay - p(t)yz \\ &= s - dx - \frac{r}{k}\left(x - \frac{k}{2}\right)^2 + \frac{rk}{4} - ay - p(t)yz + ax_0 - ax_0 \\ &\leq s - dx - ay + \frac{rk}{4} + ax_0 \\ &= \frac{4s + 4ax_0 + rk}{4}s - \tilde{d}(x+y), \end{aligned}$$

where $\tilde{d} = \min\{a, d\}$, which implies that $\limsup_{t\to\infty}(x+y) = \frac{4s+4ax_0+rk}{4\tilde{d}}$. Hence for $\epsilon_1 > 0$ there exists a $t_1 > 0$ such that for $t > t_1$

$$y' \leq \left(\beta\left(\frac{4s+4ax_0+rk}{4\tilde{d}} + \epsilon_1 - y\right) - a\right)y.$$

Consider the following differential equation

$$\begin{aligned}\tilde{y}' &= \frac{4\beta s + 4\beta a x_0 + \beta rk + 4\beta\tilde{d}\epsilon_1 - 4\beta\tilde{d}\tilde{y}(t) - 4a\tilde{d}}{4\tilde{d}}\tilde{y} \\ &= \left(\frac{4\beta s + 4\beta a x_0 + \beta rk + 4\beta\tilde{d}\epsilon_1 - 4\beta\tilde{d}\tilde{y}(t) - 4a\tilde{d}}{4\tilde{d}}\right)\tilde{y}. \end{aligned} \tag{10}$$

When $R_0 > 1$ and $\tilde{y}(0) > 0$, (10) has a unique positive equilibrium $\tilde{y}^* = \frac{4\beta s+4a(\beta x_0-\tilde{d})+\beta rk+4\beta\tilde{d}\epsilon_1}{4\beta\tilde{d}}$ which is globally asymptotically stable. By the comparison principle, choose an ϵ_2, then there exists a $t_2 > t_1$ such that

$$y \leq \tilde{y}^* + \epsilon_2 \ \ \forall t > t_2.$$

Let $y^* = \frac{4\beta s+4a(\beta x_0-\tilde{d})+\beta rk}{4\beta\tilde{d}}$, because ϵ_1 is small enough. Then

$$y \leq y^* + \epsilon_2 \ \ \forall t > t_2$$

and using the previous inequality we get

$$z'(t) \leq c(y^* + \epsilon_2)z(t-\tau) - bz \ \forall t > t_2 + \tau.$$

Choose an ϵ_2 small enough such that $R_1' + \frac{c\beta\epsilon_2}{\beta b+ac} < 1$ and $R_1' = \frac{4c\beta s+\beta crk+4ca\beta x_0}{4ca\tilde{d}+4b\beta\tilde{d}}$. By using again lemma (1) we get as before $\lim_{t\to\infty} z(t) = 0$. Therefore system (2) is asymptotic to the following homogeneous system:

$$\begin{aligned} x'(t) &= s - dx(t) + rx(t)\left(1 - \frac{x(t)}{k}\right) - \beta x(t)y(t) \\ y'(t) &= \beta x(t)y(t) - ay(t). \end{aligned} \tag{11}$$

System (11) has a unique equilibrium $(\hat{x}, \hat{y})$ where $\hat{x} = \frac{a}{\beta}$, $\hat{y} = \frac{s}{a} + \frac{r}{\beta} - \frac{d}{\beta} - \frac{ra}{\beta^2 k}$. Inspired in Hu et al.(2014) we consider the following Lyapunov functional:

$$V(t) = x - \hat{x} - \hat{x}\ln\frac{x}{\hat{x}} + y - \hat{y} - \hat{y}\ln\frac{y}{\hat{y}}$$

we get

$$\begin{aligned} V' &= \left(1 - \frac{\hat{x}}{x}\right)\left(s - dx + rx\left(1 - \frac{x}{k}\right) - \beta xy\right) + \left(1 - \frac{\hat{y}}{y}\right)(\beta xy - ay) \\ &= (x-\hat{x})\left(-\frac{s(x-\hat{x})}{x\hat{x}} - \frac{r(x-\hat{x})}{k} - \beta(y-\hat{y})\right) + (y-\hat{y})\beta(x-\hat{x}) \\ &= -\frac{s(x-\hat{x})^2}{x\hat{x}} - \frac{r(x-\hat{x})^2}{k}. \end{aligned}$$

$V' \leq 0$ and $V' = 0$ if and only if $x = \hat{x}$. The previous argument shows that the equilibrium $(\hat{x}, \hat{y})$ is globally asymptotically stable by Lyapunov-LaSalle invariance principle. Finally, by applying the theory of internally chain transitive sets (Zhao, 2003) to the two first equations of system (2) we conclude that $\lim_{t\to\infty} x(t) = \hat{x}$,$\lim_{t\to\infty} y(t) = \hat{y}$. This completes the proof. □

5. Uniform Persistence of Disease if $R_1 > 1$

Theorem 6. *If $R_1 > 1$, system (2) has a positive $T-$periodic solution, and there is an $\eta > 0$ such that for any solution $(x(t,\phi), y(t,\phi), z(t,\phi))$ of (2) in $C([-\tau, 0], \mathbb{R}^3_+)$ and $\phi_2(0) > 0$ y $\phi_3(0) > 0$ satisfies*

$$\liminf_{t\longrightarrow\infty} x(t,\phi) \geq \eta, \quad \liminf_{t\longrightarrow\infty} y(t,\phi) \geq \eta, \quad \liminf_{t\longrightarrow\infty} z(t,\phi) \geq \eta.$$

Proof. Let

$$X = C([-\tau, 0], \mathbb{R}^3_+)$$

$$X_0 = \{\phi = (\phi_1, \phi_2, \phi_3) \in X : \phi_2(0) > 0, \phi_3(0) > 0\}$$

$$\partial X_0 = X \setminus X_0.$$

Noting the form of system (2), it is easy to check that X y X_0 are positively invariant. Then ∂X_0 is relatively closed in X, and

$$\partial X_0 = \{\phi \in X : \phi_2(0) = 0 \text{ or } \phi_3(0) = 0\}.$$

Let $u(t, \phi)$ be the unique solution of system (2) with $u_0(\phi) = \phi$. Define $\Phi(t)\psi = u_t(\psi)$, $t \geq 0$ and $\psi \in X$. Let $P : X \longrightarrow X$ be the Poincaré map associated with the system (2), i.e,

$$P(\phi) = u_T(\phi) = u(T, \phi) \;\; T = 1 \;\; \forall \phi \in X.$$

Note that the lemma (2) implies that the discrete time system $P : X \longrightarrow X$ is point dissipative and P^{n_0} is compact whenever $n_0 T > \tau$. It then follows from theorem 2.9 of (Magal & Zhao, 2005) that P admits a global attractor A in X. By using the technique employed in (Lou & Zhao, 2010), we first verify that P is uniformly persistent with respect to $(X_0, \partial X_0)$.

Let $M_1 = \left(\frac{k}{2r}\left[(r-d) + \sqrt{(r-d)^2 + \frac{4rs}{k}}\right], 0, 0\right)$ and $M_2 = \left(\frac{a}{\beta}, \frac{s}{a} + \frac{r}{\beta} - \frac{d}{\beta} - \frac{ra}{\beta^2 k}, 0\right)$. Since $R_0 > R_1 > 1$, we choose a δ_1 small enough such that $R_0 - \dfrac{(\beta + p_0 + p_1)\delta_1}{a} > 1$.

By the continuity of solutions with respect to initial conditions there exists $\delta_1^*(\delta_1) > 0$ such that for all $\phi \in X_0$ with

$$\| \phi - M_1 \| \leq \delta_1^*,$$

then we have

$$\| \Phi(t)\phi - M_1 \| \leq \delta_1 \quad \forall t \in [0, T].$$

We prove the following result:

Claim 7. $\limsup_{n\to\infty} \| \Phi(nT)\phi - M_1 \| \geq \delta_1^*$ for all $\phi \in X_0$.

Suppose, by contradiction, that $\limsup_{n\to\infty} \| \Phi(nT)\psi - M_1 \| < \delta_1^*$ for some $\psi \in X_0$. Then there exists an integer $N_1 \geq 1$ such that $\| \Phi(nT)\psi - M_1 \| < \delta_1^*$ for all $n \geq N_1$. For any $t - \tau \geq N_1 T$ we have $t = nT + t'$, with $n \geq N_1, t' \in [0, T]$ and

$$\| \Phi(t)\psi - M_1 \| = \| \Phi(t')\Phi(nT)\psi - M_1 \| \leq \delta_1.$$

Then it follows that

$$x_0 - \delta_1 \leq x(t) \leq x_0 + \delta_1, 0 \leq y(t), z(t) \leq \delta_1 \;\; \forall t - \tau \geq N_1 T.$$

Hence, for $t \geq N_1 T + \tau$, it is obtained that

$$\begin{aligned} y'(t) &\geq (\beta(x_0 - \delta_1) - a - (p_0 + p_1)\delta_1)y(t) \\ &\geq (\beta x_0 - a - \beta\delta_1 - (p_0 + p_1)\delta_1)y(t). \end{aligned}$$

Solving the previous inequality we get

$$y(t) \geq y(N_1 T + \tau) e^{(\beta x_0 - a - \beta\delta_1 - (p_0 + p_1)\delta_1)(t - N_1 T - \tau)}.$$

Since $R_0 - \dfrac{(\beta + p_0 + p_1)\delta_1}{a} > 1$, $\beta x_0 - a - \beta\delta_1 - (p_0 + p_0)\delta_1 > 0$, then $\lim_{t\to\infty} y(t) = \infty$. But this is a contradiction.

In the case where $R_1 > 1$, we can choose a small positive number δ_2 such that $R_1 - \frac{\delta_2 k \beta^2}{ar} > 1$. Since $\limsup_{\phi \to M_2} (\Phi(t)\phi - M_2) = 0$ uniformly for $t \in [0, T]$, there exists $\delta_2^*(\delta_2) > 0$ with $\delta_2^* < \hat{y}$ such that

$$\| \Phi(t)\phi - M_2 \| \leq \delta_2 \quad \forall t \in [0, T] \quad \| \phi - M_2 \| < \delta_2^*.$$

Claim 8. $\limsup_{n\to\infty} \| \Phi(nT)\phi - M_2 \| \geq \delta_2^*$ for all $\phi \in X_0$.

Suppose the contrary, i.e. $\limsup_{n\to\infty} \| \Phi(nT)\psi - M_2 \| < \delta_2^*$ for some $\psi \in X_0$. Then there exists an integer $N_2 \geq 1$ such that $\| \Phi(nT)\psi - M_2 \| < \delta_2^*$ for all $n \geq N_2$. For some $t - \tau \geq N_2 T$ we have $t = nT + t'$ with $n \geq N_2$ and $t' \in [0, T]$ such that

$$\| \Phi(t)\psi - M_2 \| = \| \Phi(t')\Phi(nT)\psi - M_2 \| \leq \delta_2.$$

This implies

$$|x(t) - \hat{x}| < \delta_2, |y(t) - \hat{y}| < \delta_2, \;\; 0 < z(t) < \delta_2 \text{ for all } t - \tau \geq N_2 T.$$

From the third equation of system (2)

$$z'(t) \geq c(\hat{y} - \delta_2)z(t - \tau) - bz$$

and the inequality $R_1 - \dfrac{\delta_2 k \beta^2}{ar} > 1$, it is implied that $c(\hat{y} - \delta_2) > b$. By lemma (1) $\lim_{t\longrightarrow\infty} z(t) = \infty$. But this is a contradiction.

Define the following sets:

$$\begin{aligned} M_\partial &:= \{\phi \in \partial X_0 : P^n(\phi) \in \partial X_0, \forall n \geq 0\} \\ D_1 &:= \{\phi \in X : \phi_2(0) = 0, \phi_3(0) \geq 0\} \\ D_2 &:= \{\phi \in X : \phi_2(0) > 0, \phi_3(0) = 0\}. \end{aligned}$$

We claim that $M_\partial = D_1 \cup D_2$. We know that $D_1 \cup D_2 \subset M_\partial$. We will prove that $M_\partial \subset D_1 \cup D_2$. For some $\psi \in \partial X_0 \backslash (D_1 \cup D_2)$, from the second equation of system (2) we have

$$y(t, \psi) = y(0, \psi) e^{\int_0^t (\beta x(s,\psi) - a - p(s) z(s,\psi)) ds} \;\; t \geq 0.$$

The solution of the third equation of system (2) in the interval $[0, \tau]$ is

$$z(t, \psi) = e^{-bt} \left(z(0, \psi) + c \int_0^t e^{bs} y(s - \tau, \psi) z(s - \tau, \psi) ds \right)$$

for any $\psi \in \partial X_0 \setminus (D_1 \cup D_2)$. From the previous expression we verify that there exists $t_0 \in [0, \tau]$ such that $z(t, \psi) > 0$ for all $t \geq t_0$. Hence there exists some n with $nT \geq t_0$ such that $P^n(\psi) \notin \partial X_0$ and therefore $M_\partial \subset D_1 \cup D_2$. Then it follows that M_1 and M_2 are disjoint, compact and isolated invariant sets for P in ∂M, and $\hat{A_\partial} := \cup_{\phi \in M_\partial} \omega(\phi) = \{M_1, M_2\}$. Moreover, no subset of $\{M_1, M_2\}$ form a cycle in M_∂ (and hence in ∂X_0). By the previous claims we see that M_1 y M_2 are isolated and invariant sets for P in X, and $w^s(M_i) \cap X_0 = \emptyset$ for $i = 1, 2$, where $w^s(M_i)$ is the stable set of de M_i for P.

By the acyclicity theorem on uniform persistence for maps (see theorem 1.3.1 and the remark 1.3.1 of (Zhao, 2003)), it follows that $P : X \to X$ is uniformly persistent with respect to X_0. Then the same theorem implies that the periodic semiflow $\Phi(t) : X \longrightarrow X$ is also uniformly persistent with respect to X_0. Therefore from theorem 3.1 of (Zhao, 2008) system (2) admits a T-periodic solution (x^*, y^*, z^*) with initial condition $\phi^* \in X_0$. By a similar argument in (Lou & Zhao, 2010) and (Zhao, 2008) it is shown that there exists $\eta > 0$ such that

$$\lim_{t\longrightarrow\infty} \inf \min(x(t, \phi), y(t, \phi), z(t, \phi)) \geq \eta.$$

In particular $\lim_{t\longrightarrow\infty} \inf \min(\Phi(t)\phi^*) \geq \eta$ and $x^*, y^*, z^* \geq 0$ for all $t \geq 0$. This implies that (x^*, y^*, z^*) is a T-periodic solution. □

6. Numerical Simulations

In this section we investigate the behavior of an epidemiological model described by a nonautonomous SIR system. In addition, some comparisons among our model and the other closed model will be provided.

To explore the dynamic of system (2) and to illustrate the stability of equilibria solutions we have used, dde23 (Shampine & Thompson, 2001), based on Runge-Kutta methods.

In system (2), the parameter set will be taken from (Wang et al., 2006; Ji et al., 2010; Hu et al., 2014). Let $p(t) = 1 + 0.5\cos\left(2\pi t - \frac{\pi}{12}\right)$,$s = 190, d = 0.1, r = 0.1, k = 1200, a = 5, b = 0.1, c = 0.3, \beta = 0.002, \tau = 5$. We consider different constant history functions $x(0) = 100, 500, 800$, $y_0(\theta) = y(\theta) = 20, 25, 30$, $z_0(\theta) = z(\theta) = 1, 5, 10$.
Note that $R_1 = 0.6024 < 1$ and $R_0 = 0.6040 < 1$, then the virus eventually disappears. The numerical simulation confirms

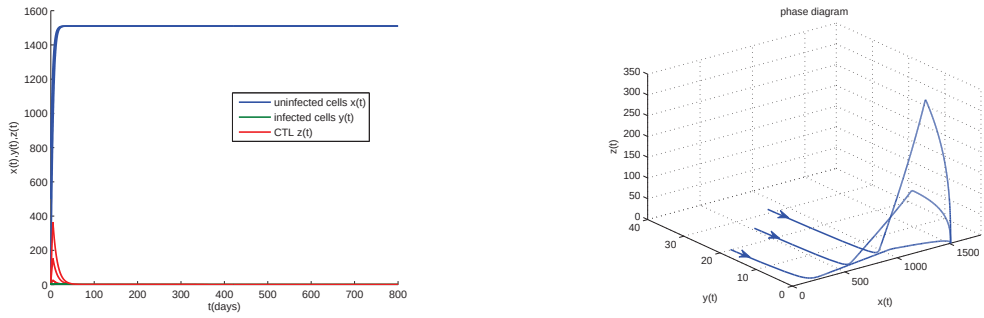

Figure 1. When $R_1 = 0.6024 < 1$ and $R_0 = 0.6040 < 1$ the disease-free equilibrium is stable. Phase space of system (2).

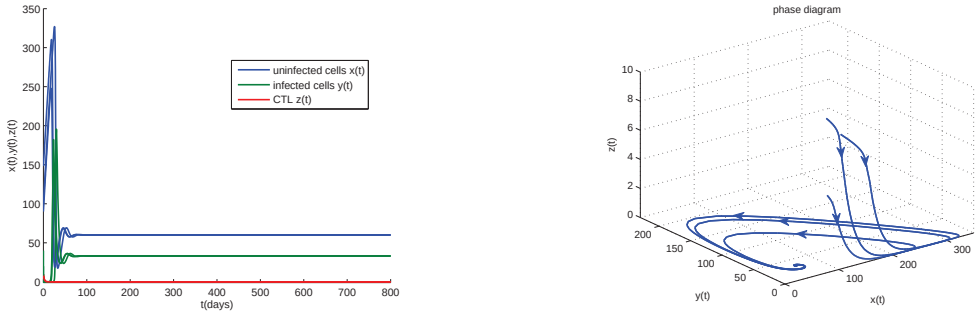

Figure 2. When $R_1 = 0.2 < 1$ and $R_0 = 12.9099 > 1$ immune-exhausted equilibrium is stable. Phase space of system (2).

that the disease-free equilibrium is stable when $R_0 < 1$. System (2) has a unique disease-free equilibrium $P_0 = (1510, 0, 0)$. See figure(1).

Next, consider the following parameter set: $p(t) = 1+0.5\cos\left(2\pi t - \frac{\pi}{12}\right)$, $s = 10, d = 0.03, r = 0.03, k = 1800, a = 0.3, b = 0.5, c = 0.003, \beta = 0.005$. We note that $R_1 = 0.2 < 1$ and $R_0 = 12.9099 > 1$.Then the immune-exhausted equilibrium is $P_1 = (60, 33.13, 0)$, and theorem (5) is satisfied. See figure (2)

In figures (3) and (6) we use the following parameters: $s = 190, \beta = 0.05, d = 0.1, a = 0.1, r = 0.1, b = 0.2, c = 0.01, \tau = 6, k = 1200, p(t) = 1+0.5\cos\left(2\pi t - \frac{\pi}{12}\right)$. The basic reproduction numbers for the viral infection and for the CLT response are $R_0 = 754.9834 > 1$ and $R_1 = 93.5417 > 1$, respectively.

The dynamic behavior of system (2) becomes more complex as the amplitude parameter p_1 increases. The numerical simulation shows that the period of the viral dynamics seems not to agree with the oscillating immune response (figure (3)). When we choose the parameters for amplitudes $p_1 = 0.2, 0.33$ and 0.55, respectively, the period of the virus dynamics is 1, 2 and 4, respectively according to figure (3).

In order to study the effect of the immune system oscillation over the behavior of the virus dynamics, the amplitude, which is represented by p_1, is used as bifurcation parameter. We obtain a similar diagram to the one obtained in (Bai and Zou, 2012). Let p_1 be in the interval $(0, 1)$. We obtain a bifurcation diagram in the plane $p_1 - y$. In this diagram the number of points in a vertical line corresponding to the amplitude represent multiples of the period of $y(t)$. For example, a point in the bifurcation diagram represents the period of $y(t)$ in T days and n points represent the period in nT days for $y(t)$.

Asp_1 increases from 0 to 1, the virus dynamics has periods of 1, 2, 4, 8, 16. In figure (3) we can observe that when p_1 is small the system dynamics is not repeating itself, it's a cyclic day. When p_1 is greater than 0.33, the dynamics repeats itself every two days, it's of two cyclic days, and when it's 0.55, the dynamics repeats itself every four days, therefore being four cyclic days. Finally, when it exceeds 0.55 the dynamics is of multiple cyclic days.

For the study of the dynamics of system (2), as the other parameters vary, we use as bifurcation parameter s, r, and p_1,respectively. In figure (4), we vary s; when $s = 90$ the virus dynamics is of one cyclic day for all the values of p_1, as s increases, as for example $s = 137$, the virus dynamics maintains its one day period, and when it exceeds certain threshold, its period is of two cyclic days occurring the the double bifurcation period. When $s = 175$ and p_1 varies, the dynamics

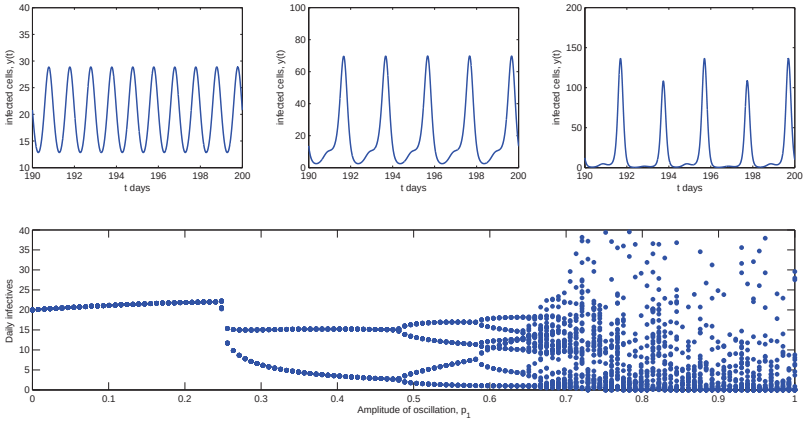

Figure 3. When $R_1 = 93.5417 > 1$ and $R_0 = 754.9834 > 1$, the numerical simulations are run with different amplitudes $p_1 = 0.2, 0.3$ ans 0.55, respectively. Bifurcation diagram for system (2) as p_1 changes.

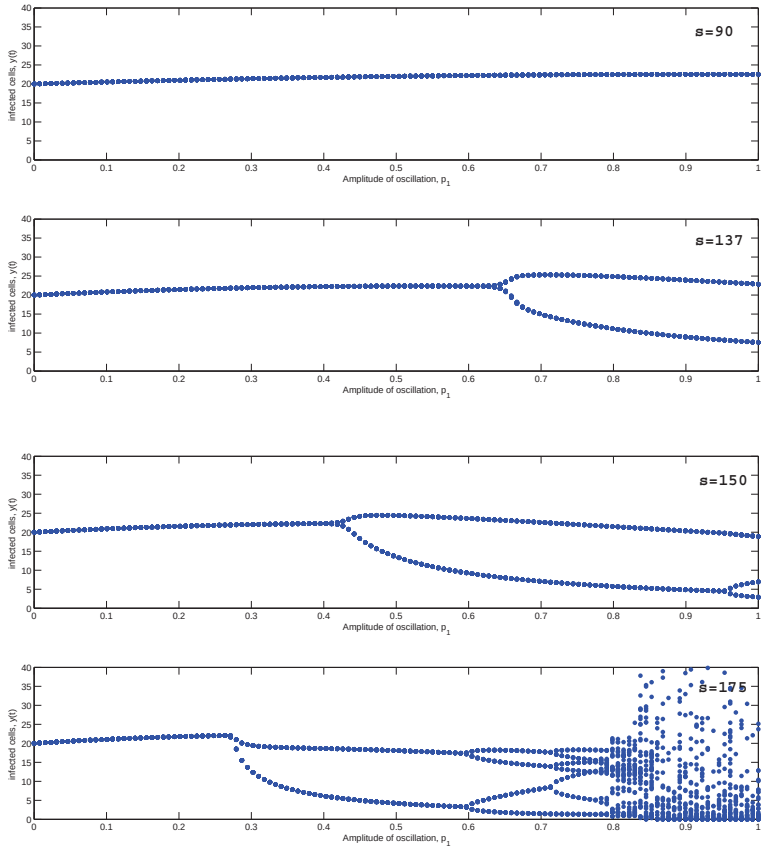

Figure 4. Bifurcation diagrams for the following parameter values: $s.\beta = 0.05, d = 0.1, a = 0.1, r = 0.1, b = 0.2, c = 0.01, \tau = 6, k = 1200, p(t) = 1 + 0.5\cos\left(2\pi t - \frac{\pi}{12}\right)$.

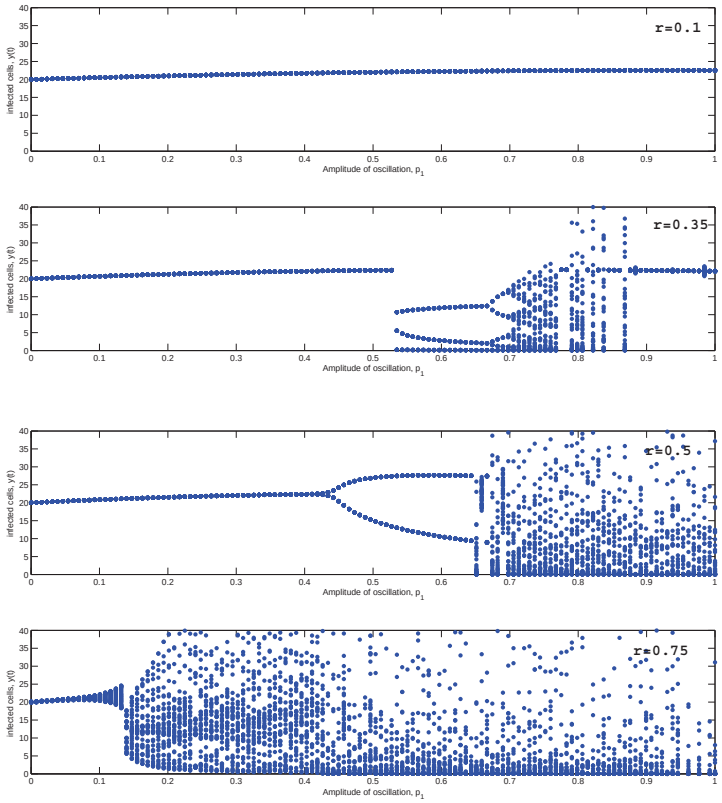

Figure 5. Bifurcation diagrams for system 2 as r changes. $\beta = 0.05, d = 0.1, a = 0.1, b = 0.2, c = 0.01, \tau = 6, k = 1200, p(t) = 1 + 0.5\cos\left(2\pi t - \frac{\pi}{12}\right)$.

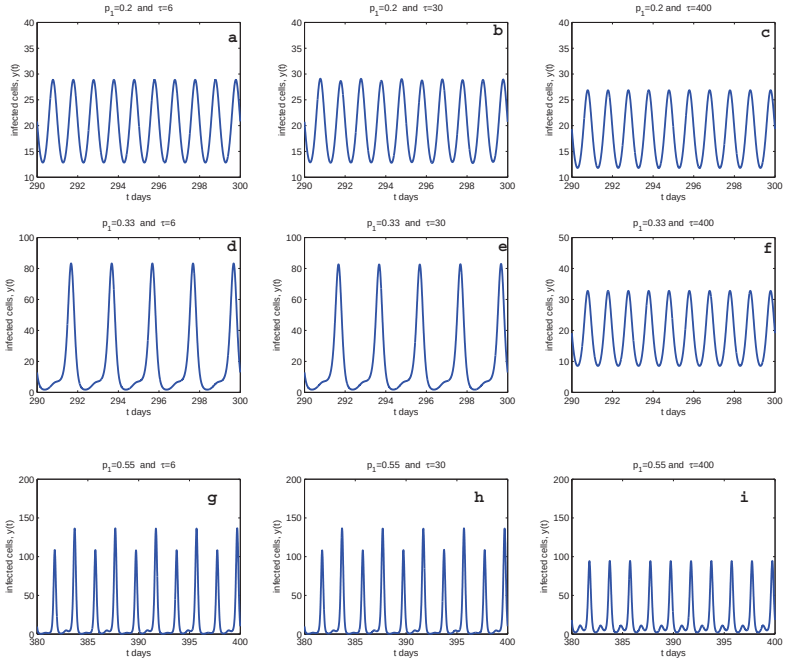

Figure 6. $y(t)$ solution as p_1 and τ changes.

has periods 1, 2, 4, 8 etc. In figure (5) we use the parameter set $s = 90, \beta = 0.05, d = 0.1, a = 0.1, b = 0.2, c = 0.01, \tau = 6, k = 1200, p(t) = 1 + 0.5\cos\left(2\pi t - \frac{\pi}{12}\right)$ and we vary r. When r is small, $r = 0.1$, the virus dynamics is the same as when p_1 varies; when $r = 0.35$ the virus dynamics has a cyclic day and when it exceeds certain threshold the dynamics is of two cyclic days, then it becomes of four cyclic days, and later it becomes of multiple days. Later it changes from multiple days to one cyclic day. When $r = 0.5$, it changes from one cyclic day to two cyclic days and then chaos. When r is greater than 0.74 it changes from one cyclic day to chaos.

Comparing figures (4) and (5), in the bifurcation diagrams we can observe that in figure (5) it changes quicker to chaos than in figure (4) as p_1 increases.

Nevertheless, as it is mentioned in (Bai & Zhou, 2012; keeling & Rohani, 2007), the bifurcation diagram cannot completely capture the dynamics behavior. To explore how the amplitude (p_1) and the delay (τ) affects dynamics of system (2), we perform numerical calculations for different amplitude rates and time delays. When τ is large and the amplitude parameter is small, the fraction of infected cells shows harmonic oscillations (Figure 6, top a-c). As p_1 increases to 0.33, we observese for small delays gives rise to subharmonic resonance (Figure 6, middle d and e). A increase in delay can alter the oscillations: from two day cycles to one day cycles (Figure 6, middle f). A further increase in p_1, for example $p_1 = 0.55$, gives rise to four-day cycles that a noticeable one-day as well as two-day cycles component (Figure 6, bottom g and h). The delay (that is big) can alter the oscillation: four day cycles to two day cycles (Figure 6, bottom f). Moreover, the third column in figure 6 shows that the subharmonic resonance occurs only when the amplitude p_1 and the delay τ are big enough.

Let $r = 0$, system (2) become the model investigated in (Bai and Zhou, 2012).

$$\begin{aligned} x'(t) &= s - dx(t) - \beta x(t)y(t) \\ y'(t) &= \beta x(t)y(t) - ay(t) - p(t)y(t)z(t) \\ z'(t) &= cy(t-\tau)z(t-\tau) - bz(t), \\ p(t) &= p_0 + p_1\cos(2\pi t - \phi), 0 \le p_1 < p_0. \end{aligned} \tag{12}$$

Comparing the viral infection model without logistic proliferation, our series of sufficient conditions for the stability of equilibrium and uniform persistence are different. Moreover, we have shown by numerical simulations that the dynamical behaviours become more and more complex with the increase of maximum proliferation rate (5).

7. Summary

In this paper, we give a delayed viral infection with the contribution of CTLs and periodic immune response, to which we incorporated logistic growth. Similar to the analysis in Bai and Zhou (2012), we obtain the basic reproduction number (R_0) and the immune response reproductive number (R_1). We verified that when $R_1 \le 1$ the disease-free equilibrium is globally asymptotically stable. For $R_1 < 1 < R_0$ the immune-exhausted equilibrium occurs and it is asymptotically stable. In the case when $R_1 > 1$ the dynamics of system (2) becomes become more complex with the increase of the amplitude parameter p_1 from 0 to 1. The delay can alter the oscillation period when p_1 is big enough. When the delay is big enough subharmonic resonance occurs with p_1 greater than 0.33. Moreover, in the simulations it is illustrated that as the noninfected cells growth rate increases the oscillation patterns of system (2) are modified (see figure(4)). It can also be observed that when we use r as bifurcation parameter we obtain in a quicker way multiple cyclic days or chaos (see figure (5)).

Our numerical results show that the growth rate of noninfected cells, the amplitude, the delay of the immune response, as well as the maximum proliferation rate of white cells, can evidently change the dynamic behavior of the viral infection. Our analytical results and numerical simulations can be used to explain the oscillating behavior of the virus population that it is observed in chronic HBV or HCV patients.

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