International Journal of Bifurcation and Chaos, Vol. 22, No. 3 (2012) 1250062 (21 pages)

DOI: 10.1142/S0218127412500629

# BIFURCATION ANALYSIS ON AN HIV-1 MODEL WITH CONSTANT INJECTION OF RECOMBINANT

PEI YU* and XINGFU ZOU
*Department of Applied Mathematics,*
*The University of Western Ontario,*
*London, Ontario, Canada N6A 5B7*
**pyu@pyu1.apmaths.uwo.ca*

Received January 17, 2011

This paper is a continuation of our previous work on an HIV-1 therapy model of fighting a virus with another virus [Jiang *et al.*, 2009]. The work in [Jiang *et al.*, 2009] investigated cascading bifurcations between equilibrium solutions, as well as Hopf bifurcation from a double-infected equilibrium solution. In this paper, we propose a modification of the model in [Revilla & Garcia-Ramos, 2003; Jiang *et al.*, 2009] by adding a constant $\eta$ to the recombinant virus equation, which accounts for the treatment of constant injection of recombinants. We study the dynamics of the new model and find that $\eta$ plays an important role in the therapy. Unlike the previous model without injection of recombinant, which has three equilibrium solutions, this new model can only allow two biologically meaningful equilibrium solutions.

It is shown that there is $R_1^\eta > 1$ depending on $\eta$, such that the HIV free equilibrium solution $E_0^\eta$ is globally asymptotically stable when the basic reproduction ratio, $\mathcal{R}_0 < R_1^\eta$; $E_0^\eta$ becomes unstable when $\mathcal{R}_0 > R_1^\eta$. In the latter case, there occurs the double-infection equilibrium solution, $E_d^\eta$, which is stable when $\mathcal{R}_0 \in (R_1^\eta, R_h^\eta)$ for some $R_h^\eta$ larger than $R_1^\eta$, and loses its stability when $\mathcal{R}_0$ passes the critical value $R_h^\eta$ and bifurcates into a family of limit cycles through Hopf bifurcation. Our results show that appropriate injection rate can help eliminate the HIV virus in the sense that the HIV free equilibrium can be made globally asymptotically stable by choosing $\eta > 0$ sufficiently large. This is in contrast to the conclusion for the case with $\eta = 0$ in which, the recombinants do not help eliminate the HIV virus but only help reduce the HIV load in the long term sense.

*Keywords*: HIV-1 therapy model; stability; bifurcation; HIV-free equilibrium; double-infected equilibrium; Hopf bifurcation; limit cycle; decease control.

## 1. Introduction

More than twenty years after its discovery in early 1980s, the acquired immunodeficiency syndrome (AIDS) still remains one of the main causes of death of human beings. It is well known that AIDS is a result of the $CD4^+T$ cells dropping below certain level, and the population of $CD4^+T$ cells is closely related to the HIV virus load within the host. Naturally, controlling the virus load has been the main goal of all therapies of AIDS. Currently there are two types of drugs for therapy of HIV infection: the protease inhibitors and the reverse transcriptase inhibitors. Recent progress in genetic engineering has offered a potentially alternative therapy: modification of a viral genome can produce recombinants capable of attaching to the HIV infected cells and hence, reducing the replication rate of HIV virus. The idea of this method is similar to that of using

*Author for correspondence

lytic bacteriophages to cure the human bacterial infections which has been used since the early 20th century, mainly in Eastern Europe and the former Soviet Union (see, e.g. [Slopek *et al.*, 1987; Carlton, 1999; Sulakvelidze *et al.*, 2001]). Indeed, this method has been used to modify rhabdovirus, including the rabies and the vesicular stomatities, making them capable of infecting and killing cells previously attacked by HIV-1. For details, see, e.g. [Mebatsion *et al.*, 1997; Nolan, 1997; Schnell *et al.*, 1997; Wagner & Hewlett, 1999].

To examine the efficacy of this approach of fighting a virus with a genetically modified virus, Revilla and Garcia-Ramos [2003] proposed a mathematical model which is a result of incorporating two more variables — the density $w$ of the recombinant (genetically modified) virus and the density $z$ of doubly-infected cells (by the wild HIV virus and the recombinants), into the standard and classic differential equation model for HIV infection (see, e.g. [Nowak & May, 2000]):

$$\begin{cases} \dot{x} = \lambda - dx - \beta xv, \\ \dot{y} = -ay + \beta xv, \\ \dot{v} = -pv + ky. \end{cases} \tag{1}$$

Here $x(t), y(t)$ and $v(t)$ are the densities of uninfected CD4$^+$T cells, infected CD4$^+$T cells and the free HIV virus respectively at time $t$. In this model, a mass action infection mechanism is adopted with an infection rate constant $\beta$. It is also assumed that the healthy cell is produced at a constant rate $\lambda$ and die at a constant rate $d$, the infected cells die at rate $a$, the virions are cleared (by immune system) at rate $p$, and each infected cell produces and release new virus at rate $k$. Based on the fact that the engineered virus only codifies the coreceptor pair CD4 and CXCR4 of the host cell membrane and bind specifically to the protein complex gp120/41 of HIV-1 expressed on the surface of infected cells (see [Schnell *et al.*, 1997]), Revilla and Garcia-Ramos [2003] came up with the following model

$$\begin{cases} \dot{x} = \lambda - dx - \beta xv, \\ \dot{y} = -ay + \beta xv - \alpha yw, \\ \dot{z} = -bz + \alpha yw, \\ \dot{v} = -pv + ky, \\ \dot{w} = -qw + cz. \end{cases} \tag{2}$$

The model (2) assumes that the recombinants are only injected initially and there will be no subsequent injections. However, as in other therapies, subsequent treatments (injection in this context) may enhance the efficacy of the therapy. In this paper, we consider a simple injection mechanism, that is, a constant injection rate $\eta$, and explore the consequence of such a treatment. Adoption of such a constant injection rate treatment adds the term $\eta$ to the last equation in (2), resulting in the following model system

$$\begin{cases} \dot{x} = \lambda - dx - \beta xv, \\ \dot{y} = -ay + \beta xv - \alpha yw, \\ \dot{z} = -bz + \alpha yw, \\ \dot{v} = -pv + ky, \\ \dot{w} = \eta - qw + cz. \end{cases} \tag{3}$$

We will investigate how the injection rate $\eta$, together with other parameters, affects the dynamics of the model. For convenience of analysis, we first simplify system (3) by the following rescalings:

$$\begin{gathered} x \to \mu_1 x, \quad y \to \mu_2 y, \quad z \to \mu_3 z, \\ v \to \mu_4 v, \quad w \to \mu_5 w, \quad \tau = \nu t \end{gathered} \tag{4}$$

$$\begin{gathered} \frac{d}{\nu} \to d, \quad \frac{a}{\nu} \to a, \quad \frac{b}{\nu} \to b, \quad \frac{p}{\nu} \to p, \\ \frac{q}{\nu} \to q, \quad \frac{\alpha c}{k\beta} \to c, \quad \frac{\alpha\eta}{\nu^2} \to \eta, \end{gathered} \tag{5}$$

where

$$\begin{gathered} \nu = (\lambda k\beta)^{1/3}, \quad \mu_1 = \mu_2 = \mu_3 = \frac{\nu^2}{k\beta}, \\ \mu_4 = \frac{\nu}{\beta}, \quad \mu_5 = \frac{\nu}{\alpha}. \end{gathered} \tag{6}$$

By the above, system (3) is transformed to the following equivalent one:

$$\begin{cases} \dfrac{dx}{d\tau} = 1 - dx - xv, \\ \dfrac{dy}{d\tau} = -ay + xv - yw, \\ \dfrac{dz}{d\tau} = -bz + yw, \\ \dfrac{dv}{d\tau} = -pv + y, \\ \dfrac{dw}{d\tau} = \eta - qw + cz. \end{cases} \tag{7}$$

Note that in the new system (7), we still use the same notations for the scaled state variables and parameters as those in (3).

In order to compare the dynamics of the new model system (7) with $\eta \neq 0$ to that of the model with $\eta = 0$ (i.e. a system equivalent to (2) which has been previously studied in [Jiang *et al.*, 2009]), we summarize the results obtained in [Jiang *et al.*, 2009] as below.

Let

$$\mathcal{R}_0 = \frac{1}{adp}, \quad \text{and} \quad R_1 = 1 + \frac{bq}{cdp}. \tag{8}$$

Then, we have the following conclusions on the dynamics of (7) with $\eta = 0$:

(i) when $\mathcal{R}_0 < 1$, the infection-free equilibrium $E_0 = (1/d,\ 0,\ 0,\ 0,\ 0)$ is globally asymptotically stable;

(ii) when $\mathcal{R}_0 > 1$, $E_0$ becomes unstable and there occurs the single-infection equilibrium

$$E_s = \left(ap, \frac{1}{a}\left(1 - \frac{1}{\mathcal{R}_0}\right), 0, \frac{1}{ap}\left(1 - \frac{1}{\mathcal{R}_0}\right), 0\right); \tag{9}$$

(iii) when $\mathcal{R}_0 \in (1, R_1)$ , $E_s$ is globally asymptotically stable;

(iv) when $\mathcal{R}_0 > R_1, E_s$ becomes unstable and there occurs the double-infection equilibrium

$$E_d = \left(\frac{1}{dR_1}, \frac{bq}{c}, \frac{aq(\mathcal{R}_0 - R_1)}{cR_1}, \frac{bq}{cp}, \frac{a(\mathcal{R}_0 - R_1)}{R_1}\right); \tag{10}$$

(v) there is a $R_2 > R_1$ such that $E_d$ is asymptotically stable when $\mathcal{R}_0 \in (R_1, R_h)$;

(vi) when $\mathcal{R}_0$ is further increased in some appropriate ways to some critical value $R_h$, $E_d$ loses its stability, giving rise to some stable periodic solution via Hopf bifurcation.

In the rest of this paper, we analyze (7) with $\eta > 0$. Our results show that appropriate injection rate can help eliminate the HIV virus in the sense that the HIV infection free equilibrium can be made globally asymptotically stable by choosing $\eta > 0$ sufficiently large. This is in contrast to the conclusion for the case with $\eta = 0$ in which, the recombinants do not help eliminate the HIV virus but only help reduce the HIV load in the long term sense. We also show that insufficient injection may still lead to the persistence of the HIV virus, with the recombinants also being persistent. In such a case, the model may allow periodic dynamics arising from Hopf bifurcation within certain range of the model parameters. Numerical simulations are also carried out, which are guided by the analytical results obtained, and in turn, support these results.

The remainder of the paper is organized as below. In Sec. 2, we confirm that the model (7) is well-posed by showing non-negativity of and boundedness of solutions corresponding to non-negative initial values, and consider the structure of equilibria for the model. In Sec. 3, we prove that there is a threshold value for $\mathcal{R}_0$, denoted by $R_1^\eta$ such that when $\mathcal{R}_0 < R_1^\eta$, the HIV free equilibrium is globally asymptotically stable; when $\mathcal{R}_0 > R_1^\eta$, the HIV free equilibrium becomes unstable and there occurs an infection equilibrium. In Sec. 4, we study the stability of the HIV infection equilibrium, and in Sec. 5, we explore Hopf bifurcation from this infection equilibrium. Section 6 is devoted to numerical demonstrations of the theoretical results. Section 7 gives some conclusions and also offers some discussion.

## 2. Non-Negativeness and Boundedness of Solutions and Equilibria

Due to their biological meanings, the negative values of the state variables of system (7) are not allowed. This requires that all solutions should remain non-negative as long as the initial values are non-negative. Moreover, solutions should remain bounded. We confirm these below.

**Theorem 1.** *When the initial values are non-negative, the solutions of system (7) remain non-negative for $\tau > 0$. Moreover, they are bounded.*

*Proof.* First, consider the first equation of (7), yielding the solution for $x(\tau)$:

$$x(\tau) = e^{-\int_0^\tau (d+v(s))ds} x(0) + \int_0^\tau e^{-\int_s^\tau (d+v(\xi))d\xi} ds \tag{11}$$

which clearly shows that $x(\tau) > 0$ for $\tau > 0$, provided that $x(0) \geq 0$.

Next, consider the second and the fourth equations in (7) as a nonautonomous system for $y$

and $v$:

$$\begin{cases} \dfrac{dy}{d\tau} = -[a + w(t)]y + x(t)v, \\ \dfrac{dv}{d\tau} = -pv + y, \end{cases} \tag{12}$$

with $x = x(t) > 0$ being proved above. By Theorem 2.1, p. 81 in [Smith, 1995], we know that a solution of (12) with $y(0) \geq 0$ and $v(0) \geq 0$ remains non-negative for all $\tau \geq 0$ in its maximal interval of existence. Applying the same argument to the subsystem consisting of the third and fifth equations in (7), we also obtain the non-negativity of $z(t)$ and $w(t)$.

It remains to prove that non-negative solutions of (7) are all bounded. Let $(x(\tau), y(\tau), z(\tau), v(\tau), w(\tau))$ be a non-negative solution and consider

$$V = x(\tau) + y(\tau) + z(\tau) + \frac{a}{2}v(\tau) + \frac{b}{2c}w(\tau). \tag{13}$$

Then, differentiating $V$ along (7) yields

$$\begin{aligned} \frac{dV}{d\tau} &= 1 + \frac{b\eta}{2c} - dx - \frac{a}{2}y - \frac{b}{2}z - \frac{ap}{2}v - \frac{bq}{2c}w \\ &= \begin{cases} < 0 & \text{for } dx + \dfrac{a}{2}y + \dfrac{b}{2}z + \dfrac{ap}{2}v + \dfrac{bq}{2c}w \\ & \qquad > 1 + \dfrac{b\eta}{2c}, \\ > 0 & \text{for } dx + \dfrac{a}{2}y + \dfrac{b}{2}z + \dfrac{ap}{2}v + \dfrac{bq}{2c}w \\ & \qquad < 1 + \dfrac{b\eta}{2c}. \end{cases} \end{aligned} \tag{14}$$

This shows that any solution starting from a non-negative initial value must be bounded. By the continuation theory of ODEs, the boundedness of a solution also implies that it exists for $\tau \geq 0$. ■

The equilibrium solutions of (7) can be obtained by setting the vector field of (7) to zero, yielding

$$\begin{aligned} E_0^\eta &= \left(\frac{1}{d},\ 0,\ 0,\ 0,\ \frac{\eta}{q}\right) \\ E_s^\eta &= \left(p(a + Z_-), \frac{b}{c}\left(q - \frac{\eta}{Z_-}\right), \frac{1}{c}(qZ_- - \eta), \frac{b}{cp}\left(q - \frac{\eta}{Z_-}\right), Z_-\right) \\ E_d^\eta &= \left(p(a + Z_+), \frac{b}{c}\left(q - \frac{\eta}{Z_+}\right), \frac{1}{c}(qZ_+ - \eta), \frac{b}{cp}\left(q - \frac{\eta}{Z_+}\right), Z_+\right), \end{aligned} \tag{15}$$

where

$$Z_\pm = \frac{(c - acdp - abq + b\eta) \pm \sqrt{(c - acdp - abq + b\eta)^2 + 4ab\eta(cdp + bq)}}{2(cdp + bq)}. \tag{16}$$

Thus, similar to the previous model without injection (i.e. $\eta = 0$), the new model (7) with $\eta > 0$ also *formally* has three equilibrium solutions. Also, as $\eta \to 0$, we have

$$\lim_{\eta \to 0} Z_- = 0 \quad \text{and} \quad \lim_{\eta \to 0} \frac{\eta}{Z_-} = \frac{-c + cadp + abq}{ab},$$

and so $\lim_{\eta \to 0} E_0^\eta = E_0$, $\lim_{\eta \to 0} E_s^\eta = E_s$, and $\lim_{\eta \to 0} E_d^\eta = E_d$, a natural expectation. However, it is obvious that $Z_- < 0 (Z_+ > 0)$ for $\eta > 0$ and thus, the equilibrium $E_s^\eta$ is biologically meaningless for this model with $\eta > 0$ and hence, will not be discussed. Note that the HIV free equilibrium $E_0^\eta$ exists for any positive parameter values, while the HIV infection equilibrium $E_d^\eta$ exists if and only if $qZ_+ - \eta > 0$.

## 3. Stability of the HIV Free Equilibrium $E_0^\eta$

In this section, we consider the stability of the HIV free equilibrium $E_0^\eta$. Let

$$R_1^\eta = 1 + \frac{\eta}{aq}. \tag{17}$$

We have the following theorem.

**Theorem 2.** *When $\mathcal{R}_0 < R_1^\eta$, the HIV free equilibrium $E_0^\eta$ is globally asymptotically stable, implying that the virus cannot invade regardless of the initial load; when $\mathcal{R}_0 > R_1^\eta$, $E_0^\eta$ becomes unstable and the HIV infection equilibrium comes into existence.*

*Proof.* The proof of the stability (instability) of $E_0^\eta$ is divided into two steps. The first step is to prove the local asymptotic stability (instability) of $E_0^\eta$ by analyzing the characteristic equation, and the second step is to show the global attractivity of $E_0^\eta$.

For the first step, we use the Jacobian matrix of (7), which is given by

$$J_{(7)} = \begin{bmatrix} -d-v & 0 & 0 & -x & 0 \\ v & -a-w & 0 & x & -y \\ 0 & w & -b & 0 & y \\ 0 & 1 & 0 & -p & 0 \\ 0 & 0 & c & 0 & -q \end{bmatrix}. \quad (18)$$

Evaluating $J_{(7)}$ at $E_0^\eta$ yields the following characteristic polynomial:

$$P_0(\xi) = (\xi+d)(\xi+b)(\xi+q)\left[\xi^2 + \left(p+a+\frac{\eta}{q}\right)\xi + ap + \frac{\eta p}{q} - \frac{1}{d}\right], \quad (19)$$

indicating that the equilibrium $E_0^\eta$ is asymptotically stable if and only if

$$ap + \frac{\eta p}{q} - \frac{1}{d} = ap\left(1 + \frac{\eta}{aq} - \frac{1}{adp}\right) = ap(R_1^\eta - \mathcal{R}_0) > 0,$$

that is, $\mathcal{R}_0 < R_1^\eta$.

For the second step, we apply the Fluctuation Lemma (see, e.g. [Hirsch *et al.*, 1985]). To achieve this, for a continuous and bounded function $g : [0,\infty) \to R$, define

$$g_\infty = \lim_{\tau\to\infty} \inf g(\tau) \quad \text{and} \quad g^\infty = \lim_{\tau\to\infty} \sup g(\tau).$$

Then, by the Fluctuation Lemma, there exists a sequence $\tau_n$ with $\tau_n \to \infty$ as $n \to \infty$ such that

$$\lim_{n\to\infty} x(\tau_n) = x^\infty, \quad \lim_{n\to\infty} \left.\frac{dx}{d\tau}\right|_{\tau=\tau_n} = 0. \quad (20)$$

Thus, it follows from the first equation of (7) that

$$\left.\frac{dx}{d\tau}\right|_{\tau=\tau_n} + dx(\tau_n) + x(\tau_n)v(\tau_n) = 1,$$

which, as $n \to \infty$, yields the following estimate:

$$dx^\infty \le (d+v_\infty)x^\infty \le 1, \quad \text{implying } x^\infty \le \frac{1}{d}. \quad (21)$$

By applying similar argument to the second, third and fourth equations of (7), we obtain respectively

$$(a+w_\infty)y^\infty \le x^\infty v^\infty, \quad (22)$$

$$bz^\infty \le y^\infty w^\infty, \quad (23)$$

$$pv^\infty \le y^\infty. \quad (24)$$

On the other hand, again by the Fluctuation Lemma, there exists a sequence $s_n$ with $s_n \to \infty$ as $n \to \infty$ such that

$$\lim_{n\to\infty} w(s_n) = w_\infty, \quad \lim_{n\to\infty} \left.\frac{dw}{d\tau}\right|_{s=s_n} = 0.$$

Substituting $s = s_n$ into the fifth equation of (7) and letting $n \to \infty$ leads to

$$qw_\infty \ge \eta + cz_\infty \ge \eta \quad (25)$$

Combining (21)–(22) and (24)–(26), we then have

$$\left(a + \frac{\eta}{q}\right) y^\infty \le (a+w_\infty)y^\infty \le \frac{1}{dp} y^\infty,$$

which implies

$$\left[\left(1 + \frac{\eta}{aq}\right) - \frac{1}{adp}\right] y^\infty \le 0,$$

that is,

$$(R_1^\eta - \mathcal{R}_0)y^\infty \le 0 \Rightarrow y^\infty = 0 \quad \text{since} \quad \mathcal{R}_0 < R_1^\eta \quad \text{and} \quad y^\infty \ge 0.$$

Hence $v^\infty = 0$ (by (24)) and $z^\infty = 0$ (by (23)). Now by the relations:

$$0 \le y_\infty \le y^\infty, \quad 0 \le z_\infty \le z^\infty \quad \text{and} \quad 0 \le v_\infty \le v^\infty,$$

we conclude that as $\tau \to \infty$,

$$y(\tau) \to 0, \quad z(\tau) \to 0 \quad \text{and} \quad v(\tau) \to 0.$$

Thus, with $z(\tau) \to 0$ and $v(\tau) \to 0$, the first and last equations of (7) become asymptotically autonomous equations with the following limit equations:

$$\frac{dx}{d\tau} = 1 - dx \quad \text{and} \quad \frac{dw}{d\tau} = \eta - qw,$$

which, by the theory for the asymptotically continuous systems (see, e.g. [Castillo-Chavez & Thieme, 1995]), results in

$$\lim_{\tau\to\infty} x(\tau) = \frac{1}{d} \quad \text{and} \quad \lim_{\tau\to\infty} w(\tau) = \frac{\eta}{q}.$$

Combining the local stability and global attactivity of the equilibrium $E_0^\eta$ under the condition $\mathcal{R}_0 < R_1^\eta$ shows that $E_0^\eta$ is globally asymptotically stable.

Finally, the occurrence of $E_d^\eta$ under $\mathcal{R}_0 > R_1^\eta$ is a result of the following claim: $\mathcal{R}_0 > R_1^\eta$ if and only if $qZ_+ > \eta$. Indeed, a direct calculation leads to

$$qZ_+ - \eta > 0 \Leftrightarrow \frac{q(c - acdp - abq + b\eta) + q\sqrt{(c - acdp - abq + b\eta)^2 + 4ab\eta(cdp + bq)}}{2(cdp + bq)} - \eta > 0$$

$$\Leftrightarrow q\sqrt{(c - acdp - abq + b\eta)^2 + 4ab\eta(cdp + bq)} > 2(cdp + bq)\eta - q(c - acdp - abq + b\eta).$$

If $c - acdp - abq + b\eta \le 0$, the right-hand side of the above inequality is obviously positive; while if $c - acdp - abq + b\eta > 0$, the absolute value of the right-hand side of the above inequality cannot be greater than that of the left-hand side of the inequality. Thus, in any case, we have

$$\begin{aligned} qZ_+ - \eta > 0 &\Leftrightarrow q^2(c - acdp - abq + b\eta)^2 + 4ab\eta(cdp + bq) \\ &\quad - [2(cdp + bq)\eta - q(c - acdp - abq + b\eta)]^2 > 0 \\ &\Leftrightarrow 4c\eta(dpc + bq)(q - qdap - \eta dp) > 0 \\ &\Leftrightarrow 4c^2d^2p^2aq\eta\left(1 + \frac{bq}{cdp}\right)\left(\frac{1}{adp} - 1 - \frac{\eta}{aq}\right) > 0 \\ &\Leftrightarrow 4c^2d^2p^2aq\eta R_1^\eta(\mathcal{R}_0 - R_1^\eta) > 0 \\ &\Leftrightarrow \mathcal{R}_0 > R_1^\eta. \end{aligned}$$

The proof is complete. ■

## 4. Stability of the HIV Infection Equilibrium $E_d^\eta$

In this section, we assume $\mathcal{R}_0 > R_1^\eta$ (equivalent to $qZ_+ - \eta > 0$) and study the stability of the HIV infection equilibrium $E_d^\eta$. Substituting the solution $E_d^\eta$ given in (15) into the Jacobian matrix (18) results in the characteristic polynomial:

$$P_d(\xi) = \xi^5 + a_1\xi^4 + a_2\xi^3 + a_3\xi^2 + a_4\xi + a_5, \tag{26}$$

where

$$\begin{aligned} a_1 &= \frac{1}{Z_+}\left[Z_+^2 + (p + q + b + a + d)Z_+ + \frac{b}{pc}Z_q\right], \\ a_2 &= \frac{1}{Z_+}\left\{(q + b + d)Z_+^2 + \left[(p + a)(q + b + d) + d(q + b) + \frac{b}{pc}Z_q\right]Z_+ + \frac{b}{pc}(b + q + p + a)Z_q + b\eta\right\}, \\ a_3 &= \frac{1}{Z_+^2}\left\{(bq + bd + dq)Z_+^3 + \left[d(b + q)(a + p) + \frac{b}{pc}(p + q + b)Z_q\right]Z_+^2\right. \\ &\quad \left. + \left[b\eta(d + p + a) + \frac{b}{pc}((b + q)(a + p) + ap)Z_q\right]Z_+ + \frac{b^2\eta}{pc}Z_q\right\}, \\ a_4 &= \frac{b}{Z_+^2}\left\{dqZ_+^3 + \left[p + \frac{1}{pc}(bq + pq + pb)\right]Z_+^2Z_q + \left[d\eta(p + a) + \frac{a}{c}(q + b)Z_q\right]Z_+ + \frac{b\eta}{pc}(p + a)Z_q\right\}, \\ a_5 &= \frac{b}{cZ_+^2}[(bq + cdp)Z_+^2 + ab\eta]Z_q, \end{aligned} \tag{27}$$

in which $Z_q := qZ_+ - \eta > 0$ since $\mathcal{R}_0 > R_1^\eta$ has been assumed. Therefore, $a_i > 0, i = 1, 2, 3, 4, 5$.

In the following, we show that there is an $R_2 > R_1^\eta$ such that HIV infection equilibrium $E_d^\eta$ is stable for $R_1^\eta < \mathcal{R}_0 < R_2$. To achieve this, we first need to show that when $\mathcal{R}_0 > R_1^\eta$, there exist parameter values such that

$$\Delta_i > 0, \quad i = 1, 2, 3, 4, 5, \tag{28}$$

where $\Delta_i$'s are Hurwitz quantities, given by

$$\begin{aligned}
\Delta_1 &= a_1,\\
\Delta_2 &= a_1a_2 - a_3,\\
\Delta_3 &= a_3\Delta_2 - a_1(a_1a_4 - a_5),\\
\Delta_4 &= a_4\Delta_3 - a_5[a_2\Delta_2 - (a_1a_4 - a_5)],\\
\Delta_5 &= a_5\Delta_4.
\end{aligned} \tag{29}$$

A direct computation yields

$$\begin{aligned}
\Delta_2 = \frac{1}{Z_+^2}\Bigg\{&(q+b+d)Z_+^4 + \left[2(a+p)(q+b+d) + q^2 + b^2 + d^2 + 2db + 2qd + qb + \frac{b}{pc}Z_q\right]Z_+^3\\
&+ \left[b\eta + (q+b+d)(p+a+d)(p+q+b+a) + \frac{b}{pc}(p+2b+2q+2a+2d)Z_q\right]Z_+^2\\
&+ \left[\frac{b^2}{p^2c^2}Z_q^2 + \frac{b}{pc}((p+q+b+a)(b+q+p+2d) + a(a+b+q))Z_q + b\eta(q+b)\right]Z_+\\
&+ \frac{b^2}{p^2c^2}(b+p+q+a)Z_q^2\Bigg\}\\
&> 0 \quad \text{since } Z_q > 0.
\end{aligned} \tag{30}$$

For $\Delta_3$ and $\Delta_4$, however, it is not easy to determine their signs for general $\mathcal{R}_0$. Thus, we use the property that $\Delta_3$ and $\Delta_4$ continuously depend on the parameters. At $\mathcal{R}_0 = R_1^\eta$, using (16), (27), (29) with a direct calculation leads to

$$\begin{aligned}
\Delta_3|_{\mathcal{R}_0=R_1^\eta} &= \frac{1}{q^3}(d+q)(b+d)(b+q)\\
&\quad\times(q^2 + qa + qp + \eta)\\
&\quad\times(\eta + dq + qa + qp)\\
&\quad\times(\eta + qp + qb + qa) > 0,\\
\Delta_4|_{\mathcal{R}_0=R_1^\eta} &= \frac{1}{q^3}bd(\eta + qp + qa)\Delta_3|_{\mathcal{R}_0=R_1^\eta} > 0\\
\Delta_5|_{\mathcal{R}_0=R_1^\eta} &= a_5\Delta_4|_{\mathcal{R}_0=R_1^\eta} > 0.
\end{aligned} \tag{31}$$

Since $\Delta_3$, $\Delta_4$ and $\Delta_5$ depend on $\mathcal{R}_0$ continuously, we can conclude that there must exist an $R_2 > R_1^\eta$ such that $\Delta_i > 0$ for $i = 3, 4, 5$ when $\mathcal{R}_0 \in (R_1^\eta, R_2)$. This together with $\Delta_1 = a_1 > 0$ and $\Delta_2 > 0$, leads to the following conclusion.

**Theorem 3.** *There exists an $R_2 > R_1^\eta$ such that when $\mathcal{R}_0 \in (R_1^\eta, R_2)$, the HIV infection equilibrium $E_d^\eta$ is asymptotically stable.*

## 5. Hopf Bifurcation Analysis

In the previous section, we have shown that when $\mathcal{R}_0$ is increased to cross the critical point $R_1^\eta$, the equilibrium $E_0^\eta$ loses its stability and bifurcates to the equilibrium $E_d^\eta$, which is stable for $\mathcal{R}_0 \in (R_1^\eta, R_2)$ where $R_2 > R_1^\eta$. Now, in this section we want to study the stability of $E_d^\eta$ when $\mathcal{R}_0$ is further increased. We show that there exists indeed an $R_h^\eta > R_2$ such that $E_d^\eta$ will lose it stability when $\mathcal{R}_0$ passes $R_h^\eta$, resulting in Hopf bifurcation. We have the following result.

**Theorem 4.** *For system (7), as $\mathcal{R}_0 > R_1^\eta$ is further increased, there exists finite $R_h^\eta > R_1^\eta$ such that the equilibrium $E_d^\eta$ loses its stability at $\mathcal{R}_0 = R_h^\eta$, giving rise to a family of limit cycles via Hopf bifurcation.*

*Proof.* First, note that when $\mathcal{R}_0 > R_1^\eta$ is further increased, $\Delta_1 = a_1, \Delta_2$ and $a_5$ remain positive, but $\Delta_3$ and $\Delta_4$ may become negative. The type of bifurcations depends on whether $\Delta_3$ or $\Delta_4$ first crosses zero. We want to prove that if $\Delta_3$ and $\Delta_4$ can ever become negative as $\mathcal{R}_0$ increases, then $\Delta_4$ must cross zero before $\Delta_3$ does.

First, assume $\Delta_4 = 0$ at $\mathcal{R}_0 = R_4 > R_2$ ($R_2$ is given in Theorem 3). Then, from (29) we have

$$a_4\Delta_3 = a_5[a_2\Delta_2 - (a_1a_4 - a_5)],$$

or

$$a_1a_4\Delta_3 = a_1a_5[a_2\Delta_2 - (a_1a_4 - a_5)]. \quad (32)$$

Now multiplying the third equation in (29) by $a_5$ results in

$$a_5\Delta_3 = a_3a_5\Delta_2 - a_1a_5(a_1a_4 - a_5). \quad (33)$$

Subtracting (33) from (32) we obtain

$$\Delta_3 = \frac{a_5(a_1a_2 - a_3)\Delta_2}{a_1a_4 - a_5} = \frac{a_5\Delta_2^2}{a_1a_4 - a_5}. \quad (34)$$

Note that $a_5 > 0$. Further, we can show that

$$\begin{aligned} &a_1a_4 - a_5 \\ &= \frac{b}{Z_+^3}\left\{qdZ_+^5 + \left[qd(p+q+b+a+d) + \frac{1}{pc}(p^2c + bq + pq + pb)Z_q\right]Z_+^4\right. \\ &\quad + \left[\frac{1}{pc}((p+q+b+a)(p^2c + q(b+p)) + p((b+q)(a+d) + b(a+b+p)) + 2bdq)Z_q + d\eta(p+a)\right]Z_+^3 \\ &\quad + \left[\frac{b}{p^2c^2}(p^2c + bq + bp + pq)Z_q^2 + \frac{1}{pc}(pa(q+b)(p+q+b+a+d) + b\eta(p+a))Z_q\right. \\ &\quad \left. + d\eta(a+p)(a+p+q+b+d)\right]Z_+^2 \\ &\quad \left. + \frac{1}{p^2c^2}\left[bap(q+b)Z_q^2 + pbc\eta((a+p)(p+b+q+2d) + a^2)Z_q\right]Z_+ + \frac{b^2}{p^2c^2}\eta(p+a)Z_q^2\right\} \\ &> 0 \quad \text{when } \mathcal{R}_0 > R_1^\eta \quad (\text{i.e. } Z_q > 0). \end{aligned} \quad (35)$$

This together with (34) shows that $\Delta_3 > 0$ when $\Delta_4 = 0$.

Conversely, assume, for the sake of contradiction, that $\Delta_3$ will change sign no later than $\Delta_4$ does. Then there exists an $R_3 > R_2$ such that $\Delta_3 > 0, \Delta_4 > 0$ for $\mathcal{R}_0 \in (R_1, R_3)$, and $\Delta_3 = 0, \Delta_4 \geq 0$ at $\mathcal{R}_0 = R_3$. Thus, at $\mathcal{R}_0 = R_3$, it follows from (29) with $\Delta_3 = 0$ that

$$a_3\Delta_2 - a_1(a_1a_4 - a_5) = 0,$$

or

$$a_1a_4 - a_5 = \frac{a_3}{a_1}\Delta_2 \quad (a_1 > 0).$$

Hence, $\Delta_4$ becomes

$$\Delta_4 = -a_5\left[a_2\Delta_2 - \frac{a_3}{a_1}\Delta_2\right] = -\frac{a_5}{a_1}\Delta_2^2 < 0 \quad (a_1 > 0, a_5 > 0, \Delta_2 > 0),$$

leading to a contradiction to $\Delta_4 \geq 0$ at $\mathcal{R}_0 = R_3$. This confirms that when $\Delta_4$ crosses zero, $\Delta_3$ must remain positive.

The above discussion, together with the Hopf critical condition obtained for high-dimensional systems [Yu, 2005] implies that there are no static bifurcation, Hopf-zero bifurcation, double-Hopf bifurcation, or double-zero Hopf bifurcation, emerging from the equilibrium $E_d^\eta$. The only possibility for $E_d^\eta$ to lose stability is occurrence of Hopf bifurcation when $\Delta_4$ crosses zero from positive to negative as $\mathcal{R}_0$ is further increased from $R_2 > R_1^\eta$.

In order to show that $\Delta_4$ can indeed change sign from positive to negative as $\mathcal{R}_0$ increases to pass some finite value $R_h^\eta$, we notice that $\Delta_4|_{\mathcal{R}_0 = R_1^\eta} > 0$. Thus, we only need to show that as $\mathcal{R}_0 > R_1^\eta$ and increases to pass some finite value $R_h^\eta$, it becomes negative. To prove this, we only need to show that $\Delta_4$ can be negative for some combination of parameter values. First note that $\mathcal{R}_0 = \frac{1}{adp}$ and $R_1^\eta = 1 + \frac{\eta}{aq}$, implying that $\mathcal{R}_0 \to +\infty$ and $R_1^\eta \to +\infty$ as $a \to 0^+$, and it is easy to satisfy $\mathcal{R}_0 > R_1^\eta$ if $d$ is chosen small enough such that $\frac{1}{d} > p(a + \frac{\eta}{q})$. Thus, we may choose

$$a = \epsilon \quad (0 < \epsilon \ll 1), \quad (36)$$

and then obtain

$$\Delta_4 = \sum_{k=0}^{10} c_k c^k + O(\epsilon), \quad (37)$$

where the leading coefficient of $c^{10}$ is

$$c_{10} = \frac{-bd}{(cdp+bq)^4(c+b\eta)^6}\left[bd^2p(1+p\eta)(d+p)+(d+b+pd^2(p+d))(d+q)+p^2qb\left(\frac{1}{dp}-\frac{\eta}{q}\right)\right]f_5(d),$$

in which $f_5(d)$ is a fifth-order polynomial of $d$, given by

$$\begin{aligned} f_5(d) = &-\eta^2p^6b(b+q)d^5-\eta p^5[p(b+q)(p+b+q)+b\eta]d^4\\ &-\eta p^3[bq(b+q)+p^2(b+p)+p(2q+3b)(p+q)+2p(pq+b^2)]d^3\\ &+p^2\{p^2q(b+p+q)-\eta[p(3b+3q+2p)+bq]\}d^2\\ &-p[q(b^2+bq+q^2-2p^2)+p\eta]d+q(p-b-q). \end{aligned} \tag{38}$$

Since $\mathcal{R}_0 > R_1^\eta$ implies that $\frac{1}{dp}-\frac{\eta}{q}$ is positive, the sign of $c_{10}$ is determined by the sign of $f_5(d)$. Indeed, $f_5(d) > 0 (< 0)$ corresponds to $c_{10} < 0 (> 0)$. Note that $f_5(0) = q(p-b-q)$ and $f(-\infty) = -\infty$. Thus, if $p, b$ and $q$ are chosen such that $p-b-q > 0$, then $f_5(d) > 0$ for small $d$. Therefore, further increasing $R_0$ to some value $R_h^\eta > R_1$ by decreasing $d$ can cause change of signs of $\Delta_4$ from $\Delta_4 > 0$ to $\Delta_4 < 0$, leading to occurrence Hopf bifurcation (see [Yu, 2005]) as long as $a > 0$ is taken sufficiently small and $c > 0$ is taken sufficiently large. For general model parameters, quantitatively determining the above "small" and/or "large" is very difficult (if not impossible). In the next section, we will numerically explore this problem by fixing some parameters, using the above analysis as a guide line. ■

*Remark 1.* The above analysis shows that if we choose the parameters such that

$$p-b-q>0, \quad 0<a\ll 1,$$

$$0<d\ll 1, \quad \text{and} \quad c\gg 1,$$

then we will have $\Delta_4 < 0$, resulting in Hopf bifurcation. However, these are only sufficient conditions; when they are not all satisfied, Hopf bifurcation may still be possible. Indeed, in the next section, for convenience of comparison with the results given by Jiang *et al.* [2009], we will choose $a = 0.93$ and $p = b = q$ (hence $p-b-q < 0$) in the numerical example of the next section, and show that we can find parameter values such that Hopf bifurcation occurs when $\mathcal{R}_0$ passes a finite value $R_h > R_1$. In such a case, the parameter $\eta$ must be restricted to small; for large values of $\eta$, one must choose small $a$. This will be illustrated in the next section by numerical examples.

*Remark 2.* Comparing the above results with those in [Jiang *et al.*, 2009], we have seen that there is a difference in the bifurcation path, as is shown below:

$$\text{System (7) without injection } (\eta=0): E_0 \xrightarrow{\mathcal{R}_0=1} E_s \xrightarrow{\mathcal{R}_0=R_1} E_d \xrightarrow{\mathcal{R}_0=R_h} \text{Hopf};$$

and

$$\text{System (7) with injection } (\eta\neq 0): E_0^\eta \xrightarrow{\mathcal{R}_0=R_1^\eta} E_d^\eta \xrightarrow{\mathcal{R}_0=R_h^\eta} \text{Hopf}.$$

It should be noted that if we consider the stability of $E_s^\eta$ purely from the mathematical view point, we can show that it is always unstable since the coefficient $a_5$ for the characteristic polynomial of $E_s^\eta$, given by

$$a_5 = \frac{b}{cZ_-^2}[(bq+cdp)Z_-^2+ab\eta](qZ_--\eta),$$

is negative for any positive parameter values due to $Z_- < 0$.

## 6. Numerical Illustration

In this section, we present numerical examples and simulations to demonstrate the theoretical results obtained in the previous sections. We choose $d$ as a bifurcation parameter, and apply normal form theorem to determine bifurcation and stability of limit cycles.

For a consistent comparison, we take the same parameter values used for the model without an

injection of recombinant (i.e. $\eta = 0$) [Jiang *et al.*, 2009]:

$$c = 40, \quad a = \frac{93}{100}, \quad b = p = q = \frac{28}{5}. \tag{39}$$

Since this modified model is a new one and there are no results in the literature about how to choose the injection parameter $\eta$, we will consider several different values of $\eta$ to see the trends of the system asymptotic dynamics and the effect of $\eta$.

Based on the bifurcation parameter $d$, we have

$$\mathcal{R}_0 = \frac{1}{adp} = \frac{125}{651d}. \tag{40}$$

The equilibrium solution:

$$E_0^\eta = \left(\frac{1}{d}, 0, 0, 0, \frac{5\eta}{28}\right)$$

is stable when $0 < \mathcal{R}_0 < R_1^\eta = 1 + \frac{125}{651}\eta$ (i.e. $d > \frac{125}{125\eta+651}$). At the critical point $\mathcal{R}_0 = 1 + \frac{125}{651}\eta (d = \frac{125}{125\eta+651})$, $E_0^\eta$ becomes unstable and bifurcates into the equilibrium solution:

$$E_d^\eta = \left(\frac{651}{125} + \frac{28Z_+}{5},\ -\frac{7\eta}{50Z_+} + \frac{98}{125},\ -\frac{\eta}{40} + \frac{7Z_+}{50}\ -\frac{\eta}{40Z_+} + \frac{7}{50},\ Z_+\right),$$

where

$$Z_+ = \frac{25}{224(50d+7)}\left[\left(\frac{6772}{625} - \frac{5208}{25}d + \frac{28}{5}\eta\right) + \sqrt{\left(\frac{6772}{625} - \frac{5208}{25}d + \frac{28}{5}\eta\right)^2 + \frac{291648}{3125}(50d+7)\eta}\right] > 0. \tag{41}$$

The equilibrium solution $E_d^\eta$ is stable when

$$1 + \frac{125}{651}\eta < \mathcal{R}_0 < R_h^\eta, \quad \text{or} \quad d_h^\eta < d < \frac{125}{125\eta+651},$$

where $d_h^\eta$ or $R_h^\eta$ is determined as follows.

Under the given parameter values, the coefficients of the characteristic polynomial for $E_d^\eta$ are:

$$\begin{aligned}
a_1 &= \frac{1}{200Z_+}[200Z_+^2 + (200d + 3574)Z_+ - 5\eta],\\
a_2 &= \frac{1}{20000Z_+}[400(50d + 567)Z_+^2 + 8(188983d + 44325)Z_+ + 103135\eta],\\
a_3 &= \frac{7}{25000Z_+^2}[400(100d + 301)Z_+^3 + 4(65300d - 375\eta + 9793)Z_+^2 + 5(4000d + 25281)\eta Z_+ - 500\eta^2],\\
a_4 &= \frac{7}{125000Z_+^2}[11200(50d + 301)Z_+^3 - 112(5375\eta - 1302)Z_+^2 + 20(32650d + 3269)\eta Z_+ - 16325\eta^2],\\
a_5 &= \frac{49}{31250Z_+^2}[80(50d + 7)Z_+^2 + 93\eta](28Z_+ - 5\eta),
\end{aligned} \tag{42}$$

and thus

$$\begin{aligned}
\Delta_2 = \frac{1}{4000000Z_+^2}&[80000(50d + 567)Z_+^4 + 4000(1000d^2 + 35740d - 25\eta + 244552)Z_+^3\\
&+ 8(8865000d^2 - 25000d\eta + 159658650d + 2423250\eta + 670164537)Z_+^2\\
&+ 10(250\eta - 354600d + 21946907)\eta Z_+ + 44325\eta^2],
\end{aligned}$$

$$\Delta_3 = \frac{7}{100000000000Z_+^4}[32000000(5000d + 57750d + 86387)Z_+^7 + 320000(500000d^3 + 19840000d^2$$
$$- 31250d\eta + 1254750\eta + 154527450d + 73119711)Z_+^6 + 3200(1073000000d^3 + 20625000d^2\eta$$
$$+ 25289905000d^2 605881250d\eta + 46875\eta^2 + 135888034450d + 7446495000\eta - 54784651243)Z_+^5$$
$$+ 32(2500000000d^3\eta + 578884500000d^3 + 64861250000d\eta - 112500000d\eta^2 + 10508879190000d^2$$
$$+ 1248995756250d\eta - 2347453125\eta^2 + 45194987681550d + 9251858981750\eta + 5398746708201)Z_+^4$$
$$+ 40(224000000000d^3 - 150000000d^2\eta + 371523285000d^2 + 8444600000d\eta$$
$$+ 1156250\eta^2 + 3930979433950d + 41653769625\eta + 16768455413388)\eta Z_+^3$$
$$- 250(268800000d^2 - 600000d\eta - 16959281440d + 39181900\eta - 116370697641)\eta^2 Z_+^2$$
$$+ 125(13440000d - 10000\eta - 924584267)\eta^3 Z_+ - 14000000\eta^4],$$

$$\Delta_4 = \frac{49}{62500000000000000Z_+^6}[358400000000(62500d^3 + 770000d^2 + 2615375d + 11876032)Z_+^{10}$$
$$+ 512000000(437500000d^4 + 7812500d^3\eta + 1157187500d^3 + 80937500d^2\eta + 8406317500d^2$$
$$+ 154809375d\eta + 19785929275d - 159152000\eta + 56343381031)Z_+^9 + 5120000(781250000d^4\eta$$
$$+ 32637500000d^4 + 55476562500d^3\eta + 39062500d^2\eta^2 + 294118562500d^3 + 544326562500d^2\eta$$
$$+ 144921875d\eta^2 - 210354305000d^2 + 1393225421875d\eta - 23618000000\eta^2 - 5438046860575d$$
$$+ 6770841609000\eta - 75962431340229)Z_+^8 - 51200(4228125000000d^4\eta - 5859375000d^3\eta^2$$
$$- 36224606250000d^4 + 127095507812500d^3\eta + 135976562500d^2\eta^2 + 48828125d\eta^3$$
$$- 628921081687500d^3 + 917508252500000d^2\eta + 1439169921875d\eta^2 - 875000000\eta^3$$
$$- 2290566634282500d^2 + 1799559791071875d\eta - 140968236281250\eta^2 + 1964727758881125d$$
$$+ 10950676362050250\eta - 761023756778439)Z_+^7 + 512(5135472656250000d^4\eta$$
$$+ 12378906250000d^3\eta^2 + 14648437500d^2\eta^3 + 105324401492187500d^3\eta + 2216748281250000d^2\eta^2$$
$$+ 492041015625d\eta^3 + 2637976666500000d^3 + 517492882714062500d^2\eta + 14458708712109375d\eta^2$$
$$+ 37552812500000\eta^3 + 47888962468830000d^2 + 294513488052765625d\eta - 164010832351406250\eta^2$$
$$+ 205953558864823350d + 215006668674033250\eta + 24602088749271957)Z_+^6$$
$$+ 640(408125000000000d^4\eta + 9450289462500000f^4 + 818154203125000d^3\eta - 1136171875000d^2\eta^2$$
$$- 97656250d\eta^3 + 172349911619625000d^3 + 26292244412812500d^2\eta - 75947388671875d\eta^2$$
$$- 23587890625\eta^3 + 750979923076897500d^2 + 158891091692003125d\eta - 1075867616687500\eta^2$$
$$+ 140938912990928850d - 211011650994607750\eta + 2880627455034042)\eta Z_+^5$$
$$+ 800(3656800000000000d^4 - 32650000000000d^3\eta + 5949268163000000d^3 + 129916613437500d^2\eta$$
$$+ 13679687500d\eta^2 + 62131744461117500d^2 + 180009575871875d\eta + 4425071359375\eta^2$$
$$+ 270135269412279250d - 13621925249009000\eta + 32901492002660442)\eta^2 Z_+^4$$

$$
\begin{aligned}
&- 1000(29254400000000d^3 - 97950000000d^2\eta - 1264442575510000d^2 + 6342784706250d\eta \\
&+ 2718750\eta^2 - 8531601925051750d - 23080719997625\eta + 3665294181509436)\eta^3 Z_+^3 \\
&+ 1250(877632000000d^2 - 1306000000d\eta - 58019234078800d + 67522139500\eta \\
&- 170731874778439)\eta^4 Z_+^2 - 3125(5850880000d(-3265000e - 302750729877)\eta^5 Z_+ \\
&+ 114275000000\eta^6)],
\end{aligned}
$$

where $Z_+$ is given in (41).

We shall consider several values of $\eta$ starting from $\eta = 0.01$. It should be noted that since we take $a = 0.93$, which is quite close to 1, and $b = p = q$ which makes the constant term in (38) negative, there might not exist $R_h^\eta$ for large values of $\eta$. So for such a set of parameter values given in (39), we need to choose small values of $\eta$. For large values of $\eta$, we need to choose small values of $a$. We will also present a couple of cases for small $a$ but large $\eta$. For brevity, we shall only present a detailed analysis on the case of $\eta = 0.01$, and summarize the results for other cases.

When $\eta = 0.01$, with other parameter values given in (39), the equilibrium solution $E_0^\eta$ is stable for

$$
\begin{aligned}
&0 < \mathcal{R}_0 < 1.192012288786482 \\
&(\text{or } d > 0.161082474226804),
\end{aligned}
\tag{43}
$$

and bifurcates into the equilibrium solution $E_d^\eta$ at the critical point $\mathcal{R}_0 = 1.192012288786482$ ($d = 0.161082474226804$). The equilibrium solution $E_d^\eta$ is stable for $1.192012288786482 < \mathcal{R}_0 < R_h^\eta$ (or $d_h^\eta < d < 0.161082474226804$), and bifurcates into a family of limit cycles at the critical point $\mathcal{R}_0 = R_h^\eta$ ($d = d_h^\eta$). A numerical scheme (e.g. bisection approach) can be used to find the solution $d$ of $\Delta_4 = 0$ as

$$
\begin{aligned}
d_h^\eta &= 0.0163983468429118, \quad \text{or} \\
R_h^\eta &= 11.709246707967994.
\end{aligned}
\tag{44}
$$

At the critical point $\mathcal{R}_0 = R_h^\eta$, except for $\Delta_4$, all other Hurwitz conditions are satisfied:

$$
\begin{aligned}
&\Delta_1 = a_1 = 18.1053876158, \quad a_5 = 6.1809019109, \\
&\Delta_2 = 1402.6217823605, \\
&\Delta_3 = 13609.5628253147, \\
&\Delta_4 = 0.3162518844 \times 10^{-10}.
\end{aligned}
$$

The eigenvalues of this characteristic polynomial $P_d(\xi)$ include a pure imaginary pair and three negative real values:

$$
\begin{aligned}
\xi = \pm 0.7981309053i, \quad &-0.1281736434, \\
&-6.7317310171, \quad -11.2454829553,
\end{aligned}
$$

where $i$ is the imaginary unit, $i^2 = -1$.

In order to obtain the approximate solution of the bifurcating family of limit cycles, we apply the normal form theory and program using computer algebra system Maple, developed by Yu [1998], to analyze the Hopf bifurcation of system (7) from the critical point $d = d_h^\eta(\mathcal{R}_0 = R_h^\eta)$. The general normal form can be written in polar coordinates as:

$$
\begin{aligned}
\frac{dr}{d\tau} &= r(v_0\mu + v_1 r^2) + \cdots, \\
\frac{d\theta}{d\tau} &= \omega_0 + \tau_0\mu + \tau_1 r^2 + \cdots,
\end{aligned}
\tag{45}
$$

where $\omega_0 = 0.7981309053, v_0, v_1, \tau_0, \tau_1$ are constants, expressed in terms of the original system parameters; $v_0$ and $v_1$ are called focus values (or Lyapunov coefficients). $v_0$ and $\tau_0$ can be found from linearization at the critical point $\mathcal{R}_0 = R_h^\eta$, while $v_1$ and $\tau_1$ must be determined by using nonlinear analysis. $r$ and $\theta$ represent the amplitude and phase of periodic motion (limit cycle), respectively. When $v_1 < 0$ ($v_1 > 0$), the Hopf bifurcation is supercritical (subcritival), giving rise to stable (unstable) limit cycles, and the periodic solutions can be approximated in terms of the steady-state solution of (45).

Let $d = d_h^\eta - \mu$, where $\mu$ is a small perturbation (bifurcation) parameter. Further, introducing the following linear transformation

$$
\begin{pmatrix} x \\ y \\ z \\ v \\ w \end{pmatrix} = \begin{pmatrix} 6.4406999294 \\ 0.7776399769 \\ 0.0305674982 \\ 0.1388642816 \\ 0.2201249874 \end{pmatrix} + T \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \\ x_5 \end{pmatrix}, \tag{46}
$$

where

$$T = \begin{bmatrix} 1.3370910031 & 0.2767729103 & -8.0633794990 & 0.9006658877 & -0.0048590515 \\ 0.1491338139 & -0.9635913372 & 0.1855705581 & -1.0407983714 & 0.0472345425 \\ -0.1313985937 & -0.0338798848 & -0.1919070400 & -0.0086936442 & -0.0766425867 \\ 0.0020651094 & -0.1723642080 & 0.0339138244 & 0.9196517155 & -0.0083667851 \\ -0.9536799068 & -0.1060774970 & -1.4028737574 & 0.3072689190 & 0.5430365290 \end{bmatrix},$$

into (7) yields

$$\frac{dx_i}{d\tau} = F_i(x_1, x_2, x_3, x_4, x_5; \mu), \quad i = 1, 2, \ldots, 5, \tag{47}$$

in which

$$\begin{aligned}
F_1 &= 0.7981309053x_2 - (2.4544677135x_1 - 21.0146351538x_2 + 4.3252758911x_3 \\
&\quad - 23.2404597695x_4 + 1.3787597052x_5)\mu + \cdots \\
&\quad + 0.4348707871x_1^2 - 0.3132788864x_2^2 + 0.7914568489x_3^2 + 0.9912263340x_4^2 \\
&\quad - 0.0784190641x_5^2 - 2.7648983162x_1x_2 + 1.1811644773x_1x_3 - 3.1546713514x_1x_4 \\
&\quad - 0.1100566813x_1x_5 - 4.0498643138x_2x_3 + 0.5692835516x_2x_4 + 1.6150680334x_2x_5 \\
&\quad - 4.7585752473x_3x_4 - 0.1044033300x_3x_5 + 1.6833860349x_4x_5, \\
F_2 &= -0.7981309053x_1 + (0.0201877283x_1 + 4.7355319755x_2 - 0.7313653103x_3 \\
&\quad - 32.0146359880x_4 + 0.3488866114x_5)\mu + \cdots \\
&\quad - 0.0238147316x_1^2 + 0.0555310017x_2^2 + 0.1904213506x_3^2 - 0.7442823567x_4^2 \\
&\quad + 0.0038423546x_5^2 + 0.3296533305x_1x_2 - 0.0824745155x_1x_3 - 0.8778051825x_1x_4 \\
&\quad + 0.0148394608x_1x_5 - 0.9743278331x_2x_3 - 0.1114882188x_2x_4 - 0.0785966765x_2x_5 \\
&\quad + 6.4342427395x_3x_4 - 0.0513312088x_3x_5 - 0.0731380752x_4x_5 \\
F_3 &= -0.1281736434x_3 - (0.5548438965x_1 - 2.8606104110x_2 - 0.3703949508x_3 \\
&\quad - 6.5240594399x_4 + 0.2501050776x_5)\mu + \cdots \\
&\quad + 0.0711256583x_1^2 - 0.0547754723x_2^2 + 0.1079022556x_3^2 + 0.2257156082x_4^2 \\
&\quad - 0.0127842286x_5^2 - 0.4686429801x_1x_2 + 0.1948260523x_1x_3 - 0.4191383638x_1x_4 \\
&\quad - 0.0188126243x_1x_5 - 0.5521379769x_2x_3 + 0.1005117728x_2x_4 + 0.2632460746x_2x_5 \\
&\quad - 1.3472952388x_3x_4 - 0.0118178142x_3x_5 + 0.2735719636x_4x_5 \\
F_4 &= -6.7317310171x_4 + (-0.0223497497x_1 + 1.1404096931x_2 - 0.2016845633x_3 \\
&\quad - 5.7954656586x_4 + 0.0501630568x_5)\mu + \cdots \\
&\quad + 0.0005120195x_1^2 + 0.0069015842x_2^2 + 0.0452202351x_3^2 - 0.1295588393x_4^2 \\
&\quad - 0.0001779833x_5^2 + 0.0305135228x_1x_2 - 0.0019798715x_1x_3 - 0.2027518607x_1x_4 \\
&\quad + 0.0015400066x_1x_5 - 0.2313806778x_2x_3 - 0.0145455868x_2x_4 + 0.0037675484x_2x_5 \\
&\quad + 1.1640435729x_3x_4 - 0.0109312340x_3x_5 + 0.0055909766x_4x_5
\end{aligned}$$

$$
\begin{aligned}
F_5 = {} & -11.2454829552x_5 + (-5.7273193778x_1 + 44.5756964879x_2 - 6.6679148882x_3 \\
& + 54.6945255400x_4 - 3.0277259802x_5)\mu + \cdots \\
& + 0.9425228123x_1^2 - 0.6847438147x_2^2 + 1.6803186075x_3^2 + 2.2518207727x_4^2 \\
& - 0.1698947743x_5^2; -6.0192671940x_1x_2 + 2.5626799918x_1x_3 - 6.6797733300x_1x_4 \\
& - 0.2398542988x_1x_5 - 8.5981550372x_2x_3 + 1.2458878774x_2x_4 + 3.4989615815x_2x_5 \\
& - 11.2393705622x_3x_4 - 0.2177247953x_3x_5 + 3.6456518531x_4x_5
\end{aligned}
$$

Here $\cdots$ denotes the terms including higher-order powers of $\mu$. Now, the Jacobian of system (47) evaluated at the equilibrium solution $x_i = 0, i = 1, 2, \ldots 5$ (i.e. $E_d^\eta$) is in the Jordan canonical form:

$$
J(E_d^\eta) = \begin{bmatrix}
0 & 0.7981309053 & 0 & 0 & 0 \\
-0.7981309053 & 0 & 0 & 0 & 0 \\
0 & 0 & -0.1281736434 & 0 & 0 \\
0 & 0 & 0 & -6.7317310171 & 0 \\
0 & 0 & 0 & 0 & -11.2454829553
\end{bmatrix}.
$$

The coefficients $v_0$ and $\tau_0$ are given by Yu and Huseyin [1988]:

$$
\begin{aligned}
v_0 &= \frac{1}{2}\left(\frac{\partial^2 F_1}{\partial x_1 \partial \mu} + \frac{\partial^2 F_2}{\partial x_2 \partial \mu}\right) = 1.1405321310, \\
\tau_0 &= \frac{1}{2}\left(\frac{\partial^2 F_1}{\partial x_2 \partial \mu} - \frac{\partial^2 F_2}{\partial x_1 \partial \mu}\right) = 10.4972237127.
\end{aligned} \tag{48}
$$

Applying the Maple program [Yu, 1998] to system (47) (setting $\mu = 0$) results in

$$
\begin{aligned}
v_1 &= -0.07469643387, \\
\tau_1 &= -0.7343312614.
\end{aligned} \tag{49}
$$

Therefore, the third-order normal form (47) is given by

$$
\begin{aligned}
\frac{dr}{d\tau} &= r(1.1405321310\mu - 0.07469643387r^2), \\
\frac{d\theta}{d\tau} &= 0.7981309053 + 10.4972237127\mu \\
&\quad - 0.7343312614r^2.
\end{aligned} \tag{50}
$$

The steady-state solutions of (50) are determined by setting $\frac{dr}{d\tau} = \frac{d\theta}{d\tau} = 0$, yielding

$$
\bar{r} = 0 \quad \text{and} \quad \bar{r}^2 = 15.26888966786\mu. \tag{51}
$$

The solution $\bar{r} = 0$ actually denotes the equilibrium solution $E_d^\eta$. A simple linearization of the first equation of (50) indicates that $\bar{r} = 0(E_d^\eta)$ is stable for $\mu < 0$, as expected. When $\mu$ increases from negative to cross zero, a Hopf bifurcation occurs and the amplitude of bifurcating periodic solutions is given by the nonzero steady-state solution

$$
\bar{r} = 3.90754356068\sqrt{\mu} \quad (\mu > 0). \tag{52}
$$

Since $v_1 < 0$, the Hopf bifurcation is supercritical, i.e. the bifurcating limit cycles are stable and the amplitude is given by Eq. (52), and the frequency is determined from the following equation:

$$
\omega = 0.7981309053 + 7.6277923208\mu. \tag{53}
$$

Now we give a comparison of the two systems, one without injection ($\eta = 0$) and one with injection $\eta = 0.01$, as follows:

$$
\begin{aligned}
&\text{System without injection } (\eta = 0) : E_0 \xrightarrow{d=0.1920} E_s \xrightarrow{d=0.0520} E_d \xrightarrow{d=0.0243} \text{Hopf} \\
&\text{System with injection } (\eta = 0.01) : E_0^\eta \xrightarrow{d=0.1611} E_d^\eta \xrightarrow{d=0.0164} \text{Hopf}.
\end{aligned}
$$

Recalling that $d$ decreases as $\mathcal{R}_0$ is increasing, we know that by adding the constant injection $\eta$, the equilibrium $E_0^\eta$ has larger stability interval, and delay the occurrence of Hopf bifurcation. This confirms that the constant injection of recombinant helps to cure disease.

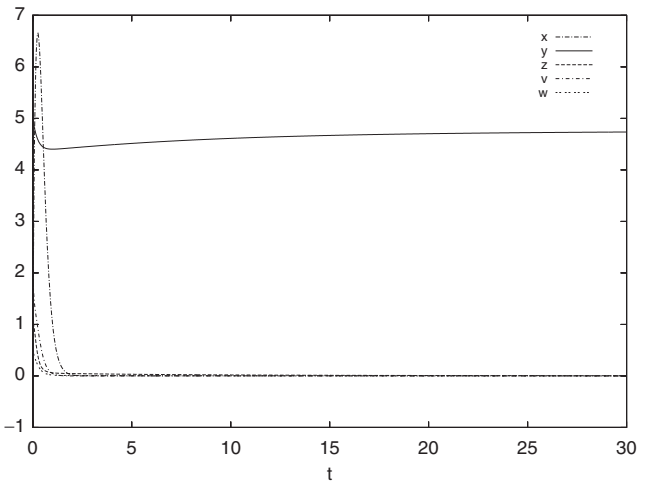



Fig. 1. Simulated time history of system (7) for $d = 0.21$, $a = 0.93$, $c = 40$, $b = p = q = 5.6$, $\eta = 0.01$, with the initial condition: $x(0) = 5.0$, $y(0) = 1.0$, $z(0) = 2.0$, $v(0) = 0.5$, $w(0) = 4.0$, converging to the stable equilibrium solution $E_0^\eta$.

To this end, we show some simulation results for the case $\eta = 0.01$, based on Eq. (7), obtained by using a fourth-order Runge–Kutta method. We take the parameter values given in Eq. (39), and choose three different values for $d$ (and so for $\mathcal{R}_0$):

$$\begin{aligned} &d = 0.21 \quad (\mathcal{R}_0 = 0.9143442323),\\ &d = 0.10 \quad (\mathcal{R}_0 = 1.9201228879),\\ &d = 0.012 \ (\mathcal{R}_0 = 16.0010240655),\\ &d = 0.008 \ (\mathcal{R}_0 = 24.0015360982). \end{aligned} \tag{54}$$

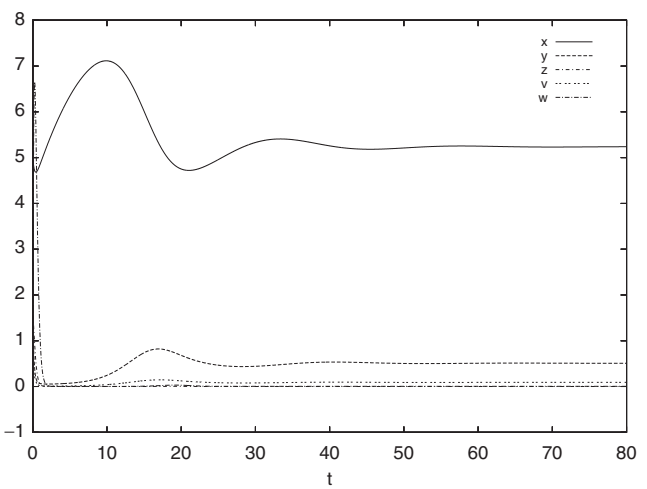
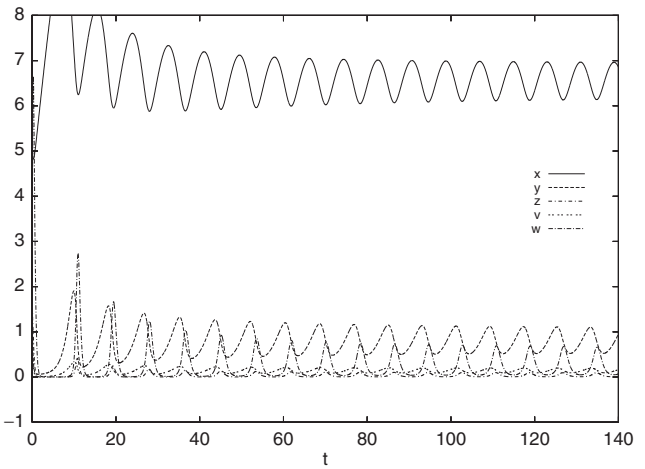


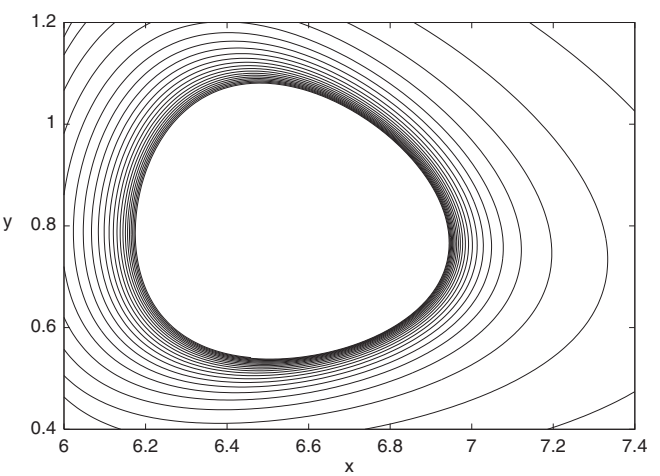

Fig. 2. Simulated time history of system (7) for $d = 0.04$, $a = 0.93$, $c = 40$, $b = p = q = 5.6$, $\eta = 0.01$, with the initial condition: $x(0) = 5.0$, $y(0) = 1.0$, $z(0) = 2.0$, $v(0) = 0.5$, $w(0) = 4.0$, converging to the stable equilibrium solution $E_d^\eta$.

According to the above theoretical analysis, the simulation results are expected to have stable equilibrium $E_0^\eta$ when $d = 0.21$, stable equilibrium $E_d^\eta$ when $d = 0.10$, and stable limit cycles when $d = 0.012$ (for which $\mu = 0.0043983468$), and $d = 0.008$ (for which $\mu = 0.0083983468$). Note that the first two numerical values of $d$ are the same as that used for the model without the injection (i.e. $\eta = 0$) [Jiang *et al.*, 2009].

The simulated time history and phase portraits for the above four cases are shown in Figs. 1–4, respectively, where the initial condition is

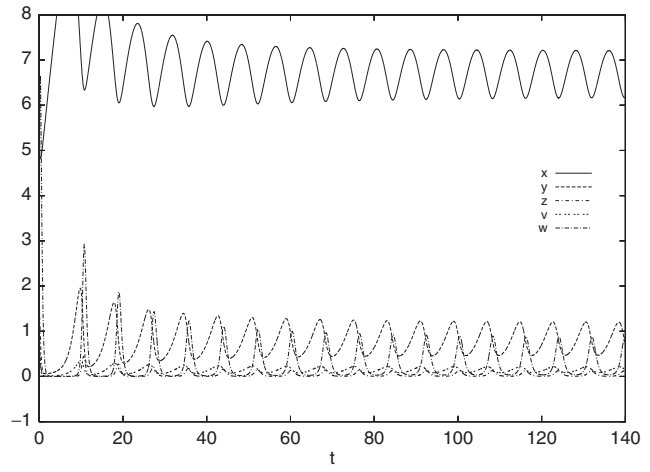



(a)

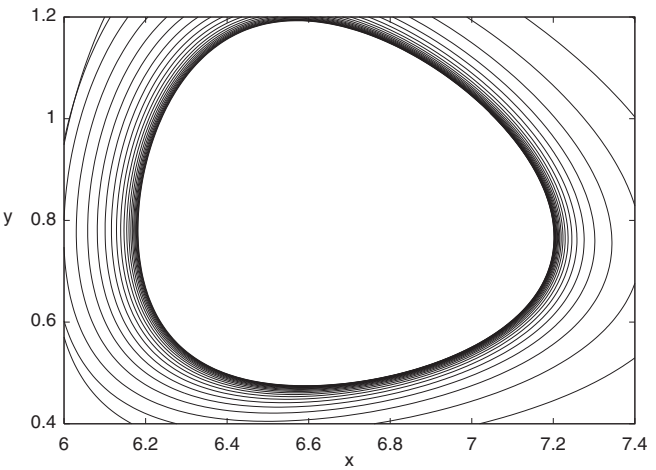



(b)

Fig. 3. Simulation results of system (7) for $d = 0.012$, $a = 0.93$, $c = 40$, $b = p = q = 5.6$, $\eta = 0.01$, with the initial condition, $x(0) = 5.0, y(0) = 1.0, z(0) = 2.0, v(0) = 0.5, w(0) = 4.0$: (a) time history showing convergence to a stable periodic solution; (b) phase portrait projected on $x$–$y$ plane indicating a stable limit cycle.




(a)




(b)

Fig. 4. Simulation results of system (7) for $d = 0.008$, $a = 0.93$, $c = 40$, $b = p = q = 5.6$, $\eta = 0.01$ with the initial condition, $x(0) = 5.0$, $y(0) = 1.0$, $z(0) = 2.0$, $v(0) = 0.5$, $w(0) = 4.0$: (a) time history showing convergence to a stable periodic solution; (b) phase portrait projected on $x$–$y$ plane indicating a stable limit cycle.

taken as

$$x(0) = 5.0, \quad y(0) = 1.0, \quad z(0) = 2.0, \quad v(0) = 0.5, \quad w(0) = 4.0. \tag{55}$$

It can be seen from these figures that the numerical simulation results agree with the analytical predictions. The solutions for the first two cases converge to the equilibrium points, $E_0^\eta$ and $E_d^\eta$, respectively. They are quite similar to the results obtained for the model without the injection (see Figs. 1 and 3 in [Jiang *et al.*, 2009]).

For the last two cases, the simulated amplitudes of the limit cycles (see Figs. 3 and 4) are close to the predicted values, $\bar{r} = 0.2591$ for Fig. 3, and $\bar{r} = 0.3581$ for Fig. 4, showing a good agreement between the theoretical prediction and numerical simulation results, not only qualitatively, but also quantitatively. It can be seen from these two figures that a small change in $\mu$ can cause large variation of the amplitudes.

The period of motion, $T = \frac{2\pi}{\omega}$ ($\omega$ is given in Eq. (53)), decreases as $\mu$ increases. In other words, $T$ decreases as $d$ decreases. However, since $\mu$ is quite small, the change of the period due to $\mu$ is not significant [hardly to observe from Figs. 3(a) and 4(a)].

By using the above process, for the fixed parameter values given in (39), we can similarly consider bifurcation of limit cycles for different values $\eta = 0.02, 0.04, 0.05, 0.1$, etc. We have found that there does not always exist $d_h^\eta$ at which a Hopf bifurcation occurs. This is because $a = 0.93$ is quite close to 1. In fact, for these fixed parameter values, $\eta$ has a limit value $\eta = 0.0412442708$ for which all the Hurwitz conditions are satisfied even as $d \to 0^+$. In other words, for such a case, the equilibrium solution $E_d^\eta$ is always stable, and no Hopf bifurcation can occur.

We summarize the results for the cases: $\eta = 0.02, \eta = 0.04$ and $\eta = 0.0412442708026295$ below. The critical points $d_h^\eta$ are given by

$$\begin{aligned} &a = 0.93, \quad c = 40, \quad b = p = q = 5.6, \\ &d_h^\eta = 0.0101558526334221 \quad \text{when } \eta = 0.02, \\ &d_h^\eta = 0.0005138201172363 \quad \text{when } \eta = 0.04, \\ &d_h^\eta = 0^+ \quad \text{when } \eta = 0.0412442708026295, \end{aligned} \tag{56}$$

and the normal forms for $\eta = 0.02$ and $\eta = 0.04$ (the case $d_h^\eta =$ does not have positive $\mu$) are

$$\eta = 0.02 : \begin{cases} \dfrac{dr}{d\tau} = r(1.1688784471\mu - 0.0269500492r^2), \\ \dfrac{d\theta}{d\tau} = 0.8710118988 + 10.2078158880\mu - 0.2138810655r^2. \end{cases} \tag{57}$$

$$\eta = 0.04 : \begin{cases} \dfrac{dr}{d\tau} = r(1.2296296415\mu - 0.0945184454r^2), \\ \dfrac{d\theta}{d\tau} = 0.9805343288 + 10.0797829783\mu - 0.6189782824r^2, \end{cases} \tag{58}$$

where $\mu = d_h^\eta - d$. It should be pointed out that the above two normal forms are obtained from the two different critical points corresponding to the two different values of $\eta = 0.02, 0.04$, though both cases use $d$ as a bifurcation parameter. Therefore, the estimate of the amplitude of the periodic motion (limit cycle) may not be consistent for comparison with respect to $\eta$, and so we cannot make a conclusion on the trend of the effectiveness of $\eta$. As a matter of fact, if taking $\mu = 0.0004$, we obtain the amplitudes of the two limit cycles estimated from the above normal forms as

$$\bar{r} = 0.1317148951 \ (\eta = 0.02)$$

$$\bar{r} = 0.0721371321 \ (\eta = 0.04),$$

which seems to imply that a larger value of $\eta$ results in a smaller motion. (For this case, double the amount of injection reduces the amplitude of the motion almost by half.) However, the simulated results for the two phase portraits, depicted in Figs. 5(a) and 5(b) respectively, indicate that the two limit cycles almost have the same size. This discrepancy does not mean that the normal forms are not appropriate, but that they are based on two different critical points. To illustrate this point, in the following we consider two different values of $\eta$, but now we fix $d$ and treat $\eta$ as a bifurcation parameter.

Take the parameter values given in (39) and choose $d = 0.0005$. Then the critical point $\eta_h = 0.040033210376566$. Let $\eta = \eta_h - \mu$. The normal is then given by

$$\begin{aligned} \frac{dr}{d\tau} &= r(0.5116283875\mu - 0.0945229057r^2), \\ \frac{d\theta}{d\tau} &= 0.9806903402 + 0.5029615211\mu \\ &\quad - 0.6188803990r^2. \end{aligned} \tag{59}$$

We compare two cases:

$$\mu = 0.01 \ (\eta = 0.0300332104) \quad \text{and}$$

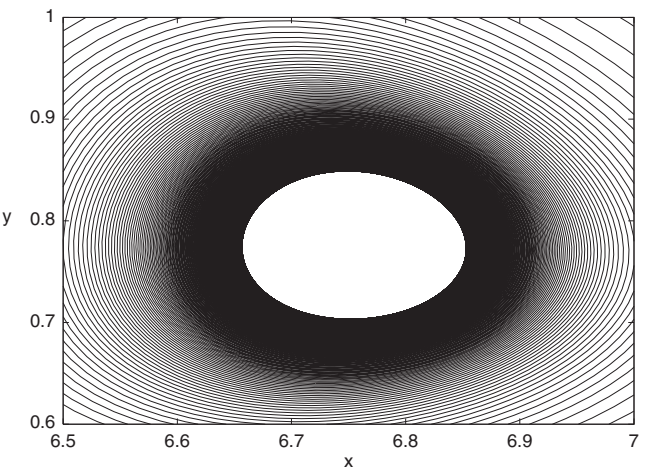
$$\mu = 0.02 \ (\eta = 0.0200332104),$$

for which the estimates of the amplitudes of the two limit cycles are obtained from the normal form (59) as:

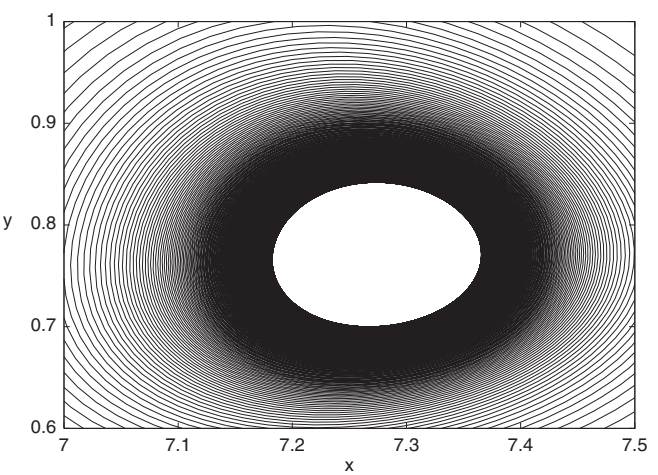
$$\bar{r} = 0.3290211246 \ (\eta = 0.0200332104) \quad \text{and}$$

$$\bar{r} = 0.2326530684 \ (\eta = 0.0300332104),$$

respectively. This shows that 50% increase in the value of $\eta$ results in 40% reduction in the amplitude of bifurcating motion.

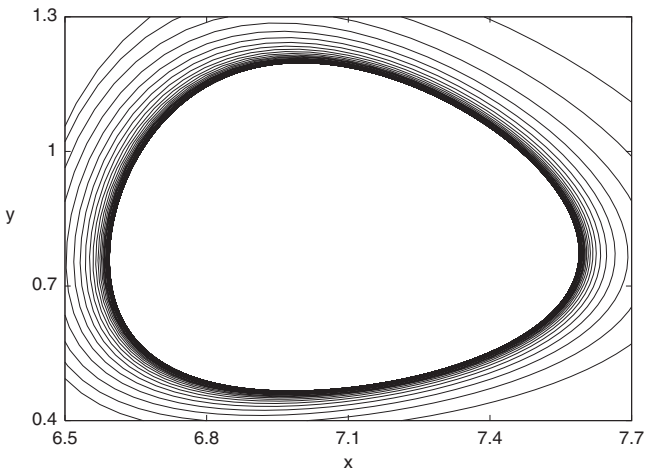



(a)

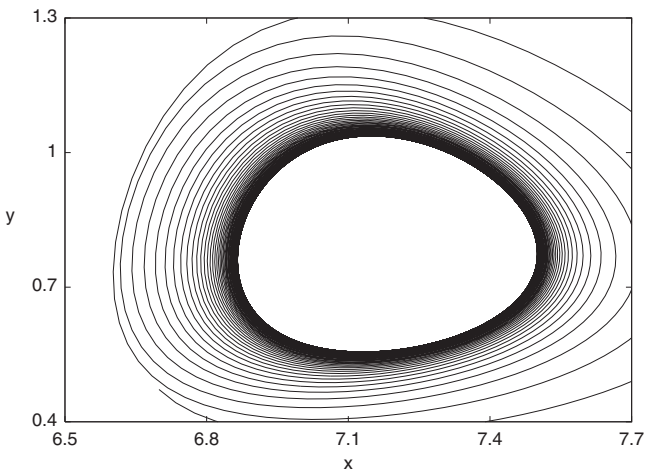



(b)

Fig. 5. Simulated phase portraits, projected on $x$–$y$ plane, for system (7) when $a = 0.93$, $c = 40$, $b = p = q = 5.6$ with the initial condition, $x(0) = 5.0$, $y(0) = 1.0$, $z(0) = 2.0$, $v(0) = 0.5$, $w(0) = 4.0$, showing stable limit cycles: (a) $\eta = 0.02, d = 0.009755852$; (b) $\eta = 0.04, d = 0.0001138201$.




(a)




(b)

Fig. 6. Simulated phase portraits, projected on $x$–$y$ plane, for system (7) when $a = 0.02$, $d = 0.0005$, $c = 40$, $b = p = q = 5.6$ with the initial condition, $x(0) = 5.0$, $y(0) = 1.0$, $z(0) = 2.0$, $v(0) = 0.5$, $w(0) = 4.0$, showing stable limit cycles: (a) $\eta = 0.0200332104$; (b) $\eta = 0.0300332104$.

The numerical simulation results for the above two cases are shown in Figs. 6(a) and 6(b), respectively. These figures indeed show a good agreement with the theoretical predictions, confirming that increasing $\eta$ does help to control the disease.

To this end, we consider a couple of cases for small $a$. Suppose $a = 0.02$, and other parameters are still the same as that given in (39). Again we treat $\eta$ as bifurcation parameter and fix $d = 0.02$.

Then it can be shown that for these parameter values, $\eta_h = 0.3995538746$. Then the normal form for this case is

$$\frac{dr}{d\tau} = r(0.1996192042\mu - 0.0624230311r^2),$$

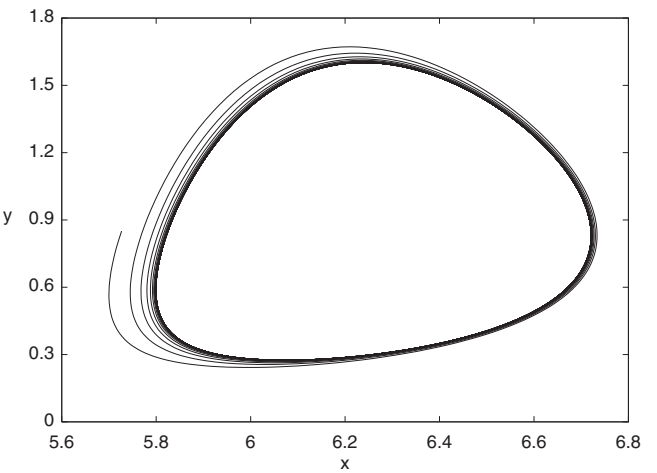
$$\frac{d\theta}{d\tau} = 1.6338126963 + 0.0051686823\mu - 0.2300113030r^2, \tag{60}$$

where $\eta = \eta_h - \mu$. For this case, we give a comparison for two relatively large values of $\mu = 0.05, 0.2$, with the corresponding values of $\eta$, given by

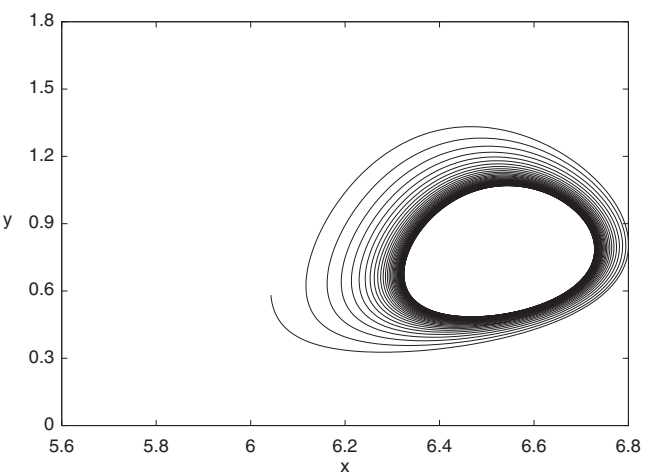
$$\eta = 0.3495538746 \ (\mu = 0.05) \quad \text{and}$$

$$\eta = 0.1995538746 \ (\mu = 0.2).$$

For the above values, the estimates for the amplitudes of the limit cycles are obtained from the




(a)




(b)

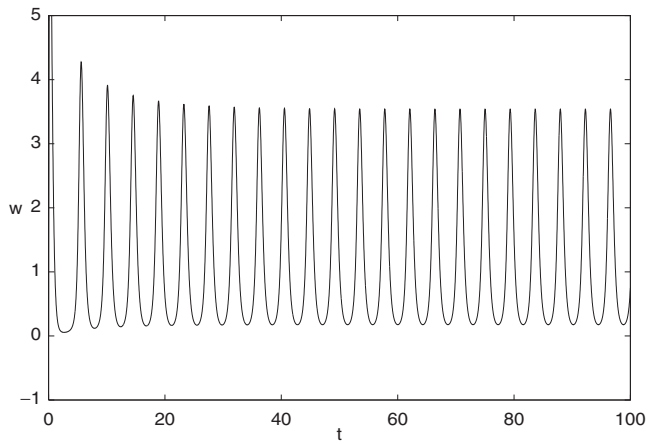
Fig. 7. Simulated phase portraits, projected on $x$–$y$ plane, for system (7) when $a = d = 0.02$, $c = 40$, $b = p = q = 5.6$, with the initial condition, $x(0) = 5.0, y(0) = 1.0, z(0) = 2.0$, $v(0) = 0.5$, $w(0) = 4.0$, showing stable limit cycles: (a) $\eta = 0.1995538746$; (b) $\eta = 0.3495538746$.

normal form (60) as:

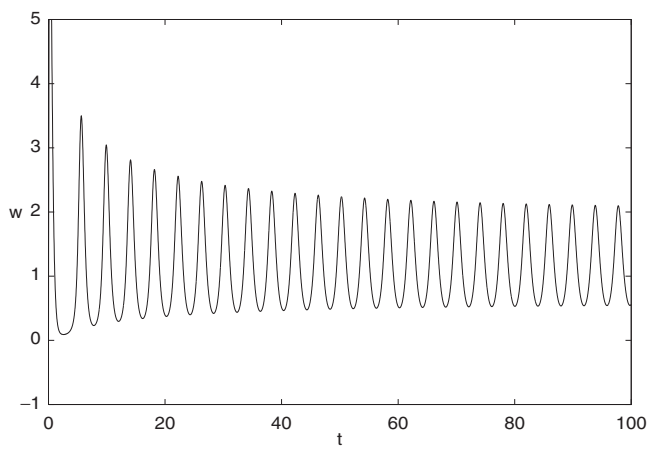
$$\bar{r} = 0.7997306324 \ (\eta = 0.1995538746) \quad \text{and}$$

$$\bar{r} = 0.3998653162 \ (\eta = 0.3495538746).$$

The numerical simulation results for the above two cases are shown in Figs. 7(a) and 7(b), respectively. These figures indeed show that large values of $\eta$ decrease the amplitudes of motion, as expected. Thus, the injection is beneficial to cure the decease. However, due to large perturbation, the error between the theoretical prediction and numerical results is larger than that of small perturbations. This can be seen by comparing Figs. 6(a) and 6(b) (for smaller perturbation) with Figs. 7(a) and 7(b) (for larger perturbation).




(a)




(b)

Fig. 8. Simulated time history of $w(t)$ for $a = d = 0.02, c = 40, b = p = q = 5.6$, with the initial condition, $x(0) = 5.0, y(0) = 1.0, z(0) = 2.0, v(0) = 0.5$, $w(0) = 4.0$, showing stable limit cycles: (a) $\eta = 0.1995538746$; (b) $\eta = 0.3495538746$.

It may be noted that the phase portraits shown in Figs. 3–7 are projected on the $x$–$y$ plane, indicating that increasing the value of $\eta$ is indeed beneficial in controlling the Hopf bifurcation, reducing the amplitude of the motion with respect to the variables $x$ and $y$. This is also true for the variables $z$ and $v$. For the variable $w$, it is not so obvious if increasing $\eta$ will also help to decrease the amplitude of $w$ since $\eta$ is a positive input for the rate of change $w$ [see the fifth equation of (7)]. However, the time history of $w$ for the last two cases [shown in Figs. 7(a) and 7(b)] actually indicates that an increase in $\eta$ is also good for controlling the motion of $w$, as depicted in Figs. 8(a) and 8(b). This is because changing the value of $\eta$ mainly affect the equilibrium solution, but not the dynamical motion. In other words, for equilibrium solutions, increasing $\eta$ can help to stabilize the equilibria, while for periodic motions, increasing $\eta$ can decrease the amplitudes of motions. Hence, we can conclude that increasing $\eta$ is beneficial in controlling the disease.

## 7. Conclusion and Discussion

In this paper, in order to study the consequence of the continuous constant injection of a genetically modified virus in the therapy of "fighting HIV virus with another virus", we incorporate a new term into the model considered in [Revilla & Garcia-Ramos, 2003; Jiang *et al.*, 2009] to describe the interaction of the $CD4^+T$ cells, the HIV virus and the recombinant virus. The added injection measurement ($\eta$) helps one understand the mechanism of therapy treatment and how to control the injection in controlling the disease. This new model includes the one in [Revilla & Garcia-Ramos, 2003; Jiang *et al.*, 2009] as a special case. However, mathematically it has been shown that the dynamics of this model with $\eta > 0$ has a significant difference from that of the model with $\eta = 0$. For example, unlike the previous model in [Revilla & Garcia-Ramos, 2003; Jiang *et al.*, 2009] which has three equilibrium solutions: infection-free equilibrium $E_0$, single-infection equilibrium $E_s$ and double-infection equilibrium $E_d$; this new model only allows two equilibrium solutions: infection-free equilibrium $E_0^\eta$ and double-infection equilibrium $E_d^\eta$. Biologically, this is reasonable because a continuous injection would keep the population of the recombinants persistent, and thus, an HIV-infection-only equilibrium becomes impossible. This has caused a difference

in the path of the cascading bifurcations for the model with $\eta > 0$ and the model with $\eta = 0$, as is shown below:

$$\text{System without injection } (\eta = 0) : E_0 \xrightarrow{\mathcal{R}_0=1} E_s \xrightarrow{\mathcal{R}_0=R_1} E_d \xrightarrow{\mathcal{R}_0=R_h} \text{Hopf};$$

$$\text{System with injection } (\eta \neq 0) : E_0^\eta \xrightarrow{\mathcal{R}_0=R_1^\eta} E_d^\eta \xrightarrow{\mathcal{R}_0=R_h^\eta} \text{Hopf},$$

where $R_1 = 1 + \frac{bq}{cdp}$ and $R_1^\eta = 1 + \frac{\eta}{aq}$.

An immediate biological implication is that, while the treatment without subsequent injection ($\eta = 0$) does not help at all eliminate the HIV virus completely, the treatment with a constant injection rate does. To see this, we first note that $\mathcal{R}_0$ is independent of $\eta$. If $\mathcal{R}_0 > 1$, then the HIV virus will remain persistent if $\eta = 0$, although the HIV load will be reduced by the introduction of the recombinants (see [Jiang *et al.*, 2009]). But with $\eta > 0$, even if $\mathcal{R}_0 > 1$, as long as $\eta > aq(\mathcal{R}_0 - 1)$, HIV virus will be eventually eliminated (Theorem 3).

When considering bifurcation to the double-infection equilibrium, we notice that $R_1^\eta$ is usually smaller than $R_1$, however the critical value $R_h^\eta$ is usually much larger than $R_h$, implying that $E_d^\eta$ is more stable than $E_d$. For the numerical example given in Sec. 6 with the parameter values given in (39) we have

$$\text{System without injection } (\eta = 0) : E_0 \xrightarrow{\mathcal{R}_0=1} E_s \xrightarrow{\mathcal{R}_0=3.6917} E_d \xrightarrow{\mathcal{R}_0=7.8911} \text{Hopf};$$

$$\text{System with injection } (\eta = 0.01) : E_0^\eta \xrightarrow{\mathcal{R}_0=1.0019} E_d^\eta \xrightarrow{\mathcal{R}_0=11.7092} \text{Hopf},$$

$$(\eta = 0.02) : E_0^\eta \xrightarrow{\mathcal{R}_0=1.0038} E_d^\eta \xrightarrow{\mathcal{R}_0=18.9066} \text{Hopf},$$

$$(\eta = 0.04) : E_0^\eta \xrightarrow{\mathcal{R}_0=1.0077} E_d^\eta \xrightarrow{\mathcal{R}_0=373.6955} \text{Hopf},$$

which shows that an increase in $\eta$ greatly increases the Hopf critical value. Moreover, the numerical example with the normal form analysis and simulation, presented in Sec. 6, indicates that an increase in $\eta$ is also beneficial in controlling the amplitudes of bifurcating periodic motions.

In summary, the results obtained in this paper based on the modified HIV-1 model (7) clearly indicates that increasing $\eta$ is beneficial for controlling/eliminating the HIV virus. We point out that the adoption of a constant injection rate is just for simplicity of analysis in this first attempt. In reality, other types of injection strategies may be more feasible. For example, impulsive injection strategy and periodic injection strategy are more reasonable injection mechanism. Of course, adopting such injection strategies will increase the difficulty level in analyzing the resulting model system.

## Acknowledgment

This work was supported by the Natural Sciences and Engineering Research Council of Canada.

## References

Carlton, R. M. [1999] "Phage therapy: Past history and future prospect," *Arch. Immun. Exp.* **47**, 267–274.

Castillo-Chavez, C. & Thieme, H. R. [1995] "Asymptotically autonomous epidemic models," in *Mathematical Population Dynamics*: *Analysis of Heterogeneity, I. Theory of Epidemics*, eds. O. Arino *et al.* (Wuerz, Winnipeg, Canada), pp. 33–50.

Hirsch, W. M., Hanisch, H. & Gabriel, J. P. [1985] "Differential equation models of some parasitic infections: Methods for the study of asymptotic behaviour," *Comm. Pure Appl. Math.* **38**, 733–753.

Jiang, X., Yu, P., Yuan, Z. & Zou, X. [2009] "Dynamics of a HIV-1 therapy model of fighting a virus with another virus," *J. Biol. Dyn.* **3**, 387–409.

Mebatsion, T., Finke, S., Weiland, F. & Conzelmann, K. [1997] "A CXCR4/CD4 pseudotype rhabdovirus that selectively infects HIV-1 envelope protein-expressing cells," *Cell* **90**, 841–847.

Nolan, G. P. [1997] "Harnessing viral devices as pharmaceuticals: Fighting HIV-1s fire with fire," *Cell* **90**, 821–824.

Nowak, M. & May, R. [2000] *Virus Dynamics* (Oxford University).

Revilla, T. & Garcia-Ramos, G. [2003] "Fighting a virus with a virus: A dynamic model for HIV-1 therapy," *Math. Bios.* **185**, 191–203.

Schnell, M. J., Johnson, E., Buonocore, L. & Rose, J. K. [1997] "Construction of a novel virus that targets HIV-1 infected cells and control HIV-1 infection," *Cell* **90**, 849–857.

Slopek, S., Wener-Dabrowska, B., Dabrowska, M. & Kucharewicz, A. [1987] "Results of bacteriophage treatment of supportive bacterial infection in the years of 1981–1986," *Arch. Immunol. Ther. Exp.* **35**, 569–583.

Smith, H. L. [1995] *Monotone Dynamical Systems*: *An Introduction to the Theory of Competitive and Cooperative Systems*, Mathematical Surveys and Monographs, Vol. 41 (American Mathematical Society, Providence, RI).

Sulakvelidze, A., Alavidze, Z. & Morris, Jr. J. [2001] "Bacteriophage therapy," *Antimicrob. Agents Chemoth.* **45**, 649–659.

Wagner, E. K. & Hewlett, M. J. [1999] *Basic Virology* (Blackwell, NY).

Yu, P. & Huseyin, K. [1988] "A perturbation analysis of interactive static and dynamic bifurcations," *IEEE Trans. Automat. Contr.* **33**, 28–41.

Yu, P. [1998] "Computation of normal forms via a perturbation technique," *J. Sound Vib.* **211**, 19–38.

Yu, P. [2005] "Closed-form conditions of bifurcation points for general differential equations," *Int. J. Bifurcation and Chaos* **15**, 1467–1483.