Journal of Biological Dynamics
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/tjbd20

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Xiamei Jiang [a], Pei Yu [b], Zhaohui Yuan [c] & Xingfu Zou [b]

[a] Department of Computer and Mathematical Sciences, University of Toronto at Scarborough, Toronto, Ont., Canada

[b] Department of Applied Mathematics, University of Western Ontario, London, Ont., Canada

[c] College of Mathematics and Econometrics, Hunan University, Changsha, Hunan, China

Version of record first published: 08 Jun 2009

To cite this article: Xiamei Jiang, Pei Yu, Zhaohui Yuan & Xingfu Zou (2009): Dynamics of an HIV-1 therapy model of fighting a virus with another virus, Journal of Biological Dynamics, 3:4, 387-409

To link to this article: http://dx.doi.org/10.1080/17513750802485007

Journal of Biological Dynamics
Vol. 3, No. 4, July 2009, 387–409

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Dynamics of an HIV-1 therapy model of fighting a virus with another virus

Xiamei Jiang[a], Pei Yu[b], Zhaohui Yuan[c] and Xingfu Zou[b]*

[a]*Department of Computer and Mathematical Sciences, University of Toronto at Scarborough, Toronto, Ont., Canada;* [b]*Department of Applied Mathematics, University of Western Ontario, London, Ont., Canada;* [c]*College of Mathematics and Econometrics, Hunan University, Changsha, Hunan, China*

(*Received 25 January 2008; final version received 11 September 2008*)

In this paper, we rigorously analyse an ordinary differential equation system that models fighting the HIV-1 virus with a genetically modified virus. We show that when the basic reproduction ratio $\mathcal{R}_0 < 1$, then the infection-free equilibrium E_0 is globally asymptotically stable; when $\mathcal{R}_0 > 1$, E_0 loses its stability and there is the single-infection equilibrium E_s. If $\mathcal{R}_0 \in (1, 1+\delta)$ where δ is a positive constant explicitly depending on system parameters, then the single-infection equilibrium E_s that is globally asymptotically stable, while when $\mathcal{R}_0 > 1+\delta$, E_s becomes unstable and the double-infection equilibrium E_d comes into existence. When $\mathcal{R}_0$ is slightly larger than $1+\delta$, E_d is stable and it loses its stability via Hopf bifurcation when $\mathcal{R}_0$ is further increased in some ways. Through a numerical example and by applying a normal form theory, we demonstrate how to determine the bifurcation direction and stability, as well as the estimates of the amplitudes and the periods of the bifurcated periodic solutions. We also perform numerical simulations which agree with the theoretical results. The approaches we use here are a combination of analysis of characteristic equations, fluctuation lemma, Lyapunov function and normal form theory.

Keywords: HIV-1 dynamics; recombinant virus; stability; Lyapunov function; LaSalle invariance principle; fluctuation lemma

AMS Subject Classification: 34K25; 34K60; 92B05; 92D30

1. Introduction

In recent years, mathematical modelling has contributed greatly to the understanding of HIV-1 infection in host and has provided valuable insight into HIV-1 pathogenesis. Among various models is the class by differential equations, which quantitatively describe the dynamics of the HIV-1 virus, healthy and infected cells and even possibly the immune responses. By studying these models, researchers have gained much knowledge about the mechanism of the interactions of these components within a host, and have thereby enhanced the progress in understanding the HIV-1 infection (see, e.g. [14–17]). Such understanding in turn may offer guidance for developing new drugs and for designing optimal combination of existing therapies (see, e.g. [6,10,18] and the references therein).

*Corresponding author. Email: xzou@uwo.ca

ISSN 1751-3758 print/ISSN 1751-3766 online

DOI: 10.1080/17513750802485007
http://www.informaworld.com

A standard and classic differential equation model for HIV infection is the following system of ordinary differential equations (ODEs) (see, e.g. [10,14,16]):

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

where $x(t)$, $y(t)$ and $v(t)$ are the densities of uninfected target cells, infected target cells and the free virus, respectively, at time t. Here a mass action infection mechanism is adopted, with an infection rate constant β. The healthy cell is assumed to be produced at a constant rate λ. It is also assumed that once cells are infected, they may die at rate a either due to the action of the virus or the immune system, and in the mean time, they each produces HIV-1 virus particles at a rate k during their life which on average has length $1/a$.

It is known that the HIV-1 virus load is a crucial measurement of the severity of an HIV-1 carrier. When the load exceeds certain level after a clinically latent phase, the CD^+ T-cell count declines drastically, indicating a transition from HIV to AIDS (see, e.g. [5,20]). Most of the existing therapies for HIV and/or AIDS employ inhibitors of the enzymes required for replication of HIV-1 virus to reduce the load (see, e.g. [3,8]). Recent progress in genetic engineering has offered an alternative approach: modification of a viral genome can produce recombinants capable of controlling infections by other virus. Indeed, this method had been used to modify rhabdovirus, including the rabies and the vesicular stomatitis, making them capable of infecting and killing cells previously attacked by HIV-1 (for details, see, e.g. [9,13,19,22]). To understand this approach of fighting a virus with a genetically modified virus, Revilla and Garcia-Ramos [18] proposed a mathematical model which is a result of incorporating into Equation (1) two more variables: the density w of the recombinant (genetically modified) virus and the density z of doubly infected cells.

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

Here it is assumed that (i) recombinant infects cells previously infected by the pathogen, turning them at rate αwy into doubly infected cells, and in the mean time, recombinants are removed at a rate qw and (ii) the doubly infected cells die at a rate of bz and release recombinants at a rate cz.

In [18], the authors only analysed the structure of the equilibria of the system (2) and performed some numerical simulations. System (2) has a *dimension higher than* 2, and it is well known that for systems with higher dimensions, equilibria cannot determine solutions' long-term behaviours, and complicated dynamics (periodic solutions and even chaos) may occur which would make the system unpredictable. Therefore, theoretically determining the global dynamics of Equation (2) is an important yet challenging problem, and this constitutes the purpose of this paper. In Section 2, we will justify the well-posedness of the model by showing the positivity and boundedness of solutions of Equation (2) and review the existence result on equilibria and the basic reproduction number $\mathcal{R}_0$. In Section 3, we show that when $\mathcal{R}_0 < 1$, the disease-free equilibrium is globally asymptotically stable, and when $\mathcal{R}_0 > 1$ it is unstable. In Section 4, we prove that there is a $\delta > 0$ depending on all parameters except for λ, such that if $1 < \mathcal{R}_0 < 1 + \delta$, then the single-infection equilibrium exists and is globally asymptotically stable, and when $\mathcal{R}_0 > 1 + \delta$, this equilibrium loses its stability. Note that $\mathcal{R}_0 > 1 + \delta$ is also the condition for the existence of double-infection

equilibrium. In Section 5, we analyse the stability of the double-infection equilibrium E_d and prove that when $\mathcal{R}_0$ is slightly larger than $1+\delta$, solutions of the model converge to the E_d; but when $\mathcal{R}_0$ is further increased in some way, E_d loses its stability via Hopf bifurcation, giving rise to stable periodic solutions. This theoretical result confirms what we stated earlier: equilibria cannot fully determine the solution dynamics, and stability analysis is important and indeed necessary. Through a numerical example, we illustrate in Section 6 how to obtain more information about the Hopf bifurcation, including the bifurcation direction, the stability, amplitude and frequency of the bifurcated periodic solution. Such information is crucial for giving good estimates of the virus load and healthy cells' density in the case that these quantities are periodic in time variable t (i.e. sustained fluctuations), based on which, a therapy is usually determined. It may also provide guidance for designing a optimal clinical sampling strategy, such as the best time intervals of sampling. The approaches we used here are a combination of analysis of characteristic equations, fluctuation lemma, Lyapunov function and normal form theory. Our numerical simulations agree with the theoretical results. In the last section, we summarize the main results and discuss possible modifications of the model.

2. Well-posedness, equilibria and basic reproduction numbers

Since the variables are densities which cannot be negative, one expects that starting from non-negative initial values, the corresponding solution remains non-negative. This can be easily confirmed as below. First, from the first equation of Equation (2), we have

$$x(t) = \mathrm{e}^{-\int_0^t (d+\beta v(s))\,\mathrm{d}s} x(0) + \lambda \int_0^t \mathrm{e}^{-\int_s^t (d+\beta v(\xi))\,\mathrm{d}\xi}\,\mathrm{d}s,$$

implying $x(t) > 0$ for $t > 0$ provided that $x(0) \geq 0$. In a similar way, one can establish non-negativity of the other four variables $y(t), z(t), v(t), w(t)$ for $t > 0$ provided that $y(0) \geq 0$, $z(0) \geq 0$, $v(0) \geq 0$ and $w(0) \geq 0$. Moreover, if in addition, $y(0) > 0$ (or $z(0) > 0$ or $v(0) > 0$ or $w(0) > 0$), then $y(t) > 0$ (or $z(t) > 0$ or $v(t) > 0$ or $w(t) > 0$) for $t > 0$.

Solutions to Equation (2) also remain bounded. To see this, let $(x(t), y(t), z(t), v(t), w(t))$ be a non-negative solution. Choose $\epsilon_1 \in (0, a/k)$ and $\epsilon_2 \in (0, b/c)$, and let

$$g(t) = x(t) + y(t) + z(t) + \epsilon_1 v(t) + \epsilon_2 w(t).$$

Then

$$\begin{aligned} g'(t) &= \lambda - dx - (a-\epsilon_1 k)y - (b-\epsilon_2 c)z - \epsilon_1 pv - \epsilon_2 qw \\ &= \begin{cases} < 0 & \text{for } dx + (a-\epsilon_1 k)y + (b-\epsilon_2 c)z + \epsilon_1 pv + \epsilon_2 qw > \lambda, \\ > 0 & \text{for } dx + (a-\epsilon_1 k)y + (b-\epsilon_2 c)z + \epsilon_1 pv + \epsilon_2 qw < \lambda. \end{cases} \end{aligned}$$

This implies that every component of (x, y, z, v, w) must be bounded. By the extension theory of ODEs, the boundedness of a solution also implies that it exists for all $t \geq 0$.

Model system (2) always has the infection-free equilibrium $E_0 : (\lambda/d, 0, 0, 0, 0)$. The other two possible biologically meaningful equilibria are

$$E_s = \left(\frac{ap}{\beta k}, \frac{\lambda}{a} - \frac{dp}{\beta k}, 0, \frac{\lambda k}{ap} - \frac{d}{\beta}, 0\right),$$

$$E_d = \left(\frac{\lambda\alpha cp}{d\alpha cp + \beta bkq}, \frac{bq}{\alpha c}, \frac{q(\alpha\beta\lambda ck - \beta abkq - \alpha acdp)}{\alpha c(\beta bkq + \alpha cdp)}, \frac{bkq}{\alpha cp}, \frac{\alpha\beta\lambda ck - \beta abkq - \alpha acdp}{\alpha(\beta bkq + \alpha cdp)}\right)$$

with the former being the singly infected equilibrium and the latter being the doubly infected equilibrium. From the biological meaning of the basic reproduction numbers, Revilla and Garcia-Ramos [18] identified $\mathcal{R}_0$ as

$$\mathcal{R}_0 = \frac{\beta\lambda k}{apd}.$$

Applying the general mathematical theory of basic reproduction numbers for disease model described by ODEs (see, e.g. [21]), we can easily confirm the above formula. It turns out that the value of $\mathcal{R}_0$ determines the existence of the single-infection equilibrium: E_s exists if and only if $\mathcal{R}_0 > 1$.

The double-infection equilibrium exists (biologically meaningful) if and only if $Q > 0$ where

$$Q = \alpha\beta\lambda ck - \beta abkq - \alpha acdp.$$

Introducing the second basic reproduction number

$$\mathcal{R}_d = \frac{c\lambda\alpha}{abq}\left(1 - \frac{1}{R_0}\right)$$

for the doubly infected cells, one can easily verify that

$$Q = a\beta bkq(\mathcal{R}_d - 1)$$

and hence

$$\mathcal{R}_d > 1 \iff Q > 0.$$

For convenience, we denote

$$D = \beta bkq + \alpha cdp.$$

With the above identities, E_s and E_d can be expressed by the following simpler formulas:

$$E_s = \left(\frac{ap}{\beta k}, \frac{\lambda}{\alpha}\left(1 - \frac{1}{R_0}\right), 0, \frac{d}{\beta}(R_0 - 1), 0\right),$$
$$E_d = \left(\frac{\lambda\alpha cp}{D}, \frac{bq}{\alpha c}, \frac{qQ}{\alpha cD}, \frac{bkq}{\alpha cp}, \frac{Q}{\alpha D}\right).$$

In order to analyse local stability of Equation (2) at an equilibrium E, we need to calculate the the Jacobian matrix of Equation (2) at $E = (\hat{x}, \hat{y}, \hat{z}, \hat{v}, \hat{w})$ as below:

$$J(E) = \begin{pmatrix} -(d + \beta\hat{v}) & 0 & 0 & -\beta\hat{x} & 0 \\ \beta\hat{v} & -\alpha\hat{w} - a & 0 & \beta\hat{x} & -\alpha\hat{y} \\ 0 & \alpha\hat{w} & -b & 0 & \alpha\hat{y} \\ 0 & k & 0 & -p & 0 \\ 0 & 0 & c & 0 & -q \end{pmatrix}. \tag{3}$$

The characteristic equation of Equation (2) at E is $\det(\lambda I - J(E)) = 0$, whose roots determine the local stability of E.

3. Stability of the infection-free equilibrium

For the infection-free equilibrium $E = E_0$, some fundamental calculations give the corresponding characteristic equation

$$(\xi + d)(\xi + b)(\xi + q)\left(\xi^2 + (p + a)\xi + \left(ap - \frac{\beta\lambda k}{d}\right)\right) = 0. \tag{4}$$

The stability of E_0 is determined by the sign of real parts of the roots of Equation (4): if all roots of Equation (4) have negative real parts, then E_0 is asymptotically stable; if there is at least one root of Equation (4) has positive real part, then E_0 is unstable. Obviously, it suffices to consider the quadratic equation

$$\xi^2 + (p + a)\xi + ap - \frac{\beta\lambda k}{d} = 0. \tag{5}$$

Using the Decarte's rule of sign, we know that whether or not the two roots of Equation (5) have negative real part is determined by the sign of $ap - \beta\lambda k/d$: the negativity (positivity) of the real parts of the two root of Equation (5) is equivalent to $ap - \beta\lambda k/d > 0$ ($ap - \beta\lambda k/d < 0$), that is, $\mathcal{R}_0 < 1$ ($\mathcal{R}_0 > 1$).

Indeed, by employing the fluctuation lemma (see, e.g. [4]), we can prove the global asymptotic stability of the infection-free equilibrium E_0 under the condition $\mathcal{R}_0 < 1$. For this purpose, we first introduce some basic notations. For a continuous and bounded function $f : [0, \infty) \to R$, let

$$f_\infty = \lim_{t\to\infty} \inf f(t), \quad f^\infty = \lim_{t\to\infty} \sup f(t).$$

In Section 2, we have shown that for any initial values $x_0 \geq 0$, $y_0 \geq 0$, $z_0 \geq 0$, $v_0 \geq 0$, $w_0 \geq 0$, the corresponding solution $(x(t), y(t), z(t), v(t), z(t))$ remains non-negative and is bounded from above. Therefore, the lim inf$_{t\to\infty}$ and lim sup$_{t\to\infty}$ exist for all these five component functions. By the fluctuation lemma (see, e.g. [4]), there exists a sequence t_n with $t_n \to \infty$ as $n \to \infty$ such that

$$\lim_{n\to\infty} x(t_n) = x^\infty, \quad \lim_{n\to\infty} \dot{x}(t_n) = 0 \quad \text{as } n \to \infty. \tag{6}$$

From the first equation of Equation (2), we obtain

$$\dot{x}(t_n) + dx(t_n) + \beta x(t_n)v(t_n) = \lambda.$$

Letting $n \to \infty$ in the above equation leads to the following estimate

$$dx^\infty \leq (d + \beta v_\infty)x^\infty \leq \lambda. \tag{7}$$

Similar treatment to the rest of the equations in Equation (2) gives

$$ay^\infty \leq (a + \alpha w_\infty)y^\infty \leq \beta x^\infty v^\infty, \tag{8}$$

$$bz^\infty \leq \alpha w^\infty y^\infty, \tag{9}$$

$$pv^\infty \leq ky^\infty, \tag{10}$$

$$qw^\infty \leq cz^\infty. \tag{11}$$

We claim that $y^\infty = 0$. Otherwise, $v^\infty > 0$ by Equation (8). From Equations (7), (8) and (10), it follows that

$$pv^\infty \leq ky^\infty \leq \frac{k\beta}{a}x^\infty v^\infty \leq \frac{k\lambda\beta}{ad}v^\infty$$

leading to

$$p \leq \frac{k\lambda\beta}{ad}.$$

This contradicts to the condition $\mathcal{R}_0 < 1$. Hence, $y^\infty = 0$ which also implies $z^\infty = 0$, $v^\infty = 0$, $w^\infty = 0$ by Equations (7)–(9). Now, by the relation $0 \leq y_\infty \leq y^\infty$, we then conclude that $y(t) \to 0$ as $t \to \infty$. Similarly, $z(t)$, $v(t)$ and $w(t)$ all approach 0 as $t \to \infty$. Finally, with $v(t) \to 0$, the first equation in Equation (2) becomes an asymptotically autonomous equation with the limiting equation being $\dot{x} = \lambda - dx$. By the theory for the asymptotically autonomous systems (see, e.g. [1]), we know that the function $x(t) \to \lambda/d$ as $t \to \infty$. The local stability of E_0 established in Section 2 under the assumption $\mathcal{R}_0 < 1$ and the global attractivity of E_0 established above give the global asymptotical stability of E_0.

Summarizing the above results, we have proved the following theorem.

THEOREM 3.1 *When $\mathcal{R}_0 < 1$, the infection-free equilibrium E_0 is globally asymptotically stable implying the virus cannot invade regardless of initial load*; *when $\mathcal{R}_0 > 1$, E_0 becomes unstable implying that virus may persist.*

4. Stability of the single-infection equilibrium

From Section 3, we know that when $\mathcal{R}_0$ increases to pass the value 1, the disease-free equilibrium loses its stability and the single-infection equilibrium E_s comes into existence. In this section, we study the stability of E_s.

For the local stability of E_s, the characteristic equation of the linearized system of the model (2) at E_s is given by

$$\xi^5 + a_4\xi^4 + a_3\xi^3 + a_2\xi^2 + a_1\xi + a_0 = 0, \tag{12}$$

where

$$\begin{aligned}
a_1 &= a + b + q + p + \frac{\beta\lambda k}{ap},\\
a_2 &= ab + aq + bq + bp + qp + \frac{\beta\lambda k}{a} + \frac{\beta\lambda k}{p} + \frac{\beta\lambda kq}{ap} + \frac{\beta\lambda bk}{ap} - \frac{\alpha\lambda c}{a} + \frac{\alpha cdp}{\beta k},\\
a_3 &= abp + bqp + abq - adp - \alpha\lambda c + \frac{\beta\lambda bk}{a} + \frac{\beta\lambda kq}{a} - \frac{\alpha\lambda cp}{a} + \frac{\alpha\lambda cd}{a}\\
&\quad + \frac{\beta\lambda bkq}{ap} - \frac{\alpha\beta\lambda^2 ck}{a^2 p} + \frac{\alpha acdp}{\beta k} + \frac{\alpha cdp^2}{\beta k} + \frac{\beta\lambda bk}{p} + \frac{\beta\lambda kq}{p},\\
a_4 &= -abdp - adqp + \beta\lambda bk + \beta\lambda kq + \alpha\lambda cd + \frac{\beta\lambda bkq}{a} + \frac{\alpha\lambda cdp}{a} - \frac{\alpha\beta\lambda^2 ck}{a^2}\\
&\quad - \frac{\alpha\beta\lambda^2 ck}{ap} + \frac{\beta\lambda bkq}{p},\\
a_5 &= -abdqp + \beta\lambda bqk + 2\alpha\lambda cdp - \frac{\alpha\beta\lambda^2 cd}{a} - \frac{\alpha acd^2 p^2}{\beta k}.
\end{aligned}$$

Equation (12) may be rewritten as

$$\left[\xi^2 + (b+q)\xi + bq - \frac{\alpha\lambda c}{a} + \frac{\alpha cdp}{\beta k}\right] \times \left[\xi^3 + (a+p+\frac{\beta\lambda k}{ap})\xi^2 + (\beta\lambda k + \frac{\beta kp}{a} + \frac{\beta\lambda k}{p})\xi + \beta\lambda k - adp\right] = 0.$$

Thus, the eigenvalues of Equation (12) are determined by the following two equations:

$$\xi^2 + (b+q)\xi + bq - \frac{\alpha\lambda c}{a} + \frac{\alpha cdp}{\beta k} = 0 \tag{13}$$

and

$$\xi^3 + \left(a + p + \frac{\beta\lambda k}{ap}\right)\xi^2 + \left(\beta\lambda k + \frac{\beta kp}{a} + \frac{\beta\lambda k}{p}\right)\xi + \beta\lambda k - adp = 0. \tag{14}$$

Equation (14) is a cubic equation of the form

$$\xi^3 + b_2\xi^2 + b_1\xi + b_0 = 0.$$

The Routh–Hurwitz theorem (see [2]) for this equation states that all roots have negative real parts if and only if $b_2 > 0$, $b_0 > 0$ and $b_1b_2 - b_0 > 0$. Now, for Equation (14),

$$b_2 = a + p + \frac{\beta\lambda k}{ap} > 0,$$
$$b_0 = \beta\lambda k - adp > 0 \quad (\text{because } \mathcal{R}_0 > 1).$$

It is also easy to verify that $b_1b_2 - b_0 > 0$. Hence, all roots of the cubic equation (14) have negative real parts.

For the quadratic equation (13), by a similar argument to that for Equation (5), we know that the two roots of Equation (13) have negative real parts if and only if

$$b + q > 0 \quad \text{and} \quad bq - \frac{\alpha\lambda c}{a} + \frac{\alpha cdp}{\beta k} > 0.$$

The first inequality holds automatically (since $b > 0$ and $q > 0$) and the second one is equivalent to $\mathcal{R}_d < 1$ (or $Q < 0$). Consequently, the single-infected equilibrium E_s exists if and only if $\mathcal{R}_0 > 1$, and is locally stable if and only if $\mathcal{R}_d < 1$ (or $Q < 0$).

Indeed, by constructing a Lyapunov function and applying the LaSalle's invariance principle, we can show that when $\mathcal{R}_0 > 1$ and $\mathcal{R}_d < 1$, E_s is *globally* asymptotically stable. To this end and for convenience for notation, denote by x_s, y_s and v_s the three positive components of the single-infection equilibrium E_s, that is, $x_s = ap/\beta k$, $y_s = \lambda/a - dp/\beta k$ and $v_s = \lambda k/ap - d/\beta$. Define

$$V = \left(x - x_s - x_s \ln\frac{x}{x_s}\right) + \left(y - y_s - y_s \ln\frac{y}{y_s}\right) + z + \frac{a}{k}\left(v - v_s - v_s \ln\frac{v}{v_s}\right) + \frac{b}{c}w \tag{15}$$

for $x > 0$, $y > 0$, $z \geq 0$, $v > 0$, $w \geq 0$. By calculus of multi-variable functions, it can be easily seen that $V(x, y, z, v, w)$ has a global minimum attained at E_s and thus, $V(x, y, z, v, w) \geq 0$ and

$V(x, y, z, v, w) = 0$ if and only $(x, y, z, v, w) = E_s$. Making use of the equilibrium equation at E_s, the derivative of V along positive solutions of Equation (2) can be estimated as

$$\begin{aligned}
V' &= x' - \frac{x_s}{x}x' + y' - \frac{y_s}{y}y' + z' + \frac{a}{k}\left(v' - \frac{v_s}{v}v'\right) + \frac{b}{c}w' \\
&= \lambda - dx - \beta x v - \frac{\lambda}{x}x_s + dx_s + \beta x_s v + \beta x v - ay - \alpha w y - \frac{\beta x v y_s}{y} + ay_s + \alpha w y_s \\
&\quad + \alpha w y - bz + ay - \frac{ap}{k}v - \frac{ayv_s}{v} + \frac{ap}{k}v_s + bz - \frac{bq}{c}w \\
&= dx_s\left(2 - \frac{x_s}{x} - \frac{x}{x_s}\right) + \beta x_s v_s - \frac{\beta {x_s}^2 v_s}{x} + \beta x_s v - \frac{\beta x v y_s}{y} + ay_s \\
&\quad + \alpha w y_s - \frac{ap}{k}v - \frac{ayv_s}{v} + \frac{ap}{k}v_s - \frac{bq}{c}w \\
&= \beta x_s v_s - \frac{\beta {x_s}^2 v_s}{x} + \beta x_s v - \frac{\beta x v y_s}{y} + \beta x_s v_s + \alpha w y_s - \frac{ap}{k}v - \frac{ayv_s}{v} + \frac{ap}{k}v_s - \frac{bq}{c}w \\
&= \beta x_s v_s - \frac{\beta {x_s}^2 v_s}{x} - \frac{\beta x v y_s}{y} + \beta x_s v_s + \alpha w y_s - \frac{ayv_s}{v} + \beta x_s v_s - \frac{bq}{c}w \\
&= 3\beta x_s v_s - \frac{\beta {x_s}^2 v_s}{x} - \frac{\beta x v y_s}{y} - \frac{ayv_s}{v} + \left(\alpha y_s - \frac{bq}{c}\right)w \\
&= \beta x_s v_s\left(3 - \frac{x_s}{x} - \frac{x v y_s}{x_s v_s y} - \frac{ay}{\beta x_s v}\right) + \left(\alpha y_s - \frac{bq}{c}\right)w \\
&= \beta x_s v_s\left(3 - \frac{x_s}{x} - \frac{x v y_s}{x_s v_s y} - \frac{ay}{\beta x_s v}\right) + \left(\frac{\alpha\beta x_s v_s}{a} - \frac{bq}{c}\right)w \\
&\le 3\beta x_s v_s\left(1 - \sqrt[3]{\frac{x_s}{x}\frac{x v y_s}{x_s v_s y}\frac{ay}{\beta x_s v}}\right) + \left(\frac{pd\alpha}{k\beta}(R_0 - 1) - \frac{bq}{c}\right)w \\
&= 3\beta x_s v_s\left(1 - \sqrt[3]{\frac{ay_s}{\beta x_s v_s}}\right) + \frac{pd\alpha}{k\beta}\left(R_0 - 1 - \frac{kbq\beta}{cpd\alpha}\right)w = \frac{pd\alpha}{k\beta}\left(R_0 - 1 - \frac{kbq\beta}{cpd\alpha}\right)w.
\end{aligned} \tag{16}$$

It is straightforward to verify that the condition $\mathcal{R}_d < 1$ (or $Q < 0$) is equivalent to

$$\mathcal{R}_0 < 1 + \frac{kbq\beta}{cpd\alpha} =: R_1. \tag{17}$$

Thus, when $\mathcal{R}_0 \in (1, R_1)$, $V' \le 0$ and $V' = 0$ if and only if $(x, y, z, v, w) = E_s$. By the LaSalle's invariance principle [7], we conclude that E_s is indeed globally asymptotically stable.

Summarizing the above analysis, we have established the following theorem.

THEOREM 4.1 *When $\mathcal{R}_0 > 1$ and $\mathcal{R}_d < 1$ (equivalently $Q < 0$ or Equation (17) holds) hold, then the single-infection equilibrium E_s is globally asymptotically stable implying that the recombinant virus cannot survive but the pathogen virus can; when $\mathcal{R}_d > 1$, E_s becomes unstable implying that recombinant virus may persist.*

5. Stability of the double-infection equilibrium E_d and Hopf bifurcation from E_d

When $\mathcal{R}_d > 1$ (equivalently $Q > 0$ or $\mathcal{R}_0 > R_1$), the single-infection equilibrium becomes unstable and there occurs the double-infection equilibrium E_d. Unlike for E_0 and E_s at which the characteristic equations can be factored into product of lower degree polynomials, we are unable to factor the characteristic equation at E_d, and thus cannot determine the stability of E_d by the same way as in Sections 3 and 4. On the other hand, our preliminary simulations show that for certain parameter values satisfying $\mathcal{R}_d > 1$, solutions of Equation (2) converge to E_d, while for other parameter values the solutions of Equation (2) do not converge to E_d; instead they converge to a periodic solution. This observation shows the necessity and importance of some theoretical analyses on the stability of E_d as well as on possible Hopf bifurcation.

For convenience in the following analysis, we first do the following rescalings to reduce the number of parameters:

$$x \longrightarrow \mu_1 x, \quad y \longrightarrow \mu_2 y, \quad z \longrightarrow \mu_3 z, \quad v \longrightarrow \mu_4 v, \quad w \longrightarrow \mu_5 w, \quad \tau = \nu t \tag{18}$$

$$\frac{d}{\nu} \longrightarrow d, \quad \frac{a}{\nu} \longrightarrow a, \quad \frac{b}{\nu} \longrightarrow b, \quad \frac{p}{\nu} \longrightarrow p, \quad \frac{q}{\nu} \longrightarrow q, \quad \frac{\alpha c}{k\beta} \longrightarrow c, \tag{19}$$

where

$$\nu = (\lambda k \beta)^{1/3}, \quad \mu_1 = \mu_2 = \mu_3 = \frac{\nu^2}{k\beta}, \quad \mu_4 = \frac{\nu}{\beta}, \quad \mu_5 = \frac{\nu}{\alpha}. \tag{20}$$

By the above, system (2) is transformed to

$$\begin{aligned} \frac{dx}{d\tau} &= 1 - dx - xv, \\ \frac{dy}{d\tau} &= -ay + xv - yw, \\ \frac{dz}{d\tau} &= -bz + yw, \\ \frac{dv}{d\tau} &= -pv + y, \\ \frac{dw}{d\tau} &= -qw + cz. \end{aligned} \tag{21}$$

Under Equations (18)–(20), the basic reproduction number $\mathcal{R}_0$ now becomes

$$\mathcal{R}_0 = \frac{1}{a\,d\,p}, \tag{22}$$

and the critical value of $\mathcal{R}_0$ for the double-infection equilibrium E_d of Equation (2) to exist becomes

$$R_1 := 1 + \frac{bq}{cdp}. \tag{23}$$

In the rest of this section, we assume $\mathcal{R}_0 > R_1$. Thus, the double-infection equilibrium E_d for Equation (21) exists and is now (by Equations (18)–(20)) given by

$$E_d = (x_d, y_d, z_d, v_d, w_d) = \left(\frac{cp}{bq + cdp}, \frac{bq}{c}, \frac{q}{bq + cdp} - \frac{a}{c}, \frac{bq}{cp}, \frac{c}{bq + cdp} - a \right). \tag{24}$$

In order to examine the stability of E_{d} for Equation (21), we compute the Jacobian matrix of system (21) as

$$J = \begin{bmatrix} -d-v & 0 & 0 & -x & 0 \\ v & -a-w & 0 & x & -y \\ 0 & w & -b & 0 & y \\ 0 & 1 & 0 & -p & 0 \\ 0 & 0 & c & 0 & -q \end{bmatrix}. \tag{25}$$

By straightforward but tedious computations, the characteristic polynomial of J at E_{d} is obtained as follows:

$$\begin{aligned} P_{\mathrm{d}}(\xi) &= \xi^2(\xi + dR_1)(\xi + b + q)\left(\xi + p + a\frac{\mathcal{R}_0}{R_1}\right) \\ &\quad + \xi(\xi + b + q)\left(\frac{R_1 - 1}{R_1}\right) + abq(\xi + dR_1)(\xi + p)\left(\frac{\mathcal{R}_0 - R_1}{R_1}\right) \\ &\equiv \xi^5 + a_1\xi^4 + a_2\xi^3 + a_3\xi^2 + a_4\xi + a_5, \end{aligned} \tag{26}$$

where

$$\begin{aligned} a_1 &= a\frac{\mathcal{R}_0}{R_1} + b + d\,R_1 + p + q, \\ a_2 &= (b+q)\left(p + a\frac{\mathcal{R}_0}{R_1}\right) + \left(b + q + p + a\frac{\mathcal{R}_0}{R_1}\right)dR_1, \\ a_3 &= (b+q)\left(p + a\frac{\mathcal{R}_0}{R_1}\right)dR_1 + \frac{R_1 - 1}{R_1} + adq\left(\frac{\mathcal{R}_0 - R_1}{R_1}\right), \\ a_4 &= (b+q)\left(\frac{R_1 - 1}{R_1}\right) + abq(p + dR_1)\left(\frac{\mathcal{R}_0 - R_1}{R_1}\right), \\ a_5 &= \frac{b\,q}{\mathcal{R}_0}(\mathcal{R}_0 - R_1). \end{aligned} \tag{27}$$

It is obvious that $a_1 > 0$ and $a_2 > 0$ for any positive parameter values. Here we apply the Routh–Hurwitz criterion to find the stability of the equilibrium solution E_{d}. The necessary and sufficient conditions for E_{d} to be stable are given by

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

where

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

It is easy to see that $a_i > 0$, $i = 1, 2, \ldots, 5$, since $R_1 > 1$ and we have assumed $\mathcal{R}_0 > R_1$. Now, we need to check the signs of Δ_i, $i = 2, 3, 4$. First, a straightforward calculation shows that

$$\Delta_2 = \left(a\frac{\mathcal{R}_0}{R_1} + b + p + q\right)\left[(b+q)p + qa\frac{\mathcal{R}_0}{R_1}\right] + ab\left(a\frac{\mathcal{R}_0}{R_1} + b + p\right)\frac{\mathcal{R}_0}{R_1} + \left[\left(a\frac{\mathcal{R}_0}{R_1} + b + d\,R_1 + q\right)\left(b + q + p + a\frac{\mathcal{R}_0}{R_1}\right) + p(b+p+q)\right]dR_1 + abq + \frac{1}{R_1}, \tag{30}$$

indicating that $\Delta_2 > 0$ for all positive parameter values.

For Δ_3 and Δ_4, the signs are not easy to determine for general $\mathcal{R}_0$, and hence we use a continuity argument below. At $\mathcal{R}_0 = R_1$, using Equation (27) and by direct calculations, we have

$$\begin{aligned}\Delta_4|_{R_0=R_1} = {} & \frac{bq(b+q)}{a^2d^2cR_1^2}\left[1 + a^2d + a^2dR_1 + ad^2(1+a^3)R_1^2 + a^3d^3R_1^3\right] \\ & \times \left\{(b+q)^2 + \left[ad(b+q)^3 + a^2d(b+q)^2 + d(b+q) + \frac{a^2bdq}{c}\right]R_1 \right. \\ & \left. + ad^2(b+q)(a+b+q)R_1^2\right\} > 0\end{aligned} \tag{31}$$

and

$$\Delta_3|_{\mathcal{R}_0=R_1} = \frac{c}{abq(b+q)}, \quad \Delta_4|_{\mathcal{R}_0=R_1} > 0. \tag{32}$$

Note that Δ_3, Δ_4 and Δ_5 depend continuously on $\mathcal{R}_0$. From Equations (27), (29)–(32) and the continuity, we know $R_2 > R_1$ such that Equation (28) holds when $\mathcal{R}_0 \in (R_1, R_2)$, leading to the following conclusion.

THEOREM 5.1 *There is an $R_2 > R_1$ such that when $\mathcal{R}_0 \in (R_1, R_2)$, the double-infection equilibrium E_{d} is asymptotically stable.*

When $\mathcal{R}_0$ is further increased, Δ_1 and Δ_2 remain positive, but Δ_3 and Δ_4 may become negative (so may Δ_5 by Equation (29) and $a_5 > 0$ as $\mathcal{R}_0 > R_1$). The following lemma identifies the order of possible sign switches for Δ_3 and Δ_4.

LEMMA 5.1 *If Δ_3 and Δ_4 can change signs from positive to negative as $\mathcal{R}_0$ is further increased after the value R_2 in Theorem* 5.1, *then Δ_4 will change before Δ_3 does.*

Proof Assume, for the sake of contradiction, that Δ_3 will change sign no later than Δ_4 does. Then there exists an $R_3 > R_2$ such that

$$\Delta_3 = \begin{cases} > 0 & \text{when } \mathcal{R}_0 \in (R_1, R_3), \\ = 0 & \text{when } \mathcal{R}_0 = R_3, \end{cases} \qquad \Delta_4 = \begin{cases} > 0 & \text{when } \mathcal{R}_0 \in (R_1, R_3), \\ \geq 0 & \text{when } \mathcal{R}_0 = R_3. \end{cases} \tag{33}$$

Then, at $\mathcal{R}_0 = R_3$,

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

from which we obtain

$$a_1a_4 - a_5 = \frac{a_3}{a_1}\Delta_2.$$

Thus,

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

leading to a contradiction to $\Delta_4 \geq 0$. This completes the proof. ■

The following lemma tells that when Δ_4 crosses zero, Δ_3 must remain positive.

LEMMA 5.2 *For any $\mathcal{R}_0 > R_1$, if $\Delta_4 = 0$, then $\Delta_3 > 0$.*

Proof Suppose $\Delta_4 = 0$ at $\mathcal{R}_0 = R_4 > R_1$. Then,

$$a_4\Delta_3 - a_5[a_2\Delta_2 - (a_1a_4 - a_5)] = 0$$

and hence

$$a_1a_4\Delta_3 = a_1a_5[a_2\Delta_2 - (a_1a_4 - a_5)]. \tag{34}$$

On the other hand, the third equation in Equation (29) leads to

$$a_5\Delta_3 = a_3a_5\Delta_2 - a_1a_5(a_1a_4 - a_5). \tag{35}$$

Subtracting Equation (35) from Equation (34) results in

$$\Delta_3 = \frac{a_5(a_1a_2 - a_3)\Delta_2}{a_1a_4 - a_5} = \frac{a_5\Delta_2^2}{a_1a_4 - a_5}. \tag{36}$$

Note that $a_5 > 0$ and $\Delta_2 > 0$. Also, a careful calculation gives

$$\begin{aligned} a_1a_4 - a_5 = {} & (b+q)\left(a\frac{\mathcal{R}_0}{R_1} + b + dR_1 + p + q\right)\left(\frac{R_1 - 1}{R_1}\right) \\ & + abq\left[\left(a\frac{\mathcal{R}_0}{R_1} + b + dR_1 + q\right)(p + dR_1) + p^2\right]\left(\frac{\mathcal{R}_0 - R_1}{R_1}\right), \end{aligned} \tag{37}$$

which clearly shows that $a_1a_4 - a_5 > 0$ when $\mathcal{R}_0 > R_1$. This together with Equation (36) confirms $\Delta_3 > 0$, completing the proof. ■

The above discussion and the results in Yu [24] imply that there are no static bifurcation, Hopf-zero bifurcation, double Hopf bifurcation and double-zero Hopf bifurcation, emerging from the equilibrium solution E_{d}; and the only possibility for E_{d} to lose stability is occurrence of Hopf bifurcation when Δ_4 crosses zero from positive to negative as $\mathcal{R}_0$ further increases from R_2 (see Theorem 5.1).

In order to show that Hopf bifurcation can occur, we need to show that Δ_4 can change sign from positive to negative as $\mathcal{R}_0$ further increases after R_1. To this end, we notice that $\mathcal{R}_0 = 1/adp$ and $R_1 = 1 + bq/cdp$, implying that as $a \to \infty$, $\mathcal{R}_0 \to +\infty$ while $\mathcal{R}_0 > R_1$ remains valid (actually, as long as $1/a > dp + bq/c$). The above observation suggests considering small values of a and large values of c. Indeed, by Equations (27), (29) and tedious but straightforward expansion, we may obtain

$$\Delta_4 = \frac{-bq}{(cdp + bq)^4}[c_4c^4 + c_3c^3 + c_2c^2 + c_1c + c_0 + c_{-1}c^{-1} + c_{-2}c^{-2} + c_{-3}c^{-3}] + \mathrm{O}(a), \tag{38}$$

where

$$c_4 = [pdq + pbd^3(d+p) + d(d+q)(pd^3 + p^2d^2 + b + d)]f(d),$$

in which

$$f(d) = p^4(b + p + q)d^2 - p(b^2 + bq + q^2 - 2p^2)d - b + p - q. \tag{39}$$

Thus, for small a and large c, the sign of Δ_4 is determined by the leading coefficient c_4, i.e. the sign of $f(d)$. In order to have $c_4 > 0$, we need $f(d) > 0$, which holds for appropriate values of d.

For example, $f(d) > 0$ when $d < d_1$ or $d > d_2$ where d_1 and d_2 are the two roots of $f(d) =$ as a quadratic function of d:

$$\begin{aligned} d_1 &= \frac{(b^2+bq+q^2-2p^2)-\sqrt{(b^2+q^2)(b+q)^2+bq(bq+4p^2)}}{2p^3(b+p+q)}, \\ d_2 &= \frac{(b^2+bq+q^2-2p^2)+\sqrt{(b^2+q^2)(b+q)^2+bq(bq+4p^2)}}{2p^3(b+p+q)}. \end{aligned} \tag{40}$$

Combining the above and the results in Yu [24], we have proved the following theorem.

THEOREM 5.2 *For some large values of c and small values of a, together with $d < d_1$ or $d > d_2$(d_1, d_2 as given in Equation* (40))(*hence $\mathcal{R}_0 \gg R_1$), the double-infection equilibrium E_{d} loses its stability through Hopf bifurcation, giving rise to a family of periodic solutions.*

By the above theorem, E_{d} can lose its stability through Hopf bifurcation when $\mathcal{R}_0$ is further increased from R_1 in some way. It should be pointed out that the conditions obtained above for Δ_4 to change sign (i.e. for large values of c and small values of a) are only sufficient conditions for the requirement $\Delta_4 < 0$, which may be quite conservative. There may be many other choices of the parameters that can satisfy this requirement. For some special choice, we may even find the critical value R_{h} for $\mathcal{R}_0$ precisely at which Hopf bifurcation occurs. This will be illustrated numerically in the following section.

6. Numerical illustrations

In this section, we use a numerical example and some simulations to demonstrate the theoretical results obtained in the previous sections. Due to the larger number of parameters, there are many choices for this purpose. For convenience, we will work on the scaled model (21) instead of the original model (2). Throughout this section, we fix

$$c = 40, \quad a = \frac{93}{100}, \quad b = p = q = \frac{28}{5}, \tag{41}$$

but choose d as the bifurcation parameter. Then,

$$\mathcal{R}_0 = \frac{1}{adp} = \frac{125}{651d} \quad \text{and} \quad R_1 = 1 + \frac{bq}{cdp} = 1 + \frac{7}{50d}. \tag{42}$$

The infection-free equilibrium becomes

$$E_0 = \left(\frac{1}{d}, 0, 0, 0, 0\right),$$

which is stable when $d > \frac{125}{651}$ (i.e. $\mathcal{R}_0 < 1$). When d decreases to pass the critical value $\frac{125}{651}$, $\mathcal{R}_0$ increases to pass the threshold value 1, and E_0 becomes unstable and there occurs the single-infection equilibrium

$$E_{\mathrm{s}} = \left(\frac{651}{125}, \frac{100}{93} - \frac{28}{5}d, 0, \frac{125}{651} - d, 0\right)$$

which is stable for $\frac{1693}{32550} < d < \frac{125}{651}$ (corresponding to $1 < \mathcal{R}_0 < R_1$). When d further decreases to pass the critical value $\frac{1693}{32550}$, $\mathcal{R}_0$ increases to pass R_1 and E_{s} loses its stability to the double-infection

equilibrium

$$E_{\mathrm{d}} = \left(1 + \frac{7}{50}d, \frac{98}{125}, \frac{1693 - 32550d}{125(50d+7)}, \frac{7}{50}, \frac{1693 - 32550d}{700(50d+7)}\right),$$

which is stable when

$$1 + \frac{7}{50d} < \mathcal{R}_0 < R_{\mathrm{h}} \quad \text{or} \quad d_{\mathrm{h}} < d < \frac{1693}{32550} = 0.05201228879,$$

where d_{h} or R_{h} is determined as follows.

For the given parameter values, the coefficients of the characteristic polynomial for E_{d} become

$$\begin{aligned}
a_1 &= \frac{2}{175(50d+7)}(4375d^2 + 74725d + 11157),\\
a_2 &= \frac{1}{3500(50d+7)}(2940000d^2 + 11830450d + 1948639),\\
a_3 &= \frac{1}{125(50d+7)}(392000d^2 - 60020d + 19789),\\
a_4 &= \frac{14}{15625(50d+7)}(573391 - 9257200d - 1627500d^2),\\
a_5 &= \frac{392}{78125}(1693 - 32550d)
\end{aligned} \tag{43}$$

and thus

$$\begin{aligned}
\Delta_2 &= \frac{1}{306250(50d+7)^2}(12862500000d^4 + 223429718750d^3 + 925986901875d^2\\
&\quad + 276209570425d + 21401583973),\\
\Delta_3 &= \frac{1}{957031250(50d+7)^3}(129541453125000000d^6 + 2289800686250000000d^5\\
&\quad + 10119907671671875000d^4 + 7454450134607656250d^3 + 1626985083652346875d^2\\
&\quad + 126603254586394425d + 2644699936366537),\\
\Delta_4 &= \frac{2}{1068115234375(50d+7)^4}(48448475332031250000000d^8\\
&\quad + 858348826387500000000000d^7 + 370216771606681835937500d^6\\
&\quad + 92493314786535113281250d^5 - 73331345083753823554687 50d^4\\
&\quad - 77556742983386341889062 5d^3 + 17502784886835387568625 0d^2\\
&\quad + 153288505938403595242 00d - 462890586754471441699).
\end{aligned} \tag{44}$$

A numerical scheme for solving the roots of polynomial can be applied here to find three positive real solutions of $\Delta_4 = 0$, given by

$$d = 0.02433284924,\ 0.1439442394,\ 1.1875365473.$$

It is seen that only the first solution satisfies the requirement, and thus

$$d_{\mathrm{h}} = 0.02433284924,$$

giving a corresponding value

$$R_{\rm h} = 7.8910729629$$

for $\mathcal{R}_0$ by the formula of $\mathcal{R}_0$ in Equation (42) in terms of d. Hence, when

$$0.02433284924 < d < 0.05201228879 \quad \text{or} \quad 3.6916715889 < \mathcal{R}_0 < 7.8910729629,$$

the equilibrium solution $E_{\rm d}$ is stable. At the critical point, $d = d_{\rm h}(\mathcal{R}_0 = R_h)$, the equilibrium solution $E_{\rm d}$ becomes unstable and a Hopf bifurcation occurs, leading to a family of periodic solutions. In fact, at the critical point $\mathcal{R}_0 = R_h$, other Routh–Hurwitz conditions are satisfied as

$$\begin{aligned} &a_1 = 18.0509776034, \quad a_2 = 77.8297845427, \quad a_3 = 18.0712652830,\\ &a_4 = 37.8582007260, \quad a_5 = 4.5206857827,\\ &\Delta_2 = 1386.8324323768, \quad \Delta_3 = 12807.7870360972,\\ &\Delta_4 = 0.1478893257 \times 10^{-11}. \end{aligned}$$

Indeed, with these given parameter values, one can numerically find the eigenvalues of the characteristic polynomial $P_{\rm d}(\xi)$ which include a pair of pure imaginary roots and three negative real roots:

$$\xi = \pm 0.6996439883{\rm i}, -0.1229130660, -6.6799164524, -11.2481480850,$$

where i is the imaginary unit, ${\rm i}^2 = -1$.

In what follows, we show, via this numerical example, how to obtain more information about the Hopf bifurcation, such as bifurcation direction and stability, magnitudes and periods of the bifurcated period solutions. To this end, we apply the normal form theory and the program using computer algebra system Maple developed by Yu [23], and Yu and Huseyin [25] to analyse the Hopf bifurcation of system (21) from the critical point $d = d_{\rm h}(\mathcal{R}_0 = R_{\rm h})$ (with other parameters given by Equation (41)).

The general normal form can be written in polar coordinates as

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

where r and θ represent the amplitude and phase of periodic motion (limit cycle), respectively. The constant $\omega_0 = 0.6996439883$ corresponds to the pair of the pure imaginary roots of $P_{\rm d}(\xi)$, v_0, v_1, τ_0, τ_1 are constants, depending on the original system parameters, with v_0 and v_1 being called focus values (or Lyapunov coefficients). When $v_1 < 0 (v_1 > 0)$, the Hopf bifurcation is supercritical (subcritival), giving stable (unstable) limit cycles, and the periodic solutions can be approximated in terms of the steady-state solution of Equation (45) (see [23] for details). v_0 and τ_0 can be found from linear analysis, while v_1 and τ_1 must be determined by using nonlinear analysis. We show how to find these constants below for this numerical example.

Let $d = d_{\rm h} - \mu$, where μ is small perturbation (bifurcation) parameter, and

$$T = \begin{bmatrix} -0.9807311131 & 1.2289461236 & 7.7132047383 & -0.5738621607 & 0.0099614719\\ 0.8839099286 & 0.5629856374 & -0.2875522037 & 0.6635527506 & -0.1024809760\\ 2.7770485106 & -3.8165262586 & 7.2480063486 & 0.1487044501 & 6.6967660754\\ 0.1677823774 & 0.0795710189 & -0.5250093840 & -0.6144482281 & 0.0181441729\\ 0.4044415553 & -0.7320520288 & 1.3233323546 & -0.1376999580 & -1.1856569578 \end{bmatrix}.$$

By the linear transformation

$$\begin{pmatrix} x \\ y \\ z \\ v \\ w \end{pmatrix} = \begin{pmatrix} 6.0852106234 \\ 0.7840000000 \\ 0.8772106234 \\ 0.1400000000 \\ 0.1566447542 \end{pmatrix} + T \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \\ x_5 \end{pmatrix}, \tag{46}$$

system (21) is transformed to

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

in which

$$\begin{aligned}
F_1 &= 0.6996439883x_2 + (12.3096075793x_1 + 7.0040169156x_2 - 4.3728592211x_3 \\
&\quad - 10.5713612773x_4 - 0.4156611553x_5)\mu + o(\mu) \\
&\quad + 0.3561346924x_1^2 - 0.4769602403x_2^2 - 0.7980855956x_3^2 + 0.1332821303x_4^2 \\
&\quad + 0.1615737524x_5^2 - 0.4646425311x_1x_2 + 2.3715629953x_1x_3 + 0.5605661618x_1x_4 \\
&\quad - 1.4591815204x_1x_5 + 1.6662710988x_2x_3 - 1.3268086927x_2x_4 - 0.7705413442x_2x_5 \\
&\quad - 2.1821003938x_3x_4 + 0.3735112628x_3x_5 - 1.0385184254x_4x_5, \\
F_2 &= -0.6996439883x_1 + (-15.7111809897x_1 - 10.0506358184x_2 + 6.2186196979x_3 \\
&\quad - 20.3255688833x_4 + 2.2407734339x_5)\mu + o(\mu) \\
&\quad - 1.1220803000x_1^2 + 1.2649183711x_2^2 + 1.0133784444x_3^2 + 0.3836952899x_4^2 \\
&\quad - 0.3638760837x_5^2 + 1.2960748880x_1x_2 - 2.7352377073x_1x_3 - 0.2812613892x_1x_4 \\
&\quad + 3.2580692528x_1x_5 - 2.6905502101x_2x_3 + 1.4372320702x_2x_4 + 1.7817905444x_2x_5 \\
&\quad - 4.2180683514x_3x_4 - 0.5714642311x_3x_5 + 2.3089964765x_4x_5, \\
F_3 &= -0.1229130660x_3 + (3.2296425652x_1 + 2.3100610142x_2 - 0.3267210453x_3 \\
&\quad + 4.3446396524x_4 - 0.4813686500x_5)\mu + o(\mu) \\
&\quad + 0.2412724663x_1^2 - 0.2717692264x_2^2 - 0.2165318633x_3^2 - 0.0832350520x_4^2 \\
&\quad + 0.0781092847x_5^2 - 0.2785323025x_1x_2 + 0.5838231750x_1x_3 + 0.0591250445x_1x_4 \\
&\quad - 0.6993381369x_1x_5 + 0.5761976189x_2x_3 - 0.3065386940x_2x_4 - 0.3825366370x_2x_5 \\
&\quad + 0.9170831803x_3x_4 + 0.1223262778x_3x_5 - 0.4956089251x_4x_5, \\
F_4 &= -6.6799164524x_4 + (1.5622567928x_1 + 0.7409792295x_2 - 0.5272185195x_3 \\
&\quad - 5.4639965627x_4 + 0.1563670175x_5)\mu + o(\mu) \\
&\quad - 0.0365555512x_1^2 + 0.0198967355x_2^2 - 0.1014961739x_3^2 + 0.0845086223x_4^2 \\
&\quad + 0.0011557773x_5^2 + 0.0271810123x_1x_2 + 0.3353347962x_1x_3 + 0.1238921958x_1x_4 \\
&\quad - 0.0138731493x_1x_5 + 0.1416788965x_2x_3 - 0.1989762704x_2x_4 + 0.0001664596x_2x_5 \\
&\quad - 1.1314177813x_3x_4 + 0.0356257344x_3x_5 - 0.0110727609x_4x_5,
\end{aligned}$$

$$
\begin{aligned}
F_5 = {} & -11.2481480850x_5 + (17.3226213739x_1 + 11.0868910462x_2 - 5.6345823041x_3 \\
& + 14.4271665998x_4 - 2.0807163549x_5)\mu + o(\mu) \\
& + 1.0878139578x_1^2 - 1.2493237453x_2^2 - 1.1278070934x_3^2 - 0.2941530028x_4^2 \\
& + 0.3668251220x_5^2 - 1.2727531528x_1x_2 + 3.1104371502x_1x_3 + 0.4164748934x_1x_4 \\
& - 3.2882835763x_1x_5 + 2.8562424959x_2x_3 - 1.6589948369x_2x_4 - 1.7899345495x_2x_5 \\
& + 3.0149660230x_3x_4 + 0.6126373064x_3x_5 - 2.3317504708x_4x_5. \qquad (48)
\end{aligned}
$$

Here $o(\mu)$ denotes a term containing only higher orders of μ. Now, the Jacobian of system (47) evaluated at the trivial equilibrium solution $x_i = 0, i = 1, 2, \ldots, 5$ (corresponding to E_d for Equation (21)) is in the Jordan canonical form:

$$
J = \begin{bmatrix}
0 & 0.6996439883 & 0 & 0 & 0 \\
-0.6996439883 & 0 & 0 & 0 & 0 \\
0 & 0 & -0.1229130660 & 0 & 0 \\
0 & 0 & 0 & -6.6799164524 & 0 \\
0 & 0 & 0 & 0 & -11.2481480850
\end{bmatrix}.
$$

By Yu and Huseyin [25], the coefficients v_0 and τ_0 are given by

$$
\begin{aligned}
v_0 &= \frac{1}{2}\left(\frac{\partial^2 F_1}{\partial x_1\,\partial\mu} + \frac{\partial^2 F_2}{\partial x_2\,\partial\mu}\right)\Bigg|_{\mu=0} = 1.1294858805, \\
\tau_0 &= \frac{1}{2}\left(\frac{\partial^2 F_1}{\partial x_2\partial\mu} - \frac{\partial^2 F_2}{\partial x_1\partial\mu}\right)\Bigg|_{\mu=0} = 11.3575989526.
\end{aligned} \qquad (49)
$$

Applying the Maple program developed in Yu [24] to system (47) (setting $\mu = 0$) results in

$$
v_1 = -0.0607814981, \quad \tau_1 = -1.0336310494. \qquad (50)
$$

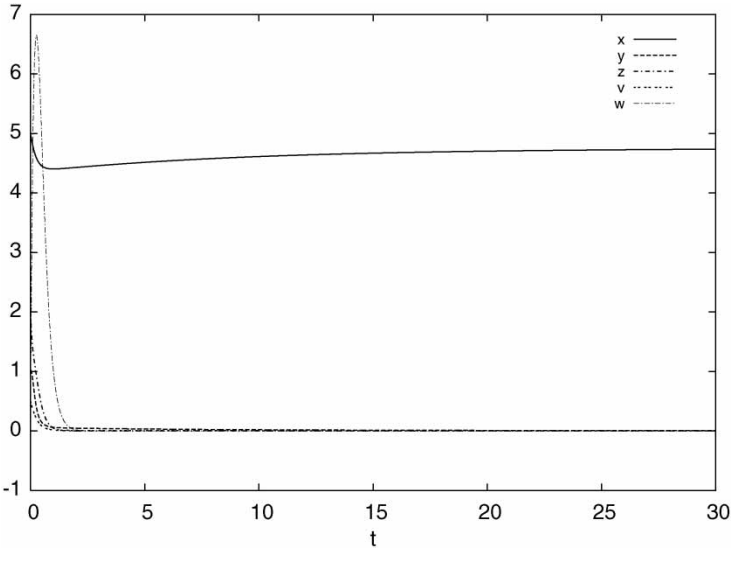

Figure 1. Simulated time history of system (21) for $d = 0.21, a = 0.93, c = 40, b = p = q = 5.6$ with the initial condition: $x(0) = 5.0$, $y(0) = 1.0$, $z(0) = 2.0$, $v(0) = 0.5$, $w(0) = 4.0$, converging to the stable equilibrium solution E_0.

Therefore, the third-order normal form Equation (45) becomes

$$\begin{aligned}\frac{\mathrm{d}r}{\mathrm{d}\tau} &= r(1.1294858805\mu - 0.0607814981r^2),\\ \frac{\mathrm{d}\theta}{\mathrm{d}\tau} &= 0.6996439883 + 11.3575989526\mu - 1.0336310494r^2.\end{aligned} \tag{51}$$

The steady-state solutions of Equation (51) are determined by setting $\mathrm{d}r/\mathrm{d}\tau = \mathrm{d}\theta/d\tau = 0$, yielding

$$\bar{r} = 0 \quad \text{and} \quad \bar{r}^2 = 18.5827252624\mu. \tag{52}$$

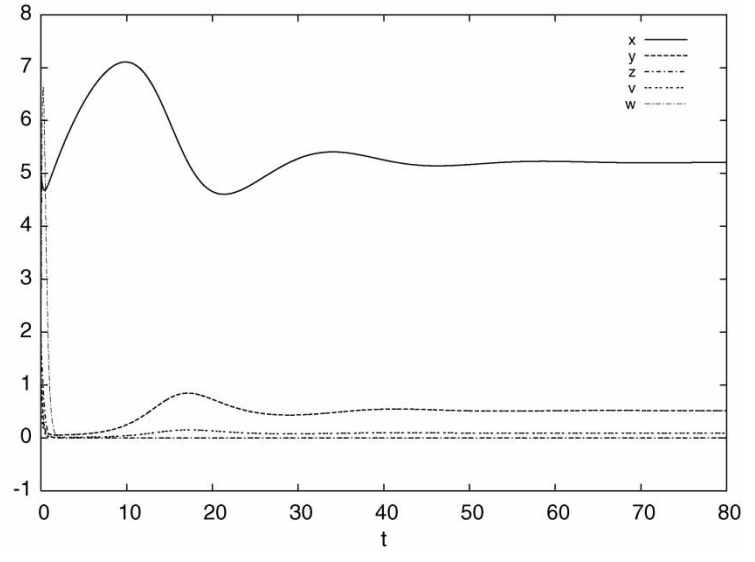

Figure 2. Simulated time history of system (21) for $d = 0.10, a = 0.93, c = 40, b = p = q = 5.6$ with the initial condition: $x(0) = 5.0$, $y(0) = 1.0$, $z(0) = 2.0$, $v(0) = 0.5$, $w(0) = 4.0$, converging to the stable equilibrium solution E_{s}.

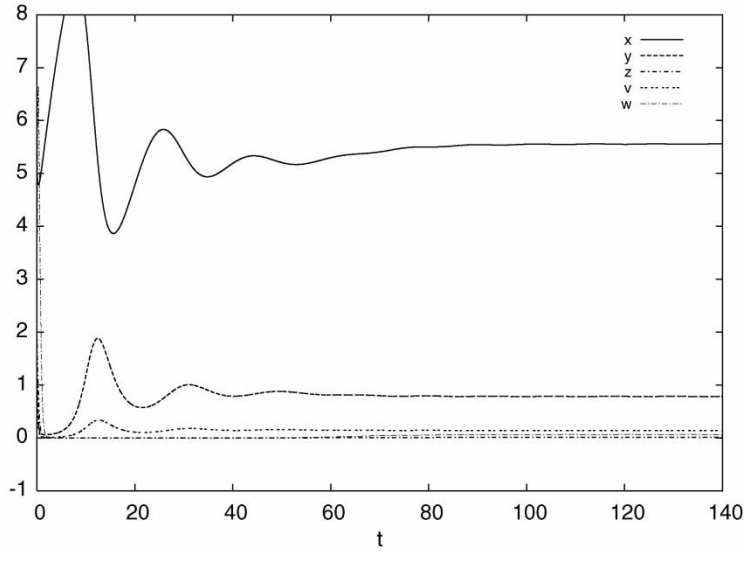

Figure 3. Simulated time history of system (21) for $d = 0.04, a = 0.93, c = 40, b = p = q = 5.6$ with the initial condition: $x(0) = 5.0$, $y(0) = 1.0$, $z(0) = 2.0$, $v(0) = 0.5$, $w(0) = 4.0$, converging to the stable equilibrium solution E_{d}.

The solution $\bar{r} = 0$ actually corresponds to the equilibrium solution E_d of Equation (21). A simple linearization of the first equation of Equation (51) indicates that $\bar{r} = 0(E_d)$ is stable for $\mu < 0$, as expected. When μ increases from negative to cross zero, a Hopf bifurcation occurs and the amplitude of the bifurcation periodic solutions is given by the non-zero steady-state solution

$$\bar{r} = 4.3107685234\sqrt{\mu} \quad (\mu > 0). \tag{53}$$

Since $v_1 < 0$, the Hopf bifurcation is supercritical and the bifurcating limit cycle is stable. The amplitude of the bifurcating limit cycle is given by Equation (53), and the frequency is determined from the following equation:

$$\omega = 0.6996439883 + 6.9018547601\mu. \tag{54}$$

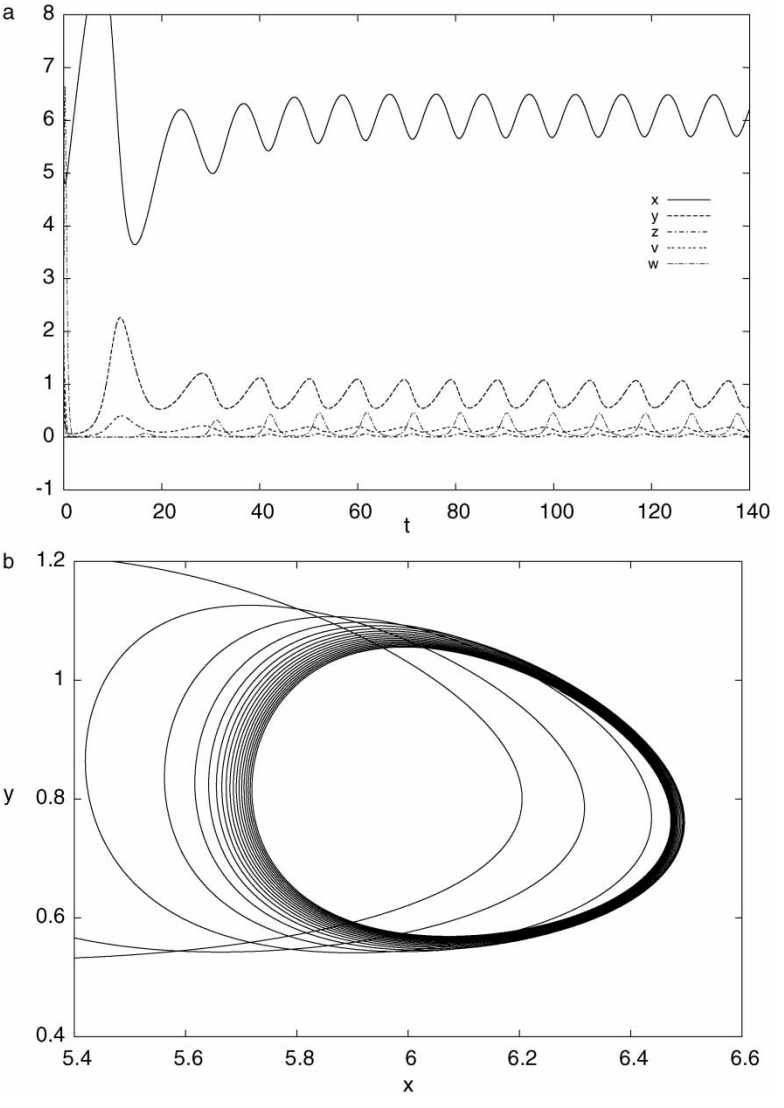

Figure 4. Simulation results of system (21) for $d = 0.022$, $a = 0.93$, $c = 40$, $b = p = q = 5.6$ with the initial condition, $x(0) = 5.0$, $y(0) = 1.0$, $z(0) = 2.0$, $v(0) = 0.5$, $w(0) = 4.0$: (a) time history showing convergence to a stable periodic solution and (b) phase portrait projected on $x - y$ plane indicating a stable limit cycle.

We have performed some numerical simulations for Equation (21) by using a fourth-order Runge–Kutta method. We take the parameter values given in Equation (41), giving $d_{\mathrm{h}} = 0.02433284924$ and $R_{\mathrm{h}} = 7.8910729629$. We choose four different values for d (and so for $\mathcal{R}_0$):

$$
\begin{aligned}
&d = 0.21 \text{ leading to } \mathcal{R}_0 = 0.9143442323 < 1 \text{ by Equation (42)};\\
&d = 0.10 \text{ leading to } \mathcal{R}_0 = 1.9201228879) \in (1, 2.4) = (1, R_1) \text{ by Equation (42)};\\
&d = 0.04 \text{ leading to } \mathcal{R}_0 = 4.8003072197 \in (4.50000000, 7.8910729629)\\
&\quad = (R_1, R_h) \text{ by Equation (42)};\\
&d = 0.022 \text{ leading to } \mathcal{R}_0 = 8.7278313085 > 7.8910729629 = R_h \text{ by Equation (42)}. \qquad (55)
\end{aligned}
$$

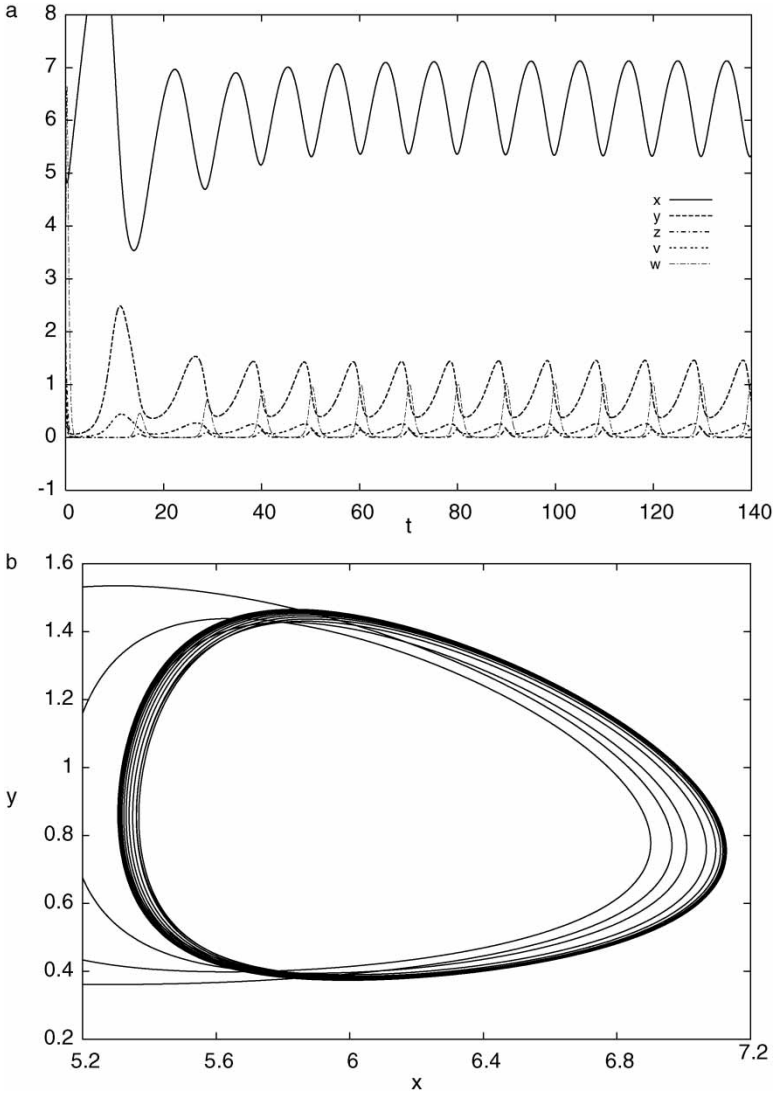

Figure 5. Simulation results of system (21) for $d = 0.012$, $a = 0.93$, $c = 40$, $b = p = q = 5.6$ with the initial condition, $x(0) = 5.0$, $y(0) = 1.0$, $z(0) = 2.0$, $v(0) = 0.5$, $w(0) = 4.0$: (a) time history showing convergence to a stable periodic solution and (b) phase portrait projected on $x - y$ plane indicating a stable limit cycle.

According to the above theoretical analysis, the simulation results are expected to have the stable equilibrium solution E_0 for $d = 0.21$, the stable equilibrium solution E_s for $d = 0.10$, the stable equilibrium solution E_d for $d = 0.04$ and a stable limit cycle for $d = 0.022$ (for which $\mu = 0.0023328492$), with approximate amplitude for the periodic motion, $\bar{r} = 0.2082083010$.

The simulated time history and phase portraits for the above four cases are shown in Figures 1–4, respectively, where the initial conditions are taken as

$$x(0) = 5.0, \quad y(0) = 1.0, \quad z(0) = 2.0, \quad v(0) = 0.5, \quad w(0) = 4.0. \tag{56}$$

It can be seen from these figures that the numerical simulation results agree with the analytical predictions. The solutions for the first three cases converge to the equilibrium points, E_0, E_s and E_d, respectively. For the last case, the simulated amplitude of the limit cycle (see Figure 4) is close to the predicted value, $\bar{r} = 0.2082$, showing a good agreement, not only qualitatively, but also quantitatively, between the theoretical prediction and numerical simulation. Also, it is seen that the period of motion, $T = 2\pi/\omega$ (ω is given in Equation (54)), decreases as μ increases. In other words, T decreases as d decreases. However, since μ is quite small, the change of the period due to μ is not significant (hardly observed, see Figures 4 and 5). Nevertheless, a small change in μ can cause large variation of the amplitude. The simulation results shown in Figure 5 uses $d = 0.012$, which gives $\mu = 0.0123328492$ and thus the approximation of the amplitude of periodic motion is $\bar{r} = 0.4787253380$, which is almost 2.3 times of that when $d = 0.022$. This can be observed from Figures 4b and 5b.

7. Conclusion and discussion

Revilla and Garcia-Ramos [18] proposed a model to describe the interaction of HIV-1 virus, a genetically modified virus, healthy T-cells and infected T-cells, and in terms of theory, they only analysed the structure of the equilibria of the model. As we emphasized in Section 1, for a higher-dimensional system, its dynamics cannot be fully determined by the structure of equilibria, and stability analysis is crucial and necessary. In this paper, we have fully analysed the stability of the infection-free equilibrium E_0, the single-infection equilibrium E_s and the double-infection equilibrium E_d and theoretically proved following:

(1) when $\mathcal{R}_0 < 1$, the disease-free equilibrium E_0 is globally asymptotically stable;
(2) when $\mathcal{R}_0 > 1$, E_0 becomes unstable and there occurs the single-infection equilibrium E_s.
(3) when $\mathcal{R}_0 \in (1, 1 + kbq\beta/cpd\alpha)$, E_s is globally asymptotically stable;
(4) when $\mathcal{R}_0 > 1 + kbq\beta/cpd\alpha$ (equivalently $\mathcal{R}_d > 1$), E_s becomes unstable, and there is the double-infection equilibrium E_d;
(5) there is a $R_2 > 1 + kbq\beta/cpd\alpha$, such that E_d is asymptotically stable when $\mathcal{R}_0 \in (1 + kbq\beta/cpd\alpha, R_2)$;
(6) when $\mathcal{R}_0$ is further increased in some appropriate ways, E_d loses it stability, giving rise to some stable periodic solution via Hopf bifurcation.

The above descriptions reveal the role that each parameter plays in determining the global dynamics of the model and give some quantitative criteria in terms of the parameters for controlling the infection.

Note that Equation (2) is a result of incorporating the variables z and w (recombinant related) into Equation (1). It can be easily seen that both Equations (1) and (2) share the same basic reproduction number $\mathcal{R}_0$, and hence the parameters in z and w equations have no impact on $\mathcal{R}_0$. In this sense, introducing the recombinant into to the host does not help completely eliminate the HIV virus. However, by comparing the healthy $CD4^+$ T-cell populations and the wild HIV

virus loads in the single-infection equilibrium $E_s = (x_s, y_s, 0, v_s, 0)$ and the double-infection equilibrium $E_d = (x_d, y_d, z_d, v_d, w_d)$, we can see that the recombinant can increase the healthy cell populations and reduce the virus load. To see this, assume $\mathcal{R}_0 > 1$. Then large c and small k will guarantee that $\mathcal{R}_0$ is slightly large than $1 + kbq\beta/cpd\alpha$, so that the double-infection equilibrium is asymptotically stable. Now simple calculations show the condition $\mathcal{R}_0 > 1 + kbq\beta/cpd\alpha$ implies (is indeed equivalent to)

$$x_d = \frac{\lambda\alpha cp}{d\alpha cp + \beta bkq} > x_s = \frac{ap}{\beta k} \quad \text{and} \quad v_d = \frac{bkq}{\alpha cp} < v_s = \frac{\lambda k}{ap} - \frac{d}{\beta}. \tag{57}$$

There have been various models for HIV drug therapies. Comparing the model (2) for the generic therapy with existing models for drug therapies, one finds that the latter is much simpler, because they are usually the result of replacing a parameter by another one reflecting the drug efficacy. For example, in considering the effectiveness of a reverse transcriptase inhibitor, the usual way is to replace the parameter β in Equation (1) by $(1 - \eta_{rt})\beta$ (see, e.g. [16]), leading to

$$\begin{aligned} \dot{x} &= \lambda - dx - (1 - \eta_{rt})\beta xv, \\ \dot{y} &= (1 - \eta_{rt})\beta xv - ay, \\ \dot{v} &= ky - pv, \end{aligned} \tag{58}$$

where η accounts for the drug efficacy. Clearly, Equation (58) has the same structure as Equation (1), and hence, demonstrate the same threshold dynamics as Equation (1), but now in terms of the new basic reproduction number $\mathcal{R}_0 = (1 - \eta_{rt})\beta\lambda k/apd$. Obviously, positive η_{rt} reduces $\mathcal{R}_0$, implying that an effective drug may help eliminate the HIV virus. This is in contrast to the generic therapy that Equation (2) models (see the above paragraph).

We point out that [18] only numerically explored solution behaviour of model (2). Now after some rigorous analysis, we have obtained conditions in terms of the model parameters on the stability of the equilibria E_0, E_s and E_d, given by the descriptions (1)–(5) above. Moreover, the description (4) above (or Theorem 5.2) identifies an important class of solutions: periodic solutions. Considering the fact that the *sustained fluctuation* of the virus load and/or the healthy cells' population *in vivo* will make the clinic measurements of these two quantities less reliable, this finding is of particular theoretical and practical significance. For example, without excluding the period dynamics, a very lower load of virus in the clinic sampling may right be the value of a periodic solution at the *lowest* moment and hence does not imply that virus is dying out. In order to avoid misleading and to make good use of clinical data in such a periodic situation, information about the frequencies and magnitudes of the oscillating densities is necessary. Through a numerical example, we have demonstrated how to obtain such information. Knowledge on the periods of oscillation of solutions may help design optimal clinical sampling strategy, e.g. the time interval for sampling.

The interaction of HIV virus and T-cells is a complicated process, which involves cell production, virus attachment to the cells and penetration into the cells, virus replication inside cells and release from cells. Now with a recombinant virus added in, the process becomes more complicated. The model we consider here is just a simple one, and there is more room to improve and expand the model. For example, one may consider the situation when there is an external source of recombinant virus. One may also consider the situation when the recombinant virus also infects susceptible cells but at a lower rate (this may occur due to possible mutation of the recombinant virus). One may also incorporate the infection latent into the model, as in [11,12], that leads to models of delay differential equations. Such modifications should more precisely describe the reality and give us more insights into the infection process, but would lead to much more challenging mathematical problems.

Acknowledgements

This research was supported by NSERC of Canada, PREA of Ontario and by China Scholarship Council.

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