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Influence of backward bifurcation in a model of hepatitis B and C viruses

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ABSTRACT

In the 1990s, liver transplantation for hepatitis B and C virus (HBV and HCV) related-liver diseases was a very controversial issue since recurrent infection of the graft was inevitable. Significant progress has been made in the prophylaxis and treatment of recurrent hepatitis B/C (or HBV/HCV infection) after liver transplantation. In this paper, we propose a mathematical model of ordinary differential equations describing the dynamics of the HBV/HCV and its interaction with both liver and blood cells. A single model is used to describe infection of either virus since the dynamics in-host (infected of the liver) are similar. Analyzing the model, we observe that the system shows either a transcritical or a backward bifurcation. Explicit conditions on the model parameters are given for the backward bifurcation to be present. Consequently, we investigate possible factors that are responsible for HBV/HCV infection and assess control strategies to reduce HBV/HCV reinfection and improve graft survival after liver transplantation.

1. Introduction

Hepatitis refers to inflammation of the liver. Such inflammation can be caused by alcohol, certain medications and chemicals or by viral infection. Hepatitis C virus (HCV) and hepatitis B virus (HBV) are two such viral pathogens which infect liver cells (hepatocytes). HBV and HCV account for over 500 million chronic infections worldwide [36].

Although hepatitis B virus and hepatitis C virus have similar names, these are distinctly different viruses both genetically and clinically. HBV is a DNA virus that infects liver cells. It leads to acute infection, where virus is cleared from the body by the immune response, or chronic infection, where virus persists. Chronic infection eventually leads to liver disease, i.e. cirrhosis and hepatocellular carcinoma [18]. Those with only acute disease still experience severe symptoms for up to a year, including jaundice, extreme fatigue, nausea, vomiting and abdominal pain. Approximately 1–5% of infected adults are unable to clear infection and become chronically infected, but this proportion is much higher in infants and children [19]. Chronic hepatitis B is a major cause of cirrhosis and hepatocellular carcinoma worldwide. Approximately 30–40% of hepatitis B patients with persistent liver inflammation progress to cirrhosis [19]. About 25% of chronic carriers die from liver cancer induced by the virus [36].

HCV is a small, enveloped, single strand RNA virus that also infects liver cells. In contrast to HBV, a large proportion of hepatitis C patients become chronically infected (approximately 60–85%), and approximately one-third of these patients will develop cirrhosis of the liver [19]. HCV alone affects an estimated 170 million people worldwide [6].

Drug therapies are used to treat patients with HBV and HCV. However, the current therapies (such as Peginterferon-aCRibavirin for HCV and Lamivudine (LMV) and Entecavir for HBV) are ineffective in eliminating the virus in a large proportion of chronic patients [11,26,19] and patients may require a liver transplant.

It is believed that liver transplantation prolongs and improves quality of life for patients with many types of chronic liver disease. Because the liver is probably the largest reservoir of HBV, it was hoped that removal of the liver, combined with blood loss and subsequent transfusions that occur with liver transplantation, that the virus would be cleared from most patients. Unfortunately, the early results of transplantation for patients with chronic HBV were discouraging [35]. Survival was poor, and HBV reinfection of the liver graft often resulted in a rapidly progressive course of disease. Historically, in the absence of prevention, the spontaneous risk for HBV reinfection after transplantation is approximately 80%

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related to the initial liver disease and the presence of HBV replication at time of transplantation [13,35].

The result of liver transplantation in chronic HCV carriers has an equally troubling story. It has been found that recurrent HCV infection of the new liver occurs in almost all patients and that the natural history of recurrent HCV after transplantation is significantly accelerated [2].

The fact that reinfection of the liver after transplantation occurs suggests that virus is present in other reservoirs. Thus, virus can be circulating in the blood which ultimately reinfects the new liver if drug therapies cannot clear it. We have developed a mathematical model that describes the pathogenesis of HBV or HCV infection that takes into account free virus in the blood as well as the liver. Since the dynamics of HBV and HCV are similar in that they infect liver cells and may infect cells in the blood, only one model is needed. We use the model to determine conditions that allow extra-hepatic HBV/HCV DNA to persist in patients who have liver transplants. We demonstrate that the model produces a transcritical bifurcation as well as backward bifurcation, both related to the production of virus from infected cells in the liver and in the blood. This has clear implications towards drug therapy strategies before, after and during liver transplantation.

In Section 2, we describe some early models of HBV and HCV. We then build on the basic model to describe infection in both the liver and blood. Section 2 is devoted to the presentation and the well-posedness of our model, that originally takes the form of a system of compartmental ordinary differential equations. In Section 3, we describe the dynamics of the full model such as the existence of steady states and global asymptotic stability of the disease-free equilibrium (DFE) using a Lyapunov function. Next, we demonstrate that the model produces a transcritical bifurcation as well as backward bifurcation in Section 4. In Section 5 we determine if there are any effects or phenomena that may eliminate the existence of the backward bifurcation. Finally, we discuss implications of the backward bifurcation in terms of drug therapy strategies.

2. Mathematical models

Mathematical models have aided in the understanding of viral infections, such as HBV and HCV (see [30,31]). Such models build on the basic model of in-host infection considering uninfected (x) and infected (y) cells and free virus (v):

$$\begin{aligned}\frac{dx}{dt} &= \lambda - \beta x v - dx,\\ \frac{dy}{dt} &= \beta x v - ay,\\ \frac{dv}{dt} &= ky - uv.\end{aligned} \tag{2.1}$$

Here, target cells (cells susceptible to infection, i.e. hepatocytes or liver cells) are produced at a constant rate λ, die at per capita rate d, and become infected at a rate $\beta x v$, proportional to both the target cell concentration and the virus concentration. Infected cells are thus produced at rate $\beta x v$ and are assumed to die at constant rate a per cell. Upon infection, infected cells produce virus at rate k per infected cell, and virus is cleared at rate u.

To decrease or eliminate HBV or HCV virus production, ky, or viral infection in the liver, $\beta x v$, must be reduced. Several studies [23,24,30,35] have modified the system (2.1) to include antiviral therapy, including a therapy-induced block in virus production (protease inhibitors (PI)) with efficacy ϵ to obtain $(1-\epsilon)ky$, and a block in viral infection (reverse transcriptase (RT) inhibitors) with efficacy η to obtain $(1-\eta)\beta x v$. The models were then fit to viral load data from patients under therapy and patient specific parameters were estimated (see [33] for details). However, even in patients undergoing drug therapy interventions viral replication may not be halted and these patients may require a liver transplant. Also, even after a liver transplant HBV or HCV infection may still persist [12,34] since extra-hepatic viral DNA could not be cleared by this procedure. Thus, the model (2.1) should be improved by considering another area of infection.

Recently, Dahari et al. [5] extended the basic model (2.1) to include two compartments of infection. This model demonstrated that the second compartment could predict the viral kinetics of patients from the anhepatic phase until first viral increase data, where the single compartmental model could not. This model, however, did not determine a quantitative estimation of the responsible factors of the persistence of the virus and its clearance. Furthermore, this model did not give a picture of the asymptotic viral dynamics after transplantation of the liver, and bifurcation analysis was not made.

Several modeling studies have highlighted the bifurcation behaviors of compartmental models when reinfection is considered [9,10,14]. Taking a more abstract approach, van den Driessche and colleagues have demonstrated the occurrence of backward bifurcations in a number of general models describing infectious disease dynamics [9,14]. This type of bifurcation behavior allows for the existence of multiple positive steady states, leading to different threshold conditions for the onset of an epidemic and its elimination.

A common drawback of the models mentioned above is that they neglect that fact a virion is lost when it infects a healthy cell [17]. This may play a major role in HBV/HCV dynamics, especially when the viral load is small, i.e. when a patient is under drug therapy. Adding $-\beta x v$ to the virus equation, (v) in the basic model we obtain:

$$\begin{aligned}\frac{dx}{dt} &= \lambda - \beta x v - dx,\\ \frac{dy}{dt} &= \beta x v - ay,\\ \frac{dv}{dt} &= ky - uv - \beta x v.\end{aligned} \tag{2.2}$$

In the next section, a compartmental model will be developed to describe HBV/HCV dynamics in the liver as well as the blood. This model is an extension of Eq. (2.2). We demonstrate that the model produces a transcritical bifurcation as well as a backward bifurcation.

3. Full model and basic properties

Our model uses the structure in Eqs. (2.1) and (2.2) with significant changes. As mentioned in the preceding section, we consider the infection of both liver and blood cells and the interaction of these cells through viral particles which are allowed to circulate freely between the liver and blood compartments. A schematic of our model is shown in Fig. 1. The liver–virus–blood (LVB) system is as follows:

$$\begin{aligned}\frac{dx}{dt} &= \lambda_x - \beta_x x v - d_x x,\\ \frac{dy}{dt} &= \beta_x x v - a_y y,\\ \frac{dv}{dt} &= k_x y + k_z w - uv - \beta_x x v - \beta_z z v,\\ \frac{dz}{dt} &= \lambda_z - \beta_z z v - d_z z,\\ \frac{dw}{dt} &= \beta_z z v - a_w w,\end{aligned} \tag{3.3}$$

where x, y and v are defined as before and $\lambda_x, \beta_x, d_x, k_x, a_x$ and u are the associated parameters. Here, the virus interacts with both liver

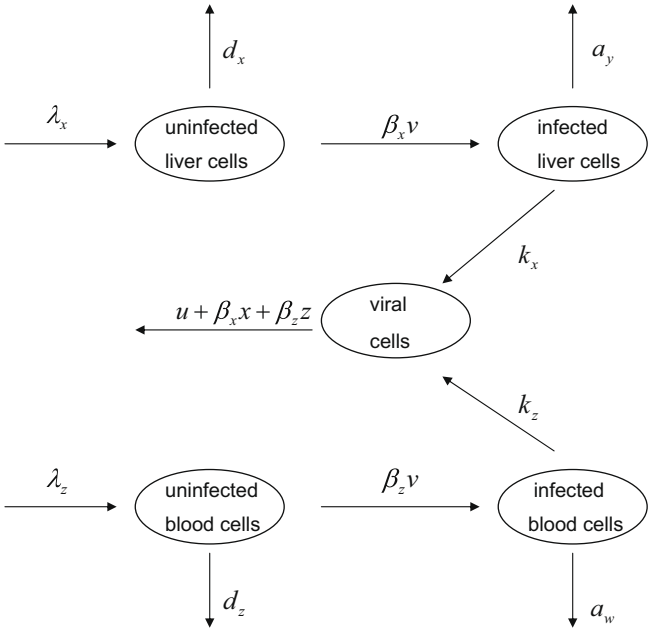

Fig. 1. Flow diagram for hepatitis Liver–Virus–Blood model structure.

cells, x, producing infected cells y, and blood cells, z, producing infected cells w. λ_z and d_z are the birth rate and death rate of healthy blood cells, respectively. Also, in the blood compartment, β_z is the infection rate, k_z is the production rate of virions and a_w is the death rate of infected cells.

Even when acute infections appear to be lytic, for chronic HBV and HCV it may not be completely clear whether the virus is intrinsically cytopathic. Results suggest that CTL-mediated lysis is sufficiently fast to eliminate a large fraction of productively infected cells and thereby greatly reduce virus production [31]. Also, based on previous studies where patient specific parameters were estimated (see [33] for details), it seems reasonable to assume that infected cells in the blood and liver may have shorter lifespans than their uninfected counterparts. Thus, hereafter, we will assume that $d_x \leqslant a_y$ and $d_z \leqslant a_w$. Note that CTL is not modeled explicitly in (3.3).

Lemma 1. *The region*

$$\Omega = \left\{(x,y,v,z,w) \in \mathbb{R}^4_+ : x+y \leqslant \frac{\lambda_x}{d_x}, z+w \leqslant \frac{\lambda_z}{d_z}, v \leqslant v_M\right\},$$

where

$$v_M := \frac{1}{u}\left(\frac{k_x\lambda_x}{d_x}+\frac{k_z\lambda_z}{d_z}\right)$$

is positively invariant and attracting with respect to the system (3.3).

Proof. For the invariance property it suffices to show that the vector field, on the boundary, does not point to the exterior.

From Eq. (3.3) we have, on the boundary of Ω,

$$\frac{d}{dt}(x+y) = \lambda_x - d_x x - a_y y = (d_x - a_y)y \leqslant 0.$$

Similarly, we get

$$\frac{d}{dt}(z+w) \leqslant (d_z - a_w)w \leqslant 0,$$

and

$$\frac{dv}{dt} \leqslant \frac{k_x\lambda_x}{d_x}+\frac{k_z\lambda_z}{d_z} - uv = 0.$$

Therefore, solutions starting in Ω will remain there for $t \geqslant 0$.

Attractiveness. Since $d_x \leqslant a_y$ and $d_z \leqslant a_w$, we have

$$\frac{d}{dt}(x+y) \leqslant \lambda_x - d_x(x+y),$$

and

$$\frac{d}{dt}(z+w) \leqslant \lambda_z - d_z(z+w).$$

Therefore

$$\limsup_{t\to\infty}(x+y)(t) \leqslant \frac{\lambda_x}{d_x},$$
$$\limsup_{t\to\infty}(z+w)(t) \leqslant \frac{\lambda_z}{d_z}.$$

Similarly, we prove that $v(t)$ approaches v_M if $v > v_M$. Hence, Ω is attracting, that is, all solutions of (3.3) eventually enters Ω. □

Thus, in Ω the model (3.3) is well-posed epidemiologically and mathematically. Hence, it is sufficient to study the dynamics of the basic model with initial data from Ω.

4. Existence and stability of equilibria

4.1. Disease-free equilibrium (DFE)

The (LVB) model (3.3) has a DFE given by,

$$I_0 = (\bar{x},0,0,0,\bar{z}) = \left(\frac{\lambda_x}{d_x},0,0,0,\frac{\lambda_z}{d_z}\right),$$

in which there is no infection.

Let R_0 be given by

$$R_0 = \frac{k_x}{a_y}\frac{\beta_x\bar{x}}{u+\beta_z\bar{z}+\beta_x\bar{x}} + \frac{k_z}{a_w}\frac{\beta_z\bar{z}}{u+\beta_z\bar{z}+\beta_x\bar{x}}. \tag{4.4}$$

The threshold parameter R_0 defined by (4.4) is called the basic reproductive ratio, and is defined as the average number of secondary infections produced when one infected individual is introduced into a host virgin population [8,9,16]. The value of this parameter plays a central role in the dynamics of system (3.3) with important implications in the treatment of HBV/HCV. The parameter R_0 has an interesting biological meaning. Assume that one infectious virion is introduced into a healthy organism with $\bar{x}$ healthy liver cells and $\bar{z}$ healthy blood cells. This virion then produces, on average, $\frac{\beta_x\bar{x}}{u+\beta_z\bar{z}+\beta_x\bar{x}}$ infected liver cells and $\frac{\beta_z\bar{z}}{u+\beta_z\bar{z}+\beta_x\bar{x}}$ infected blood cells during its lifespan. Since each infected liver cell and (respectively) infected blood cell produces $\frac{k_x}{a_y}$ virions and (respectively) $\frac{k_z}{a_w}$ virions during its lifespan, $(\frac{k_x}{a_y}\frac{\beta_x d_x\bar{x}}{ud_z+\lambda_z\beta_z+\beta_x d_z\bar{x}} + \frac{k_z}{a_w}\frac{\beta_z d_x\bar{z}}{ud_x+\lambda_x\beta_x+\beta_z d_x\bar{z}}) = R_0$ is the average number of new virions produced by an initial virion in a healthy organism.

In what follows, we show the role of R_0 in the study of the stability properties of the uninfected equilibrium I_0.

Theorem 2. *The disease-free equilibrium is locally asymptotically stable for $R_0 < 1$ and unstable for $R_0 > 1$.*

Proof. The local stability of I_0 is governed by the eigenvalues of the Jacobian matrix, of system (3.3),

$$J(I_0) = \begin{pmatrix} -d_x & 0 & -\beta_x\frac{\lambda_x}{d_x} & 0 & 0 \\ 0 & -a_y & -\beta_x\frac{\lambda_x}{d_x} & 0 & 0 \\ 0 & k_x & u-\beta_x\frac{\lambda_x}{d_x}-\beta_z\frac{\lambda_z}{d_z} & 0 & k_z \\ 0 & 0 & -\beta_z\frac{\lambda_z}{d_z} & -d_z & 0 \\ 0 & 0 & \beta_z\frac{\lambda_z}{d_z} & 0 & -a_w \end{pmatrix}, \tag{4.5}$$

which clearly are $-d_x$ and $-d_z$ and the roots of the following equation:

$$\delta(\lambda) = \lambda^3 + \alpha_1\lambda^2 + \alpha_2\lambda + \alpha_3, \tag{4.6}$$

where

$$\alpha_1 = \frac{a_y d_x d_z + a_w d_x d_z + u d_x d_z + \beta_x\lambda_x d_z + \beta_z\lambda_z d_x}{d_x d_z},$$
$$\alpha_2 = \frac{(a_y d_x d_z + a_w d_x d_z)u + a_y a_w d_x d_z + a_y\beta_z\lambda_z d_x + a_w\beta_x\lambda_x d_z}{d_x d_z} + \frac{(a_y - k_x)\beta_x\lambda_x d_z + (a_w - k_z)\beta_z\lambda_z d_x}{d_x d_z},$$
$$\alpha_3 = \frac{-k_x\beta_x\lambda_x d_z a_w - k_z\beta_z\lambda_z d_x a_y + u d_x d_z a_y a_w + \lambda_x\beta_x d_z a_y a_w + \lambda_z\beta_z d_x a_y a_w}{d_x d_z}.$$

We can see that

$$\alpha_3 = \frac{u d_x d_z a_y a_w + \lambda_x\beta_x d_z a_y a_w + \lambda_z\beta_z d_x a_y a_w}{d_x d_z}(1 - R_0), \tag{4.7}$$

and

$$a_y a_w\alpha_2 - (a_y + a_w)\alpha_3 = \frac{a_y^2 a_w^2 d_x d_z + a_y^2 k_z\beta_z\lambda_z d_x + a_w^2 k_x\beta_x\lambda_x d_z}{d_x d_z}. \tag{4.8}$$

It follows that, for $R_0 < 1$, the coefficients of the polynomial (4.6) are positive. Using the Routh–Hurwitz criteria, the local stability of the uninfected equilibrium I_0 will be established if we show that

$$\alpha_1\alpha_2 - \alpha_3 > 0. \tag{4.9}$$

Note that $\alpha_1 > a_y + a_w$. Using this and (4.8) we find that

$$\alpha_1\alpha_2 > (a_y + a_w)\alpha_2 > \frac{(a_y + a_w)^2}{a_y a_w}\alpha_3 > \alpha_3.$$

Therefore I_0 is locally asymptotically stable for $R_0 < 1$.

For $R_0 \geqslant 1$ or equivalently $\alpha_3 < 0$, we have $\delta(0) < 0$ and $\lim \delta(\lambda) \to +\infty$ when $\lambda \in \mathbb{R}$ and $\lambda \to +\infty$. Then, there exists $\lambda^* > 0$ such that $\delta(\lambda^*) = 0$, which proves the instability of the disease-free equilibrium. □

A global stability result for the DFE I_0 is given below.

Theorem 3. *Assume that $R_0 \leqslant 1$ and $(k_x - a_y)(k_z - a_w) \geqslant 0$. Then, the uninfected steady state I_0 of system (3.3) is unique and globally asymptotically stable in the region Ω.*

Proof. To prove this, we use the Lyapunov function

$$U(x, y, v, z, w) = k_x y + a_y v + \frac{a_y k_z}{a_w} w.$$

The orbital derivative of U is given by

$$\dot{U} = (k_x - a_y)\beta_x x v + a_y\left(\frac{k_z}{a_w} - 1\right)\beta_z z v - a_y u v = \left((k_x - a_y)\beta_x x + a_y\left(\frac{k_z}{a_w} - 1\right)\beta_z z - a_y u\right)v.$$

Then $\dot{U} \leqslant 0$ when $k_x - a_y \leqslant 0$ and $k_z - a_w \leqslant 0$. If $k_x - a_y \geqslant 0$ and $k_z - a_w \geqslant 0$, since $x \leqslant \frac{\lambda_x}{d_x}$ and $z \leqslant \frac{\lambda_z}{d_z}$, we obtain

$$\dot{U} \leqslant -\frac{u d_x d_z a_y a_w + \lambda_x\beta_x d_z a_y a_w + \lambda_z\beta_z d_x a_y a_w}{d_x d_z a_w}(1 - R_0)v,$$

which is negative for $R_0 \leqslant 1$. Therefore, $\dot{U} \leqslant 0$ in Ω.

The subset where $\dot{U} = 0$ is defined by the following two cases:

(i) If $R_0 < 1$, then $v = 0$;
(ii) If $R_0 = 1$, then $v = 0$ or $(k_x - a_y)\beta_x x + a_y(\frac{k_z}{a_w} - 1)\beta_z z - a_y u = 0$.

From system (3.3), it can be seen that the maximum invariant set contained in $\dot{U} = 0$ is the plane $v = 0,\ y = 0,\ w = 0$. In this set, system (3.3) is given by

$$\frac{dx}{dt} = \lambda_x - d_x x,$$
$$\frac{dy}{dt} = \frac{dw}{dt} = \frac{dv}{dt} = 0,$$
$$\frac{dz}{dt} = \lambda_z - d_z z,$$

which implies that solutions started at $v = 0,\ y = 0,\ w = 0$ tend to the equilibrium I_0 as t goes to infinity. Therefore, applying the LaSalle–Lyapunov Invariance Principal in [15], it follows that I_0 is locally stable and all trajectories starting in Ω approach I_0. □

5. Endemic equilibria and bifurcation behavior

In order to find endemic equilibria of the (LVB) system (that is, equilibria where at least one of the infected components of the model (3.3) is non-zero), the following steps are taken.

Let $I^* = (x^*, y^*, v^*, z^*, w^*)$ represent any arbitrary endemic equilibrium of the model (3.3). Solving the equations in (3.3) at steady state gives

$$x^* = \frac{\lambda_{x^*}}{\beta_x v^* + d_x}, \quad y^* = \frac{\beta_x\lambda_{x^*} v^*}{(\beta_x v^* + d_z)a_y}, \quad z^* = \frac{\lambda_{z^*}}{\beta_z v^* + d_z},$$
$$w^* = \frac{\beta_z\lambda_{z^*} v^*}{(\beta_z v^* + d_z)a_w}.$$

If $v^* \neq 0$, then substituting $x^*,\ y^*,\ z^*$ and w^* in the third equation of (3.3) at steady state, we obtain after some calculations that v^* must satisfy the following quadratic equation:

$$h(v^*) = A v^{*2} + B v^* + C = 0, \tag{5.10}$$

where

$$A = u\beta_x\beta_z, \tag{5.11}$$
$$B = u d_z\beta_x + u d_x\beta_z + \lambda_x\beta_x\beta_z\left(1 - \frac{k_x}{a_y}\right) + \lambda_z\beta_x\beta_z\left(1 - \frac{k_z}{a_w}\right), \tag{5.12}$$
$$C = u d_x d_z + \lambda_x\beta_x d_z\left(1 - \frac{k_x}{a_y}\right) + \lambda_z\beta_z d_x\left(1 - \frac{k_z}{a_w}\right). \tag{5.13}$$

We state the following Lemma.

Lemma 4. *The endemic equilibrium, when it exists, belongs to the positively invariant subset Ω.*

Proof. Using relations $d_x \leqslant a_y$ and $d_z \leqslant a_w$, we see that if (5.10) has a solution, v^*, then $0 < v^* < v_M$. In fact,

$$h(v_M) = A v_M^2 + B v_M + C > 0, \tag{5.14}$$

and

$$\dot{h}(v_M) = 2A v_M + B > 0. \tag{5.15}$$

Thus, the endemic equilibrium, whenever there exists, is given by

$$I^* = (x^*, y^*, v^*, z^*, w^*) = \left(\frac{\lambda_x}{\beta_x v^* + d_x}, \frac{\beta_x\lambda_x v^*}{(\beta_x v^* + d_x)a_x}, v^*, \frac{\lambda_z}{\beta_z v^* + d_z}, \frac{\beta_z\lambda_z v^*}{(\beta_z v^* + d_z)a_z}\right).$$

and belongs to the positively invariant subset Ω. □

Since $A > 0$, the existence of the positive solutions of Eq. (5.10) will depend on the signs of B and C. Note that C is given by

$$C = \frac{u d_x d_z + \lambda_x\beta_x d_z + \lambda_z\beta_z d_x}{d_x d_z}(1 - R_0) \tag{5.16}$$

and, thus, $C < 0$ is equivalent to $R_0 > 1$.

One can show that $C > 0$ and $B < 0$ can occur for some parameter values and thus, we have the following result.

Theorem 5. *The system (3.3) has:*

(i) *a unique endemic equilibrium in Ω if $C < 0 \iff R_0 > 1$;*
(ii) *a unique endemic equilibrium in Ω if $B < 0$, and $C = 0$ or $B^2 - 4AC = 0$;*
(iii) *two endemic equilibria in Ω if $C > 0$, $B < 0$ and $B^2 - 4AC > 0$;*
(iv) *no endemic equilibrium otherwise.*

Remark 6. Notice that

$$a_y a_w d_x d_z B = a_y a_w(\beta_x d_z + \beta_z d_x)C + \beta_x d_z^2 \lambda_x\left(\frac{k_x}{a_y} - 1\right) + \beta_z d_x^2 \lambda_z\left(\frac{k_z}{a_w} - 1\right).$$

Thus, $B \geqslant 0$ when $C \geqslant 0$, $k_x - a_y \geqslant 0$ and $k_z - a_w \geqslant 0$. Furthermore, from (5.12) and (5.13), $B \geqslant 0$ and $C \geqslant 0$ for $k_x - a_y \leqslant 0$ and $k_z - a_w \leqslant 0$. Hence, system (3.3) has no endemic equilibrium if $R_0 \leqslant 1$ and $(k_x - a_y)(k_z - a_w) \geqslant 0$.

Many epidemiological models have defined a threshold condition that indicates whether an infection introduced into a population will be eliminated or become endemic [1]. In models with only two steady states and a transcritical bifurcation, $R_0 > 1$ implies that the endemic state is stable (i.e., the infection persists), and $R_0 \leqslant 1$ implies that the uninfected state is stable (i.e., the infection is eliminated).

Bifurcation analysis of the basic model (2.2) exhibits only the usual transcritical bifurcation. However, since multiple non-negative steady states occur for values of $R_0 \leqslant 1$ and close to one for (3.3) this may not be the case (see case (iii) in Theorem 5). In the following, we show that system (3.3) undergoes two possible options of bifurcation, shown in Figs. 2 and 3, depending on the parameters chosen.

5.1. Transcritical bifurcation of the endemic equilibrium

Remark 6 indicates the uniqueness of the DFE when $k_x \geqslant a_y$, $k_z \geqslant a_w$ and $R_0 \leqslant 1$. For $R_0 > 1$, the equilibrium I_0 becomes an unstable hyperbolic point, and the endemically infected

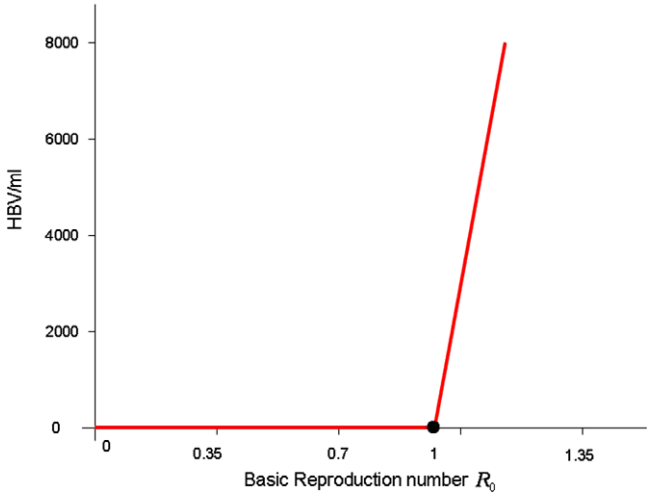

Fig. 2. *Forward (transcritical) bifurcation.* Endemic states exist only above the critical basic reproduction number $R_0 = 1$.

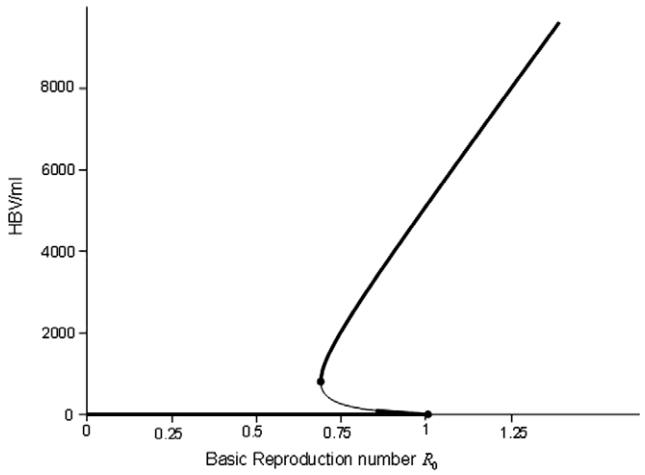

Fig. 3. *Backward bifurcation.* Bifurcation branch with turning point. Endemic states exist below the critical basic reproduction number $R_0 = 1$.

equilibrium, I^* emerges in the region Ω. The local stability of I^* is given by the Jacobian, $J(I^*)$, of (3.3) evaluated in this point

$$J(I^*) = \begin{pmatrix} -\frac{\lambda_x}{x^*} & 0 & -\beta_x x^* & 0 & 0 \\ \beta_x v^* & -a_y & -\beta_x x^* & 0 & 0 \\ -\beta_x v^* & k_x & \frac{1}{v^*}(k_x y^* + k_z w^*) & -\beta_z z^* & k_z \\ 0 & 0 & \beta_z z^* & -\frac{\lambda_z}{z^*} & 0 \\ 0 & 0 & \beta_z z^* & \beta_z v^* & -a_w \end{pmatrix}.$$

In the following, we discuss the existence of a transcritical bifurcation of the positive steady state when $k_x \geqslant a_y$, $k_z \geqslant a_w$ and $R_0 = 1$.

Note that, when $k_x \geqslant a_y$ and $k_z \geqslant a_w$, $R_0 > 1$ is equivalent to

$$0 < u < \bar{u} := \frac{\lambda_x \beta_x d_z\left(1 - \frac{k_x}{a_y}\right) + \lambda_z \beta_z d_x\left(1 - \frac{k_z}{a_w}\right)}{d_x d_z}. \tag{5.17}$$

The next lemma will be useful to analyze the eigenvalues of $J(I^*)$.

Lemma 7. *Let M be an $n \times n$ square matrix. Write M as*

$$M = \begin{pmatrix} N & Q \\ R & e \end{pmatrix},$$

where N is an $(n-1) \times (n-1)$ square matrix, Q is a column vector, R is a row vector and $e \in \mathbb{R}$. If $e \neq 0$, then

$$\det(M) = \frac{1}{(e)^{n-2}} \det(\widetilde{M}),$$

where $\widetilde{M}$ is the $(n-1) \times (n-1)$ matrix

$$\widetilde{M} = eN - QR.$$

Proof. The result follows from the formula

$$\begin{pmatrix} N & Q \\ R & e \end{pmatrix}\begin{pmatrix} eI_{n-1} & 0 \\ -R & 1 \end{pmatrix} = \begin{pmatrix} \widetilde{M} & Q \\ 0 & e \end{pmatrix}. \qquad \square$$

Applying Lemma 7 twice to matrix $\lambda I - J(I^*)$, the associated characteristic equation, denoted by $\Delta(\lambda, u)$, is given by

$$\Delta(\lambda, u) = -Q_1\left(\frac{\lambda_x}{x^*} + \lambda\right)(a_y + \lambda)(a_w + \lambda) - Q_2\left((a_y + \lambda)\beta_x v^* + d_y k_x + \lambda k_x\right), \tag{5.18}$$

where

$$Q_1 = \left(\left((a_w+\lambda)\left(\frac{1}{v^*}(k_x y + k_z w)\right) - z^*\beta_z k_z\right)\left(\frac{\lambda_z}{z^*}+\lambda\right) + (a_w+\lambda-k_z)\beta_z^2 z^* v^*\right),$$

$$Q_2 = (a_w+\lambda)\left(\frac{\lambda_z}{z^*}+\lambda\right)\beta_x x^*.$$

Taking account of the third equation of system (3.3) evaluated at the equilibrium I^*, we obtain

$$a_w\frac{k_x y^* + k_z w^*}{v^*} = \frac{a_w k_x \beta_x \lambda_x}{a_y(\beta_x v^* + d_y)} + z^*\beta_z k_z.$$

Then

$$a_w\frac{k_x y^* + k_z w^*}{v^*} - z^*\beta_z k_z = \frac{a_w k_x \beta_x}{a_y}x^*$$

and Q_1 becomes

$$Q_1 = \lambda\left(\frac{k_z\beta_z}{a_w}z^* + \frac{k_x\beta_x}{a_y}x^* + \lambda + a_w\right)\left(\frac{\lambda_z}{z^*}+\lambda\right) + \lambda\frac{a_w k_x\beta_x}{a_y}x^* + \lambda\beta_z^2 z^* v^* + \left(\frac{a_w k_x\beta_x\lambda_z}{a_y}\frac{x^*}{z^*} + (a_w-k_z)\beta_z^2 z^* v^*\right). \quad (5.19)$$

Next, we will show that, for positive parameter u and close to $\bar{u}$, which is defined in (5.17), the endemic equilibrium is stable. To prove this, the following lemma is used, which is the consequence the of continuity of principal eigenvalues of the matrices on the parameters.

Lemma 8. *Let $Z(\mu)$ be a $2n\times 2n$ real matrix satisfying the following conditions:*

(i) *$Z(\mu)$ is continuous fo μ close to μ_0;*
(ii) *$Z(\mu_0)$ has a zero eigenvalue, which is simple, and all other eigenvalues of $Z(\mu_0)$ have negative real parts.*

If $\det(Z(\mu))>0$, then all eigenvalues of $Z(\mu)$ have negative real parts, while if $\det(Z(\mu))<0$, then $Z(\mu)$ has a positive eigenvalue, where $|\mu-\mu_0|$ is sufficiently small.

It follows from Lemma 7 that

$$\det(\lambda I - J(I^*)) = (\lambda + a_w)\det(\lambda I - Z(u)), \quad (5.20)$$

where $Z(u)$ is the following 4×4 square submatrix

$$Z(u) = \begin{pmatrix} -\frac{\lambda_x}{x*} & 0 & -\beta_x x^* & 0 \\ \beta_x v^* & -a_y & -\beta_x x^* & 0 \\ -\beta_x v^* & k_x & \frac{k_x y^* k_z w^*}{v^*} + z^*\beta_z k_z & -\beta_z v^* + k_z\beta_z v^* \\ 0 & 0 & -\beta_z z^* & -\frac{\lambda_z}{z*} \end{pmatrix}.$$

Then one eigenvalue of $J(I^*)$ is $-a_w$ and the rest of the eigenvalues are those of the matrix Z. Now we will use Lemma 8 to determine the sign of the eigenvalues of Z.

The matrix $Z(\bar{u})$ is given by

$$Z(\bar{u}) = \begin{pmatrix} -d_x & 0 & -\beta_x\frac{\lambda_x}{d_x} & 0 \\ 0 & -a_y & -\beta_x\frac{\lambda_x}{d_x} & 0 \\ 0 & k_x & \frac{\beta_x k_x\lambda_x}{a_y d_x} & 0 \\ 0 & 0 & -\beta_z\frac{\lambda_z}{d_z} & -d_z \end{pmatrix},$$

and its eigenvalues satisfy

$$\delta(\lambda) = \lambda(d_x+\lambda)(d_x+\lambda)\left(\frac{\beta_x k_x\lambda_x}{a_y d_x}+\lambda\right). \quad (5.21)$$

Then $\lambda=0$ is a simple eigenvalue for the matrix $Z(\bar{u})$ and all other eigenvalues have negative real parts. Then, Lemma 8implies the local stability of I^* if $\det(Z(u))>0$. From (5.20) is equivalent to $\det J(I^*)<0$. Notice that v^* converges to zero when u converge to $\bar{u}$. Hence, Q_1 given by (5.19) is positive. Furthermore, for R_0 near 1, we deduce from (5.18) that $\det J(I^*) = \Delta(0,u)<0$. Therefore, the local stability of I^* is given by the following theorem.

Theorem 9. *Assume that $k_x \geqslant a_y$ and $k_z \geqslant a_w$. When $R_0=1$, the endemically infected state I^* undergoes a transcritical bifurcation, that is for $R_0>1, R_0$ close to 1, the positive steady state is locally asymptotically stable whereas the trivial steady state (DFE) is unstable, and for $R_0\leqslant 1$ the trivial steady state (DFE) is locally asymptotically stable and is the only steady state of (3.3).*

The epidemiological implication of Theorem 9 is that, in general, when R_0 is less than unity, a small influx of virus particles into the liver and the blood will not generate a large outbreak, and the disease will die out in time (since the DFE is globally asymptotically stable). Furthermore, the will disease persist when R_0 is larger then unity (Fig. 2). However, we show in the next subsection that the disease may still persist even when $R_0<1$.

5.2. Backward bifurcation

Case (iii) of Theorem 6 indicates the possibility of a backward bifurcation (where the locally-asymptotically stable DFE co-exists with a locally-asymptotically endemic equilibrium when $R_0<1$). To check for this, the discriminant B^2-4AC is set to be zero and solved for the critical value of R_0, denoted R_c, given by

$$R_c = 1 - \frac{a_y a_w B^2}{4A(ud_x d_z + \lambda_z\beta_z d_x + \lambda_x\beta_x d_z)}.$$

Thus, $R_c<R_0$ is equivalent to $B^2-4AC>0$ and, therefore, backward bifurcation would occur for values of R_0 such that $R_c<R_0<1$.

Consider the case when $R_0=1$. Let $\overline{k_x}$ be given by

$$\overline{k_x} := \frac{a_y(ud_x d_z a_w + \lambda_x\beta_z d_x(a_w-k_z) + \lambda_x\beta_x d_z a_w)}{\lambda_x\beta_x d_z a_w}.$$

We state and prove the following result.

Theorem 10. *Assume that $(k_z-a_w)(k_x-a_y)<0$. The LVB model (3.3) exhibits a backward bifurcation when the coefficient a defined by*

$$p = \frac{\lambda_x\beta_x^2}{d_x^2}\left(1-\frac{\overline{k_x}}{a_y}\right) + \frac{\lambda_z\beta_z^2}{d_z^2}\left(1-\frac{k_z}{a_w}\right)$$

is negative.

If $(k_z-a_w)(k_x-a_y)\geqslant 0$, then the LVB model (3.3) does not undergo a backward bifurcation.

Proof. The proof is based on the center manifold theory. To apply this method, the following simplification and change of variables are made on the LVB model (3.3). First of all, let $x_1=x,\ x_2=y,\ x_3=v,\ x_4=z,\ x_5=w$. Further, by using the vector notation $X=(x_1,x_2,x_3,x_4,x_5)^T$, the system (3.3) can be written in the form $\frac{dX}{dt}=(f_1,f_2,f_3,f_4,f_5)^T$ as follows:

$$\begin{aligned} \frac{dx_1}{dt} &= f_1 = \lambda_x - \beta_x x_1 x_3 - d_x x_1, \\ \frac{dx_2}{dt} &= f_2 = \beta_x x_1 x_3 - a_y x_2, \\ \frac{dx_3}{dt} &= f_3 = k_x x_2 + k_z x_5 - u x_3 - \beta_x x_1 x_3 - \beta_z x_4 x_3, \\ \frac{dx_4}{dt} &= f_4 = \lambda_z - \beta_z x_4 x_3 - d_z x_4, \\ \frac{dx_5}{dt} &= f_5 = \beta_z x_4 x_3 - a_w x_5. \end{aligned} \quad (5.22)$$

Assume that $(k_z - a_w)(k_x - a_y) < 0$. Without loss of generality, we consider the case when $k_z < a_w$ and $k_x > a_y$. Choose k_x as a bifurcation parameter (the case when $k_z < a_w$ and $k_x > a_y$ is similar by taking k_z as a bifurcation parameter). Solving $R_0 = 1$ gives

$$k_x = \overline{k_x} := \frac{a_y(ud_xd_za_w + \lambda_x\beta_zd_x(a_w - k_z) + \lambda_x\beta_xd_za_w)}{\lambda_x\beta_xd_za_w}.$$

Let J_0 denote the Jacobian of the system (3.3), evaluated at the DFE I_0 with $k_x = \overline{k_x}$,

$$J_0 = \begin{pmatrix} -d_x & 0 & -\beta_x\frac{\lambda_x}{d_y} & 0 & 0 \\ 0 & -a_y & -\beta_x\frac{\lambda_x}{d_y} & 0 & 0 \\ 0 & k_x & u - \beta_x\frac{\lambda_x}{d_y} - \beta_z\frac{\lambda_z}{d_w} & 0 & k_z \\ 0 & 0 & -\beta_z\frac{\lambda_z}{d_w} & -d_z & o \\ 0 & 0 & \beta_z\frac{\lambda_z}{d_w} & 0 & -a_w \end{pmatrix}.$$

Let

$$\delta(\lambda) = \lambda(\lambda + d_z)(\lambda + d_x)(\lambda^2 + \alpha_1\lambda + \alpha_2), \tag{5.23}$$

where

$$\alpha_1 = \frac{a_yd_xd_z + a_wd_xd_z + ud_xd_z + \beta_x\lambda_xd_z + \beta_z\lambda_zd_x}{d_xd_z},$$

$$\alpha_2 = \frac{(a_yd_xd_z + a_wd_xd_z)u + a_ya_wd_xd_z + a_y\beta_z\lambda_zd_x + a_w\beta_x\lambda_xd_z}{d_xd_z} + \frac{(a_y - k_x)\beta_x\lambda_xd_z + (a_w - k_z)\beta_z\lambda_zd_x}{d_xd_z}.$$

Thus, the Jacobian J_0 of the linearized system has a simple zero eigenvalue and all the other eigenvalues have negative real parts. Hence, the center manifold theory [2,3,6] can be used to analyze the dynamics of the system (3.3). In particular, a theorem in [4], reproduced in the appendix for convenience, will be used.

For the case when $R_0 = 1$, it can be shown that the J_0 has a right eigenvector (corresponding to the zero eigenvalue), given by $w = [w_1, w_2, w_3, w_4, w_5]^T$, where

$$w_1 = -\frac{\beta_x\lambda_x}{d_x^2}w_3, \quad w_2 = \frac{\beta_x\lambda_x}{a_yd_x}w_3, \quad w_3 = w_3,$$
$$w_4 = -\frac{\beta_z\lambda_z}{d_z^2}w_3, \quad w_5 = \frac{\beta_z\lambda_z}{a_wd_z}w_3. \tag{5.24}$$

Similarly, the components of the left eigenvector of J_0 (corresponding to the zero eigenvalue), denoted by $w = [w_1, w_2, w_3, w_4, w_5]^T$, are given by

$$v_1 = 0, \quad v_2 = \frac{k_x}{a_y}v_3, \quad v_3 = v_3, \quad v_4 = 0, \quad v_5 = \frac{k_z}{a_w}x_3. \tag{5.25}$$

Let a and b be the coefficients defined as in Theorem 11 (see Appendix A).

Computation of a. For the transformed model (3.3), the associated non-zero partial derivatives of f (evaluated at the DFE I_0) are given by

$$\frac{\partial^2f_1}{\partial x_1\partial x_3} = -\beta_x, \quad \frac{\partial^2f_2}{\partial x_1\partial x_3} = \beta_x, \quad \frac{\partial^2f_3}{\partial x_1\partial x_3} = -\beta_x,$$
$$\frac{\partial^2f_3}{\partial x_3\partial x_4} = -\beta_z, \quad \frac{\partial^2f_4}{\partial x_3\partial x_4} = -\beta_z, \quad \frac{\partial^2f_5}{\partial x_3\partial x_4} = \beta_z. \tag{5.26}$$

Using the expressions in Eqs. 5.24, 5.25 and 5.26, it follows that

$$a = \left(-\frac{\overline{k_x}\lambda_x\beta_x^2}{a_yd_x^2} + \frac{\lambda_x\beta_x^2}{d_x^2} - \frac{\overline{k_z}\lambda_z\beta_x^2}{a_wd_z^2} + \frac{\lambda_z\beta_z^2}{d_z^2}\right)v_3w_3^2$$
$$= \frac{\lambda_x\beta_x^2}{d_x^2}\left(1 - \frac{\overline{k_x}}{a_y}\right)v_3w_3^2 + \frac{\lambda_z\beta_z^2}{d_z^2}\left(1 - \frac{k_z}{a_w}\right)v_3w_3^2. \tag{5.27}$$

Computation of b. Substituting the vectors v and w and the respective partial derivatives (evaluated at the DFE I_0) into the expression

$$b = \sum_{k,i=1}^{5} v_kw_i\frac{\partial^2f_k}{\partial x_i\partial k_x}(0,0),$$

gives $b = v_3w_2 > 0$. Since the coefficient b is automatically positive, it follows from Theorem 11 that the LVB (3.3) will undergo backward bifurcation if the coefficient a, given by (5.27), is negative (Fig. 3).

Now, if $(k_z - a_w)(k_x - a_y) \geqslant 0$ then, for $R_0 \leqslant 1$, Theorem 3 indicates that the uninfected steady state I_0 of system (3.3) is unique and globally asymptotically stable and, therefore, no backward bifurcation occurs in this case. This completes the proof. □

6. Discussion

In this paper, a mathematical model for HBV/HCV that explores the interaction of viral particles in both the liver and the blood is developed. We have found that the LVB model is well-posed and useful for the description of hepatitis infection dynamics. The analysis of the LVB model (3.3) is quite extensive and involved. The model has both a disease-free equilibrium and endemic state, similar to the basic model. However, a backward bifurcation can take place. The existence of a backward bifurcation is an interesting artifact since this means that the disease cannot be eradicated by simply reducing the value of the basic reproduction number R_0 below 1. This can have important implications on drug therapy protocols, since it sheds light on possible control mechanisms for disease eradication.

For example, the conditions for the backward bifurcation ($(k_z - a_w)(k_x - a_y) < 0$) demonstrate that variable efficacy of therapy may sustain infection. Suppose that $k_z = (1 - \epsilon_z)k_z$ and that $k_x = (1 - \epsilon_x)k_x$, where $0 < \epsilon_x < 1$ and $0 < \epsilon_z < 1$ represent the efficacy of drug therapy on viral production in the liver and the blood respectively. It is possible that drug therapy may be effective at reducing $k_x < a_y$ in the liver, but may not be successful in reducing $k_z < a_w$ and therefore, the virus can not be eradicated (see Theorem 10). This demonstrates that drug therapies must be accompanied by testing virus production in both the liver and the blood in order to fully determine if the drug will be fully effective.

It is well known that HBV or HCV liver transplant patients will ultimately incur infection in the liver again [21,28]. This may be due to the variable efficacy of drug therapy in either the liver or blood compartments as discussed above. Unexpectedly, using PEGylated IFN drug before liver transplantation and five weeks after PEG-IFN treatment, clearance of hepatitis C for a patient was achieved just one month after the successful liver transplantation [20]. In a future project, we shall use the LVB model to predict the levels of infection in target cells in the blood that are needed to reinfect the liver under timescales observed in transplant patients. This prediction will be helpful to study the impact of antiviral therapy and post-liver transplantation on viral eradication and will aid in determining the efficacy of drug therapy that is needed in a transplant patient in both the liver and the blood so that viral clearance can be achieved.

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Appendix A

Theorem 11 (Castillo-Chavez and Song [3]). *Consider the following general system of ordinary differential equations with a parameter ϕ,*

$$\frac{dx}{dt} = f(x,\phi), \quad f:\mathbb{R}^n\times\mathbb{R}\to\mathbb{R}, \quad \text{and} \quad f\in\mathbb{C}^2(\mathbb{R},\mathbb{R}). \tag{6.28}$$

Without loss of generality, it is assumed that 0 is an equilibrium for system (5.22) for all values of the parameter ϕ, (that is $f(0,\phi)=0$ for all ϕ). Assume

(A1): *$A = D_x f(0,0) = (\frac{\partial f}{\partial x_j}, 0, 0)$ is the linearized matrix of system (5.22) around the equilibrium 0 with ϕ evaluated at 0: zero is a simple eigenvalue of A and all other eigenvalue of A have negative real parts;*

(A2): *Matrix A has a non-negative right eigenvector w and a left eigenvector v corresponding to the zero eigenvalue.*

Let f_k be the kth component of f and

$$a = \sum_{k,i,j=1}^{n} v_k w_i w_j \frac{\partial f_k^2}{\partial x_i \partial x_j}(0,0),$$

$$b = \sum_{k,j=1}^{n} v_k w_j \frac{\partial f_k^2}{\partial x_i \partial \phi}(0,0).$$

The local dynamics of system (5.22) around 0 are totally determined by a and b.

(i) *In the case where $a>0, b>0$, we have that when $\phi<0$ with $|\phi|$ close to zero, 0 is locally asymptotically stable and there exists a positive unstable equilibrium; when $0<\phi\ll 1$, 0 is unstable and there exists a negative and locally asymptotically stable equilibrium;*

(ii) *In the case where $a<0,\ b<0$, we have that when $\phi<0$ with $|\phi|$ close to zero, 0 is unstable; when $0<\phi\ll 1$, 0 is locally asymptotically stable, and there exists a positive unstable equilibrium;*

(iii) *In the case where $a>0,\ b<0$, we have that when $\phi<0$ with $|\phi|$ close to zero, 0 is unstable and there exists a locally asymptotically stable negative equilibrium; when $0<\phi\ll 1$, 0 is stable and a positive unstable equilibrium appears;*

(iv) *In the case where $a<0,\ b>0$, we have that when ϕ changes from negative to positive, 0 changes its stability from stable to unstable. Correspondingly a negative unstable equilibrium becomes positive and locally asymptotically stable. Particularly, if $a>0$ and $b>0$, then a backward bifurcation occurs at $\phi=0$.*

References

[1] F. Brauer, C. Castillo-Chávez, Mathematical Models in Population Biology and Epidemiology, Texts in Applied Mathematics, Springer, New York, NY, 2001.

[2] M. Berenguer, M. Prieto, F. San Juan, J.M. Rayon, F. Martinez, D. Carrasco, et al., Contribution of donor age to the recent decrease in patient survival among HCV-infected liver transplant recipients, Hepatology 36 (2002) 202.

[3] J. Carr, Applications of centre manifolds, in: Applied Mathematical Sciences, Springer, NY, USA, 1981, p. 35.

[4] C. Castillo-Chávez, B. Song, Dynamical models of tuberculosis and their applications, Math. Biosci. Eng. 1 (2) (2004) 361.

[5] H. Dahari, A. Feliu, M. Garcia-Retortillo, X. Forns, A.U. Neumann, Second hepatitis C replication compartment indicated by viral dynamics during liver transplantation, J. Hepatol. 42 (2005) 491.

[6] S.E. Davies, B.C. Portmann, O'J.G. Grady, P.M. Aldis, K. Chaggar, G.J. Alexander, et al., including an unique pattern of fibrosing cholestatic hepatitis, Hepatology 13 (1991) 150.

[8] O. Diekmann, J.A.P. Heesterbeek, J.A.J. Metz, On the definition and computation of the basic reproduction ratio R_0 in models for infections diseases in heterogeneous populations, J. Math. Biol. 28 (1990) 365.

[9] P. van den Driessche, J. Watmough, Reproduction number and sub-threshold endemic equilibria for compartmental models of disease transmission, Math. Biosci. 180 (2002) 29.

[10] Z. Feng, C. Castillo-Chavez, A. Capurro, A model for tuberculosis with exogenous reinfection, Theor. Populat. Biol. 57 (2000) 235.

[11] M.W. Fried, M.L. Shiffman, K.R. Reddy, C. Smith, G. Marinos, F.L. Goncales Jr., D. Haussinger, M. Diago, G. Carosi, D. Dhumeaux, A. Craxi, A. Lin, J. Hoffman, J. Yu, Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection, N. Engl. J. Med. 347 (2002) 975.

[12] J.G. O'Grady, H.M. Smith, S.E. Davies, H.M. Daniels, P.T. Donaldson, K.C. Tan, et al., J. Hepatol. 14 (1992) 104.

[13] L. Grellier, D. Multimer, M. Ahmed, et al., Lamivudine prophylaxis against reinfection in liver transplantation for hepatitis B cirrhosis, Lancet 1 (1996) 1212.

[14] K. Hadeler, P. van den Driessche, Backward bifurcation in epidemic control, Math. Biosci. 146 (1997) 15.

[15] J.K. Hale, Ordinary Differential Equations, Wiley, New York, 1969.

[16] J.M. Heffernan, R.J. Smith, L.M. Wahl, Perspectives on the basic reproductive ratio, J.R. Soc. Interf. 2 (2005) 281.

[17] J.M. Heffernan, L.M. Wahl, Monte Carlo estimates of natural variation in HIV infection, J. Theor. Biol. 236 (2005) 137.

[18] F.B. Hollinger, T.J. Liang, Hepatitis B virus, in: D.M. Knipe, P.M. Howley (Eds.), Fields Virology, vol. 2, Lippincott Williams and Wilkins, Philadelphia, PA, 2001, p. 2971.

[19] K.K. Holmes, P.F. Sparling, W.E. Stamm, P. Piot, J.N. Wasserheit, L. Corey, M.S. Cohen, D.H. Watts, Sexually Transmitted Diseases, fourth ed., McGraw Hill, Toronto, Canada, 2008.

[20] T. Ichikawa et al., Clearance of hepatitis C virus after living-donor liver transplantation in spite of residual viremia on end date of interferon therapy before transplantation, World J. Gastroenterol. 13 (30) (2007) 4149.

[21] A. Powers Kimberly, M. Ruy Ribeiro, Kinetics of hepatitis C virus reinfection after liver transplantation, Liver Transplant. 12 (2006) 207.

[23] G. Lau, M. Tsiang, J. Hou, S. Yuen, W. Carman, L. Zhang, C. Gibbs, S. Lam, Combination therapy with lamivudine and famciclovir for chronic hepatitis B infected Chinese patients: a viral dynamics study, Hepatology 32 (2000) 394.

[24] S. Lewin, R. Ribeiro, T. Walters, G. Lau, S. Bowden, S. Locarnini, A. Perelson, Analysis of hepatitis B viral load decline under potent therapy: complex decay profiles observed, Hepatology 34 (2001) 1012.

[26] M.P. Manns, J.G. McHutchison, S.C. Gordon, V.K. Rustgi, M. Shiffman, R. Reindollar, Z.D. Goodman, K. Koury, M. Ling, J.K. Albrecht, Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial, Lancet 358 (2001) 958.

[28] V. Mazzaferro et al., Risk of HBV reinfection after liver transplantation in HBsAg-positive cirrhosis. Primary hepatocellular carcinoma is not a predictor for HBV recurrence. The European Cooperative Study Group on Liver Cancer and Transplantation, Liver 16 (2) (1996) 117.

[30] M.A. Nowak, S. Bonhoeffer, A.M. Hill, R. Boehme, H.C. Thomas, H. McDade, Viral dynamics in Hepatitis B Virus infection, Proc. Natl. Acad. Sci. USA 93 (1996) 4398.

[31] M.A. Nowak, R.M. May, Virus Dynamics, Oxford University, 2000.

[33] R. Ribeiro, A. Lo, A. Perelson, Dynamics of hepatitis B virus infection, Microb. Infect. 4 (2002) 829.

[34] S. Todo, A.J. Demetris, D. Van Thiel, L. Teperman, J.J. Fung, T.E. Starzl, Orthotopic liver transplantation for patients with hepatitis B virus-related liver disease, Hepatology 13 (1991) 619.

[35] M. Tsiang, J. Rooney, J. Toole, C. Gibbs, Biphasic clearance kinetics of hepatitis B virus from patients during adefovir dipivoxil therapy, Hepatology 29 (1999) 1863.

[36] World Health Organization. Heptatitis B fact sheet No. 204, WHO website, 2009.