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Analysis of a Model for the Dynamics of Hepatitis B with Noncytolytic Loss of Infected Cells*

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Abstract. We consider the basic model of virus dynamics with noncytolytic loss of infected cells for the infection with viral hepatitis B. Stability of the infection-free steady state and existence, uniqueness and stability of the infected steady state is investigated. The stability results are given in terms of the basic reproductive number R_0. Here, we perform the global stability analysis using two techniques, the method of Lyapunov functions and the theory of competitive three dimensional systems. We shall use suitable linear combinations of known functions, common quadratic, composite quadratic and Volterra-type functions, for obtain a suitable Lyapunov function for each steady state. Numerical simulations are presented to illustrate the results.

Keywords: virus dynamics, hepatitis B, Lyapunov functions, compound matrices, competitive systems, periodic orbit, global stability

1 Introduction

The hepatitis B virus (HBV) is a noncytopathic, hepatotropic, DNA virus (hepadnavirus). It has a strong preference for infecting liver cells, but small amounts of hepadnaviral DNA can be found in the kidneys, pancreas and mononuclear cells[23].

HBV can be transmitted by sexual contact, through the skin, by inoculation with contaminated blood or blood products, by transplantation of organs from infected donors, and perinatally from infected mothers.

Although HBV replication is only mildly cytopathic, cellular immune responses directed against the virus can produce substantial liver damage and result in chronic hepatitis, cirrhosis and hepatocellular carcinoma[23].

Chronic HBV infections remain a major public health problem worldwide. An estimated 350 million people worldwide have been infected with HBV[30], with 5% developing chronic HBV as a result[13].

The major characteristics of the replication cycle are the following:
(1) HBV replication does not induce a cytopathic effect in infected cells, which in turn is one of the factors involved in viral persistence;
(2) viral covalently closed circular DNA (cccDNA) is the transcriptionally active form of viral genome and has been shown to have a long half-life in infected cells;
(3) viral genome replication occurs via a reverse transcription step that leads to the production of viral DNA genome within nucleocapsids, which are then enveloped prior to virion release.

Furthermore, viral nucleocapsids may also be recycled back to the nucleus to initially amplify and then maintain a stable pool of viral cccDNA in the liver[45].

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Potent agent inhibitors of viral polymerase are administered long-term in tissue culture and in vivo experiments have shown that does not lead to complete clearance of viral cccDNA from infected cells[45]. Chronic infection is believed to be maintained by HBV cccDNA[40].

Considering the long half-life of hepatocytes, the limiting factor in eliminating infection is thought to be the clearance of cccDNA reservoirs from infected cells[6, 33]. One immune mechanism that has been proposed to mediate cccDNA clearance is a non-cytolytic mechanism, cytokine-induced "curing" of infected cells[14]. In addition, infected cells may also revert to the uninfected state by loss of all cccDNA from their nucleus[14]. There is evidence from animal models supporting this mechanism, it is currently unclear how infection is resolved in patients.

The mathematical models of viral dynamics are based on a set of assumptions that are spelled out clearly. The first models of HBV dynamics have been introduced by Marchuk and co-workers[31], and Nowak[36]. The interactions between HBV and the immune system have been studied by using different models[7, 21, 31]. In particular, Nowak developed the basic model to study HIV infection[37], which was later adapted to HBV[36] and HCV[35] infection.

Lewin et al. [25] developed a mathematical model that describes the dynamics of the hepatitis B and the noncytolytic loss of infected cells. The model is formulated by the following system of non-linear differential equations:

$$\begin{cases} H'(t) = \lambda - \mu H(t) - \beta H(t)V(t) + \delta I(t), \\ I'(t) = \beta H(t)V(t) - \sigma I(t), \\ V'(t) = \kappa I(t) - \gamma V(t). \end{cases} \tag{1}$$

Here, H, I and V denote the concentration of uninfected hepatocytes, infected hepatocytes, and free virions, respectively. The model (1) is based on the following assumptions.

Target cells are produced at a rate λ and die at (natural) rate μ. The infection process is described by the mass-action term βHV, that describes the infection rate as proportional to the product of the concentrations of the virions and the target cells, where β is the rate of infection of target cells. Infected cells may be killed because of viral or immune effects, or they may be lost by noncytolytic elimination of the cccDNA in their nucleus. The loss rate of infected cells is given by $\sigma := \alpha + \delta$, where α is the death rate of infected cells and δ is the reversion rate into the uninfected state. The term δI into first line of Eq. (1) gives a measure of the uninfected cells which are created through "cure", per unit time. Finally, it is assumed that free virions are produced at a constant rate κ per infected cell and γ is the clearance rate of viral particles i.e. by humoral immunity.

Thus reasonable initial conditions for infection by free virus only are $H(0) = H_0 > 0$, $I(0) = I_0 \geq 0$, $V(0) = V_0 > 0$. Here H, I and $V \in \mathbb{R}_+$, and all parameters are assumed to be positive, with the exception of δ, which can be non-negative.

The qualitative analysis of the models reveals the existence of scenarios possible of a viral infection. A first scenario is that the viral population is eventually totally eliminated. Mathematically, this means that the infection-free steady state is globally asymptotically stable. A second scenario is that the infection becomes established, and that the virus population grows with damped oscillations, or unimodal growth, is that the infected steady state (positive interior steady state) is globally asymptotically stable. A third scenario is that the virus population grows with self-sustained oscillations, is that the interior steady state is unstable.

In the study of solutions of nonlinear systems of ordinary differential equations, a very interesting problem is that of proving the global stability of the interior steady state by using the method of Lyapunov functions or other sophisticated techniques developed recently.

Many authors have studied the global stability of biological models using the second Lyapunov method. The Lyapunov function candidate for population biology models is often the Volterra-type function. This function has been extensively used to prove the global stability of the steady state of Lotka-Volterra systems[12], infectious disease models[20], and virus dynamic models[19, 42, 43]. Generalized Lyapunov functions are developed in[11, 17] to study the global stability properties of several different predator-prey models with nonlinear functional response. A peculiar Lyapunov function, that are not of Volterra type function, is constructed in[4] for an epidemic model with general nonlinear incidence rate. The method of Lyapunov function is also an

effective technique for multi-dimensional systems. Recently, Volterra-type functions were used to prove the global stability of a unique endemic equilibrium for several multi-group epidemic models[15, 16].

In case when we do not succeed in constructing an appropriate Lyapunov function, we need to use other techniques. For example, the generalization of the Poincaré–Bendixson criterion for three-dimensional competitive systems has been applied in several papers (see, e.g., [9, 10, 24, 44]). In particular, Buonomo and Lacitignola[3] analyze the global dynamics of several three-dimensional epidemic models by applying the geometrical approach developed by Li and Muldowney[26].

In this paper we will use the method of Lyapunov functions and the theory of competitive systems for studying the global stability of infected steady state of a three-dimensional model for the viral dynamics of HBV[25]. We shall construct suitable linear combination of common quadratic, composite quadratic and Volterra-type functions.

The paper is organized as follows: the basic properties of model are presented in Section 2. The global asymptotic stability of the infection-free steady state is described in Section 3. The local stability of the infected equilibrium and the uniform persistence of system are analyzed in Section 4. In Section 5, the Lyapunov method is applied to study the global stability of the infected steady state. In Section 6, the global dynamics is studied by means of the theory of competitive systems. In Section 7, we introduce some simulation figures to illustrate our main result. Conclusions are given in Section 8.

2 Positive invariance, boundedness and steady states

It is easy to see that the non-negative octant

$$\mathbb{R}^3_+ = \left\{(H, I, V) \in \mathbb{R}^3 : H \geq 0, I \geq 0 V \geq 0\right\},$$

is positively invariant with respect to Eq. (1).

Now we shall show that the system (1) is uniformly bounded.

Proposition 1. *All the solutions of system (1) are uniformly bounded in the compact subset*

$$\Delta = \left\{(H, I, V) \in \mathbb{R}^3_+ : H + I \leq \frac{\lambda}{\eta}, V \leq \frac{\kappa\lambda}{\eta\gamma}\right\}.$$

Proof. Let $(H(t), I(t), V(t))$ be any solution with positive initial conditions (H_0, I_0, V_0). From the first two equations of (1) we define a function $U(H, I) = H(t) + I(t)$. The time derivative along a solution of Eq. (1) is $U' \leq \lambda - \eta U$, where $\eta = \min\{\alpha, \mu\}$. It follows that $U' + \eta U \leq \lambda$. Applying the theory of differential inequalities[2], we obtain

$$U(H, I) \leq \frac{\lambda}{\eta}(1 - \exp(-\eta t)) + U(H_0, I_0)\exp(-\eta t),$$

and for $t \to \infty$, we have $\limsup_{t\to\infty} U \leq \frac{\lambda}{\eta}$. On the other hand, from the third equation of system (1) we obtain

$$V' = \kappa I - \gamma V \leq \frac{\kappa\lambda}{\eta} - \gamma V.$$

By a standard comparison theorem, we can conclude that

$$\limsup_{t\to\infty} V \leq \frac{\kappa\lambda}{\eta\gamma}.$$

Hence all the solutions of Eq. (1) which start in $\mathbb{R}^3_+$ are eventually confined in the region Δ. This completes the proof.

Obviously, the set Δ is positively invariant with respect to Eq. (1) and convex.

Here we derive the basic reproduction number for viral infection using the next generation operator[8]. Using the notation in [8], the non-negative matrix, F, of the new infection terms, and the M-matrix, V, of the transition terms associated with the model (1), are given, respectively, by

$$F := \begin{pmatrix} 0 & \beta H^\circ \\ 0 & 0 \end{pmatrix} \text{ and } V := \begin{pmatrix} \sigma & 0 \\ -\kappa & \gamma \end{pmatrix}.$$

It follows that the basic reproduction number, denoted by $R_0 = \rho(FV^{-1})$, where ρ is the spectral radius, is given by

$$R_0 = \frac{\beta\lambda\kappa}{\gamma\mu\sigma}. \tag{2}$$

The basic reproductive number is formally defined as the average number of secondary infected cells produced by each infected cell at the beginning of the infection.

We now show that in $\mathbb{R}^3_+$ there are two possible steady states of Eq. (1) and they must satisfy the following algebraic equations:

$$\begin{aligned} 0 &= \lambda - \mu H - \beta HV + \delta I, \\ 0 &= \beta HV - \sigma I, \\ 0 &= \kappa I - \gamma V. \end{aligned} \tag{3}$$

We have the following result.

Proposition 2. *System (1) always has the infection-free steady state $E^\circ = (\lambda/\mu, 0, 0)$. If $R_0 > 1$, there is a unique infected steady state $E^* = (H^*, I^*, V^*)$ in the interior of $\mathbb{R}^3_+$, where*

$$H^* = \frac{\gamma\sigma}{\beta\kappa}, \quad I^* = \frac{\lambda}{\alpha} - \frac{\gamma\mu\sigma}{\alpha\beta\kappa}, \quad V^* = \frac{\kappa\lambda}{\alpha\gamma} - \frac{\mu\sigma}{\alpha\beta}. \tag{4}$$

Rewriting E^* in terms of basic reproductive number,

$$H^* = \frac{\lambda}{\mu R_0}, \quad I^* = \frac{\lambda}{\alpha}\left(1 - \frac{1}{R_0}\right), \quad V^* = \frac{\kappa\lambda}{\alpha\gamma}\left(1 - \frac{1}{R_0}\right). \tag{5}$$

The infection-free steady state E° corresponds to the case in which all cells are healthy, while the infected steady state E^* corresponds to the case where the viral infection persists in the populations of cells.

3 Stability of the infection-free steady state

We now study the local stability behavior of the infection-free steady state E° for system (1). The Jacobian matrix for system (1) with $x = (H, I, V)$ is given by

$$\frac{\partial f}{\partial x} = \begin{pmatrix} -(\mu + \beta V) & \delta & -\beta H \\ \beta V & -\sigma & \beta H \\ 0 & \kappa & -\gamma \end{pmatrix}. \tag{6}$$

We get the following local stability result for E°.

Proposition 3. *If $R_0 < 1$, then the infection-free steady state E° is locally asymptotically stable; if $R_0 > 1$, then it is unstable.*

Proof. The Jacobian matrix (6) of the vector field corresponding to system (1), evaluated at E°, is

$$\frac{\partial f}{\partial x}(E^\circ) = \begin{pmatrix} -\mu & \delta & -\beta H^\circ \\ 0 & -\sigma & \beta H^\circ \\ 0 & \kappa & -\gamma \end{pmatrix}.$$

So one eigenvalue of $\frac{\partial f}{\partial x}(E^\circ)$ is $-\mu$. The other two eigenvalues are determined by the quadratic equation

$$\tau^2 + (\gamma+\sigma)\tau + \gamma\sigma - \beta\kappa H^\circ = 0. \tag{7}$$

Rewriting Eq. (7) in terms of basic reproductive number

$$\tau^2 + (\gamma+\sigma)\tau + \gamma\sigma(1-R_0) = 0,$$

and consequently the eigenvalues have negative real parts if and only if $R_0 < 1$. Therefore E° is locally asymptotically stable for $R_0 < 1$. If $R_0 > 1$ one eigenvalue is positive. Therefore E° is unstable.

The following result shows that if $R_0 \leq 1$ then the infection-free steady state is globally stable, and all solutions starting in $\mathbb{R}^3_+$ approach E°.

Theorem 1. *If $R_0 \leq 1$, then the infection-free steady state E° of Eq. (1) is globally asymptotically stable in $\mathbb{R}^3_+$.*

Proof. Define the *global Lyapunov function* $W : \left\{(H,I,V) \in \mathbb{R}^3_+ : H > 0\right\} \to \mathbb{R}$ by

$$W(H,I,V) = H^\circ\left(\frac{H}{H^\circ} - 1 - \ln\frac{H}{H^\circ}\right) + \frac{\delta}{2(\alpha+\mu)H^\circ}\left[(H-H^\circ)+I\right]^2 + I + \frac{\sigma}{\kappa}V.$$

Then W is C^1 on the interior of $\mathbb{R}^3_+$, E° is the global minimum of W on $\mathbb{R}^3_+$, and $W(H^\circ,0,0) = 0$. The time derivative of W computed along solutions of Eq. (1) is

$$\begin{aligned}
W' &= \frac{(H-H^\circ)}{H}H' + \frac{\delta}{(\alpha+\mu)H^\circ}\left[(H-H^\circ)+I\right](H'+I') + I' + \frac{\sigma}{\kappa}V', \\
&= \frac{(H-H^\circ)}{H}\left(\lambda - \mu H - \beta HV + \delta I\right) \\
&\quad + \frac{\delta}{(\alpha+\mu)H^\circ}\left[(H-H^\circ)+I\right](\lambda - \mu H - \alpha I) \\
&\quad + (\beta HV - \sigma I) + \frac{\sigma}{\kappa}(\kappa I - \gamma V).
\end{aligned}$$

Using $\lambda = \mu H^\circ$, we obtain

$$\begin{aligned}
W' &= \frac{(H-H^\circ)}{H}\left(-\mu(H-H^\circ) - \beta HV + \delta I\right) \\
&\quad + \frac{\delta}{(\alpha+\mu)H^\circ}\left[(H-H^\circ)+I\right](-\mu(H-H^\circ) - \alpha I) \\
&\quad + \left(\beta HV - \frac{\sigma\gamma}{\kappa}V\right).
\end{aligned}$$

Notice that

$$\delta I\frac{(H-H^\circ)}{H} = -\delta I\frac{(H-H^\circ)^2}{HH^\circ} + \frac{\delta}{H^\circ}I(H-H^\circ).$$

Substituting and simplifying, we get

$$W' = -\left(\mu H^\circ + \frac{\delta\mu}{(\alpha+\mu)}H + \delta I\right)\frac{(H-H^\circ)^2}{HH^0} - \frac{\alpha\delta I^2}{(\alpha+\mu)H^\circ} - \frac{\sigma\gamma}{\kappa}\left(1 - \frac{\beta\kappa H^\circ}{\sigma\gamma}\right)V.$$

Rewriting W' in terms of basic reproductive number, we have

$$W' = -\left(\mu H^\circ + \frac{\delta\mu}{(\alpha+\mu)}H + \delta I\right)\frac{(H-H^\circ)^2}{HH^\circ} - \frac{\alpha\delta I^2}{(\alpha+\mu)H^\circ} - \frac{\sigma\gamma}{\kappa}(1-R_0)V.$$

If $R_0 \leq 1$, then $W' \leq 0$; and $W' = 0$ if and only if $H = H^\circ$ and $I = V = 0$ or $R_0 = 1$, $H = H^\circ$ and $I = 0$. Therefore the largest compact invariant set in $\left\{(H,I,V) \in \mathbb{R}^3_+ : W' = 0\right\}$ is the singleton $\{E^\circ\}$, where E° is the infection-free steady state. By LaSalle's invariance principle[22] then implies that E° is globally asymptotically stable in $\mathbb{R}^3_+$. This proves Theorem 1.

Remark 1. As is well known, the Lyapunov functions are not unique. We construct another Lyapunov function for the infection-free steady state, and we proved Theorem 1 using the following function,

$$\widehat{W}(H,I,V)=\frac{1}{2H^{\circ}}\left(H-H^{\circ}\right)^{2}+\frac{\delta}{2(\alpha+\mu)H^{\circ}}\left[\left(H-H^{\circ}\right)+I\right]^{2}+I+\frac{\sigma}{\kappa}V,$$

obtained by means of suitable combinations of common quadratic, composite quadratic and linear functions. The time derivative of $\widehat{W}$ along the solutions of system (1), and using $\lambda=\mu H^{\circ}$ and $HV(H-H^{\circ})=V(H-H^{\circ})^{2}+H^{\circ}V(H-H^{\circ})$, we get

$$\widehat{W}'=-\left(\mu+\frac{\delta\mu}{(\alpha+\mu)}+\beta V\right)\frac{\left(H-H^{\circ}\right)^{2}}{H^{\circ}}-\frac{\alpha\delta}{(\alpha+\mu)H^{\circ}}I^{2}-\frac{\gamma\sigma}{\kappa}\left(1-R_{0}\right)V.$$

We thus have shown that if all solutions of system (1) which starting in $\mathbb{R}^{3}_{+}$ converge to E° when $R_{0}\leq 1$. Thus, Δ is subset of $\mathbb{R}^{3}_{+}$, we obtain the following corollary.

Corollary 1. *If $R_{0}\leq 1$, then the infection-free steady state E° of Eq. (1) is globally asymptotically stable in Δ.*

4 Local stability of the infected steady state and persistence

For $R_{0}>1$, the steady state E° becomes an unstable hyperbolic point, and the infected steady state E^{*} emerges in the region $\mathbb{R}^{3}_{+}$.

The local stability of E^{*} is given by the Jacobian matrix (6) of Eq. (1) evaluated in this point:

$$\frac{\partial f}{\partial x}(E^{*})=\begin{pmatrix}-(\mu+\beta V^{*}) & \delta & -\beta H^{*}\\ \beta V^{*} & -\sigma & \beta H^{*}\\ 0 & \kappa & -\gamma\end{pmatrix}.$$

that can be rewritten as

$$\frac{\partial f}{\partial x}(E^{*})=\begin{pmatrix}-\left(\mu+\sigma\frac{I^{*}}{H^{*}}\right) & \delta & -\sigma\frac{I^{*}}{V^{*}}\\ \sigma\frac{I^{*}}{H^{*}} & -\sigma & \sigma\frac{I^{*}}{V^{*}}\\ 0 & \kappa & -\kappa\frac{I^{*}}{V^{*}}\end{pmatrix}.$$

when we take into account the identities:

$$\begin{cases}\mu+\beta V^{*}=\mu+\sigma\frac{I^{*}}{H^{*}},\\ \beta H^{*}=\sigma\frac{I^{*}}{V^{*}},\\ \beta V^{*}=\sigma\frac{I^{*}}{H^{*}},\\ \gamma=\kappa\frac{I^{*}}{V^{*}},\end{cases}\tag{8}$$

which are obtained from nonlinear algebraic system (3).

The following lemma[1, 32] is used to demonstrate the local stability of the infected steady state.

Lemma 1. *Let $\frac{\partial f}{\partial x}(E^{*})$ be a 3×3 real matrix. If $tr\left(\frac{\partial f}{\partial x}(E^{*})\right)$, $det\left(\frac{\partial f}{\partial x}(E^{*})\right)$ and $det\left(\frac{\partial f^{[2]}}{\partial x}(E^{*})\right)$ are all negative, then all of the eigenvalues of $\frac{\partial f}{\partial x}(E^{*})$ have negative real parts.*

The second additive compound $\frac{\partial f^{[2]}}{\partial x}(E^{*})$ of the Jacobian matrix, $\frac{\partial f}{\partial x}(E^{*})$[1, 28] is given by

$$\begin{aligned}\frac{\partial f^{[2]}}{\partial x}(E^{*}):&=\begin{pmatrix}j_{11}+j_{22} & j_{23} & -j_{13}\\ j_{32} & j_{11}+j_{33} & j_{12}\\ -j_{31} & j_{21} & j_{22}+j_{33}\end{pmatrix}\\ &=\begin{pmatrix}-\left(\mu+\sigma+\sigma\frac{I^{*}}{H^{*}}\right) & \sigma\frac{I^{*}}{V^{*}} & \sigma\frac{I^{*}}{V^{*}}\\ \kappa & -\left(\mu+\sigma\frac{I^{*}}{H^{*}}+\kappa\frac{I^{*}}{V^{*}}\right) & \delta\\ 0 & \sigma\frac{I^{*}}{H^{*}} & -\left(\sigma+\kappa\frac{I^{*}}{V^{*}}\right)\end{pmatrix},\end{aligned}$$

where j_{kl} is the (k,l)th entry of the Jacobian matrix $\frac{\partial f}{\partial x}(E^{*})$.

Proposition 4. *If $R_0 > 1$, then the infected steady state E^* is locally asymptotically stable for system (1).*

Proof. Clearly $tr\left(\frac{\partial f^{[2]}}{\partial x}(E^*)\right) < 0$. The determinant of J_{E^*} is given by

$$det\left(\frac{\partial f}{\partial x}(E^*)\right) = -\alpha\kappa\sigma\frac{(I^*)^2}{H^*V^*}.$$

The determinant of $\frac{\partial f^{[2]}}{\partial x}(E^*)$ is

$$\begin{aligned} det\left(\frac{\partial f^{[2]}}{\partial x}(E^*)\right) =& -\left(\mu+\sigma+\sigma\frac{I^*}{H^*}\right)\left[\left(\sigma+\kappa\frac{I^*}{V^*}\right)\left(\mu+\alpha\frac{I^*}{H^*}+\kappa\frac{I^*}{V^*}\right)+\delta\kappa\frac{(I^*)^2}{H^*V^*}\right] \\ &+\kappa\sigma\frac{I^*}{V^*}\left(\sigma+\kappa\frac{I^*}{V^*}\right)+\kappa\sigma^2\frac{(I^*)^2}{H^*V^*}, \\ =& -\mu\left[\left(\sigma+\kappa\frac{I^*}{V^*}\right)\left(\mu+\alpha\frac{I^*}{H^*}+\kappa\frac{I^*}{V^*}\right)+\delta\kappa\frac{(I^*)^2}{H^*V^*}\right] \\ &-\sigma\left[\left(\sigma+\kappa\frac{I^*}{V^*}\right)\left(\mu+\alpha\frac{I^*}{H^*}\right)+\delta\kappa\frac{(I^*)^2}{H^*V^*}\right] \\ &-\sigma\frac{I^*}{H^*}\left[\left(\sigma+\kappa\frac{I^*}{V^*}\right)\left(\mu+\alpha\frac{I^*}{H^*}\right)+\left(\kappa\frac{I^*}{V^*}\right)^2+\delta\kappa\frac{(I^*)^2}{H^*V^*}\right] < 0. \end{aligned}$$

Thus, the result follows from Lemma 1.

Next, we deal with the uniform persistence of Eq. (1).

Theorem 2. *When $R_0 > 1$, the system (1) is uniformly persistent, i.e., there exists $\epsilon > 0$ (independent of initial conditions), such that $\liminf_{t\to\infty} Y(t) > \epsilon$ for $Y = H, I, V$.*

Proof. The result follows from an application of *Theorem 4.6* in [38], with $Y_1 = int(\mathbb{R}^3_+)$ and $Y_2 = bd(\mathbb{R}^3_+)$. Since the proof is similar to that of Lemma 3.5 in [24], we only sketch the modifications that E° is a weak repeller for Y_1. Since $R_0 > 1$, we can choose $\epsilon > 0$ small enough such that

$$\frac{\beta\kappa}{\gamma\sigma}\left(H^\circ-\epsilon\right) > 1. \tag{9}$$

Suppose there exists a solution $(H(t), I(t), V(t))$ such that $(H(t), I(t), V(t)) \to (H^\circ, 0, 0)$. For this ϵ, we can select $t_0 > 0$ large enough such that if $t > t_0$ then

$$H^\circ - \epsilon < H(t) < H^\circ + \epsilon, \quad I(t) \le \epsilon,\ V(t) \le \epsilon.$$

From the last two equations of system (1), for $t > t_0$, we obtain

$$\begin{aligned} I'(t) &= \beta H(t)V(t) - \sigma I(t) \ge \beta\left(H^\circ-\epsilon\right)V(t) - \sigma I(t), \\ V'(t) &= \kappa I(t) - \gamma V(t). \end{aligned}$$

Let us consider the matrix A_ϵ defined by

$$A_\epsilon = \begin{pmatrix} -\sigma & \beta\left(H^\circ-\epsilon\right) \\ \kappa & -\gamma \end{pmatrix}.$$

Since A_ϵ admits positive off–diagonal element, the Perron–Frobenius theorem implies that there is positive eigenvector $v = (v_1, v_2)$ for the maximum eigenvalue ω_1 of A_ϵ. Moreover, by Eq. (9), we see that the maximum eigenvalue ω_1 is positive

$$\begin{aligned} y_1'(t) &= \beta\,(H^\circ - \epsilon)\,y_2(t) - \sigma y_1(t), \\ y_2'(t) &= \kappa y_1(t) - \gamma y_2(t). \end{aligned} \tag{10}$$

Let $y(t) = (y_1(t), y_2(t))$ be a solution of Eq. (10) through (rv_1, rv_2) at $t = t_0$, where $r > 0$ satisfies $rv_1 < I(t_0)$, $rv_2 < V(t_0)$. Since the semiflow of Eq. (10) is monotone and $A_\epsilon v > 0$, it follows that $y_i(t)$ is strictly increasing and $y_i(t) \to +\infty$, as $t \to +\infty$, contradicting the eventual boundedness of positive solution of Eq. (1). Thus, no positive orbit of Eq. (1) tends to $(H^\circ, 0, 0)$ as t tends to infinity. Then an application of the techniques given in [5] establishes the uniform persistence of Eq. (1). The proof of Theorem 2 is complete.

Biologically, the uniform persistence characterizes chronic infection of hepatocytes.

5 Global stability of the infected steady state: Method of Lyapunov functions

In this section, we establish a sufficient condition for the global asymptotic stability of a unique infected steady state E^* in $int(\mathbb{R}^3_+)$ when $R_0 > 1$.

Theorem 3. *Let $R_0 > 1$. If*

$$\mu H^* \geq \delta I^*, \tag{11}$$

then the infected steady state E^* of Eq. (1) is globally asymptotically stable in the interior of $\mathbb{R}^3_+$. In particular, Eq. (11) is equivalent to

$$1 < R_0 \leq \frac{\alpha}{\delta} + 1. \tag{12}$$

Proof. Define the *global Lyapunov function* $L : \left\{(H, I, V) \in \mathbb{R}^3_+ : H, I, V > 0\right\} \to \mathbb{R}$ by

$$\begin{aligned} L(H, I, V) = {} & H^* \left(\frac{H}{H^*} - 1 - \ln \frac{H}{H^*} \right) + I^* \left(\frac{I}{I^*} - 1 - \ln \frac{I}{I^*} \right) \\ & + \frac{\delta}{2(\alpha + \mu)H^*} \left[(H - H^*) + (I - I^*) \right]^2 + \frac{\beta H^* V^*}{\kappa I^*} V^* \left(\frac{V}{V^*} - 1 - \ln \frac{V}{V^*} \right). \end{aligned}$$

Then L is C^1 on the interior of $\mathbb{R}^3_+$, E^* is the global minimum of L on $\mathbb{R}^3_+$, and $L(H^*, I^*, V^*) = 0$. The time derivative of L computed along solutions of Eq. (1) is

$$\begin{aligned} L' = {} & \left(1 - \frac{H^*}{H} \right) H' + \left(1 - \frac{I^*}{I} \right) I' \\ & + \frac{\delta}{(\alpha + \mu)H^*} \left[(H - H^*) + (I - I^*) \right] (H' + I') + \frac{\beta H^* V^*}{\kappa I^*} \left(1 - \frac{V^*}{V} \right) V', \\ = {} & \left(1 - \frac{H^*}{H} \right) (\lambda - \mu H - \beta H V + \delta I) + \left(1 - \frac{I^*}{I} \right) (\beta H V - \sigma I) \\ & + \frac{\delta}{(\alpha + \mu)H^*} \left[(H - H^*) + (I - I^*) \right] (\lambda - \mu H - \alpha I) \\ & + \frac{\beta H^* V^*}{\kappa I^*} \left(1 - \frac{V^*}{V} \right) (\kappa I - \gamma V). \end{aligned}$$

At the infected steady state, we have

$$\lambda = \mu H^* + \beta H^* V^* - \delta I^*, \tag{13}$$

$$\sigma = \frac{\beta H^* V^*}{I^*}, \tag{14}$$

$$\lambda = \mu H^* + \alpha I^*, \tag{15}$$

$$\gamma = \kappa \frac{I^*}{V^*}. \tag{16}$$

Using Eqs. (13) $\sim$ (16), we obtain

$$\begin{aligned} L' = & \left(1-\frac{H^*}{H}\right)\left(-\mu\left(H-H^*\right)-\beta HV+\beta H^*V^*+\delta\left(I-I^*\right)\right) \\ & +\left(1-\frac{I^*}{I}\right)\left(\beta HV-\beta H^*V^*\frac{I}{I^*}\right) \\ & -\frac{\delta}{(\alpha+\mu)H^*}\left[(H-H^*)+(I-I^*)\right]\left(\mu(H-H^*)+\alpha(I-I^*)\right) \\ & +\frac{\beta H^*V^*}{\kappa I^*}\left(1-\frac{V^*}{V}\right)\left(\kappa I-\kappa I^*\frac{V}{V^*}\right). \end{aligned}$$

Notice that

$$\delta\left(1-\frac{H^*}{H}\right)(I-I^*)=-\delta(I-I^*)\frac{(H-H^*)^2}{HH^*}+\frac{\delta}{H^*}(H-H^*)(I-I^*).$$

Thus,

$$\begin{aligned} L' = & -\left(\mu H^*+\delta(I-I^*)\right)\frac{(H-H^*)^2}{HH^*}+\frac{\delta}{H^*}(H-H^*)(I-I^*) \\ & +\left(\beta H^*V^*-\beta HV-\beta H^*V^*\frac{H^*}{H}+\beta H^*V\right) \\ & +\left(\beta HV-\beta H^*V^*\frac{I}{I^*}-\beta H^*V^*\frac{HI^*V}{H^*IV^*}+\beta H^*V^*\right) \\ & -\frac{\mu\delta}{(\alpha+\mu)H^*}(H-H^*)^2-\frac{(\alpha+\mu)\delta}{(\alpha+\mu)H^*}(H-H^*)(I-I^*)-\frac{\alpha\delta}{(\alpha+\mu)H^*}(I-I^*)^2 \\ & +\frac{\beta H^*V^*}{\kappa I^*}\left(\kappa I-\kappa I^*\frac{V}{V^*}-\kappa I^*\frac{IV^*}{I^*V}+\kappa I^*\right). \end{aligned}$$

After some calculations we obtain

$$\begin{aligned} L' = & -\left(\mu H^*-\delta I^*+\delta I+\frac{\mu\delta H}{(\alpha+\mu)}\right)\frac{(H-H^*)^2}{HH^*}-\frac{\alpha\delta}{(\alpha+\mu)H^*}(I-I^*)^2 \\ & +\beta H^*V^*\left(3-\frac{H^*}{H}-\frac{IV^*}{I^*V}-\frac{HI^*V}{H^*IV^*}\right). \end{aligned}$$

If $\mu H^*-\delta I^*\geq 0$ then L' is negative for all $H,I,V>0$, and $L'=0$ if and only if $H=H^*$, $I=I^*$ and $V=V^*$ holds. The largest compact invariant set in $\left\{(H,I,V)\in\mathbb{R}^3_+ : L'=0\right\}$ is the singleton $\{E^*\}$, where E^* is the infected steady state. By LaSalle's invariance principle[22] then implies that E^* is globally asymptotically stable in the interior of $\mathbb{R}^3_+$.

Finally, we show that the condition Eq. (11) is equivalent to the condition Eq. (12). Using H^* and I^* of Eq. (5), we have

$$\mu H^*-\delta I^*\equiv\lambda\left[\frac{1}{R_0}\left(1+\frac{\delta}{\alpha}\right)-\frac{\delta}{\alpha}\right]\equiv\frac{\delta\lambda}{\alpha R_0}\left[\left(1+\frac{\alpha}{\delta}\right)-R_0\right]\geq 0.$$

Therefore, we obtain the condition $R_0\leq\frac{\alpha}{\delta}+1$. The Theorem 3 is proved.

Remark 2. Recently, A. Korobeinikov [19, 20] used the Volterra-type Lyapunov function to prove global stability of the steady states of a basic viral dynamic model and $SEIR$ epidemic model with constant population. The constructions of the Lyapunov functions exploit the equivalent between the differential equations of $SEIR$ model and the basic model. C. Vargas-De-León [41] used combinations of common quadratic, composite quadratic and Volterra-type functions, constructed suitable Lyapunov functions and obtained the global stability for the SIS, SIR and $SIRS$ epidemic models with disease-induced death. Motivated by the works [19, 20, 41–43] in this paper, we construct a Lyapunov function for each steady state, using suitable combinations of common quadratic, composite quadratic and Volterra-type functions.

6 Global stability of the infected steady state: Poincaré–Bendixson property

In this section, we investigate the global asymptotic stability of the unique infected steady state E^* in the interior of feasible region Δ when $R_0 > 1$. To do so, we shall use the results about three–dimensional competitive systems that live in convex sets and the theory of second compound matrix to prove the asymptotic orbital stability of periodic solutions[29].

Theorem 4. *[29]. Consider the following autonomous dynamical systems:*

$$x' = f(x), \tag{17}$$

where $f : \Delta \to \mathbb{R}^n$, $\Delta \subset \mathbb{R}^n$ open set and $f \in C^1(\Delta)$. If the following conditions are satisfied:
(i) The system (17) has a compact absorbing set $K \subset \Delta$ and has a unique steady state E^* in $int(\Delta)$;
(ii) E^* is local asymptotically stable;
(iii) The system (17) satisfies a Poincaré–Bendixson property;
(iv) Any periodic orbit of the system (17) is asymptotically orbitally stable.
Then the only steady state E^* is the globally asymptotically stable in $int(\Delta)$.

(i) Uniform persistence. The uniform persistence property of the solution of the system (1) is satisfied, see Theorem 2. On the other hand, the uniform persistence together with boundedness of Δ is equivalent to the existence of a compact set of the condition *(i)* of Theorem 4, which is absorbing for Eq. (1), in the interior of Δ, see [18].
(ii) Local stability. The proof of local stability of infected steady state, E^*, is given in *Proposition 4*.
(iii) Poincaré–Bendixson property. As is well known, a three–dimensional competitive system satisfies the Poincaré–Bendixson property in a convex region Δ.

Theorem 5. *[29]. Assume that $n = 3$ and Δ is convex. Suppose that (17) is competitive in Δ. Then it satisfies the Poincaré–Bendixson property.*

Theorem 6. *When $R_0 > 1$, the system (1) is competitive.*

Proof. We choose the matrix M as

$$M = \begin{pmatrix} 1 & 0 & 0 \\ 0 & -1 & 0 \\ 0 & 0 & 1 \end{pmatrix}.$$

Then from the matrix M and the Jacobian given in Eq. (6) we get

$$M\frac{\partial f}{\partial x}M = \begin{pmatrix} -(\mu + \beta V) & -\delta & -\beta H \\ -\beta V & -\sigma & -\beta H \\ 0 & -\kappa & -\gamma \end{pmatrix}.$$

It can easily be seen that the system (1) is competitive Δ.

(iv) Orbital stability of periodic orbits.

Theorem 7. *[34]. A sufficient condition for a periodic orbit $\Gamma = \{\varphi(t) : 0 \leq t \leq \nu\}$ of Eq. (17) to be asymptotically orbitally stable with asymptotic phase is that the linear system equation*

$$Y'(t) = \left(\frac{\partial f^{[2]}}{\partial x}(\varphi(t))\right) Y(t).$$

is asymptotically stable, where $\frac{\partial f^{[2]}}{\partial x}$ is the second additive compound matrix of the Jacobian matrix of $\frac{\partial f}{\partial x}$ of $f(x)$. The system (17) is called the second compound system of the orbit $\varphi(t)$.

Theorem 8. *Any periodic solution to the system (1), if it exists, is asymptotically orbitally stable.*

Proof. Assume that $\varphi(t) = (H(t), I(t), V(t))$ is a periodic solution containing in $int(\Gamma)$. By Theorem 7, we only need to prove that the following periodic linear system

$$\overline{Y}'(t) = \left(\frac{\partial f^{[2]}}{\partial x} (\varphi(t)) \right) \overline{Y}(t), \tag{18}$$

is asymptotically stable, where $\overline{Y} = (X, Y, Z)^T$ and $\frac{\partial f^{[2]}}{\partial x}$ is the second additive compound matrix of the Jacobian $\frac{\partial f}{\partial x}$ of system (1). This matrix has the form

$$\frac{\partial f^{[2]}}{\partial x} = \begin{pmatrix} -(\alpha + \delta + \mu + \beta V) & \beta H & \beta H \\ \kappa & -(\gamma + \mu + \beta V) & \delta \\ 0 & \beta V & -(\alpha + \gamma + \delta) \end{pmatrix}.$$

Substituting $\varphi(t)$ into (18) gives

$$\begin{aligned} X'(t) &= -(\alpha + \delta + \mu + \beta V) X(t) + \beta H Y(t) + \beta H Z(t), \\ Y'(t) &= \kappa X(t) - (\gamma + \mu + \beta V) Y(t) + \delta Z(t), \\ Z'(t) &= \beta V Y(t) - (\alpha + \gamma + \delta) Z(t). \end{aligned} \tag{19}$$

To show the asymptotic stability of the system (18) we consider the following Lyapunov function:

$$\widetilde{L}(t) = \widetilde{L}(X(t), Y(t), Z(t); H(t), I(t), V(t)) = \sup \left\{ |X(t)|, \frac{I(t)}{V(t)} [|Y(t)| + |Z(t)|] \right\}. \tag{20}$$

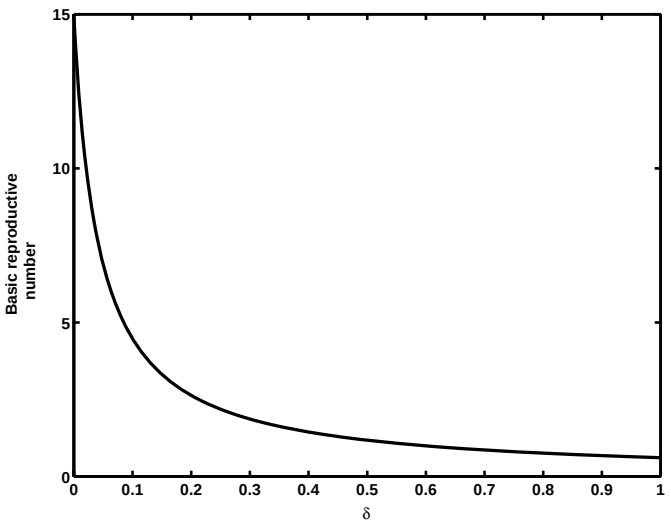

Fig. 1. Plot of the basic reproductive number R_0 in Eq. (2) as a function of the cure rate δ.

Eq. (20) is positive, but not differentiable everywhere. We next calculate the right-hand derivative of $\widehat{L}(t)$, denoted as $D_+\widehat{L}(t)$, and obtain the following differential inequalities:

$$D_+ |X(t)| \leq -(\alpha + \delta + \mu + \beta V) |X(t)| + \beta H \frac{V}{I} \left[\frac{I}{V} [|Y(t)| + |Z(t)|] \right], \tag{21}$$

$$D_+ |Y(t)| \leq \kappa |X(t)| - (\gamma + \mu + \beta V) |Y(t)| + \delta |Z(t)|, \tag{22}$$

$$D_+ |Z(t)| \leq \beta V |Y(t)| - (\alpha + \gamma + \delta) |Z(t)|. \tag{23}$$

From Eqs. (22) and (23) we get

Table 1. Parameter estimates and initial data values for the model of hepatitis B, reported in [39].

Initial data values and parameters	Values
Initial data values	
$H(0)$ initial value of uninfected target cells	1.7×10^8 cells/mL
$I(0)$ initial value of infected hepatocytes	0
$V(0)$ initial value of free virions	400 copies/mL
Parameters	
λ production rate of uninfected target cells	5×10^5 cells/(mL.d)
μ per-cell death rate of uninfected target cells	$0.003/d$
β rate of infection of target cells	4×10^{-10} mL/(copies.d)
α per-cell death rate of infected hepatocytes	$0.043/d$
δ reversion rate of cells to uninfected state	Varies
κ production rate of free virions from an infected cell	$6.24/d$
γ clearance rate constant of virions	$0.65/d$

$$D_+ \left[|Y(t)| + |Z(t)|\right] \leq -(\gamma + \eta) \left[|Y(t)| + |Z(t)|\right] + \kappa \left|X(t)\right|. \tag{24}$$

Therefore

$$\begin{aligned} D_+ \left[\frac{I}{V} \left[|Y(t)| + |Z(t)|\right]\right] &= \left(\frac{I'}{I} - \frac{V'}{V}\right) \frac{I}{V} \left[|Y(t)| + |Z(t)|\right] + \frac{I}{V} D_+ \left[|Y(t)| + |Z(t)|\right] \\ &\leq \kappa \frac{I}{V} \left|X(t)\right| + \left(\frac{I'}{I} - \frac{V'}{V} - \gamma - \eta\right) \frac{I}{V} \left[|Y(t)| + |Z(t)|\right]. \end{aligned} \tag{25}$$

From Eqs. (21) and (25) we get:

$$D_+ \widetilde{L}(t) = \sup\left\{h_1(t), h_2(t)\right\} \widetilde{L}(t), \tag{26}$$

where

$$h_1(t) = -\left(\alpha + \delta + \mu + \beta V\right) + \beta H \frac{V}{I}, \tag{27}$$

$$h_2(t) = \kappa \frac{I}{V} + \frac{I'}{I} - \frac{V'}{V} - \gamma - \eta. \tag{28}$$

We rewrite the last two Eq. (1) as

$$\beta H \frac{V}{I} = \frac{I'}{I} + \alpha + \delta, \tag{29}$$

$$\kappa \frac{I}{V} = \frac{V'}{V} + \gamma. \tag{30}$$

Substituting Eq. (29) into Eq. (27) and Eq. (30) into Eq. (28), we have

$$h_1(t) = \frac{I'}{I} - \eta - \beta V, \tag{31}$$

$$h_2(t) = \frac{I'}{I} - \eta. \tag{32}$$

From Eqs. (31) and (32) we find

$$\sup\left\{h_1(t), h_2(t)\right\} \leq \frac{I'}{I} - \eta,$$

and thus, from Eq. (26) and Gronwall's inequality, we obtain

$$\widetilde{L}(t) \leq \widetilde{L}(0)I(t)\exp(-\eta t) \leq \frac{\lambda}{\eta}\widetilde{L}(0)\exp(-\eta t),$$

which implies that $\widetilde{L}(t) \to 0$ as $t \to \infty$. It turns out that $(X(t), Y(t), Z(t)) \to 0$ as $t \to \infty$. This implies that the linear system Eq. (18) is asymptotically stable and therefore $\varphi(t)$ is asymptotically orbitally stable. This completes the proof.

Now, we are ready to prove the global stability of the infected steady state E^*.

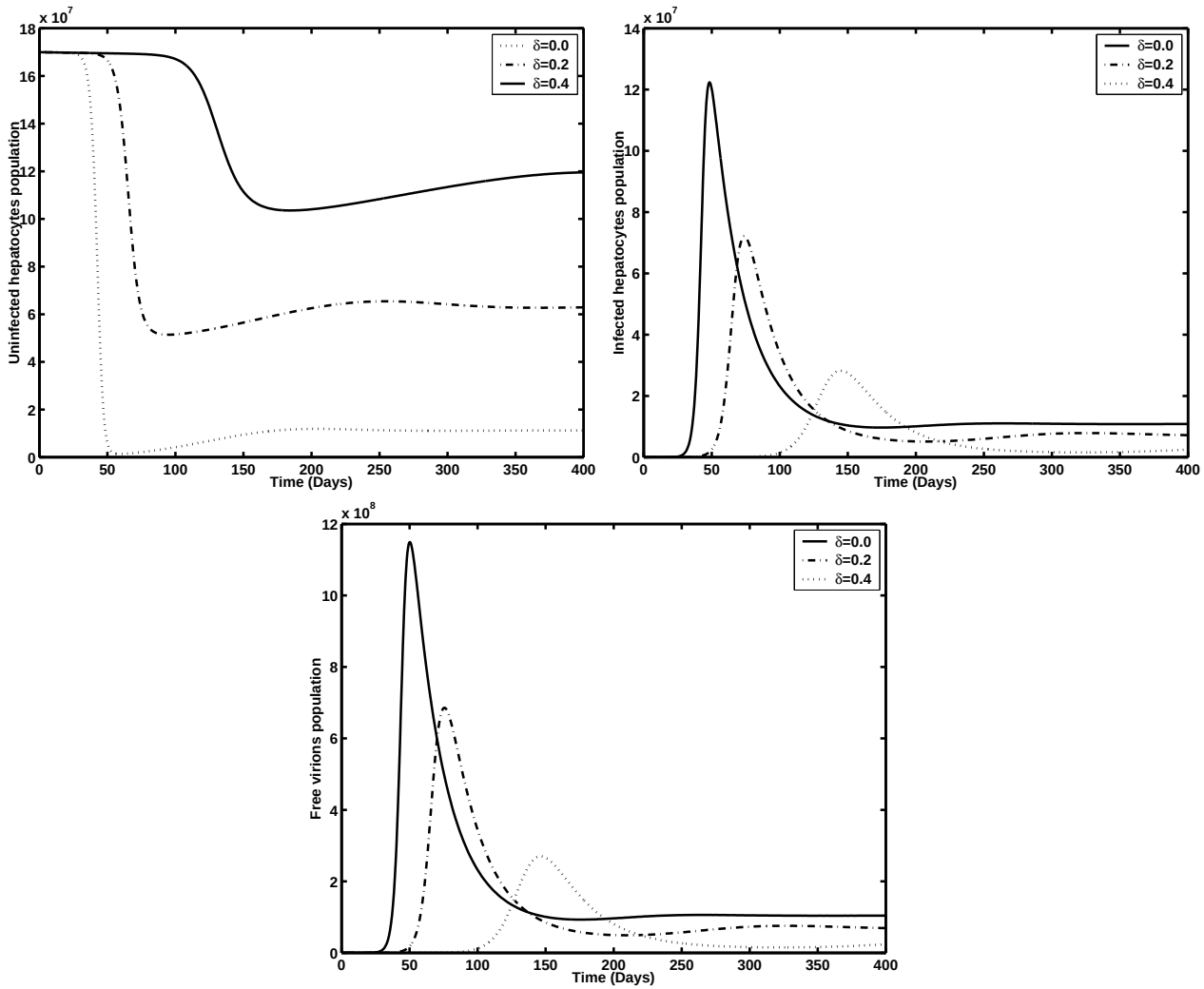

Fig. 2. Numerical solution of model (1)

Theorem 9. *If $R_0 > 1$ then the infected steady state E^* of Eq. (1) is globally asymptotically stable in the interior of Δ.*

Proof. Since system (1) is competitive and persistent, the infected steady state E^* is locally asymptotically stable for $R_0 > 1$ and that any periodic orbit is asymptotically orbitally stable. By Proposition 4 and Theorems 2, 6 and 8 we know that the system (1) is satisfied with every condition of Theorem 4, so the unique infected steady state E^* is globally asymptotically stable in the interior of Δ.

Remark 3. Li and Muldowney [27, 29] used the Lyapunov function $\widetilde{L}$ to prove global stability of the positive steady states of $SEIR$ epidemiological models. Various authors have used this function to study global stability in predator–prey model[10], host–vector model[9] and viral infections models [24, 44].

7 Numerical simulations

In this section, we use numerical simulations to visualise qualitative and quantitative properties of the trajectories of model (1) with respect to different values of reversion rate constant δ, that reflect the noncytolytic loss of infected cells through reversion to the uninfected state by loss of all cccDNA from their nucleus.

The time courses of uninfected hepatocytes, infected hepatocytes, and free virion populations were obtained by numerical integration using MATLAB. We use a set of clinical data reported in [39], and vary the values of δ because the estimation of the parameter is not available in the literature. All the parameters involved in model (1) are summarized in Tab. 1.

We use the values of the parameters given in Tab. 1 and the definition of basic reproductive number in Eq. (2), we plot R_0 vs δ, and vary the values of δ between (0,1), see Fig. 1.

In Fig. 1, we notice that if $\delta = 0$ then $R_0 = 14.88$ and if it increases the value of cure rate of the infected cells it approaches unity, then the basic reproductive number decreases to near zero. This is very important for the control of the viral infection.

We perform a series of numerical simulations for model (1), using three values of δ, 0.0/day, 0.2/day and 0.4/day. In Fig. 2, it shows the uninfected cells, infected cells and free virions populations. Respectively, in these cases the basic reproductive number is greater than unity.

The Fig. 2 show uninfected hepatocytes cells, infected hepatocytes cells and viral particles versus time. In these cases the values of δ, 0.0/day, 0.2/day and 0.4/day, and the basic reproductive numbers are $R_0 = 14.88$, $R_0 = 2.63$ and $R_0 = 1.44$, respectively.

Next we perform other series of numerical simulations for values of basic reproductive numbers less than or equal to unity. We use three values of δ, 0.6/day, 0.605/day and 0.8/day. In Fig. 3, it shows the uninfected cells, infected cells and virus populations, respectively.

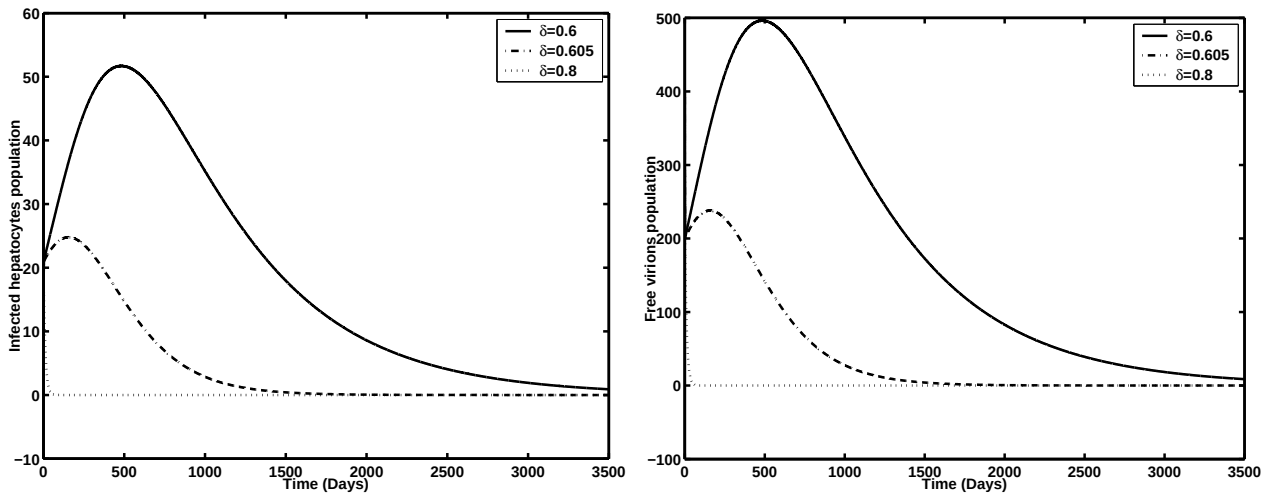

Fig. 3. Numerical solution of model (1)

The graphs show infected hepatocytes cells and free virions versus time. In these cases the values of δ, 0.6/day, 0.605/day and 0.8/day, and the basic reproductive numbers are $R_0 = 0.995$, $R_0 = 0.987$ and $R_0 = 0.759$, respectively.

8 Conclusions

In this paper, we studied a mathematical model that describes the interaction between HBV virus and hepatocyte with the mechanism of noncytolytic loss of infected cells.

Our main goal was to investigate the qualitative behavior of the model such as positive invariance, the boundedness, the persistence, the local and global stability of the steady states and numerically explore the mechanism of the "cure" of infected cells.

We proved that the global stability is completely determined by the basic reproductive number R_0. We have shown in Theorem 1, that if $R_0 \leq 1$, the infection-free steady state is globally asymptotically stable in the interior of the non-negative octant and the cellular infection by the hepatitis B virus will always die out. The reversion rate of infected cells into the uninfected state is a very important parameter. A result relevant of model (1) is that the viral infection eradicates if δ is larger. The local stability of infected steady state is proved in Proposition 4 using a recent stability criterion[1, 32] for the stability of 3×3 matrices with real entries. Verification of the local stability conditions is less technical and more manageable than the Routh–Hurwitz conditions. Also, in Theorem 3, it has been proved that if $R_0 > 1$, a unique infected steady state exists and is globally asymptotically stable, and viral infection becomes chronic.

Usually, it is difficult to obtain the global properties of population models in dimensions greater than or equal to three. We constructed two Lyapunov function to proved the global stability of infection-free steady state. We used the Lyapunov function method and obtained the global stability of the infected steady state in the interior of the non-negative octant under a sufficient condition in terms of the parameters of Eq. (1). The global stability of the infected steady state in the interior of the feasible region is proved unrestricted in the parameters using the Poincaré–Bendixson property for three-dimensional competitive systems and the stability criterion of Muldowney [34] for periodic orbits.

Our results of model (1) can be used to prove the global stability of the following system,

$$\begin{cases} H'(t) = \lambda - \mu H(t) - (1-\theta)\beta H(t)V_I(t) + \delta I(t), \\ I'(t) = (1-\theta)\beta H(t)V_I(t) - \sigma I(t), \\ V_I'(t) = (1-\phi)\kappa I(t) - \gamma_I V_I(t), \\ V_{NI}'(t) = \phi\kappa I(t) - \gamma_{NI} V_{NI}(t), \end{cases} \tag{33}$$

that incorporates the combination of two drug therapies[25, 39]. There V_I and V_{NI} denote infectious and non-infectious viral particles, respectively.

Parameters θ and ϕ are defined as follows: θ the efficiency of drug therapy in preventing new infections, and ϕ the efficiency of drug therapy in inhibiting viral production, with $0 \leq \theta, \phi \leq 1$. An efficacy of 0 indicates that there is no inhibition, whereas an efficacy of 1 (100%) indicates complete inhibition. Values of the efficacy between 0 and 1 indicate partial inhibition.

Note that the first three equations are decoupled from the last one and that this subsystem is essentially similar to Eq. (1). We can calculate the basic reproductive number $\widetilde{R_0}$ under combination therapy:

$$\widetilde{R_0} = (1-\theta)(1-\phi)\frac{\beta\lambda\kappa}{\gamma\mu\sigma} = (1-\theta)(1-\phi)R_0. \tag{34}$$

System (33) has two possible steady states in the non-negative octant $\mathbb{R}^3_+$: the free-infection steady state $\widetilde{E^\circ} = (\lambda/\mu, 0, 0)$ and the infected steady state

$$\widetilde{E^*} = \left(\lambda/\mu\widetilde{R_0}, \lambda(\widetilde{R_0}-1)/\alpha\widetilde{R_0}, \kappa\lambda(\widetilde{R_0}-1)/\alpha\gamma\widetilde{R_0}\right). \tag{35}$$

Thus, we obtain the following corollary.

Corollary 2. *If $\widetilde{R_0} \leq 1$, then the infection-free steady state $\widetilde{E^\circ}$ of Eq. (33) is globally asymptotically stable in Δ. If $\widetilde{R_0} > 1$, then the infected steady state $\widetilde{E^*}$ of Eq. (33) is globally asymptotically stable in the interior of Δ.*

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