Global Journal of Pure and Applied Mathematics.
ISSN 0973-1768 Volume 12, Number 3 (2016), pp. 2297–2312

http://www.ripublication.com/gjpam.htm

Sensitivity and Stability Analysis of Hepatitis B Virus Model with Non-Cytolytic Cure Process and Logistic Hepatocyte Growth

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Abstract

We study a mathematical model for hepatitis B consisting of populations of uninfected liver cells, infected liver cells and free virus. The model includes a non-cytolytic cure process term and a logistic growth term. We show that the model has a disease free equilibrium point and an endemic equilibrium point and then analyze the stability of these points for a range of parameter values. We find the basic reproduction number R_0 and then use a Lyapunov function to prove that the disease free equilibrium point is globally asymptotically stable for $R_0 < 1$. We analyze the sensitivity of R_0 with respect to changes in five parameters of the model. We show that R_0 has the highest sensitivity to changes in the rate of release of free virus by infected cells (γ), followed by rate of infection of uninfected cells by free virus (β), death rate of free virus (μ), cytolytic cure rate of infected cells (p) and finally death rate of infected cells (a). We have also studied the sensitivity of the endemic equilibrium populations to changes in parameter values. The results show that free viruses have the highest sensitivity to changes in the rate of release of free viruses by infected cells (γ), followed by changes to μ and β. For the infected cell population, the highest sensitivity indices are the rate of infection of uninfected cells (β), followed by p and K. Numerical simulations for a range of parameter values have been carried out using the Matlab program.

AMS subject classification:
Keywords: HBV model, basic reproduction number, global stability, sensitivity.

1. Introduction

The first record of an epidemic caused by hepatitis B virus (HBV) was in 1885. The virus was first identified in 1966 by Baruch Blumberg at the National Institutes of Health in the USA [1] and it has now become a major public health problem. In recent years, many researchers have used mathematical modelling to study HBV infection. In 1996, Nowak et al.(1996) [2], proposed a basic model to study the spread of hepatitis B virus infection which described the interaction between uninfected cells, infected cells and free virus. In 2010, Wang et al. [3] modified the model of Nowak et al. by replacing the rate of infection term by a mass action incidence term and by assuming that infected cells could be cured. They showed that their model had two equilibrium points and that these two points were globally asymptotically stable. In 2011, Hattaf et al. [4] generalized the Nowak et al. model by including the effects of drug therapy and they also replaced the assumption of constant infusion of healthy hepatocytes with a logistic growth term. They showed that their model had two globally asymptotically stable equilibrium points. In 2011, Xinjian Zhuo [6], [7] considered a model which included the loss of free virus particles when free virus infected an uninfected cell and the loss of infected cells due to a non-cytolytic cure process. They showed that an endemic equilibrium point of their model was globally asymptotically stable.

In this paper, we consider a model which includes a logistic growth term for uninfected cells, a mass action term for infection of uninfected cells, a free virus term, a loss of free viruses on infection of a cell, and a non-cytolytic cure process. We study the equilibrium points of the model, prove their global asymptotic stability, and study their sensitivity to changes in parameter values.

2. The Mathematical Model

The proposed model is as follows:

$$\begin{aligned} \frac{dx}{dt} &= rx\left(1-\frac{x+y}{K}\right)-\frac{\beta xv}{x+v}+py, \\ \frac{dy}{dt} &= \frac{\beta xv}{x+v}-(a+p)y, \\ \frac{dv}{dt} &= \gamma y-\mu v-\frac{\beta xv}{x+v}, \end{aligned} \tag{1}$$

where $x(t)$ is the number of uninfected liver cells at time t, $y(t)$ is the nnumber of infected liver cells at time t, $v(t)$ is the concentration of free viruses in the blood at time t, and the parameters in the model are defined in Table 1. Note that all populations must be nonnegative and all parameters are assumed to be positive.

The feasible region of the model is the region in which all populations are nonnegative and bounded above. We now prove that this region is invariant, i.e., if the initial populations are in the feasible region then they remain in the feasible region for all time.

Table 1: Meaning of parameters in the HBV model

Parameters	Meaning
r	intrinsic growth rate of liver cells
K	carrying capacity of the liver for liver cells
β	rate of infection of uninfected cells by free virus
a	death rate of infected cells
p	rate of cure of infected cells by non-cytolytic cure process
γ	rate of release of free viruses by an infected cell
μ	death rate of free virus

Lemma 2.1. The feasible region Ω of model (1) is defined as

$$\Omega = \left\{(x(t), y(t), v(t)) \in \Re^3_+ \cup (0,0,0) |\ 0 \le x(t) + y(t) \le K, \right.$$
$$\left. 0 \le v(t) \le \frac{\gamma K}{\mu} \right\}. \tag{2}$$

Then, if $(x(0), y(0), v(0)) \in \Omega$, the solution $(x(t), y(t), v(t)) \in \Omega$ for all $t \ge 0$.

Proof. We can assume that all populations are nonnegative. By combining the first and second equations in the system (1), we obtain

$$\frac{d(x+y)}{dt} = rx\left(1 - \frac{x+y}{K}\right) - ay.$$

Then, if $x(t) + y(t) \le K$, we have

$$\frac{d(x+y)}{dt} = rx\left(1 - \frac{x+y}{K}\right) - ay \le r(x+y)\left(1 - \frac{x+y}{K}\right)$$
$$- ay \le r(x+y)\left(1 - \frac{x+y}{K}\right).$$

It follows that if $x(0) + y(0) \le K$, then

$$0 \le x(t) + y(t) \quad \le \quad \frac{K(x(0) + y(0))}{x(0) + y(0) + (K - x(0) - y(0))\exp(-rt)} \le K. \tag{3}$$

Thus $\lim_{t\to\infty} \sup(x(t) + y(t)) \le K$, and therefore the two functions x and y are also bounded above by the constant K. From the third equation in (1), we obtain

$$\frac{dv}{dt} = \gamma y - \mu v - \frac{\beta x v}{x+v} \le \gamma y - \mu v \le \gamma K - \mu v,$$

and therefore if $v(0) \leq \dfrac{\gamma K}{\mu}$, we have

$$0 \leq v(t) \quad \leq \quad \frac{\gamma K}{\mu} + \left(v(0) - \frac{\gamma K}{\mu} \right) \exp(-\mu t) \leq \frac{\gamma K}{\mu}. \tag{4}$$

Therefore $\lim\limits_{t \to \infty} \sup v(t) \leq \dfrac{\gamma K}{\mu}$.

Therefore, if $(x(0), y(0), v(0)) \in \Omega$, then $(x(t), y(t), v(t)) \in \Omega$. ■

3. Analysis of the disease-free solutions of the model

3.1. Equilibrium points

The equilibrium points of the model (1) are solutions of the following algebraic equations.

$$\begin{aligned} rx^* \left(1 - \frac{x^* + y^*}{K} \right) - \frac{\beta x^* v^*}{x^* + v^*} + py^* &= 0, \\ \frac{\beta x^* v^*}{x^* + v^*} - (a + p) y^* &= 0, \\ \gamma y^* - \mu v^* - \frac{\beta x^* v^*}{x^* + v^*} &= 0. \end{aligned} \tag{5}$$

For these equations, there are two disease-free equilibria and one endemic equilibrium point. We will discuss the endemic equilibrium point in section 4. The two disease-free equilibria are a trivial equilibrium $E_0(x^*, y^*, v^*) = (0, 0, 0)$ and a disease-free equilibrium point $E_1(x^*, y^*, v^*) = (K, 0, 0)$. The trivial equilibrium point E_0 means that there are no liver cells and it can therefore be ignored.

3.2. The basic reproduction number (R_0)

The basic reproduction number R_0 of a system can be defined so that if $R_0 < 1$ then a disease-free equilibrium point is stable and if $R_0 > 1$ then it is unstable. The basic reproduction number can be calculated using either the next-generation method of van den Driessche and Watmough [8] or from Lyapunov's first method of computing the eigenvalues of the Jacobian matrix of the linearized system at an equilibrium point (see, e.g., [12]).

In this section, we will use the next-generation method. We will discuss the eigenvalue method in section 3.4. To apply the next-generation method, we look for the condition that the infected cells y decrease with time. For simplicity, we arrange (1) as

follows:

$$\begin{aligned}
\frac{dy}{dt} &= \frac{\beta x v}{x+v} - (a+p)y, \\
\frac{dv}{dt} &= \gamma y - \mu v - \frac{\beta x v}{x+v}, \\
\frac{dx}{dt} &= rx\left(1 - \frac{x+y}{K}\right) - \frac{\beta x v}{x+v} + py.
\end{aligned} \tag{6}$$

We let $X = (y, v, x)^T$ and rewrite the system (6) in the form:

$$\frac{dX}{dt} = F(X) - G(X),$$

where

$$F(X) = \begin{bmatrix} \dfrac{\beta x v}{x+v} \\ 0 \\ 0 \end{bmatrix}, \quad G(X) = \begin{bmatrix} (a+p)y \\ -\gamma y + \mu v + \dfrac{\beta v x}{x+v} \\ -rx(1 - \dfrac{x+y}{K}) + \dfrac{\beta v x}{x+v} - py \end{bmatrix}.$$

Then, following the next-generation method, we linearize the functions $F(X)$ and $G(X)$ at the disease-free equilibrium E_1 to obtain the Jacobian matrices J_F and J_G and then compute the product $J_F J_G^{-1}$. We obtain

$$\begin{aligned}
J_F &= \begin{bmatrix} 0 & \beta & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}, \quad J_G = \begin{bmatrix} a+p & 0 & 0 \\ -\gamma & \mu+\beta & 0 \\ r-p & \beta & r \end{bmatrix}, \\
J_F J_G^{-1} &= \begin{bmatrix} \dfrac{\beta\gamma}{(\beta+\mu)(a+p)} & \dfrac{\beta}{\mu+\beta} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}.
\end{aligned} \tag{7}$$

The basic reproduction number R_0 is the largest eigenvalue of $J_F J_G^{-1}$ and therefore

$$R_0 = \frac{\beta\gamma}{(\beta+\mu)(a+p)}. \tag{8}$$

Therefore if $R_0 = \dfrac{\beta\gamma}{(\beta+\mu)(a+p)} < 1$, then the disease-free equilibrium is stable and the HBV infection in the liver and blood stream dies out. On the other hand, if $R_0 = \dfrac{\beta\gamma}{(\beta+\mu)(a+p)} > 1$, then the disease-free equilibrium is unstable and the HBV infection increases.

In order to understand the epidemiological meaning of R_0 we denote

$$h_1 = \frac{\beta}{\beta + \mu}, \quad h_2 = \frac{\gamma}{a + p},$$

where h_1 is the fraction of free viruses that move into infected cells $y(t)$ and h_2 is the fraction of infected cells that release free virus $v(t)$. So $R_0 = h_1 h_2$ is the fraction of free viruses that move from the blood to infect a cell and are then released back into the blood from an infected cell as free viruses. If this fraction is less than 1 then the free virus and infected cells die out, otherwise the free virus and infected cells increase.

3.3. Sensitivity analysis of the basic reproduction number

The basic reproduction number R_0 is a function of five parameters β, p, a, γ and μ. In order to cure the disease it is necessary to control the parameter values to make $R_0 < 1$. We are therefore interested in finding the rate of change of R_0 as the parameter values are changed.

The rate of change of R_0 for a change in value of parameter h can be estimated from a normalized sensitivity index, $SI(h)$ (see, e.g., [10]) defined as follows:

$$SI(h) = \frac{h}{R_0} \frac{\partial R_0}{\partial h}. \tag{9}$$

The normalized sensitivity indices of the reproduction number with respect to β, p, a, γ and μ are given by

$$\begin{aligned} SI(\beta) &= 1 - \frac{1}{\mu + \beta}, \quad SI(p) = -\frac{p}{a + p}, \\ SI(a) &= -\frac{a}{a + p}, \quad SI(\gamma) = 1, \quad SI(\mu) = -\frac{1}{\mu + \beta}. \end{aligned} \tag{10}$$

The sensitivity indices $SI(\beta)$ and $SI(\gamma)$ are positive, i.e., the value of R_0 increases as β and γ values increase. The remaining indices are negative, i.e., the value of R_0 decreases as p, a and μ values increase. Since all of the indices, except $SI(\gamma)$, are functions of other parameters, the sensitivity indices will change with change in values of these other parameters.

As an example, we have computed the normalized sensitivity indices for the special case of parameter values given in [11]. These values are shown in Table 2.

The sensitivity indices and corresponding % values in Table 3 represent the changes in parameter value required to give a 1% decrease in R_0.

For example, in order to get a 1% decrease in the value of R_0, it is necessary to decrease the values of β and γ by 1.0004% and 1%,respectively. Also, in order to get a 1% decrease in the value of R_0, it is necessary to increase the values of p, a and μ by 1.693%, 2.443% and 1.0004%, respectively. Therefore, from the sensitivity indices the most effective methods of reducing the value of R_0 are to decrease the rate of release of free virus from an infected cell (γ), the infection rate of an uninfected cell (β) and to increase the death rate of free virus (μ), respectively.

Table 2: Parameter values corresponding to disease-free equilibrium [11]

Parameter	Value	Unit
Intrinsic growth rate of liver cells (r)	0.1	$\text{mm}^{-3}\ \text{day}^{-1}$
Carrying capacity of the liver for liver cells (K)	1000	$\text{mm}^{-3}\ \text{day}^{-1}$
Rate of infection of uninfected cells (β)	0.0014	$\text{mm}^{-3}\ \text{day}^{-1}$
Rate infected cells can be cured (p)	0.1	day^{-1}
Death rate of infected cells (a)	0.0693	day^{-1}
Rate of release of free viruses by an infected cell (γ)	230	none
Death rate of free virus (μ)	3.693	day^{-1}

Table 3: Normalized sensitivity indices of R_0 and % change in parameter for 1% change in R_0

Parameter	Sensitivity indices of R_0	corresponding % changes
β	$+0.9996$	-1.0004%
p	-0.5907	$+1.6930\%$
a	-0.4093	$+2.4430\%$
γ	$+1.0000$	-1.0000%
μ	-0.9996	$+1.0004\%$

3.4. Local stability of the disease-free equilibrium

As stated in section 3.2, the basic reproduction number can also be computed from the eigenvalues of the Jacobian matrix of the linearized system about an equilibrium point. This method can be used to check the local asymptotic stability of any equilibrium point. We will apply this method in section 4.2 to check the local stability of the endemic equilibrium point.

We summarize the results for the disease-free equilibrium in the following theorem.

Theorem 3.1. The disease-free equlibrium $E_1(x^*, y^*, z^*) = (K, 0, 0)$ of the model (1) is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

Proof. The Jacobian matrix of the model (1) at E_1 is

$$J(E_1) = \begin{bmatrix} -r & -r+p & -\beta \\ 0 & -a-p & \beta \\ 0 & \gamma & -\mu-\beta \end{bmatrix}. \tag{11}$$

A necessary condition for local stability of E_1 is that the real parts of all eigenvalues of the Jacobian must be negative.

Clearly, one eigenvalue of $J(E_1)$ is $\lambda_1 = -r$ which is always negative. The other two eigenvalues are the roots of the characteristic polynomial

$$P(\lambda) = \lambda^2 + (a + p + \mu + \beta)\lambda + (a + p)(\mu + \beta) - \beta\gamma = 0. \tag{12}$$

The two solutions of the characteristic equation (12) are the eigenvalues

$$\begin{aligned} \lambda_2 &= \frac{1}{2}\big(-(a + p + \mu + \beta) + \sqrt{(a + p + \mu + \beta)^2 - 4[(a + p)(\beta + \mu) - \beta\gamma)]}\big), \\ \lambda_3 &= \frac{1}{2}\big(-(a + p + \mu + \beta) - \sqrt{(a + p + \mu + \beta)^2 - 4[(a + p)(\beta + \mu) - \beta\gamma]}\big). \end{aligned} \tag{13}$$

From (13) it can be seen that the real part of λ_3 is always negative and that the real part of λ_2 is negative if and only if $(a + p)(\beta + \mu) - \beta\gamma > 0$, i.e., if and only if $R_0 = \dfrac{\beta\gamma}{(a + p)(\beta + \mu)} < 1$. ■.

Therefore, the disease-free equilibrium $E_1 = (K, 0, 0)$ is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$ in agreement with the result from the next-generation method. For $R_0 = 1$, the linear test fails and higher order terms must be examined.

3.5. Global stability of disease-free equilibrium

We apply Lyapunov's second method (see, e.g., [12]) to prove global stability of E_1 for $R_0 < 1$.

Theorem 3.2. If $R_0 < 1$, then the disease free equilibrium $E_1(K, 0, 0)$ of the model (1) is globally asymptotically stable.

Proof. We define the Lyapunov function

$$V(t) = y(t) + mv(t), \quad m > 0$$

To prove global stability, we must prove that

(1) V is a continuous function of t,

(2) V has a minimum at $(x^*, y^*, z^*) = (K, 0, 0)$ and

(3) that the time derivative $\dot{V}$ is less than or equal to zero for all t with $\dot{V} = 0$ only at the minimum.

Clearly, conditions (1) and (2) are satisfied because $y(t)$ and $v(t)$ are nonnegative continuous functions of t.

We therefore check the derivative of V with repect to time. We have

$$\begin{aligned}\frac{dV}{dt} &= \frac{dy}{dt} + m\frac{dv}{dt} \\ &= \frac{\beta x v}{x+v} - (a+p)y + m\left(\gamma y - \mu v - \frac{\beta x v}{x+v}\right) \\ &= \frac{\beta x v}{x+v}(1-m) - m\mu v + (\gamma m - a - p)y \\ &\leq \beta v(1-m) - m\mu v + (\gamma m - a - p)y.\end{aligned}$$

Choosing $m = \dfrac{a+p}{\gamma}$, we obtain

$$\begin{aligned}\frac{dV}{dt} &\leq \frac{\beta v(\gamma - a - p) - (a+p)\mu v}{\gamma} \\ &= \frac{v}{\gamma}(\beta\gamma - (a+p)(\beta+\mu)) \\ &= \frac{v(a+p)(\beta+\mu)}{\gamma}\left(\frac{\beta\gamma}{(a+p)(\beta+\mu)} - 1\right) \\ &= \frac{(a+p)(\beta+\mu)}{\gamma}(R_0 - 1)v \leq 0. \qquad (14)\end{aligned}$$

Therefore $\dot{V} \leq 0$ and $\dot{V} = 0$ only when $v(t) = 0$. Then substituting $v(t) = 0$ into the system of (1),we obtain $x \to K$, $y \to 0$ as $t \to \infty$. Therefore, the disease-free equilibrium point is globally asymptotically stable when $R_0 < 1$. ■

4. Endemic Equilibrium Enalysis

An endemic equilibrium point of (1) is an equilibrium point with positive values of $x(t)$, $y(t)$ and $v(t)$, i.e., it is a positive solution of (5). A positive solution of (5) exists and is given by

$$\begin{aligned}x^* &= \frac{K}{r}\left[\frac{r(\gamma - a - p) - a(\beta+\mu)(R_0 - 1)}{(\gamma - a - p) + (\beta+\mu)(R_0 - 1)}\right], \\ y^* &= x^*\frac{\beta+\mu}{\gamma - a - p}(R_0 - 1), \qquad (15) \\ v^* &= x^*\frac{\beta+\mu}{\mu}(R_0 - 1).\end{aligned}$$

So, the endemic equilibrium in (15) exists with positive x^*, y^* and v^* values if and only if $\gamma - a - p > 0$ and $R_0 > 1$. Therefore, the endemic equilibrium exists if and only if the disease-free equilibrium is unstable.

4.1. Sensitivity analysis of the endemic equilibrium point

Sensitivity analysis of the endemic equilibrium point can be used to determine the relative changes in the endemic equilibrium populations (x^*, y^*, v^*) when parameter values are changed. The sensitivity analysis can be used to determine the relative importance of different parameters in the level of HBV infection. The sensitivity indices for parameter values can be calculated either by using the method of Chitnis et al. [9] or by direct differentiation of the endemic equilibrium populations in (15). Since the expressions for these sensitivity indices are complicated, we will not give them in this paper. However, the indices can easily be computed both symbolically and numerically using packages such as Maple, Matlab or Mathematica.

We have used the Maple program to compute the sensitivity indices for the three endemic equilibrium populations with respect to the seven input parameters for the parameter values given in [11]. These values are shown in Table 4.

Table 4: Parameter values corresponding to endemic equilibrium [11]

Parameter	Value	Unit
Intrinsic growth rate of liver cells (r)	0.3	$\text{mm}^{-3}\ \text{day}^{-1}$
Carrying capacity of the liver for liver cells (K)	1000	$\text{mm}^{-3}\ \text{day}^{-1}$
Rate of infection of uninfected cells (β)	0.000903	$\text{mm}^{-3}\ \text{day}^{-1}$
Rate infected cells can be cured (p)	0.12	day^{-1}
Death rate of infected cells (a)	0.0693	day^{-1}
Rate of release of free viruses by an infected cell (γ)	300	none
Death rate of free virus (μ)	0.693	day^{-1}

The results for the sensitivity indices are shown in Table 5.

Table 5: Sensitivity indices of the endemic equilibrium populations

parameters	*Sensitivity indices*		
	x^*	y^*	v^*
r	$+0.0007$	$+0.0007$	$+0.0007$
K	$+0.9999$	$+0.9999$	$+0.9999$
β	-0.0066	$+1.7582$	$+1.7582$
p	$+0.0039$	-1.0387	-1.0391
a	$+0.0020$	-0.7206	-0.2708
γ	-0.00284	$+0.7623$	$+1.7629$
μ	$+0.00283$	-0.7619	-1.7619

Table 5 shows that the most sensitive parameter for the uninfected cell population x^* is the carrying capacity of the liver $K = 0.9999$ followed by β, p, γ, μ, a and

r respectively. The most sensitive parameter for the infected cell population y^* is the infection rate $\beta = 1.7582$ followed by p, K, γ, μ, a and r respectively. For the free virus population, the most sensitive parameter is the rate of release of free virus $\gamma = 1.7629$ followed by μ, β, p, K, a and r respectively.

4.2. Local stability of the endemic steady state

In this section, we study the local stability of the endemic equilibrium (x^*, y^*, v^*) of the model, where x^*, y^*, v^* are defined in (15). For the endemic equilibrium point, the Jacobian matrix of the model (1) is

$$J = \begin{bmatrix} r - M_1\left(\dfrac{(\beta+\mu)(R_0-1)}{\gamma-a-p}\right) - \beta M_2 & -M_1 + p & -M_3 \\ \beta M_2 & -a-p & M_3 \\ -\beta M_2 & \gamma & -\mu - M_3 \end{bmatrix}, \tag{16}$$

where

$$\begin{aligned} M_1 &= \frac{r(\gamma-a-p) - a(\beta+\mu)(R_0-1)}{(\gamma-a-p)+(\beta+\mu)(R_0-1)}, \\ M_2 &= \left(\frac{(\beta+\mu)(R_0-1)}{(\mu+(\beta+\mu)(R_0-1)}\right)^2 \\ M_3 &= \frac{\beta\mu^2}{(\mu+(\beta+\mu)(R_0-1))^2}. \end{aligned}$$

It is difficult to obtain analytical formulas for the eigenvalues of this Jacobian either by direct computation or by finding the zeros of the characteristic polynomial. It is also very difficult to obtain useful analytical formulas by the alternative method of checking local stability based on the characteristic polynomial and the Routh-Hurwitz criteria (see, e.g. [12]). However, it is very easy with modern software packages such as Maple, Matlab or Mathematica to compute the eigenvalues of the Jacobian numerically or to numerically test the Routh-Hurwitz criteria and check if the real parts of the eigenvalues are all negative (local asymptotic stability) or if one or more has a positive real part (unstable).

The results of numerical calculations for the selected parameter values given in Table 4 are given in section 5.

5. Numerical Simulation

5.1. Disease-free solutions

We use the parameter values in Table 2 which correspond to a disease-free equilibrium. We first compute the basic reproduction number and obtain the value $R_0 = 0.5146 < 1$ which means that the disease-free equilibrium is locally asymptotically stable and the HBV infection dies out. The numerical solutions for uninfected cells (x), infected cells

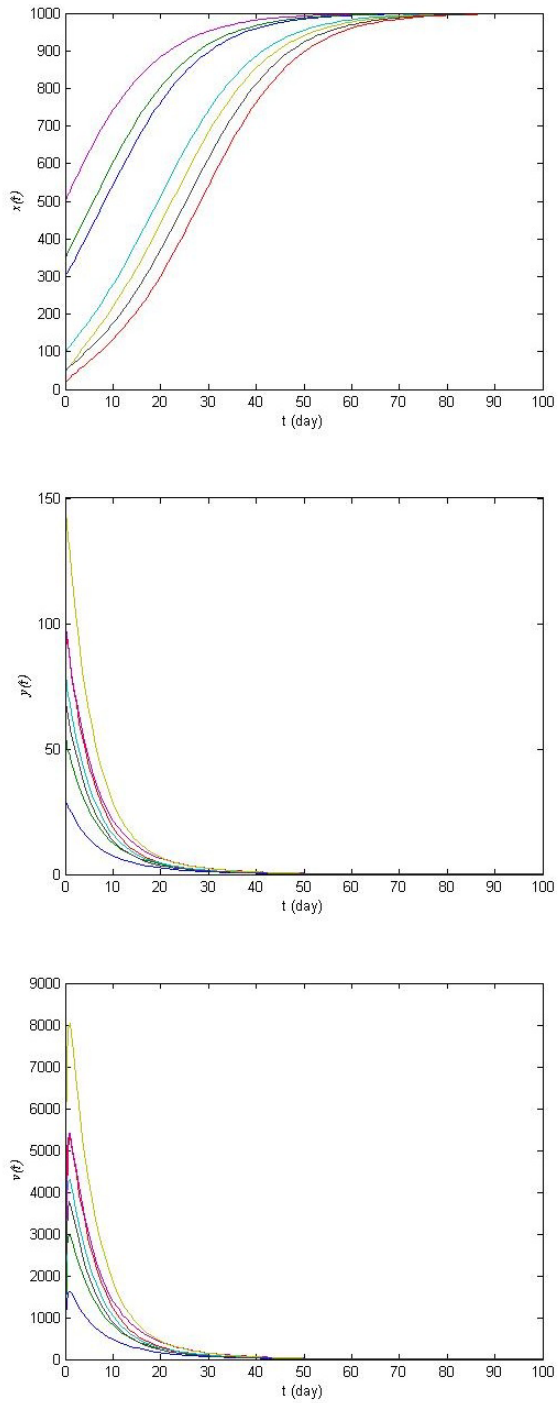

Figure 1: Graphs of numerical solutions showing the global stability of the disease-free equilibrium (1000, 0, 0) when $R_0 = 0.5146 < 1$.

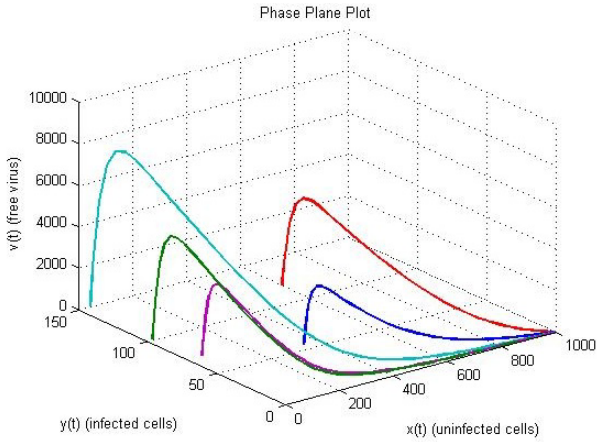

Figure 1: (Continued.)

(y) and free virus (v) for seven different initial conditions $x(0)$, $y(0)$, $v(0)$ are shown in Figure 1. It can be seen that the populations of uninfected cells (x), infected cells (y) and free virus (v) converge to the disease-free equilibrium values $E_1 = (1000, 0, 0)$ in agreement with the global asymptotic stability

5.2. Endemic solutions

We use the parameter values in Table 4 which correspond to an endemic equilibrium point $(x^*, y^*, v^*) = (996.98, 2.45, 1060.50)$. For these values, the value of $R_0 = 2.0637 > 1$ which shows that the disease-free equilibrium is unstable and that the endemic equilibrium exists. For these parameter values the eigenvalues of the Jacobian in Fig. 16 are:

$$\lambda_1 = -0.085, \quad \lambda_2 = -0.2989, \quad \lambda_3 = -0.7978. \tag{17}$$

Since the real parts of all eigenvalues are negative, the endemic equilibrium is locally asymptotically stable. We have also numerically checked the Routh Hurwitz conditions which also show that the endemic equilibrium is locally asymptotically stable.

We have also computed the numerical solutions of the system (1) corresponding to the parameter values in Table 4 for the same seven initial conditions used for the disease-free equilibrium case. The results are in Fig 5.2, the uninfected cell population (x), the infected cell population (y) and the free virus population (v) are converging. We found that the populations are converging to $(x, y, v) = (996.98, 2.45, 1060.50)$ in good agreement with the endemic equilibrium $E_+ = (996.98, 2.45, 1060.50)$.

6. Conclusion

In this paper, we have constructed a novel HBV epidemic model which includes a logistic growth term and a non-cytolytic cure process of infected cells. Using the next generation method, we obtained a formula for the basic reproduction number R_0. We then derived

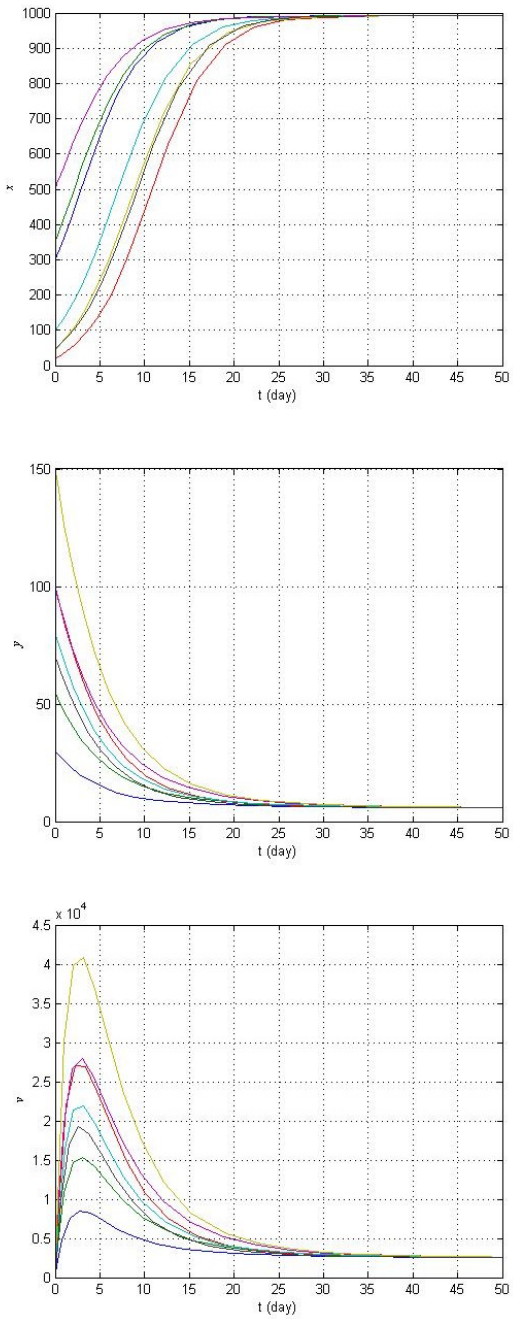

Figure 2: Graphs of numerical solutions and the global stability of the endemic equilibrium $E^*(996.98, 2.45, 1060.50)$ and the basic reproduction number $R_0 = 2.0637 > 1$.

formulas for the sensitivity indices of R_0 for changes in the parameters of the model. We found that the parameters that have the most effect in reducing the value of R_0 for the disease-free equilibrium are γ, β, μ, p, a, respectively. From the sensitivity indices

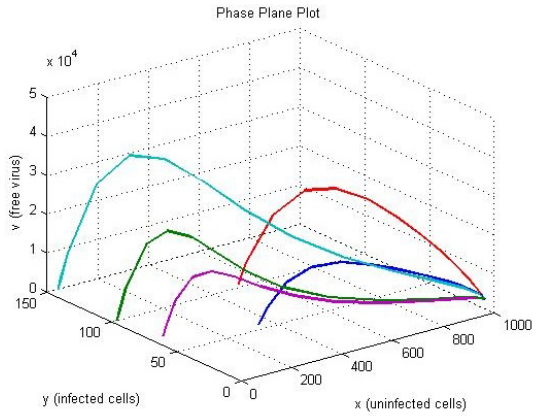

Figure 2: (Continued.)

for the endemic equilibrium, we found that the parameters that have the most effect in reducing the number of infected cells are β, p and that the parameters β, γ have the most effect in reducing the free-virus population. We also proved that the disease-free equilibrium is globally asymptotically stable for $R_0 < 1$. We also showed that an endemic equilibrium exists only if $R_0 > 1$. Numerical simulations were conducted to support our analytic results.

Acknowledgements

This research was supported by the Science and Technology Research Institute of King Mongkuts University of Technology North Bangkok. We would also like to the Department of Mathematics, Faculty of Applied Science, King Mongkuts University of Technology North Bangkok for partial financial support.

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