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Research Article

Modeling the effect of drug therapy on hepatitis B virus infection

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Abstract - With an increase in hepatitis B virus (HBV) infection every year around the world, particularly in developing countries, a mathematical model involving the relationship between HBV and the cytotoxic T lymphocytes (CTL)-mediated immunity is constructed. The model also includes non-cytolytic cure process and drug therapy of HBV. The basic reproduction number R_0 is calculated and becomes threshold for equilibrium point stabilities. Sensitivity analysis is carried out to seek for potential parameters that could reduce overall spread of HBV infection. The numerical and sensitivity analyses show that both effectiveness of drug therapy in blocking new infection and non-cytolytic cure process play a key role in reducing the concentration of infected hepatocytes and free virus. Therefore, HBV drug therapy should be encouraged as one of the approaches to reduce overall chronic HBV infection.

Keywords: Hepatitis B virus, cytotoxic T lymphocytes, hepatocyte, sensitivity, drug therapy

1. Introduction

Hepatitis is a leading cause of inflammation of the liver. Hepatitis viruses are the most common cause of hepatitis in the world. There are five main hepatitis viruses, called hepatitis A, B, C, D and E (Zuckerman, 1996). Among these, types B and C lead to chronic disease in hundreds of millions of people and, together, are the most common cause of liver cirrhosis and cancer. In particular, hepatitis B virus (HBV) is the most serious type of viral hepatitis, which is now also as a major infectious disease that is spreading around the world especially in Western Pacific and South-East Asia (Hou *et al*., 2005; Richard and Hock Foong, 2011; WHO, 2017; Henry *et al*., 2014). There are two types of hepatitis B which are acute and chronic. Infection of the hepatitis B virus can be transmitted in a variety of ways and is thought to be 50–100 times more infectious than HIV (Foundation for Liver Research, 2004; Liaw *et al*., 2012; WHO, 2017). In general, anyone can get HBV infected from person to person through blood, semen or other body fluids, through injecting drugs by sharing syringes, unprotected sexual intercourse and the most common way of infection is the vertical transmission from mother to infant at birth (Lim *et al*., 1997; Behrouz *et al*., 2011). The WHO has reported that an estimated 257 million people worldwide have been infected with HBV. In 2015, hepatitis B resulted in 887,000 deaths mostly from complications (WHO, 2017). However, most of new infections could be prevented through vaccination and new techniques in molecular/cellular biology and immune processes for chronic HBV.

Chronic hepatitis B is not curable, but it is treatable. The goal of therapy is to reduce the risk of complications, including premature death. Treatment can help to prevent cirrhosis, liver failure and liver cancer by reducing hepatitis B viral. Current treatments for hepatitis B are divided into two general categories. The first are immune modulator drugs which are interferon type drugs that boost the immune system to help get rid of the hepatitis B virus. They are given as a dosage over 6 months to 1 year, where the amount of interferon for each dosage and the number of times taking in a week depending on doctor's decision for each patient. The second are antiviral drugs which are drugs that stop or reduce the hepatitis B virus from reproducing, leading to a decrease in inflammation and damage to the liver. These are taken as a pill once a day for at least 1 year and usually longer (Perrillo, 2009; Richard and Hock Foong, 2011).

Furthermore, several pieces of evidence have shown that the immune cells in the body could also kill the virus. Cytotoxic cells are also called Cytotoxic T lymphocytes (CTL) and are a type of immune cell that can kill other cells and are thought to play a major role in viral clearance during acute infections, including hepatitis B virus (HBV) infection (Andersen *et al*., 2006, Kerkvliet *et al*., 2010).

Many researchers have studied and increased understanding of the interaction between HBV and immune system through mathematical models (e.g. Nowak *et al*., 1996; Lewin *et al*., 2001; Wodarz, 2003; Ciupe *et al*., 2006, 2007a,b; Koonprasert *et al*., 2016).

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In this paper we formulate a mathematical modeling of chronic HBV infection of hepatocytes. The model includes the interaction between HBV and cytotoxic cells, a non-cytolytic cure process, and drug therapy of HBV. Equilibrium points and their stability are determined including the basic reproduction number and its sensitivity analysis. Finally, numerical solutions are carried out to seek possible parameters that could lead to a decrease in HBV infection.

2. Model formulation

The mathematical model in this study is modified from the work by (Long *et al*., 2007) and (Mboya *et al*., 2015). This model contains four variables at time t : x is the concentration of the uninfected hepatocytes, y is the concentration of the infected hepatocytes, v is the concentration of free virus, and z is the concentration of cytotoxic T lymphocyte (CTL) cells.

The schematic diagram of this model is shown in Figure 1.

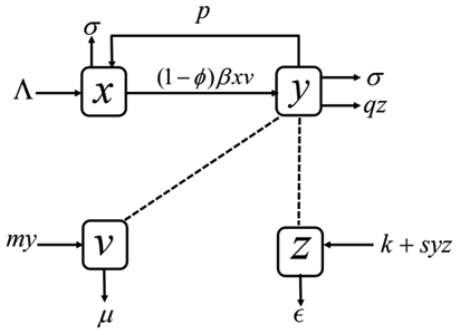

Figure 1. A schematic diagram of hepatitis B virus infection model.

The model is given by the following nonlinear system of differential equations.

$$\frac{dx}{dt} = \Lambda - (1-\phi)\beta xv + py - \sigma x \tag{1}$$

$$\frac{dy}{dt} = (1-\phi)\beta xv - py - \sigma y - qyz \tag{2}$$

$$\frac{dv}{dt} = my - \mu v \tag{3}$$

$$\frac{dz}{dt} = k + syz - \grave{o}z \tag{4}$$

with initial condition

$$x(0) \geq 0,\ y(0) \geq 0,\ v(0) \geq 0,\ z(0) \geq 0\,.$$

The parameters used in this model are defined as Λ is the constant production rate of uninfected hepatocytes, β is the rate of infection of uninfected hepatocytes by free virus, ϕ is the efficiency of drug therapy in blocking new infection, p is the rate of cure of infected hepatocytes by non-cytolytic cure process, σ is the natural death rate of hepatocytes, q is the death rate of infected hepatocytes due to immune-mediated killing, m is the rate of free virus generated from infected hepatocytes, μ is the death rate of free virus, k is the production rate of CTL cell, s is the activation rate of CTL cells by infected hepatocytes and $\grave{o}$ is the death rate of CTL cells.

2.1 Equilibrium point of the model

There are two equilibrium points in this model which are:

1. Disease-free equilibrium point $E_0 = (x_0, y_0, v_0, z_0)$ $= (\frac{\Lambda}{\sigma}, 0, 0, \frac{k}{\grave{o}})$.

2. Endemic equilibrium point $E_1 = (x^*, y^*, v^*, z^*)$ where x^* is a positive solution of

$$(((1-\phi)\beta m)^2\varepsilon + (1-\phi)\beta m\sigma\mu s)x^2 + (-((1-\phi)(p+\sigma)\beta m\mu + (1-\phi)$$
$$\beta mqk\mu + (1-\phi)\beta mp\mu\varepsilon + (1-\phi)\beta m\Lambda\mu s + (p+\sigma)\sigma s\mu^2))x +$$
$$(p+\sigma)p\varepsilon\mu^2 + pqk\mu^2 + \Lambda s(p+\sigma)\mu^2 = 0,$$

$$y^* = \frac{(\Lambda - \sigma x^*)\mu}{(1-\phi)\beta x^* m - p\mu}, v^* = \frac{my^*}{\mu} \text{ and } z^* = \frac{k}{\varepsilon - sy^*}.$$

2.2 Basic reproduction number (R_0)

The basic reproduction number of this model is calculated by using next generation matrix method (van den Driessche *et al*., 2002). From our model, we have

$$R_0 = \frac{(1-\phi)\beta\Lambda m\varepsilon}{\sigma\mu(\varepsilon p + \varepsilon\sigma + qk)}.$$

2.3 Stability analysis

The local stability of each equilibrium point within this model is determined from the Jacobian matrix at that equilibrium point of the system of equations (1)-(4).

The Jacobian matrix is

$$J(x,y,v,z) = \begin{bmatrix} -(1-\phi)\beta v - \sigma & p & -(1-\phi)\beta x & 0 \\ (1-\phi)\beta v & -(p+\sigma+qz) & (1-\phi)\beta x & -qy \\ 0 & m & -\mu & 0 \\ 0 & sz & 0 & sy - \grave{o} \end{bmatrix}.$$

Theorem 2.1 (local stability at E_0) If $R_0 < 1$, then the disease-free equilibrium point (E_0) is locally asymptotically stable. If $R_0 > 1$, then the disease-free equilibrium point (E_0) is unstable.

Proof. The Jacobian matrix of the system of equations (1)-(4) at E_0 is

$$J(x_0,y_0,v_0,z_0) = \begin{bmatrix} -\sigma & p & -\frac{(1-\phi)\beta\Lambda}{\sigma} & 0 \\ 0 & -(p+\sigma+\frac{qk}{\grave{o}}) & \frac{(1-\phi)\beta\Lambda}{\sigma} & 0 \\ 0 & m & -\mu & 0 \\ 0 & \frac{sk}{\grave{o}} & 0 & -\grave{o} \end{bmatrix}.$$

From Jacobian matrix above, we set $det(J(E_0) - \lambda I) = 0$ to

find eigenvalues, then we obtain

$$(-\sigma-\lambda)(-\varepsilon-\lambda)(\lambda^2+(p+\sigma+\mu+\frac{qk}{\grave{o}})\lambda+\mu(p+\sigma+\frac{qk}{\grave{o}})-\frac{(1-\phi)\beta\Lambda m}{\sigma})=0.$$

Thus, $\lambda_1=-\sigma<0, \lambda_2=-\varepsilon<0$ and $\lambda^2+(p+\sigma+\mu+\frac{qk}{\grave{o}})\lambda$ $+\mu(p+\sigma+\frac{qk}{\grave{o}})-\frac{(1-\phi)\beta\Lambda m}{\sigma}=0$ which is considered in the form of $\lambda^2+a_1\lambda+a_2=0.$ Therefore, we have $a_1=p+\sigma+\mu+\frac{qk}{\grave{o}}$ and $a_2=\mu(p+\sigma+\frac{qk}{\grave{o}})-\frac{(1-\phi)\beta\Lambda m}{\sigma}=$

$\mu(p+\sigma+\frac{qk}{\grave{o}})(1-R_0).$

We obtain that $a_1>0$ and $a_2>0$ when $R_0<1$. Hence, by the criteria of Routh-Hurwitz, E_0 is locally asymptotically stable when $R_0<1$, and E_0 is unstable when $R_0>1$. This completes the proof.

Theorem 2.2 (local stability at E_1) When $R_0>1$, the endemic equilibrium point (E_1) is stable.

Proof. Consider Jacobian matrix of endemic equilibrium point, we have

$$J(x^*,y^*,v^*,z^*)=\begin{bmatrix}-(1-\phi)\beta v^*-\sigma & p & -(1-\phi)\beta x^* & 0\\ (1-\phi)\beta v^* & -(p+\sigma+qz^*) & (1-\phi)\beta x^* & -qy^*\\ 0 & m & -\mu & 0\\ 0 & sz^* & 0 & sy^*-\grave{o}\end{bmatrix}.$$

By calculating $det(J(E_0)-\lambda I)=0$, we have

$$\lambda^4+(\varepsilon+(1-\phi)\beta v^*+2\sigma+p+qz^*+\mu-sy^*)\lambda^3+(qsy^*z^*+$$
$$((1-\phi)\beta v^*+\sigma)\varepsilon+((1-\phi)\beta v^*+\sigma)(p+\sigma+qz^*+\mu)$$
$$+(p+\sigma+qz^*)\mu-((1-\phi)\beta v^*+\sigma)sy^*-(p+\sigma+qz^*+\mu)sy^*+$$
$$\varepsilon(p+\sigma+qz^*+\mu)-(1-\phi)\beta x^*m-(1-\phi)\beta pv^*)\lambda^2$$
$$+(qs\mu y^*z^*+qsy^*z^*((1-\phi)\beta v^*+\sigma)+(1-\phi)s\beta mx^*y^*$$
$$+\varepsilon(p+\sigma+qz^*)\mu+((1-\phi)\beta v^*+\sigma)(p+\sigma+qz^*)\mu+(1-\phi)\beta spy^*v^*$$
$$+(1-\phi)^2\beta^2mx^*v^*-((1-\phi)\beta v^*+\sigma)(p+\sigma+qz^*+\mu)sy^*-s\mu y^*$$
$$(p+\sigma+qz^*)-((1-\phi)\beta v^*+\sigma)(p+\sigma+qz^*+\mu)\varepsilon-(1-\phi)\beta\varepsilon mx^*$$
$$-((1-\phi)\beta v^*+\sigma)(1-\phi)\beta mx^*-(1-\phi)\beta p\mu v^*-(1-\phi)\beta\varepsilon pv^*).$$
$$\lambda+qs\mu y^*z^*((1-\phi)\beta v^*+\sigma)+((1-\phi)\beta v^*+\sigma)(1-\phi)\beta msx^*y^*$$
$$+((1-\phi)\beta v^*+\sigma)(p+\sigma+qz^*)\varepsilon u+(1-\phi)\beta sp\mu y^*v^*+\varepsilon(1-\phi)^2$$
$$\beta^2mx^*v^*-((1-\phi)\beta v^*+\sigma)(p+\sigma+qz^*)s\mu y^*-((1-\phi)\beta v^*+\sigma)$$
$$(1-\phi)\beta m\varepsilon\hat{x}-(1-\phi)\beta\varepsilon upv^*-(1-\phi)^2\beta^2msx^*y^*v^*=0.$$

Consider the above equation in the form $\lambda^4+a_1\lambda^3+a_2\lambda^2+$ $+a_3\lambda+a_4=0$, therefore by the criteria of Routh-Hurwitz, E_1 is stable when $a_1>0$, $a_3>0$, $a_4>0$ and $a_1a_2a_3>a_3^2+a_1^2a_4$.

2.3 Sensitivity analysis

The sensitivity indices of the basic reproduction number R_0 of the model are determined to seek for the best strategies to reduce the HBV infection of hepatocytes. They are calculated by using the technique of the normalized forward sensitivity index (Ngoteya and Gyekye, 2015; Samsuzzoha *et al*., 2013) i.e. the normalized forward sensitivity index of R_0 with respect to a parameter value P is given by:

$$S_P^{R_0}=\frac{\partial R_0}{\partial P}\times\frac{P}{R_0}.$$

Therefore, by using the parameters value from Table 2, the sensitivity indices are given in Table 1. We obtained that the positive sign of sensitivity index of R_0 (i.e. with respect to $\Lambda, \beta, m, \varepsilon$) leads to the result that when these parameters increase, the value of R_0 increases. Hence, we should try to reduce these mentioned parameters to reduce the value of R_0. On the contrary, the negative sign of sensitivity index of R_0 (i.e. with respect to ϕ,p,σ,μ,q,k) gives a result that when these parameters increase, the value of R_0 decreases.

Table 1. Numerical values of sensitivity indices of R_0

Parameters	Index at Parameter Value	Sign
Λ	+1	positive
β	+1	positive
m	+1	positive
ε	+0.0045	positive
k	-0.0045	negative
ϕ	-1	negative
p	-0.9641	negative
σ	-1.0313	negative
μ	-1	negative
q	-0.0045	negative

3. Numerical simulation

In this section, the system of equations (1)-(4) are solved numerically. The parameters within this model are chosen as appropriate and are shown in Table 2. The numerical results are shown in figures 2-5.

Table 2. Parameters values used in numerical study.

Parameter	Description	Value	Reference
Λ	Constant production rate of uninfected hepatocytes.	10000 cell/ml/day	Yousfi *et al*. (2011)
β	Rate of infection of uninfected hepatocytes by free virus.	6.1×10^{-10}ml vir^{-1}day^{-1}	Ciupe *et al*. (2014)
ϕ	The efficiency of drug therapy in blocking new infection.	0.5 day^{-1}	Assume
p	Rate of cure of infected hepatocytes by non-cytolytic cure process.	0.12 day^{-1}	Koonprasert *et al*. (2016)
σ	Natural death rate of hepatocytes.	0.0039 day^{-1}	Bralet *et al*. (1994); MacDonald (1961); Eikenberry *et al*. (2009)
q	Death rate of infected hepatocytes due to immune-mediated killing.	7×10^{-4} ml^{-1}cell^{-1}day^{-1}	Ciupe *et al*. (2007b)
m	Rate of free virus generated from infected hepatocytes.	300 vir cell day^{-1}	Whalley *et al*. (2001)
μ	Death rate of free virus.	0.67 day^{-1}	Nowak and May (2000)
k	Production rate of cytotoxic cell.	0.403	Mboya *et al*. (2015)
s	Activation rate of CTL cells by infected hepatocytes.	4.4×10^{-7} ml^{-1}cell^{-1}day^{-1}	Ciupe *et al*. (2007b)
ε	Death rate of CTL cells.	0.5 day^{-1}	Ahmed and Gray (1996)

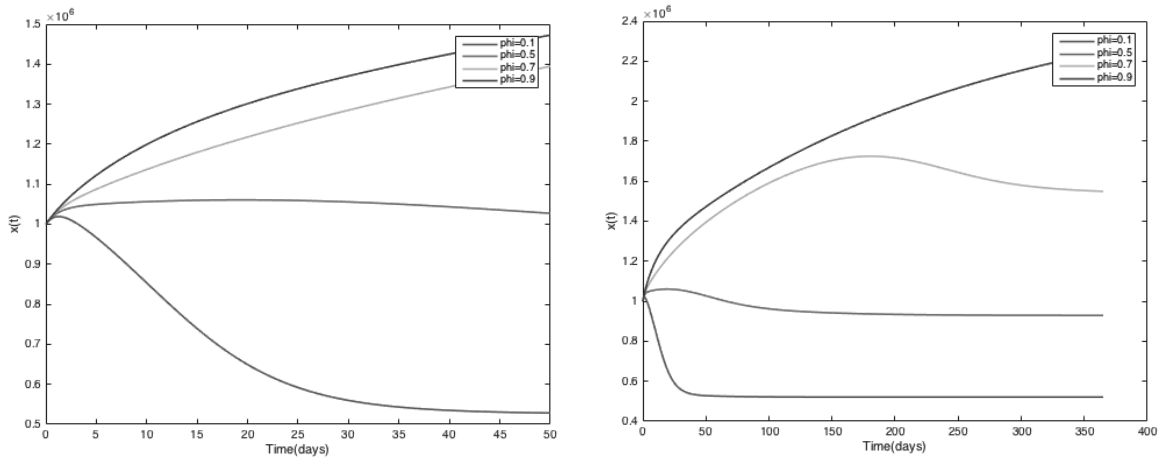

Figure 2. Numerical solution of the concentration of the uninfected hepatocytes (x) obtained using parameters: $\Lambda=10000,\ \beta=0.61\times10^{-10}, p=0.12, \sigma=0.0039, q=7\times10^{-4}, m=300, s=0.67,\ \varepsilon=0.5$ when $\phi=0.1, 0.5, 0.7, 0.9$ varies. (left) 50 days of time and (right) 365 days of time.

Figure 2 shows that when the efficiency of drug therapy of free virus increases from $\phi=0.1$ to $\phi=0.9$, the result demonstrates an increase in number of uninfected hepatocytes. It shows that with higherϕ, the equilibrium value of x is higher.

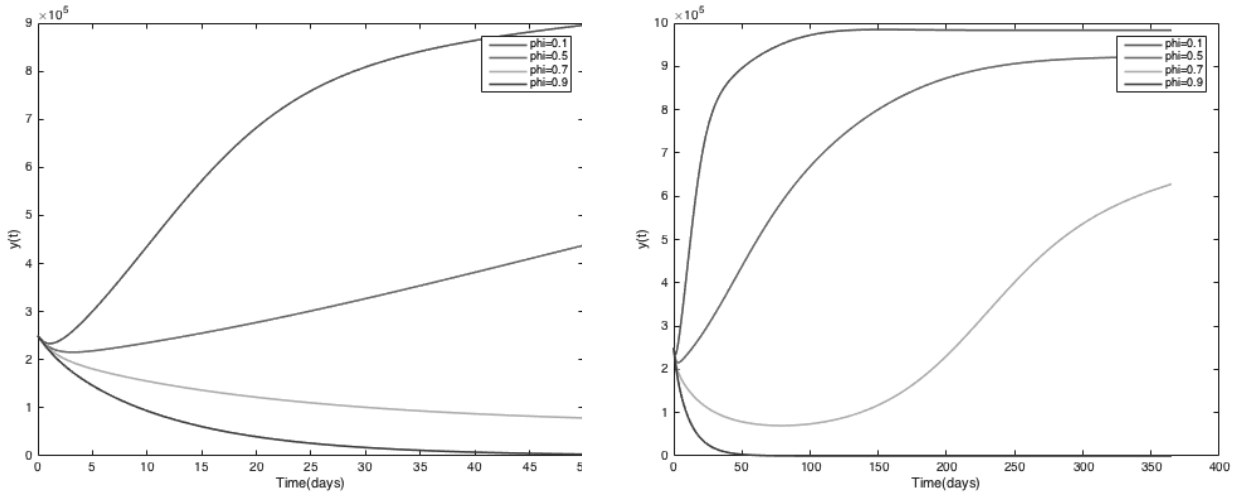

Figure 3. Numerical solution of the concentration of the infected hepatocytes (y) obtained using parameters: $\Lambda = 10000,\ \beta = 0.61\times10^{-10}, p = 0.12, \sigma = 0.0039, q = 7\times10^{-4}, m = 300, s = 0.67,\ \varepsilon = 0.5$ when $\phi = 0.1, 0.5, 0.7, 0.9$ varies**.** (left) 50 days of time and (right) 365 days of time.

Figure 3 shows the dynamic of the number of infected hepatocytes at $\phi = 0.1$ to $\phi = 0.9$, it can be seen that when ϕ increases, the concentration of infected hepatocytes decreases and reaches lower equilibrium values. Interestingly, the concentration of infected hepatocytes decreases since the starting point.

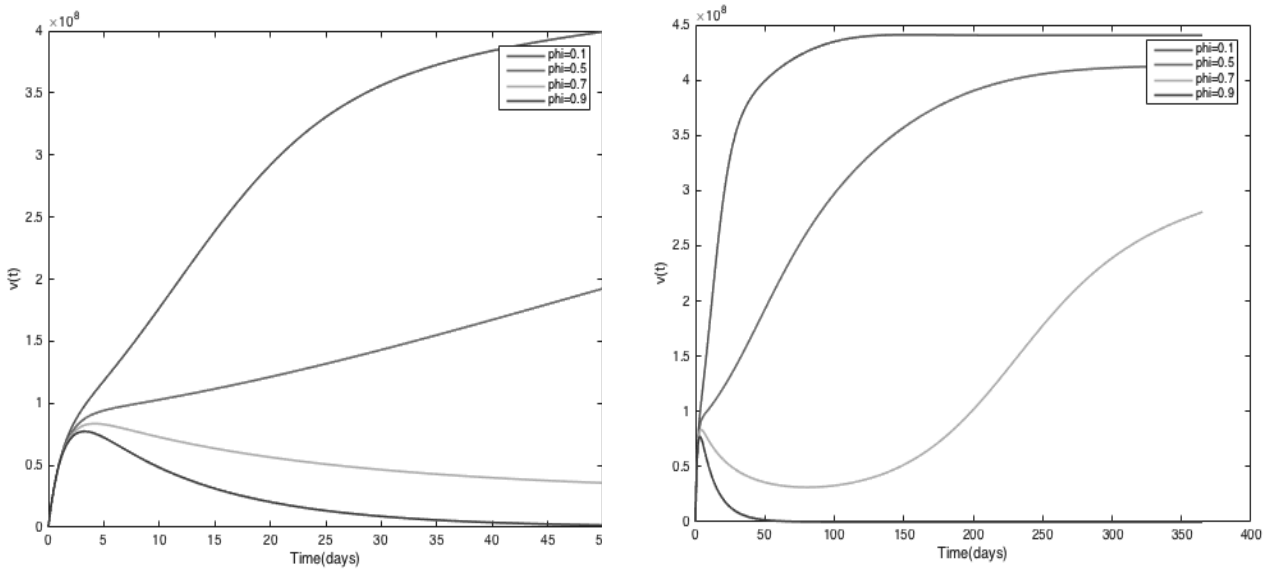

Figure 4. Numerical solution of the concentration of the free virus (v) obtained using parameters: $\Lambda = 10000,\ \beta = 0.61\times10^{-10}, p = 0.12, \sigma = 0.0039, q = 7\times10^{-4}, m = 300, s = 0.67,\ \varepsilon = 0.5$ when $\phi = 0.1, 0.5, 0.7, 0.9$ varies**.** (left) 50 days of time and (right) 365 days of time.

Figure 4 shows the dynamic of the concentration of free virus over time at $\phi = 0.1$ to $\phi = 0.9$. For $\phi = 0.1$ to $\phi = 0.5$, it can be seen that the concentration of free virus in the blood stream increases, and reaches equilibrium values of about 4.4×10^8 and 4.2×10^8, respectively. For $\phi = 0.7$, the dynamic decreases in the first stage after which it increases and reaches an equilibrium value of about 2.8×10^8. At $\phi = 0.9$, the peak occurs rapidly in the first 5 days, after which it decreases dramatically.

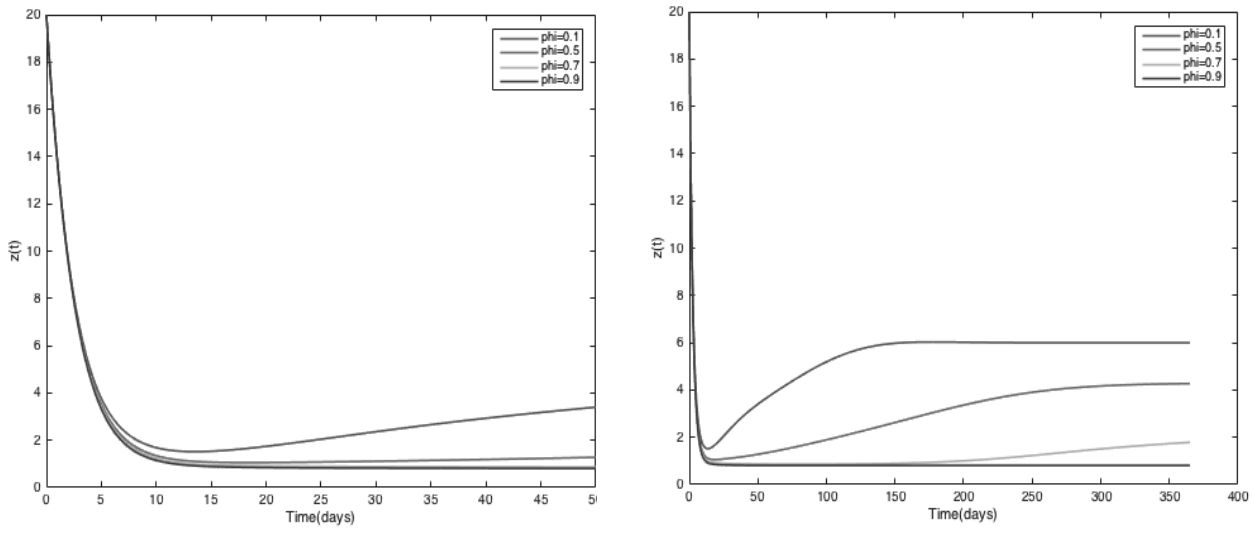

Figure 5. Numerical solution of the concentration of the cytotoxic T lymphocytes (CTL) cells (z) obtained using parameters: $\Lambda = 10000,\ \beta = 0.61\times10^{-10}, p = 0.12, \sigma = 0.0039, q = 7\times10^{-4}, m = 300, s = 0.67,\ \varepsilon = 0.5$ when $\phi = 0.1, 0.5, 0.7, 0.9$ varies**.** (left) 50 days of time and (right) 365 days of time.

Figure 5 shows the dynamic of CTL cells when $\phi = 0.1$ to $\phi = 0.9$, the results demonstrate a decrease with lower equilibrium value when ϕ is higher, respectively.

4. Conclusions

In this paper, we construct a mathematical model of HBV infection of hepatocytes. We obtain two main equilibrium points (the disease-free and the endemic ones) and the basic reproduction number is $R_0 = \frac{(1-\phi)\beta\Lambda m\varepsilon}{\sigma\mu(\varepsilon p + \varepsilon\sigma + qk)}$. Our results show that the disease-free equilibrium point is locally asymptotically stable if $R_0 < 1$ and unstable when $R_0 > 1$. As for the endemic equilibrium point, it is locally asymptotically stable since the real parts of all eigenvalues are negative. Our sensitivity analysis and numerical simulations indicate that the efficiency of drug therapy in blocking new infection (ϕ) is an important factor that could reduce the number of HBV infection of hepatocytes dramatically, therefore it could be encouraged as a promising approach to overall disease control.

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