Global Analysis of a General HBV Infection Model

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***Abstract*—Mathematical models have been used to understand the factors that govern infectious disease progression in viral infections. Two basic models of within-host viral infection, proposed by Nowak et. al. and Perelson et. al. respectively, have been widely used in the studies of HBV and HIV infections. However, the loss term of viral particles when it enters the target cells are both ignored by these two models. Leenheer and Smith provided a general virus dynamic model with the loss term of viral particles, which make the above two basic models only be special cases. But the basic reproduction numbers of all above models are proportional to the number of total cells of the host's organ prior to the infection(when used for HBV infection) or the normal target cell level(when used for HIV infection). On the other hand, the global asymptotically stable condition of the endemic equilibrium about Leenheer and Smith's model is related to the initial value of the growth function of uninfected cell. In this paper, we formulate an amended Leenheer and Smith's model with standard incidence, the basic reproduction numbers were no more dependent on the number of total cells of the host's organ. If the basic reproduction number of virus is less than one, the infection-free equilibrium is globally asymptotically stable and the virus is cleared; if the basic reproduction number is great than one, then the virus persist in the host, and solutions approach either an endemic equilibrium or a periodic orbit. The periodic orbit can be ruled out in some cases but not in general. The globally asymptotically stable condition of the endemic equilibrium is only determined by the model parameters.**

I. Introduction

The infection with Hepatitis B virus (HBV) is a major health problem in the world. The WHO has reported that more than 2 billion people worldwide has been infected by HBV. There are over 350 millions who are chronically infected with HBV[1]. 25-40% of these chronic infection carriers will die from liver cirrhosis or primary hepatocellular carcinoma[2].

Using mathematical models to enhance our understanding of the dynamics of chronic viral infections has been proved fruitful([3], [4], [5]), and using mathematical models to interpret experimental and clinical results has made a significant contribution to the fields of anti- HIV, HBV and or HCV infections([6], [7], [8]). Mathematical analysis of the HBV dynamics not only provide important quantitative insights into the pathogenesis, but also lead to design treatment strategies which would more effectively bring the infection under control[9].

The basic models of within-host viral infection, proposed by Nowak et. al. [2] and Perelson et. al. [10] have been widely used in the studies of HBV and HIV infections. The basic models, describing the dynamics of interaction between uninfected cells $x(t)$, infected cells $y(t)$ and free virus $v(t)$, take the form of

$$\begin{cases} \dot{x} = f(x) - \beta vx \\ \dot{y} = \beta vx - ay \\ \dot{v} = ky - uv \end{cases} \tag{1}$$

where the functional form of f is defined differently by:
1). Nowak and May[2]: $f(x) = f_1(x) = \lambda - dx$.
2). Perelson and Nelson[10]:

$$f(x) = f_2(x) = \lambda - dx + px(1 - \frac{x}{x_{\max}}).$$

Uninfected cells are assumed to be produced at the constant rate λ, die at the rate of dx and become infected at the rate of βxv. Infected cells are thus produced at the rate of βxv and die at the rate ay. Free virions are generated from infected cells at the rate of ky and decay at the rate of uv. Parameter p is the maximum proliferation rate of uninfected cells and $x_{\max}$ is the maximum capacity of host's organ cells.

Obviously, as pointed by Leenheer and Smith[11], both Perelson et. al. and Nowak et. al. ignored that the loss term βvx should appear in the v equation, i.e.,

$$\dot{v} = ky - uv - \beta vx \tag{2}$$

representing the loss of free virus particles when they enter the target. Leenheer and Smith discussed a more general model as follows:

$$\begin{cases} \dot{x} = f(x) - \beta vx \\ \dot{y} = \beta vx - ay \\ \dot{v} = ky - uv - i\beta vx \end{cases} \tag{3}$$

which $f(x)$ is a smooth function satisfying:

$$\begin{array}{l} f(x) > 0, 0 \le x < \bar{x}, \\ f(\bar{x}) = 0, f'(\bar{x}) < 0, \\ f(x) < 0, x > \bar{x} \end{array} \tag{4}$$

where $\bar{x}$ represents the number of total cells of the host's organ prior to the infection when it is used for HBV infection or normal target cell level when it is used for HIV infection. Here $i = 0$ means ignoring the loss of viral particle, $i = 1$ otherwise. Thus $f_1(x) = \lambda - dx$ and $f_2(x) = \lambda - dx + px(1 - x/x_{\max})$ are the special cases. Leenheer and Smith also gave the stable analysis of the model (3) and oscillation behaviors when $f(x) = f_2(x)$. Obviously the rate of infection in model (3) is bilinear in the virus v and the uninfected target cells x, the basic reproduction number of models (3) is given by $R_0 = \bar{x}(\beta k - ia)/au$, since R_0 is proportional to $\bar{x}$, which implies that an individual with a smaller organ or smaller target cell level may be more resistent to virus infection. Hence, it

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may not be reasonable for the basic mathematical models to describe virus infection in a sense. Paper[12] pointed out that actual incidence rates are probably not strictly linear, then, they proposed a HIV model with saturated mass action $\beta xv/(1+\alpha v)$ under the assumption that a less than linear response in v could occur due to saturation at high virus concentration. Paper [13], [14] employed a standard incidence function to describe the hepatitis B virus infection as follows:

$$\begin{cases} \dot{x} = \lambda - dx - \dfrac{\beta vx}{x+y} \\ \dot{y} = \dfrac{\beta vx}{x+y} - ay \\ \dot{v} = ky - uv. \end{cases} \tag{5}$$

The basic reproduction number of model (5) is $R_0 = \beta k/au$ which is independent of the number of total cells of human liver λ/d. It is proved that if $R_0 < 1$, then the infection-free steady state is globally asymptotically stable[13]. If $R_0 > 1$, then the endemic steady state is globally asymptotically stable[14].

Mover, the other amended mother model based on Perelson and Nelson's model was discussed by Yu Ji[15] as follows:

$$\begin{cases} \dot{x} = \lambda - dx + px(1 - \dfrac{x}{x_{\max}}) - \dfrac{\beta vx}{x+y} \\ \dot{y} = \dfrac{\beta vx}{x+y} - ay \\ \dot{v} = ky - uv. \end{cases} \tag{6}$$

The basic reproduction number of model (6) is $R_0 = \beta k/au$ which is also independent of the number of human liver cells. The result showed that if $R_0 < 1$, then the infection-free equilibrium is globally asymptotically stable and the virus is cleared; if $R_0 > 1$, then the virus persists in the host, and solutions approach either an endemic equilibrium or a periodic orbit. But the local stability which is needed for globally asymptotical stability of the endemic equilibrium was given with another additional condition $a_1a_2 > a_3$.

Obviously, both model (5) and model (6) all ignored the loss term of viral particles. In this paper, we formulate a general model as follows:

$$\begin{cases} \dot{x} = f(x) - \dfrac{\beta vx}{x+y} \\ \dot{y} = \dfrac{\beta vx}{x+y} - ay \\ \dot{v} = ky - uv - i\dfrac{\beta vx}{x+y}. \end{cases} \tag{7}$$

Here $f(x)$ satisfy the condition (4), and $i = 0$ means we ignore the loss of viral particles when it enters target cell, otherwise, we choose $i = 1$. Thus model (5) and model (6) are only two special cases of our model (7) when $i = 0$. The basic reproduction number of our model is $R_0 = \beta(k - ia)/au$, which also make the basic reproduction number of Model (5) and (6) the special case when $i = 0$. If $R_0 \geqslant 1$, our model has two steady states:

$$E_0 = (\bar{x}, 0, 0), E_e = (x_e, y_e, v_e). \tag{8}$$

which $f(\bar{x})$=0, $v_e = \dfrac{k - ia}{u} y_e, y_e = \dfrac{f(x_e)}{a}$, and x_e satisfy

$$f(x_e) - a(R_0 - 1)x_e = 0. \tag{9}$$

Since $f(x)$ satisfy condition (4), we know that there must exist $x_e \in (0, \bar{x})$ which satisfy (9). These two steady states represent the infection-free steady state and the endemic steady state respectively. Note the biological meaning, E_e does not exist if $R_0 < 1$, and it becomes E_0 when $R_0 = 1$. It is easy to see that $x_e < \bar{x}$ when $R_0 > 1$. This means the infection of the virus will reduce the total number of uninfected cells in host.

The main purpose of this paper is to discuss the globally asymptotical stability of E_0 and E_e for both $i = 0, i = 1$. For the endemic equilibrium E_e, when $i = 0, f(x) = f_2(x)$, the local stable condition $a_1a_2 > a_3$ was proved without any additional condition. We also consider the oscillation behaviors of system (7), and give some parameter condition of oscillation behaviors when $f(x) = f_2(x)$, for both $i = 0, i = 1$. Simulations were also given to test the theoretical conclusion.

II. Stability Analysis of the Infection-Free Steady State

Before the analysis of the stability of the equilibria, we will show that the solution of model (7) always positive and bounded. The proof of positive solution is easy, the bound proof is similar to lemma 3.1 in [11], we only describe the result as follows:

Theorem 2.1: There is an $M > 0$ such that all solutions satisfy $x(t) < M,\ y(t) < M,\ v(t) < M$ for all large t.
Define

$$D = \{(x,\ y,\ v) \in R^3_+ : 0 < x(t) \leqslant \bar{x}, 0 \leqslant y(t), v(t) \leqslant M\}.$$

If $x(0) \leqslant \bar{x}$, from the first equation of model (7), we have $x(t) \leqslant \bar{x}$ when $t > 0$. It is easy to see that D is a positively invariant region for model (7).

Theorem 2.2: the disease-free state E_0 is globally asymptotically stable when $R_0 < 1$, and becomes unstable when $R_0 > 1$.

Proof: First, we will analyze the locally asymptotical stability of E_0. The Jacobian matrix of the vector field corresponding to model (7) is

$$J = \begin{pmatrix} f'(x) - \dfrac{\beta yv}{(x+y)^2} & \dfrac{\beta xv}{(x+y)^2} & -\dfrac{\beta x}{x+y} \\ \dfrac{\beta yv}{(x+y)^2} & -a - \dfrac{\beta xv}{(x+y)^2} & \dfrac{\beta x}{x+y} \\ -i\dfrac{\beta yv}{(x+y)^2} & k + i\dfrac{\beta xv}{(x+y)^2} & -u - i\dfrac{\beta x}{x+y} \end{pmatrix}.$$

The above Jacobian matrix evaluted at E_0 is

$$J_{E_0} = \begin{pmatrix} f'(\bar{x}) & 0 & -\beta \\ 0 & -a & \beta \\ 0 & k & -u - i\beta \end{pmatrix}. \tag{10}$$

Here $f'(\bar{x}) < 0$ is an eigenvalue, since the trace of the two-by-two lower right submatrix is negative and the determinant is $au(1 - R_0)$, if $R_0 < 1$, the remaining two eigenvalues are

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also negative, so E_0 is locally asymptotically stable. If $R_0 > 1$, there must exist a positive eigenvalue, so E_0 is unstable.

Next, we'll discuss the globally asymptotical stability. Consider the Lyapunov function

$$V_2 = y(t) + \frac{a}{k}v(t).$$

Calculating the derivative of V_2 along the solutions of the model (7) gives

$$\begin{aligned} V_2'(t) &= \frac{\beta xv}{x+y} - \frac{au}{k}v - \frac{ia}{k}\frac{\beta xv}{x+y} \\ &= \frac{\beta xv}{x+y}(1-\frac{ia}{k}) - \frac{au}{k}v \\ &\leqslant \beta v(1-\frac{ia}{k}) - \frac{au}{k}v \\ &= (1-\frac{1}{R_0})\frac{\beta(k-ia)}{k}v \leqslant 0. \end{aligned}$$

Let $E = \{(x,y,v) \in D | V_2'(t) = 0\}$, it is clear that $E \subset \{(x,y,v) \in D | v = 0\}$. Let M be the largest positively invariant subset of the set E, in the set M, $y'(t) = -ay$, so that $y(t) \to 0$ when $t \to \infty$. By the Lyapunov - Lasalle Theorem[16], $\lim_{t\to\infty} y(t) = 0, \lim_{t\to\infty} v(t) = 0$. Thus, the first equation of model (7) is asymptotically equivalent to $\dot{x} = f(x)$, because $f(x) > 0, x \leq \bar{x}$ and $f(x) < 0, x > \bar{x}$, we can know that $x(t) \to \bar{x}$. By the theorem on limiting systems[17], we can know the infection-free equilibrium E_0 is globally attractive, combine with the the locally asymptotical stability, E_0 is globally asymptotically stable. ■

III. Stability Analysis of the Endemic Steady State

A. Local stability of the endemic steady state

We first consider the local stability of the endemic steady state E_e:

Theorem 3.1: If $R_0 > 1$ and $f'(x_e) \leq 0$, then the endemic steady state E_e is locally asymptotically stable for $i = 0, 1$.

Proof: Note that

$$\begin{aligned} \frac{x_e}{x_e+y_e} &= \frac{1}{R_0}, \\ \frac{\beta x_e v_e}{(x_e+y_e)^2} &= \frac{a(R_0-1)}{R_0}, \\ \frac{\beta y_e v_e}{(x_e+y_e)^2} &= \frac{a(R_0-1)^2}{R_0}, \end{aligned}$$

the Jacobian matrix of the vector field corresponding to model (7) evaluated at E_e is

$$J_{E_e} = \begin{pmatrix} J_{11} & \frac{a(R_0-1)}{R_0} & -\frac{\beta}{R_0} \\ \frac{a(R_0-1)^2}{R_0} & -\frac{a(R_0-1)}{R_0} - a & \frac{\beta}{R_0} \\ -i\frac{a(R_0-1)^2}{R_0} & k + i\frac{a(R_0-1)}{R_0} & -u - i\frac{\beta}{R_0} \end{pmatrix}.$$

which $J_{11} = f'(x_e) - a(R_0-1)^2/R_0$ The characteristic equation associated with J_{E_e} is given by

$$|lE - J_{E_e}| = l^3 + a_1 l^2 + a_2 l + a_3 = 0, \tag{11}$$

where

$$\begin{aligned} a_1 &= aR_0 + u - f'(x_e) + i\frac{\beta}{R_0} > 0, \\ a_2 &= -f'(x_e)(a + u + \frac{a(R_0-1)}{R_0} + i\frac{\beta}{R_0}) \\ &\quad + au(R_0-1) + \frac{a^2(R_0-1)^2}{R_0} > 0, \\ a_3 &= \frac{a^2u(R_0-1)^2}{R_0} - f'(x_e)\frac{au(R_0-1)}{R_0} > 0. \end{aligned}$$

Let

$$a_1 = u + C, \;\; a_2 = -f'(x_e)\frac{a(R_0-1)}{R_0} + \frac{a^2(R_0-1)^2}{R_0} + D,$$

which

$$\begin{aligned} C &= aR_0 - f'(x_e) + i\frac{\beta}{R_0} > 0, \\ D &= -f'(x_e)(a + u + i\frac{\beta}{R_0}) + au(R_0-1) > 0. \end{aligned}$$

then

$$\begin{aligned} a_1a_2 - a_3 &= uD + C(-f'(x_e)\frac{a(R_0-1)}{R_0}) \\ &\quad + C(\frac{a^2(R_0-1)^2}{R_0} + D) > 0. \end{aligned}$$

By Routh-Hurwitz criterion, E_e is locally asymptotically stable. ■

B. Globally asymptotic stability of the disease steady state

In order to prove the global stability, we need to show the uniform persistence of system (7) when $R_0 > 1$. By Theorem 4.3 in paper [20], we choose $X = R^3$ and $E = D$. The maximal invariant set N on the boundary ∂D is the singleton E_0 and is isolated, so the uniform persistence is equivalent to the unstability of E_0. Hence, by theorem 2.2, we know if $R_0 > 1$, the system (7) is uniform persistence. Consequently, there exists a compact absorbing set $K \subset D$[21].

Theorem 3.2: Suppose that $R_0 > 1$, $f'(x) < 0$ for $x \in [0, \bar{x}]$, and denote $0 < \alpha* = -\max_{x\in[0,\bar{x}]} f'(x)$. If $i = 0$ or if $i = 1$ and $\beta < \min(\alpha*, a)$, then E_e is globally asymptotically stable with initial conditions in D but not on the x axis.

Proof: By the first statement of theorem 3.3, if the omega limit set does contain E_e, because $x_e < \bar{x}$, we must have $f'(x_e) < 0$, combine with the first statement of theorem 3.1, we establish the claim. If system (7) possesses a nontrival periodic solution, similar to the arguments in Muldowney'paper[19], we will show the periodic solution must be asymptotically orbitaly stable. Denote the periodic solution by $p(t) \equiv (p_1, p_2, p_3)^T$ and suppose its minimal period is $\omega > 0$, by the positive invariance of D, we know

$$0 \leq p_1 \leq \bar{x}, \forall t \in [0, \omega]. \tag{12}$$

Next, we only need to prove the system

$$\dot{z} = (DF^{[2]}(p(t)))z(t). \tag{13}$$

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is asymptotically stable, where $DF^{[2]}$ is the second additive compound matrix of Jacobian (11).

$$DF^{[2]} = \begin{pmatrix} D_{11} & \frac{\beta x}{x+y} & \frac{\beta x}{x+y} \\ k + i\frac{\beta xv}{(x+y)^2} & D_{22} & \frac{\beta xv}{(x+y)^2} \\ i\frac{\beta yv}{(x+y)^2} & \frac{\beta yv}{(x+y)^2} & D_{33} \end{pmatrix}.$$

which

$$\begin{aligned} D_{11} &= f'(x) - a - \frac{\beta v}{x+y}, \\ D_{22} &= f'(x) - \frac{\beta yv}{(x+y)^2} - u - i\frac{\beta x}{x+y}, \\ D_{33} &= -a - u - \frac{\beta xv}{(x+y)^2} - i\frac{\beta x}{x+y} \end{aligned}$$

We will show that the function

$$V(z_1, z_2, z_3; p(t)) = \sup\left\{|z_1|, \frac{p_2}{p_3}(|z_2| + |z_3|)\right\}$$

is a Lyapunov function for system (25). We have

$$\begin{aligned} D_+(|z_1(t)|) &\leq -(-f'(p_1) + a + \frac{\beta p_3}{p_1+p_2})|z_1| \\ &\quad + \frac{\beta p_1}{p_1+p_2}\frac{p_3}{p_2}\frac{p_2}{p_3}(|z_2| + |z_3|) \end{aligned}$$

$$\begin{aligned} & D_+\left(\frac{p_2}{p_3}(|z_2| + |z_3|)\right) \\ &= \left(\frac{\dot{p}_2(t)}{p_2} - \frac{\dot{p}_3(t)}{p_3}\right)\frac{p_2}{p_3}(|z_2| + |z_3|) \\ &\quad + \frac{p_2}{p_3}D_+(|z_2| + |z_3|) \\ &= \frac{p_2}{p_3}\left(k + i\frac{\beta p_3}{p_1+p_2}\right)|z_1| - \frac{p_2}{p_3}(-f'(p_1)|z_2| + a|z_3|) \\ &\quad + \left(\frac{\dot{p}_2(t)}{p_2} - \frac{\dot{p}_3(t)}{p_3} - u - i\frac{\beta p_1}{p_1+p_2}\right)\frac{p_2}{p_3}(|z_2| + |z_3|) \\ &\leq \frac{p_2}{p_3}\left(k + i\frac{\beta p_3}{p_1+p_2}\right)|z_1| - \min(\alpha*, a)\frac{p_2}{p_3}(|z_2| + |z_3|) \\ &\quad + \left(\frac{\dot{p}_2(t)}{p_2} - \frac{\dot{p}_3(t)}{p_3} - u - i\frac{\beta p_1}{p_1+p_2}\right)\frac{p_2}{p_3}(|z_2| + |z_3|) \end{aligned}$$

Thus , we obtain that

$$D_+V(t) \leq \sup(g_1(t), g_2(t))V(t). \tag{14}$$

where

$$\begin{aligned} g_1(t) &= -(-f'(p_1) + a + \frac{\beta p_3}{p_1+p_2}) + \frac{\beta p_1}{p_1+p_2}\frac{p_3}{p_2} \\ &= -(-f'(p_1) + \frac{\beta p_3}{p_1+p_2}) + \frac{\dot{p}_2(t)}{p_2} \\ &\leq -\alpha* + \frac{\dot{p}_2(t)}{p_2}. \end{aligned}$$

$$\begin{aligned} g_2(t) &= k\frac{p_2}{p_3} + i\frac{\beta p_2}{p_1+p_2} + \frac{\dot{p}_2(t)}{p_2} - \frac{\dot{p}_3(t)}{p_3} - u \\ &\quad -i\frac{\beta p_1}{p_1+p_2} - \min(\alpha*, a) \\ &= i\frac{\beta p_2}{p_1+p_2} + \frac{\dot{p}_2(t)}{p_2} - \min(\alpha*, a). \end{aligned}$$

Hence $g_1(t) < g_2(t)$, so we have

$$D_+V(t) \leq g_2(t)V(t). \tag{15}$$

If the following holds:

$$\int_0^\omega g_2(t)dt < 0,$$

it follows that V must be a lyapunov function for system(13). when $i = 0$,

$$\begin{aligned} \int_0^\omega g_2(t)dt &= \int_0^\omega \left(\frac{\dot{p}_2(t)}{p_2} - \min(\alpha*, a)\right)dt \\ &= -\min(\alpha*, a)\omega < 0. \end{aligned}$$

when $i = 1$,

$$\begin{aligned} \int_0^\omega g_2(t)dt &= \int_0^\omega \left(\frac{\beta p_2}{p_1+p_2} + \frac{\dot{p}_2(t)}{p_2} - \min(\alpha*, a)\right)dt \\ &\leq \int_0^\omega \beta dt + \int_0^\omega \left(\frac{\dot{p}_2(t)}{p_2} - \min(\alpha*, a)\right)dt \\ &= (\beta - \min(\alpha*, a))\omega < 0. \end{aligned}$$

Combine with (15) we know that $\lim_{t\to\infty} V(t) = 0$, which means $z_1(t), z_2(t), z_2(t) \to 0$, so the system (13) is asymptotically stable, this completes the proof. ■

IV. Oscillations

When $f(x) = f_2(x)$, if the condition $f'(x_e) \leq 0$ in theorem 3.1 couldn't be satisfied, there would exist an orbitally asymptotically stable periodic solution, and we have the following theorem.

Theorem 4.1: If $R_0 > 1$ and $a_1a_2 < a_3$, then model (6) exists an orbitally asymptotically stable periodic solution.

Proof: When $f = f_2$,

$$E_e = (x_e, (R_0 - 1)x_e, \frac{(k - ia)(R_0 - 1)}{u}v_e).$$

which

$$x_e = \frac{x_{\max}}{2p}[p - d - a(R_0 - 1) + \sqrt{\Delta}]$$

which$\Delta = (p - d - a(R_0 - 1))^2 + \frac{4p\lambda}{x_{\max}} > \frac{a^2(R_0-1)^2}{R_0^2}$.
The jacobian matrix of the vector field corresponding to model (7) evaluated at E_e when $f = f_2$ is

$$J = \begin{pmatrix} -B & \frac{a(R_0-1)}{R_0} & -\frac{\beta}{R_0} \\ \frac{a(R_0-1)^2}{R_0} & -\frac{a(R_0-1)}{R_0} - a & \frac{\beta}{R_0} \\ -i\frac{a(R_0-1)^2}{R_0} & k + i\frac{a(R_0-1)}{R_0} & -u - i\frac{\beta}{R_0} \end{pmatrix}.$$

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which $B = \sqrt{\Delta} - \dfrac{a(R_0-1)}{R_0}$. The parameters of equation (11) become as follows:

$$\begin{aligned} a_1 &= \sqrt{\Delta} + a + u + i\frac{\beta}{R_0} > 0, \\ a_2 &= \sqrt{\Delta}(a + u + \frac{a(R_0-1)}{R_0} + i\frac{\beta}{R_0}) \\ &\quad -(R_0-1)(a^2 + i\frac{\beta a}{R_0}), \\ a_3 &= \sqrt{\Delta}\frac{au(R_0-1)}{R_0} > 0 \end{aligned}$$

When $R_0 > 1$, the second part of a_2 is positive, so we can choose a proper parameters p and a large enough $x_{\max}$ such that $\sqrt{\Delta}$ be very small, so a_2 may be negative and $a_1 a_2 < a_3$ holds, which means E_e is unstable.

The conclusion follows from Theorem 1.2 [22] and the fact that nonlinearities in model (7) are analytic in D. In order to apply that result, we take the domain for (7) to be the interior of the positive orthant, in which the only steady state is Q_2. If $R_0 > 1$ and $a_1 a_2 < a_3$, then Q_2 is unstable. The dissipativity hypothesis of Theorem 1.2 [22] follows from Theorem 2.1 and the persistence of model (7). By looking at the Jacobian matrix J and choosing the matrix $H = diag\{1, -1, 1\}$, then HJH is a matrix with non-positive off-diagonal elements. Hence, the model (7) is competitive in D. Taking $l = 0$ in the characteristic equation (11), we have $|J_{Q_2}| = -a_3 < 0$. Hence, all conditions of Theorem 1.2 [22] are satisfied. This completes the proof. ■

V. Numerical simulations

In this section, we will give some numerical simulations of system (7) when $f(x) = f_2(x)$. When we simulate the orbitally asymptotical stability of stable periodic solution, by the theorem 4.1, we only need to choose parameters satisfying $R_0 > 1$ and $a_1 * a_2 - a_3 < 0$. When $i = 0$, we choose parameters as follows: $\lambda = 2.5267e+005$, $d = 0.00379$, $u = 0.16$, $p = 3$, $a = 0.0533$, $\beta = 1.6891e+003$, $k = 2.4500e-004$, $X_{max} = 6.6667e+007$, $R_0 = 48.52 > 1$, thus we have $a_1 * a_2 - a_3 = -2.5024e+003 < 0$, which satisfy the theorem 4.1, we choose the initial condition $X_0 = [3.3333 * 10^7, 3.3333 * 10^7, 10^2]$, the system (7) has an orbitally asymptotically stable periodic solution(see fig.1) which is consistent with the statement of theorem 4.1.

When $i = 1$, we choose $\lambda = 2.5267e+005$, $d = 0.00379$, $u = 0.650$, $p = 0.0311$, $a = 0.00379$, $\beta = 2.8957e-004$, $k = 70$, $X_{max} = 6.6667e+12$, $R_0 = 8.2276 > 1$, $a1 * a2 - a3 = -2.2537e-005 < 0$, which satisfy the note of the theorem 4.1, we choose $X_0 = [6 * 10^7, 6.6667e+006, 10^3]$, the system 7 has an orbitally asymptotically stable periodic solution(see fig.2).

VI. Concluding remarks

In this paper, based on Leenheer and Smith's model[11], we consider an amended viral infection model with standard incidence. By stability analysis we give sufficient conditions for the global stability of infection-free steady-state and the the endemic steady state. That is when $R_0 = \beta(k - ia)/au < 1$, the infection-free equilibrium E_0 is globally asymptotically stable and becomes unstable when $R_0 > 1$. If $R_0 > 1$, the globally asymptotical stability of endemic equilibrium E_e is related to $f(x)$ which determine the dynamic behavior of uninfected cell in system (7) both for $i = 0$ and $i = 1$. But when $i = 1$, another condition of parameters must hold , that is $\beta < \min(\alpha*, a)$. We also show that periodic oscillations of system (7) are possible. When $f(x) = f_2(x)$, we give the sufficient condition of the parameters to obtain the periodic oscillations. The numerical simulation results confirm our analytic results.

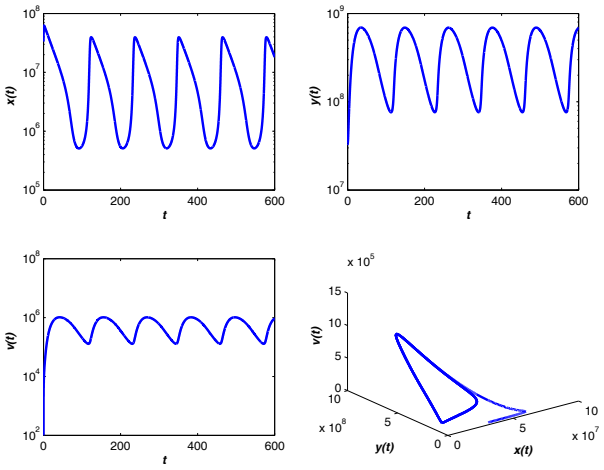

Fig. 1. an orbitally asymptotically stable periodic solution of system (7) when $i = 0$.

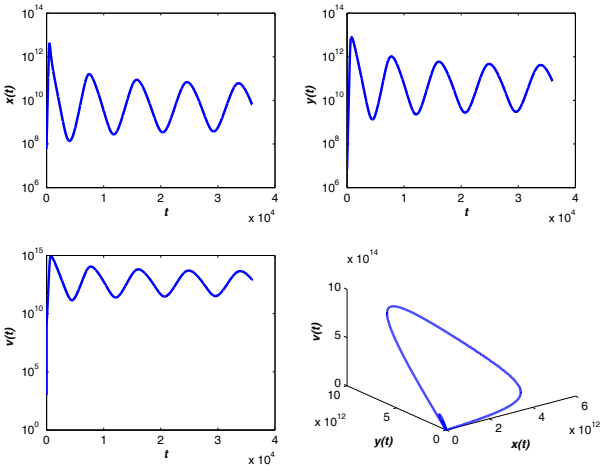

Fig. 2. an orbitally asymptotically stable periodic solution of system $i = 1$

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