GLOBAL STABILITY OF THE VIRUS DYNAMICS MODEL WITH CROWLEY-MARTIN FUNCTIONAL RESPONSE

SHENGHU XU

ABSTRACT. In this paper, a virus dynamics model with Crowley-Martin functional response of the infection rate is investigated. By analyzing the corresponding characteristic equations, the local stability of an infection-free equilibrium point and infection equilibrium point are discussed. By constructing suitable Lyapunov functions and using LaSalles invariance principle, the global stability also are established, it is proved that if the basic reproductive number, R_0, is less than or equal to one, the infection-free equilibrium point is globally asymptotically stable, if R_0, is more than one, the infection equilibrium point is globally asymptotically stable.

1. Introduction

Mathematical models have been used to model the dynamic of viral infections, such as human immunodeficiency virus type I (HIV-I), hepatitis C virus (HCV), hepatitis B virus (HBV), and human T-cell lymphotropic virus I (HTLV-I) (Perelson *et al.*, 1993, 1996; Bonhoeffer *et al.*, 1997; Perelson and Nelson, 1999; Nowak and May, 2000; Nowak *et al.*, 1996; Korobeinikov, 2004). Nowak *et al.*(1996) and Nowak and May(2000) proposed a basic mathematical model for uninfected susceptible host cells, T, infected host cells, I, and free virus particles, V, as follows:

$$\frac{dT}{dt} = \lambda - dT - \beta TV, \quad t > 0,$$
$$\frac{dI}{dt} = \beta TV - pI, \quad t > 0, \tag{1.1}$$
$$\frac{dV}{dt} = kI - \mu V, \quad t > 0,$$

where susceptible cells are produced at rate λ, die at rate dT and become infected at rate βTV; infected cells are produced at rate βTV and die at rate pI; free viruses are produced from infected cells at rate kI and are removed at rate μV.

In this paper, we consider the following more general the virus dynamics model with Crowley-Martin functional response

$$\frac{dT}{dt} = \lambda - dT - \frac{\beta TV}{(1+aT)(1+bV)}, \quad t > 0,$$
$$\frac{dI}{dt} = \frac{\beta TV}{(1+aT)(1+bV)} - pI, \quad t > 0, \tag{1.2}$$
$$\frac{dV}{dt} = kI - \mu V, \quad t > 0,$$

and with the following initial conditions:

$$T(0) \geq 0, I(0) \geq 0, V(0) \geq 0. \tag{1.3}$$

Here the state variables T, I and V, and all parameters $\lambda, \beta, \mu, d, k, p$ have the same biological meanings as in model (1.1), the term βTV has been replaced with Crowley-Martin the functional response term, $\frac{\beta TV}{(1+aT)(1+bV)}$, where $a, b \geq 0$ are constants. The Crowley-Martin type of functional response was introduced by Growley and Martin(1989).

Note that when $a = b = 0$, (1.2) reduces to the system (1.1); when $a > 0, b = 0$, the Crowley-Martin functional response reduces to the Holling type II functional response (e.g., Ma and Li, 2007); when $a = 0, b > 0$, it expresses a saturation response (see, Song and Neumann, 2007); Huang *et al.* (2009) considered a mathematical model with Beddington-DeAngelis functional response of the infection rate, and sufficient conditions were derived for the global stability of an infected steady state and uninfected steady state.

Recently, Zhou and Cui (2010) proposed the model (1.2), and showed that the infection equilibrium E^* is globally asymptotically stable if the following conditions

$$R_0 = \frac{k\lambda\beta}{p\mu(d + a\lambda)} > 1, \tag{1.4}$$

$$p\mu \left(\frac{\beta V^* + b\beta(V^*)^2}{(1 + aT^*)^2(1 + bV^*)^2} \right) > \frac{dk(\beta T^* + b\beta(T^*)^2)}{(1 + aT^*)^2(1 + bV^*)^2}, \tag{1.5}$$

$$\left(\mu + d + p + \frac{\beta V^* + b\beta(V^*)^2}{(1+aT^*)^2(1+bV^*)^2} \right) \left[\mu d + dp + (p+\mu)\frac{\beta V^* + b\beta(V^*)^2}{(1+aT^*)^2(1+bV^*)^2} \right] + \mu p(\mu + p)$$
$$> k\left(\mu + p + 2dk + \frac{\beta V^* + b\beta(V^*)^2}{(1+aT^*)^2(1+bV^*)^2} \right) \frac{\beta T^* + b\beta(T^*)^2}{(1+aT^*)^2(1+bV^*)^2}, \tag{1.6}$$

$$d > \frac{ap\lambda}{b} \tag{1.7}$$

hold. The proof uses the theory of competitive systems as developed in Smith (1987), with conditions (1.4), (1.5) and (1.6) being used to establish the local stability of E^*.

In this article, we will study the global dynamics of (1.2) by constructing a suitable Lyapunov function and using LaSalle's invariance principle rather than by using the theory of competitive systems, as has been done in Zhou and Cui (2010). This will enable us to obtain the global asymptotic stability of the infection equilibrium point under weaker hypotheses than those used in Zhou and Cui (2010) and by a simpler method. In our setting, the persistence condition $R_0 > 1$ used in Zhou and Cui (2010) will appear in a natural way as a monotonicity condition. Finally, we will discuss the biological significance of our results and indicate possible extensions to the study of more comprehensive models in section 4.

2. **Boundedness, Equilibria and their stability**

2.1. **Boundedness.** First, we shows that the solution of system (1.2) is bounded.

Theorem 2.1. *Let $(T(t), I(t), V(t))$ be a solution of (1.2) with initial conditions (1.3), and let $[0, T)$ be the maximal existence interval of the solution.. Then there is an $M > 0$ such that*

$$T(t), I(t), V(t) < M.$$

Further $T = +\infty$.

Proof. Let $Z(t) = T(t) + I(t)$. Then

$$\begin{aligned} \frac{dZ}{dt} &= \lambda - dT - pI \\ &\leq \lambda - \min\{d, p\}Z(t). \end{aligned}$$

Denote $m = \min\{d, p\}$, it follows that

$$Z(t) \leq \frac{\lambda}{m} + (Z(0) - \frac{\lambda}{m})e^{-mt}.$$

Therefore, there exists a $t_1 > 0$ and $M_1 > 0$ such that $Z(t) < M_1$ for $t > t_1$. So that $T(t)$ and $I(t)$ are bounded. On the other hand, by the third of system (1.2) we obtain

$$\frac{dV}{dt} = kI - \mu V \leq M_1 - \mu V.$$

Similar to the argument on $Z(t)$, we can conclude that $V(t)$ is also ultimately bounded. Therefore, from the extension theorem of solutions, we have $T = +\infty$. This completes the proof. $\qquad \square$

2.2. **Equilibria.** Let $\delta = \frac{pu}{k}$. The basic reproduction number of model (1.2) is

$$R_0 = \frac{\beta \lambda}{\delta(d + a\lambda)},$$

which is independent of the number of total cells of liver.

Now we consider the stability of equilibrium points of (1.2). By the simple calculation, system (1.2) has the following three equilibrium points:

(i) the trivial equilibrium point $E_0 = (0, 0, 0)$, E_0 symbolizes complete liver failure;

(ii) if $R_0 \leq 1$, then the (1.2) has a unique infection-free equilibrium point $E_f = (T_0, 0, 0)$, where $T_0 = \frac{\lambda}{d}$, E_f is a healthy, disease free, mature liver;

(iii) if $R_0 > 1$, then the system (1.2) has a unique infection equilibrium point $E^* = (T^*, I^*, V^*)$, E^* represents persistent, chronic HBV infection. E^* is given by

$$T^* = \frac{bd + \beta - a(b\lambda + \delta) + \sqrt{(bd + \beta - a(b\lambda + \delta))^2 + 4abd(b\lambda + \delta)}}{2abd}, I^* = \frac{\mu}{bk}(R^* - 1), V^* = \frac{1}{b}(R^* - 1)$$

if and only if

$$R^* = \frac{\beta T^*}{\delta(1 + aT^*)} > 1.$$

We note that $R_0 = \frac{\beta T_0}{\delta(d + aT_0)} > \frac{\beta T^*}{\delta(1 + aT^*)}$, since $I^* = \frac{1}{dp}(\frac{\lambda}{d} - T^*)$. Hence, the system (1.2) has a unique infection equilibrium point $E^* = (T^*, I^*, V^*)$ if $R_0 > 1$.

2.3. **Local stability,** $R_0 < 1$ **and** $R_0 > 1$**.** Next, we analyze the stability of non-negative equilibria of (1.2).

Theorem 2.2.
(i) $E_0 = (0, 0, 0)$ *is stable.*
(ii) *If* $R_0 < 1$*, then* E_f *is locally asymptotically stable; if* $R_0 > 1$*, then* E_f *is unstable.*
(iii) *If* $R^* > 1$*, then* E^* *is locally asymptotically stable.*

Remark 2.2. *Notice that* $R_0 > R^*$*, therefore, Theorem 2.2.(iii) becomes:*
(iii)$'$ *If* $R_0 > 1$ *holds, then* E^* *is also locally asymptotically stable.*

Proof. (i) The linearization matrix of the system (1.2) at E_0 is

$$J(E_0) = \begin{pmatrix} -d & 0 & 0 \\ 0 & -p & 0 \\ 0 & k & -\mu \end{pmatrix}.$$

The characteristic equation at E_0 is $(\lambda + d)(\lambda + p)(\lambda + \mu) = 0$, then E_0 is stable.

(ii) The linearization matrix of the system (1.2) at E_f is

$$J(E_f) = \begin{pmatrix} -d & 0 & -\frac{\beta T_0}{1+aT_0} \\ 0 & -p & \frac{\beta T_0}{1+aT_0} \\ 0 & k & -\mu \end{pmatrix}.$$

The characteristic equation at E_f is

$$\lambda^3 + A_1\lambda^2 + A_2\lambda + A_3 = 0,$$

where

$$A_1 = d + p + \mu > 0,$$
$$A_2 = pd + d\mu + p\mu - \frac{k\beta T_0}{1+aT_0} = pd + d\mu + p\mu(1 - R_0),$$
$$A_3 = p\mu d(1 - R_0),$$
$$A_1 A_2 - A_3 = d^2(p + \mu) + (p + \mu)[d(p + \mu) + p\mu(1 - R_0)].$$

If $R_0 < 1$, then $A_1, A_3, A_1 A_2 - A_3 > 0$. Therefore, by the Routh-Hurwitz criterion, if $R_0 < 1$ hold, then E_f is locally asymptotically stable.

(iii) The linearization matrix of the system (1.2) at E^* is

$$J(E^*) = \begin{pmatrix} b_{11} & b_{12} & b_{13} \\ b_{21} & b_{22} & b_{23} \\ b_{31} & b_{32} & b_{33} \end{pmatrix},$$

where $b_{11} = -d - b_{21}, b_{12} = 0, b_{13} = -b_{23}, b_{21} = \frac{\beta V^*(1+bV^*)}{(1+aT^*+bV^*+abT^*V^*)^2}, b_{22} = -p, b_{23} = \frac{\beta(1+aT^*)}{(1+aT^*+bV^*+abT^*V^*)^2}, b_{31} = 0, b_{32} = k, b_{33} = -\mu.$

The characteristic equation at E^* is

$$\lambda^3 + B_1\lambda^2 + B_2\lambda + B_3 = 0,$$

where

$$B_1 = (d + p + \mu + b_{21}) > 0,$$
$$B_2 = (p + \mu)(d + b_{21}) + (p\mu - kb_{23}),$$
$$B_3 = (d + b_{21})(pu - kb_{23}) + b_{21}b_{23}k,$$
$$B_1 B_2 - B_3 = (p + \mu)(p\mu - kb_{23}) + (p + \mu)(d + b_{21})^2 + (p^2 + p\mu + \mu^2)(d + b_{21}) + p\mu d + b_{21}(p\mu - kb_{23}).$$

Furthermore,

$$
\begin{aligned}
B_2 \;>\;& p\mu - kb_{23} \\
=\;& p\mu - \frac{\beta(1+aT^*)}{(1+aT^*+bV^*+abT^*V^*)^2} \\
=\;& \frac{p\mu}{(1+bV^*)^2}[(1+bV^*)^2 - R^*] \\
=\;& \frac{p\mu}{(1+bV^*)^2}\{[1+(R^*-1)]^2 - R^*\} \\
=\;& \frac{p\mu}{R^*}(R^*-1).
\end{aligned}
$$

If $R^* > 1$, then $B_2 > 0$. It follows that $B_3 > 0$, $B_1B_2 - B_3 > 0$ if $R^* > 1$.

Then by the Routh-Hurwitz criterion, we have that $E^* = (T^*, I^*, V^*)$ is locally asymptotically stable if $R^* > 1$. $\hfill\square$

2.4. **Analysis at $R_0 = 1$.** To use the center manifold theory, as described in Castillo-Chavez and Song (2004) (Theorem 4.1). To apply this method, the following simplification and change of variables are made first. Let $T = x_1$, $I = x_2$, $V = x_3$, the system (1.2) becomes

$$
\begin{aligned}
\frac{dx_1}{dt} &= \lambda - dx_1 - \frac{\beta x_1 x_3}{(1+ax_1)(1+bx_3)} \doteq f_1, \\
\frac{dx_2}{dt} &= \frac{\beta x_1 x_3}{(1+ax_1)(1+bx_3)} - px_2 \doteq f_2, \\
\frac{dx_3}{dt} &= kx_2 - \mu x_3, \doteq f_3,
\end{aligned}
\tag{2.1}
$$

with $R_0 = 1$ corresponding to $\beta = \beta^* = \frac{\delta(d+a\lambda)}{\lambda}$. The infection-free equilibrium is $(x_1^* = \frac{\lambda}{d}, x_2^* = 0, x_3^* = 0)$. The linearization matrix of system (2.1) around the infection-free equilibrium when $\beta = \beta^*$ is

$$
D_x f = \begin{pmatrix} -d & 0 & -\frac{\beta^* T_0}{1+aT_0} \\ 0 & -p & \frac{\beta^* T_0}{1+aT_0} \\ 0 & k & -\mu \end{pmatrix}.
$$

The matrix $D_x f$ has eigenvalues $(0, -d, -p - \mu)^T$, which meets the requirement of a simple zero eigenvalue and others having negative real part. A right eigenvector w corresponding to the zero eigenvalue is $w = (-\frac{p}{d}, 1, \frac{k}{\mu})^T$, and the left eigenvector satisfying $v \cdot w = 1$ is $v = (0, \frac{\mu}{\mu+p}, \frac{p(\mu+p)}{k\mu})$. For system (2.1) the associated non-zero the second partial derivative of f_2, f_3 are given by

$$
\frac{\partial^2 f_2}{\partial x_1 \partial x_3} = \frac{\partial^2 f_2}{\partial x_3 \partial x_1} = \frac{\beta^*}{(1+aT_0)^2}, \quad \frac{\partial^2 f_2}{\partial x_3^2} = -\frac{2b\beta^* T_0}{1+aT_0}, \quad \frac{\partial^2 f_2}{\partial x_3 \partial \beta} = \frac{T_0}{1+aT_0}.
$$

It follows that

$$
\begin{aligned}
a \;=\;& v_2 \sum_{i,j=1}^{3} w_i w_j \frac{\partial f_2}{\partial x_i \partial x_j} + v_3 \sum_{i,j=1}^{3} w_i w_j \frac{\partial f_3}{\partial x_i \partial x_j} \\
=\;& 2w_1 w_3 \frac{\beta^*}{(1+aT_0)^2} - w_3^2 \frac{2b\beta^* T_0}{1+aT_0} \\
=\;& -\frac{2pk}{d\mu} \frac{\beta^*}{(1+aT_0)^2} - \frac{k^2}{\mu^2} \frac{2b\beta^* T_0}{1+aT_0} < 0.
\end{aligned}
$$

$$b = v_2 \sum_{i=1}^{3} w_i \frac{\partial f_2}{\partial x_i \partial \beta} + v_3 \sum_{i=1}^{3} w_i \frac{\partial f_3}{\partial x_i \partial \beta}$$

$$= v_2 w_3 \frac{T_0}{1 = aT_0} > 0.$$

Thus, $a < 0$, $b > 0$, by item (iv) of Theorem 4.1 in Castillo-Chavez and Song (2004), we can give the following result:

Theorem 2.3. *The infection equilibrium point E^* is locally asymptotically stable for R_0 near 1.*

Note that the result in Theorem 2.3 holds for $R_0 > 1$ but close to 1.

3. **Global stability and uniformly persistent**

3.1. **Global stability.** The following two theorems is the global stability results of the infection-free equilibrium point E_f and infection equilibrium point E^*.

Theorem 3.1.
(i) If $R_0 \leq 1$, then E_f is globally asymptotically stable.
(ii) If $R_0 > 1$, then E^* is globally asymptotically stable.

Proof. (i) Let us consider the Lyapunov function

$$V_1(T, I, V) = \frac{1}{1 + aT_0}(T - T_0 - T_0 ln\frac{T}{T_0}) + I + \frac{p}{k}V.$$

It is easily seen that $V_1(T, I, V) \geq 0$ and $V_1(T, I, V) = 0$ if and only if $T = T_0, I = V = 0$. We now compute the time derivative of V_1 along the solutions of (1.2). One then has

$$\begin{aligned}
\dot{V}_1(t) &= \frac{1}{1 + aT_0}\dot{T} - \frac{1}{1 + aT_0}\frac{T_0}{T}\dot{T} + \dot{I} + \frac{p}{k}\dot{V} \\
&= \frac{1}{1 + aT_0}\left(\lambda - dT - \frac{\beta TV}{(1 + aT)(1 + bV)}\right) - \frac{1}{1 + aT_0}\frac{T_0}{T}\left(\lambda - dT - \frac{\beta TV}{(1 + aT)(1 + bV)}\right) \\
&\quad + \frac{\beta TV}{(1 + aT)(1 + bV)} - \frac{p\mu}{k}V \\
&= \frac{1}{1 + aT_0}\left[-d(T - T_0) + d\frac{T_0}{T}(T - T_0)\right] + \frac{1}{1 + aT_0}\frac{\beta T_0 V}{(1 + aT)(1 + bV)} + \frac{\beta TV}{(1 + aT)(1 + bV)} \\
&\quad - \frac{1}{1 + aT_0}\frac{\beta TV}{(1 + aT)(1 + bV)} - \frac{p\mu}{k}V \\
&= \frac{-d}{T(1 + aT_0)}(T - T_0)^2 + \frac{p\mu}{k}\frac{V}{(1 + bV)}\left[\frac{k}{p\mu}\left(\frac{-1}{1 + aT_0}\frac{\beta T}{1 + aT} + \frac{\beta T_0}{1 + aT_0}\frac{1}{1 + aT} + \frac{\beta T}{1 + aT}\right) - (1 + bV)\right] \\
&= -\left[\frac{d}{T(1 + aT_0)}(T - T_0)^2 + \frac{p\mu b}{k(1 + bV)}V^2\right] + \frac{p\mu}{k}\frac{V}{(1 + bV)}(R_0 - 1).
\end{aligned}$$

It follows from $R_0 \leq 1$ that $\dot{V}_1 \leq 0$ for all $T, I, V > 0$. Hence, the uninfected steady E_f is stable. And $\dot{V}_1 = 0$, when $T = T_0$ and $V = 0$. Let Σ_0 be the largest invariant set in set

$$\Sigma = \{T, I, V)|\dot{V}_1(T, I, V) = 0\} = \{T, I, V)|T = T_0, I \geq 0, V = 0\}.$$

We have from the third equation of (1.2) that $\Sigma_0 = \{E_f\}$. By the Lyapunov-LaSalle invariance principle (LaSalle, 1976), E_f is global asymptotically stable.

(ii) Let us consider the Lyapunov function

$$V_2(T, I, V) = T - T^* - \int_{T^*}^{T} \frac{pI^*}{\frac{\beta\tau V^*}{(1+a\tau)(1+bV^*)}} d\tau + I - I^* - I^* ln\frac{I}{I^*} + \frac{p}{k}(1 + bV^*)\left(V - V^* - \int_{V^*}^{V} \frac{pI^*}{\frac{\beta\tau T^*}{(1+aT^*)(1+b\tau)}} d\tau\right)$$

It is easily seen that $V_2(T, I, V) \geq 0$ and $V_2(T, I, V) = 0$ if and only if $T = T^*, I = I^*, V = V^*$. Calculating the time derivative of $V_2(T, I, V)$ along the positive solutions of model (1.2), satisfies

$$
\begin{aligned}
\dot{V}_2(t) &= \dot{T} + \dot{I} + \frac{p}{k}(1 + bV^*)\dot{V} - pI^*\frac{(1+aT)(1+bV^*)}{\beta TV^*}\dot{T} - \frac{I^*}{I}\dot{I} - \frac{p}{k}(1 + bV^*) \cdot pI^* \cdot \frac{(1+aT^*)(1+bV)}{\beta T^*V}\dot{V} \\
&= \dot{T} + \dot{I} + \frac{p}{k}\dot{V} - pI^*\frac{(1+aT)(1+bV^*)}{\beta TV^*}\dot{T} - \frac{I^*}{I}\dot{I} - \frac{p}{k}\frac{V^*}{V}\dot{V} \\
&= \left\{\lambda - dT - \frac{p\mu}{k}V\right\} - \left\{pI^*\frac{(1+aT)(1+bV^*)}{\beta TV^*}\left[\lambda - dT - \frac{\beta TV}{(1+aT)(1+bV)}\right]\right\} \\
&\quad - \left\{\frac{I^*}{I}\left[\frac{\beta TV}{(1+aT)(1+bV)} - pI\right]\right\} - \left\{\frac{p}{k}\frac{V^*}{V}(kI - \mu V)\right\}.
\end{aligned}
$$

Since $\lambda = dT^* + pI^*$, $\frac{p\mu}{k} = \frac{pI^*}{V^*}$, $pI^* = \frac{\beta T^*V^*}{(1+aT^*)(1+bV^*)}$, this yields

$$
\begin{aligned}
\dot{V}_2(t) &= \left\{dT^* + pI^* - dT - pI^*\frac{V}{V^*}\right\} \\
&\quad - \left\{\frac{T^*}{T}\frac{1+aT}{1+aT^*}dT^* - \frac{T^*}{T}\frac{1+aT}{1+aT^*}pI^* + \frac{1+aT}{1+aT^*}dT^* + \frac{V}{V^*}\frac{1+bV^*}{1+bV}pI^*\right\} \\
&\quad + \left\{pI^*\left[1 - \frac{TI^*V}{T^*IV^*}\frac{(1+aT^*)(1+bV^*)}{(1+aT)(1+bV)}\right]\right\} + \left\{pI^*\left(1 - \frac{I}{I^*}\frac{V^*}{V}\right)\right\} \\
&= dT^*\left[1 - \frac{T}{T^*} - \frac{T^*}{T}\frac{1+aT}{1+aT^*} + \frac{1+aT}{1+aT^*}\right] + pI^*\left[1 - \frac{T^*I^*V}{TIV^*}\frac{(1+aT^*)(1+bV^*)}{(1+aT)(1+bV)}\right] \\
&\quad + pI^*\left[1 - \frac{V}{V^*} - \frac{I}{I^*}\frac{V^*}{V}\right] \\
&= -\frac{d}{T(1+aT^*)}(T - T^*)^2 + pI^*\left[-1 - \frac{V}{V^*} + \frac{V}{V^*}\frac{1+bV^*}{1+bV} + \frac{1+bV}{1+bV^*}\right] \\
&\quad + pI^*\left[4 - \frac{T^*}{T}\frac{1+aT}{1+aT^*} - \frac{T}{T^*}\frac{I^*}{I}\frac{V}{V^*}\frac{(1+aT^*)(1+bV^*)}{(1+aT)(1+bV)} - \frac{I}{I^*}\frac{V^*}{V} - \frac{1+bV}{1+bV^*}\right] \\
&= -\frac{d}{T(1+aT^*)}(T - T^*)^2 - \frac{bpI^*}{V^*(1+bV)(1+bV^*)}(V - V^*)^2 \\
&\quad + pI^*\left[4 - \frac{T^*}{T}\frac{1+aT}{1+aT^*} - \frac{T}{T^*}\frac{I^*}{I}\frac{V}{V^*}\frac{(1+aT^*)(1+bV^*)}{(1+aT)(1+bV)} - \frac{I}{I^*}\frac{V^*}{V} - \frac{1+bV}{1+bV^*}\right].
\end{aligned}
$$

From the $AM - GM$ inequality, we get

$$4 - \frac{T^*}{T}\frac{1+aT}{1+aT^*} - \frac{T}{T^*}\frac{I^*}{I}\frac{V}{V^*}\frac{(1+aT^*)(1+bV^*)}{(1+aT)(1+bV)} - \frac{I}{I^*}\frac{V^*}{V} - \frac{1+bV}{1+bV^*} \leq 0,$$

with equality if and only if $T = T^*, I = I^*, V = V^*$.

Therefore, $\dot{V}_2 \leq 0$ for all $T, I, V > 0$, and $\dot{V}_2 = 0$ if and only if $T = T^*$, $I = I^*$, $V = V^*$. The largest compact invariant set in $M = \{(T, I, V)|\dot{V}_2 = 0\}$ is $\widetilde{M} = \{E^*\}$. From Lyapunov-LaSalle invariance principle one then obtains the desired conclusion. $\qquad\square$

3.2. **Uniformly persistent.** We recall that the system (1.2) is said to be *uniformly persistent* if there is ε_0 such that any solution of (1.2) which starts with $T(0), I(0), V(0)$ satisfies

$$\liminf_{t\to\infty} T(t) \geq \varepsilon_0, \quad \liminf_{t\to\infty} I(t) \geq \varepsilon_0, \quad \liminf_{t\to\infty} V(t) \geq \varepsilon_0.$$

Theorem 3.2. *If $R_0 > 1$, then the system (1.2) is uniformly persistent.*

Proof. Let us consider the Lyapunov function

$$V_3(T, I, V) = I + \frac{p}{k}V.$$

Then the derivative of V_3 along the solutions of (1.2) is

$$\begin{aligned}
\dot{V}_3(t) &= \left(\frac{\beta TV}{(1+aT)(1+bV)} - pI\right) + \frac{p}{k}(kI - \mu V) \\
&= \left(f(T, I, V) - \frac{p\mu}{k}\right)V,
\end{aligned}$$

where $f(T, I, V) = \frac{\beta TV}{(1+aT)(1+bV)}$. If $R_0 > 1$, that is, $f(T_0, 0, 0) - \frac{p\mu}{k} > 1$, then $\dot{V}_3$ is positive in all strictly positive points of a vicinity of $(T_0, 0, 0)$, and so $(T_0, 0, 0)$ is unstable. Since the only invariant subsets on the boundary of $(0, \infty)^3$ are $\{(T_0, 0, 0)\}$ and $\{(0, 0, 0)\}$ and their stable manifolds are also contained in the boundary of $(0, \infty)^3$, it follows from a result of Hofbauer and So (1989) that the system (1.2) is uniformly persistent. $\qquad\square$

4. **Discussion.**

This paper presents a mathematical study on the global dynamics of virus dynamic model with Crowley-Martin functional response. At first, we discussed the existence and local stability of the infection-free and infection equilbria. The results (see, Theorem 2.2.) showed that the basic reproduction number of virus R_0 is a sharp threshold parameter. Next, the global asymptotical stability for infection-free equilibrium E_f when $R_0 < 1$ and infection equilibrium E^* when $R_0 > 1$ are proved (see, Theorem 3.1.). The proof relies on the construction of a global Lyapunov function that are motivated by earlier works (Korobeinikov, 2004; Huang *et al.*, 2009)

Now, we discuss the biological significance of our results. Theorem 3.1 (i) implies that a person with $R_0 < 1$ cannot be infected by virus forever. Theorem 3.1 (ii) implies that a person with $R_0 > 1$ will be very difficult to prevent to be infected. Consequently, HBV vaccines may be the first line choice for preventing HBV infection. It also implies that if a patient's $R_0 > 1$, and drug anti-virus therapy cannot activate the patient's immune response, then the anti-virus treatment cannot stop until all virus has been cleared.

In another approach, Zhou and Cui (2010) studied the model (1.2), and obtained global asymptotic stability of the infection equilibrium E^* result by the theory of competitive systems. However, their results (see, Theorem 5.2 of Zhou and Cui (2010)) need more hypotheses than our results here (Theorem 3.1).

Furthermore, our considerations may be easily extended to systems of the form

$$\frac{dT}{dt} = n(T) - f(T, V),$$
$$\frac{dI}{dt} = f(T, V) - pI, \tag{4.1}$$
$$\frac{dV}{dt} = kI - \mu V,$$

to encompass different type of functional responses, under appropriate assumptions on the functions $f(T, V)$. Some examples of f and $n(T)$ which fit into our framework are $f(T, V) = \beta TV$, $f(T, V) = \frac{\beta TV^q}{1+mV^q}$, $f(T, V) = \frac{\beta TV}{1+aT+bV}$, $n(T) = \lambda - dT$.

On the other hand, we can consider with "intracellular" delay (see, Herz *et al.*, 1996)

$$\frac{dT}{dt} = \lambda - dT - \frac{\beta TV}{(1+aT)(1+bV)},$$
$$\frac{dI}{dt} = e^{-m\tau} \frac{\beta T(t-\tau)V(t-\tau)}{(1+aT(t-\tau))(1+bV(t-\tau))} - pI, \tag{4.2}$$
$$\frac{dV}{dt} = kI - \mu V.$$

And, we also consider the system (1.2) with CTL immune response (Nowak and Bangham, 1996):

$$\frac{dT}{dt} = \lambda - dT - \frac{\beta TV}{(1+aT)(1+bV)},$$
$$\frac{dI}{dt} = \frac{\beta TV}{(1+aT)(1+bV)} - pI - mIC,$$
$$\frac{dV}{dt} = kI - \mu V, \tag{4.3}$$
$$\frac{dC}{dt} = hIC - nC.$$

The model (4.2) and (4.3) are left to the future work.

5. **Acknowledgment**

REFERENCES

Bonhoeffer, S., May, R. M., Shaw, G. M., Nowak, M. A., (1997). Virus dynamics and drug therapy. Proc. Natl. Acad. Sci. USA. 94, 6971-6976.

Crowley, P. H., Martin, E. K., (1989). Functional responses and interference within and between year classes of a dragonfly population. J. North. Am. Benth. Soc. 8, 211-221.

Hofbauer, J., So, J. W. H., (1989). Uniform persistence and repellors for maps. Proc. Amer. Math. Soc. 107, 1137-1142.

Herz, V., Bonhoeffer, S., Anderson, R., May, R. M., Nowak, M. A., (1996). Viral dynamics in vivo: limitations on estimations on intracellular delay and virus delay. Proc. Natl. Acad. Sci. USA. 93, 7247-7251.

Huang, G., Ma, W. B., Takeuchi, Y., (2009). Global properties for virus dynamics model with Beddington-DeAngelis functional response. Appl. Math. Lett. 22, 1690-1693.

Korobeinikov, A., (2004). Global properties of basic virus dynamics models. Bull. Math. Biol. 66, 879-883.

LaSalle, J. P., (1976). The Stability of Dynamical Systems, CBMS-NSF Regional Conf. Ser. in Appl. Math. 25, SIAM, Philadelphia, 1976.

Li, D., Ma, W. B., (2007). Asymptotic properties of an HIV-1 infection model with time delay. J. Math. Anal. Appl. 335, 683-691.

Nowak, M. A., Bangham, C. R. M.,(1996). Population dynamics of immune responses to persistent viruses. Science. 272, 74-79.

Nowak, M.A., Bonhoeffer, S., Hill, A. M., Boehme, R., Thomas, H. C., (1996). Viral dynamics in hepatitis B virus infection. Proc. Natl. Acad. Sci. USA 93, 4398-4402.

Nowak, M. A., May, R. M., (2000). Virus Dynamics. Cambridge University Press, Cambridge.

Perelson, A. S., Kirschner, D. E., de Boer, R., (1993). Dynamics of HIV infection of CD4 T cells. Math. Biosci. 114, 81-125.

Perelson, A. S., Neumann, A. U., Markowitz, M., Leonard, J. M., Ho, D. D., (1996). HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time. Science. 271, 1582-1586.

Perelson, A. S., Nelson, P. W., (1999). Mathematical analysis of HIV-I dynamics in vivo. SIAM Rev. 41, 3-44.

Smith, H. L., (1987). A classification theorem for three dimensional competitive systems. J. Differ. Equs. 70, 325-332.

Song, X. Y., Neumann, A. U., (2007). Global stability and periodic solution of the viral dynamics. J. Math. Anal. Appl. 329, 281-297.

Zhou, X. Y., Cui, J. A., (2011). Global stability of the viral dynamics with Crowley-Martin functional response. Bull. Korean. Math. Soc. 48, 555-574.

Castillo-Chavez, C., Song, B. J., (2004). Dynamical models of tuberculosis and their applications. Math. Biosci. Eng. 1, 361-404.

(Received August 10, 2011)

Shenghu Xu

School of Mathematics and Statistics,
Lanzhou University, Lanzhou, Gansu 730000, People's Republic of China

School of Mathematics and Statistics,
Longdong University, Qingyang, Gansu, 745000, People's Republic of China
E-mail:xuluck2001@163.com