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ANALYSIS OF A VIRUS DYNAMICS MODEL WITH BEDDINGTON-DEANGELISH INFECTION RATE AND CTL IMMUNE RESPONSE

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Abstrak

Penelitian ini menganalisis sebuah model dinamika virus dengan laju infeksi Beddington-DeAngelis dan respon imun CTL. Hal ini terbuktik bahwa pemecahan-pemecahan dengan nilai-nilai awal positif semuanya positif dan dibatasi. Stabilitas global titik ekuilibrium untuk model dinamika virus dieksplorasi dengan menggunakan fungsi Lyapunov. Dinamika global dari model ini ditentukan oleh nilai-nilai bilangan reproduksi dasar R_0. Hal ini membuktikan bahwa jika $R_0<1$, terdapat keadaan tetap yang unik, keseimbangan bebas virus yang stabil asimtotik global. Jika $R_0>1$, terdapat keadaan tetap lain, keseimbangan endemik yang stabil asimptotik secara global. Selain itu, kami menunjukkan bahwa respon CTL memiliki peran penting dalam pengendalian kepadatan partikel virus bebas dan sel yang terinfeksi. Simulasi-simulasi numerik disajikan untuk menggambarkan hasil-hasil.

Abstract

A virus dynamics model with Beddington-DeAngelis infection rate and CTL immune response is analyzed. It is proved that the solutions with positive initial values are all positive and bounded. The global stability of equilibrium points for dynamics virus model are explored by using appropriate Lyapunov functions. The global dynamics of the model are determined by the values of the basic reproduction number R_0. It is proved that if $R_0<1$, there is a unique steady state, the virus-free equilibrium, which is globally asymptotically stable. If $R_0>1$ there is another steady state, the endemic equilibrium, which is globally asymptotically stable. In addition, we show that the CTL response have important role in controlling of the density of free virus particles and of infected cells. Numerical simulations are presented to illustrate the results.

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Introduction

Recently, many mathematical models have been developed to describe the the dynamics of virus and the responsiveness of immune system such as human immunodeciency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV) (Adams et al. 2004; Ciupe et al. 2007; Yousfi et al. 2009). By investigating these models, researchers have enhanced progress in the understanding of virus infection and have gained much important knowledge about immune response. Note that cytotoxic T lymphocyte cells (CTLs) are the main host immune factor that determines virus load by attack infected cells (Wang et al. 2011). The basic model for virus dynamics with and without CTL response may be described by the following system.

$$\begin{aligned} \dot{Z} &= \alpha - mZ - rVZ,\ t \geq 0, \\ \dot{I} &= rVZ - \mu I,\ t \geq 0, \\ \dot{V} &= kI - cV,\ t \geq 0, \end{aligned} \tag{1}$$

and

$$\begin{aligned} \dot{Z} &= \alpha - mZ - rVZ,\ t \geq 0, \\ \dot{I} &= rVZ - \mu I - sIT,\ t \geq 0, \\ \dot{V} &= kI - cV,\ t \geq 0, \\ \dot{T} &= dIT - nT,\ t \geq 0, \end{aligned} \tag{2}$$

respectively, with given constants a, m, r, u, k, c, s, d, n, p, g, h>0. Here Z, I, V, and T represent the density of uninfected host cells, infected cells, free virus particles, and CTLs at time t, respectively.

Usually the rate of infection in most virus dynamics models is assumed to be bilinear in the virus V and the uninfected cells Z. However, the actual incidence rate is probably not linear over the entire range of V and Z. Thus, it is reasonable to assume that the infection rate of virus is given by Beddington-DeAngelis functional response, rVZ/(1+ aZ+bV) , where a,b≥0 are constants. Huang et al. (2009) and Wang et al. (2011) have incorporated a Beddington-DeAngelis into model (1) and model (2), respectively. In the first model we have the model:

$$\begin{aligned} \dot{Z} &= \alpha - mZ - \frac{rVZ}{1+aZ+bV},\ t \geq 0, \\ \dot{I} &= \frac{rVZ}{1+aZ+bV} - \mu I,\ t \geq 0, \\ \dot{V} &= kI - cV,\ t \geq 0, \end{aligned} \tag{3}$$

and for the second model this leads to the following model:

$$\begin{aligned} \dot{Z} &= \alpha - mZ - \frac{rVZ}{1+aZ+bV},\ t \geq 0, \\ \dot{I} &= \frac{rVZ}{1+aZ+bV} - \mu I - sIT,\ t \geq 0, \\ \dot{V} &= kI - cV,\ t \geq 0, \\ \dot{T} &= dIT - nT,\ t \geq 0. \end{aligned} \tag{4}$$

The global stability of equilibria of model (3) and (4) have been discussed in Huang et al. (2009) and Wang et al. (2011), respectively; whereas Korobeinikov constructed Lyapunov functions for the global stability analysis of model (1) in Korobeinikov (2004). Motivated by the works in Huang et al. (2009), Korobeinikov (2004) and Wang et al. (2011), in this paper, some preliminaries such as the positive invariance of model (4), the existence of equilibria, and the boundedness of solutions are presented. Thereafter, the global stability of equilibria of model (4) is analyzed. The Lyapunov functions are constructed (different with the functions in Wang et al. (2011) to analyze the global stability of endemic equilibrium points. Moreover, the numerical simulations are presented to observe the dynamics of the model with some sets of parameter, include the changing of value of a and b. In particular, model (2) is compared with model (4) to find the difference of the infection rate. The role of CTL immune response can be described by comparing endemic equilibrium point of model (3) with model (4).

Some Preliminary Results

In this section, we give some basic properties of model (4).

Positive Invariance

Proposition 1. Let X:[0,+$] menjadi R^4, X(t)= (Z(t), I(t), V(t), T(t)), be a solution of model (4). If $X(0) \in R_+^4$, then $X(t) \in R_+^4$ for all $t \in [0,+\infty]$.

Proof. The model (4) can be written in the form

$$\dot{X}(t) = F\big(X(t)\big), \tag{5}$$

Where X(t)= (x1, x2, x3, x4) T (Z, I, V, T) T, X(0)= XER+4 and
is easy to check that Fi (X) |(xi= 0)≥0,i= 1,2,3,4.

$$F(X) = \begin{pmatrix} F_1(X) \\ F_2(X) \\ F_3(X) \\ F_4(X) \end{pmatrix} = \begin{pmatrix} \alpha - mZ - \frac{rVZ}{1+aZ+bV} \\ \frac{rVZ}{1+aZ+bV} - \mu I - sIT \\ kI - cV \\ dIT - nT \end{pmatrix}$$

Due to the well known theorem by Nagumo (1942), any solution of model (4) with initial point $X_0 \in R_+^4$, say $X(t)= X(t;X_0)$, is such that $X(t) \in R_+^4$ for all $t \in [0,+\infty)$.

Boundedness of Solutions

The set of continuous and bounded functions defined on the interval I is denoted by $C_b(I)$.

Proposisition 2. Let $X:[0,+\infty]$ menjadi R+4, $X(t)=(Z(t),I(t),V(t),T(t))$, be a solution of model (4). If $X(0) \in R+4$, then $X \in Cb([0,+\infty))$. Moreover

(i) $Z(t) \le Z_0 + \frac{\alpha}{m}$,

(ii) $I(t) \le I_0 + \max\left(1, 2 - \frac{m}{\mu}\right) Z_0 + \max\left(\frac{\alpha}{\mu}, \frac{\alpha}{m}\right)$,

(iii) $V(t) \le V_0 + \frac{k}{c}\|I\|_\infty$,

(iv) $T(t) \le T_0 + \frac{d}{s}\left[\max\left(1, 2 - \frac{m}{n}\right) Z_0 + I_0 + \max\left(\frac{\alpha}{n}, \frac{\alpha}{m}\right) + \max\left(0, 1 - \frac{\mu}{n}\right)\|I\|_\infty\right]$.

Proof. From Proposition 1, $X(t) \in \Re_+^4$. From $\dot{Z} = \alpha - mZ - \frac{rVZ}{1+aZ+bV}$, it is deduced that $\dot{Z} + mZ \le \alpha$, then $\frac{d}{dt}(Ze^{mt}) \le \alpha e^{mt}$. Hence,

$$Z(t) \le Z_0 e^{-mt} + \frac{\alpha}{m}(1 - e^{-mt}). \quad (6)$$

Since $0 \le e^{-mt} \le 1$, thus $Z(t) \le Z_0 + \frac{\alpha}{m}$. From

$$\dot{I} + \mu I = \frac{rVZ}{1+aZ+bV} - sIT \le \frac{rVZ}{1+aZ+bV} = \alpha - mZ - \dot{Z},$$

then

$$\dot{I} + \mu I \le \alpha - (\dot{Z} + mZ).$$

Thus,

$$I(t)e^{\mu t} - I_0 \le \frac{\alpha}{\mu}(e^{\mu t} - 1) - \int_0^t e^{(\mu - m)s}\frac{d}{ds}(Z(s)e^{ms})ds.$$

Using the integration by parts,

$$\int_0^t e^{(\mu-m)s}\frac{d}{ds}(Z(s)e^{ms})ds = [Z(s)e^{\mu s}]_0^t - (\mu - m)\int_0^t Z(s)e^{\mu s}ds.$$

Hence,

$$I(t) \le (Z_0 + I_0)e^{-\mu t} + \frac{\alpha}{\mu}(1 - e^{-\mu t}) - Z(t) + (\mu - m)\int_0^t Z(s)e^{\mu(s-t)}ds. \quad (7)$$

If $\mu - m \le 0$, then

$$I(t) \le Z_0 + I_0 + \frac{\alpha}{m}. \quad (8)$$

If $\mu - m \ge 0$, then

$$I(t) \le Z_0 + I_0 + \frac{\alpha}{m} + (\mu - m)\int_0^t Z(s)e^{\mu(s-t)}ds.$$

According to (i),

$$I(t) \le Z_0 + I_0 + \frac{\alpha}{m} + \frac{\mu - m}{\mu}\left(Z_0 + \frac{\alpha}{m}\right)(1 - e^{-\mu t}).$$

Hence,

$$I(t) \le I_0 + \left(2 - \frac{m}{\mu}\right)Z_0 + \frac{\alpha}{m}. \quad (9)$$

From (8) and (9), it is deduced that

$$I(t) \le I_0 + \max\left(1, 2 - \frac{m}{\mu}\right) Z_0 + \max\left(\frac{\alpha}{\mu}, \frac{\alpha}{m}\right).$$

The equation $\dot{V}(t) = kI - cV$ implies that

$$V(t) = V_0 e^{-ct} + k\int_0^t I(s) e^{(s-t)c} ds. \quad (10)$$

Then,

$$V(t) \le V_0 + \frac{k}{c}\|I\|_\infty (1 = e^{-tc}).$$

Since $1 - e^{-tc} \le 1$, then

$$V(t) \le V_0 + \frac{k}{c}\|I\|_\infty.$$

The equation $\dot{T}(t) = dIT - nT$ implies that

$$\dot{T}(t) + nT = dIT = \frac{d}{s}\left[\alpha - \left(\dot{Z} + mZ\right) - \left(\dot{I} + \mu I\right)\right].$$

Using the same technic to show (7), it is obtained that

$$T(t) = \left[\frac{d}{s}\left(Z_0 + I_0 - \frac{\alpha}{n}\right) + T_0\right] e^{-nt} + \frac{d}{s}\left[\frac{\alpha}{n} - Z(t) - I(t)\right.$$
$$\left. + \int_0^t [(n-m)Z(s) + (n-\mu)I(s)e^{(s-t)n} ds\right].$$

If $n - m \le 0$ and $n - \mu \le 0$, then

$$T(t) \le T_0 + \frac{d}{s}\left(\frac{\alpha}{n} + Z_0 + I_0\right). \quad (11)$$

If $n - m \le 0$ and $n - \mu \ge 0$, then

$$T(t) \le T_0 + \frac{d}{s}\left[\frac{\alpha}{n} + Z_0 + I_0 + \left(1 - \frac{\mu}{n}\right)\|I\|_\infty\right]. \quad (12)$$

If $n - m \ge 0$ and $n - \mu \le 0$, then

$$T(t) \le T_0 + \frac{d}{s}\left[\frac{\alpha}{m} + \left(2 - \frac{m}{n}\right) Z_0 + I_0\right]. \quad (13)$$

If $n - m \ge 0$ and $n - \mu \ge 0$, then

$$T(t) \le T_0 + \frac{d}{s}\left[\frac{\alpha}{m} + \left(2 - \frac{m}{n}\right) Z_0 + I_0 + \left(1 - \frac{\mu}{n}\right)\|I\|_\infty\right]. \quad (14)$$

From (11) – (14), it is deduced that

$$T(t) \le T_0 + \frac{d}{s}\left[\max\left(1, 2 - \frac{m}{n}\right) Z_0 + I_0 + \max\left(\frac{\alpha}{n}, \frac{\alpha}{m}\right) + \max\left(0, 1 - \frac{\mu}{n}\right)\|I\|_\infty\right]. \square$$

Analysis of the Model

The basic reproduction number of model (4) is R_0=ark/(uc(m+qa)). It is defined as the total number of infected cells that arise from one infected cell when almost all cells are noninfected (Kurdhi & Aryati 2011; Wodarz 2007). If R_0 is less than unity, every infected cell on the average produces less than one infected cell. Thus, the virus will not spread. If R_0 is greater than unity, every infected cell produces more than one newly infected cell. Then the disease will spread. Hence, R_0 determines the persistence or extinction of an infection over a long period of time (Pruss et al., 2008).

Model (4) always has virus-free equilibrium point of the form

$$\bar{E} = (\bar{Z}, \bar{I}, \bar{V}, \bar{T}) = \left(\frac{\alpha}{m}, 0,0,0\right), \quad (15)$$

and two endemic equilibrium points

$$E_*(Z_*, I_*, V_*, T_*) = \left(\frac{\mu c+\alpha bk}{mbk+rk-a\mu c}, \frac{\alpha rkZ_*}{\mu(\mu c+\alpha bk)}\left(1-\frac{1}{R_0}\right), \frac{k}{c}I_*, 0\right), \quad (16)$$

$$\hat{E}(\hat{Z}, \hat{I}, \hat{V}, \hat{T}) = \left(\hat{Z}, \frac{n}{d}, \frac{k}{c}\hat{I}, \frac{\alpha-m\hat{Z}-\mu\hat{I}}{s\hat{I}}\right), \quad (17)$$

where

$$\hat{Z} = -\frac{m(1+b\hat{V})+r\hat{V}-\alpha a+\sqrt{4\alpha am(1+b\hat{V})+(mb\hat{V}+r\hat{V}+m-\alpha a)^2}}{2am}. \quad (18)$$

The equilibrium points E always positive; whereas E and E are positive if and only if R_0>1 and R_1>1, respectively, where

$$R_1 = \frac{\alpha rkd}{\mu n(mbk+rk-a\mu c)}\left(1-\frac{1}{R_0}\right) \quad (19)$$

Here, R_1 is called basic reproduction number for CTL response of model (4). When R_0>1, the persistence or extinction of the CTL response depends on the value of R_1 . The global asymptotic stability of the equilibrium points of model (4) is described in the following theorems.

Theorem 3. If R_0<1, E is globally asymptotically stable.

Proof. The following Lyapunov function has been constructed by Wang et al. (2011):

$$\Phi_0(Z, I, V, T) = \frac{\bar{Z}}{1+a\bar{Z}}\left(\frac{Z}{\bar{Z}} - \ln\frac{Z}{\bar{Z}} - 1\right) + I + \frac{\mu}{k}V + \frac{s}{d}T$$

The function satisfies

$$\dot{\Phi}_0(Z, I, V, T) = \frac{m\bar{Z}}{1+a\bar{Z}}\left(2 - \frac{Z}{\bar{Z}} - \frac{\bar{Z}}{Z}\right) + \frac{\mu c(1+aZ)V}{k(1+aZ+bV)}(R_0 - 1) - \frac{b\mu cV^2}{k(1+aZ+bV)} - \frac{\mu c}{k}V - \frac{sn}{d}T.$$

Since the arithmetical mean is greater than or equal to the geometrical mean, the function

Z/Z+Z /Z≥2

Is non-negative for Z>0, and the equality holds only for Z=Z . It is obvious that R_0<1 ensures O:0 (Z,I,V,T)≤0 for all V,T≥0.

Theorem 4. If R_0>1 and R_1<1, E is globally asymptotically stable.

Proof. The function 0:O menjadi R is introduced, where O={(Z,I,V,T)ER^4:Z,I,V>0,T≥0} and

$$\Phi_*(Z, I, V, T) = \frac{(1+bV_*)Z_*}{1+aZ_*+bV_*}\left(\frac{Z}{Z_*} - \ln\frac{Z}{Z_*} - 1\right) + I_*\left(\frac{I}{I_*} - \ln\frac{I}{I_*} - 1\right) + \frac{\mu}{k}V_*\left(\frac{V}{V_*} - \ln\frac{V}{V_*} - 1\right) + \frac{s}{d}T.$$

Clearly,0 is C^1 on 0, E is the global minimum of 0 on O, and 0 (Z,I,V,T)=0. The time derivative of 0 computed along solution of (4) is

$$\dot{\Phi}_*(Z, I, V, T) = -\frac{m(1+bV_*)(Z-Z_*)^2}{Z(1+aZ_*+bV_*)} + \mu I_*\left(-1 - \frac{V}{V_*} + \frac{V(1+aZ+bV_*)}{V_*(1+aZ+bV)} + \frac{1+aZ+bV}{1+aZ+bV_*}\right) + \mu I_*\left(4 - \frac{Z_*(1+aZ+bV_*)}{Z(1+aZ_*+bV_*)} - \frac{ZI_*V(1+aZ_*+bV_*)}{Z_*IV_*(1+aZ+bV)} - \frac{IV_*}{I_*V} - \frac{1+aZ+bV}{1+aZ+bV_*}\right) + sT\left(I_* - \frac{n}{d}\right).$$

Since the arithmetical mean is greater than or equal to the geometrical mean, the function

$$\frac{Z_*(1+aZ+bV_*)}{Z(1+aZ_*+bV_*)} + \frac{ZI_*V(1+aZ_*+bV_*)}{Z_*IV_*(1+aZ+bV)} + \frac{IV_*}{I_*V} + \frac{1+aZ+bV}{1+aZ+bV_*} - 4$$

is non-negative for all Z,I,V>0 and the equality hold only for Z=Z*,I=I* and V=V*. Furthermore, since R1<1, then I*<n/d. Hence 0* (Z,I,V,T)≤0 for all (Z,I,V,T)EO*. Note that 0* (Z,I,V,T)=0 if and only if Z=Z*,I=I*,V=V*, and T=0. Therefore the largest compact invariant set in {(Z,I,V,T)EO*: 0* (Z,I,V,T)=0} is the singleton {E*}. LaSalle's invariant principle (Kurdhi & Aryati 2011) then implies that the endemic equilibrium E* is globally asymptotically stable in O*.

Theorem 5. If $R_0>1$ and $R_1>1$, E is globally asymptotically stable.

Proof. The function ^{0*}:O menjadi R, where O={(Z,I,V,T)ER^4:Z,I,V,T>0} and

$$\Phi^*(Z,I,V,T)=\frac{\left(1+b\hat{\hat{V}}\right)\hat{Z}}{1+a\hat{Z}+b\hat{V}}\left(\frac{Z}{\hat{Z}}-\ln\frac{Z}{\hat{Z}}-1\right)+\hat{I}\left(\frac{I}{\hat{I}}-\ln\frac{I}{\hat{I}}-1\right)$$
$$+\frac{\mu+s\hat{\hat{T}}}{k}\hat{V}\left(\frac{V}{\hat{V}}-\ln\frac{V}{\hat{V}}-1\right)+\frac{s}{d}\hat{T}\left(\frac{T}{\hat{T}}-\ln\frac{V}{\hat{T}}-1\right)$$

Clearly, Φ^* is C^1 on $\Omega\hat{}$, E$\hat{}$ is the global minimum of Φ^* on $\Omega\hat{}$, and Φ^*(Z$\hat{}$, I$\hat{}$, V$\hat{}$, T$\hat{}$) =0. The time derivative of Φ^* computed along solution of (4) is

$$\dot{\Phi}^*(Z,I,V,T)=-\frac{m\left(1+b\hat{V}\right)\left(Z-\hat{Z}\right)^2}{Z\left(1+a\hat{Z}+b\hat{V}\right)}-\left(\frac{b(1+aZ)\left(\mu\hat{I}+s\hat{I}\hat{T}\right)\left(V-\hat{V}\right)^2}{\hat{V}(1+aZ+bV)\left(1+a\hat{Z}+b\hat{V}\right)}\right)+\left(\mu\hat{I}+s\hat{I}\hat{T}\right)$$
$$\left(4-\frac{\hat{Z}(1+aZ+b\hat{V})}{Z(1+a\hat{Z}+b\hat{V})}-\frac{Z\hat{I}V(1+a\hat{Z}+b\hat{V})}{\hat{Z}I\hat{V}(1+aZ+bV)}-\frac{I\hat{V}}{\hat{I}V}-\frac{1+aZ+bV}{1+aZ+b\hat{V}}\right).$$

Since the arithmetical mean is greater than or equal to the geometrical mean, the function

$$\frac{\hat{Z}\left(1+aZ+b\hat{V}\right)}{Z\left(1+a\hat{Z}+b\hat{V}\right)}+\frac{Z\hat{I}V\left(1+a\hat{Z}+b\hat{V}\right)}{\hat{Z}I\hat{V}(1+aZ+bV)}+\frac{I\hat{V}}{\hat{I}V}+\frac{1+aZ+bV}{1+aZ+b\hat{V}}-4$$

is non-negative for all Z,I,V>0, and the equality hold only for Z=Z,I=I, and V=V. Hence, 0 (Z,I,V,T)≤0 for all (Z,I,V,T)E O. Not that 0 (Z,I,V,T)=0 if and if only Z=Z,I=I,V=V, and T=T. Therefore the largest compact invariant set in {(Z,I,V,T)EO:0* (Z,I,V,T)=0} is the singleton {E}. LaSalle's invariant principle (Kurdhi & Aryati 2011) then implies that the endemic equilibrium E is globally asymptotically stable in O.

We observe that for $R_1<1$, the solution of (4) converges to the equilibrium given by T = 0. This means that the CTL response have no influence for large t. In this case, the threshold condition $R_1<1$ is equivalent to I<n/d and that the number of CTLs decreases strictly if and only if I<n/d, due to (4). Hence, in order to trigger a significant CTL response the reproduction rate must be large enough to push I over the critical value n/d. In this case it holds $V_*/V = I_*/I=((n/d)\ R_1)/(n/d)=R_1$. Compared with the model (3), the CTL response thus decrease the density of free virus particles and of infected cells.

Numerical Simulation

To get a better understanding of the dynamics of viral infection over time, the numerical simulations of model (4) are presented by three sets of parameter values in Table 1. The values of parameters are obtained from (Adams et al. 2004; Kurdhi 2012, Kurdhi & Aryati 2011; Nowak & May 2000; Perelson et al. 1993; Wodarz 2007). The first set of parameter values is given by Va-lues 1 of Table 1. It easy to show that R_0 = 0.643<1. By Theorem 3.1, the virus-free equilibrium point E=(1000,0,0,0) is globally asymptotically stable. Numerical simulation illustrate it (see Figure 1).

Table 1. Values of parameters used for models dynamics calculations.

Parameters	Description	Range of the parameters	Values 1	Values 2	Values 3
α	Uninfected cell production rate	0-10 cells $mm^{-3}day^{-1}$	10	10	10
m	Uninfected cell death rate	0.01-0.02 day^{-1}	0.01	0.01	0.01
μ	Infected cell production rate	0.2398-0.7 day^{-1}	0.7	0.7	0.7
r	The rate of uninfected cells to be infected	2.4×10^{-5} - 2×10^{-4} $mm^3cell^{-1}day^{-1}$	1.5×10^{-4}	1.5×10^{-4}	2×10^{-4}
k	Free virus production rate	3-100 day^{-1}	75	75	100
c	Free virus death rate	3.33-12.5 day^{-1}	10	5	5
s	The rate of infected cells to be Eliminated by the CTL response	10^{-5} – 1 $mm^3cell^{-1}day^{-1}$	10^{-2}	10^{-2}	10^{-2}
d	CTL production rate	0.1-1 $mm^3cell^{-1}day^{-1}$	0.7	0.7	0.7
n	CTL death rate	0.05-0.25 day^{-1}	0.1	0.1	0.1
a	Positive parameters that describe the effects of capture rate	Assumed	0.0015	0.0015	0.0015
b	Positive parameters that describe the effects of capture rate	Assumed	0.4	0.4	0.4

For comparison purposes, the model (4) is also simulated for set of parameter values in Values 2 and Values 3 of Table 1. The second set of parameter values (Values 2) give R_0 = 1.286>1 and R_1 = 0.817<1. By Theorem 4, the endemic equilibrium E= (991.83,0.117,1.751,0) is globally asymptotically stable. The result of numerical simulation is illustrated in Figure 2. Now from the third set of parameter values (Values 2), it is obtained that R_0 = 2.286>1 and R_1 = 2.712>1. By Theorem 5, the endemic equilibrium E= (984.458,0.142857,2.85714,38.7936) is globally asymptotically stable. Numerical simulation illustrate it in Figure 3.

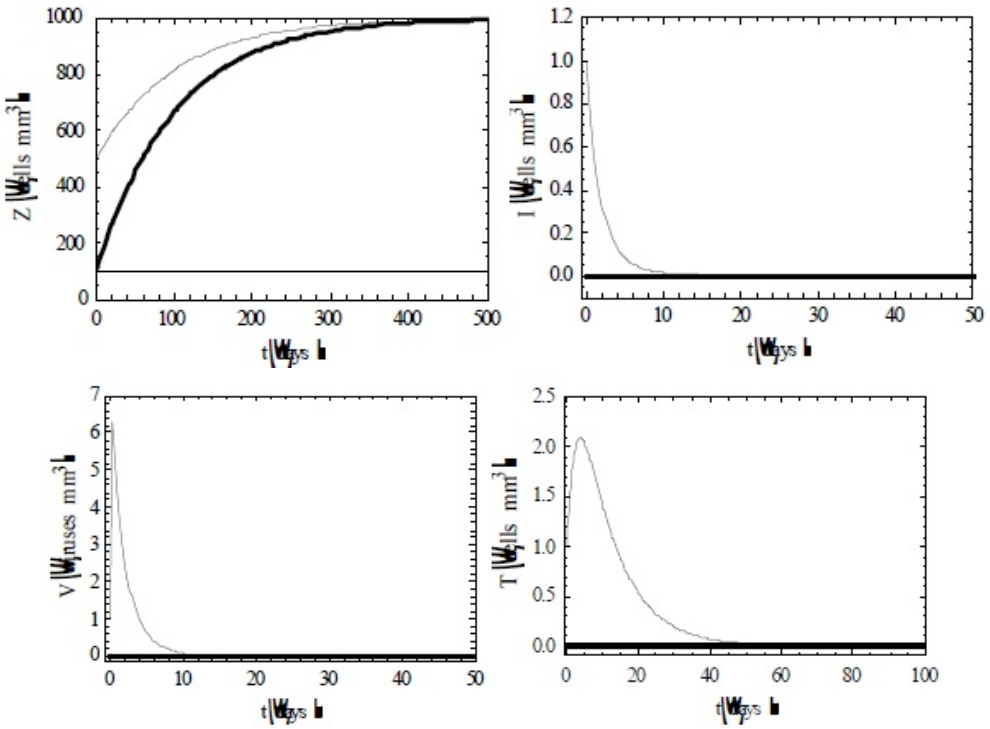

Figure 1. The density of noninfected cells (Z), infected cells (I), free virus particles (V), and CTLs (T) for parameter values in Table 1, R_0<1, and initial values (Z_0,I_0,V_0,T_0)=(100,0,0.001,0.001) (thick line) and (500,1,1,1) (thin line).

Here the effect of the dynamical system due to the change in parametric values of model (4) will be analyzed graphically. Figure 4 and Figure 5 are a plot of a solution for the model variables Z,I,V, and T for different values a and b, respectively. In Figure 4, it is shown that if a decreases from 0.0015 to 0.0010, to 0.0005, the density of infected cell and free virus population increase only at peak level and the density of CTL population increase at equilibrium level. If b decreases from 0.4 to 0.2 to 0.05 similar qualitative features observe as shown for a (see Figure 5).

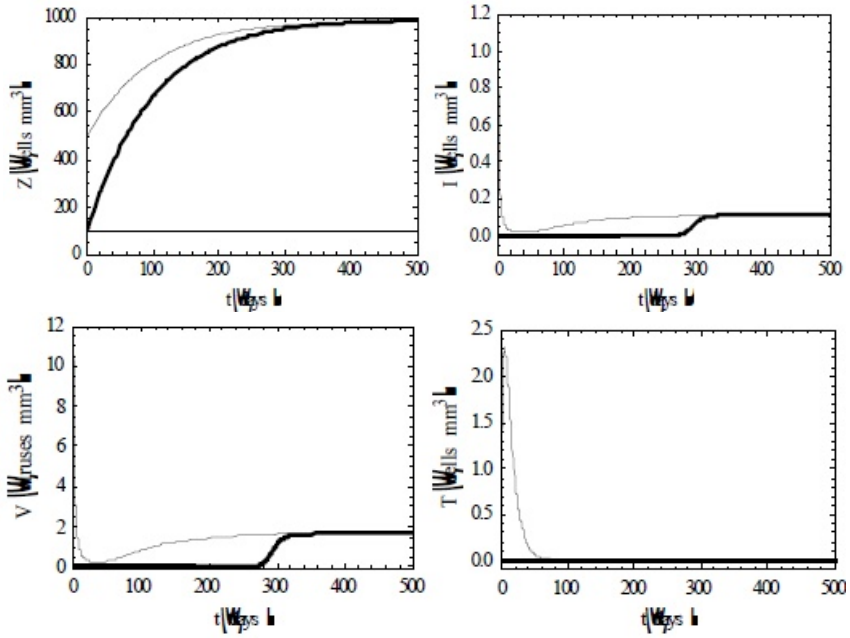

Figure 2. The density of noninfected cells (Z), infected cells (I), free virus particles(V), and CTLs (T) for parameter values in Table 1, $R_0>1$ and $R_1<1$,and initial values $(Z_0,I_0,V_0,T_0)=(100,0,0.001,0.001)$ (thick line) and (500,1,1,1) (thin line).

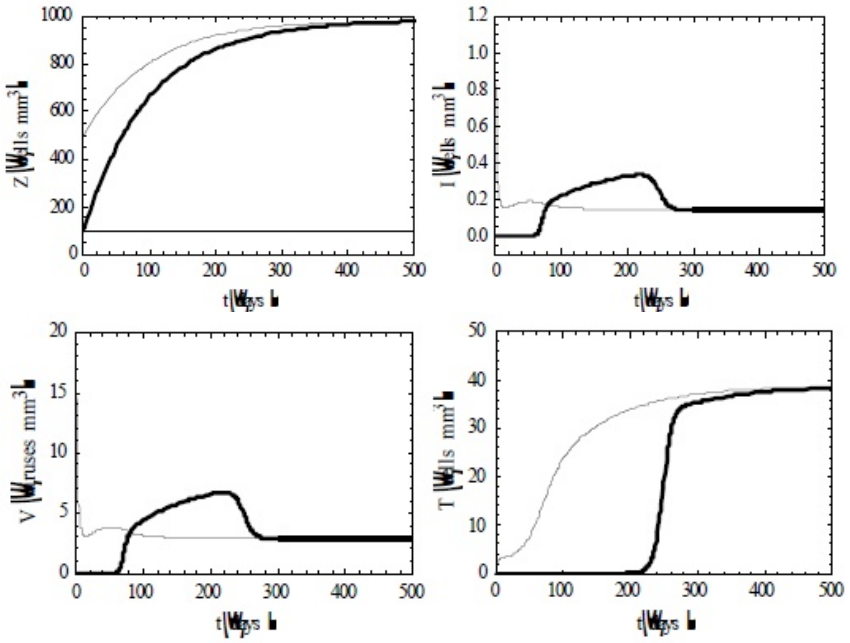

Figure 3. The density of noninfected cells (Z), infected cells (I), free virus particles (V), and CTLs (T) for parameter values in Table 1, $R_0>1,R_1>1$ and initial values $(Z_0,I_0,V_0,T_0)= (100,0,0.001,0.001)$ (thick line) and (500,1,1,1) (thin line).

The difference between Beddington-DeAngelis and bilinear infection rate can be seen by comparing model (4) with the basic model (2) by simulation. In Figure 6, it is shown that infected cell and virus load decreases because of the difference of the infection rate. Furthermore, to understand the role of CTL response numerically, the comparison of noninfected cells, infected cells, and free virus particles population between model (3) and (4) is illustrated in Figure 7. From the figure and the endemic equilibria E_* and E, the CTL response will increase the density of noninfected cells and decrease the density of free virus particles and infected cells at equilibrium level. From the simulations, it can be seen that the CTL response have a very realistic control over the population of infected cells and free virus particles.

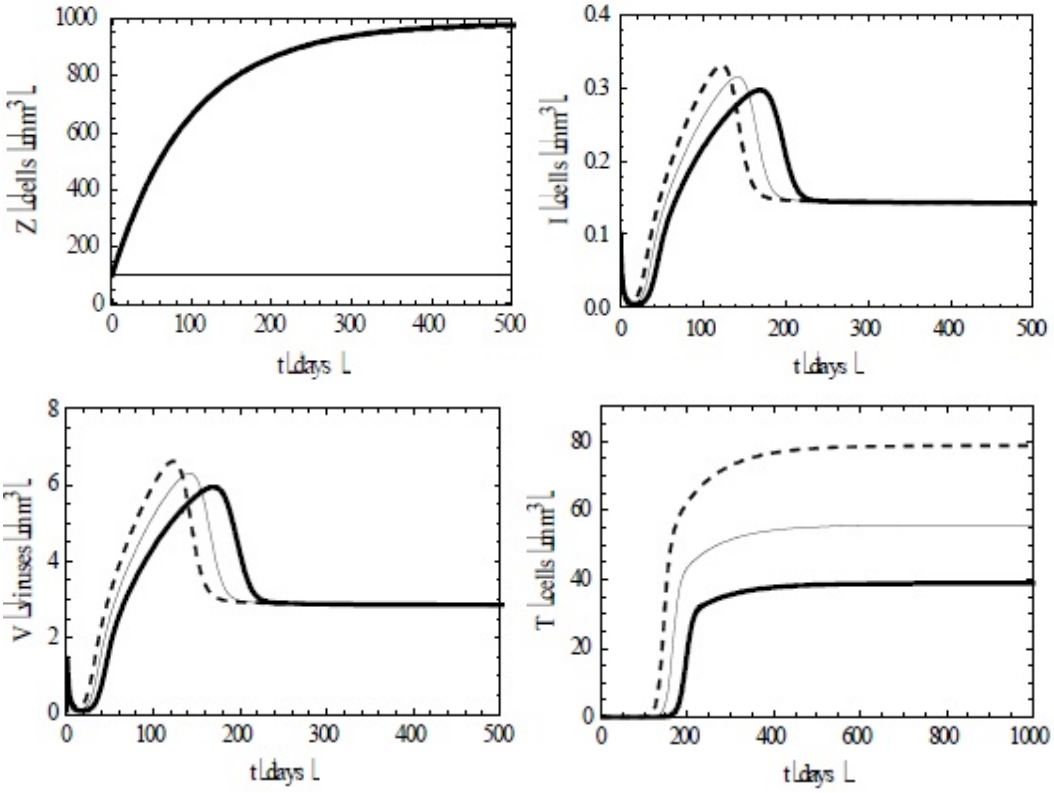

Figure 4. Variation of noninfected cells (Z), infected cells (I), free virus particles (V), and CTLs population (T) for different values a:0.0015 (thick line), 0.0010 (thin line), 0.0005 (dashed line).

Concluding Remarks

In this work, the global analysis of virus dynamics model with Beddington-DeAngelish infection rate and CTL immune response is given. If the basic reproduction number for virus infection $R_0<1$, the virus-free equilibrium is globally asymtotically stable, and in case $R_0>1$ there is a unique endemic equilibrium which is globally asymptotically stable. The stability of the two endemic equilibrium points is also dependent upon the basic reproduction number for CTL response R_1, which determine the persistence or extinction of CTL response at equilibrium level; If $R_1<1<R_0$, the equilibrium E_* is globally asymptotically stable and the infection becomes chronic but without CTL immune response; If $1<R_0$ and $1<R_1$, the equilibrium E is globally asymptotically stable and the infection turns to chronic with CTL immune response. Moreover, the solution of model (4) with positive initial conditions are all positive and bounded.

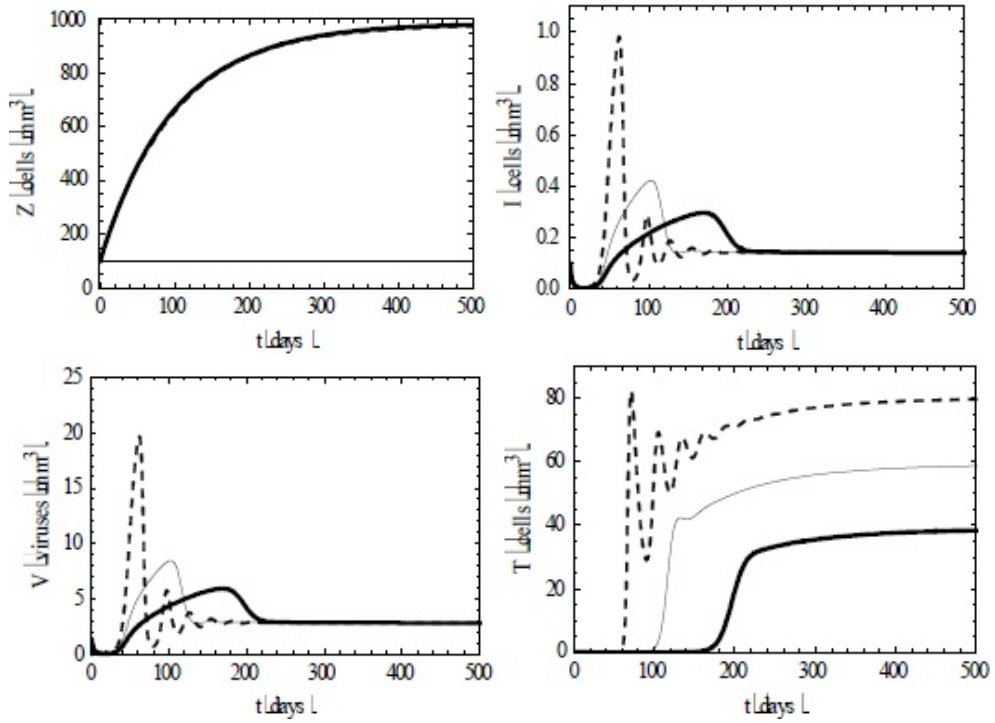

Figure 5. Variation of noninfected cells (Z), infected cells (I), free virus particles (V), and CTLs population (T) for different values b:0.4 (thick Line), 0.2 (thin line), 0.05 (dashed line).

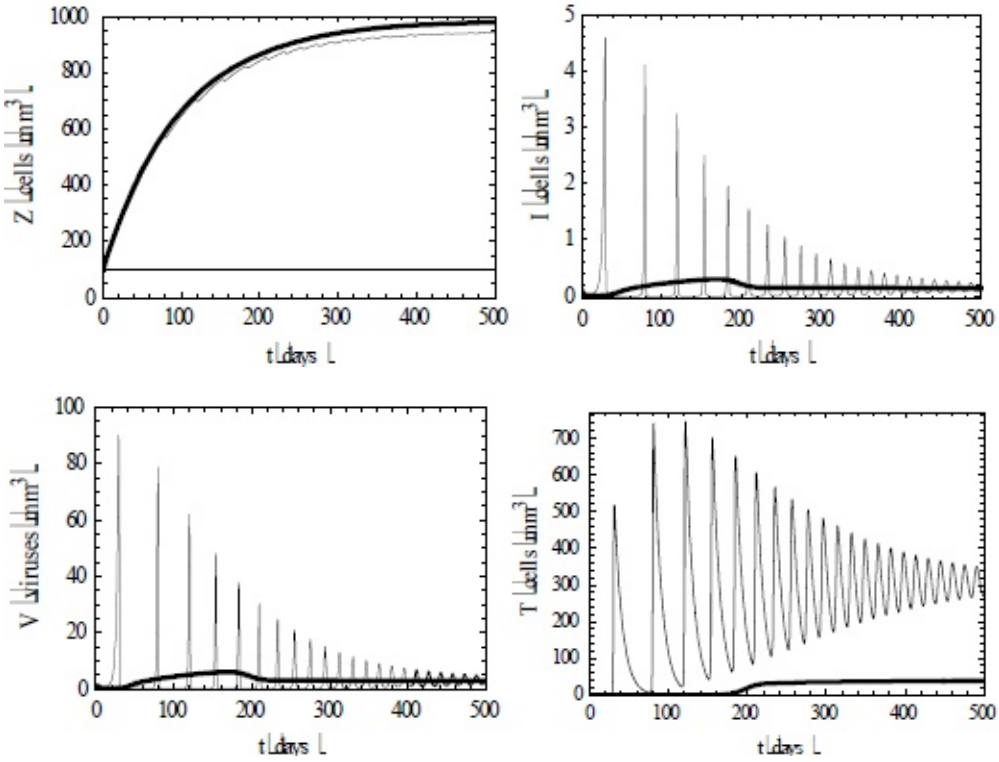

Figure 6. Comparison of noninfected cells (Z), infected cells (I), free virus particles (V), and CTLs population (T) for model (2) (thin line) and model (4) (thick line).

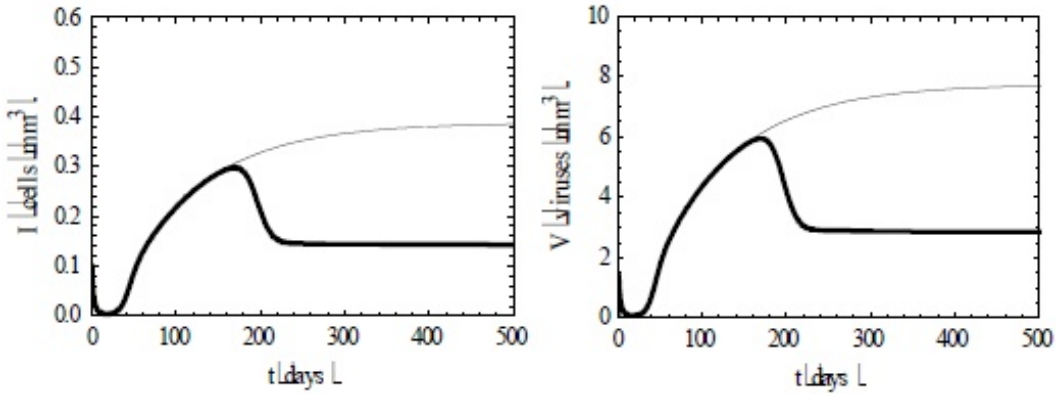

Figure 7. Comparison of infected cells (I) and free virus particles (V) for model (2) (thin line) and model (4) (thick line).

By comparing model (4) and model (2), it is deduced that the virus load decreases because of the difference in the infection rate. From the formula of R_0 and the results of numerical simulation, it is obtained that parameter a is important to model (4). Although parameter b is independent with R_0, it changes the count of noninfected cells and CTLs at equilibrium level, and it also changes the equilibrium level of viral load during chronic infection, especially at the peak level. Hence, b is also important to model (4). That is model (4) is more reasonable than (2).

From numerical simulations, it is deduced that the persistence of the CTL immune response will decrease the density of infected cells and of free virus particles at equilibrium condition. Hence, the CTL immune response plays an important role in the reduction of the virus infection.

References

Adams BM, Banks HT, Davidian M, Kwon HD & Tran HT. 2004. Dynamic multidrug the-rapies for HIV: Optimal and STI control approaches. Math Biosci Eng 1:223–241.

Ciupe SM, Ribeiro RM, Nelson PW & Perelson AS. 2007. Modeling the Mecha-nisms of Acute Hepatitis B Virus Infection. J Theor Biol 247: 23-35.

Huang G, Ma WB & Takeuchi. 2009. Global properties of 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.

Kurdhi NA. 2012. Analysis of a virus dynamics model with multiple infection. Proceeding of the Fifth International Symposium on Computational Science Vol. 1:185–197.

Kurdhi NA & Aryati L. 2011. Global asymptotic stability of virus dynamics models and the effects of CTL and antibody responses. Proceeding of the 6 SEAMS-GMU International Conference on Mathematics and Its Applications pp. 481-498.

Nagumo N. 1942. Uber die Lage der Integralkurven Gewohnlicher Differential Gleichungen. Proc.Phys-Math. Soc. Japan 24, 551 – 559.

Nowak MA & May RM. 2000. Virus Dynamics. Oxford University Press, Inc., New York.

Perelson AS, Kirschner DE & Boer RD. 1993. Dynamics of HIV infection of CD4+ T Cells. Math Biosci 114:81–225.

Pruss J, Zacher R & Schnaubelt R. 2008. Global asymptotic stability of equilibria in models for virus dynamics. Math Model Nat 3(7):126-142.

Yousfi N, Hattaf K & Rachik M. 2009. Analysis of a HCV model with CTL and antibody responses. Appl Math Sci.3(57):2835–2846.

Wang X, Tao Y & Song X. 2011. Global stability of a virus dynamics model with Beddington-DeAngelis incidence rate and CTL immune response. Springer Science.

Wodarz D. 2007. Killer Cells Dynamics. Mathematical and Computational Approaches to Immunolog. Springer-Verlag, New York.