

## VIRAL DYNAMICS OF HIV-1 WITH CTL IMMUNE RESPONSE

AIPING WANG

School of Mathematics and Physics  
North China Electric Power University  
Beijing, 102206, China

MICHAEL Y. LI\*

Department of Mathematical and Statistical Sciences  
University of Alberta  
Edmonton, Alberta, T6G 2G1, Canada

**ABSTRACT.** In this paper, we investigate an in-host model for the viral dynamics of HIV-1 infection and its interaction with the CTL immune response. The model is sufficiently general to allow nonlinear forms for both viral infection and CTL response. Threshold parameters are identified that completely determine the global dynamics and outcomes of the virus-target cell-CTL interactions. Impacts of key parameter values for CTL functions and viral budding rate on the HIV-1 viral load and CD4 count are investigated using numerical simulations. Results support clinical evidence for important differences between HIV-1 nonprogressors and progressors.

**1. Introduction.** In peripheral blood, the human immunodeficiency virus type 1 (HIV-1) mainly infects CD4<sup>+</sup> T helper lymphocyte cells. HIV-1 infection promotes strong immune responses from the body [1]. For infected individuals, the slow depletion of CD4<sup>+</sup> T-cells due to HIV-1 infection and the killing of cytotoxic T-lymphocytes (CTL) is a hallmark of HIV-1 infection. The CD4 count, together with the viral load, is an important measure of the progression of the HIV-1 infection [1, 12, 42]. When the CD4 count gradually decreases from a normal level of 1000 cells mm<sup>-3</sup> to below 200 mm<sup>-3</sup>, acquired immune deficiency syndrome (AIDS) develops and opportunistic infections can cause death [1, 43]. Understanding the viral dynamics of HIV-1 infection and its interaction with the CTL responses is crucial for eventual goal of virus clearance and a cure of AIDS.

Mathematical models have been developed to describe and investigate the HIV-1 infection dynamics. Analysis of these models can help improve our understanding of the pathogenesis HIV-1 within the host, explain the disease progression, and identify the possible risk factors for infection and diseases; It can also provide insights for limiting virus spread and developing vaccines, and inform potential treatment and intervention measures [2, 34, 36, 38]. The basic within-host viral infection model of HIV takes into consideration three variables: healthy CD4<sup>+</sup> T cells  $x$ , infected

---

2020 *Mathematics Subject Classification.* Primary: 34C60, 34D23; Secondary: 92C60.

*Key words and phrases.* HIV-1 infection, CTL immune response, viral dynamics, global stability, HIV nonprogressors.

Dedicated to Professor Sze-Bi Hsu on the occasion of his retirement.

\* Corresponding author: Michael Y. Li.

CD4<sup>+</sup> T cells  $y$ , and free virus particles  $v$ . The interaction of the three variables can be described by a set of nonlinear differential equations [30, 31]:

$$\begin{aligned}\dot{x} &= \lambda - \mu_1 x - \beta xv, \\ \dot{y} &= \beta xv - \mu_2 y, \\ \dot{v} &= ky - \mu_3 v.\end{aligned}\tag{1}$$

In this model, it is assumed that target cells  $x$  are produced at a constant rate  $\lambda$  and have a death rate  $\mu_1$ . The infection of healthy cells by free virus is given by the simple mass-action term  $\beta xv$ , where  $\beta$  is the transmission coefficient. The infected cells have a death rate  $\mu_2$ . The free virus are produced at a rate  $k$  and die at a natural decay rate  $\mu_3$ . The viral dynamics described by this model are quite simple. Outcomes of the infection are completely determined by a basic reproduction number for the viral infection  $R_0 = \frac{\lambda\beta k}{\mu_1\mu_2\mu_3}$ . More specifically, if  $R_0 \leq 1$ , then the infection-free equilibrium  $(\lambda/\mu_1, 0, 0)$  is globally asymptotically stable in the feasible region and the infection will be cleared irrespective of the initial viral loads; if  $R_0 > 1$ , then a unique chronic-infection equilibrium  $(x^*, y^*, v^*)$ ,  $x^*, y^*, v^* > 0$ , exists and is globally asymptotically stable, and the infection becomes chronic irrespective of the initial (positive) viral loads [33, 34].

Improved models for HIV-1 viral dynamics incorporated mitotic division in CD4<sup>+</sup> T cells when stimulated by antigen or mitogen in model (1) ([33, 34, 41]), using a standard logistic growth term in the equation for  $x$ :

$$rx \left[ 1 - \frac{x+y}{x_{max}} \right],$$

where  $r$  is the intrinsic growth rate for the mitotic growth, and  $x_{max}$  is the maximum level of CD4<sup>+</sup> T cells in the body. In addition to threshold dynamics, in some range of the parameter region, periodic oscillations are shown to exist ([41]). When logistic growth term are coupled with ART treatment in a model, it was shown in [26] that backward bifurcations can occur. The bi-stability accompanying the backward bifurcation can have significant implications for the control of HIV-1 infection. Model (1) are further extended to incorporate intracellular delays. Interested readers are referred to [6, 29, 37, 45].

The human immune system reacts to HIV-1 infection with a strong CTL response by killing infected cells and suppressing viral replications [18, 22, 32]. Mathematical models of HIV-1 dynamics with CTL response have been proposed to study the complex interaction between virus infection and CTL response, see [4, 27, 30, 32, 35, 37, 44, 45] and references therein.

To derive a simple HIV-1 infection model with immune response, we consider the fourth variable  $z$  of the number of CTLs, in addition to the three variables in model (1): healthy cells  $x$ , infected cells  $y$ , free virus  $v$ , and describe the interaction between HIV-1 infection and the CTL response by the following system of nonlinear differential equations:

$$\begin{aligned}\dot{x} &= \lambda - \mu_1 x - \beta x f(v) \\ \dot{y} &= \sigma \beta x f(v) - \mu_2 y - \alpha y z \\ \dot{v} &= ky - \mu_3 v \\ \dot{z} &= cyg(z) - \mu_4 z\end{aligned}\tag{2}$$

Compartments  $x$ ,  $y$ ,  $v$ , and  $z$  have death rates  $\mu_1, \mu_2, \mu_3$  and  $\mu_4$ , respectively. The killing of infected cells by CTL action is given by the term  $\alpha y z$ , and production of

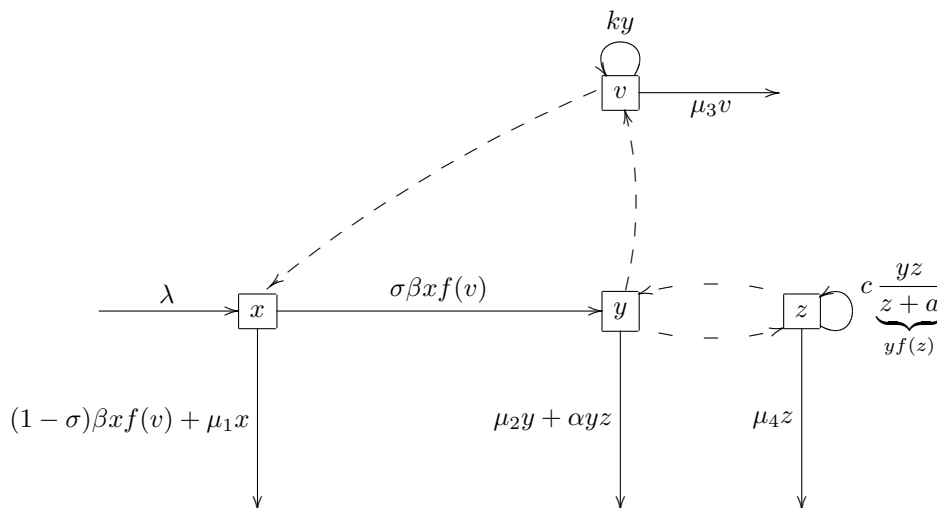


FIGURE 1. Transfer-infection diagram of model (2). Solid lines indicate cell transfer and dotted lines indicated virus-cell or cell-cell interaction.

CTLs in response to HIV-1 infection is described by term  $cyg(z)$ , where  $g(z)$  is called the CTL response function. We also included effects of antibody immune responses to HIV-1 infection indirectly by assuming that only a fraction  $\sigma$  ( $0 \leq \sigma \leq 1$ ) of newly-infected cells escape the killing of antibody-dependent cellular cytotoxicity by effector cells such as natural killer cells ([39, 40]). The infection of healthy cells infected by free virus is described by a nonlinear mass-action term  $\beta x f(v)$ , where  $\beta$  is the transmission coefficient. We make the following biologically motivated assumptions on the function  $f(v)$  in the incidence term.

(H). Assume that  $f(v)$  is continuous,  $f(0) = 0$ ,  $f(v) \geq 0$ ,  $f'(v) > 0$ , and  $f''(v) \leq 0$ , for  $v \geq 0$ .

Nonlinear incidence terms satisfying assumption (H) include the bilinear form  $\beta xv$  and saturation form  $\beta xv/(v + b)$  commonly used in the literature. All parameters in the model are assumed to be positive.

Several forms of CTL response function  $g(z)$  have been considered in the modeling literature of immune responses to viral infections. The most common form is  $g(z) = z$  [31]. Given the complex process of immune responses, nonlinear forms of immune response function are justified. These include  $g(z) = z/(z + a)$  [11, 31] and more generally  $g(z) = z^n/(z^n + a)$  [22]. In [11], for a model of HTLV-I infection with CTL response, the response function  $g(z) = \frac{z}{z+a}$  was used and the global dynamics of the model were completely determined mathematically. It is the primary objective of our study to establish the complete global dynamics of model (2) assuming

$$g(z) = \frac{z}{z + a}, \quad a > 0, \tag{3}$$

and derive the associated the threshold parameters. The main mathematical tool for establishing the global stability of equilibria is the Lyapunov functions of form  $x - x^* \log x$ , which was first used by Goh for ecological models [10] and S-Z. Hsu for predator-prey systems [17] and for chemostat models [3], and later by Korobeinikov for epidemic models [19, 20]. Lyapunov function of this form for complex models were constructed by Guo, Li, and Shuai using a graph theoretic method [13, 14, 24, 25].

We completely establish the global dynamics of model (1) for general nonlinear incidence form  $\beta x f(v)$ , with  $f$  satisfying assumption **(H)** and a nonlinear CTL response functions  $g(z)$  as in (3). The global stability of the positive equilibrium for HIV infection models with nonlinear response functions  $g(z)$  has not previously been established in the literature.

We note that, in a model of HTLV-I infection with CTL response using  $g(z) = z^2/(z^2 + a)$ ,  $a > 0$ , global stability of the positive equilibrium is no longer true, and completely different dynamics including transient periodic oscillations were discovered in [22]. It is of interest to determine if this type of unstable robust periodic oscillations that lasts only for finite time can exist for model (2).

Our simulations of model (1) using biologically plausible parameter values show that several key parameters including the CTL response rate  $c$ , CTL killing rate  $\alpha$ , and viral budding rate  $N$  can greatly influence the HIV viral load. These findings are consistent with previous modeling study results (see e.g. [4, 5] and references therein), and suggest that these factors might help to explain differences between HIV nonprogressors and progressors [9] and are worthy of further modeling study.

**2. Feasible region and equilibria.** Since populations of cells are non-negative, we study model (2) in  $\mathbb{R}_+^4$ . By examining directions of the vector field associated with model (2) on the boundaries of  $\mathbb{R}_+^4$ , we can verify that  $\mathbb{R}_+^4$  is positively invariant with respect to model (2). This implies that solutions with nonnegative initial conditions will remain nonnegative for  $t \geq 0$ , and the model is well defined.

We show that all solutions of model (2) are uniformly ultimately bounded. From the first equation of (2), we have that  $\dot{x} \leq \lambda - \mu_1 x$ . This implies that  $x(t) \leq \frac{\lambda}{\mu_1}$  for  $t \geq 0$  if  $x(0) \leq \frac{\lambda}{\mu_1}$ , and that  $\lim_{t \rightarrow \infty} \sup x(t) \leq \frac{\lambda}{\mu_1}$ . Using the first two equations of (2), we have  $\dot{x} + \dot{y} \leq \lambda - \min\{\mu_1, \mu_2\}(x + y)$ . Denote  $\tilde{\mu} = \min\{\mu_1, \mu_2\}$ . Then we obtain that

$$x(t) + y(t) \leq \frac{\lambda}{\tilde{\mu}} \quad \text{for } t \geq 0 \text{ if } x(0) + y(0) \leq \frac{\lambda}{\tilde{\mu}},$$

and that  $\lim_{t \rightarrow \infty} \sup(x(t) + y(t)) \leq \frac{\lambda}{\tilde{\mu}}$ . Using a similar argument, we can obtain that

$$v(t) \leq \frac{k\lambda}{\tilde{\mu}\mu_3} \quad \text{for } t \geq 0, \text{ if } v(0) \leq \frac{k\lambda}{\tilde{\mu}\mu_3},$$

and  $\lim_{t \rightarrow \infty} \sup v(t) \leq \frac{k\lambda}{\tilde{\mu}\mu_3}$ , and that

$$z(t) \leq \frac{c\lambda}{\tilde{\mu}\mu_4} \quad \text{for } t \geq 0, \text{ if } z(0) \leq \frac{c\lambda}{\tilde{\mu}\mu_4},$$

and  $\lim_{t \rightarrow \infty} \sup z(t) \leq \frac{c\lambda}{\tilde{\mu}\mu_4}$ . In summary, the bounded region

$$\Gamma = \left\{ (x, y, v, z) \in \mathbb{R}_+^4 : x \leq \frac{\lambda}{\mu_1}, x + y \leq \frac{\lambda}{\tilde{\mu}}, v \leq \frac{k\lambda}{\tilde{\mu}\mu_3}, z \leq \frac{c\lambda}{\tilde{\mu}\mu_4} \right\} \quad (4)$$

is positively invariant with respect to model (2) and contains its global attractor. It suffices to study that global dynamics of model (2) in the feasible region  $\Gamma$ .

From equilibrium equations:

$$\begin{aligned} \lambda - \mu_1 x - \beta x f(v) &= 0, \\ \sigma \beta x f(v) - \mu_2 y - \alpha y z &= 0, \\ ky - \mu_3 v &= 0, \\ cy \frac{z}{z+a} - \mu_4 z &= 0, \end{aligned} \tag{5}$$

we see that the infection-free equilibrium  $P_0 = (\frac{\lambda}{\mu_1}, 0, 0, 0)$  always exists. Two chronic-infection equilibria are possible:  $P_1 = (\bar{x}, \bar{y}, \bar{v}, 0)$  with no CTL response, and  $P_2 = (x^*, y^*, v^*, z^*)$  with CTL response, where  $\bar{x}, \bar{y}, \bar{v}, x^*, y^*, v^*, z^* > 0$ . Biological significances of these chronic equilibria are discussed in the next section.

By equation (5), when  $z = 0$  and  $v \neq 0$ , we have  $\frac{\mu_3 v}{k} = \frac{\sigma \beta x f(v)}{\mu_2}$  and  $x = \frac{\lambda}{\mu_1} - \frac{\mu_2 \mu_3 v}{k \sigma \mu_1}$ . Then we obtain the chronic-infection equilibrium with no CTL response

$$P_1 = \left( \frac{\lambda}{\mu_1} - \frac{\mu_2 \mu_3 \bar{v}}{k \sigma \mu_1}, \frac{\mu_3 \bar{v}}{k}, \bar{v}, 0 \right).$$

This equilibrium exists if  $\bar{v}$  satisfies the following equation

$$F(v) := \frac{\lambda \sigma \beta k f(v)}{\mu_2 \mu_3 (\mu_1 + \beta f(v))} - v = 0, \tag{6}$$

and the first coordinate of  $P_1$  is positive, namely,

$$0 < \bar{v} < \frac{k \sigma \lambda}{\mu_2 \mu_3} := v_0.$$

Direct calculation shows that

$$F''(v) = \frac{\lambda \sigma \beta k \mu_1 f''(v) [\mu_1 + \beta f(v)] - 2 \beta [f'(v)]^2}{\mu_2 \mu_3 [\mu_1 + \beta f(v)]^3}.$$

By the assumption that  $f''(v) \leq 0$  and  $f'(v) > 0$  for for all  $v > 0$ , we get that  $F''(v) < 0$  for  $v > 0$ , and thus  $F(v)$  is concave down for  $0 \leq v \leq v_0$ . Let

$$R_0 = \frac{\lambda \sigma \beta k}{\mu_1 \mu_2 \mu_3} f'(0). \tag{7}$$

Then,  $F'(0) = \frac{\lambda \sigma \beta k}{\mu_1 \mu_2 \mu_3} f'(0) - 1 = R_0 - 1$  and  $F'(0) > 0$  if and only if  $R_0 > 1$ . Since  $F(0) = 0$  and

$$F(v_0) = -\frac{k \sigma \lambda \mu_1}{\mu_2 \mu_3 (\mu_1 + \beta f(v_0))} < 0,$$

we know that  $F(v) = 0$  has a unique positive root  $0 \leq \bar{v} \leq v_0$  if and only if  $R_0 > 1$ . As a consequence, a unique chronic-infection equilibrium  $P_1 = (\frac{\lambda}{\mu_1} - \frac{\mu_2 \mu_3 \bar{v}}{k \sigma \mu_1}, \frac{\mu_3 \bar{v}}{k}, \bar{v}, 0)$  exists if and only if  $R_0 > 1$ .

From equilibrium equation (5), a positive equilibrium  $P_2 = (x^*, y^*, v^*, z^*)$  satisfies

$$\begin{aligned} x^* &= \frac{\lambda}{\mu_1} + \left( \frac{\alpha \mu_3 a}{\mu_1 \sigma k} - \frac{\mu_2 \mu_3}{\mu_1 \sigma k} \right) v^* - \frac{\alpha c \mu_3^2}{\mu_1 \sigma \mu_4 k^2} v^{*2}, \\ y^* &= \frac{\mu_3 v^*}{k}, \\ z^* &= \frac{c \mu_3}{k \mu_4} v^* - a, \end{aligned} \tag{8}$$

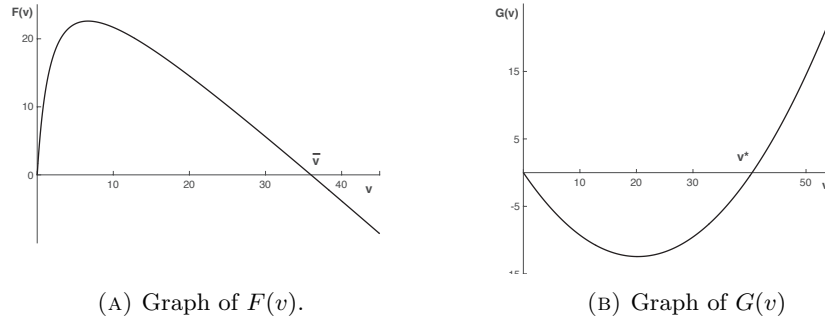


FIGURE 2. Graphs of functions  $F(v)$  and  $G(v)$  and a geometric demonstration of existence of chronic-infection equilibria  $P_1$  and  $P_2$ .

and  $z^* > 0$ . Set

$$G(v) = \frac{\lambda}{\mu_1 + \beta f(v)} - \left[ -\frac{\alpha c \mu_3^2}{\mu_1 \mu_4 \sigma k^2} v^2 + \left( \frac{\alpha \mu_3 a}{\mu_1 \sigma k} - \frac{\mu_2 \mu_3}{\mu_1 \sigma k} \right) v + \frac{\lambda}{\mu_1} \right].$$

Then  $v^*$  satisfies

$$v^* > \frac{ak\mu_4}{c\mu_3} = v^0 \tag{9}$$

and

$$G(v^*) = 0.$$

It can be verified that  $G(0) = 0$ ,  $G'(0) < 0$  if  $R_0 > 1$ , and  $G''(v) > 0$  for  $v > 0$ , since  $f''(v) \leq 0$ . The strict convexity of  $G(v)$  implies that a unique positive equilibrium with  $v^* > v^0$  exists if and only if

$$G(v^0) < 0. \tag{10}$$

By direct calculation we can verify that condition (10) is equivalent to

$$\beta f(v^0)(\lambda \sigma c - a \mu_2 \mu_4) > a \mu_1 \mu_2 \mu_4.$$

Using  $f(0) = 0$  and convex property of  $f(v)$  we obtain  $f(v) \leq v f'(0)$  for  $v > 0$ . The above relation can be rewritten as

$$\frac{\lambda \sigma \beta k c f'(0)}{c \mu_1 \mu_2 \mu_3 + a k \beta \mu_2 \mu_4 f'(0)} = \frac{c \mu_1 \mu_2 \mu_3}{c \mu_1 \mu_2 \mu_3 + a k \beta \mu_2 \mu_4 f'(0)} R_0 > 1,$$

which is equivalent to

$$R_0 > 1 + \frac{ak\beta\mu_2\mu_4}{c\mu_1\mu_2\mu_3} f'(0). \tag{11}$$

We summarize the above analysis and results in the following theorem.

**Theorem 2.1.** Assume that function  $f$  satisfies assumption **(H)**.

- (i) The infection-free equilibrium  $P_0 = (\frac{\lambda}{\mu_1}, 0, 0, 0)$  always exists;
- (ii) A unique chronic-infection equilibrium with no CTL response  $P_1 = (\frac{\lambda}{\mu_1} - \frac{\mu_2 \mu_3 \bar{v}}{k \sigma \mu_1}, \frac{\mu_3 \bar{v}}{k}, \bar{v}, 0)$ ,  $\bar{v} > 0$ , exists if and only if  $R_0 = \frac{\lambda \sigma \beta k}{\mu_1 \mu_2 \mu_3} f'(0) > 1$ ;
- (iii) A unique positive equilibrium  $P_2 = (x^*, y^*, v^*, z^*)$ ,  $x^*, y^*, v^*, z^* > 0$  exists if and only if

$$R_0 > 1 + \frac{ak\beta\mu_4}{c\mu_1\mu_3} f'(0).$$

- Corollary 1.** (i) If  $R_0 \leq 1$ , then  $P_0$  is the only equilibrium of system (2) in  $\Gamma$ ;  
 (ii) If  $1 < R_0 \leq 1 + \frac{ak\beta\mu_4}{c\mu_1\mu_3} f'(0)$ , then only  $P_0$  and  $P_1$  exist in  $\Gamma$ , and they are on the boundary of  $\Gamma$ .  
 (iii) If  $R_0 > 1 + \frac{ak\beta\mu_4}{c\mu_1\mu_3} f'(0)$ , then  $P_0$ ,  $P_1$  and  $P_2$  all exist in  $\Gamma$ .

**3. Global dynamics and outcomes of infection.** In this section, we investigate the global dynamics of model (2). Mathematical results are interpreted in terms of the outcomes of interactions of HIV-1 infection and the immune responses.

**3.1. Global dynamics.** We assume that function  $f$  satisfies assumption (H) and establish the following result.

- Theorem 3.1.** (i) If  $R_0 \leq 1$ , then the infection-free equilibrium  $P_0 = (\frac{\lambda}{\mu_1}, 0, 0, 0)$  is globally asymptotically stable in  $\Gamma$  and the infection clears. If  $R_0 > 1$ , then  $P_0$  is unstable, and system (2) is uniformly persistent.  
 (ii) If  $1 < R_0 \leq 1 + \frac{ak\beta\mu_4}{c\mu_1\mu_3} f'(0)$ , then the unique chronic-infection equilibrium without CTL response,  $P_1 = (\frac{\lambda}{\mu_1} - \frac{\mu_2\mu_3\bar{v}}{k\sigma\mu_1}, \frac{\mu_3\bar{v}}{k}, \bar{v}, 0)$ ,  $\bar{v} > 0$ , is globally asymptotically stable in  $\Gamma$ .  
 (iii) If  $R_0 > 1 + \frac{ak\beta\mu_4}{c\mu_1\mu_3} f'(0)$ , then both  $P_0$  and  $P_1$  are unstable, and a unique positive equilibrium  $P_2 = (x^*, y^*, v^*, z^*)$ ,  $x^*, y^*, v^*, z^* > 0$  is globally asymptotically stable in the interior of  $\Gamma$ .

Theorem 3.1 completely determines the global dynamics of model (2). It establishes sharp threshold values in term of the basic reproduction number  $R_0$ . Biological implications of Theorem 3.1 are the following:

- (i) If the basic reproduction number  $R_0$  is below 1, the any initial infection will eventually clear irrespective of the initial viral load. If  $R_0$  is greater than 1, any initial infection will become chronic.
- (ii) If the basic reproduction number  $R_0$  is in the range  $(1, 1 + \frac{ak\beta\mu_4}{c\mu_1\mu_3} f'(0))$ , then the longtime outcome of any initial infection will be at the equilibrium  $P_1 = (\frac{\lambda}{\mu_1} - \frac{\mu_2\mu_3\bar{v}}{k\sigma\mu_1}, \frac{\mu_3\bar{v}}{k}, \bar{v}, 0)$ , namely, the infection becomes chronic while the body will not mount a persistent CTL response.
- (iii) If  $R_0$  exceeds the threshold value  $1 + \frac{ak\beta\mu_4}{c\mu_1\mu_3} f'(0)$ , then the longtime outcome of any initial infection will be at the positive equilibrium  $P_2 = (x^*, y^*, v^*, z^*)$ ,  $x^*, y^*, v^*, z^* > 0$ , namely, the infection becomes chronic and the body mounts a persistent CTL response.

Technical proofs of global stability will be provided in the Appendix. We present the proof of local stability of  $P_0$  in the following, to establish  $R_0$  as a threshold parameter for the stability of  $P_0$ .

The Jacobian matrix of system (2) at  $P_0$  is

$$J(P_0) = \begin{pmatrix} -\mu_1 & 0 & -\frac{\lambda\beta}{\mu_1} f'(0) & 0 \\ 0 & -\mu_2 & \frac{\lambda\sigma\beta}{\mu_1} f'(0) & 0 \\ 0 & k & -\mu_3 & 0 \\ 0 & 0 & 0 & -\mu_4 \end{pmatrix}.$$

The characteristic polynomial of  $J(P_0)$  is as follows:

$$\begin{aligned} |sI - J(P_0)| &= \begin{vmatrix} s + \mu_1 & 0 & \frac{\lambda\beta}{\mu_1} f'(0) & 0 \\ 0 & s + \mu_2 & -\frac{\lambda\sigma\beta}{\mu_1} f'(0) & 0 \\ 0 & -k & s + \mu_3 & 0 \\ 0 & 0 & 0 & s + \mu_4 \end{vmatrix} \\ &= (s + \mu_1)(s + \mu_4) \left[ (s + \mu_2)(s + \mu_3) - \frac{\lambda\sigma\beta k}{\mu_1} f'(0) \right] \\ &= (s + \mu_1)(s + \mu_4) [s^2 + (\mu_2 + \mu_3)s + \mu_2\mu_3(1 - R_0)]. \end{aligned}$$

When  $R_0 > 1$ , a positive root exists and  $P_0$  is unstable. If  $R_0 < 1$ , real parts of all roots are negative and  $P_0$  is asymptotically stable. When  $R_0 = 1$ , one of the root is 0 and the method of linearization is not applicable. The case is proved using a Lyapunov function in the Appendix.

### 3.2. Threshold values for CTL response and implications to HIV vaccines.

Our mathematical analysis in previous sections has identified two key values for the threshold parameter  $R_0$ , the basic reproduction number, namely,  $R_0 = 1$  and  $R_0 = 1 + \frac{ak\beta\mu_4}{c\mu_1\mu_3} f'(0)$ .

When  $R_0$  is below the first threshold value 1, namely,  $R_0 < 1$ , then Theorem 3.1 implies that all initial infection will eventually clear. Since most, if not all, of the HIV-1 infected persons can not clear the virus, the biologically relevant parameter region should be  $R_0 > 1$ , in which case, Theorem 3.1 implies that all initial HIV-1 infection will become chronic. Note that  $R_0 > 1$  is expressed as, using (7),

$$\frac{\lambda\sigma\beta k}{\mu_1\mu_2\mu_3} f'(0) > 1.$$

This expression does not involve parameters related to the CTL immune response. Therefore, in this parameter region, an initial HIV-1 infection will become chronic with or without any effective CTL response. In another word, our model predicts that CTL response alone can not clear the HIV-1 virus.

The second threshold value for  $R_0$  is related to the interaction between viral infection and the CTL response that aims at controlling the viral infection. In the parameter range

$$1 < R_0 < 1 + \frac{ak\beta\mu_4}{c\mu_1\mu_3} f'(0),$$

all positive solutions of model (1) converge to the boundary equilibrium  $P_1 = (\bar{x}, \bar{y}, \bar{v}, 0)$ . Outcome of any initial infection is that the HIV-1 infection becomes chronic and the body does not mount a persistent CTL response. Clinical evidence has established that HIV-1 infected individuals develop persistent CTL responses [9], this suggests that the equilibrium  $P_1$  may not be biologically relevant to HIV-1 infection.

Based on model (2) and our analysis, the most biologically relevant parameter range for HIV-1 infection is

$$R_0 > 1 + \frac{ak\beta\mu_4}{c\mu_1\mu_3} f'(0). \quad (12)$$

While it is not feasible to discuss viral clearance in this parameter range, there are other important biological issues regarding HIV-1 infection, on which our model



can provide insight, in particular for HIV vaccine development. Cellular vaccines such as the one in the STEP trial [16] aim at boosting effective HIV-specific CTL responses in the body. These vaccines, if effective, will help to control the viral infection through effective killing of HIV infected cells. Our modeling result based on the discussion of  $R_0$  show that cellular vaccines alone will not be able to achieve clearance of HIV virus. In contrast, vaccines that elicit broad neutralizing antibody responses will allow antibodies to bind to viral antigens on the surface viruses and render the virus noninfectious. The effect is to reduce the number of infectious viruses and hence to reduce the transmission rate  $\beta$ . This will reduce the basic reproduction number, ideally to below 1, and achieve viral clearance. Another effect of antibody responses is the antibody dependent cellular cytotoxicity (ADCC), in which antibodies bind to viral antigens on the surface of infected cells and allow effector cells such as natural killer cells to kill the infected cell. This effect is to reduce the fraction  $\sigma$  of newly infected CD4 T cells that survived ADCC. Reducing  $\sigma$  will also directly reduce the basic reproduction number  $R_0$  and help to achieve viral clearance. Our results agree with the current HIV vaccine strategies that aim to stimulate more than one branch of the immune responses, from antibody responses, to primary responses and CTL responses [8].

**3.3. Key factors for differences between a progressor and a nonprogressor.** The progression of HIV-1 infection is marked by increasingly higher level of viral load and decreasing CD4 count. Anti-retroviral therapies (ART) can effectively suppress HIV-1 replication, reduce the viral load to undetectable levels and restore CD4 count. A subset of HIV-1 patients are known to be able to control the viral load at low levels for long periods of time without undertaking ART. These patients are called “nonprogressors” [9]. Since both progressors and nonprogressors maintain persistent CTL responses, they are both represented in our model by the positive equilibrium  $P_2 = (x^*, y^*, v^*, z^*)$ . An interesting biological question is the following: what parameters in our model can be used to explain differences between nonprogressors and progressors?

Clinical evidence has suggested that frequency of CTL  $z^*$  is not a good biomarker to separate progressors and long-term nonprogressors and that there is no clear correlation between the frequency of CTL  $z^*$  and viral load  $y^*$  in the plasma [9]. Recent clinical research has discovered a key clinical difference between nonprogressors and progressors. It is shown in [9, 28] that the nonprogressors maintain an increased proliferation capacity for the HIV-1 specific CD8<sup>+</sup> T cells linked to effector functions. Translated into our model setting, CTL response parameters  $c$ , and CTL killing rate parameter  $\alpha$  are key parameters that may help to characterize nonprogressors. We will investigate the effects of these parameters on the temporal viral load  $v(t)$ . We also examine effects of the average number of virus particles that bud out each of each infected CD4<sup>+</sup> cells on the viral load  $v(t)$ .

In the following numerical simulations, we have chosen  $f(v) = v$  and taken the following values for model parameters:  $\lambda = 20$ ,  $\beta = 0.00048$ ,  $\mu_1 = 0.04$ ,  $\mu_2 = 0.055$ ,  $\mu_3 = 0.1$ ,  $\mu_4 = 0.05$ ,  $\sigma = 0.8$ ,  $k = 0.04$ ,  $c = 0.02$ ,  $a = 2.45$ , and  $\alpha = 0.04$ . These parameter values are adapted from the literature [2, 5, 11, 30, 31, 33]. These parameter values give  $R_0 = 38$ , which fall in the parameter range of interest  $R_0 > 1 + \frac{ak\beta\mu_4}{c\mu_1\mu_3}$  ( $f'(0) = 1$ ). Simulations were carried out using the ODE45 package of Matlab. Simulation results are given in Figure 3 - Figure 5.

**(I). Effects of CTL response parameter  $c$  on HIV-1 viral load**

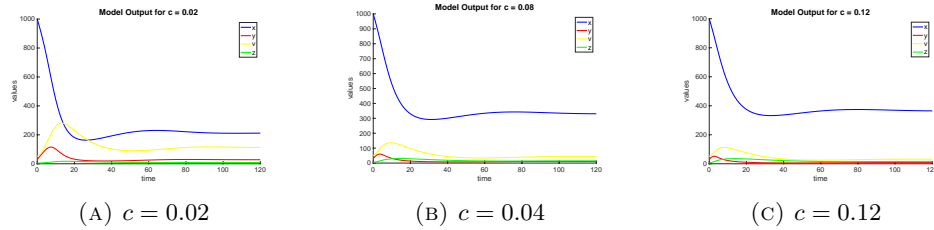


FIGURE 3. Effects of CTL response parameter  $c$  on HIV-1 viral load and CD4 count.

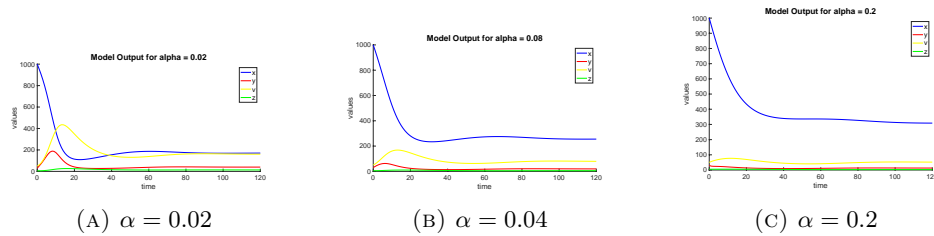


FIGURE 4. Effects of CTL killing rate  $\alpha$  on HIV-1 viral load and CD4 count.

In Figure 3, we have shown that an increase in CTL response parameter  $c$  can effectively decrease the HIV-1 viral load  $v(t)$  to very low levels and increase the CD4<sup>+</sup> count  $x(t) + y(t)$  to healthy levels.

### (II). Effects of CTL killing rate $\alpha$ on HIV-1 viral load

In Figure 4, we have shown that an increase in CTL killing rate  $\alpha$  can also effectively decrease the HIV-1 viral load  $v(t)$  to very low levels and increase the CD4<sup>+</sup> count  $x(t) + y(t)$  to healthy levels.

Our simulation results in both (I) and (II) support the clinical results in [9, 28], providing further evidence that CTL functions might constitute a major difference between HIV-1 progressors and nonprogressors.

### (III). Effects of viral budding rate $N$ on HIV-1 viral load

We have also examined the effects of changing the average number  $N$  of HIV-1 virus particles that bud out of an infected CD4<sup>+</sup> cell at the end of replication cycle. The parameter  $k$  for the production term  $ky(t)$  of HIV-1 virus can be written as  $k = N\mu_2$ . In Figure 5, we have increased  $N$  from 7 to 20 and observed a drastic effects on the rise of the HIV-1 viral load and the decline of CD4<sup>+</sup> count. This suggests that the nonprogressors may harbour HIV-1 viruses that have a low replication rate or of shortened replication cycle inside an infected cell. It will be of interest to explore clinical evidence that may support this difference.

**Acknowledgments.** AW acknowledges the support of National Science Foundation of China. Research of MYL is supported in part by Natural Sciences and Engineering Research Council of Canada (NSERC) and Canada Foundation of Innovation (CFI). The authors wish to thank an anonymous referee whose critique of an earlier draft has improve the presentation of the manuscript.

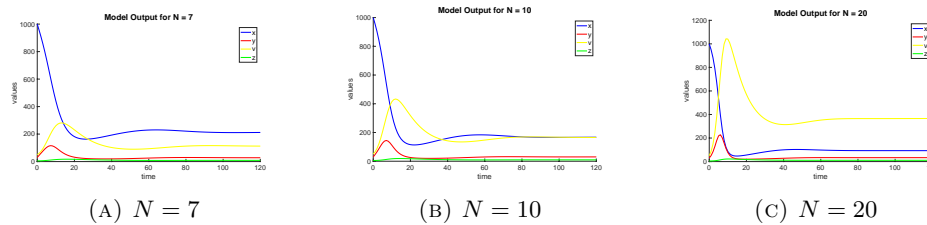


FIGURE 5. Effects of viral budding number  $N$  on HIV-1 viral load and CD4 count.

### REFERENCES

- [1] J. B. Alimonti, T. B. Ball and K. R. Fowke, [Mechanisms of CD4<sup>+</sup> T lymphocyte cell death in human immunodeficiency virus infection and AIDS](#), *J. Gen. Virol.*, **84** (2003), 1649–1661.
- [2] R. A. Arnaout, M. A. Nowak and D. Wodarz, [HIV-1 dynamics revisited: Biphasic decay by cytotoxic T lymphocyte killing?](#) *Proc. R. Soc. Lond. B*, **267** (2000), 1347–1354.
- [3] G. J. Butler, S. B. Hsu and P. Waltman, [A mathematical model of the chemostat with periodic washout rate](#), *SIAM J. Appl. Math.*, **45** (1983), 435–449.
- [4] J. M. Conway and R. M. Ribeiro, [Modeling the immune response to HIV infection](#), *Curr. Opin. Syst. Biol.*, **12** (2018), 61–69.
- [5] J. M. Conway and A. S. Perelson, [Post-treatment control of HIV infection](#), *Proc. Natl. Acad. Sci. USA*, **112** (2015), 5467–5472.
- [6] T. Dumrongpokaphan, Y. Lenbury, R. Ouncharoen and Y. S. Xu, [An intracellular delay-differential equation model of the HIV infection and immune control](#), *Math. Model. Nat. Phenom. Epidemiol.*, **2** (2007), 75–99.
- [7] H. I. Freedman, M. X. Tang and S. G. Ruan, [Uniform persistence and flows near a closed positively invariant set](#), *J. Dynam. Diff. Equat.*, **6** (1994), 583–600.
- [8] Y. Gao, P. F. McKay and J. F. S. Mann, [Advances in HIV-1 vaccine development](#), *Viruses*, **10** (2018), 167.
- [9] J. C. Gea-Banacloche, S. A. Migueles and L. Martino, et al., [Maintenance of large numbers of virus-specific CD8 + T cells in HIV-infected progressors and long-term nonprogressors](#), *J. Immunol.*, **165** (2000), 1082–1092.
- [10] B. S. Goh, [Global stability in many-species systems](#), *Amer. Natur.*, **111** (1997), 135–143.
- [11] H. Gomez-Acevedo, M. Y. Li and S. Jacobson, [Multi-stability In a model for CTL response to HTLV-1 infection and its implications to HAM/TSP development and prevention](#), *Bull. Math. Biol.*, **72** (2010), 681–696.
- [12] R. A. Gruters, C. A. van Baalen and A. D. M. E. Osterhaus, [The advantage of early recognition of HIV-infected cells by cytotoxic T-lymphocytes](#), *Vaccine*, **20** (2002), 2011–2015.
- [13] H. Guo, M. Y. Li and Z. Shuai, [Global stability of the endemic equilibrium of multigroup SIR epidemic models](#), *Canadian Appl. Math. Quart.*, **14** (2006), 259–284.
- [14] H. Guo, M. Y. Li and Z. Shuai, [A graph-theoretic approach to the method of global Lyapunov functions](#), *Proc. Amer. Math. Soc.*, **136** (2008), 2793–2802.
- [15] J. K. Hale, *Ordinary Differential Equations*, John Wiley & Sons, New York, 1969.
- [16] S. M. Hammer, M. E. Sobieszczyk and H. Janes, et al., [Efficacy trial of a DNA/rAd5 HIV-1 preventive vaccine](#), *N. Engl. J. Med.*, **369** (2013), 2083–2092.
- [17] S. B. Hsu, [On global stability of a predator-prey systems](#), *Math. Biosci.*, **39** (1978), 1–10.
- [18] S. Imlach, S. McBreen and T. Shirafuji, et al., [Activated peripheral CD8 lymphocytes express CD4 in vivo and are targets for infection by human immunodeficiency virus type 1](#), *J. Virol.*, **75** (2001), 11555–11564.
- [19] A. Korobeinikov, [A Lyapunov function for Leslie-Gower predator-prey models](#), *Appl. Math. Lett.*, **14** (2001), 697–699.
- [20] A. Korobeinikov and P. K. Maini, [A Lyapunov function and global properties for SIR and SEIR epidemiological models with nonlinear incidence](#), *Math. Biosci. Eng.*, **1** (2004), 57–60.
- [21] J. P. LaSalle, *The Stability of Dynamical System*, Regional Conference Series in Applied Mathematics, SIAM, Philadelphia, 1976.

- [22] J. Lang and M. Y. Li, [Stable and transient periodic oscillations in a mathematical model for CTL response to HTLV-I infection](#), *J. Math. Biol.*, **65** (2012), 181–199.
- [23] M. Y. Li, J. R. Graef, L. Wang and J. Karsai, [Global dynamics of a SEIR model with varying total population size](#), *Math. Biosci.*, **160** (1999), 191–213.
- [24] M. Y. Li and Z. Shuai, [Global-stability problem for coupled systems of differential equations on networks](#), *J. Differential Equations*, **248** (2010), 1–20.
- [25] M. Y. Li, Z. Shuai and C. Wang, [Global stability of multi-group epidemic models with distributed delays](#), *J. Math. Anal. Appl.*, **361** (2010), 38–47.
- [26] M. Y. Li and L. Wang, [Backward bifurcation in a mathematical model for HIV infection in vivo with anti-retroviral treatment](#), *Nonl. Anal. RWA*, **17** (2014), 147–160.
- [27] J. Lin, R. Xu and X. Tian, [Threshold dynamics of an HIV-1 model with both viral and cellular infections, cell-mediated and humoral immune responses](#), *Math. Biosci. Engin.*, **16** (2018), 292–319.
- [28] S. A. Migueles, A. C. Laborico and W. L. Shupert, et al., [HIV-specific CD8+ T cell proliferation is coupled to perforin expression and is maintained in nonprogressors](#), *Nature Immunol.*, **3** (2002), 1061–1068.
- [29] P. W. Nelson and A. S. Perelson, [Mathematical analysis of delay differential equation models of HIV-1 infection](#), *Math. Biosci.*, **179** (2002), 73–94.
- [30] M. A. Nowak and C. R. M. Bangham, [Population dynamics of immune responses to persistent viruses](#), *Science*, **272** (1996), 74–79.
- [31] M. Nowak and R. M. May, *Virus Dynamics: Mathematical Principles of Immunology and Virology*, Oxford University Press, Oxford, 2000.
- [32] G. S. Ogg and X. Jin, et al., [Quantitation of HIV-1-specific cytotoxic T lymphocytes and plasma load of viral RNA](#), *Science*, **279** (1998), 2103–2106.
- [33] A. S. Perelson, D. E. Kirschner and R. de Boer, [Dynamics of HIV infection of CD4+ T cells](#), *Math. Biosci.*, **114** (1993), 81–125.
- [34] A. S. Perelson and P. W. Nelson, [Mathematical analysis of HIV-1 dynamics in vivo](#), *SIAM Rev.*, **41** (1999), 3–44.
- [35] A. S. Perelson and R. M. Ribeiro, [Modeling the within-host dynamics of HIV infection](#), *BMC Biol.*, **11** (2013), 96.
- [36] L. B. Rong and A. S. Perelson, [Modeling HIV persistence, the latent reservoir, and viral blips](#), *J. Theor. Biol.*, **260** (2009), 308–331.
- [37] H. Shu, L. Wang and J. Watmough, [Global stability of a nonlinear viral infection model with infinitely distributed intracellular delays and CTL immune responses](#), *SIAM J. Appl. Math.*, **73** (2013), 1280–1302.
- [38] V. Simon and D. D. Ho, [HIV-1 dynamics in vivo: Implications for therapy](#), *Nat. Rev. Microbiol.*, **1** (2003), 181–190.
- [39] G. D. Tomarasa and B. F. Haynes, [HIV-1-specific antibody responses during acute and chronic HIV-1 infection](#), *Curr. Opin. HIV AIDS*, **4** (2009), 373–379.
- [40] J. Overbaugh and L. Morris, [The Antibody Response against HIV-1](#), *Cold Spring Harb. Perspect. Med.*, **2** (2012), a007039.
- [41] L. Wang and M. Y. Li, [Mathematical analysis of the global dynamics of a model for HIV infection of CD4+ T cells](#), *Math. Biosci.*, **200** (2006), 44–57.
- [42] Y. Wang, Y. C. Zhou, F. Brauer and J. M. Heffernan, [Viral dynamics model with CTL immune response incorporating antiretroviral therapy](#), *J. Math. Biol.*, **67** (2013), 901–934.
- [43] J. Weber, [The pathogenesis of HIV-1 infection](#), *Br. Med. Bull.*, **58** (2001), 61–72.
- [44] D. Wodarz and M. A. Nowak, [Correlates of cytotoxic t-lymphocyte-mediated virus control: Implications for immunosuppressive infections and their treatment](#), *Phil. Trans. R. Soc. Lond. B*, **355** (2000), 1059–1070.
- [45] H. Y. Zhu and X. F. Zou, [Dynamics of a HIV-1 Infection model with cell-mediated immune response and intracellular delay](#), *DCDS B*, **12** (2009), 511–524.

**Appendix.** We provide technical proofs of Theorem 3.1.

For the conclusion (i) of Theorem 3.1, we assume that  $R_0 \leq 1$  and define a Lyapunov function  $V_1$  as follows:

$$V_1(x, y, v, z) = ky + \mu_2 v, \quad (x, y, v, z) \in \mathbb{R}_+^4.$$

Then  $V_1 \geq 0$  and  $V_1(P_0) = 0$ . Differentiating  $V_1$  along the solution of system (2) we obtain

$$\dot{V}_1 = k\dot{y} + \mu_2\dot{v} = k\sigma\beta x f(v) - k\alpha y z - \mu_2\mu_3 v \leq k\sigma\beta x f(v) - \mu_2\mu_3 v.$$

When  $v = 0$ , the derivative  $\dot{V}_1 \leq 0$ . If  $v > 0$ , then

$$\begin{aligned} \dot{V}_1 &\leq k\sigma\beta x f(v) - \mu_2\mu_3 v = \mu_2\mu_3 v \left[ \frac{k\sigma\beta x f(v)}{\mu_2\mu_3 v} - 1 \right] \leq \mu_2\mu_3 v \left[ \frac{k\sigma\beta\lambda f(v)}{\mu_1\mu_2\mu_3} - 1 \right] \\ &\leq \mu_2\mu_3 v \left[ \frac{k\sigma\beta\lambda f'(0)}{\mu_1\mu_2\mu_3} - 1 \right] = \mu_2\mu_3 v (R_0 - 1) \leq 0, \end{aligned}$$

Therefore  $\dot{V}_1 = 0$  if and only if  $v = 0$  or  $R_0 = 1$ . It can be verified that the largest invariant subset of the set where  $\dot{V}_1 = 0$  is the singleton  $\{P_0\}$ . Using the LaSalle's invariant principle [21], we conclude that  $P_0$  is globally asymptotically stable in  $\Gamma$ .

If  $R_0 > 1$  and  $v \neq 0$ , we know that, since  $f(v)/v \rightarrow f'(0)$  as  $v \rightarrow 0^+$ ,

$$\frac{k\sigma\beta x f(v)}{\mu_2\mu_3 v} - 1 > 0,$$

and hence  $\dot{V}_1 > 0$  for points in the interior of  $\Gamma$  and sufficiently close to  $P_0$ . Therefore, for initial points sufficiently close to  $P_0$ , solutions move away from  $P_0$ . This implies that  $P_1$  is unstable. Using a uniform persistence result from [7] and a similar argument as in the proof of Proposition 3.3 of [23], we can show that, when  $R_0 > 1$ , the instability of  $P_0$  implies the uniform persistence of system (2). This completes the proof of conclusion (i).

For conclusion (ii), we note that the coordinates of equilibrium  $P_1$  satisfy the following equations:

$$\begin{aligned} \lambda - \mu_1\bar{x} - \beta\bar{x}f(\bar{v}) &= 0, \\ \sigma\bar{x}f(\bar{v}) - \mu_2\bar{y} &= 0, \\ k\bar{y} &= \mu_3\bar{v}. \end{aligned} \tag{13}$$

Define a Lyapunov function

$$V_2(x, y, v, z) = x - \bar{x} \ln x + \frac{1}{\sigma}(y - \bar{y} \ln y) + \frac{\mu_2}{\sigma k}(v - \bar{v} \ln v) + \frac{\alpha a}{c\sigma} z.$$

Then,  $V_2$  has a global minimum at  $P_1$ . Differentiating  $V_2$  along the solution of system (2) and using equations (13), we obtain

$$\begin{aligned} \dot{V}_2 &= \lambda - \mu_1 x - \frac{\alpha}{\sigma} y z - \frac{\mu_2\mu_3 v}{\sigma k} - \frac{\bar{x}}{x} \lambda + \mu_1 \bar{x} + \beta \bar{x} f(v) - \frac{\beta x \bar{y}}{y} f(v) \\ &\quad + \frac{\mu_2 \bar{y}}{\sigma} + \frac{\alpha \bar{y} z}{\sigma} - \frac{\mu_2 y \bar{v}}{\sigma v} + \frac{\mu_2 \mu_3 \bar{v}}{\sigma k} + \frac{a \alpha y z}{\sigma(z+a)} - \frac{\alpha a \mu_4}{c\sigma} z \\ &= 2\mu_1 \bar{x} + 2\beta \bar{x} f(\bar{v}) - \mu_1 x - \frac{v}{\bar{v}} \beta \bar{x} f(\bar{v}) - \frac{\mu_1}{x} \bar{x}^2 - \frac{\beta}{x} \bar{x}^2 f(\bar{v}) + \beta \bar{x} f(v) - \frac{\beta x \bar{y}}{y} f(v) \\ &\quad - \frac{y \bar{v} \beta \bar{x}}{y \bar{v}} f(\bar{v}) + \beta \bar{x} f(v) - \frac{\alpha}{\sigma} y z + \frac{\alpha}{\sigma} \bar{y} z + \frac{a \alpha y z}{\sigma(z+a)} - \frac{\alpha a \mu_4}{c\sigma} z \\ &= \mu_1 \bar{x} \left[ 2 - \frac{\bar{x}}{x} - \frac{x}{\bar{x}} \right] + \beta \bar{x} f(\bar{v}) \left[ 3 - \frac{\bar{x}}{x} - \frac{x \bar{y} f(v)}{\bar{x} y f(\bar{v})} - \frac{v}{\bar{v}} + \frac{f(v)}{f(\bar{v})} - \frac{\bar{v} y}{v \bar{y}} \right] \\ &\quad + \left[ -\frac{\alpha}{\sigma} y z + \frac{\alpha}{\sigma} \bar{y} z + \frac{a \alpha y z}{\sigma(z+a)} - \frac{\alpha a \mu_4}{c\sigma} z \right]. \end{aligned}$$

Let  $\Phi(x) = 1 - x + \ln x$ . We have

$$\begin{aligned}
 & 3 - \frac{\bar{x}}{x} - \frac{x\bar{y}f(v)}{\bar{x}yf(\bar{v})} - \frac{v}{\bar{v}} + \frac{f(v)}{f(\bar{v})} - \frac{\bar{v}y}{v\bar{y}} \\
 &= \Phi\left(\frac{\bar{x}}{x}\right) + \Phi\left(\frac{x\bar{y}f(v)}{\bar{x}yf(\bar{v})}\right) + \Phi\left(\frac{\bar{v}y}{v\bar{y}}\right) + \ln \frac{vf(\bar{v})}{\bar{v}f(v)} - \frac{v}{\bar{v}} + \frac{f(v)}{f(\bar{v})} \\
 &= \Phi\left(\frac{\bar{x}}{x}\right) + \Phi\left(\frac{x\bar{y}f(v)}{\bar{x}yf(\bar{v})}\right) + \Phi\left(\frac{\bar{v}y}{v\bar{y}}\right) + \Phi\left(\frac{vf(\bar{v})}{\bar{v}f(v)}\right) + \left[\frac{f(v)}{f(\bar{v})} - 1\right] \left[1 - \frac{vf(\bar{v})}{\bar{v}f(v)}\right] \\
 &= \Phi\left(\frac{\bar{x}}{x}\right) + \Phi\left(\frac{x\bar{y}f(v)}{\bar{x}yf(\bar{v})}\right) + \Phi\left(\frac{\bar{v}y}{v\bar{y}}\right) + \Phi\left(\frac{vf(\bar{v})}{\bar{v}f(v)}\right) + \frac{(f(v) - f(\bar{v}))}{f(v)} \left[\frac{f(v)}{f(\bar{v})} - \frac{v}{\bar{v}}\right].
 \end{aligned} \tag{14}$$

Since  $f(v)$  is concave and monotonically increasing on  $v \geq 0$ , we have

$$(f(v) - f(\bar{v}))\left(\frac{f(v)}{f(\bar{v})} - \frac{v}{\bar{v}}\right) \leq 0,$$

which, together with the fact that  $\Phi(x) \leq 0$  for  $x > 0$ , yields that

$$3 - \frac{\bar{x}}{x} - \frac{x\bar{y}f(v)}{\bar{x}yf(\bar{v})} - \frac{v}{\bar{v}} + \frac{f(v)}{f(\bar{v})} - \frac{\bar{v}y}{v\bar{y}} \leq 0.$$

Next, we consider the third group of terms in  $\hat{V}_2$ :

$$\begin{aligned}
 -\frac{\alpha}{\sigma}yz + \frac{\alpha}{\sigma}\bar{y}z + \frac{\alpha\alpha yz}{\sigma(z+a)} - \frac{\alpha a\mu_4}{c\sigma}z &= \frac{\alpha z}{\sigma} \left[ \frac{ay}{z+a} - y \right] + \frac{\alpha z}{\sigma} \text{Big} \left[ \bar{y} - \frac{a\mu_4}{c} \right] \\
 &= \frac{\alpha z}{\sigma} \frac{-yz}{z+a} + \frac{\alpha z}{\sigma} \left[ \bar{y} - \frac{a\mu_4}{c} \right].
 \end{aligned}$$

Let  $F(v)$  be defined by (6) and  $v^0 = \frac{ak\mu_4}{c\mu_3}$  be defined by (9). Then we have

$$\begin{aligned}
 F(v^0) &= \frac{\lambda\sigma\beta k f(v^0)}{\mu_2\mu_3(\mu_1 + \beta f(v^0))} - v^0 = \frac{(\lambda\sigma\beta k - v^0\mu_2\mu_3\beta)f(v^0) - v^0\mu_1\mu_2\mu_3}{\mu_2\mu_3(\mu_1 + \beta f(v^0))} \\
 &= \frac{1}{\mu_2\mu_3(\mu_1 + \beta f(v^0))} \frac{1}{c} [(\lambda\sigma\beta kc - ak\mu_2\mu_4\beta)f(v^0) - ak\mu_1\mu_2\mu_4] \\
 &\leq \frac{(\lambda\sigma\beta kc - ak\mu_2\mu_4\beta)f'(0) - c\mu_1\mu_2\mu_3}{c[\mu_2\mu_3(\mu_1 + \beta f(v^0))] \cdot \frac{c\mu_3}{ak\mu_4}},
 \end{aligned}$$

where the last inequality follows from  $f(v) \leq v f'(0)$  for all  $v > 0$ . From

$$R_0 \leq 1 + \frac{ak\beta\mu_2\mu_4}{c\mu_1\mu_2\mu_3} f'(0),$$

namely,

$$\lambda\sigma\beta kc f'(0) \leq c\mu_1\mu_2\mu_3 + ak\beta\mu_2\mu_4 f'(0),$$

we obtain

$$(\lambda\sigma\beta kc - ak\beta\mu_2\mu_4) f'(0) \leq c\mu_1\mu_2\mu_3.$$

Therefore,  $F(v^0) \leq 0$ . Using the properties of  $F(v)$  and the uniqueness of  $P_1$ , we have the relation

$$\bar{v} \leq v^0.$$

Using the equilibrium equation (13),  $\bar{y} = \frac{\mu_3\bar{v}}{k}$ , we obtain

$$\bar{y} - \frac{a\mu_4}{c} = \frac{c\mu_3\bar{v} - ak\mu_4}{kc} \leq \frac{c\mu_3v^0 - ak\mu_4}{kc} = \frac{c\mu_3 \cdot \frac{ak\mu_4}{c\mu_3} - ak\mu_4}{kc} = 0,$$

and thus,

$$-\frac{\alpha}{\sigma}yz + \frac{\alpha}{\sigma}\bar{y}z + \frac{a\alpha yz}{\sigma(z+a)} - \frac{\alpha a\mu_4}{c\sigma}z \leq 0,$$

which implies that  $\dot{V}_2 \leq 0$  for all  $x, y, v, z > 0$ .

Using the expression of  $\dot{V}_2$  and equation (14) we can show that  $\dot{V}_2 = 0$  only at  $P_1$ . This implies  $\dot{V}_2$  is negative definite with respect to equilibrium  $P_1$ , and thus  $P_1$  is locally asymptotically stable by the classical Lyapunov stability result [15], and  $P_1$  attracts all points in  $\Gamma$ . This implies that  $P_1$  is globally asymptotically stable in  $\Gamma$  when  $1 < R_0 < 1 + \frac{ak\beta\mu_2\mu_4}{c\mu_1\mu_2\mu_3} f'(0)$ .

To show conclusion (iii), we assume that

$$R_0 > 1 + \frac{ak\beta\mu_2\mu_4}{c\mu_1\mu_2\mu_3} f'(0),$$

and consider the Lyapunov function

$$V_3 = x - x^* \ln x + \frac{1}{\sigma}(y - y^* \ln y) + \frac{\beta x^* f(v^*)}{ky^*}(v - v^* \ln v) + \frac{\alpha(z^* + a)}{\sigma c}(z - z^* \ln z).$$

It can be verified that  $V$  has a global minimum at the equilibrium  $P_2$ . We will be using the equilibrium equations for the coordinates of  $P_2$ :

$$\begin{aligned} \lambda &= \mu_1 x^* + \beta x^* f(v^*), & \mu_2 &= \frac{\sigma \beta x^* f(v^*)}{y^*} - \alpha z^*, \\ \mu_3 &= \frac{ky^*}{v^*}, & \mu_4 &= \frac{cy^*}{z^* + a}. \end{aligned} \tag{15}$$

Differentiating  $V_3$  along the solution of system (2) and using (15), we obtain

$$\begin{aligned} \dot{V}_3 &= \lambda - \mu_1 x - \frac{\mu_2}{\sigma}y - \frac{\alpha}{\sigma}yz + \frac{\alpha yz(z^* + a)}{\sigma(z+a)} - \frac{\alpha \mu_4(z^* + a)z}{\sigma c} - \frac{x^*}{x}\lambda + \mu_1 x^* \\ &+ \beta x^* f(v) - \frac{y^*}{y}\beta x f(v) + \frac{\mu_2 y^*}{\sigma} + \frac{\alpha y^* z}{\sigma} - \frac{\beta x^* v^* f(v^*)y}{y^* v} + \frac{\beta x^* v^* \mu_3 f(v^*)}{ky^*} \\ &- \frac{\alpha yz^*(z^* + a)}{\sigma(z+a)} + \frac{\alpha \mu_4 z^*(z^* + a)}{\sigma c} + \frac{y\beta x^* f(v^*)}{y^*} - \frac{\beta x^* f(v^*)}{v^*}v \\ &= 2\mu_1 x^* - \mu_1 x - \frac{\mu_1 x^{*2}}{x} + 3\beta x^* f(v^*) - \frac{\beta x^{*2} f(v^*)}{x} + \beta x^* f(v) - \frac{y^*}{y}\beta x f(v) \\ &- \frac{\beta x^* v^* f(v^*)y}{y^* v} - \frac{\beta x^* f(v^*)v}{v^*} + \frac{\alpha yz^*}{\sigma} - \frac{\alpha yz}{\sigma} + \frac{\alpha yz(z^* + a)}{\sigma(z+a)} - \frac{\alpha yz^*(z^* + a)}{\sigma(z+a)} \\ &= \mu_1 x^* \left[ 2 - \frac{x}{x^*} - \frac{x^*}{x} \right] + \beta x^* f(v^*) \left[ 3 - \frac{x^*}{x} + \frac{f(v)}{f(v^*)} - \frac{xy^* f(v)}{yx^* f(v^*)} - \frac{v}{v^*} - \frac{v^* y}{y^* v} \right] \\ &+ \frac{\alpha y}{\sigma} \left[ (z^* - z) + \frac{(z^* + a)(z - z^*)}{z + a} \right]. \end{aligned}$$

We can use the same method as in the proof of conclusion (ii) and obtain

$$3 - \frac{x^*}{x} + \frac{f(v)}{f(v^*)} - \frac{xy^* f(v)}{yx^* f(v^*)} - \frac{v}{v^*} - \frac{v^* y}{y^* v} \leq 0.$$

Furthermore, we have

$$\begin{aligned} \frac{\alpha y}{\sigma} \left[ (z^* - z) + \frac{(z^* + a)(z - z^*)}{z + a} \right] &= \frac{\alpha y(z^* - z)}{\sigma} \left[ 1 - \frac{(z^* + a)(z - z^*)}{z + a} \right] \\ &= -\frac{\alpha y(z^* - z)^2}{\sigma(z + a)} \leq 0. \end{aligned}$$

Therefore  $\dot{V}_3 \leq 0$  for all  $x, y, v, z > 0$ .

It can be verified that  $\dot{V}_3$  is negatively definite with respect to the equilibrium  $P_2$ , and thus  $P_2$  is locally asymptotically stable and globally attracting in the interior of  $\Gamma$  when  $R_0 > 1 + \frac{ak\beta\mu_2\mu_4}{c\mu_1\mu_2\mu_3} f'(0)$ . This completes the proof of Theorem 3.1.

Received June 2019; revised November 2019.

*E-mail address:* [aiping@ncepu.edu.cn](mailto:aiping@ncepu.edu.cn)

*E-mail address:* [myli@ualberta.ca](mailto:myli@ualberta.ca)