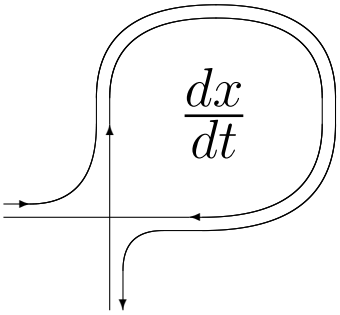

DIFFERENTIAL EQUATIONS
AND
CONTROL PROCESSES N 4, 2013
Electronic Journal,
reg. N ΦC77-39410 at 15.04.2010
ISSN 1817-2172

http://www.math.spbu.ru/diffjournal
e-mail: jodiff@mail.ru

Ordinary differential equations

Global properties for an HIV-1 infection model including an eclipse stage of infected cells and saturation infection

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Abstract

In this paper, we study a fourth-dimensional human immunodeficiency virus (HIV) model including an eclipse stage of infected cells and saturation infection. One feature of this model is that an eclipse stage for the infected cells is included and cells in this stage may revert to the uninfected class . The other feature is that system has nonlinear incidence of infection of health $CD4^+T$ cells. For the analysis of nonlinear autonomous differential equations with or without time delay, the stability of equilibria is important. We will obtain sufficient conditions for the global stability of the equilibria system by using Lyapunov direct method and the geometric approach to stability, based on the generalization of the Poincare-Bendixson criterion for system of n ordinary differential equations.

Keywords: HIV-1 infection, LaSalle invariant principle, Global stability, Compound matrices, Lozinskiĭ measure.

1 Introduction

From the advances in immunology over the past few decades, we are now able to understand the dynamics of infections at the cellular level. In recent years, considerable attention has been paid to study the dynamics of HIV-1 infection model. Mathematical modeling combined with experimental measurements has

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yielded important insights into HIV-1 pathogenesis [1, 2, 3, 4]. Many authors use differential equations to study the dynamical properties of HIV-1 infection models and obtained much knowledge about the HIV-1 infection [5]. In 2007, Rong and coworkers, [6], studied an extension of the basic model of HIV-1 infection. One main feature of their model is that an eclipse stage for the infected cells is included and a portion of these cells is reverted to the uninfected class and in 2011, Buonomo and Vargas-De-León obtained sufficient conditions for global stability of this model [7].
Models used to study HIV-1 infection have involved the concentration of uninfected $CD4^+T$ cells x, productively infected cells y, infected cells in the eclipse stage w and free virus v. It is given by the following set of differential equations [7]:

$$\begin{aligned}
\dot{x} =& \lambda - \beta x(t)v(t) - \mu x(t) + \delta w(t),\\
\dot{y} =& \varphi w(t) - \alpha y(t),\\
\dot{w} =& \beta x(t)v(t) - (\delta + \eta + \varphi)w(t),\\
\dot{v} =& \sigma y(t) - \gamma v(t),
\end{aligned} \tag{1}$$

where parameters are described in Table 1 The cells in the eclipse stage are

Table 1: Parameters for system (1)

Parameter	Description
λ	Rate of which new $CD4^+T$ cells are generated
β	Infection rate of uninfected $CD4^+T$ cells by virus
μ	Natural death rate of uninfected $CD4^+T$ cells
δ	Rate at which the $CD4^+T$ cells in the eclipse phase may revert to the uninfected class
φ	Rate at which infected $CD4^+T$ cells in the eclipse stage become productively infected cells
η	Death rate of infected cells in the eclipse stage
α	Death rate of productively infected cells
σ	Rate of production of virions by infected cells
γ	Rate at which cleared from plasma

already infected and may be killed by immune cells or cytopathic effects [8]. Then it is reasonable to assume that the average life span of uninfected cells $(1/\mu)$ should be greater than, or equal to, the life span of cells in the eclipse stage $(1/\eta)$.

It is assumed in model (1) that the infection process is governed by the mass-action principle, i.e. that the infection rate per host and per virus is a constant. However, experiments reported in [9] strongly suggested that the infection rate of microparasitic infections is an increasing function of the parasite dose, and is usually sigmoidal in shape (see, for example, [10]), in fact the relationship between virus and host cells is nonlinear. In principle, the rate of infection should saturate at high virus. In [10], to place the model on more sound biological grounds, Regoes et al. replaced the mass-action infection rate with a dose-dependent infection rates.

Thus, it is reasonable to assume that the infection rate of modeling viral infection in saturated mass action, $\beta x v^m/(1+av^n)$, where $m, n, a > 0$ are constants. In this paper we assume $m = n = 1$, so the model is given by:

$$\begin{aligned}
\dot{x} =& \lambda - \frac{\beta x(t)v(t)}{1+av(t)} - \mu x(t) + \delta w(t),\\
\dot{y} =& \varphi w(t) - \alpha y(t),\\
\dot{w} =& \frac{\beta x(t)v(t)}{1+av(t)} - (\delta+\eta+\varphi)w(t),\\
\dot{v} =& \sigma y(t) - \gamma v(t),
\end{aligned} \tag{2}$$

2 Well-posedness and equilibria of system (2)

By a standard argument for population models, one can show that for given system (2) with initial conditions in $\mathbb{R}^4_+ = \{(x,y,w,v) \in \mathbb{R}^4 : x \geq 0, y \geq 0, w \geq 0, v \geq 0\}$ has a unique solution which exists for $t \in (0,\infty)$, remains positive and bounded in the compact subset $\Theta \subset \mathbb{R}^4_+$, where $\Theta = \{(x,y,w,v) \in \mathbb{R}^4 : 0 \leq x,y,w \leq \frac{\lambda}{\psi},\ 0 \leq v \leq \frac{\lambda\sigma}{\gamma\psi},\ \psi = \min\{\alpha,\mu,\eta\}\}$, [7].

Define now the basic reproduction number for the viral infection as

$$R_\circ = \frac{\beta\lambda\sigma\varphi}{\alpha\gamma\mu(\delta+\eta+\varphi)},$$

The basic reproduction number describes the average number of newly infected cells generated from one infected cell at the beginning of the infectious process. Usually, $\mathbb{R}_0 > 1$ is a sufficient condition for the persistence of the infection in the host cells, and this condition is also necessary for a large number of epidemic models. The uninfected state always exists. If this state is the only state, then it is globally asymptotically stable. If the infected steady state exists, then

this state is globally asymptotically stable. These different cases depend on the value of the basic reproduction number. The system (2) has the infection-free equilibrium $E_0(\lambda/\mu, 0, 0, 0)$ and if $\mathbb{R}_0 > 1$, this system admits unique infected equilibrium, that is with positive components:

$$x^* = \frac{\lambda}{\mu R_0}(1 + \frac{\sigma\varphi w}{\lambda}), \quad y^* = \frac{\varphi}{\alpha}w^*, \quad w^* = \frac{\lambda\left(1 - \frac{1}{R_0}\right)}{\left(\eta + \varphi + \frac{\lambda\sigma\varphi}{\gamma R_0}\right)}, \quad v^* = \frac{\sigma\varphi w^*}{\alpha\gamma}$$

3 Global stability of virus-free equilibrium by means of Lyapunov functions

In this section we show the global stability of the viral-free equilibrium by using a Lyapunov approach can be established as follows:

Theorem 1. *If $\mathbb{R}_0 \leq 1$, then E_0 is globally asymptotically stable in $\mathbb{R}^4_+$.*

Proof. Define the global Lyapunov function $L : \{(x, y, w, v) \in \mathbb{R}^4_+ : x > 0\} \to \mathbb{R}$,

$$\begin{aligned} L(x, y, w, v) =& (x - x^\circ - x^\circ \ln\frac{x}{x^\circ}) + \frac{\delta}{2(\mu + \eta + \varphi)x^\circ}[(x - x^\circ) + w]^2 \\ &+ \frac{(\delta + \eta + \varphi)}{\varphi}y + w + \frac{\alpha(\delta + \eta + \varphi)}{\sigma\varphi}v + \frac{a\alpha\gamma(\delta + \eta + \varphi)}{\sigma\varphi}\int_0^t \frac{v^2}{1 + av} \end{aligned} \tag{3}$$

Then L is C^1 on the interior of $\mathbb{R}^4_+$, E° is the global minimum of L on $\mathbb{R}^4_+$, and $L(x^\circ, 0, 0, 0) = 0$ where $x^\circ = (\lambda/\mu)$. The derivative of (3) along the solution curves of (2) is given by the equation:

$$\begin{aligned} \dot{L}|_{(2)} =& \frac{(x - x^\circ)}{x}\dot{x} + \frac{\delta}{(\mu + \eta + \varphi)x^\circ}[(x - x^\circ) + w](\dot{x} + \dot{w}) + \frac{(\delta + \eta + \varphi)}{\varphi}\dot{y} \\ &+ \dot{w} + \frac{\alpha(\delta + \eta + \varphi)}{\sigma\varphi}\dot{v} + \frac{a\alpha\gamma(\delta + \eta + \varphi)}{\sigma\varphi}\frac{v^2}{1 + av} \end{aligned}$$

that is,

$$\begin{aligned}\dot{L}|_{(2)} =&\frac{(x-x^\circ)}{x}\left(\lambda-\mu x-\frac{\beta xv}{1+av}+\delta w\right)+\frac{\delta}{(\mu+\eta+\varphi)x^\circ}[(x-x^\circ)+w]\\&\times(\lambda-\mu x-(\eta+\varphi)w)+\frac{(\delta+\eta+\varphi)}{\varphi}(\varphi w-\alpha y)\\&+\left(\frac{\beta xv}{1+av}-(\delta+\eta+\varphi)w\right)+\frac{\alpha(\delta+\eta+\varphi)}{\sigma\varphi}(\sigma y-\gamma v)+\\&\frac{a\alpha\gamma(\delta+\eta+\varphi)}{\sigma\varphi}\frac{v^2}{1+av}.\end{aligned}$$

Using $\lambda=\mu x^\circ$, we obtain

$$\begin{aligned}\dot{L}|_{(2)} =&\frac{(x-x^\circ)}{x}\left(-\mu(x-x^\circ)-\frac{\beta xv}{1+av}+\delta w\right)+\frac{\delta}{(\mu+\eta+\varphi)x^\circ}[(x-x^\circ)+w]\\&\times(-\mu(x-x^\circ)-(\eta+\varphi)w)+\frac{\beta xv}{1+av}-\frac{\alpha\gamma(\delta+\eta+\varphi)}{\sigma\varphi}v\\&+\frac{a\alpha\gamma(\delta+\eta+\varphi)}{\sigma\varphi}\frac{v^2}{1+av}.\end{aligned}$$

notice that:

$$\delta w\frac{(x-x^\circ)}{x}=-\delta w\frac{(x-x^\circ)^2}{xx^\circ}+\delta w\frac{x^\circ}{(x-x^\circ)}. \tag{4}$$

Substituting (4), we have:

$$\begin{aligned}\dot{L}|_{(2)} =&-\left(\mu x^\circ+\frac{\delta\mu}{(\eta+\mu+\varphi)}x+\delta w\right)\frac{(x-x^\circ)^2}{xx^\circ}-\frac{\delta(\eta+\varphi)w^2}{(\eta+\mu+\varphi)x^\circ}\\&-\frac{\alpha\gamma(\delta+\eta+\varphi)}{\sigma\varphi}(1-\frac{\beta\sigma\varphi x^\circ}{\alpha\gamma(\delta+\eta+\varphi)(1+av)})v\\&+\frac{a\alpha\gamma(\delta+\eta+\varphi)}{\sigma\varphi}\frac{v^2}{1+av}.\end{aligned}$$

By rewriting $\dot{L}|_{(2)}$ in terms of basic reproduction number, we get

$$\begin{aligned}\dot{L}|_{(2)} =&-\left(\mu x^\circ+\frac{\delta\mu}{(\eta+\mu+\varphi)}x+\delta w\right)\frac{(x-x^\circ)^2}{xx^\circ}-\frac{\delta(\eta+\varphi)w^2}{(\eta+\mu+\varphi)x^\circ}\\&-\frac{\alpha\gamma(\delta+\eta+\varphi)}{\sigma\varphi}(1-R_0)\frac{v}{1+av}.\end{aligned}$$

Since $x(t)$, $y(t)$, $v(t)$, $z(t)$ are positive, it follows from $R_0\le 1$ that $\dot{L}|_{(2)}\le 0$, $\dot{L}|_{(2)}=0$ if and only if $(x,y,v,z)=E_0$. By LaSalles invariance principle, E_0 is globally asymptotically stable. □

Corollary 1. *If $R_0 \leq 1$, then the virus-free equilibrium E° of (1) is globally asymptotically stable in Θ.*

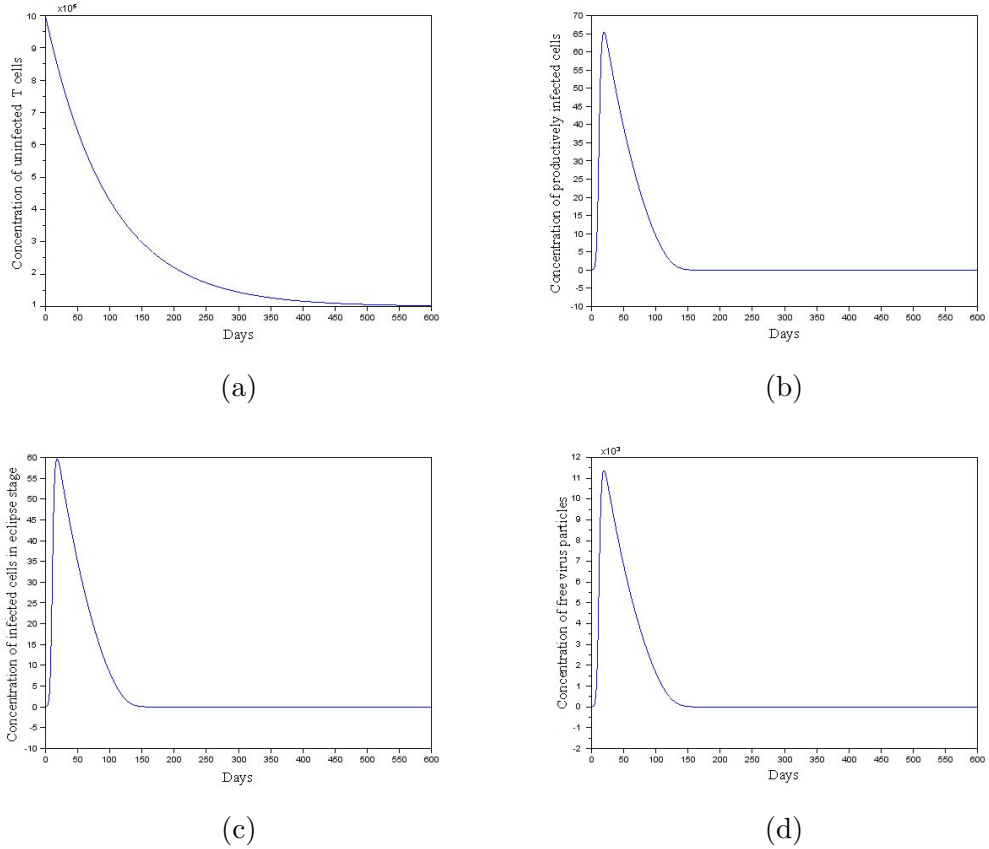

Figure 1: Numerical solution of system (2) with $\lambda = 10^3$, $\beta = 2.4 \cdot 10^{-8}$, $\mu = 0.01$, $\delta = 0.01$, $\varphi = 1.1$, $\alpha = 1$, $\eta = 0.7$ $\sigma = 4000$, $\gamma = 23$, $a = 0.0001$. $x(0) = 10^6$, $y(0) = 0$, $w(0) = 0$, $v(0) = 10^2$. It is easy to verify that $R_0 = 0.2536632 < 1$.

4 Global stability of the infected equilibrium by means of the geometric approach

In this section, we will use the geometric approach to study the global stability of the endemic equilibrium [11, 12, 13]. Due to technical difficulties, applications to four dimensional systems are still few in the literature, [14, 15]. Here we follow the approach used in [15] for a SVEIR (the development of the mathematical model is based on subdividing a given SARS-affected community into five compartments: susceptible, S, vaccinated, V , asymptomatic, E, symptomatic, I, and recovered, R, individuals.) model of severe acute respiratory syndrome (SARS) epidemic spread. As far as we know, all the applications

available in the literature do not completely report all the involved theoretical cases into details. Here we choose to explicitly report all of them, in order to give an exhaustive framework to those interested in applying the method to similar models. Consider the autonomous dynamical system:

$$\dot{x} = f(x), \tag{5}$$

where $f : D \to \mathbb{R}^n$, $D \subset \mathbb{R}^n$ open set and simply connected and $f \in C^1(D)$. Let x^* be an equilibrium of (5), i.e.$f(x^*) = 0$.

Let $Q(x)$ be an $\binom{n}{2} \times \binom{n}{2}$ matrix-valued function that is C^1 on D and consider:

$$A = Q_f Q^{-1} + QMQ^{-1},$$

where the matrix Q_f is

$$(q_{ij}(x))_f = (\partial q_{ij}/\partial x)^T . f(x) = \nabla q_{ij} . f(x),$$

and the matrix M is the second additive compound matrix of the Jacobian matrix J . Consider the Lozinskiĭ measure $\overline{\mu}$ of A with respect to a vector norm $||\cdot||$ in $\mathbb{R}^{\binom{n}{2}}$, that is:

$$\overline{\mu} = \lim_{h \to \circ^+} \frac{||I + hA|| - 1}{h}$$

We will apply the following [12]:

Theorem 2. *(See [12, corollary2.6].)Suppose*

(a) D is simply connected,

(b) D_1 is a compact absorbing subset in the interior of D,

(c) there exist $\zeta > \circ$ and the Lozinskiĭ measure $\overline{\mu}(A) \leq -\zeta$ for all $x \in D_1$,

(d) the system (2) has a unique equilibrium x^*.

Then x^* is globally asymptotically stable.

In Section 2, we discussed about the existence of equilibria and we knew that if $R_0 > 1$, then there exists a unique infected equilibrium E^*. Furthermore,the characteristic equation of system (2) at the virus-free equilibrium E° is of the form:

$$(s+\mu)[s^3+(\delta+\eta+\varphi+\alpha+\gamma)s^2+((\alpha+\gamma)(\delta+\eta+\varphi)+\alpha\gamma)s+\alpha\gamma(\delta+\eta+\varphi)(1-R_0)],$$

by using of Routh-Hurwitz criterion, if $R_0 > 1$, then the virus-free equilibrium E° is unstable. The instability of E°, together with $E^\circ \in \partial\Theta$, imply the uniform persistence of the state variables, [16], i.e. there exists a constant $\epsilon > 0$ such that:

$$\liminf_{t\to\infty} x_i > \epsilon, \qquad \text{for} \quad x_i = x, y, w, v,$$

where the x_i's indicate the state variables of system (2). The uniform persistence, together with boundedness of Θ, is equivalent to the existence of a compact set in the interior of Θ which is absorbing for (2), see [17]. Hence Theorem 2 may be applied, with $D = \Theta$.

According to [18], the Lozinskiĭ measure in Theorem 2 can be evaluated as:

$$\overline{\mu}(A) = \inf\{c : D_+||\mathbf{z}|| \le c||\mathbf{z}||, \quad \text{for all solutions of } \mathbf{z}' = A\mathbf{z}\},$$

where D_+ is the right-hand derivative. In order to use Theorem 2 and get the global asymptotic stability, it is necessary to find a norm $||\cdot||$ such that $\overline{\mu}(A) < 0$ for all x in the interior of D.

The Jacobian matrix J of (2) is given by:

$$J = \begin{pmatrix} -\dfrac{\beta v}{1+av} - \mu & 0 & \delta & -\dfrac{\beta x}{(1+av)^2} \\ 0 & -\alpha & \varphi & 0 \\ \dfrac{\beta v}{1+av} & 0 & -(\delta+\eta+\varphi) & \dfrac{\beta x}{(1+av)^2} \\ 0 & \sigma & 0 & -\gamma \end{pmatrix}.$$

the second additive compound matrix of J is given by:

$$M = \begin{pmatrix} M_{11} & \varphi & 0 & -\delta & \dfrac{\beta x}{(1+av)^2} & 0 \\ 0 & M_{22} & \dfrac{\beta x}{(1+av)^2} & 0 & 0 & \dfrac{\beta x}{(1+av)^2} \\ \sigma & 0 & M_{33} & 0 & 0 & \delta \\ -\dfrac{\beta v}{1+av} & 0 & 0 & M_{44} & \dfrac{\beta x}{(1+av)^2} & 0 \\ 0 & 0 & 0 & 0 & M_{55} & \varphi \\ 0 & 0 & \dfrac{\beta v}{(1+av)} & -\sigma & 0 & M_{66} \end{pmatrix}$$

$$M_{11} = -\frac{\beta v}{1+av} - \mu - \alpha; \quad M_{22} = -\frac{\beta v}{1+av} - \mu - (\delta+\eta+\varphi);$$

$$M_{33} = -\frac{\beta v}{1+av} - \mu - \gamma; \quad M_{44} = -\alpha - (\delta + \eta + \varphi);$$
$$M_{11} = -\alpha - \gamma; \qquad M_{66} = -(\delta + \eta + \varphi) - \gamma;$$

Consider now the matrix Q , where:

$$q_{11} = q_{22} = q_{34} = 1/w; \quad q_{43} = q_{55} = q_{66} = 1/v$$

and all the other entries q_{ij} are zero.

Then we obtain the matrix $A = Q_f Q^{-1} + QMQ^{-1}$, where Q_f is the derivative of Q in the direction of the vector field f . More precisely, we have:

$$Q_f Q^{-1} = -\mathrm{diag}(\dot{w}/w, \dot{w}/w, \dot{w}/w, \dot{v}/v, \dot{v}/v, \dot{v}/v)$$

$$QMQ^{-1} = \begin{pmatrix} M_{11} & \varphi & -\delta & 0 & \beta\frac{xv}{w(1+av)^2} & 0 \\ 0 & M_{22} & 0 & \beta\frac{xv}{w(1+av)^2} & 0 & \beta\frac{xv}{w(1+av)^2} \\ -\frac{\beta v}{1+av} & 0 & M_{44} & 0 & \beta\frac{xv}{w(1+av)^2} & 0 \\ \sigma\frac{w}{v} & 0 & 0 & M_{33} & 0 & \delta \\ 0 & 0 & 0 & 0 & M_{55} & \varphi \\ 0 & 0 & -\sigma\frac{w}{v} & \frac{\beta v}{1+av} & 0 & M_{66} \end{pmatrix} \tag{6}$$

Hence, according to:

$$\frac{\dot{w}}{w} = \beta\frac{xv}{w(1+av)^2} - (\delta + \eta + \varphi); \qquad \frac{\dot{v}}{v} = \sigma\frac{y}{v} - \gamma,$$

we have the matrix A, where:

$$A_{11} = -\frac{\beta v}{1+av} - \mu - \alpha - \beta\frac{xv}{w(1+av)^2} + (\delta + \eta + \varphi);$$
$$A_{22} = -\frac{\beta v}{1+av} - \mu - \beta\frac{xv}{w(1+av)^2};$$
$$A_{33} = -\alpha - \beta\frac{xv}{w(1+av)^2}; \qquad A_{44} = -\frac{\beta v}{1+av} - \mu - \sigma\frac{y}{v};$$
$$A_{55} = -\alpha - \sigma\frac{y}{v}; \qquad A_{66} = -(\delta + \eta + \varphi) - \sigma\frac{y}{v};$$

and all the other entries are as in the matrix (6). We consider the following norm on R^6:

$$||\mathbf{z}|| = \max\{U_1, U_2\}, \tag{7}$$

where $\mathbf{z} \in \mathbb{R}^6$, with components $z_i, i = 1, ..., 6$, and $U_1(z_1, z_2, z_3)$ is defined as:

$$\begin{cases} \max\{|z_1|, |z_2| + |z_3|\} & \text{if } \operatorname{sgn}(z_1) = \operatorname{sgn}(z_2) = \operatorname{sgn}(z_3), \\ \max\{|z_2|, |z_1| + |z_3|\} & \text{if } \operatorname{sgn}(z_1) = \operatorname{sgn}(z_2) = -\operatorname{sgn}(z_3), \\ \max\{|z_1|, |z_2|, |z_3|\} & \text{if } \operatorname{sgn}(z_1) = -\operatorname{sgn}(z_2) = \operatorname{sgn}(z_3), \\ \max\{|z_1| + |z_3|, |z_2| + |z_3|\} & \text{if } -\operatorname{sgn}(z_1) = \operatorname{sgn}(z_2) = \operatorname{sgn}(z_3), \end{cases}$$

and $U_2(z_4, z_5, z_6)$ is defined as:

$$\begin{cases} |z_4| + |z_5| + |z_6| & \text{if } \operatorname{sgn}(z_4) = \operatorname{sgn}(z_5) = \operatorname{sgn}(z_6), \\ \max\{|z_4| + |z_5|, |z_4| + |z_6|\} & \text{if } \operatorname{sgn}(z_4) = \operatorname{sgn}(z_5) = -\operatorname{sgn}(z_6), \\ \max\{|z_5|, |z_4| + |z_6|\} & \text{if } \operatorname{sgn}(z_4) = -\operatorname{sgn}(z_5) = \operatorname{sgn}(z_6), \\ \max\{|z_4| + |z_6|, |z_5| + |z_6|\} & \text{if } -\operatorname{sgn}(z_4) = \operatorname{sgn}(z_5) = \operatorname{sgn}(z_6), \end{cases}$$

We will use the following inequalities:

$$|z_1|, |z_2|, |z_3|, |z_2 + z_3| \leq U_1.$$

and

$$|z_i|, |z_i + z_j|, |z_4 + z_5 + z_6| \leq U_2; \quad i = 4, 5, 6; i \neq j$$

Set:

$$\theta = \frac{\lambda}{\psi\epsilon}$$

where ϵ is the constant of uniform persistence. We state the following theorem:

Theorem 3. *If $R_0 > 1$, then system (2) admits a unique infected equilibrium. It is globally asymptotically stable provided that*

$$\eta + 2\varphi + 2\delta < \mu < \alpha, \tag{8}$$

and

$$2\sigma\theta + \nu < \eta, \tag{9}$$

for some positive constant .

Proof. The proof is based on the estimate of the right derivative $D_+||\mathbf{z}||$ of the norm (7). This involves sixteen different cases according to the different orthants and the definition of the norm (7) within each orthant.

Case 1: $U_1 > U_2$, $z_1, z_2, z_3 > 0$, and $|z_1| > |z_2| + |z_3|$. Then:

$$||\mathbf{z}|| = |z_1|, \tag{10}$$

so that:

$$\begin{aligned} D_+||\mathbf{z}|| =& z_1' \\ =& A_{11}z_1 + A_{12}z_2 + A_{13}z_3 + A_{15}z_5 \\ \leq& \left[-\frac{\beta v}{1+av} - \mu - \alpha - \beta\frac{xv}{w(1+av)^2} + (\delta+\eta+\varphi)\right]|z_1| + \varphi|z_2| \\ & - \delta|z_3| + \beta\frac{xv}{w(1+av)^2}|z_5|. \end{aligned}$$

Using $|z_2| < |z_1|$, $-\delta|z_3| < 0$, $|z_5| < U_2 < |z_1|$, and (10), it follows:

$$D_+||\mathbf{z}|| \leq [-(\mu+\alpha) + (\eta+\delta+2\varphi)]||\mathbf{z}||.$$

Taking into account of (8), we get

$$D_+||\mathbf{z}|| \leq -\alpha||\mathbf{z}||.$$

Case 2: $U_1 > U_2, z_1, z_2, z_3 > 0$, and $|z_1| < |z_2| + |z_3|$. Then:

$$||\mathbf{z}|| = |z_2| + |z_3|, \tag{11}$$

so that:

$$\begin{aligned} D_+||\mathbf{z}|| =& z_2' + z_3' \\ =& A_{31}z_1 + A_{22}z_2 + A_{23}z_3 + A_{24}z_4 + A_{35}z_5 + A_{26}z_6 \\ \leq& -\frac{\beta v}{1+av}|z_1| + \left(-\frac{\beta v}{1+av} - \mu - \beta\frac{xv}{w(1+av)^2}\right)|z_2| \\ & - \left(\alpha + \beta\frac{xv}{w(1+av)^2}\right)|z_3| + \beta\frac{xv}{w(1+av)^2}|z_4+z_5+z_6|. \end{aligned}$$

Using now $|z_4+z_5+z_6| < U_2 < |z_2|+|z_3|$, $-\dfrac{\beta v}{1+av}(|z_1|+|z_2|) \leq 0$, and taking into account of and (11), we get:

$$D_+||\mathbf{z}|| \leq -\min(\alpha,\mu)||\mathbf{z}||.$$

From (8):

$$D_+||\mathbf{z}|| \leq -\mu||\mathbf{z}||.$$

Case3: $U_1 > U_2$, $z_1 < 0$, $z_2, z_3 > 0$, and $|z_1| > |z_2|$, Then:

$$||\mathbf{z}|| = |z_1| + |z_3|, \tag{12}$$

so that:

$$\begin{aligned} D_+||\mathbf{z}|| =& -z_1' + z_3' \\ \leq& \left[-\frac{\beta v}{1+av} - \mu - \alpha - \beta\frac{xv}{w(1+av)^2} + (\delta+\eta+\varphi)\right]|z_1| - \varphi|z_2| \\ &+ \delta|z_3| - \beta\frac{xv}{w(1+av)^2}|z_5| + \frac{\beta v}{1+av}|z_1| - \left(\alpha + \beta\frac{xv}{w(1+av)^2}\right)|z_3| \\ &+ \beta\frac{xv}{w(1+av)^2}|z_5|. \end{aligned}$$

Using $-\varphi|z_2| < \varphi|z_2| < \varphi|z_1|$ together with (12), we have:

$$D_+||\mathbf{z}|| \leq (-\alpha + \delta)||\mathbf{z}||,$$

now using (8) and (9), we get:

$$D_+||\mathbf{z}|| \leq -\nu||\mathbf{z}||$$

Case4: $U_1 > U_2$, $z_2, z_3 > 0, z_1 < 0$, and $|z_1| < |z_2|$.Then

$$||\mathbf{z}|| = |z_2| + |z_3|, \tag{13}$$

so that

$$\begin{aligned} D_+||\mathbf{z}|| =& z_2' + z_3' \\ \leq& \frac{\beta v}{1+av}|z_1| - \left(\frac{\beta v}{1+av} + \mu + \beta\frac{xv}{w(1+av)^2}\right)|z_2| \\ &- \left(\alpha + \beta\frac{xv}{w(1+av)^2}\right)|z_3| + \beta\frac{xv}{w(1+av)^2}|z_4 + z_5 + z_6|. \end{aligned}$$

Using $|z_4 + z_5 + z_6| < U_2 < |z_2| + |z_3|$ and in view of $|z_1| < |z_2|$, (13), it follows:

$$D_+||\mathbf{z}|| \leq -\min(\alpha, \mu)||z||.$$

Now using (8):

$$D_+||\mathbf{z}|| \leq -\mu||\mathbf{z}||.$$

Case5: $U_1 > U_2,\ z_1, z_2 > 0, z_3 < 0$ and $|z_2| > |z_1| + |z_3|$.Then:

$$||\mathbf{z}|| = |z_2|, \tag{14}$$

so that:

$$\begin{aligned} D_+||\mathbf{z}|| =& z_2' \\ &\leq -\left(\frac{\beta v}{1+av} + \mu + \beta\frac{xv}{w(1+av)^2}\right)|z_2| + \beta\frac{xv}{w(1+av)^2}|z_4 + z_6|. \end{aligned}$$

Using $|z_4 + z_6| \leq U_2 < |z_2|$ and (14), it follows:

$$D_+||\mathbf{z}|| \leq -\mu||\mathbf{z}||.$$

Case6: $U_1 > U_2,\ z_1, z_2 > 0, z_3 < 0,\ |z_2| < |z_1| + |z_3|$. Then

$$||\mathbf{z}|| = |z_1| + |z_3|, \tag{15}$$

so that:

$$\begin{aligned} D_+||\mathbf{z}|| =& z_1' - z_3' \\ &\leq \left[-\frac{\beta v}{1+av} - \mu - \alpha - \beta\frac{xv}{w(1+av)^2} + (\delta + \eta + \varphi)\right]|z_1| + \varphi|z_2| \\ &+\delta|z_3| + \beta\frac{xv}{w(1+av)^2}|z_5| + \frac{\beta v}{1+av}|z_1| - (\alpha + \beta\frac{xv}{w(1+av)^2})|z_3| \\ &- \beta\frac{xv}{w(1+av)^2}|z_5|. \end{aligned}$$

Using $\varphi|z_2| < \varphi(|z_1| + |z_3|)$ and taking into account of (15), we have:

$$D_+||\mathbf{z}|| \leq (-\alpha + \delta)||\mathbf{z}||,$$

now using (8) and (9), we get:

$$D_+||\mathbf{z}|| \leq -\nu||\mathbf{z}||.$$

The remaining ten cases are omitted for brevity (a complete analysis for a similar problem may be found in [19]). Their combination allow to obtain the following estimate:

$$D_+||\mathbf{z}|| \leq -\nu||\mathbf{z}||,$$

so that the global stability follows according to Theorem 2. □

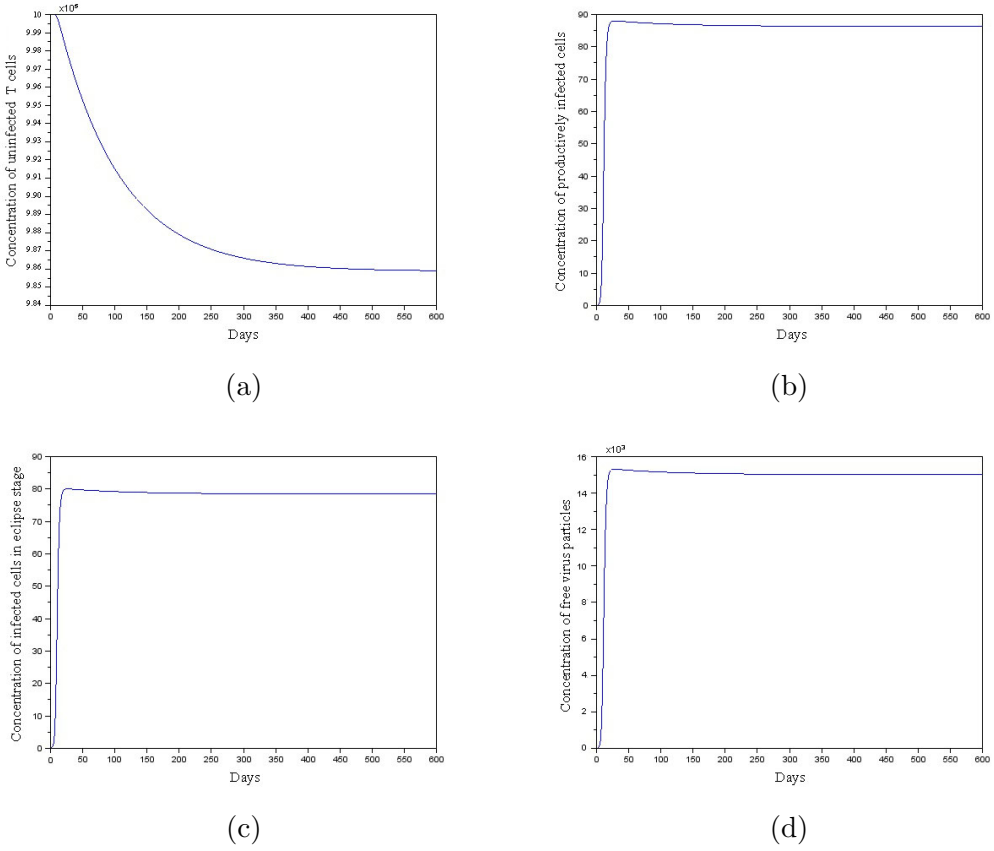

Figure 2: Numerical solution of system (2) with $\lambda = 10^4$, $\beta = 2.4 \cdot 10^{-8}$, $\mu = 0.01$, $\delta = 0.01$, $\varphi = 1.1$, $\alpha = 1$, $\eta = 0.7$ $\sigma = 4000$, $\gamma = 23$, $a = 0.0001$. $x(0) = 10^6$, $y(0) = 0$, $w(0) = 0$, $v(0) = 10^2$. It is easy to verify that $R_0 = 2.5366322 > 1$ and inequality (8) fails to hold.

5 Conclusions

in this paper, we have studied the global dynamics of an HIV-1 infection model including an eclipse stage of infected cells. By using the Lyapunov direct method we see that if the basic reproduction number R_0 is less than unity, the infection-free equilibrium is globally asymptotically stable, and by the Li and Muldowney's geometric approach to global stability we see that if the basic reproduction number R_0 is greater than unity, the infected equilibrium is globally asymptotically stable provided that inequality (8) and (9), in fact we show that R_0 play important roles in the global stabilites of the two equilibria.

As for the sufficient conditions (8) and (9), we note that (8) is satisfied if the average life span of productively infected cells, $1/\alpha$, is less than the average life span of uninfected cells,$1/\mu$; and the average life span of uninfected cells is less than the average residence time in the infected stage in the eclipse state, $1/(\delta + \eta + \varphi)$. For η sufficiently large (i.e., a sufficiently short average life span

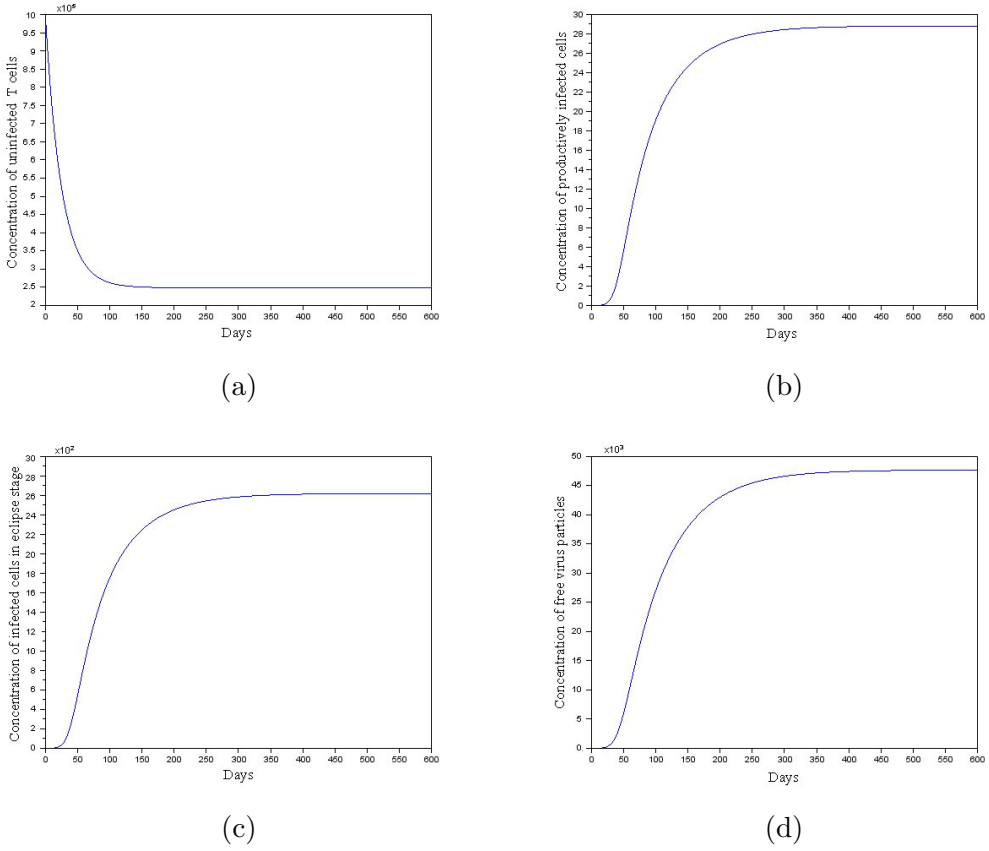

Figure 3: Numerical solution of system (2) with $\lambda = 10^4$, $\beta = 2.4 \cdot 10^{-8}$, $\mu = 0.04$, $\delta = 0.001$, $\varphi = .01$, $\alpha = 1$, $\eta = 0.007$ $\sigma = 40000$, $\gamma = 23$, $a = 0.0001$. $x(0) = 10^6$, $y(0) = 0$, $w(0) = 0$, $v(0) = 10^2$. It is easy to verify that $R_0 = 5.7971014 > 1$ and inequality (8) holds.

of cells in the eclipse state), inequality (9) holds and Theorem 2 holds.

We know that the range of parameter values guaranteeing the global stability of the infected equilibrium is larger than that indicated by our conditions.

As a final consequence, we emphasize that the sufficient conditions here obtained may be, in principle, improved. For example, by different choices of the matrix Q and of the vector norm (7) we can get to better sufficient conditions than those found here, in the sense that the restrictions on the parameters may be weakened.

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