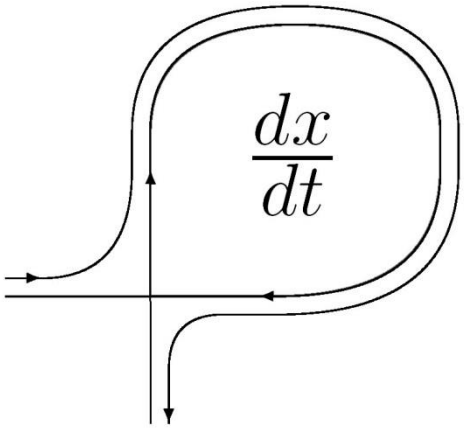

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Dynamical systems in medicine

Immune impairment and immunodeficiency thresholds in HIV infection with general incidence rate

Hajar Ansari[1] , Mahmoud Hesaaraki[2]

[1,2] Department of mathematics, Sharif University of Technology,
P.O.Box: 11155-9414,Tehran, Iran.

Abstract

In [1] and [2], the authors used a linear incidence rate into a mathematical model to examine the immune impairment for a proliferation model of CTL responses in the immune response to HIV. Under the assumption that the immune impairment increases over the HIV infection, they classified four processes of the disease progression dynamics, according to their virological properties. In particular they showed that a typical disease progression presents a risky threshold and an immunodeficiency threshold. Moreover the immune system might collapse when the impairment rate of HIV exceeds a threshold value. On the other hand if the immune impairment rate never exceeds the threshold value, the viral replication is well controlled by CTL responses. In this paper we show that all of the above results remain valid if we use a general functional response, $\varphi(x)$ instead of βx as the incidence rate into the above mathematical model.

Keywords: HIV infection, Global stability, Functional response, Immune impairment, immunodeficiency.
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1 Introduction

The origin of various disease progression in HIV(i.e. Human Immunodeficiency Virus is a lentivirus(i.e. a member of retrovirus family, that causes acquired

[1] E-mail address: hajar_ansari@yahoo.com
[2] E-mail address: hesaraki@sharif.ed

immunodeficiency syndrome,AIDS.) infection is largely unresolved but many researchers have been trying to explain it. An important factor in understanding the unusual incubation period distribution in the development of AIDS(i.e. Acquired Immunodeficiency Syndrome) is the dynamics of the long-lasting struggle between HIV and our immune system [3]. In early models of HIV infection [4] an explosion in the virus load caused by increased HIV variants diversity explains the immune system collapse in [5]. The CTL(i.e. Cytotoxic T Cells or killer T cell or Cytotoxic T-lymphocyte are a sub-group of T cells which induce the death of cells that are infected with viruses or are otherwise damaged or dysfunctional.) exhaustion induced by an evolutionary increase of viral infectivity accounts for immune deficiency. Moreover, in [6] the functional deteriorations of T and B cells caused by accumulations of deleterious mutations are considered as a reason for development of AIDS.

In [1,2] the authors present discussion of an immune impairment effect caused by the depletion and dysfunction of DC(i.e. Dendritic cells are immune cells forming part of the mammalian immune system.) on HIV disease progression. Because the progressive decrease of DC number and function during the course of HIV-1 is observed [7,8,9]. The authors in [1,2] simply assumed that the immune impairment effect increases over HIV infection.

The authors in [1,2] by using the discussion of the immune impairment effect caused by the depletion and dysfunction of DC on HIV disease program, extend the standard virus-immune model including the effect of immune impairment cause by HIV infection [4] to the following equations:

$$\begin{cases} \dot{x} = \lambda - dx - y\varphi(x), \\ \dot{y} = y\varphi(x) - ay - pyz, \\ \dot{z} = \dfrac{cxyz}{1+\varepsilon y} - bz. \end{cases} \tag{1.1}$$

Here, $x(t), y(t)$ and $z(t)$ denote the concentration of the susceptible or uninfected target cells, the exposed or infected cells that produce virus and the infective or HIV-1 virus particles at time t, respectively. The positive constants $\lambda, d, a, p, c, \varepsilon$ and b are the proliferation rate of $CD4^+$ T cells(i.e. helper T cells are immune response mediators and play an important role in establishing and maximizing the capabilities of the adaptive immune response. These cells have no cytotoxic or phagocytic activity and cannot kill infected cells or clear pathogens, but in essence manage the immune response, by directing other cells or perform these tasks.), the decay rate of infected $CD4^+$ T cells, the killing rate of infected $CD4^+$ T cells, the proliferation rate of CTLs, the immune impairment rate of HIV and the decay rate of CTLs, per day, respectively. Finally, $y\varphi(x)$ is the incidence rate of the transmission of the infection or the rate of infection and $\varphi(x)$ is a saturation response or functional response of uninfected cells into the exposed cells.

Here we assume that the saturation response $\varphi(x)$ satisfies the following natural hypotheses:

H_1) $\varphi(0) = 0$.

H_2) $\varphi(x) > 0$, for all $x > 0$.

H_3) $\varphi'(x) > 0$, for all $x > 0$.

Moreover we assume:

H_4) $\frac{d^2}{dy^2}[y^2\varphi\left(\frac{b(1+\varepsilon y)}{cy}\right)] \geq 0$, for all $y > 0$.

Notice that most of the famous functional responses such as: Lotka-Voltra, Michealis-Menten, Holling type II, Holling type IV, Monod-Haldane, Ivlev and Rosenzweig satisfy the above hypotheses. See the appendix.

The authors in [1] studied the mathematical analysis of the system (1.1) by assuming that the rate of infection is bilinear i.e. $y\varphi(x) = \beta xy$. However, the actual incidence rate is probably not linear over the entire range of x. Thus, it is reasonable to assum that the infected rate is given by one of the famous functional responses such as Michealis-Menten, Holling type II and IV, Monod-Haldane, Ivlev and Rosenzweig. Since all of these functional responses satisfy hypotheses H_1-H_4, we consider the system (1.1) with the general functional response $\varphi(x)$, for mathematical analysis investigation of HIV infection.

In this paper, we will analyze the global stability of the viral free equilibrium and the local and global stability of the infected equilibrium points for general incidence rate. In fact, we will show that the results which are obtained in [2] remain valid for general functional response, $\varphi(x)$. In fact the model (1.1) has four possible equilibria: uninfected equilibrium, shortage state equilibrium, immunodeficiency equilibrium and controlled state equilibrium. In section 2, we consider the stability of the uninfected and the shortage state equilibria. In section 3, we study the stability of the other equilibria. In section 4, we will discuss the biological results.

2 Equilibrium Points and Stability

In this section and the next one, we will find the equilibrium points of the system (1.1) and then we will consider the stability property of them. In order to do this, we will find the eigenvalues of the linearized system of this system at these points.

At an equilibrium point of the system (1.1) we must have

$$\begin{cases} \lambda - dx - y\varphi(x) = 0, \\ y\varphi(x) - ay - pyz = 0, \\ \dfrac{cxyz}{1+\varepsilon y} - bz = 0. \end{cases} \tag{2.1}$$

From the third equation we obtain $z = 0$ or $\frac{cxy}{1+\varepsilon y} = b$.

In the following, we consider the case $z = 0$ and the other case will be considered in section 3.

By substituting $z = 0$ into the second equation yields, $y(\varphi(x) - a) = 0$. If $y = 0$, then from the first equation we must have $x = \frac{\lambda}{d}$. Thus $E_0 = (\frac{\lambda}{d}, 0,0)$ is one of the equilibrium points which is called uninfected steady state of the system. If $\varphi(x) - a = 0$, by using this in the first equation of (2.1) we get $y = \frac{\lambda - dx}{a}$. Hence at the second equilibrium point, if exists we must have

$$\varphi(x) = a. \tag{2.2}$$

By hypothesis, H_3, we have $\dot{\varphi} > 0$. Since at an equilibrium point we must have $y = \frac{\lambda - dx}{a} \geq 0$ the acceptable root of (2.2) must be in the interval, $(0, \frac{\lambda}{d}]$. Therefore the

second equilibrium point exists if and only if, $\varphi(\frac{\lambda}{d}) > a$. Let $R_0 := \frac{\varphi(\frac{\lambda}{d})}{a}$. This number is called the basic reproductive ratio of the virus for the system. Thus we have the following theorem.

Theorem 2.1 . For $z = 0$, if $R_0 \leq 1$, then the uninfected steady state $E_0 := (\frac{\lambda}{d}, 0,0)$ is the unique equilibrium point of the system (1.1). If $R_0 > 1$, then in addition to the uninfected steady state , there is another equilibrium point $E_1 := (x_1, y_1, 0)$ with $x_1 \epsilon (0, \frac{\lambda}{d})$ and $y_1 > 0$.

Here we will analyze the local asymptotical stability of these equilibrium points. In order to do this, we check the sign of the eigenvalues of Jacobi matrix of (1.1) at these points. This matrix is given by

$$J(X) = \begin{bmatrix} -d - y\varphi'(x) & -\varphi(x) & 0 \\ y\varphi'(x) & \varphi(x) - a - pz & -py \\ \frac{cyz}{1+\varepsilon y} & \frac{cxz}{(1+\varepsilon y)^2} & \frac{cyx}{1+\varepsilon y} - b \end{bmatrix} \qquad (2.3)$$

where $X := (x, y, z)$.

At first we consider the local stability of the equilibrium point E_0. Hence, we calculate the eigenvalues of $J(E_0)$:

$$\det\left(SI_{3\times 3} - J(E_0)\right) = 0,$$

$$det\begin{bmatrix} S + d & \varphi(\frac{\lambda}{d}) & 0 \\ 0 & S + a - \varphi(\frac{\lambda}{d}) & 0 \\ 0 & 0 & S + b \end{bmatrix} = 0.$$

Therefore, the eigenvalues of $J(E_0)$ are the roots of the characteristic polynomial

$$(S + d)\left(S + a - \varphi\left(\frac{\lambda}{d}\right)\right)(S + b) = 0.$$

Thus, $S_1 = -d$,$S_2 = -a + \varphi\left(\frac{\lambda}{d}\right)$ and $S_3 = -b$ are the eigenvalues of $J(E_0)$. Clearly, S_1 and S_3 have negative real part. If, $S_2 = -a + \varphi\left(\frac{\lambda}{d}\right) < 0$, then the rest point E_0 is locally asymptotically stable. This condition is the same as, $R_0 < 1$. Therefore, we have proved the following theorem.

Theorem 2.2. If $R_0 < 1$, the equilibrium point E_0 is locally asymptotically stable and if $R_0 > 1$, this equilibrium point is unstable.

Now we will show that if $R_0 < 1$, the equilibrium point E_0 is globally asymptotically stable. First of all, consider the following domain in the (x, y, z) space,

$$D_\alpha = \left\{(x, y, z) \,\middle|\, 0 < x < \alpha \,, y > 0 \,, z > 0\right\} \,, \alpha \geq \frac{\lambda}{d}.$$

It follows from hypotheses H_1 and H_2 and the equations of the system (1.1), if an orbit initiating on the boundary of D_α, then this orbit gets into D_α immediately as time increases. This means that the flow generated by that system gets into D_a on the boundary of D_a. Let $D = D_a$, for $\alpha = \frac{\lambda}{d}$ and consider the following set for $\sigma > 0$:

$$Q_\sigma = \left\{(x,y,z): 0 < x < \frac{\lambda}{d}\,, y > 0\,, z > 0 \text{ and } V(x,y,z) < \sigma\right\},$$

where, $V(x,y,z) = (a-\varphi^*)\left(\frac{\lambda}{d} - x\right) + \varphi^* y + \frac{\varphi^* pd}{c\lambda} z$, and $\varphi^* := \varphi(\frac{\lambda}{d})$.
If we differentiate $V(x,y,z)$ along the orbits of the system (1.1), we obtain:

$$\frac{dV}{dt} = -(a-\varphi^*)\dot{x} + \varphi^*\dot{y} + \frac{\varphi^* pd}{c\lambda}\dot{z} = -(a-\varphi^*)(\lambda - dx - y\varphi(x)) +$$
$$\varphi^*(y\varphi(x) - ay - pyz) + \frac{\varphi^* pd}{c\lambda}\left(\frac{cxyz}{1+\varepsilon y} - bz\right) = -(a-\varphi^*)(\lambda - dx)$$
$$+ay(\varphi(x) - \varphi^*) - \frac{\varphi^* bpd}{c\lambda} z + \left[-p\varphi^* yz + \frac{\varphi^* pd}{c\lambda}\frac{cxyz}{1+\varepsilon y}\right].$$

Since on that part of the surface, $V(x,y,z) = \sigma$ which is some part of the boundary of the set Q_σ, we have $\lambda - dx > 0$ and $\varphi - \varphi^* < 0$ and $-p\varphi^* yz + \frac{\varphi^* pd}{c\lambda}\frac{cxyz}{1+\varepsilon y} \leq -p\varphi^* yz + \frac{\varphi^* pd}{c\lambda}\frac{c\lambda}{d} yz \leq 0$, therefore $\frac{dV}{dt} < 0$. Thus, the flow gets into Q_σ on $V(x,y,z) = \sigma$. Hence the flow gets into Q_σ from its boundery. Therefore, if an orbit starts outside of Q_σ in D, then that orbit must get into Q_σ in a finite positive time. But, $E_0 = \cap_{\sigma \geq 0} \bar{Q}_\sigma$. Hence, if an orbit start in D, then it must approach to E_0 as time tends to infinity. Hence we have proved the following theorem.

Theorem 2.3. If $R_0 < 1$, then E_0 is the only rest point of the system (1.1). This rest point is globally asymptotically stable.

Now we consider the local asymptotical stability of E_1. Notice that from (2.3) we have

$$J(E_1) = \begin{bmatrix} -d - y_1\varphi'(x_1) & -a & 0 \\ y_1\varphi'(x_1) & 0 & -py_1 \\ 0 & 0 & \frac{cy_1x_1}{1+\varepsilon y_1} - b \end{bmatrix}.$$

Therefore, the eigenvalues of $J(E_1)$ are the roots of the characteristic polynomial

$$\left(S - \frac{cy_1x_1}{1+\varepsilon y_1} + b\right)(S^2 + AS + B) = 0,$$

where $A = d + y_1\varphi'(x_1)$ and $B = ay_1\varphi'(x_1)$. Thus, $S_1 = \frac{cy_1x_1}{1+\varepsilon y_1} - b$ is one of the eigenvalues and the other two are the roots of $S^2 + AS + B = 0$. We call them S_2 *and* S_3. We know that $S_2 + S_3 = -A$ and $S_1.S_2 = B$. It follows from the hypotheses H_3, $A, B > 0$. Thus, S_2 and S_3 have negative real parts. So if $S_1 = \frac{cy_1x_1}{1+\varepsilon y_1} - b < 0$, then the equilibrium E_1 is locally asymptotically stable. This is possible for $\varepsilon \gg 0$ as x_1 and y_1 are independent of ε.
Therefore, we have proved the following theorem.

Theorem 2.4. If $R_0 > 1$ and $\frac{cy_1x_1}{1+\varepsilon y_1} - b < 0$, then the equilibrium point $E_1 = (x_1, y_1, 0)$ exists and is locally asymptotically stable.

As we know the basic reproductive ratio of the virus for the system (1.1) is R_0 and for $R_0 > 1$ both, E_0 and E_1 exist. In this case, we show that the equilibrium point E_1 is globally asymptotical stable in D under the condition $y_1 \le \frac{bd}{c\lambda}$. In order to see this, consider the following positive function on D:

$$V(x,y,z) = \int_{x_1}^{x} (1 - \frac{\varphi(x_1)}{\varphi(s)})ds + y - y_1 - y_1 \ln\frac{y}{y_1} + \frac{py_1}{b}z,$$

where, $E_1 = (x_1, y_1, 0)$ as before. Calculating the time derivative of $V(x,y,z)$ along the positive solutions of the system (1.1) gives

$$\dot{V} = \left(1 - \frac{\varphi(x_1)}{\varphi(x)}\right)\dot{x} + \dot{y} - \frac{y_1\dot{y}}{y} + \frac{py_1}{b}\dot{z} = \left(\lambda - dx - y\varphi(x)\right)\left(1 - \frac{\varphi(x_1)}{\varphi(x)}\right)$$
$$+\left(1 - \frac{y_1}{y}\right)(y\varphi(x) - ay - pyz) + \frac{py_1}{b}\left(\frac{cxyz}{1+\varepsilon y} - bz\right).$$

At the equilibrium point $(x_1, y_1, 0)$ we have

$$\lambda = dx_1 + y_1\varphi(x_1), a = \varphi(x_1).$$

By considering these equalities we can write

$$\dot{V} = \left(1 - \frac{\varphi(x_1)}{\varphi(x)}\right)\left(dx_1 + y_1\varphi(x_1) - dx - y\varphi(x)\right)$$
$$+\left(1 - \frac{y_1}{y}\right)(y\varphi(x) - \varphi(x_1)y - pyz) + \frac{py_1}{b}\left(\frac{cxyz}{1+\varepsilon y} - bz\right)$$
$$= (dx_1 - dx)\left(1 - \frac{\varphi(x_1)}{\varphi(x)}\right) + \left(y_1\varphi(x_1) - y\varphi(x)\right)\left(1 - \frac{\varphi(x_1)}{\varphi(x)}\right)$$
$$+y\varphi(x) - \varphi(x_1)y - y_1\varphi(x) + y_1\varphi(x_1) + \left(\frac{py_1}{b}\frac{cxyz}{1+\varepsilon y} - pyz\right)$$
$$= dx_1\left(1 - \frac{x}{x_1}\right)\left(1 - \frac{\varphi(x_1)}{\varphi(x)}\right) + \left(y_1\varphi(x_1) - y_1\varphi(x) + y_1\varphi(x) - y\varphi(x)\right)$$
$$\left(1 - \frac{\varphi(x_1)}{\varphi(x)}\right) + y\varphi(x) - \varphi(x_1)y - y_1\varphi(x) + y_1\varphi(x_1) + \left(\frac{py_1}{b}\frac{cxyz}{1+\varepsilon y} - pyz\right)$$
$$= dx_1\left(1 - \frac{x}{x_1}\right)\left(1 - \frac{\varphi(x_1)}{\varphi(x)}\right) + \left(y_1\varphi(x_1) - y_1\varphi(x)\right)\left(1 - \frac{\varphi(x_1)}{\varphi(x)}\right)$$
$$+y_1\varphi(x) - y\varphi(x) - y_1\varphi(x_1) + y\varphi(x_1) + y\varphi(x) - \varphi(x_1)y - y_1\varphi(x)$$
$$+y_1\varphi(x_1) + \left(\frac{py_1}{b}\frac{cxyz}{1+\varepsilon y} - pyz\right) = dx_1\left(1 - \frac{x}{x_1}\right)\left(1 - \frac{\varphi(x_1)}{\varphi(x)}\right) +$$
$$y_1\varphi(x_1)\left(1 - \frac{\varphi(x)}{\varphi(x_1)}\right)\left(1 - \frac{\varphi(x_1)}{\varphi(x)}\right) + \left(\frac{py_1}{b}\frac{cxyz}{1+\varepsilon y} - pyz\right).$$

Since $\varphi' > 0$, the first and second term must be negative for $x \neq x_1$. Since $\frac{cxyz}{1+\varepsilon y} \le \frac{c\lambda}{d}yz$ so by using $y_1 \le \frac{bd}{c\lambda}$, the third term is nonpositive. Moreover the equality holds only at the point E_1.

Since $\dot{V}(x,y,z) < 0$ for $(x,y,z) \neq E_1$ and, $\dot{V}(x_1,y_1,0) = 0$ and $V(x,y,z) > 0$ for $(x,y,z) \neq E_1$ and $(x_1,y_1,0) = 0$, thus $V(x,y,z)$ is a Lyapunov function of the system (1.1) for $R_0 > 1$ on D. Therefore, we have proved the following theorem.

Theorem 2.5. If the infected equilibrium point $E_1 = (x_1,y_1,0)$ exists and $y_1 \leq \frac{bd}{c\lambda}$, then this equilibrium point is globally asymptotically stable in D.

Remark 2.1. If Theorem 2.5 holds, E_0 and E_1 are all of the equilibrium points of the system (1.1).

3 Other Equilibrium Points and Their Stability

In this section, we will find the equilibrium points of the system (1.1) for $z \neq 0$ and $\frac{cxy}{1+\varepsilon y} = b$. Then we will consider the stability of these points.

From $\frac{cxy}{1+\varepsilon y} = b$ we obtain

$$x = \frac{b(1+\varepsilon y)}{cy}, \tag{3.1}$$

and from the second equation of (2.1) we get

$$z = \frac{\varphi - a}{p}, \tag{3.2}$$

where $\varphi := \varphi(x)$. If $\varphi < a$, then the system (1.1) does not have any rest point in $\mathbb{R}^3_+$. Hence we look for a rest point in the set $\varphi(x) > a$.

By substituting x from (3.1) into the first equation of (2.1) we obtain

$$(\lambda c - bd\varepsilon)y - c\varphi\left(\frac{b(1+\varepsilon y)}{cy}\right)y^2 - bd = 0. \tag{3.3}$$

Hence if (1.1) has another equilibrium point, it must satisfy in (3.1), (3.2) and (3.3). In the following, we discuss in more detail about the existence of such solution. From (3.3) we can write

$$c\varphi\left(\frac{b(1+\varepsilon y)}{cy}\right)y^2 = (\lambda c - bd\varepsilon)y - bd. \tag{3.4}$$

The right hand side of (3.4) is a straight line and by hypothesis H_4, the left hand side is a concave upward curve with positive values.

If $\lambda c - bd\varepsilon \leq 0$, then $(\lambda c - bd\varepsilon)y - bd$ is negative in $y > 0$, but the left hand side of (3.4) is positive. Therefore, in this case, the equation (3.4) does not have any solution. This means that (3.3) cannot have any solution if $\lambda c - bd\varepsilon \leq 0$.

If $\lambda c - bd\varepsilon > 0$ and bd is very small or $-bd\varepsilon \gg 0$, then as the concavity of $c\varphi\left(\frac{b(1+\varepsilon y)}{cy}\right)y^2$does not change, the line $(\lambda c - bd\varepsilon)y - bd$ intersects the curve $c\varphi\left(\frac{b(1+\varepsilon y)}{cy}\right)y^2$ in one point or two points. Hence (3.3) admits at most two solutions in $y > 0$. Notice that the line $(\lambda c - bd\varepsilon)y - bd$ is decreasing with respect to ε and the curve $c\varphi(\frac{b(1+\varepsilon y)}{cy})y^2$ is increasing with respect to it. Thus if ε decreases these two curves may intersect each others in two points.

If the line is tangent to the curve, then (3.4) and therefore, (3.3) has one solution. Hence the system (1.1) admits another rest point. Let $E^* = (x^*, y^*, z^*)$ be this point, where $x^* = \frac{b(1+\varepsilon y^*)}{cy^*}$, $z^* = \frac{\varphi(x^*)-a}{p}$ and y^*satisfies in (3.4).

We show the corresponding ε to this rest point by ε^*. This number is called the immunodeficiency threshold.

If $\varepsilon > \varepsilon^*$, then the line cuts the curve in two different points and the equation (3.4) has two different solutions. In this case, the system (1.1) has two other rest points. Let $E^{\pm} = (x^{\pm}, y^{\pm}, z^{\pm})$ be these points, with $y^+ < y^-$. Thus $x^+ > x^-$ and $z^+ > z^-$. If $\varphi(x^*) \le a$, then E^* and $E^-$are not in R_+^3, but $E^+$is in R_+^3 for small values of ε. If $\varphi(x^*) > a$, then $E^+ \epsilon R_+^3$ for $0 < \varepsilon < \varepsilon^*$ and $E^- \epsilon R_+^3$ for $\varepsilon < \varepsilon^*$ and $\varepsilon - \varepsilon^*$ small. That is, there is an $\varepsilon_0 < \varepsilon^*$ such that $\varphi(x^-)_{|\varepsilon=\varepsilon_0} = a$ and $E^-$is in R_+^3 for $\varepsilon_0 < \varepsilon < \varepsilon^*$. Thus we have proved the following theorem.

Theorem3.1. If the line $w = (\lambda c - bd\varepsilon)y - bd$ and the curve $w = cy^2\varphi(\frac{b(1+\varepsilon y)}{cy})$ intersect each other, then there is $\varepsilon_0 < \varepsilon^*$ such that $E^+ \epsilon R_+^3$ for $o < \varepsilon < \varepsilon^*$ and $E^- \epsilon R_+^3$ for $\varepsilon_0 < \varepsilon < \varepsilon^*$.

The number ε_0 is called the risky threshold rate of immune impairment.

Now we consider the stability of $E^{\pm}$. From (2.3) we have

$$J(E^{\pm}) = \begin{bmatrix} -d - y^{\pm}\varphi'(x^{\pm}) & -\varphi(x^{\pm}) & 0 \\ y^{\pm}\varphi'(x^{\pm}) & 0 & -py^{\pm} \\ \frac{cy^{\pm}z^{\pm}}{1+\varepsilon y^{\pm}} & \frac{cx^{\pm}z^{\pm}}{(1+\varepsilon y^{\pm})^2} & 0 \end{bmatrix}. \quad (3.5)$$

By substituting $x^{\pm} = \frac{b(1+\varepsilon y^{\pm})}{cy^{\pm}}$, $z^{\pm} = \frac{\varphi(\frac{b(1+\varepsilon y^{\pm})}{cy^{\pm}})-a}{p}$ in (3.5) yield

$$J(E^{\pm}) = \begin{bmatrix} -d - y^{\pm}\varphi'(x^{\pm}) & -\varphi(x^{\pm}) & 0 \\ y^{\pm}\varphi'(x^{\pm}) & 0 & -py^{\pm} \\ \frac{cy^{\pm}(\varphi^{\pm}-a)}{p(1+\varepsilon y^{\pm})} & \frac{b(\varphi^{\pm}-a)}{py^{\pm}(1+\varepsilon y^{\pm})} & 0 \end{bmatrix}, \quad (3.6)$$

where $\varphi^{\pm} := \varphi(\frac{b(1+\varepsilon y^{\pm})}{cy^{\pm}})$. Therefore, the characteristic polynomial of $J(E^{\pm})$ is

$$S^3 + a_1S^2 + a_2S + a_3 = 0, \quad (3.7)$$

Where $a_1 = d + y^{\pm}\varphi_x(x^{\pm})$, $a_2 = y^{\pm}\varphi_x(x^{\pm})\varphi^{\pm} + \frac{b(\varphi^{\pm}-a)}{(1+\varepsilon y^{\pm})}$ and $a_3 = (\frac{\varphi^{\pm}-a}{1+\varepsilon y^{\pm}})\left(bd + by^{\pm}\varphi_x(x^{\pm}) - cy^{\pm^2}\varphi^{\pm}\right)$.

From the Routh-Hurwitz criterion, all eigenvalues have negative real parts if

$$a_1 > 0\,,\ a_2 > 0, a_3 > 0\,, a_1a_2 - a_3 > 0.$$

By hypothesis H_3, we have $\varphi'(x^{\pm}) > 0$, thus $a_1 > 0$ and $a_2 > 0$. Now we determine the sign of a_3 and $a_1a_2 - a_3$. Since $y^{\pm}$ satisfy in (3.4) and $y^+ < y^-$, at y^+ we have

$$\frac{d}{dy}\left(c\varphi\left(\frac{b(1+\varepsilon y)}{cy}\right)y^2\right) < (\lambda c - bd\varepsilon).$$

By substituting $\varphi^+ := \varphi(\frac{b(1+\varepsilon y^+)}{cy^+})$ we get

$$2cy^+\varphi^+ - b\varphi'\left(\frac{b(1+\varepsilon y^+)}{cy^+}\right) < (\lambda c - bd\varepsilon). \qquad (3.8)$$

By using (3.8) and (3.4) we obtain

$$a_3 > \left(\frac{\varphi^+ - a}{1+\varepsilon y^+}\right)\left(bd - y^+(\lambda c - bd\varepsilon) + cy^{+2}\varphi^+\right) = 0.$$

Hence, $a_3 > 0$. Now we show that $a_1a_2 - a_3 > 0$.

$$a_1a_2 - a_3 = \frac{bd(\varphi^+ - a)}{1+\varepsilon y^+} + y^{+2}\varphi'^2\varphi^+ + \frac{by^+\varphi'(\varphi^+ - a)}{1+\varepsilon y^+} - \frac{bd(\varphi^+ - a)}{1+\varepsilon y^+} -$$

$$\frac{by^+\varphi'(\varphi^+ - a)}{1+\varepsilon y^+} + \frac{cy^{+2}\varphi'(\varphi^+ - a)}{1+\varepsilon y^+} = y^{+2}\varphi'^2\varphi^+ + \frac{cy^{+2}\varphi^+(\varphi^+ - a)}{1+\varepsilon y^+} > 0,$$

where $\varphi' := \varphi'\left(\frac{b(1+\varepsilon y^+)}{cy^+}\right)$.

Therefore, we establish the local asymptotical stability of E^+.

For E^-, at y^-we have,

$$\frac{d}{dy}\left(c\varphi\left(\frac{b(1+\varepsilon y)}{cy}\right)y^2\right) > (\lambda c - bd\varepsilon).$$

From the above inequality and $\varphi^- := \varphi(\frac{b(1+\varepsilon y^-)}{cy^-})$ we obtain

$$2cy^-\varphi^- - b\varphi'\left(\frac{b(1+\varepsilon y^-)}{cy^-}\right) > (\lambda c - bd\varepsilon). \qquad (3.9)$$

Therefore, by using (3.16) and (3.4)

$$a_3 < (\frac{\varphi^- - a}{1+\varepsilon y^-})(bd - y^-(\lambda c - bd\varepsilon) + cy^{-2}\varphi^- \le 0.$$

Since $a_3 < 0$ we conclude that the real part of one of three roots of the equation (3.14) is positive. Hence, $E^-$is always unstable. Therefore we have the following theorem.

Theorem 3.2. Suppose that the equilibrium $E^\pm = (x^\pm, y^\pm, z^\pm)$ exist. The equilibrium point $E^-$is always unstable and the equilibrium point E^+ is always locally asymptotically stable.

4 Discussion

The model which is given by the system (1.1) has four possible equilibria:

$$E_0 = \left(\frac{\lambda}{d}, 0, 0\right), E_1 = (x_1, y_1, 0), E^- = (x^-, y^-, z^-), E^+ = (x^+, y^+, z^+).$$

The basic reproductive number for one infected cell is definable as $R_0 = \frac{1}{a}\varphi(\frac{\lambda}{d})$, which represents the average number of cells infected by a single infected cell in an otherwise susceptible cell population.

In a healthy human only activated CD4$^+$T cells attain an equilibrium level of $x = \frac{\lambda}{d}$. This homeostatic equilibrium is designated by E_0 in the above.

By Theorem 2.1, E_0, the uninfected equilibrium or healthy state always exists and by Theorem 2.2 for $R_0 < 1$, it is the unique equilibrium and is globally asymptotically stable. This means that the infected CD4$^+$Tcells decreases to zero.

After infection of HIV, if $R_0 > 1$, then infected CD4$^+$T cells increase to high level and uninfected CD4$^+$T cells decrease to a low level. This situation is appeared by the infected equilibrium E_1.

By Theorem 2.1, E_1 exists if and only if $R_0 > 1$. It is locally asymptotically stable if $\frac{cx_1y_1}{1+\varepsilon y_1} < b$. In this case the infected equilibrium E_1 is the steady state of the model. This means that infected CD4$^+$T cells increase initially to high level and subsequently converge to an equilibrium value y_1 and the activated CD4$^+$T cells attain an equilibrium level of x_1. This equilibrium E_1 represents a state in which the virus load of HIV is balanced with no immune response, because of a shortage of activated CD4$^+$T cells during a primary pose of HIV infection. In this case, E_1 is designated as the shortage state. If $R_0 > 1$ and $\frac{cx_1y_1}{1+\varepsilon y_1} > b$, then E_1 is not acceptable or it is unstable.

In addition to the two equilibria E_0 and E_1, at the end of the primary phase, if CTL responses are induced, then the infected cells are regulated by them for a long time at some steady state. Actually, if c is large and ε is small, then from the equation (3.4) our model must have two possible interior equilibria $E^- = (x^-, y^-, z^-)$ and $E^+ = (x^+, y^+, z^+)$ with, $x^- < x^+$, $y^- > y^+$, $z^- < z^+$. However, by Theorem 3.2, E^- is always unstable if exists. Therefore the equilibrium E^+ is considered as a controlled state, in which effective and sustained CTLs have been established and the virus load is suppressed at a low level. In fact if c increases or ε decreases, y^+ tends to a lower level.

On the other hand, if CTLs are not induced at the end of the primary phase, then $\frac{cx_1y_1}{1+\varepsilon y_1} < b$ and by Theorem 2.4 or 2.5, E_1 is the only state equilibrium of the model for small values of c and large values of ε. This means that infected individuals immediately develop AIDS after the acute infection. Consequently, when a complete breakdown of the immune system occurs, implying that z converge zero, activated and infected CD4$^+$T cells also converge to the same equilibrium values E_1. In this case, the steady state E_1 is called the immunodeficiency state.

The immune impairment rate is low at the beginning of the infection. Therefore, sustained CTL responses are established and the viral replication is suppressed at a low level in the stable controlled state E^+ after the CTL naives begin to expand and differentiate. Consequently, the virus load of HIV equilibrates and remains at a virological set point immediately after the acute infection.

By Theorem 3.2, E^+ always is stable and the shortage state E_1 is stable in x-y space, but is unstable in all space if ε is small which implies that convergent steady state of model (1.1) always transfers from E_1 to E^+ if z becomes positive. Furthermore, even if the immune impairment rate, ε increases the viral replication is well controlled by CTL responses at E^+ until the rate exceeds the risky threshold ε_0 i.e.$\varepsilon < \varepsilon_0$. On the other hand, when the impairment rate becomes greater than the immunodeficiency threshold (i.e.$\varepsilon^* < \varepsilon$) the shortage state becomes the immunodeficiency state i.e. E_1. In this situation the immunodeficiency state E_1 becomes a unique stable steady state of model (1.1). This means that the risky zone expands into total space and the patients always develop AIDS.

Appendix

In this section, we investigate the hypothesis H_4 for some famous functional responses.

The following lemma helps us to show easier the concavity of the functional responses.

Lemma. The function $w = y^2\varphi\left(\frac{b(1+\varepsilon y)}{cy}\right)$ is concave upward if the function $w = y^2\varphi(A + \frac{1}{y})$ is concave upward.

Proof: We can write, $w = y^2\varphi(\frac{b\varepsilon}{c} + \frac{b}{cy})$. Let $t = \frac{cy}{b}$ and $A = \frac{b\varepsilon}{c}$, then $w = t^2\varphi(A + \frac{1}{t})$. Since change of scale of independent variable does not change the concavity of the function, the proof is complete.

i) Lotka-Volterra or Holling I: we let $\varphi(x) = \beta x$. For this functional response we have:

$$\frac{d}{dy}\left[y^2\varphi\left(A + \frac{1}{y}\right)\right] = \frac{d}{dy}[\beta(Ay^2 + y)] = \beta(2Ay + 1).$$

Therefore,

$$\frac{d^2}{dy^2}\left[y^2\varphi\left(A + \frac{1}{y}\right)\right] = \frac{d^2}{dy^2}[\beta(Ay^2 + y)] = 2\beta Ay > 0.$$

ii) Holling II or Michealis-Menten or Rosenzweig: Thus we have $\varphi(x) = \frac{\beta x}{1+x}$ and

$$\frac{d}{dy}\left[y^2\varphi\left(A + \frac{1}{y}\right)\right] = \frac{d}{dy}\left[\frac{\beta(y^2 + Ay^3)}{(1 + A)y + 1}\right] = \frac{\beta[2A(1 + A)y^3 + (1 + 4A)y^2 + 2y]}{((1 + A)y + 1)^2}.$$

Therefore,

$$\frac{d^2}{dy^2}\left[y^2\varphi\left(A + \frac{1}{y}\right)\right] = \frac{d^2}{dy^2}\left[\frac{\beta(y^2 + Ay^3)}{(1 + A)y + 1}\right] = \frac{\beta[2A(1 + A)^2y^3 + 6A(1 + A)y^2 + 6Ay + 2]}{((1 + A)y + 1)^3} > 0.$$

iii) Holling type IV or Monod-Haldane: we get $\varphi(x, y) = \frac{\beta x}{1+x+x^2}$. Hence we have

$$\frac{d}{dy}\left[y^2\varphi\left(A + \frac{1}{y}\right)\right] = \frac{d}{dy}\left[\frac{\beta(y^3 + Ay^4)}{(1 + A + A^2)y^2 + (1 + 2A)y + 1}\right] = \frac{\beta}{((1 + A + A^2)y^2 + (1 + 2A)y + 1)^2}[3y^2 + [2 + 8A]y^3 + [7A^2 + 4A + 1]y^4 + 2A(1 + A + A^2)y^5],$$

and

$$\frac{d^2}{dy^2}\left[y^2\varphi\left(A + \frac{1}{y}\right)\right] = \frac{d^2}{dy^2}\left[\frac{\beta(y^3 + Ay^4)}{(1 + A + A^2)y^2 + (1 + 2A)y + 1}\right] = \frac{\beta}{\left((1 + A + A^2)y^2 + (1 + 2A)y + 1\right)^3}[2A(1 + A + A^2)^2y^6 + 6A(1 + 2A)(1 + A + A^2)y^5 + [12A + 30A^2 + 26A^3]y^4 + [(1 + 2A)(2 + 8A) + 4(1 + 4A + 7A^2 - 6(1 + A + A^2)]y^3 + 3(2 + 8A)y^2 + 6y = \frac{\beta}{\left((1 + A + A^2)y^2 + (1 + 2A)y + 1\right)^3}[2A(1 + A + A^2)^2y^6 + 6A(1 + 2A)(1 + A + A^2)y^5 +$$

$$[12A + 30A^2 + 26A^3]y^4 + [22A + 38A^2]y^3 + 3(2 + 8A)y^2 + 6y > 0$$

iv) Ivlev: we let $\varphi(x) = \alpha(1 - e^{-\beta x})$ and we have

$$\frac{d}{dy}\left[y^2\varphi\left(A + \frac{1}{y}\right)\right] = \frac{d}{dy}\left[\alpha y^2\left(1 - e^{-\beta\left(A+\frac{1}{y}\right)}\right)\right] =$$

$$\alpha[2y\left(1 - e^{-\beta(A+\frac{1}{y})}\right) - \beta e^{-\beta(A+\frac{1}{y})}].$$

So

$$\frac{d^2}{dy^2}\left[y^2\varphi\left(A + \frac{1}{y}\right)\right] = \frac{d^2}{dy^2}\left[\alpha y^2\left(1 - e^{-\beta\left(A+\frac{1}{y}\right)}\right)\right]$$

$$= \alpha[2 - \left(2 + \frac{\beta}{y} + \frac{\beta^2}{y^2}\right)e^{-\beta\left(A+\frac{1}{y}\right)}] = \alpha e^{-\beta(A+\frac{1}{y})}[2e^{\beta(A+\frac{1}{y})} - \left(2 + \frac{\beta}{y} + \frac{\beta^2}{y^2}\right)]$$

$$\geq \alpha e^{-\beta(A+\frac{1}{y})}[2\left(1 + \beta\left(A + \frac{1}{y}\right) + \frac{1}{2}\left(\beta\left(A + \frac{1}{y}\right)\right)^2\right) -$$

$$\left(2 + \frac{\beta}{y} + \frac{\beta^2}{y^2}\right)] \geq \alpha e^{-\beta(A+\frac{1}{y})}\left[2\beta A + (\beta A)^2 + \frac{\beta}{y} + 2\frac{\beta^2 A}{y}\right] > 0.$$

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