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STABILITY ANALYSIS OF AN HIV PATHOGENESIS MODEL WITH SATURATING INFECTION RATE AND TIME DELAY†

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ABSTRACT. In this paper, a mathematical model for HIV infection with saturating infection rate and time delay is established. By some analytical skills, we study the global asymptotical stability of the viral free equilibrium of the model, and obtain the sufficient conditions for the local asymptotical stability of the other two infection equilibria. Finally, some related numerical simulations are also presented to verify our results.

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1. Introduction

In recent years, much great attention has been paid to the HIV pathogenesis model, and a lot of meaningful results have been obtained (for example, see [1-12, 16, 18]). By analysing these models, scholars had obtained much knowledge about the mechanism of HIV infection, which enhanced the progress in understanding of HIV and its drug therapies.

It is well known that the following HIV infection model with immune response was investigated by Perelson et al. in [2].

$$\begin{cases} \frac{dx(t)}{dt} = s - dx(t) - kx(t)v(t), \\ \frac{dy(t)}{dt} = kx(t)v(t) - \delta y(t) - py(t)z(t), \\ \frac{dv(t)}{dt} = N\delta y(t) - \mu v(t), \\ \frac{dz(t)}{dt} = f(x,y,z) - bz(t), \end{cases} \tag{1}$$

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where $x(t), y(t), v(t)$ and $z(t)$ represent the concentrations of susceptible cells, infected cells, virus particles and CTLs at time t, respectively. The parameter $s(s > 0)$ is the rate of the new target cells generated from sources. The uninfected cells die at a rate of d, and $k(k \geq 0)$ is the constant which describes the infection rate. Once susceptible cells are infected we can assume that they die at rate δ due to the action of free virus particles, and release N new virus particles during their lifetime. Thus, on average, the virus is produced at rate $N\delta y(t)$ and μ is its death rate. The infected cells die at a rate of p due to the action of immune system. The function $f(x, y, z)$ characterizes the rate of immune response which is activated by the infected cells. Finally, b stands for the death rate for CTLs.

In [15], Nowak and Bangham assumed that the production of CTLs is not only dependent on the concentration of the infected cells, but also on the concentration of the CTLs, and choose $f(x, y, z) = cy(t)z(t)$ (see, [2]), the model (1) can be modified as follows:

$$\begin{cases} \dfrac{dx(t)}{dt} = s - dx(t) - kx(t)v(t), \\ \dfrac{dy(t)}{dt} = kx(t)v(t) - \delta y(t) - py(t)z(t), \\ \dfrac{dv(t)}{dt} = N\delta y(t) - \mu v(t), \\ \dfrac{dz(t)}{dt} = cy(t)z(t) - bz(t). \end{cases} \tag{$1'$}$$

Liu [20] analyzed the stability of model ($1'$). The infection rate between the HIV virus and susceptible cells may not be a simple linear relationship in [1], therefore we can consider the saturating infection rate into the model, which is mentioned in [12]. In addition, time delay can not ignored in model for virus production, since susceptible cells which is infected by virus generating new virus may need a period of time. Hence, time delays paly a significant role in the dynamical properties of HIV pathogenesis models.

Zhu and Zou [4] incorporated a delay into the cell infection equation in model ($1'$) and proposed the following model:

$$\begin{cases} \dfrac{dx(t)}{dt} = s - dx(t) - kx(t)v(t), \\ \dfrac{dy(t)}{dt} = ke^{-\delta\tau}x(t-\tau)v(t-\tau) - \delta y(t) - py(t)z(t), \\ \dfrac{dv(t)}{dt} = N\delta y(t) - \mu v(t), \\ \dfrac{dz(t)}{dt} = cy(t)z(t) - bz(t). \end{cases} \tag{2}$$

In this paper, we incorporate a delay into the virus production equation and saturating infection rate into the infection equation in model (2). Moreover, we consider the lower activity function $\frac{x(t)v(t)}{1+av(t)}$ of the virus particles to susceptible cells. Further, we propose the following model:

$$\begin{cases} \dfrac{dx(t)}{dt} = s - dx(t) - \dfrac{kx(t)v(t)}{1+av(t)}, \\ \dfrac{dy(t)}{dt} = \dfrac{kx(t)v(t)}{1+av(t)} - \delta y(t) - py(t)z(t), \\ \dfrac{dv(t)}{dt} = N\delta e^{-m\tau} y(t-\tau) - \mu v(t), \\ \dfrac{dz(t)}{dt} = cy(t)z(t) - bz(t), \end{cases} \tag{3}$$

where the state variables $x(t), y(t), v(t), z(t)$ and the parameters in system (3) have the same biological meanings as in the system (1). a is a constant which is greater than zero. τ denotes the lag between the time that the virus infects susceptible cells and the time that the infected cells generates new virus. the term $e^{-m\tau}$ accounts for cells that have been infected at time t but die before releasing productively virus τ time units later.

The novelty of the model (3) is that it includes both saturating infection rate in the infection equation and time delay in the virus production equation, and that we consider the lower activity function $\frac{x(t)v(t)}{1+av(t)}$ of the virus particles to susceptible cells.

The remainder of the paper is organized as follows. In Section 2, some useful preliminaries are given. Section 3 is dedicated to the stability of the viral free equilibrium, which is obtained by employing Liapunov function. In Section 4 and Section 5, by carrying out a detailed analysis on the transcendental characteristic equation of the linearized systems at the two infected equilibria, we respectively get sufficient conditions for locally asymptotical stability of the two equilibria. Further, some related numerical simulations are illustrated to verify conclusions in Section 6. Finally, some conclusions are given.

2. Preliminaries

In this section, in order to prove our main results in this paper, we shall consider the positivity and boundaries of solutions of system (3). After that, three equilibria and the basic reproduction number R_0 are also given.

Let $X = C([-\tau, 0]; R^4)$ be the Banach space of continuous function form $[-\tau, 0]$ to R^4 equipped with the norm

$$\| \varphi \| = \sup_{-\tau \leq \theta \leq 0} | \varphi(\theta) |,$$

where $\varphi \in C$. By fundamental theory of FDEs and biological reasons, there is a unique solution $(x(t), y(t), v(t), z(t))$ to system (3) with initial conditions:

$$\begin{cases} x(\theta) \geq 0, y(\theta) \geq 0, v(\theta) \geq 0, z(\theta) \geq 0, \theta \in [-\tau, 0] \\ (x(\theta), y(\theta), v(\theta), z(\theta)) \in X. \end{cases} \tag{4}$$

The following Lemmas are useful.

Lemma 2.1. *Suppose that $x(t), y(t), v(t), z(t)$ is the solution of system (3) satisfying initial conditions (4). Then $x(t) \geq 0, y(t) \geq 0, v(t) \geq 0, z(t) \geq 0$ for all $t \geq 0$.*

Proof. Form each equation of the system (3), we can obtain

$$\begin{aligned}
x(t) &= x(0)e^{-\int_0^t (d+k\frac{v(\varepsilon)}{1+av(\varepsilon)})d\varepsilon} + \int_0^t se^{-\int_\eta^t (d+k\frac{v(\varepsilon)}{1+av(\varepsilon)})d\varepsilon} d\eta, \\
y(t) &= y(0)e^{-\int_0^t (\delta+pz(\varepsilon))d\varepsilon} + \int_0^t k\frac{x(\eta)v(\eta)}{1+av(\eta)} e^{-\int_\eta^t (\delta+pz(\varepsilon))d\varepsilon} d\eta, \\
v(t) &= v(0)e^{-\mu t} + \int_0^t N\delta y(\eta-\tau)e^{-m\tau}e^{-\mu(t-\eta)}d\eta, \\
z(t) &= z(0)e^{\int_0^t (cy(\varepsilon)-b)d\varepsilon}.
\end{aligned}$$

Obviously, $x(t) \geq 0, z(t) \geq 0$ for all $t > 0$. Next we only prove $y(t) \geq 0, v(t) \geq 0$.

Suppose that $y(t) \geq 0$ does not hold. Then there exists $t_1 > 0$, t_1 is the first point which pass through the x-axis and make $y(t) < 0$, which satisfies $y(t_1) = 0$ and $y'(t_1) < 0$. We can obtain by the second equation of the system (3) as follows:

$$y'(t_1) = k\frac{x(t_1)v(t_1)}{1+av(t_1)} - \delta y(t_1) - py(t_1)z(t_1) = k\frac{x(t_1)v(t_1)}{1+av(t_1)} < 0. \tag{5}$$

If $t \in [0, t_1]$, then

$$y(t_1) \geq 0, v(t_1) = v(0)e^{-\mu t_1} + \int_0^{t_1} N\delta y(\eta-\tau)e^{-m\tau}e^{-\mu(t_1-\eta)}d\eta \geq 0,$$

and $x(t) \geq 0$ for all $t \geq 0$. We get

$$y'(t_1) = k\frac{x(t_1)v(t_1)}{1+av(t_1)} \geq 0.$$

This is contradicted with (5), then $y(t) \geq 0$. By a recursive demonstration and initial conditions, we can easily get $v(t) \geq 0$. The proof is complete. □

Lemma 2.2. *Suppose that $x(t), y(t), v(t), z(t)$ are the solution of system (3), each of them is bounded.*

Proof. We define

$$F(t) = x(t) + y(t) + \frac{e^{m\tau}}{2N}v(t+\tau) + \frac{p}{c}z(t), q = \min\{d, \frac{\delta}{2}, \mu, b\}.$$

For boundedness of the solution, we define

$$\begin{aligned}
F'(t) &= x'(t) + y'(t) + \frac{e^{m\tau}}{2N}v'(t+\tau) + \frac{p}{c}z'(t) \\
&= s - dx(t) - \frac{\delta}{2}y(t) - \frac{e^{m\tau}}{2N}\mu v(t+\tau) - \frac{pb}{c}z(t)
\end{aligned}$$

$$< s - q[x(t) + y(t) + \frac{e^{m\tau}}{2N}v(t+\tau) + \frac{p}{c}z(t)]$$
$$= s - qF(t).$$

From Lemma 2.1 we know the solution of system (3) is positive, which implies that $F(t)$ is bounded, and so are $x(t), y(t), v(t)$ and $z(t)$. The proof is complete. □

Now, we give three equilibria for system (3) and the basic reproduction number R_0. Define that

$$R_0 = \frac{ksNe^{-m\tau}}{d\mu},$$

where R_0 is the basic reproduction number.

(1) When $R_0 < 1$, we can obtain the first equilibrium

$$E_0 = (\frac{s}{d}, 0, 0, 0)$$

which implies that the virus are absent. E_0 is the only biologically meaningful equilibrium.

(2) When $R_0 > 1$, $R_1 = \frac{kscN}{dc\mu e^{m\tau}+(da+k)N\delta b} < 1$. Besides E_0, system (3) has the second biologically meaningful equilibrium E_1 which represents that the virus are present and CTLs are absent, that is,

$$E_1 = (x_1, y_1, v_1, z_1) = \left(\frac{sNa + \mu e^{m\tau}}{N(da+k)}, \frac{d\mu e^{m\tau}}{N(da+k)}(R_0 - 1), \frac{d}{da+k}(R_0 - 1), 0\right).$$

(3) When $R_1 > 1$, the last equilibrium in system (3) is E_2 which represents that both virus and CTLs are present.

$$E_2 = (x_2, y_2, v_2, z_2) = \left(\frac{s(c\mu e^{m\tau} + N\delta ab)}{dc\mu e^{m\tau} + (da+k)N\delta b}, \frac{b}{c}, \frac{N\delta b}{c\mu e^{m\tau}}, \frac{\delta}{p}(R_1 - 1)\right).$$

3. Stability of the viral free equilibrium E_0

In this section, we mainly consider the stability of the viral free equilibrium E_0 by employing Liapunov funtion.

Theorem 3.1. *If $R_0 < 1$, the viral free equilibrium E_0 of system (3) is globally asymptotical stable for any time delay $\tau \geq 0$.*

Proof. In order to discuss the stability of the viral free equilibrium $E_0 = (\frac{s}{d}, 0, 0, 0)$ for system (3), we define the following Lyapunov function.

$$V(t) = \frac{e^{-m\tau}}{2}\left(x(t) - \frac{s}{d}\right)^2 + \frac{se^{-m\tau}}{d}y(t) + \frac{s}{Nd}v(t) + \frac{spe^{-m\tau}}{dc}z(t) + \frac{s\delta e^{-m\tau}}{d}\int_{t-\tau}^{t} y(\theta)d\theta.$$

Calculating the derivative of V along the solution of system (3), we get

$$V' \mid_{(3)} = e^{-m\tau}\left(x(t) - \frac{s}{d}\right)\left(-d\left(x(t) - \frac{s}{d}\right) - k\frac{(x(t) - \frac{s}{d}) + \frac{s}{d}}{1 + av(t)}v(t)\right)$$
$$+ \frac{se^{-m\tau}}{d}\left[k\frac{(x(t) - \frac{s}{d}) + \frac{s}{d}}{1 + av(t)}v(t) - \delta y(t) - py(t)z(t)\right] + \frac{s\delta e^{-m\tau}}{d}[y(t) - y(t-\tau)]$$

$$
\begin{aligned}
&+\frac{s}{Nd}\big(N\delta e^{-m\tau}y(t-\tau)-\mu v(t)\big)+\frac{spe^{-m\tau}}{dc}\left(cy(t)z(t)-bz(t)\right)\\
=&-e^{-m\tau}\left(d+k\frac{v(t)}{1+av(t)}\right)\left(x(t)-\frac{s}{d}\right)^2+\frac{ks^2e^{-m\tau}}{d^2}\frac{v(t)}{1+av(t)}\\
&-\frac{s\mu}{Nd}v(t)-\frac{spbe^{-m\tau}}{dc}z(t)\\
\leq&-e^{-m\tau}\left(d+k\frac{v(t)}{1+av(t)}\right)\left(x(t)-\frac{s}{d}\right)^2+\frac{ks^2e^{-m\tau}}{d^2}v(t)-\frac{s\mu}{Nd}v(t)-\frac{spbe^{-m\tau}}{dc}z(t)\\
=&-e^{-m\tau}\left(d+k\frac{v(t)}{1+av(t)}\right)\left(x(t)-\frac{s}{d}\right)^2-\frac{s\mu}{Nd}(1-R_0)v(t)-\frac{spbe^{-m\tau}}{dc}z(t).
\end{aligned}
$$

From Lemma 2.1, $x(t)\geq 0, y(t)\geq 0, v(t)\geq 0, z(t)\geq 0$, $R_0<1$, we can get

$$V'\mid_{(3)}\leq 0.$$

If and only if $(x(t),y(t),v(t),z(t))=(\frac{s}{d},0,0,0)$, we obtain $V'\mid_{(3)}=0$. Hence, the viral free equilibrium E_0 of system (3) is globally asymptotically stable from Lyapunov-LaSalle in [13]. The proof is complete. □

4. Stability of equilibrium E_1 inactivated by CTLs

In this section, we mainly discuss the stability of the CTL-inactivated infection equilibrium E_1 by analyzing the characteristic equation. First, we linearize system (3) at E_1 to obtain

$$
\begin{cases}
\dfrac{dx}{dt}=(-d-\dfrac{kv_1}{1+av_1})x(t)-\dfrac{kx_1}{(1+av_1)^2}v(t),\\
\dfrac{dy}{dt}=\dfrac{kv_1}{1+av_1}x(t)-\delta y(t)+\dfrac{kx_1}{(1+av_1)^2}v(t)-py_1z(t),\\
\dfrac{dv}{dt}=N\delta e^{-m\tau}y(t-\tau)-\mu v(t),\\
\dfrac{dz}{dt}=(cy_1-b)z(t).
\end{cases}\tag{6}
$$

The associated characteristic equation of system (3) at E_1 becomes

$$(\lambda+b-cy_1)\big((\lambda+\delta)(\lambda+\mu)(\lambda+d+\frac{kv_1}{1+av_1})-N\delta e^{-m\tau}(\lambda+d)\frac{kx_1}{(1+av_1)^2}e^{-\lambda\tau}\big)=0.\tag{7}$$

It is clear that a root of the equation (7) is

$$\lambda_1=cy_1-b=\frac{kscN-dc\mu e^{m\tau}-(da+k)N\delta b}{N\delta(da+k)}$$

which has a negative real part by calculating under $R_1<1$. We can give the remaining roots by the solutions of the transcendental equation as follows

$$(\lambda+\delta)(\lambda+\mu)\big(\lambda+d+\frac{kv_1}{1+av_1}\big)-N\delta e^{-m\tau}(\lambda+d)\frac{kx_1}{(1+av_1)^2}e^{-\lambda\tau}=0.\tag{8}$$

Rewrite equation (8) as

$$\lambda^3+A_2(\tau)\lambda^2+A_1(\tau)\lambda+A_0(\tau)-\big(B_1(\tau)\lambda+B_0(\tau)\big)e^{-\lambda\tau}=0,\tag{9}$$

where

$$\begin{aligned} A_2(\tau) &= \delta + \mu + d + \frac{kv_1}{1+av_1}, \\ A_1(\tau) &= \delta\mu + (\delta+\mu)(d + \frac{kv_1}{1+av_1}), \\ A_0(\tau) &= \delta\mu(d + \frac{kv_1}{1+av_1}), \\ B_1(\tau) &= \frac{kx_1 N\delta e^{-m\tau}}{(1+av_1)^2}, \\ B_0(\tau) &= \frac{dkx_1 N\delta e^{-m\tau}}{(1+av_1)^2}. \end{aligned}$$

If $\tau = 0$, equation (9) becomes

$$\lambda^3 + A_2(0)\lambda^2 + \big(A_1(0) - B_1(0)\big)\lambda + \big(A_0(0) - B_0(0)\big) = 0. \tag{10}$$

Next, we consider the distribution of all roots of Eq.(10). Noting that $R_0 > 1$ and

$$\begin{aligned} &A_2(0) = \delta + \mu + d + \frac{kv_1(0)}{1+av_1(0)} > 0, \\ &A_0(0) - B_0(0) = \frac{d\delta\mu^2(da+k)\big(R_0(0)-1\big)}{k(\mu+asN)} > 0, \\ &A_2(0)\big(A_1(0) - B_1(0)\big) - \big(A_0(0) - B_0(0)\big) = \delta^2\mu + \delta(\delta+\mu)\left(d + \frac{kv_1(0)}{1+av_1(0)}\right) \\ &\quad + \delta\mu^2 + \mu(\delta+\mu)\left(d + \frac{kv_1(0)}{1+av_1(0)}\right) + (\delta+\mu)\left(d + \frac{kv_1(0)}{1+av_1(0)}\right)^2 \\ &\quad - N\delta\frac{kx_1(0)}{(1+av_1(0))^2}\left(\delta + \mu + \frac{kx_1(0)}{1+av_1(0)}\right). \end{aligned}$$

For

$$\delta\mu - \delta N\frac{kx_1(0)}{(1+av_1(0))^2} = \frac{d\delta\mu^2 a(R_0(0)-1)}{k(\mu+sNa)} > 0,$$

we can get

$$\begin{aligned} \delta^2\mu - \delta N\delta\frac{kx_1(0)}{(1+av_1(0))^2} &> 0, \\ \delta\mu^2 - \mu N\delta\frac{kx_1(0)}{(1+av_1(0))^2} &> 0, \\ \delta\mu\frac{kv_1(0)}{1+av_1(0)} - \delta N\frac{kx_1(0)}{(1+av_1(0))^2}\frac{kv_1(0)}{1+av_1(0)} &> 0. \end{aligned}$$

So we can obtain

$$A_2(0)[A_1(0) - B_1(0)] - [A_0(0) - B_0(0)] > 0.$$

Note that the case $R_0 > 1$ holds and the Routh-Hurwitz criterion in [14] for cubic polynomials is applicable, we can get that all roots of (10) have negative real parts for $\tau = 0$.

We know that all roots of (9) continuously depends on τ, which can be verified in [17]. As τ increases, this steady state will remain stable until one or many roots cross the imaginary axis. Clearly, if $R_0 > 1$, then $\lambda = 0$ is not a solution of (9) since $A_0(0) - B_0(0) > 0$, thus this crossing may occur only at pure imaginary roots. We consider $\lambda = i\omega$ with $\omega \geq 0$. Then

$$-\omega^3 i - A_2(\tau)\omega^2 + A_1(\tau)\omega i + A_0(\tau) = [B_1(\tau)\omega i + B_0(\tau)]e^{-\tau\omega i}.$$

Separating the real parts and imaginary parts,we may get

$$\begin{cases} A_0(\tau) - A_2(\tau)\omega^2 = B_1(\tau)\omega \sin\tau\omega + B_0(\tau)\cos\tau\omega, \\ A_1(\tau)\omega - \omega^3 = B_1(\tau)\omega\cos\tau\omega - B_0(\tau)\sin\tau\omega. \end{cases}$$

which, together with $\tau > 0$, implies that

$$\begin{aligned} N(\omega) = {} & \omega^6 + [A_2^2(\tau) - 2A_1(\tau)]\omega^4 + [A_1^2(\tau) - 2A_0(\tau)A_2(\tau) \\ & - B_1^2(\tau)]\omega^2 + A_0^2(\tau) - B_0^2(\tau) \\ = {} & 0. \end{aligned} \tag{11}$$

A straightforward calculation shows that

$$\begin{aligned} N'(\omega) = {} & 6\omega^5 + 4[A_2^2(\tau) - 2A_1(\tau)]\omega^3 + 2[A_1^2(\tau) - 2A_0(\tau)A_2(\tau) \\ & - B_1^2(\tau)]\omega, \omega \in (0, +\infty). \end{aligned}$$

By computing, we have

$$\begin{aligned} \delta\mu - B_1(\tau) &= \frac{d\delta\mu^2 a(R_0 - 1)}{k(\mu + sNae^{-m\tau})} > 0, \\ A_0(\tau) - B_0(\tau) &= \frac{d\delta\mu^2 e^{m\tau}(da + k)(R_0 - 1)}{k(\mu e^{m\tau} + asN)} > 0. \end{aligned}$$

Further, we get

$$A_2^2(\tau) - 2A_1(\tau) = \delta^2 + \mu^2 + (d + \frac{kv_1}{1 + av_1})^2 > 0,$$
$$A_1^2(\tau) - 2A_0(\tau)A_2(\tau) - B_1^2(\tau) = (\delta\mu + B_1(\tau))(\delta\mu - B_1(\tau)) + (\delta^2 + \mu^2)(d + \frac{kv_1}{1 + av_1})^2 > 0,$$
$$A_0^2(\tau) - B_0^2(\tau) = [A_0(\tau) + B_0(\tau)][A_0(\tau) - B_0(\tau)] > 0.$$

Therefore, $N'(\omega) > 0$ holds and $N(\omega)$ is monotonically increasing function in $\omega \in (0, +\infty)$, and we have calculated $N(0) = A_0^2(\tau) - B_0^2(\tau) > 0$. So, equation (11) has no positive solutions, which implies that all roots of (9) has no pure imaginary roots for $\tau > 0$ under $R_0 > 1$.

Hence, we can summarize the above results and obtain the following theorem.

Theorem 4.1. *Let $R_0 > 1$. Then (1) if $R_1 < 1$, equilibrium E_1 which is not activated by CTLs is locally asymptotically stable; (2) if $R_1 > 1$, equilibrium E_1 becomes unstable and there appears the other equilibrium E_2.*

5. Stability of equilibrium E_2 activated by CTLs

In this section, we discuss the stability of the CTL-activated infection equilibrium E_2 by analyzing the characteristic equation. Assume

$$R_1 = \frac{kscN}{dc\mu e^{m\tau} + (da+k)N\delta b} > 1.$$

Then E_2 exists and we linearize system (3) at $E_2(\frac{s(c\mu e^{m\tau}+N\delta ab)}{dc\mu e^{m\tau}+(da+k)N\delta b}, \frac{b}{c}, \frac{N\delta b}{c\mu e^{m\tau}}, \frac{\delta}{p}(R_1 - 1))$ is given by

$$\begin{cases} \dfrac{dx}{dt} = (-d - \dfrac{kv_2}{1+av_2})x(t) - \dfrac{kx_2}{(1+av_2)^2}v(t), \\ \dfrac{dy}{dt} = \dfrac{kv_2}{1+av_2}x(t) - (\delta + pz_2)y(t) + \dfrac{kx_2}{(1+av_2)^2}v(t) - py_2z(t), \\ \dfrac{dv}{dt} = N\delta e^{-m\tau}y(t-\tau) - \mu v(t), \\ \dfrac{dz}{dt} = cz_2y(t) + (cy_2 - b)z(t). \end{cases} \tag{12}$$

At E_2, $cy_2 - b = 0$ holds. Let $\alpha = d + \frac{kx_2}{1+av_2}, \beta = \frac{kx_2}{(1+av_2)^2}, \gamma = \delta + pz_2 = \delta R_1$. The characteristic equation of system (3) near E_2 is given by

$$\lambda^4 + a_3\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 - \big(b_2\lambda^2 + b_1\lambda\big)e^{-\lambda\tau} = 0. \tag{13}$$

where

$$\begin{aligned} a_3 &= \mu + \alpha + \delta R_1, \\ a_2 &= \delta R_1\mu + \alpha(\mu + \delta R_1) + b\delta(R_1 - 1), \\ a_1 &= \delta R_1\alpha\mu + b\delta(R_1 - 1)(\alpha + \mu), \\ a_0 &= \alpha\mu b\delta(R_1 - 1), \\ b_2 &= \delta\mu R_1, \\ b_1 &= d\delta\mu R_1. \end{aligned}$$

By the well-known Routh-Hurwitz criterion in [14], we easily obtain that any roots of (13) have negative real part for $\tau = 0$. Further, we get equilibrium E_2 is also locally asymptotically stable when $\tau > 0$.

Rewrite the equation (13) as

$$D(\lambda) = \lambda^4 + a_3\lambda^3 + a_2\lambda^2 + a_1\lambda + a_0 - \big(b_2\lambda^2 + b_1\lambda\big)e^{-\lambda\tau} = 0. \tag{14}$$

The characteristic equation (14) is a fourth-order transcendental equation. Moreover, $D(\lambda)$ is defined as characteristic function corresponding to corollary 2.38 in [19]. Therefore, we may introduce corollary 2.38 in [19] to discuss the stability of equilibrium E_2.

Let $\lambda = i\omega(\omega > 0)$. Then we have

$$D(i\omega) = \omega^4 - a_3 i\omega^3 - a_2\omega^2 + a_1 i\omega + a_0 - \big(- b_2\omega^2 + b_1 i\omega\big)e^{-i\omega\tau} = 0.$$

Let $R(\omega)$ and $I(\omega)$ is the real parts and imaginary parts of $D(i\omega)$, respectively. We obtain

$$R(\omega) = ReD(i\omega) = \omega^4 - a_2\omega^2 + a_0 + b_2\omega^2\cos\omega\tau - b_1\omega\sin\omega\tau,$$
$$I(\omega) = ImD(i\omega) = -a_3\omega^3 + a_1\omega - b_1\omega\cos\omega\tau - b_2\omega^2\sin\omega\tau.$$

For $|\sin\omega\tau| < \omega\tau(\omega, \tau > 0)$ and $|\cos\omega\tau| \le 1$, we have

$$\begin{aligned} R(\omega) &< \omega^4 - (a_2 - b_2 - b_1\tau)\omega^2 + a_0, && \omega \in (0, +\infty),\\ R(\omega) &> \omega^4 - (a_2 + b_2 + b_1\tau)\omega^2 + a_0, && \omega \in (0, +\infty),\\ I(\omega) &< \omega(a_1 + b_1 - a_3\omega^2 + b_2\omega^2\tau), && \omega \in (0, +\infty),\\ I(\omega) &> \omega(a_1 - b_1 - a_3\omega^2 - b_2\omega^2\tau), && \omega \in (0, +\infty). \end{aligned}$$

Let

$$\begin{aligned} R^+(\omega) &= \omega^4 - (a_2 - b_2 - b_1\tau)\omega^2 + a_0,\\ R^-(\omega) &= \omega^4 - (a_2 + b_2 + b_1\tau)\omega^2 + a_0,\\ I^+(\omega) &= \omega(a_1 + b_1 - a_3\omega^2 + b_2\omega^2\tau),\\ I^-(\omega) &= \omega(a_1 - b_1 - a_3\omega^2 - b_2\omega^2\tau). \end{aligned}$$

Then, according to theorem 2.37 in [13], we easily get

$$\begin{aligned} R^-(\omega) &< R(\omega) < R^+(\omega), && \omega \in (0, +\infty),\\ I^-(\omega) &< I(\omega) < I^+(\omega), && \omega \in (0, +\infty). \end{aligned}$$

In addition, when

$$\tau < \bar{\tau} = \min\left\{\frac{1}{\mu}, \frac{1}{m}\ln\frac{kscN - (da + k)N\delta b}{dc\mu}\right\}, \tag{15}$$

we have

$$a_3 - b_2\tau = \mu + \alpha + \delta R_1(1 - \mu\tau) > 0,$$
$$a_1 - b_1 = \delta R_1\mu\frac{kv_2}{1 + av_2} + b\delta\alpha(R_1 - 1) + b\delta\mu(R_1 - 1) > 0.$$

Therefore, the equation $I^+(\omega) = 0$ only has one positive solution $\eta_1 = \sqrt{\frac{a_1+b_1}{a_3-b_2\tau}}$; the equation $I^-(\omega) = 0$ also only has one positive $\eta_2 = \sqrt{\frac{a_1-b_1}{a_3+b_2\tau}}$. Further, we have $\eta_2 < \eta_1$.

When (15) holds, we can still get that

$$a_2 - b_2 - b_1\tau = \mu d + \delta R_1 d(1 - \mu\tau) + \delta b(R_1 - 1) + (\mu + \delta R_1)\frac{kv_2}{1 + av_2} > 0.$$

$$\begin{aligned} (a_2 - b_2 - b_1\tau)^2 - 4a_0 &= [(\mu + \delta R_1)\alpha + \delta b(R_1 - 1) - d\mu\delta R_1\tau]^2 - 4\mu b\delta(R_1 - 1)\alpha\\ &\ge 2\delta[\frac{kv_2}{1 + av_2} + d(1 - \tau\mu)][\mu R_1\alpha + R_1 b\delta(R_1 - 1)]\\ &> 0. \end{aligned}$$

Thus, the equation $R^+(\omega) = 0$ has two real positive roots ζ_1^+ and ζ_2^+ satisfying

$$\zeta_1^+ = \left(\frac{(a_2 - b_2 - b_1\tau) + \sqrt{(a_2 - b_2 - b_1\tau)^2 - 4a_0}}{2} \right)^{\frac{1}{2}}$$

and

$$\zeta_2^+ = \left(\frac{(a_2 - b_2 - b_1\tau) - \sqrt{(a_2 - b_2 - b_1\tau)^2 - 4a_0}}{2} \right)^{\frac{1}{2}}.$$

Clearly, we have $\zeta_2^+ < \zeta_1^+$.

Similarly, we can obtain that the equation $R^-(\omega) = 0$ has two real positive roots ζ_1^- and ζ_2^- satisfying

$$\zeta_1^- = \left(\frac{(a_2 + b_2 + b_1\tau) + \sqrt{(a_2 + b_2 + b_1\tau)^2 - 4a_0}}{2} \right)^{\frac{1}{2}}$$

and

$$\zeta_2^-) = \left(\frac{(a_2 + b_2 + b_1\tau) - \sqrt{(a_2 + b_2 + b_1\tau)^2 - 4a_0}}{2} \right)^{\frac{1}{2}}.$$

Further, we have $\zeta_2^- < \zeta_1^-$,

Thus, under (15), both $R^+(\omega)$ and $R^-(\omega)$ have two real positive roots, respectively. It is also easy to verify the following:

$$Q_1 = [\min(\zeta_1^-, \zeta_1^+), \max(\zeta_1^-, \zeta_1^+)] = [\zeta_1^+, \zeta_1^-],$$
$$Q_2 = [\min(\zeta_2^-, \zeta_2^+), \max(\zeta_2^-, \zeta_2^+)] = [\zeta_2^-, \zeta_2^+].$$

Hence, the intervals Q_1 and Q_2 are disjoint.

Thus, by summarizing the above result, we know that corollary 2.38 in [19] is applicable if the following two conditions are satisfied.
(1) $R^-(0) > 0$;
(2) $I^-(\omega) > 0$, for $\omega \in Q_2$.

In fact,

$$R^-(0) = \lim_{\omega \to 0^+} R(\omega) = a_0 = \mu b\delta\alpha(R_1 - 1) > 0.$$

Furthermore, when $\omega \in (0, \eta_2)$, we have

$$I^-(\omega) = \omega(a_1 - b_1 - a_3\omega^2 - b_2\omega^2\tau) > 0.$$

Note that $Q_2 = [\zeta_2^-, \zeta_2^+]$, therefore, if $\zeta_2^+ \leq \eta_2$, then the second condition (2) holds. In turn, we knows that $\zeta_2^+ \leq \eta_2$ is equivalent to

$$\sigma(\tau) = (a_1 - b_1)(a_3 + b_2\tau)(a_2 - b_2 - b_1\tau) - (a_1 - b_1)^2 - a_0(a_3 + b_2\tau)^2 > 0.$$

Hence, we have following conclusions according to corollary 2.38 in [19].

Theorem 5.1. *When $R_1 > 1$ and the case (15) holds. If $\sigma(\tau) > 0$, then the equilibrium E_2 is locally asymptotically stable.*

Remark. $\sigma(\tau) > 0$ is clearly a sufficient but not necessary condition of stability for the equilibrium E_2.

6. Numerical Simulations

In order to illustrate feasibility of the results of Theorem 5.1, we use the software Matlab to perform numerical simulations.

Example 1. Consider the following system:

$$\begin{cases} \dfrac{dx(t)}{dt} = 5 - 0.03x(t) - 0.0014453\dfrac{x(t)v(t)}{1+0.06v(t)}, \\ \dfrac{dy(t)}{dt} = 0.0014453\dfrac{x(t)v(t)}{1+0.06v(t)} - 0.33y(t) - 0.05y(t)z(t), \\ \dfrac{dv(t)}{dt} = 158.4e^{-0.28\tau}y(t-\tau) - 1.8v(t), \\ \dfrac{dz(t)}{dt} = 0.2y(t)z(t) - 0.3z(t). \end{cases} \tag{16}$$

For the parameters from (16), we calculate by using the software Matlab

$$R_1 = 4.1717 > 1, \tau = 0.4 < \min\{0.5556, 13.9684\}, \sigma(0.4) = 0.2782 > 0.$$

Numerical simulations show that the equilibrium E_2 is locally asymptotically stable (See Fig. 1).

Example 2. Consider the following system:

$$\begin{cases} \dfrac{dx(t)}{dt} = 5 - 0.03x(t) - 0.001\dfrac{x(t)v(t)}{1+0.036v(t)}, \\ \dfrac{dy(t)}{dt} = 0.001\dfrac{x(t)v(t)}{1+0.036v(t)} - 0.32y(t) - 0.05y(t)z(t), \\ \dfrac{dv(t)}{dt} = 12.8e^{-0.28\tau}y(t-\tau) - 2.8v(t), \\ \dfrac{dz(t)}{dt} = 0.2y(t)z(t) - 0.3z(t). \end{cases} \tag{17}$$

For the parameters from (17), we calculate by using the software Matlab

$$R_1 = 1.5531 > 1, \tau = 0.2 < \min\{0.3571, 2.3027\}, \sigma(0.2) = -0.0015 < 0.$$

Numerical simulations show that $\sigma(\tau) > 0$ is clearly a sufficient but not necessary condition of stability for the equilibrium E_2; even if $\sigma(\tau) < 0$, E_2 is locally asymptotically stable (See Fig. 2).

7. Conclusion

In this paper, we have established a mathematical model for HIV with saturating infection rate and time delay by considering the lower activity function $\frac{x(t)v(t)}{1+av(t)}$ of the virus particles to susceptible cells, and have carried out a compete analysis on the stability of the the three equilibria of the model.

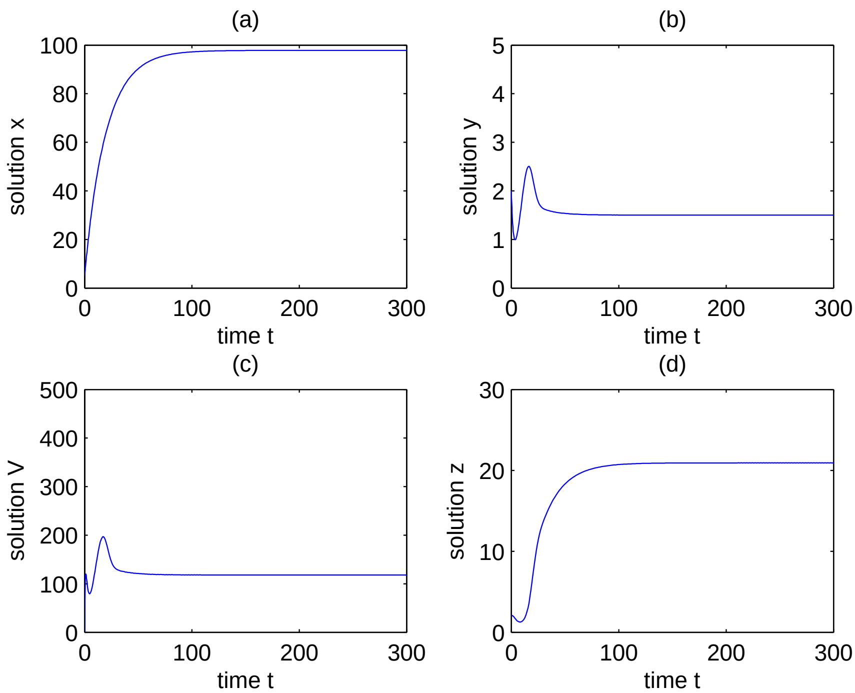

FIGURE 1. Numerical simulations show that the equilibrium E_2 is locally asymptotically stable when $\tau = 0.4 < \bar{\tau} = 0.5556$ and $\sigma(0.4) = 0.2782 > 0$.

Our results show that viral free equilibrium E_0 of system (3) is globally asymptotically stable for any time delay $\tau \geq 0$ by using the well-known Lyapunov-LaSalle theorem when the basic reproduction number $R_0 = \frac{ksNe^{-m\tau}}{d\mu} < 1$; When $R_0 > 1$ and $R_1 < 1$, E_0 becomes unstable and there occurs the second biologically meaning equilibrium E_1 which is not activated by CTLs, and the equilibrium E_1 is asymptotically stable by carrying out a detailed analysis on the transcendental characteristic equation of the linearized system (3) at E_1; When $R_1 > 1$, E_1 becomes unstable and there occurs internal equilibrium E_2 which is activated by CTLs. We have proved and numerically confirmed the asymptotical stability of E_2 satisfying the case $\sigma(\tau) > 0$ and under additional conditions (15).

However, for the case $\sigma(\tau) < 0$ under (15), we are unable to make a conclusion because numerical simulations have shown the possibility that may still be stable, which requires us to further study.

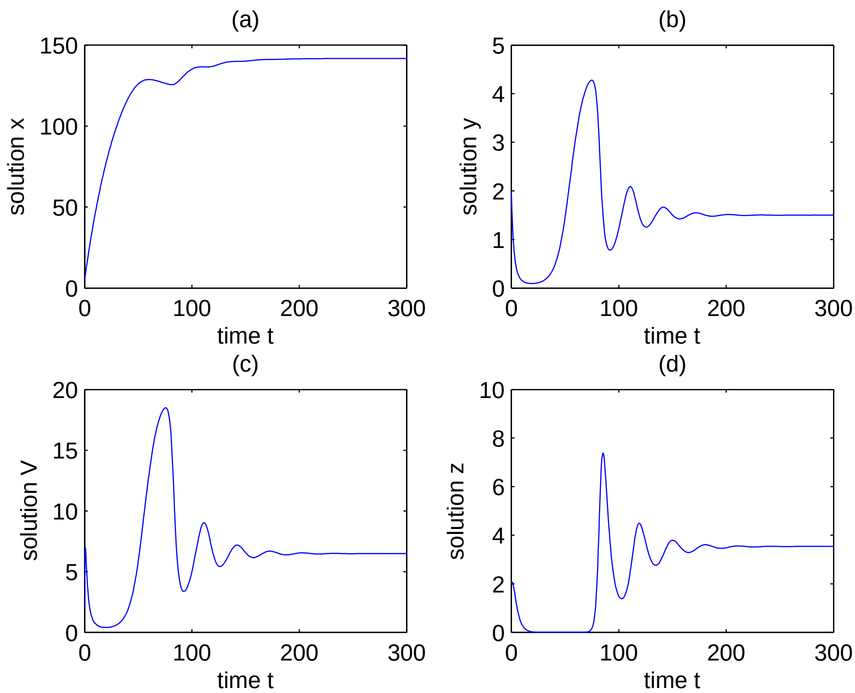

FIGURE 2. Numerical simulations show that the equilibrium E_2 is locally asymptotically stable when $\tau = 0.2 < \bar{\tau} = 0.3571$ and $\sigma(0.2) = -0.0015 < 0$.

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