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A delayed HIV-1 infection model with Beddington–DeAngelis functional response

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Abstract In this paper, a mathematical model for HIV-1 infection with intracellular delay and Beddington–DeAngelis functional response is investigated. We obtain a necessary and sufficient condition for the global stability of the infection-free equilibrium and give some sufficient conditions for the local stability of the infected equilibrium.

Keywords HIV-1 infection · Intracellular delay · Stability · Beddington–DeAngelis

1 Introduction

Mathematical models have been proven to be valuable in understanding the dynamics of the HIV-1 pathogenesis. Some authors use differential equations to study the dynamical properties of HIV-1 infection models with or without delays and they obtained much knowledge about the HIV-1 infection (see [1–10] and references therein).

Usually the rate of infection in most HIV-1 models is assumed to be bilinear in the virus V and the uninfected target cells T. However, the actual incidence rate is probably not linear over the entire range of V and T. Thus, it is reasonable to assume that the infection rate of HIV-1 model is given by the Beddington–DeAngelis functional response, $\frac{\beta TV}{1+aT+bV}$, where $a, b \geq 0$ are constants. The functional response $\frac{\beta TV}{1+aT+bV}$ was introduced by Beddington [11] and DeAngelis et al. [12].

For a specific nonlinear incidence rate, Li and Ma [13] studied the following delayed HIV-1 infection model:

$$\begin{cases} \dot{T}(t) = s - dT(t) - \frac{\beta T(t)V(t)}{1+bV(t)}, \\ \dot{I}(t) = \frac{\beta T(t-\tau)V(t-\tau)}{1+bV(t-\tau)} - pI(t), \\ \dot{V}(t) = kI(t) - uV(t), \end{cases} \tag{1}$$

where $T(t)$, $I(t)$, and $V(t)$ denote the concentration of uninfected target cells, infected cells that produce virus, and HIV-1 virus particles at time t, respectively. The positive constant s is the rate at which new target cells are generated. The positive constant d is the death rate of uninfected target cells. The positive constant p is the death rate of infected cells either due to the action of the HIV-1 virus particles or the im-

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mune system. Free virus is produced from the infected cells at the rate $kI(t)$. The positive constant u is the rate at which HIV-1 virus particles are removed from the system. And the form $\frac{\beta TV}{1+bV}$, expresses a saturation response, where b is the positive constant; $\tau > 0$ denotes the lag between the time of the virus contacts the target cell and the time of the cell becomes actively infected.

Motivated by the above discussions, in this paper, we consider the delayed HIV-1 infection model with Beddington–DeAngelis incidence rate as follows:

$$\begin{cases} \dot{T}(t) = s - dT(t) - \frac{\beta T(t)V(t)}{1+aT(t)+bV(t)}, \\ \dot{I}(t) = e^{-p\tau}\frac{\beta T(t-\tau)V(t-\tau)}{1+aT(t-\tau)+bV(t-\tau)} - pI(t), \\ \dot{V}(t) = kI(t) - uV(t), \end{cases} \tag{2}$$

where $a > 0$ is a constant. We will investigate the effects of the time delay and the Beddington–DeAngelis incidence rate on the dynamical behavior of HIV-1 infection model.

2 Positive invariance and boundedness

We begin by presenting some notations that will be used throughout this paper. Let $C = C([-\tau, 0], R^3_+)$ be the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into R^3_+, where $R^3_+ = \{(x_1, x_2, x_3) : x_i \geq 0,\ i = 1, 2, 3\}$. It is biologically reasonable to consider the following initial conditions for (2):

$$\begin{aligned} &T(\theta) = \varphi_1(\theta) \geq 0, \qquad I(\theta) = \varphi_2(\theta) \geq 0, \\ &V(\theta) = \varphi_3(\theta) \geq 0, \quad \theta \in [-\tau, 0], \\ &\varphi_1(0), \varphi_2(0), \varphi_3(0) > 0, \end{aligned} \tag{3}$$

where $(\varphi_1(0), \varphi_2(0), \varphi_3(0)) \in C$. From the fundamental theory of functional differential equations [15] and [16], it is easy to see that the solution $(T(t), I(t), V(t))$ of system (2) with the initial condition (3) exists for all $t \geq 0$ and is unique.

The model (2) can be rewritten in the following form:

$$\dot{X}(t) = G\big(X(t)\big), \tag{4}$$

where $X(t) = (x_1, x_2, x_3)^{\mathrm{T}} \triangleq (T, I, V)^{\mathrm{T}}$, $X(0) = (T(0), I(0), V(0))^{\mathrm{T}} \in R^3_+$ and

$$\begin{aligned} G(X) &= \begin{pmatrix} G_1(X) \\ G_2(X) \\ G_3(X) \end{pmatrix} \\ &= \begin{pmatrix} s - dT - \frac{\beta TV}{1+aT+bV} \\ e^{-p\tau}\frac{\beta T(t-\tau)V(t-\tau)}{1+aT(t-\tau)+bV(t-\tau)} - pI \\ kI - uV \end{pmatrix}. \end{aligned}$$

It is easy to check that $G_i(X)|_{x_i} \geq 0, i = 1, 2, 3$. Due to the well-known theorem by Nagumo [14], any solution of system (2) with initial $X(0) \in R^3_+$, say $X(t) = X(t; X(0))$, is such that $X(t) \in R^3_+$ for all $t > 0$.

In what follows, we consider the boundedness of the solutions of system (2).

Theorem 2.1 *Let $(T(t), I(t), V(t))$ be the solution of system (2) satisfying conditions (3). Then $T(t)$, $I(t)$, and $V(t)$ are all bounded for all $t \geq 0$ at which the solution exists.*

Proof Define

$$F(t) = ke^{-p\tau}T(t) + kI(t+\tau) + \frac{p}{2}V(t+\tau),$$

and $\delta = \min\{d, \frac{p}{2}, u\}$. By nonnegativity of the solution, it follows that

$$\begin{aligned} \dot{F}(t) &= ke^{-p\tau}\left(s - dT - \frac{\beta TV}{1+aT+bV}\right) \\ &\quad + k\left(e^{-p\tau}\frac{\beta TV}{1+aT+bV} - pI(t+\tau)\right) \\ &\quad + \frac{p}{2}\big(kI(t+\tau) - uV(t+\tau)\big) \\ &= ske^{-p\tau} - dke^{-p\tau}T(t) - \frac{p}{2}kI(t+\tau) \\ &\quad - \frac{p}{2}uV(t+\tau) \\ &< ske^{-p\tau} - \delta F(t). \end{aligned}$$

This implies that $F(t)$ is bounded, and so are $T(t)$, $I(t)$, and $V(t)$. This completes the proof. □

3 Equilibria and their stabilities

It is easy to see that system (2) always has an infection-free equilibrium $E_0(T_0, 0, 0) = E_0(\frac{s}{d}, 0, 0)$. To find the positive (interior) equilibrium, set

$$R_0 = \frac{T_0}{T^*}.$$

If $R_0 > 1$, that is $\frac{sk\beta e^{-p\tau}}{aups+dpu} \triangleq R_0^* > 1$, then system (2) also has an interior equilibrium $E^*(T^*, I^*, V^*)$, where

$$T^* = \frac{pu + kbse^{-p\tau}}{(k\beta + kbd)e^{-p\tau} - aup},$$

$$I^* = \frac{s - dT^*}{pe^{p\tau}} = \frac{s(1 - \frac{1}{R_0})}{pe^{p\tau}},$$

$$V^* = \frac{kI^*}{u} = \frac{ks(1 - \frac{1}{R_0})}{pue^{p\tau}}.$$

3.1 Stability of the infection-free equilibrium E_0

Theorem 3.1

(i) *If $R_0 < 1$, then the infection-free equilibrium E_0 of system (2) is locally asymptotically stable*;
(ii) *If $R_0 = 1$, then the infection-free equilibrium E_0 of system (2) is degenerated*;
(iii) *If $R_0 > 1$, then the infection-free equilibrium E_0 of system (2) is unstable*.

Proof Consider the infection-free equilibrium $E_0(\frac{s}{d}, 0, 0)$, we calculate the linearization of system (2) at E_0 and obtain the characteristic equation

$$(\lambda + d)\left[\lambda^2 + (u + p)\lambda + pu - \frac{k\beta s}{d + as}e^{-p\tau}e^{-\lambda\tau}\right] = 0. \tag{5}$$

Obviously, $\lambda = -d < 0$ is a characteristic root of (5). Hence, the stability of E_0 is determined by the distribution of the roots of equation

$$\lambda^2 + (u + p)\lambda + pu - \frac{k\beta s}{d + as}e^{-p\tau}e^{-\lambda\tau} = 0. \tag{6}$$

When $\tau = 0$, the three assertions are obvious. Therefore, we only check the conclusions as $\tau > 0$.

If $R_0 < 1$, then $\lambda = 0$ is not a root of (6) since

$$pu - \frac{k\beta s}{d + as}e^{-p\tau} > 0.$$

Note that all roots of (6) depend continuously on τ (see [17]) and the assumption (ii) of [18] holds and this ensures $\mathrm{Re}(\lambda) < +\infty$ for any root of (6). Therefore, as the delay τ increases, the roots of (6) can only enter the right-half in the complex plane by crossing the imaginary axis. Let $\lambda = i\omega(\omega > 0)$ be a purely imaginary root of (6), then

$$-\omega^2 + i\omega(u + p) + pu = \frac{k\beta s}{d + as}e^{-p\tau}e^{-i\omega\tau}. \tag{7}$$

Taking moduli in both sides of the above equation gives

$$\omega^4 + \left(u^2 + p^2\right)\omega^2 + u^2p^2 - \left(\frac{k\beta s}{d + as}e^{-p\tau}\right)^2 = 0.$$

Let $y = \omega^2$, then

$$y^2 + \left(u^2 + p^2\right)y + u^2p^2 - \left(\frac{k\beta s}{d + as}e^{-p\tau}\right)^2 = 0. \tag{8}$$

If $R_0 < 1$, then (8) has no nonnegative real root. Therefore, there is no root $\lambda = i\omega$ with $\omega > 0$ for (6), implying that the roots of (6) cannot cross the purely imaginary axis. Hence, all roots of (6) have negative real parts provided $R_0 < 1$. This proves the conclusion (i).

If $R_0 = 1$, then (6) becomes

$$\lambda^2 + (u + p)\lambda + pu - pue^{-\lambda\tau} = 0. \tag{9}$$

It is obvious that $\lambda = 0$ is a simple root of (9). We further show that any root of (9) has a negative real part except $\lambda = 0$. If (9) has imaginary roots $\lambda = v \pm i\omega$; here, $v \geq 0, \omega \geq 0$ and $\tau > 0$. Then

$$\begin{cases} pue^{-v\tau}\cos\omega\tau = v^2 - \omega^2 + (u + p)v + pu, \\ -pue^{-v\tau}\sin\omega\tau = 2v\omega + (u + p)\omega, \end{cases}$$

which implies that

$$\left[v^2 - \omega^2 + (u + p)v + pu\right]^2 + \left[2v\omega + (u + p)\omega\right]^2 = p^2u^2e^{-2v\tau} \leq p^2u^2.$$

It is easy to see that the above inequality is not correct. So, we obtain that any root of (9) has a negative real part except $\lambda = 0$. This proves conclusion (ii).

If $R_0 > 1$, then it is easy to prove that (6) has a positive real root for all $\tau > 0$. This proves conclusion (iii). This completes the proof.

To study the globally asymptotically stability of the infection-free equilibrium E_0 of system (2), we have the following lemma. □

Lemma 3.1 *For any solution $(T(t), I(t), V(t))$ of system (2), we have that*

$$\lim_{t\to+\infty} \sup T(t) \le \frac{s}{d}.$$

Proof From the first equation of system (2), we have

$$\dot{T}(t) = s - dT(t) - \frac{\beta T(t)V(t)}{1 + aT(t) + bV(t)} \le s - dT(t).$$

So, it is easy to obtain the conclusion. This completes the proof. □

Theorem 3.2 *If $R_0 \le 1$, then the infection-free equilibrium E_0 of system (2) is globally asymptotically stable for any time delay $\tau \ge 0$.*

Proof Define

$$\Omega = \left\{ \varphi = (\varphi_1, \varphi_2, \varphi_3) \in C \,\middle|\, 0 \le \varphi_1 \le \frac{s}{d},\ \varphi_2 \ge 0,\ \varphi_3 \ge 0 \right\}.$$

From Lemma 3.1, we can see that Ω attracts all solutions of system (2). For any $\varphi = (\varphi_1, \varphi_2, \varphi_3) \in \Omega$, let $(T(t), I(t), V(t))$ be the solution of system (2) with the initial function φ. We show that for any $t \ge 0$, $T(t) \le \frac{s}{d}$. In fact, if there is $t_0 > 0$ such that $T(t_0) > \frac{s}{d}$ and $\dot{T}(t_0) > 0$, then we get

$$\begin{aligned}\dot{T}(t_0) &= s - dT(t_0) - \frac{\beta T(t_0)V(t_0)}{1 + aT(t_0) + bV(t_0)} \\ &\le -\frac{\beta T(t_0)V(t_0)}{1 + aT(t_0) + bV(t_0)} \le 0.\end{aligned}$$

This contradiction to $\dot{T}(t_0) > 0$. Hence, Ω is a positive invariant with respect to system (2).

Consider the Lyapunov function L in the region Ω as follows:

$$\begin{aligned}L(\varphi) = {} & \frac{k}{p}\varphi_2(0) + \varphi_3(0) \\ & + \frac{s\beta k e^{-p\tau}}{p(d+as)} \int_{-\tau}^{0} \varphi_3(\xi)\, d\xi. \end{aligned} \tag{10}$$

Then we have

$$\begin{aligned}&\dot{L}(\varphi)|_{(1.2)} \\ &= \frac{k\beta e^{-p\tau}}{p} \frac{\varphi_1(-\tau)\varphi_3(-\tau)}{1 + a\varphi_1(-\tau) + b\varphi_3(-\tau)} \\ &\quad - k\varphi_2(0) + k\varphi_2(0) - u\varphi_3(0) \\ &\quad + \frac{s\beta k e^{-p\tau}}{p(d+as)}\big(\varphi_3(0) - \varphi_3(-\tau)\big), \\ &= \frac{k\beta e^{-p\tau}}{p}\left(\frac{\varphi_1(-\tau)}{1 + a\varphi_1(-\tau) + b\varphi_3(-\tau)} \right. \\ &\quad \left. - \frac{s}{d+as} \right)\varphi_3(-\tau) + \left(\frac{s\beta k e^{-p\tau}}{p(d+as)} - u \right)\varphi_3(0) \\ &\le \frac{k\beta e^{-p\tau}}{p}\left(\frac{\varphi_1(-\tau)}{1 + a\varphi_1(-\tau)} - \frac{s}{d+as} \right)\varphi_3(-\tau) \\ &\quad + \left(\frac{s\beta k e^{-p\tau}}{p(d+as)} - u \right)\varphi_3(0).\end{aligned}$$

Define $G = \{\varphi \in \Omega | \dot{L}(\varphi)|_{(1.2)} = 0\}$ and let M be the largest set in G which is invariant with respect to (2). If $R_0 < 1$, that is, $R_0^* = \frac{s\beta k e^{-p\tau}}{pu(d+as)} < 1$, then we obtain

$$\dot{L}(\varphi)|_{(1.2)} \le \varphi_3(0)u\left(\frac{s\beta k e^{-p\tau}}{pu(d+as)} - 1 \right) \le 0,$$

for any $\varphi \in \Omega$. Hence, $G \subset \{\varphi \in \Omega | \varphi_3(0) = 0\}$. It follows from system (2) that $M = \{(\frac{s}{d}, 0, 0)\}$.

If $R_0 = 1$, we have

$$\begin{aligned}&\dot{L}(\varphi)|_{(1.2)} \\ &\le \frac{k\beta e^{-p\tau}}{p}\left(\frac{\varphi_1(-\tau)}{1 + a\varphi_1(-\tau)} - \frac{s}{d+as} \right)\varphi_3(-\tau) \le 0.\end{aligned}$$

Therefore, $G \subset \{\varphi \in \Omega \mid \varphi_3(-\tau) = 0 \text{ or } \varphi_1(-\tau) = \frac{s}{d}\}$. Thus, for each $t \in \mathrm{R}$, we have that

$$T(t-\tau) = \frac{s}{d} \quad \text{or} \quad V(t-\tau) = 0.$$

If $T(t-\tau) = \frac{s}{d}$ for some t, we must have that $\dot{T}(t-\tau) = 0$ by $T(t) \le \frac{s}{d}$ and the differentiability of

$T(t)$. Therefore, the first equation of (2) implies that

$$s - d\cdot\frac{s}{d} - \frac{s}{d}\frac{\beta V(t-\tau)}{1+\frac{as}{d}+bV(t-\tau)} = -\frac{s}{d}\frac{\beta V(t-\tau)}{1+\frac{as}{d}+bV(t-\tau)} = 0.$$

Hence, we have that $V(t)\equiv 0$ for any $t\in R$. By a completely similar proof as for the case $R_0<1$, we can also obtain that $M=\{(\frac{s}{d},0,0)\}$. By the LaSalle invariant principle, we know that the disease-free equilibrium $E_0(\frac{s}{d},0,0)$ of system (2) is globally asymptotically stable in the region Ω. This completes the proof. □

3.2 Stability of the infected equilibrium E^*

In this subsection, we now consider the local stability of the infected equilibrium $E^*(T^*,I^*,V^*)$ when $R_0>1$. By computation, we obtain that the associated transcendental characteristic equation of system (2) at E^* becomes

$$\lambda^3+a_2(\tau)\lambda^2+a_1(\tau)\lambda+a_0(\tau) - \big(b_1(\tau)\lambda+b_0(\tau)\big)e^{-\lambda\tau}=0, \tag{11}$$

where

$$a_2(\tau)=d+h_1+p+u,$$
$$a_1(\tau)=(d+h_1)(p+u)+pu,$$
$$a_0(\tau)=pu(d+h_1),$$
$$b_1(\tau)=kh_2e^{-p\tau},\qquad b_0(\tau)=dh_2ke^{-p\tau},$$
$$h_1=\frac{\beta V^*(1+bV^*)}{(1+aT^*+bV^*)^2},$$
$$h_2=\frac{\beta T^*(1+aT^*)}{(1+aT^*+bV^*)^2}.$$

When $\tau=0$, (11) becomes

$$\lambda^3+a_2(0)\lambda^2+\big(a_1(0)-b_1(0)\big)\lambda + a_0(0)-b_0(0)=0,$$

where

$$a_1(0)-b_1(0)=(d+h_1)(p+u)+pu-kh_2>0,$$
$$a_0(0)-b_0(0)=pu(d+h_1)-dh_2k>0,$$
$$pu-kh_2=pu-\frac{(k\beta+kbd+akbs)p^2u^2}{k\beta(pu+kbs)}>0$$

if $R_0>1$ holds.

Then

$$\begin{aligned}&a_2(0)\big(a_1(0)-b_2(0)\big)-\big(a_0(0)-b_0(0)\big)\\&\quad=(d+h_1+p+u)\big((d+h_1)(p+u)+pu-kh_2\big)\\&\qquad-d(pu-h_2k)-puh_1\\&\quad=(d+h_1)^2(p+u)+(d+h_1)\big(p^2+u^2\big)\\&\qquad+2pu\left(d+\frac{h_1}{2}\right)+(h_1+p+u)(pu-kh_2)\\&\quad>0\end{aligned}$$

under $R_0>1$. Hence, all roots of (11) have negative real parts when $\tau=0$. Note that a root of (11) depends continuously on τ([17]). Notice that also that the assumption (ii) of [18] holds and this ensures that $\mathrm{Re}(\lambda)<+\infty$ for any toot of (11). Therefore, as delay τ increases, a root of (11) can only enter the right-half of the complex plane by crossing the imaginary axis. Let $\lambda=i\omega$ with $\omega\geq 0$ be a purely imaginary root of (11). Then

$$\begin{aligned}&-\omega^3-a_2(\tau)\omega^2+a_1(\tau)\omega i+a_0(\tau)\\&\quad=\big(b_1(\tau)\omega i+b_0(\tau)\big)e^{-\tau\omega i}.\end{aligned}$$

Taking moduli in the above equation and grouping in terms of the powers of ω gives

$$\omega^6+\big(a_2^2(\tau)-2a_1(\tau)\big)\omega^4 + \big(a_1^2(\tau)-2a_0(\tau)a_2(\tau)-b_1^2(\tau)\big)\omega^2 + a_0^2(\tau)-b_0^2(\tau)=0. \tag{12}$$

Let $z=\omega^2$ and denote

$$\begin{aligned}p(\tau)&=a_2^2(\tau)-2a_1(\tau)\\&=\big((d+h_1)+p+u\big)^2-2(d+h_1)(p+u)\\&\quad-2pu\\&=(d+h_1)^2+p^2+u^2>0,\\q(\tau)&=a_1^2(\tau)-2a_0(\tau)a_2(\tau)-b_1^2(\tau)\\&=\big((d+h_1)(p+u)+pu\big)^2\\&\quad-2\big((d+h_1)+p+u\big)pu(d+h_1)\\&\quad-k^2h_2^2e^{-2p\tau}\\&=(d+h_1)^2\big(p^2+u^2\big)\\&\quad+\big(pu+kh_2e^{-p\tau}\big)\big(pu-kh_2e^{-p\tau}\big)>0,\end{aligned}$$

$$r(\tau) = a_0^2(\tau) - b_0(\tau)$$
$$= \big(pu(d+h_1)\big)^2 - \big(dh_2ke^{-p\tau}\big)^2 > 0,$$

here, $pu - kh_2e^{-p\tau} > pu - kh_2 > 0$ when $R_0 > 1$. Then, (12) becomes

$$H(z) := z^3 + p(\tau)z^2 + q(\tau)z + r(\tau) = 0. \tag{13}$$

Thus, the function $H(z)$ is monotonically increasing in $z \in [0, +\infty)$ with $H(0) = r(\tau) > 0$ and hence (13) has no real nonnegative root. This implies that no root can cross the imaginary axis as τ increases, ensuring that under $R_0 > 1$ all roots of (11) have negative real parts for all $\tau \geq 0$.

Summarizing the above, we have obtained the following theorem.

Theorem 3.3 *If $R_0 > 1$, then the infected equilibrium E^* of system (2) is locally asymptotically stable for any time delay $\tau \geq 0$.*

4 Discussion

We have studied a HIV-1 infection model with intracellular delay and Beddington–DeAngelis functional response, that is, model (2). From the theoretical results summarized above, we see that the basic reproduction number R_0 determines the dynamics of the model (2). Since $R_0 = R_0(\tau) > 1$ is equivalent to $R_0^* = R_0^*(\tau) > 1$, so we consider $R_0^*(\tau) = \frac{sk\beta e^{-p\tau}}{dpu+aups}$ as a function of τ, we see that it is decreasing in τ with $R_0^*(\infty) = 0$. An implication of this observation is that the intracellular delay τ plays a positive role in preventing the virus, because with all other parameters fixed, larger τ can bring R_0 to a level lower than 1 (regardless of either $R_0^*(0) < 1$ or $R_0^*(0) > 1$), making the infection free equilibrium globally asymptotically stable. By combining the analysis of the characteristic equation and the Lyapunov–LaSalle method, we have proved that the infection-free equilibrium E_0, corresponding to the absence of virus, is globally asymptotically stable when the basic reproduction number $R_0 < 1$, i.e., the nonlinear incidence rate and the time delay do not effect on the global stability of the viral free equilibrium, which extend the results in [13]. In this case, the virus is unable to maintain the infection and will go extinct (the uninfected cell population will converge to the value s/d). When $R_0 > 1$, E_0 becomes unstable and there occurs infection equilibrium (the endemic equilibrium) E^*. When $R_0 > 1$, $E^*$is asymptotically stable.

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