Global stability analysis of a delayed HIV model with saturated infection rate

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Abstract. In this paper, the global stability of a delayed HIV model with saturated infection rate infection is investigated. We incorporate two discrete delays into the model; the first describes the intracellular delay in the production of the infected cells, while the second describes the needed time for virions production. We also derive the global properties of this two-delay model as function of the basic reproduction number \(R_0\). By using some suitable Lyapunov functions, it is proved that the free-equilibrium point is globally asymptotically stable when \(R_0 \leq 1\), and the endemic equilibrium point is globally asymptotically stable when \(R_0 \geq 1\). Finally, in order to support our theoretical findings we have illustrate some numerical simulations.

Keywords: delay model, HIV infection, viral dynamics, global stability, numerical simulation.

1 Introduction

The human immunodeficiency virus (HIV) is a virus that gradually weakens the immune system. It is considered as the main cause for several deadly diseases after the resulting acquired immunodeficiency syndrome (AIDS) is reached. With 36.7 million people living with HIV, 2.1 million people becoming newly infected by HIV and more than 1.1 million deaths annually, HIV becomes a major global public health issue [1]. For this reason, several mathematical models describing the dynamics of HIV infection have been developed and studied [2–6]. The basic of them was suggested in [2]:

\[
\begin{align*}
\dot{x} &= \lambda - d_1 x(t) - k_1 x(t) v(t), \\
\dot{y} &= k_1 x(t) v(t) - d_2 y(t), \\
\dot{v} &= a y(t) - d_3 v(t),
\end{align*}
\]

where \(x\), \(y\) and \(v\) denote the concentration of uninfected CD4\(^+\) T cells, infected CD4\(^+\) T cells and free virus, respectively. Susceptible host cells CD4\(^+\) T cells are produced at a rate \(\lambda\), die at a rate \(d_1\) and become infected by virus at a rate \(k_1 x v\). Infected cells die at a rate \(d_2\). Finally, the free virus is produced by infected cells at a rate \(a\) and decays at a rate \(d_3\). In our model we propose to change the mass action rate in (1) by a saturated infection rate \(\frac{k_1 x(t) v(t)}{x(t) + v(t)}\), called the saturated mass action [7] which describes better the rate of viral infection, then the viral infection model becomes

\[
\begin{align*}
\dot{x}(t) &= \lambda - d_1 x(t) - \frac{k_1 x(t) v(t)}{x(t) + v(t)}, \\
\dot{y}(t) &= \frac{k_1 x(t) v(t)}{x(t) + v(t)} - d_2 y(t), \\
\dot{v}(t) &= a y(t) - d_3 v(t),
\end{align*}
\]

with the initial conditions \(x(0) = x_0\), \(y(0) = y_0\) and \(v(0) = v_0\). The theoretical analysis of the epidemic models [9–12] show that the time delay plays a crucial role in the dynamical properties of the HIV infection models, in order to study the influence of time delay on the spread of HIV, we have illustrated the following model:

\[
\begin{align*}
\dot{x}(t) &= \lambda - d_1 x(t) - \frac{k_1 x(t) v(t)}{x(t) + v(t)}, \\
\dot{y}(t) &= \frac{k_1 x(t - \tau_1) v(t - \tau_1)}{x(t - \tau_1) + v(t - \tau_1)} - d_2 y(t), \\
\dot{v}(t) &= a y(t - \tau_2) - d_3 v(t).
\end{align*}
\]

In this model, \(x\), \(y\) and \(v\) denote the concentration of uninfected cells, infected cells and free virus respectively. Where \(\tau_1\) represents the delay in the production of productively infected cells and \(\tau_2\) represents the delay in the production of virus. With the initial conditions of model (3) are given by \(x(\theta) > 0\), \(y(\theta) > 0\) and \(v(\theta) > 0\) for \(\theta \in [-\rho, 0]\), where \(\rho = \max(\tau_1, \tau_2)\).
2 Global analysis of the delay model

2.1 Steady states

For our model (2), the basic reproduction number of the virus is given by
\[ R_0 = \frac{ak_1}{d_2d_3}. \] (4)

The model (2) has two steady states:
- The disease-free steady state \( E_f = (\frac{\lambda}{d_1}, 0, 0) \).
- The endemic steady state
  \[ E^* = (x_1, y_1, v_1), \]
  where
  \[ x_1 = \frac{\lambda}{d_1 + k_1(1 - \frac{1}{R_0})}, \quad y_1 = \frac{\lambda k_1(1 - \frac{1}{R_0})}{d_2(d_1 + k_1(1 - \frac{1}{R_0}))}, \]
  and \( v_1 = \frac{\lambda(R_0 - 1)}{d_1 + k_1(1 - \frac{1}{R_0})} \).

2.2 Global analysis

In this subsection, we study the global asymptotic stability of the steady states using a suitable Lyapunov functional. For this reason, we consider the function
\[ F(x) = x - 1 - \ln(x) \forall x > 0. \]

Note that \( F(x) > 0, \forall x > 0 \) and that \( F(x) = 0 \) if and only if \( x = 1 \). We consider the positive real numbers \( x_1, x_2, ..., x_n \), then
\[ 1 - x_i + \ln x_i = -F(x_i) \leq 0, \quad \forall i = 1, ..., n \] (5)

By summing for \( i = 1, ..., n \), we get:
\[ n - \sum_{i=1}^{n} x_i + \ln \prod_{i=1}^{n} x_i \leq 0, \] (6)

If we take \( x_i = \frac{p_i}{q_i} \), we will have
\[ n - \sum_{i=1}^{n} \frac{p_i}{q_i} + \ln \prod_{i=1}^{n} \frac{p_i}{q_i} \leq 0, \] (7)

**Theorem 1** If \( R_0 \leq 1 \), then the disease-free steady state \( E_f \) is globally asymptotically stable for any delays \( \tau_1 > 0 \) and \( \tau_2 > 0 \).

**Proof.** Let the following Lyapunov functional:
\[
\begin{align*}
\mathcal{L}_1(x, y, v) &= y + \frac{d_2}{a} \dot{v} \\
&\quad + k_1 \int_{t-\tau_1}^{t} \frac{x(\xi)}{x(\xi) + v(\xi)} \, d\xi + d_2 \int_{t-\tau_2}^{t} y(\xi) \, d\xi.
\end{align*}
\]

The time derivative is given by:
\[
\dot{\mathcal{L}}_1(x, y, v) = \dot{y} + \frac{d_2}{a} \dot{v} \\
&\quad + k_1 \left( \frac{x(t)v(t)}{x(t) + v(t)} - \frac{x(t-\tau_1)v(t-\tau_1)}{x(t-\tau_1) + v(t-\tau_1)} \right) \\
&\quad + d_2 \left( y(t) - y(t-\tau_2) \right) \\
&\quad = k_1x(t)v(t) \left( \frac{1}{x(t) + v(t)} - \frac{1}{x(t-\tau_1) + v(t-\tau_1)} \right) \\
&\quad \leq k_1v(t) - \frac{d_2d_3}{a} v(t) \\
&\quad \leq \frac{d_2d_3}{a} (R_0 - 1) v(t).
\]

If \( R_0 < 1 \); then \( \dot{\mathcal{L}} \leq 0 \). Moreover, \( \dot{\mathcal{L}} \leq 0 \) when \( v = 0 \). The largest compact invariant is
\[ E = \{(x, y, v) \in R^*_+ | v = 0 \}. \]

According to LaSalle’s invariance principle, \( \lim_{t \to \infty} v(t) = 0 \), the limit system of equations is:
\[
\begin{align*}
\dot{x} &= \lambda - d_1 x \\
\dot{y} &= -d_2 y
\end{align*}
\]

We define:
\[
\mathcal{L}_1(x, y) = \frac{1}{x_0} \left( x - x_0 - x_0 \ln \frac{x}{x_0} \right) + y.
\]

Since \( x_0 = \frac{\lambda}{\lambda}, \) then
\[
\dot{\mathcal{L}}_1(x, y) = d_1 \left( 2 - \frac{x}{x_0} \right) - d_2 y.
\]

Since the arithmetic mean is greater than or equal to the geometric mean, it follows
\[ 2 - \frac{x}{x_0} - \frac{x_0}{x} \leq 0 \]

Therefore \( \dot{\mathcal{L}} \leq 0 \) and the equality holds if \( x = x_0 \) and \( y = 0 \), which complete the proof.

**Theorem 2** The endemic steady state \( E^* \) is globally asymptotically stable when \( R_0 > 1 \), for any delays \( \tau_1 > 0 \) and \( \tau_2 > 0 \).

**Proof.** Let the following Lyapunov functional:
\[
\begin{align*}
\mathcal{L}_2(x, y, v) &= x - x_1 - \int_{x_1}^{x} \frac{d_2y_1}{u_1v_1} \, du + y - y_1 \\
&\quad - y_1 \ln \frac{y}{y_1} + \frac{d_2}{a} \left( v - v_1 - v_1 \ln \frac{v}{v_1} \right) \\
&\quad + k_1 \int_{x_1v_1}^{x} F(x(\xi)v(\xi)) \, d\xi \int_{x_1v_1}^{x} \frac{x_1v_1}{x(\xi) + v(\xi)} \, d\xi \\
&\quad + d_2y_1 \int_{x_1v_1}^{x} F(y(\xi)/y_1) \, d\xi.
\end{align*}
\]
then, we have
\[
\dot{L}_2(x, y, v) = -\frac{d_1y_1}{x(x_1 + v)}(x - x_1)^2 \\
- (d_2 + k_2)y_1 \left( \frac{x(v - v_1)^2}{v_1(x + v_1)(x + v)} \right) \\
+ d_2y_1 \left( 4 - \frac{x_1 + v_1}{x_1} - \frac{y_1}{y} \right)y_1 \\
\times \frac{x_1 + v_1}{x(t - \tau_1) + v(t - \tau_1) - y_1} \\
+ \ln \left( \frac{x(t - \tau_1) + v(t - \tau_1)}{x(t - \tau_1) + v(t - \tau_1)} \right) \\
\frac{y(t - \tau_2)}{y} \right),
\]
Taking \( p_1 = x_1(x + v_1), p_2 = y_1(x(t - \tau_1)v(t - \tau_1)), \)
\( p_3 = y(t - \tau_2)v_1, p_4 = x + v, q_1 = x(x_1 + v_1), q_2 = y(x_1v_1), q_3 = y_1v, q_4 = x + v_1 \) and using the inequality
(7) for \( n = 4 \), we obtain
\[
4 - \frac{x_1 + v_1}{x_1} - \frac{y_1}{y} \left( \frac{x(t - \tau_1)v(t - \tau_1)}{x(t - \tau_1) + v(t - \tau_1)} - \frac{x_1}{x_1} - \frac{y_1}{y} \right) \leq 0
\]
Therefore, \( \dot{L}_2 \leq 0 \). Assume that \( M \) is the largest invariant set in \( (x, y, v) | \dot{L}_2 = 0 \). Note that \( \dot{L}_2 = 0 \) if and only if \( x = x_1, y = y_1 \) and \( v = v_1 \). Hence, \( M = E^* \). Since \( E^* \) exists whenever \( R_0 > 1 \), then by the Lyapunov-LaSalle invariance theorem \( E^* \) is globally asymptotically stable if \( R_0 > 1 \).

### 3 Numerical results and simulations

In order to perform the numerical simulations, the system (1.1) will be solved numerically using the fourth order Runge-Kutta iterative scheme. The used parameter values are taken from Table 1.

Figure 1 represents the uninfected cells, the infected cells and the virus as function of time. The solid curves represent the case of \((\tau_1, \tau_2) = (5, 5), (10, 10)\) and \((30, 30)\). For the parameters used in this figure, the basic reproduction number is \( R_0 = 0.39 < 1 \); we clearly see that the delays do not affect the global asymptotic stability behavior of the disease-free equilibrium point \( E_1 = (719.42, 0, 0) \). This numerical result is consistent with the theoretical result concerning the stability of \( E_1 \). Finally, Fig. 2 represents the uninfected cells, the infected cells and the virus as function of time. The solid curves represent the case of \((\tau_1, \tau_2) = (5, 5), (10, 10)\) and \((30, 30)\). For the parameters used in this figure, the basic reproduction number is \( R_0 = 19.98 > 1 \); we clearly see that the magnitude of the two delays does not affect the global asymptotic stability of the endemic equilibrium point \( E^* = (214.49, 172.09, 2.97 \times 10^4, 0, 0) \). This numerical result is consistent with the theoretical result concerning the stability of \( E^* \).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Meaning</th>
<th>Value</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \lambda )</td>
<td>Source rate of CD4+ T cells</td>
<td>([0, 10])</td>
<td>[5]</td>
</tr>
<tr>
<td>( k_1 )</td>
<td>Average of infection</td>
<td>([2.5 \times 10^{-4}, 0.5])</td>
<td>[3]</td>
</tr>
<tr>
<td>( d_1 )</td>
<td>Decay rate of healthy cells</td>
<td>0.0139</td>
<td>[3]</td>
</tr>
<tr>
<td>( d_2 )</td>
<td>Death rate of infected CD4+ T cells</td>
<td>0.5776</td>
<td>[3]</td>
</tr>
<tr>
<td>( a )</td>
<td>The rate of production the virus by infected CD4+ T cells</td>
<td>([2, 1250])</td>
<td>[3]</td>
</tr>
<tr>
<td>( d_3 )</td>
<td>Clearance rate of virus</td>
<td>([0.3466, 2.4])</td>
<td>[3]</td>
</tr>
</tbody>
</table>

**Fig. 1.** The behavior of the infection dynamics for \( \lambda = 10, d_1 = 0.0139, k_1 = 0.04, d_2 = 0.5776, a = 2, d_3 = 0.3466 \)
and \( D_1 : (\tau_1, \tau_2) = (5, 5); D_2 : (\tau_1, \tau_2) = (10, 10); D_3 : (\tau_1, \tau_2) = (30, 30) \).
time for the virus production. These two delays have been included in the model to check if these delays can affect the global stability. The results show that inclusion of these delays does not influence the global dynamics of the delay model. Finally, the numerical simulations are performed in order to show the behavior of infection during the days of observation and to support the theoretical findings.

References