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Research Article

A Discrete Model for HIV Infection with Distributed Delay

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We give a consistent discretization of a continuous model of HIV infection, with distributed time delays to express the lag between the times when the virus enters a cell and when the cell becomes infected. The global stability of the steady states of the model is determined and numerical simulations are presented to illustrate our theoretical results.

1. Introduction

Nowadays, human immunodeficiency virus (HIV) that causes acquired immunodeficiency syndrome (AIDS) is a major health problem worldwide. From the World Health Organization (WHO), more than 35 million people are living with HIV/AIDS, and 1.6 million people died of this disease in 2012 [1]. Recent studies have been developed to know the dynamics of HIV infection, such as [2–9]. All these studies are based on continuous mathematical models. In reality, the statistical data are collected in discrete time, and the numerical simulations of continuous-time models are obtained by discretizing the models.

In this paper, we consider the model presented in [9] and we ignore the effect of the adaptive immune response. This model becomes as follows:

$$\begin{aligned} \dot{x}(t) &= \lambda - dx(t) - \beta x(t) v(t), \\ \dot{y}(t) &= \beta \int_0^\theta f(\tau) e^{-m\tau} x(t-\tau) v(t-\tau) d\tau - ay(t), \\ \dot{v}(t) &= ky(t) - \mu v(t), \end{aligned} \tag{1}$$

where $x(t)$, $y(t)$, and $v(t)$ denote the concentration of uninfected cells, infected cells, and free virus particles at time t, respectively. The uninfected cells are produced at a constant λ, die at a rate dx, and become infected by free virus at a rate βxv. Infected cells are lost at a rate ay. Free viruses are produced by infected cells at a rate ky and cleared at a rate μv. The authors [9] assumed that the uninfected cells are contacted by the virus particles at time $t-\tau$ and become infected cells at time t, where τ is a random variable with a probability distribution $f(\tau)$ over the interval $[0,\theta]$ and θ is limit superior of this delay. This probability distribution is assumed, for simplicity, to be a positive and integrable function on $[0,\theta]$, satisfying $\int_0^\theta f(\tau)d\tau = 1$. The term $e^{-m\tau}$ is the probability of surviving from time $t-\tau$ to time t, where m is the death rate of infected but not yet virus-producing cells.

Using the result presented in [9], it is not hard to see that the basic reproduction number of system (1) is given by $R_0^* = (\lambda k\beta/ad\mu)\int_0^\theta f(\tau)e^{-m\tau}d\tau$.

We recall that the number R_0^* is defined as the average number of secondary infections produced by one infected cell over its average life time, when all cells are uninfected.

In addition, the system (1) always has a disease-free equilibrium $E_0(\lambda/d,0,0)$ which is globally asymptotically stable if $R_0^* \le 1$ and a unique endemic equilibrium $E^*((\lambda/d)(1/R_0^*),(\mu d/k\beta)(R_0^*-1),(d/\beta)(R_0^*-1))$ is globally asymptotically stable when $R_0^* > 1$.

Motivated by the works [10–15] and that the statistical data are collected in discrete time, we propose the following discrete model obtained from (1) by using the rectangle method to approximate the integral and by applying the backward Euler discretization:

$$\frac{x_{n+1}-x_n}{h} = \lambda - dx_{n+1} - \beta x_{n+1} v_{n+1},$$
$$\frac{y_{n+1}-y_n}{h} = \beta \sum_{i=0}^{N} f(i) e^{-mi} x(n-i) v(n-i) - a y_{n+1}, \quad (2)$$
$$\frac{v_{n+1}-v_n}{h} = k y_{n+1} - \mu v_{n+1},$$

where $N = \theta - 1$ if θ is an integer, and if not, N is the integer part of θ ($N = [\theta]$). The sequences x_n, y_n, and v_n denote the concentration of uninfected cells, infected cells, and free virus particles at time n, respectively. The parameters in the system (2) are the same as those in (1). For simplicity, we may assume that $\sum_{i=0}^{N} f(i) = 1$. Similar to the continuous system (1), system (2) always has a disease-free equilibrium $E_0(\lambda/d, 0, 0)$ and an endemic equilibrium point $E^*((\lambda/d)(1/R_0), (\mu d/k\beta)(R_0 - 1), (d/\beta)(R_0 - 1))$, where R_0 is the basic reproduction number of (2) which is defined by

$$R_0 = \frac{\lambda k \beta}{a d \mu} \sum_{i=0}^{N} f(i) e^{-mi}. \quad (3)$$

The aim of this work is to show that the discretization scheme used in system (2) preserves the positivity and boundedness of solutions and the global stability of both equilibria for the continuous model (1). Therefore, this discretization is dynamically consistent which means that all of the critical, qualitative properties of the solutions to the system of differential equations should also be satisfied by the solutions of the discrete scheme.

The paper is organized as follows. Section 2 deals with positivity and boundedness of solutions. In Section 3, we discuss the global stability of the equilibria. The numerical simulations are presented in Section 4 and the paper ends with a conclusion in Section 5.

2. Positivity and Boundedness of Solutions

Model (2) describes the evolution of a cell population that the cell number is nonnegative and bounded. For these biological reasons, we assume that the initial data for system (2) satisfy

$$x(s) \geq 0, \quad y(s) \geq 0, \quad v(s) \geq 0 \quad \forall s = -N, -(N-1), \ldots, 0. \quad (4)$$

Proposition 1. *All solution of system* (2) *subject to condition* (4) *remains nonnegative and bounded.*

Proof. From (2), we have

$$x_{n+1} = \frac{\lambda h + x_n}{1 + dh + \beta h v_{n+1}}$$
$$y_{n+1} = \frac{y_n + h\beta \sum_{i=0}^{N} f(i) e^{-mi} x(n-i) v(n-i)}{1 + ah} \quad (5)$$
$$v_{n+1} = \frac{v_n + hk y_{n+1}}{1 + h\mu}.$$

Hence, by recurrence and (4), we have y_n nonnegative and, thereafter, v_n and x_n are nonnegative.

For the boundedness, we put $T_n = e^m x_n + y_n + h\beta \sum_{i=0}^{N} f(i) \sum_{j=n-i}^{n} e^{-m(n-j)} x(j) v(j)$.

We have

$$\begin{aligned} T_{n+1} - T_n &= h e^m [\lambda - d x_{n+1} - \beta x_{n+1} v_{n+1}] \\ &\quad + h \left[\beta \sum_{i=0}^{N} f(i) e^{-mi} x(n-i) v(n-i) - a y_{n+1} \right] \\ &\quad + h\beta \sum_{i=0}^{N} f(i) \sum_{j=n+1-i}^{n+1} e^{-m(n+1-j)} x(j) v(j) \\ &\quad - h\beta \sum_{i=0}^{N} f(i) \sum_{j=n-i}^{n} e^{-m(n-j)} x(j) v(j) \\ &= h [e^m \lambda - e^m d x_{n+1} - a y_{n+1}] \\ &\quad + h [1 - e^m] \beta \sum_{i=0}^{N} f(i) \sum_{j=n+1-i}^{n+1} e^{-m(n+1-j)} x(j) v(j) \\ &\leq h [\lambda e^m - \delta T_{n+1}], \end{aligned} \quad (6)$$

with $\delta = \inf\{d, a, (e^m - 1)/h\}$. Then,

$$\begin{aligned} T_{n+1} &\leq \left(\frac{1}{1+h\delta}\right)^{(n+1)} T_0 + \frac{\lambda e^m}{\delta} \left(1 - \left(\frac{1}{1+h\delta}\right)^{(n+1)}\right) \\ &\leq T_0 + \frac{\lambda e^m}{\delta}. \end{aligned} \quad (7)$$

Then, x_n and y_n are bounded.

By the third equation of (2), we have $v_{n+1} = (1/(1 + h\mu))v_n + (hk/(1 + h\mu))y_{n+1}$. Since y_n is bounded, then there is M such that $y_n \leq M$, for all $n \in \mathbb{N}$. Then, $v_{n+1} \leq (1/(1 + h\mu))v_n + (hk/(1 + h\mu))M$; hence, $v_{n+1} \leq (1/(1 + h\mu))^{n+1} v_0 + (kM/\mu)[1 - (1/(1 + h\mu))^{n+1}] \leq v_0 + (kM/\mu)$, and then v_n is bounded. □

3. Global Stability

In this section, we will give the following main result that characterizes the global behavior of our model.

Theorem 2.

(i) *If $R_0 \leq 1$, then E_0 is globally asymptotically stable.*

(ii) *$R_0 > 1$; then E^* is globally asymptotically stable.*

Proof. For (i), we consider the following sequence $\{U_n\}_{n=0}^{+\infty}$ defined by

$$\begin{aligned} U_n &= A x^* g\left(\frac{x_n}{x^*}\right) + y_n \\ &\quad + h\beta \sum_{i=0}^{N} f(i) e^{-mi} \left[\sum_{j=0}^{i} x(n-j) v(n-j) \right] + \frac{a}{k} v_n, \end{aligned} \quad (8)$$

with $A = \sum_{i=0}^{N} f(i) e^{-mi}$, $x^* = \lambda/d$, and $g(s) = s - 1 - \ln(s)$.

It is clear that $g(s) \geq 0$ for any $s > 0$ and g has the global minimum $g(1) = 0$.

Consider

$$\begin{aligned}
U_{n+1} - U_n &= Ax^* \left[\frac{x_{n+1}}{x^*} - \frac{x_n}{x^*} + \ln\left(\frac{x_n}{x_{n+1}}\right) \right] + y_{n+1} - y_n \\
&\quad + h\beta \sum_{i=0}^{N} f(i) e^{-mi} [x(n+1) v(n+1) \\
&\quad - x(n-i) v(n-i)] \\
&\quad + \frac{a}{k} [v_{n+1} - v_n] \\
&\leq A \left[(x_{n+1} - x_n) \left(1 - \frac{x^*}{x_{n+1}}\right) \right] + y_{n+1} - y_n \\
&\quad + h\beta \sum_{i=0}^{N} f(i) e^{-mi} [x(n+1) v(n+1) \\
&\quad - x(n-i) v(n-i)] \\
&\quad + \frac{a}{k} [v_{n+1} - v_n] \\
&\leq hA \left(1 - \frac{x^*}{x_{n+1}}\right) [\lambda - dx_{n+1} - \beta x_{n+1} v_{n+1}] \\
&\quad + h\beta \sum_{i=0}^{N} f(i) e^{-mi} x(n-i) v(n-i) - hay_{n+1} \\
&\quad + h\beta \sum_{i=0}^{N} f(i) e^{-mi} [x(n+1) v(n+1) \\
&\quad - x(n-i) v(n-i)] \\
&\quad + h\frac{a}{k} [ky_{n+1} - \mu v_{n+1}].
\end{aligned} \tag{9}$$

Since $x^* = \lambda/d$, we have that

$$\begin{aligned}
&U_{n+1} - U_n \\
&\leq h \Bigg[-\frac{A}{x_{n+1}} (x_{n+1} - x^*)^2 \\
&\quad - A\beta x_{n+1} v_{n+1} + A\beta x^* v_{n+1} \\
&\quad + \beta \sum_{i=0}^{N} f(i) e^{-mi} x(n-i) v(n-i) \\
&\quad - \frac{a\mu}{k} v_{n+1} + \left(\beta \sum_{i=0}^{N} f(i) e^{-mi}\right) x(n+1) v(n+1) \\
&\quad - \beta \sum_{i=0}^{N} f(i) e^{-mi} [x(n-i) v(n-i)] \Bigg] \\
&\leq h \left[-\frac{A}{x_{n+1}} (x_{n+1} - x^*)^2 - (1 - R_0) \frac{a\mu}{k} v_{n+1} \right] \leq 0.
\end{aligned} \tag{10}$$

We consider the set $S = \{(x_n, y_n, v_n) \in \mathbb{R}_+^3 / U_{n+1} - U_n = 0\}$.

We have $(x_n, y_n, v_n) \in S \Rightarrow x_n = x^*$ and, by (2), we have $y_n = v_n = 0$. By LaSalle's invariance principle (see [16, Theorem 4.24]), we have E_0 that is globally asymptotically stable. □

For (ii), we consider the following sequence $\{w_n\}_{n=0}^{+\infty}$ defined by

$$\begin{aligned}
w_n &= x^* g\left(\frac{x_n}{x^*}\right) + \frac{1}{A} y^* g\left(\frac{y_n}{y^*}\right) + \frac{\beta x^* v^*}{A} \\
&\quad \times h \sum_{i=0}^{N} f(i) e^{-mi} \sum_{j=0}^{i} g\left(\frac{x(n-j) v(n-j)}{x^* v^*}\right) \\
&\quad + \frac{a}{kA} v^* g\left(\frac{v_n}{v^*}\right),
\end{aligned} \tag{11}$$

with $x^* = \lambda/dR_0$, $y^* = \mu d/k\beta(R_0 - 1)$, and $v^* = d/\beta(R_0 - 1)$.

Consider

$$\begin{aligned}
&w_{n+1} - w_n \\
&= x^* \left[\frac{x_{n+1} - x_n}{x^*} + \ln\left(\frac{x_n}{x_{n+1}}\right) \right] \\
&\quad + \frac{y^*}{A} \left[\frac{y_{n+1} - y_n}{y^*} + \ln\left(\frac{y_n}{y_{n+1}}\right) \right] \\
&\quad + \frac{\beta x^* v^*}{A} h \sum_{i=0}^{N} f(i) e^{-mi} \\
&\quad \times \sum_{j=0}^{i} \left(\frac{x(n+1-j) v(n+1-j) - x(n-j) v(n-j)}{x^* v^*} \right) \\
&\quad + \frac{\beta x^* v^*}{A} h \\
&\quad \times \sum_{i=0}^{N} f(i) e^{-mi} \sum_{j=0}^{i} \left(\ln\left(\frac{x(n-j) v(n-j)}{x(n+1-j) v(n+1-j)} \right) \right) \\
&\quad + \frac{av^*}{kA} \left[\frac{v_{n+1} - v_n}{v^*} + \ln\left(\frac{v_n}{v_{n+1}}\right) \right] \\
&\leq \left[(x_{n+1} - x_n) \left(1 - \frac{x^*}{x_{n+1}}\right) \right] \\
&\quad + \frac{1}{A} \left[(y_{n+1} - y_n) \left(1 - \frac{y^*}{y_{n+1}}\right) \right] \\
&\quad + \frac{\beta x^* v^*}{A} h \\
&\quad \times \sum_{i=0}^{N} f(i) e^{-mi} \left(\frac{x(n+1) v(n+1) - x(n-i) v(n-i)}{x^* v^*} \right) \\
&\quad + \frac{\beta x^* v^*}{A} h \\
&\quad \times \sum_{i=0}^{N} f(i) e^{-mi} \sum_{j=0}^{i} \left(\ln\left(\frac{x(n-j) v(n-j)}{x(n+1-j) v(n+1-j)} \right) \right)
\end{aligned}$$

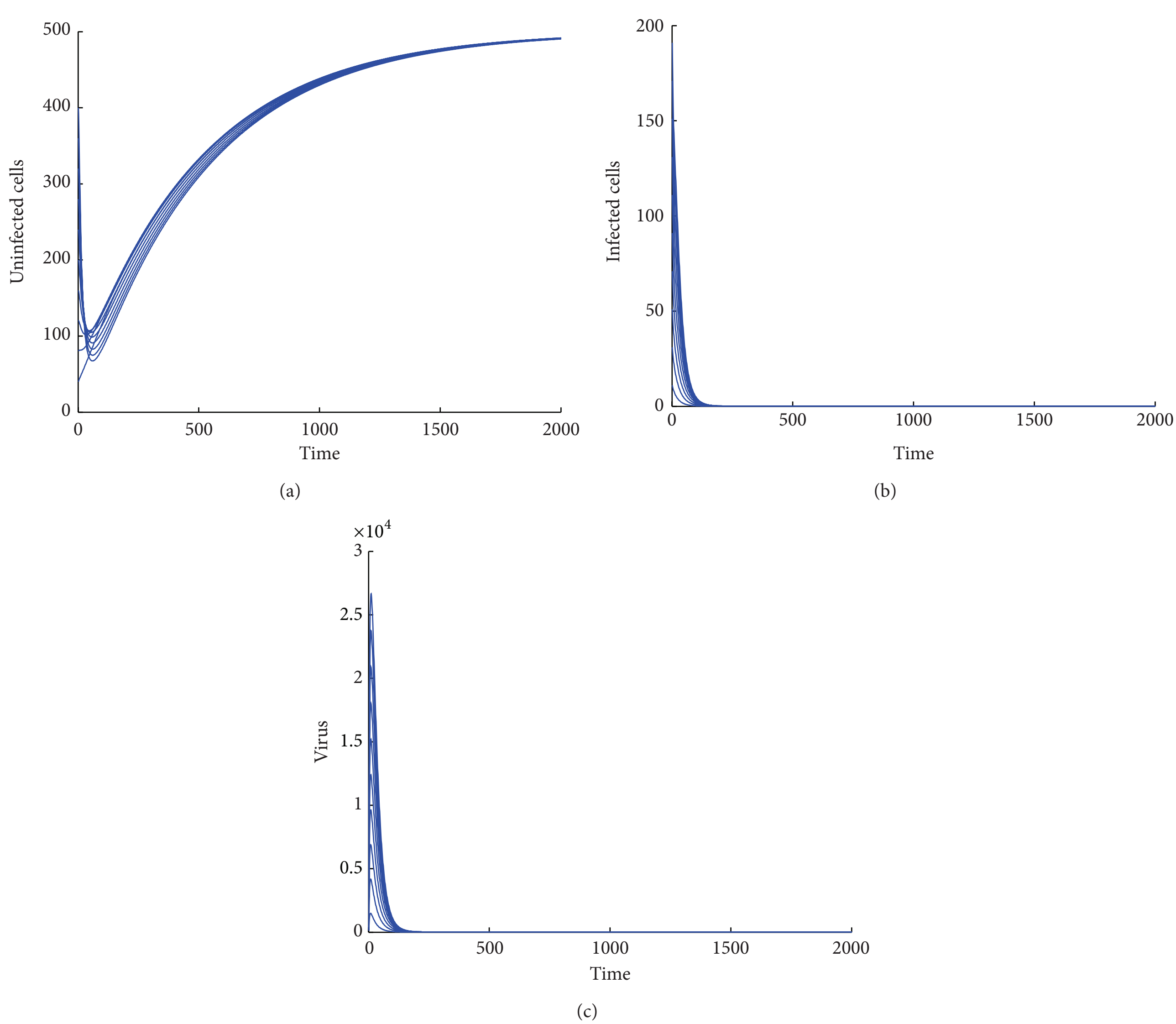

FIGURE 1: Demonstration of the stability of E_0.

$$
\begin{aligned}
&+\frac{a}{kA}\left[\left(v_{n+1}-v_{n}\right)\left(1-\frac{v^{*}}{v_{n+1}}\right)\right]\\
&\le h\Bigg[\left[\left(\lambda-dx_{n+1}-\beta x_{n+1}v_{n+1}\right)\left(1-\frac{x^{*}}{x_{n+1}}\right)\right]\\
&\quad+\frac{1}{A}\left[\left(\beta\sum_{i=0}^{N}f\left(i\right)e^{-mi}x\left(n-i\right)v\left(n-i\right)-ay_{n+1}\right)\right.\\
&\qquad\left.\times\left(1-\frac{y^{*}}{y_{n+1}}\right)\right]\\
&\quad+\beta x_{n+1}v_{n+1}-\frac{\beta x^{*}v^{*}}{A}\\
&\quad\times\sum_{i=0}^{N}f\left(i\right)e^{-mi}\left(\frac{x\left(n-i\right)v\left(n-i\right)}{x^{*}v^{*}}\right)\\
&\quad+\frac{\beta x^{*}v^{*}}{A}\sum_{i=0}^{N}f\left(i\right)e^{-mi}\left(\ln\left(\frac{x\left(n-i\right)v\left(n-i\right)}{x\left(n+1\right)v\left(n+1\right)}\right)\right)\\
&\quad+\frac{a}{kA}\left[\left(ky_{n+1}-\mu v_{n+1}\right)\left(1-\frac{v^{*}}{v_{n+1}}\right)\right]\Bigg].
\end{aligned}
\tag{12}
$$

Using the fact that $\lambda = dx^* + \beta x^* v^*$, we have

$$
\begin{aligned}
&w_{n+1}-w_{n}\\
&\le h\left[\frac{-d}{x_{n+1}}\left(x_{n+1}-x^{*}\right)^{2}+\beta x^{*}v^{*}-\beta x^{*}v^{*}\frac{x^{*}}{x_{n+1}}\right.\\
&\quad-\frac{\beta y^{*}}{Ay_{n+1}}\sum_{i=0}^{N}f\left(i\right)e^{-mi}x\left(n-i\right)v\left(n-i\right)+\frac{a}{A}y^{*}
\end{aligned}
$$

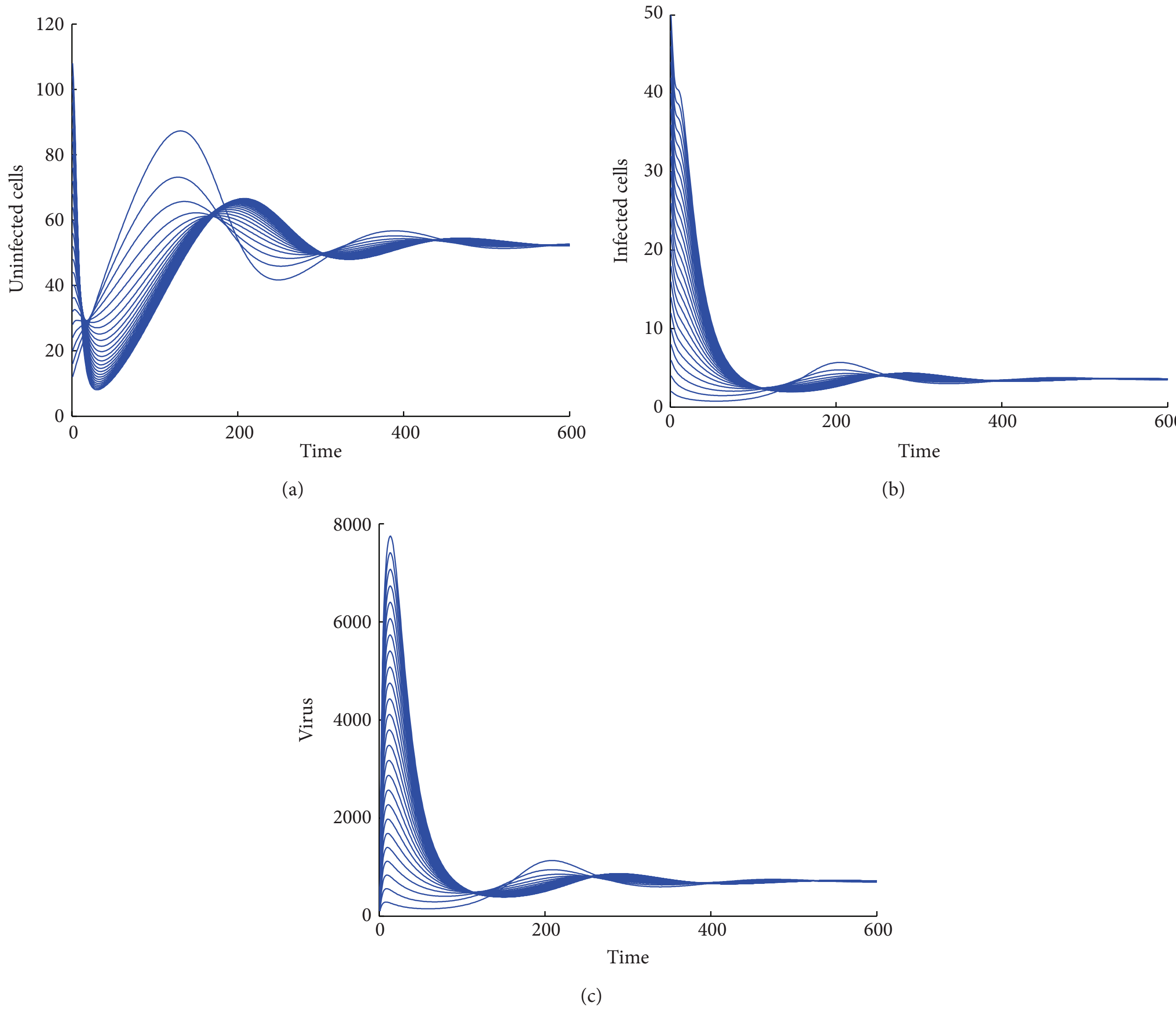

FIGURE 2: Demonstration of the stability of E^*.

$$+\frac{\beta x^* v^*}{A}\sum_{i=0}^{N} f(i)\, e^{-mi}\left(\ln\left(\frac{x(n-i)\,v(n-i)}{x(n+1)\,v(n+1)}\right)\right) + \frac{a}{kA}\left[\frac{-kv^* y_{n+1}}{v_{n+1}} + \mu v^*\right]\Bigg]. \tag{13}$$

Using the relations $\ln(x(n-i)v(n-i)/x(n+1)v(n+1)) = \ln(x(n-i)v(n-i)y^*/x^*v^*y(n+1)) + \ln(x^*/x(n+1)) + \ln(v^*y(n+1)/v(n+1)y^*)$, $\beta A x^* v^* = ay^*$, and $ky^* = \mu v^*$, we obtain

$$\begin{aligned} w_{n+1} - w_n &\le h\Bigg[\frac{-d}{x_{n+1}}(x_{n+1}-x^*)^2 - \beta x^* v^* \times \left[\frac{x^*}{x_{n+1}} - 1 - \ln\left(\frac{x^*}{x_{n+1}}\right)\right] \\ &\quad - \frac{\beta x^* v^*}{A} \times \sum_{i=0}^{N} f(i)\, e^{-mi}\left[\frac{x(n-i)\,v(n-i)\,y^*}{x^* v^* y_{n+1}} - 1 - \ln\left(\frac{x(n-i)\,v(n-i)\,y^*}{x^* v^* y_{n+1}}\right)\right] \\ &\quad - \beta x^* v^*\left[\frac{v^*}{y^*}\frac{y_{n+1}}{v_{n+1}} - 1 - ln\left(\frac{v^*}{y^*}\frac{y_{n+1}}{v_{n+1}}\right)\right]\Bigg] \\ &\le h\Bigg[\frac{-d}{v_{n+1}}(x_{n+1}-x^*)^2 - \beta x^* v^* g\left(\frac{x^*}{x_{n+1}}\right) \\ &\quad - \frac{\beta x^* v^*}{A}\sum_{i=0}^{N} f(i)\, e^{-mi} g\left(\frac{x(n-i)\,v(n-i)\,y^*}{x^* v^* y_{n+1}}\right) \\ &\quad - \beta x^* v^* g\left(\frac{v^*}{y^*}\frac{y_{n+1}}{v_{n+1}}\right)\Bigg] \end{aligned} \tag{14}$$

since $g(s) \ge 0$ for any $s > 0$; then $w_{n+1} - w_n \le 0$.

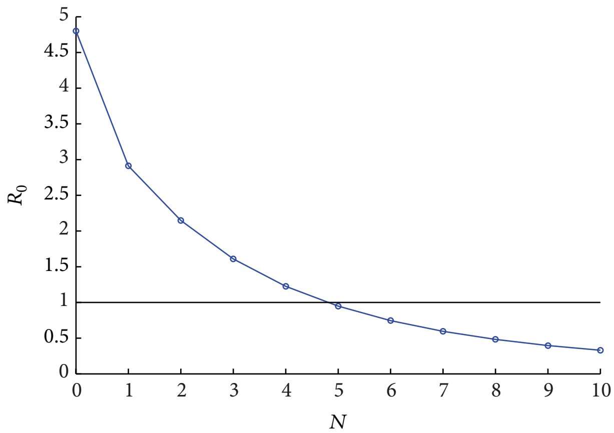

FIGURE 3: Plot of the basic reproduction number R_0 as a function of the delay N. Here, $\lambda = 10$, $d = 0.02$, $\beta = 0.000024$, $m = 0.5$, $a = 0.5$, $k = 600$, $\mu = 3$, and $h = 0.1$.

We consider the set $T = \{(x_n, y_n, v_n) \in \mathbb{R}^3_+ / w_{n+1} - w_n = 0\}$.

We have $(x_n, y_n, v_n) \in T \Rightarrow x_n = x^*$ and, by (2), we have $y_n = y^*$ and $v_n = v^*$. From LaSalle's invariance principle, we deduce that E^* is globally asymptotically stable.

4. Numerical Simulations

In this section, we present the numerical simulations to illustrate our theoretical results. In this section, we choose $f(x) = 2x/N(N+1)$. First, we use the following data set: $\lambda = 10$, $d = 0.02$, $\beta = 0.000024$, $m = 0.5$, $a = 0.5$, $k = 600$, $\mu = 3$, $N = 5$, and $h = 0.1$. In this case, the basic infection reproduction number R_0 is 0.9483. By using Theorem 2 (i), we deduce that E_0 is globally asymptotically stable. Numerical simulation illustrates our result (see Figure 1).

In Figure 2, we choose $\beta = 0.00024$ and do not change the other parameter values. By calculation, we have $R_0 = 9.4830$ which satisfies the condition (ii) of Theorem 2. Hence, E^* is globally asymptotically stable. Numerical simulation illustrates our result (see Figure 2).

In Figure 3, the parameter values are the same as those in Figure 1. Figure 3 gives R_0 in function of N and shows that the growth of N decreases the value of R_0 below 1, making the disease-free equilibrium globally asymptotically stable.

5. Conclusion

In this work, we have proposed a discrete mathematical model of HIV infection by applying the backward Euler discretization, with distributed time delay. We have proved that, when $R_0 \leq 1$, the disease-free equilibrium E_0 is globally asymptotically stable. When $R_0 > 1$, the endemic equilibrium E^* is globally asymptotically stable. More precisely, it is proved that this discretization guarantees the correct dynamic behavior regardless of the size of the time step.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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