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ORIGINAL ARTICLE

A numerical method for a delayed viral infection model with general incidence rate

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Abstract In this paper, we construct a numerical method for a delayed viral infection model with general incidence rate. We prove that the obtained discrete model has the same dynamics as the corresponding continuous model, such as positivity, boundedness and global behaviors of solutions with no restriction on the time step size. Furthermore, numerical simulations are given to illustrate and confirm our main analytical results.

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1. Introduction

In recent years, several authors are interested in the study of the dynamics of viral infections by proposing the continuous mathematical models with delays and different forms of incidence rate, such as mass action process (Zhu and Zou, 2008; Li and Shu, 2010; Hattaf and Yousfi, 2011; Vargas-De-León, 2012), standard incidence function (Gourley et al., 2008; Eikenberry et al., 2009; Tian and Xu, 2010), saturated mass action (Li and Ma, 2007; Xu, 2011), Beddington–DeAngelis functional response (Huang et al., 2011; Xiang et al., 2013) and Crowley–Martin functional response (Zhou and Cui, 2011). In 2013, the authors (Hattaf et al. (2013)) have generalized all previous forms by proposing the following model:

$$\begin{cases} \dot{x}(t) = \lambda - dx(t) - f(x(t), y(t), v(t))v(t), \\ \dot{y}(t) = f(x(t-\tau_1), y(t-\tau_1), v(t-\tau_1))v(t-\tau_1)e^{-\alpha_1\tau_1} - ay(t), \\ \dot{v}(t) = ky(t-\tau_2)e^{-\alpha_2\tau_2} - uv(t), \end{cases} \tag{1}$$

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 parameter λ is the recruited rate of uninfected cells, k is the production rate of free virus by infected cells, d, a and u are, respectively, the death rates of uninfected cells, infected cells and free virus. The first delay τ_1 represents the time needed for infected cells to produce virions after viral entry and the factor $e^{-\alpha_1\tau_1}$ accounts for the probability of surviving from time $t-\tau_1$ to time t, where α_1 is the death rate for infected but not yet virus-producing cells. The second delay τ_2 denotes the time necessary for the newly produced virions to become mature and then infectious particles. The probability

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of survival of immature virions is given by $e^{-\alpha_2\tau_2}$ and the average life time of an immature virus is given by $\frac{1}{\alpha_2}$. The incidence function $f(x,y,v)$ is assumed to be continuously differentiable in the interior of $\mathbb{R}^3_+$ and satisfies the three fundamental hypotheses given in Hattaf et al. (2012) and used in Hattaf et al. (2014), Hattaf and Yousfi (2014) and Wang et al. (2013), that are:

$$f(0,y,v)=0, \quad \text{for all } y\geqslant 0 \text{ and } v\geqslant 0, \tag{H1}$$

$$\frac{\partial f}{\partial x}(x,y,v)>0, \quad \text{for all } x>0,\ y\geqslant 0 \text{ and } v\geqslant 0, \tag{H2}$$

$$\frac{\partial f}{\partial y}(x,y,v)\leqslant 0 \text{ and } \frac{\partial f}{\partial v}(x,y,v)\leqslant 0, \quad \text{for all } x\geqslant 0,\ y\geqslant 0 \text{ and } v\geqslant 0. \tag{H3}$$

From the biological point of view, the three hypotheses are reasonable. Indeed, the first means that the incidence rate is equal to zero if there are no susceptible cells. The second one signifies that the incidence rate is increasing when the numbers of infected cells and virus are constant and the number of susceptible cells increases. Hence, the second hypothesis means the more the amount of susceptible cells, the more the average number of cells which are infected by each virus in the unit time will occur. Similarly, the third assumption means the more the amount of infected cells or virus, the less the average number of cells which are infected by each virus in the unit time will be. On the other hand, the infectious process is not instantaneous. For this reason, we choose to use delay differential equations in order to take into account the time needed for infected cells to produce new virions after viral entry and the time necessary for the newly produced virions to become mature and infectious.

In Hattaf et al. (2013), Hattaf et al. proved the positivity and boundedness of solutions. Also, they identified the basic reproduction number of model (1) as follows

$$R_0=\frac{k}{au}f\left(\frac{\lambda}{d},0,0\right)e^{-\alpha_1\tau_1-\alpha_2\tau_2}.$$

Moreover, they established the global stability of equilibria.

In reality, scientists often collect the data and analyze the results at discrete times. In addition, the numerical simulations of continuous models are obtained by discretizing these models. For these reasons, we will discretize the model (1) by using 'mixed' Euler method which is a mixture of both forward and backward Euler methods. Furthermore, we will show that the discrete model obtained by the mixed Euler method maintains essential dynamical properties, such as positivity, boundedness and global behaviors of solutions with no restriction on the time step size.

The remainder of this paper is organized as follows. In the next section, we introduce our discrete virus dynamics model with general and two delays, and establish some preliminary results. The stability of the disease-free equilibrium and the chronic infection equilibrium of the new delayed discrete model is investigated in Sections 3 and 4. Numerical simulations are given to verify the main theoretical results in Section 5. The paper ends with a conclusion in Section 6.

2. Delayed discrete model and preliminaries

Let h be a time step size. Assume that there exist integers $(m_1,\ m_2)\in\mathbb{N}$ with $\tau_1=m_1h$ and $\tau_2=m_2h$. The grids points are $t_n=nh$ for $n\in\mathbb{N}$. By applying both forward and backward Euler methods and using the approximations $x(t_n)\approx x_n,\ y(t_n)\approx y_n$ and $v(t_n)\approx v_n$, we obtain the following delayed discrete model

$$\begin{cases} x_{n+1}=x_n+h(\lambda-dx_{n+1}-f(x_{n+1},y_n,v_n)v_n),\\ y_{n+1}=y_n+h\big(f(x_{n-m_1+1},y_{n-m_1},v_{n-m_1})v_{n-m_1}e^{-\alpha_1\tau_1}-ay_{n+1}\big),\\ v_{n+1}=v_n+h\big(ky_{n-m_2+1}e^{-\alpha_2\tau_2}-uv_{n+1}\big). \end{cases} \tag{2}$$

The sequences $\{x_n\},\{y_n\}$ and $\{v_n\}$ represent the concentrations of cells and free virus at time n. Biologically, these concentrations are positives and bounded. For this, we assume that the initial values of model (2) satisfy:

$$x(s)\geqslant 0,\quad y(s)\geqslant 0,\qquad v(s)\geqslant 0,\quad \text{for all } s=-m,-m+1,\ldots,0, \tag{3}$$

where $m=\max(m_1,m_2)$.

The following result establishes the positivity and boundedness of solutions of the discrete model (2).

Proposition 2.1. *All solutions of system (2) subject to condition (3) remain nonnegative and bounded for all $n\in\mathbb{N}$.*

Proof. First, we prove the positivity of solutions by using mathematical induction. When $n=0$, we have

$$(1+hd)x_1+hf(x_1,y_0,v_0)v_0=x_0+h\lambda.$$

Let $g(x)=(1+hd)x+hf(x,y_0,v_0)v_0-x_0-h\lambda$. Clearly, g(x) is a continuous function for $x, g(\mathbb{R})=\mathbb{R}$ and

$$g'(x)=1+hd+hv_0\frac{\partial f}{\partial x}(x,y_0,v_0)>0.$$

Then $g(x)$ is monotonically increasing on $\mathbb{R}$. Hence, the equation $g(x)=0$ has a unique solution on $\mathbb{R}$. Since

$$g(0)=-x_0-h\lambda<0 \text{ and } g\left(\frac{x_0+h\lambda}{1+hd}\right)=hf\left(\frac{x_0+h\lambda}{1+hd},y_0,v_0\right)v_0>0,$$

we have $\bar{x}\in\left(0,\frac{x_0+h\lambda}{1+hd}\right)$. Hence, $\bar{x}=x_1>0$. From (2), we obtain

$$y_1=\frac{y_0+hf(x_{-m_1+1},y_{-m_1},v_{-m_1})v_{-m_1}e^{-\alpha_1\tau_1}}{1+ah},$$
$$v_1=\frac{v_0+hky_1}{1+uh}.$$

Then $y_1\geqslant 0$ and $v_1\geqslant 0$. Therefore, by using the induction, we get $x_n\geqslant 0,\ y_n\geqslant 0$ and $v_n\geqslant 0$ for all $n\geqslant 0$. This proves the positivity of solutions.

Next, we prove the boundedness of solutions. Let

$$T_n=x_n+y_n+h\sum_{j=n-m_1}^{n-1}f(x_{j+1},y_j,v_j)v_je^{-h\alpha_1(n-j)}.$$

Then,

$$\begin{aligned} T_{n+1}-T_n &= h(\lambda - dx_{n+1} - f(x_{n+1},y_n,v_n)v_n) \\ &\quad + h(f(x_{n-m_1+1},y_{n-m_1},v_{n-m_1})v_{n-m_1}e^{-\alpha_1\tau_1} - ay_{n+1}) \\ &\quad + h\sum_{j=n-m_1+1}^{n} f(x_{j+1},y_j,v_j)v_j e^{-h\alpha_1(n+1-j)} \\ &\quad - h\sum_{j=n-m_1}^{n-1} f(x_{j+1},y_j,v_j)v_j e^{-h\alpha_1(n-j)} \\ &= h(\lambda - dx_{n+1} - ay_{n+1}) \\ &\quad + h(1-e^{h\alpha_1})\sum_{j=n-m_1+1}^{n} f(x_{j+1},y_j,v_j)v_j e^{-h\alpha_1(n+1-j)} \\ &\leqslant h(\lambda - \delta T_{n+1}) \end{aligned}$$

where $\delta = \min\{d, a, \frac{e^{h\alpha_1}-1}{h}\}$. Hence,

$$T_{n+1} \leqslant \frac{1}{1+h\delta}T_n + \frac{h\lambda}{1+h\delta}.$$

By using the induction, we get the following inequality

$$T_n \leqslant \left(\frac{1}{1+h\delta}\right)^n T_0 + \frac{\lambda}{\delta}\left[1-\left(\frac{1}{1+h\delta}\right)^n\right].$$

Then,

$$\limsup_{n\to+\infty} T_n \leqslant \frac{\lambda}{\delta}.$$

This implies that $\{T_n\}$ is bounded. Therefore, $\{x_n\}$ and $\{y_n\}$ are also bounded.

By the third equation of (2), we obtain

$$v_{n+1} = \frac{1}{1+hu}v_n + \frac{hke^{-\alpha_2\tau_2}}{1+hu}y_{n-m_2+1}.$$

As $\{y_n\}$ is bounded, then there exists a M such that $y_n \leqslant M$ for all $n \in \{-m_2, -m_2+1, \ldots, 0, 1, \ldots\}$. Thus,

$$v_{n+1} \leqslant \frac{1}{1+hu}v_n + \frac{hke^{-\alpha_2\tau_2}}{1+hu}M.$$

By induction, we get

$$v_n \leqslant \left(\frac{1}{1+hu}\right)^n v_0 + \frac{kM}{u}e^{-\alpha_2\tau_2}\left[1-\left(\frac{1}{1+hu}\right)^n\right] \leqslant v_0 + \frac{kM}{u}e^{-\alpha_2\tau_2},$$

Therefore, $\{v_n\}$ is bounded. This completes the proof. □

If in addition we assume that $x_0 > 0$, $y_0 > 0$ and $v_0 > 0$, it is easy to get the following result.

Remark 2.2. If $x_0 > 0$, $y_0 > 0$ and $v_0 > 0$, then all solutions of system (2) subject to condition (3) are positive for any $n > 0$. In this case, the mixed Euler numerical scheme for the system (1) is called unconditionally positive.

Next, we find the steady states of system (2). By a simple computation, it is easy to see that the system (2) has the same steady states as those of the corresponding continuous system (1).

Theorem 2.3. *Let us define* $R_0 = \frac{k}{au}f(\frac{\lambda}{d},0,0)e^{-\alpha_1\tau_1-\alpha_2\tau_2}$.

1. *If* $R_0 \leqslant 1$, *then the system (2) has a unique disease-free equilibrium of the form* $E_f(\frac{\lambda}{d},0,0)$.
2. *If* $R_0 > 1$, *then the system (2) has a unique chronic infection equilibrium of the form* $E^*(x^*,y^*,v^*)$ *besides* E_f, *where* $x^* \in (\frac{\lambda}{d},0)$, $y^* = \frac{\lambda - dx^*}{ae^{\alpha_1\tau_1}}$ *and* $v^* = \frac{ky^*}{ue^{\alpha_2\tau_2}}$.

3. Stability of the disease-free equilibrium

In this section, we investigate the stability of the disease-free equilibrium.

Theorem 3.1. *The disease-free equilibrium* E_f *of system (2) is globally asymptotically stable whenever* $R_0 \leqslant 1$, *and unstable otherwise.*

Proof. We construct a discrete Lyapunov functional as follows

$$\begin{aligned} L_n &= x_n - x^0 - \int_{x^0}^{x_n}\frac{f(x^0,0,0)}{f(s,0,0)}ds + e^{\alpha_1\tau_1}y_n + \frac{a}{k}e^{\alpha_1\tau_1+\alpha_2\tau_2}(1+uh)v_n \\ &\quad + h\sum_{j=n-m_1}^{n-1} f(x_{j+1},y_j,v_j)v_j + ae^{\alpha_1\tau_1}h\sum_{j=n-m_2}^{n-1} y_{j+1}, \end{aligned}$$

Calculating the first difference of L_n along the positive solution of system (2), we have

$$\begin{aligned} \Delta L_n &= L_{n+1} - L_n \\ &= x_{n+1} - x_n - \int_{x_n}^{x_{n+1}}\frac{f(x^0,0,0)}{f(s,0,0)}ds + e^{\alpha_1\tau_1}(y_{n+1}-y_n) \\ &\quad + \frac{a}{k}(1+uh)e^{\alpha_1\tau_1+\alpha_2\tau_2}(v_{n+1}-v_n) \\ &\quad + h\big(f(x_{n+1},y_n,v_n)v_n - f(x_{n-m_1+1},y_{n-m_1},v_{n-m_1})v_{n-m_1}\big) \\ &\quad + ae^{\alpha_1\tau_1}h\big(y_{n+1}-y_{n-m_2+1}\big) \\ &\leqslant \left(1-\frac{f(x^0,0,0)}{f(x_{n+1},0,0)}\right)(x_{n+1}-x_n) + e^{\alpha_1\tau_1}(y_{n+1}-y_n) \\ &\quad + \frac{a}{k}(1+uh)e^{\alpha_1\tau_1+\alpha_2\tau_2}(v_{n+1}-v_n) \\ &\quad + h\big(f(x_{n+1},y_n,v_n)v_n - f(x_{n-m_1+1},y_{n-m_1},v_{n-m_1})v_{n-m_1}\big) \\ &\quad + ae^{\alpha_1\tau_1}h\big(y_{n+1}-y_{n-m_2+1}\big). \end{aligned}$$

Using the equality $\lambda = dx^0$, we get

$$\begin{aligned} \Delta L_n &\leqslant hdx^0\left(1-\frac{x_{n+1}}{x^0}\right)\left(1-\frac{f(x^0,0,0)}{f(x_{n+1},0,0)}\right) \\ &\quad + \frac{auh}{k}e^{\alpha_1\tau_1+\alpha_2\tau_2}\left(\frac{f(x_{n+1},y_n,v_n)}{f(x_{n+1},0,0)}R_0 - 1\right)v_n \\ &\leqslant hdx^0\left(1-\frac{x_{n+1}}{x^0}\right)\left(1-\frac{f(x^0,0,0)}{f(x_{n+1},0,0)}\right) \\ &\quad + \frac{auh}{k}e^{\alpha_1\tau_1+\alpha_2\tau_2}(R_0-1)v_n. \end{aligned}$$

Since $f(x,y,v)$ is strictly monotonically increasing with respect to x, we have

$$\left(1-\frac{x_{n+1}}{x^0}\right)\left(1-\frac{f(x^0,0,0)}{f(x_{n+1},0,0)}\right) \leqslant 0.$$

Since $R_0 \leqslant 1$, we have $\Delta L_n = L_{n+1} - L_n \leqslant 0$ for all $n \geqslant 0$. Then, $\{L_n\}$ is a monotonically decreasing sequence. Since $L_n \geqslant 0$, we have $\lim_{n\to+\infty} L_n \geqslant 0$. Hence $\lim_{n\to+\infty}(L_{n+1}-L_n) = 0$, from which we obtain $\lim_{n\to+\infty} x_{n+1} = x^0$ and $\lim_{n\to+\infty}((R_0-1)v_n) = 0$. We discuss two cases:

- If $R_0 < 1$, then $\lim_{n\to+\infty} v_n = 0$. By the third equation of (2), we get $\lim_{n\to+\infty} y_n = 0$.
- If $R_0 = 1$. Using $\lim_{n\to+\infty} x_n = x^0$ and the first equation of (2), it is not hard to have $\lim_{n\to+\infty} v_n = 0$.

By the above discussion, we deduce that E_f is globally asymptotically stable if $R_0 \le 1$.

Now, we prove that the disease-free equilibrium E_f is unstable when $R_0 > 1$. Calculating the linearization system of model (2) at equilibrium E_f, we get a new system of the form

$$\begin{cases} X_{n+1} = X_n + h\big(-dX_{n+1} - f(\frac{\lambda}{d},0,0)V_n\big), \\ Y_{n+1} = Y_n + h\big(e^{-\alpha_1\tau_1} f(\frac{\lambda}{d},0,0)V_{n-m_1} - aY_{n+1}\big), \\ V_{n+1} = V_n + h(ke^{-\alpha_2\tau_2} Y_{n-m_2+1} - uV_{n+1}), \end{cases} \tag{4}$$

where $X_n = x_n - \frac{\lambda}{d}$, $Y_n = y_n$ and $V_n = v_n$. Let $Z_n = (X_n, Y_n, V_n)^T$. Then, system (4) is equivalent to

$$Z_{n+1} = AZ_n + BZ_{n-m_1} + CZ_{n-m_2} + DZ_{n-m_1-m_2}, \tag{5}$$

where

$$A = \begin{pmatrix} \frac{1}{1+hd} & 0 & -\frac{hf(\frac{\lambda}{d},0,0)}{1+hd} \\ 0 & \frac{1}{1+ha} & 0 \\ 0 & 0 & \frac{1}{1+hu} \end{pmatrix}, \quad B = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & \frac{hf(\frac{\lambda}{d},0,0)}{1+ha} e^{-\alpha_1\tau_1} \\ 0 & 0 & 0 \end{pmatrix},$$

$$C = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & \frac{hk}{(1+ha)(1+hu)} e^{-\alpha_2\tau_2} & 0 \end{pmatrix}, \quad D = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & \frac{h^2kf(\frac{\lambda}{d},0,0)}{(1+ha)(1+hu)} e^{-\alpha_1\tau_1-\alpha_2\tau_2} \end{pmatrix}.$$

Hence, the characteristic equation corresponding to linearized system (5) is given by

$$\det(A - \xi I + \xi^{-m_1}B + \xi^{-m_2}C + \xi^{-m_1-m_2}D) = 0.$$

Therefore, this characteristic equation can be rewritten as

$$\left(\frac{1}{1+hd} - \xi\right) P(\xi) = 0,$$

where

$$P(\xi) = (1+ha)(1+hu)\xi^{m_1+m_2+1} - (2+ha+hu)\xi^{m_1+m_2} + \xi^{m_1+m_2-1} - h^2kf(\frac{\lambda}{d},0,0)e^{-\alpha_1\tau_1-\alpha_2\tau_2}.$$

Clearly, $\xi = \frac{1}{1+hd}$ is the root of this equation. The remaining roots are given by the solutions of the equation $P(\xi) = 0$.

We have $P(1) = h^2au(1-R_0) < 0$, $\lim_{\xi\to+\infty} P(\xi) = +\infty$ and P is a continuous function on interval $\in [1,+\infty)$. Then there exists a $\bar{\xi} \in (1,+\infty)$ such that $P(\bar{\xi}) = 0$. Therefore, E_f is unstable when $R_0 > 1$. This completes the proof. □

4. Stability of the chronic infection equilibrium

In this section, we establish the global stability of the chronic infection equilibrium E^*, by assuming that $R_0 > 1$ and the function f satisfies the following hypothesis

$$\left(1 - \frac{f(x,y,v)}{f(x,y^*,v^*)}\right)\left(\frac{f(x,y^*,v^*)}{f(x,y,v)} - \frac{v}{v^*}\right) \le 0, \quad \text{for all } x,\ y,\ v > 0. \tag{H4}$$

First, we give the following important remark.

Remark 4.1. The assumption (H4) is satisfied by various types of the incidence rate including the mass action when $f(x,y,v) = \beta x$, the saturation incidence when $f(x,y,v) = \frac{\beta x}{1+\alpha v}$, the incidence function was used in Zhuo (2012) and Sun and Min (2014) when $f(x,y,v) = \frac{\beta x}{x+v}$, Beddington–DeAngelis response when $f(x,y,v) = \frac{\beta x}{1+\alpha_1 x+\alpha_2 v}$, Crowley-Martin response when $f(x,y,v) = \frac{\beta x}{1+\alpha_1 x+\alpha_2 v+\alpha_1\alpha_2 xv}$ and the more generalized response introduced by Hattaf et al. (see Section 5 in Hattaf et al. (2013)) when $f(x,y,v) = \frac{\beta x}{1+\alpha_1 x+\alpha_2 v+\alpha_3 xv}$, where β is a positive constant rate describing the infection process, $\alpha, \alpha_1, \alpha_2$ and α_3 are nonnegative constants. Further, the fourth hypothesis given in Wang et al. (2013) on the incidence function depending only of x and v is a particular case of the assumption (H4).

The following theorem establish the global stability of E^*.

Theorem 4.2. *Assume $R_0 > 1$ and (H4) hold. Then the chronic infection equilibrium E^* of system (2) is globally asymptotically stable.*

Proof. We define a discrete Lyapunov functional as follows

$$\begin{aligned} W_n = {} & x_n - x^* - \int_{x^*}^{x_n} \frac{f(x^*,y^*,v^*)}{f(s,y^*,v^*)}ds + e^{\alpha_1\tau_1} y^* \phi\left(\frac{y_n}{y^*}\right) \\ & + \frac{a}{k}(1+uh)e^{\alpha_1\tau_1+\alpha_2\tau_2} v^* \phi\left(\frac{v_n}{v^*}\right) \\ & + f(x^*,y^*,v^*)v^* h \sum_{j=n-m_1}^{n-1} \phi\left(\frac{f(x_{j+1},y_j,v_j)v_j}{f(x^*,y^*,v^*)v^*}\right) \\ & + ae^{\alpha_1\tau_1} y^* h \sum_{j=n-m_2}^{n-1} \phi\left(\frac{y_{j+1}}{y^*}\right), \end{aligned}$$

where $\phi(x) = x - 1 - \ln x$, $x \in \mathbb{R}^+$. Clearly, $\phi : \mathbb{R}^+ \to \mathbb{R}^+$ attains its strict global minimum at $x = 1$ and $\phi(1) = 0$.

The function $\psi : x \mapsto x - x^* - \int_{x^*}^{x} \frac{f(x^*,y^*,v^*)}{f(s,y^*,v^*)}ds$ has the global minimum at $x = x^*$ and $\psi(x^*) = 0$. So, $\psi(x) \ge 0$ for all $x > 0$. Thus, $W_n \ge 0$ with equality holding if and only if $\frac{x_n}{x^*} = \frac{y_n}{y^*} = \frac{v_n}{v^*} = 1$ for all $n \ge 0$.

The first difference of W_n satisfies

$$\begin{aligned} \Delta W_n &= W_{n+1} - W_n \\ &= x_{n+1} - x_n - \int_{x_n}^{x_{n+1}} \frac{f(x^*,y^*,v^*)}{f(s,y^*,v^*)}ds \\ &\quad + e^{\alpha_1\tau_1}\left(y_{n+1} - y_n + y^* \ln\left(\frac{y_n}{y_{n+1}}\right)\right) \\ &\quad + \frac{a}{k}(1+uh)e^{\alpha_1\tau_1+\alpha_2\tau_2}\left(v_{n+1} - v_n + v^* \ln\left(\frac{v_n}{v_{n+1}}\right)\right) + f(x^*,y^*,v^*)v^* h \\ &\quad \times \left(\phi\left(\frac{f(x_{n+1},y_n,v_n)v_n}{f(x^*,y^*,v^*)v^*}\right) - \phi\left(\frac{f(x_{n-m_1+1},y_{n-m_1},v_{n-m_1})v_{n-m_1}}{f(x^*,y^*,v^*)v^*}\right)\right) \\ &\quad + ae^{\alpha_1\tau_1} y^* h\left(\phi\left(\frac{y_{n+1}}{y^*}\right) - \phi\left(\frac{y_{n-m_2+1}}{y^*}\right)\right) \\ &\le \left(1 - \frac{f(x^*,y^*,v^*)}{f(x_{n+1},y^*,v^*)}\right)(x_{n+1} - x_n) + e^{\alpha_1\tau_1}\left(y_{n+1} - y_n + y^* \ln\left(\frac{y_n}{y_{n+1}}\right)\right) \\ &\quad + \frac{a}{k}(1+uh)e^{\alpha_1\tau_1+\alpha_2\tau_2}\left(v_{n+1} - v_n + v^* \ln\left(\frac{v_n}{v_{n+1}}\right)\right) \\ &\quad + hf(x_{n+1},y_n,v_n)v_n - hf(x_{n-m_1+1},y_{n-m_1},v_{n-m_1})v_{n-m_1} \\ &\quad + f(x^*,y^*,v^*)v^* h \ln\left(\frac{f(x_{n-m_1+1},y_{n-m_1},v_{n-m_1})v_{n-m_1}}{f(x_{n+1},y_n,v_n)v_n}\right) \\ &\quad + ae^{\alpha_1\tau_1} h\left(y_{n+1} - y_{n-m_2+1} + y^* \ln\left(\frac{y_{n-m_2+1}}{y_{n+1}}\right)\right). \end{aligned}$$

By the inequality $\ln x \leqslant x-1$, we get

$$\begin{aligned}\Delta W_n \leqslant & \left(1-\frac{f(x^*,y^*,v^*)}{f(x_{n+1},y^*,v^*)}\right)(x_{n+1}-x_n)\\ & + e^{\alpha_1\tau_1}\left(1-\frac{y^*}{y_{n+1}}\right)(y_{n+1}-y_n)\\ & + \frac{a}{k}e^{\alpha_1\tau_1+\alpha_2\tau_2}\left(1-\frac{v^*}{v_{n+1}}\right)(v_{n+1}-v_n)\\ & + \frac{auh}{k}e^{\alpha_1\tau_1+\alpha_2\tau_2}\left(v_{n+1}-v_n+v^*\ln\left(\frac{v_n}{v_{n+1}}\right)\right)\\ & + hf(x_{n+1},y_n,v_n)v_n - hf(x_{n-m_1+1},y_{n-m_1},v_{n-m_1})v_{n-m_1}\\ & + f(x^*,y^*,v^*)v^*h\ln\left(\frac{f(x_{n-m_1+1},y_{n-m_1},v_{n-m_1})v_{n-m_1}}{f(x_{n+1},y_n,v_n)v_n}\right)\\ & + ae^{\alpha_1\tau_1}h\left(y_{n+1}-y_{n-m_2+1}+y^*\ln\left(\frac{y_{n-m_2+1}}{y_{n+1}}\right)\right).\end{aligned}$$

Using $\lambda = dx^* + ay^*e^{\alpha_1\tau_1}$, $f(x^*,y^*,v^*)v^* = ay^*e^{\alpha_1\tau_1}$ and $\frac{u}{k}e^{\alpha_2\tau_2} = \frac{v^*}{y^*}$, we obtain

$$\begin{aligned}\Delta W_n \leqslant & hdx^*\left(1-\frac{x_{n+1}}{x^*}\right)\left(1-\frac{f(x^*,y^*,v^*)}{f(x_{n+1},y^*,v^*)}\right) + hay^*e^{\alpha_1\tau_1}\left(1-\frac{f(x^*,y^*,v^*)}{f(x_{n+1},y^*,v^*)}+\frac{v_n}{v^*}\frac{f(x_{n+1},y_n,v_n)}{f(x_{n+1},y^*,v^*)}\right)\\ & + hay^*e^{\alpha_1\tau_1}\left(1-\frac{y^*}{y_{n+1}}\frac{v_{n-m_1}}{v^*}\frac{f(x_{n-m_1+1},y_{n-m_1},v_{n-m_1})}{f(x^*,y^*,v^*)}\right) + hay^*e^{\alpha_1\tau_1}\left(1-\frac{v_n}{v^*}-\frac{y_{n-m_2+1}v^*}{y^*v_{n+1}}\right)\\ & + hay^*e^{\alpha_1\tau_1}\ln\left(\frac{f(x_{n-m_1+1},y_{n-m_1},v_{n-m_1})v_{n-m_1}y_{n-m_2+1}}{f(x_{n+1},y_n,v_n)v_{n+1}y_{n+1}}\right) = hdx^*e^{\alpha_1\tau_1}\left(1-\frac{x_{n+1}}{x^*}\right)\left(1-\frac{f(x^*,y^*,v^*)}{f(x_{n+1},y^*,v^*)}\right)\\ & + hay^*e^{\alpha_1\tau_1}\left[4-\frac{f(x^*,y^*,v^*)}{f(x_{n+1},y^*,v^*)}-\frac{y^*}{y_{n-m_2+1}}\frac{v_n}{v^*}\frac{f(x_{n+1},y_n,v_n)}{f(x^*,y^*,v^*)}-\frac{y_{n-m_2+1}v^*}{y^*v_{n+1}}-\frac{f(x_{n+1},y^*,v^*)}{f(x_{n+1},y_n,v_n)}\right]\\ & + hay^*e^{\alpha_1\tau_1}\left(-1-\frac{v_n}{v^*}+\frac{f(x_{n+1},y^*,v^*)}{f(x_{n+1},y_n,v_n)}+\frac{v_n}{v^*}\frac{f(x_{n+1},y_n,v_n)}{f(x_{n+1},y^*,v^*)}\right)\\ & + hay^*e^{\alpha_1\tau_1}\left(\frac{y^*}{y_{n-m_2+1}}\frac{v_n}{v^*}\frac{f(x_{n+1},y_n,v_n)}{f(x^*,y^*,v^*)}-\frac{y^*}{y_{n+1}}\frac{v_{n-m_1}}{v^*}\frac{f(x_{n-m_1+1},y_{n-m_1},v_{n-m_1})}{f(x^*,y^*,v^*)}\right)\\ & + hay^*e^{\alpha_1\tau_1}\ln\left(\frac{f(x_{n-m_1+1},y_{n-m_1},v_{n-m_1})v_{n-m_1}y_{n-m_2+1}}{f(x_{n+1},y_n,v_n)v_{n+1}y_{n+1}}\right)\\ = & hdx^*e^{\alpha_1\tau_1}\left(1-\frac{x_{n+1}}{x^*}\right)\left(1-\frac{f(x^*,y^*,v^*)}{f(x_{n+1},y^*,v^*)}\right) + hay^*e^{\alpha_1\tau_1}\left(-1-\frac{v_n}{v^*}+\frac{f(x_{n+1},y^*,v^*)}{f(x_{n+1},y_n,v_n)}+\frac{v_n}{v^*}\frac{f(x_{n+1},y_n,v_n)}{f(x_{n+1},y^*,v^*)}\right)\\ & - hay^*e^{\alpha_1\tau_1}\left[\phi\left(\frac{f(x^*,y^*,v^*)}{f(x_{n+1},y^*,v^*)}\right)+\phi\left(\frac{y_{n-m_2+1}v^*}{y^*v_{n+1}}\right)+\phi\left(\frac{f(x_{n+1},y^*,v^*)}{f(x_{n+1},y_n,v_n)}\right)+\phi\left(\frac{y^*}{y_{n+1}}\frac{v_{n-m_1}}{v^*}\frac{f(x_{n-m_1+1},y_{n-m_1},v_{n-m_1})}{f(x^*,y^*,v^*)}\right)\right].\end{aligned}$$

Since $f(x,y,v)$ is strictly monotonically increasing with respect to x, we obtain that

$$\left(1-\frac{x_{n+1}}{x^*}\right)\left(1-\frac{f(x^*,y^*,v^*)}{f(x_{n+1},y^*,v^*)}\right)\leqslant 0.$$

According to (H4), we have

$$\begin{aligned}&-1-\frac{v_n}{v^*}+\frac{f(x_{n+1},y^*,v^*)}{f(x_{n+1},y_n,v_n)}+\frac{v_n}{v^*}\frac{f(x_{n+1},y_n,v_n)}{f(x_{n+1},y^*,v^*)}\\ &= \left(1-\frac{f(x_{n+1},y_n,v_n)}{f(x_{n+1},y^*,v^*)}\right)\left(\frac{f(x_{n+1},y^*,v^*)}{f(x_{n+1},y_n,v_n)}-\frac{v_n}{v^*}\right)\leqslant 0.\end{aligned}$$

Since $\phi(x)\geqslant 0$ for $x>0$, we deduce that $\Delta W_n\leqslant 0$ for all $n\geqslant 0$. Then, $\{W_n\}$ is a monotonically decreasing sequence. Since $W(n)\geqslant 0$, it follows that $\lim_{n\to+\infty}W(n)\geqslant 0$. Hence, we obtain that $\lim_{n\to+\infty}(W_{n+1}-W_n)=0$, which implies that $\lim_{n\to+\infty}x_n = x^*$ and $\lim_{n\to+\infty}\frac{y_{n-m_2+1}}{v_{n+1}} = \frac{y^*}{v^*}$. From system (2), we obtain $\lim_{n\to+\infty}v_n = v^*$ and $\lim_{n\to+\infty}y_n = y^*$. Therefore, we conclude that E^* is globally asymptotically stable. □

5. Numerical simulations

In this section, we will confirm and illustrate our previous theoretical results by numerical simulations. For this, we consider the following delayed discrete model for HIV infection:

$$\begin{cases} x_{n+1} = x_n + h(\lambda - dx_{n+1} - \beta x_{n+1}v_n),\\ y_{n+1} = y_n + h\left(e^{-\alpha_1\tau_1}\beta x_{n-m_1+1}v_{n-m_1} - ay_{n+1}\right),\\ v_{n+1} = v_n + h\left(ke^{-\alpha_2\tau_2}y_{n-m_2+1} - uv_{n+1}\right).\end{cases} \tag{6}$$

The model (6) is a special case of (2) with $f(x,y,v)=\beta x$. The basic reproduction number of (2) is given by

$$R_0 = \frac{\lambda\beta k}{dau}e^{-\alpha_1\tau_1-\alpha_2\tau_2}. \tag{7}$$

In addition, the hypotheses (H1), (H2), (H3) and (H4) are satisfied.

Firstly, we simulate the model (6) by using the following parameter values: $\lambda = 10$ cells mm^{-3} day^{-1} (Perelson et al., 1993), $d = 0.02$ day^{-1} (Perelson et al., 1993), $a = 0.5$ day^{-1} (Perelson et al., 1996), $u = 3$ day^{-1} (Perelson et al., 1996), $\beta = 0.000024$ mm^3 virion^{-1} day^{-1} (Perelson et al., 1996; Stafford et al., 2000), $\alpha_1 = d$ (Perelson et al., 1993), $k = 600$ virions cell^{-1} day^{-1} (Hattaf and Yousfi, 2012) $\alpha_2 = 0.65$ day^{-1}, $\tau_1 = 3.5$ days, $\tau_2 = 2.5$ days and $h = 0.1$ days. By calculating, we have $R_0 = 0.8813 < 1$. By Theorem 3.1, we deduce that the disease-free equilibrium $E_f(500,0,0)$ of (6) is globally asymptotically stable, which means that the virus is cleared and the infection dies out. Fig. 1 validates the above analysis.

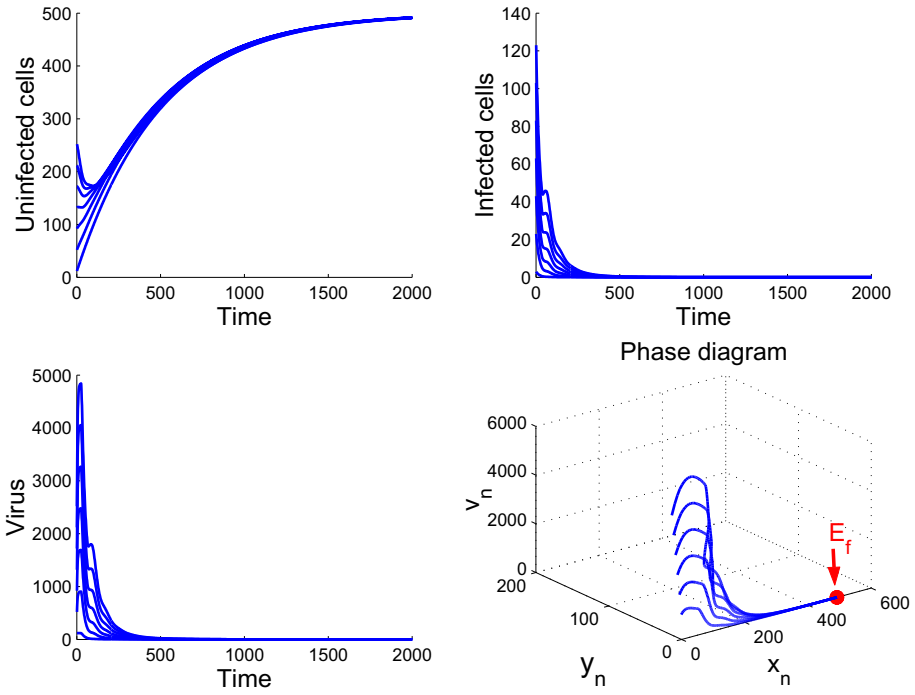

Figure 1 Plot demonstrates the global stability of E_f.

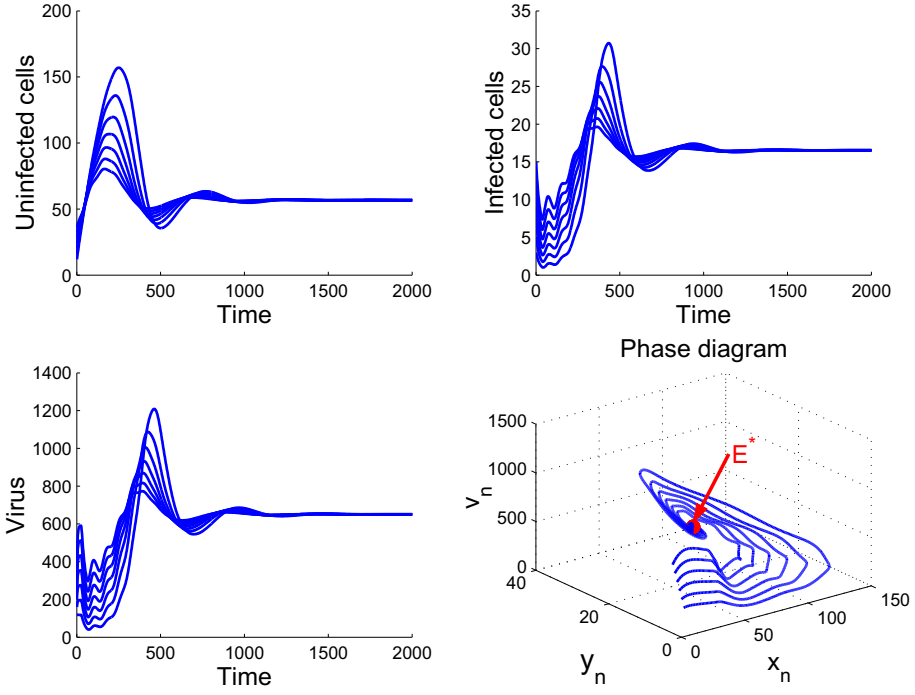

Figure 2 Plot demonstrates the global stability of E^*.

Secondly, we choose $\beta = 0.00024\,\mathrm{mm}^3\,\mathrm{virion}^{-1}\,\mathrm{day}^{-1}$ (Perelson et al., 1996; Stafford et al., 2000) and the other parameter values are the same as above. The reason to just modify the parameter β is based on the fact that R_0 is an increasing function with respect to β (see the explicit formula (7) for R_0). By calculating, we have $R_0 = 8.8128 > 1$. Then, system (6) has a unique chronic infection equilibrium $E^*(56.7359, 16.5319, 651.0636)$. By applying Theorems 3.1 and 4.2, we see that E_f becomes unstable and E^* is globally asymptotically stable. In this case, the virus persists in the host and the infection becomes chronic. Fig. 2 confirms this observation.

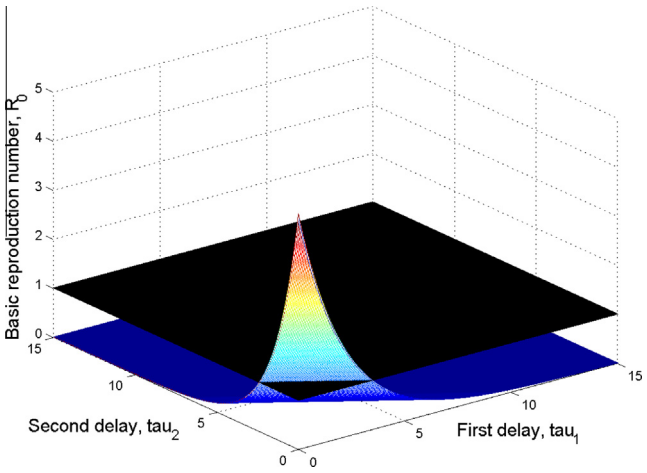

Figure 3 Plot of the basic reproduction number R_0 as a function of the time delays τ_1 and τ_2.

According to the above, we deduce a strategy to control the viral infection. This strategy is based on reducing the value of R_0 and making it less than or equal to one. From the explicit expression of R_0 in (7), it is clear that with the increase in time delays τ_1 and τ_2, the value of R_0 decreases which is demonstrated in Fig. 3.

6. Conclusion

In this work, we have proposed a discrete mathematical model with two delays to describe the dynamics of viral infection, such as human immunodeficiency virus (HIV), the hepatitis B virus (HBV) and the hepatitis C virus (HCV). The discrete model is derived from the continuous system (1) by using a mixed Euler method. Also, the infection transmission process is modeled by a general incidence function that includes various types of incidence rate existing in the literature. We have proved that the proposed mixed Euler method is unconditionally positive. Furthermore, the dynamical behaviors of the the delayed discrete model are investigated by linearization method and by constructing suitable discrete Lyapunov functionals. More precisely, we have proved that the disease-free equilibrium E_f is globally asymptotically stable if the basic reproduction number satisfies $R_0 \leqslant 1$, which means that the virus is cleared and the infection dies out. When $R_0 > 1, E_f$ becomes unstable and the chronic infection equilibrium E^* is globally asymptotically stable. In this case, the virus persists in the host and the infection becomes chronic. Therefore, we conclude that the discrete model has the same qualitative properties as the corresponding continuous viral infection model (1) with no restriction on the time step size.

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