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Mathematical Analysis of Virus Dynamics Model with Multitarget Cells in Vivo

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Abstract: This paper investigates the qualitative behavior of viral infection model with multitarget cells in vivo. The infection rate is given by Crowley-Martin functional response. By assuming that the virus attack n classes of uninfected target cells, we study a viral infection model of dimension $2n+1$ with discrete delay. To describe the latent period for the contacted target cells with viruses to begin producing viruses, two types of discrete delay are incorporated into the model. The basic reproduction number R_0 of the model is defined which determines the dynamical behaviors of the model. Utilizing Lyapunov functionals and LaSalle's invariance principle, we have proven that if $R_0 \leq 1$ then the uninfected steady state is globally asymptotically stable, and if $R_0 > 1$ then the infected steady state is globally asymptotically stable.

Keywords: Global stability; time delay; virus dynamics; multitarget cells.

1 Introduction

Mathematical modelling of virus dynamics has become an important area of research [1]. The interatcion of the virus and target cells has been formulated as ordinary differential equations in several works (see e.g. [2], [3], [4], [5], [14], [12], [6], [30] and [7]). The basic mathematical model describing the dynamics of viral infection is given by [2], [3]:

$$\dot{x} = \lambda - dx - \beta xv, \tag{1}$$
$$\dot{y} = \beta xv - \delta y, \tag{2}$$
$$\dot{v} = ky - rv, \tag{3}$$

where x, y and v represent the populations of the uninfected target cells, infected cells and free virus particles, respectively. The uninfected cells are generated from sources within the body at rate λ. The parameter β is infection rate constant and d is the death rate constant of the uninfected target cells. Eq. (2) describes the population dynamics of the infected cells and shows that they die with rate constant δ. The virus particles are produced by the infected cells with rate constant k, and are cleared from plasma with rate constant r.

Model (1)-(3) is based on the assumption that, once the virus contacts a target cell, the cell begins producing new virus particles. More realistic models incorporate the delay between the time of viral entry into the target cell and the time the production of new virus particles, modeled with discrete time delay using functional differential equations. Many researchers have devoted their effort in developing various mathematical models of viral infections with delay and studying their qualitative behaviors (see e.g. [9], [11], [24], [10], [28], [29], [25], [22], [27] [21], [34], [31], [32]). The infection rate in model (1)-(3) is given by bilinear functional response which is usually unsuitable for many viral infections. In the present paper, the infection rate is given by Crowley-Martin functional response. The Crowley-Martin type of functional response was first introduced by Crowley and Martin [33].

In the literature, most of the proposed mathematical models for viral infection assume that the virus has one class of target cells, (e.g. $CD4^+$ T cells in case of HIV or hepatic cells in case of HCV and HBV) (see e.g. [2], [3], [4] and the book Nowak and May [1]). In [8], [26], [13], [17], [15], [14] and [18], some HIV models with two classes of target cells, $CD4^+$ T cells and macrophages

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have been proposed. The global stability of these models has been investigated in ([13], [17], [14] and [18]). Because the interactions of some types of viruses in *vivo* is complex and is not known clearly, we would suppose that the virus may attack n classes of target cells where $n \geq 1$ [16], [19]. In [19], models with discrete-time delays and saturated incidence rate have been studied. Elaiw [16] studied a class of virus infection models with multitarget cells without time delay.

The purpose of this paper is to propose viral infection models with multitarget cells and Crowley-Martin functional response and investigate their qualitative behaviors. We incorporate discrete delay into the model which represents an intracellular latent period for the contacted uninfected target cells with virus to begin producing new virus particles. The global stability of the model is established using Lyapunov functionals and LaSalle's invariance principle. We prove that the global dynamics of these models are determined by the basic reproduction number R_0. If $R_0 \leq 1$, then the uninfected steady state is globally asymptotically stable (GAS) and if $R_0 > 1$, then the infected steady state exists and is GAS.

2 Model with discrete-time delays

In this section we propose a viral infection model with multitarget cells and Crowley-Martin functional response. We incorporate two types of discrete-time delays τ_i and $\mu_i, i = 1,...,n$ into the model. We assume that the virus attacks n classes of uninfected cells.

$$\dot{x}_i = \lambda_i - d_i x_i - \frac{\beta_i x_i v}{(1+a_i x_i)(1+b_i v)}, \qquad i = 1,...,n, \tag{4}$$

$$\dot{y}_i = \frac{e^{-m_i\tau_i}\beta_i x_i(t-\tau_i)v(t-\tau_i)}{(1+a_i x_i(t-\tau_i))(1+b_i v(t-\tau_i))} - \delta_i y_i, \qquad i = 1,...,n, \tag{5}$$

$$\dot{v} = \sum_{i=1}^{n} e^{-n_i\mu_i} k_i y_i(t-\mu_i) - rv, \tag{6}$$

where x_i and y_i represent the populations of the uninfected target cells and infected cells of class i, respectively, v is the population of the virus particles. Here the parameter τ_i accounts for the time between the target cells of class i are contacted by the virus particles and the contacting viruses inter the cells. The recruitment of virus producing cells at time t is given by the number of cells that were newly infected cells at time $t-\tau_i$ and are still alive at time. The factor $e^{-m_i\tau}$ accounts for the loss of target cells during delay period where m_i is positive constant. The time between the virus has penetrated into a target cell of class i, and the emission of infectious (matures) virus particles is represented by μ_i. The factor $e^{-n_i\tau}$ account for the cells loss during this delay period where n_i is positive constant. All the other parameters of the model have the same biological meaning as given in model (1)-(3).

The initial conditions for system (4)-(6) takes the form

$$x_j(\theta) = \varphi_j(\theta),\ y_j(\theta) = \varphi_{j+n}(\theta),\ \ j = 1,...,n,\ v(\theta) = \varphi_{2n+1}(\theta),$$
$$\varphi_j(\theta) \geq 0,\ \theta \in [-\ell, 0),\ \varphi_j(0) > 0,\ j = 1,...,2n+1, \tag{7}$$

where $\ell = \max\{\tau_1,...,\tau_n,\mu_1,...,\mu_n\}$, $(\varphi_1(\theta),\varphi_2(\theta),...,\varphi_{2n+1}(\theta)) \in C$ and $C = C([-\ell,0],\mathbb{R}_+^{2n+1})$ is the Banach space of continuous functions mapping the interval $[-\ell,0]$ into $\mathbb{R}_+^{2n+1}$. By the fundamental theory of functional differential equations [20], system (4)-(6) has a unique solution satisfying initial conditions (7).

We note that, model (4)-(6) can be considered as a generalization of the model with one class of target cells and without delay (i.e. $n = 1$ and $\tau_1 = \mu_1 = 0$) presented in ([32] and [31]).

2.1 Non-negativity and boundedness of solutions

In the following, we establish the non-negativity and boundedness of solutions of (4)-(6) with initial conditions (7). Let $\mathbf{x} = (x_1, x_2, ..., x_n)^T$ and $\mathbf{y} = (y_1, y_2, ..., y_n)^T$.

Proposition 1. Let $(\mathbf{x}(t), \mathbf{y}(t), v(t))$ be any solution of (4)-(6) satisfying the initial conditions (7), then $\mathbf{x}(t), \mathbf{y}(t)$ and $v(t)$ are all non-negative for $t \geq 0$ and ultimately bounded.

Proof. First, we prove that $x_i(t) > 0$, $i = 1,...,n$, for all $t \geq 0$. Assume that $x_i(t)$ lose its non-negativity on some local existence interval $[0,\omega]$ for some constant ω and let $t_1 \in [0,\omega]$ be such that $x_i(t_1) = 0$. From Eq. (4) we have $\dot{x}_i(t_1) = \lambda_i > 0$. Hence $x_i(t) < 0$ for some $t \in (t_1 - \varepsilon, t_1)$, where $\varepsilon > 0$ is sufficiently small. This leads to a contradiction and hence $x_i(t) > 0$, for all $t \geq 0$. Further, from Eqs. (5) and (6) we have

$$y_i(t) = y_i(0)e^{-\delta_i t} + e^{-m_i\tau_i}\beta_i \int_0^t e^{-\delta_i(t-\eta)} \frac{x_i(\eta-\tau_i)v(\eta-\tau_i)}{(1+a_i x_i(\eta-\tau_i))(1+b_i v(\eta-\tau_i))} d\eta, \quad i = 1,...,n,$$
$$v(t) = v(0)e^{-rt} + \sum_{i=1}^{n} k_i e^{-n_i\mu_i} \int_0^t e^{-r(t-\eta)} y_i(\eta-\mu_i) d\eta.$$

confiming that $y_i(t) \geq 0$, $i = 1,...,n$, and $v(t) \geq 0$ for all $t \in [0,\ell]$. By a recursive argument, we obtain $y_i(t) \geq 0$, $i = 1,...,n$, and $v(t) \geq 0$ for all $t \geq 0$.

Next we show that the solution is ultimately bounded. From (4) we have $\dot{x}_i \leq \lambda_i - d_i x_i$. Thus $\limsup_{t\to\infty} x_i(t) \leq \frac{\lambda_i}{d_i}$ and $x_i(t)$ is ultimately bounded. Let $X_i(t) = e^{-m_i\tau_i}x_i(t-\tau_i) + y_i(t)$, then

$$\dot{X}_i(t) \leq \lambda_i e^{-m_i\tau_i} - \sigma_i X_i(t),$$

where $\sigma_i = \min\{d_i, \delta_i\}$. It follows that $\limsup_{t\to\infty} X_i(t) \leq L_i$, where $L_i = \frac{\lambda_i e^{-m_i\tau_i}}{\sigma_i}$. This in turn implies, by the non-negativity of $x_i(t)$ and $y_i(t)$, that $\limsup_{t\to\infty} y_i(t) \leq L_i$ and $y_i(t)$ is ultimately bounded. On the other hand, from Eq. (6) we have

$$\dot{v}(t) \leq \sum_{i=1}^{n} e^{-n_i\mu_i} k_i L_i - rv,$$

then $\limsup_{t\to\infty} v(t) \leq L^*$, where $L^* = \sum_{i=1}^{n} \frac{e^{-n_i\mu_i} k_i L_i}{r}$ and $v(t)$ is ultimately bounded. □

2.2 Steady states

It is clear that, system (4)-(6) has an uninfected steady state $E_0 = (\mathbf{x}^0, \mathbf{y}^0, v^0)$, where $x_i^0 = \frac{\lambda_i}{d_i}$, $y_i^0 = 0$, $i = 1,...,n$ and $v^0 = 0$. The system can also has a positive infected steady state $E_1(\mathbf{x}^*, \mathbf{y}^*, v^*)$. The coordinates of the infected steady state, if they exist, satisfy the equalities:

$$\lambda_i = d_i x_i^* + e^{m_i\tau_i}\delta_i y_i^*, \qquad i = 1,...,n, \tag{8}$$

$$\delta_i y_i^* = \frac{e^{-m_i\tau_i}\beta_i x_i^* v^*}{(1+a_i x_i^*)(1+b_i v^*)}, \qquad i = 1,...,n, \tag{9}$$

$$rv^* = \sum_{i=1}^{n} e^{-n_i\mu_i} k_i y_i^*. \tag{10}$$

We define the intracellular delay-dependent basic reproduction number for system (4)-(6) as

$$R_0 = \sum_{i=1}^{n} R_i = \sum_{i=1}^{n} \frac{e^{-(m_i\tau_i + n_i\mu_i)}\beta_i k_i x_i^0}{\delta_i r(1+a_i x_i^0)},$$

where R_i is the basic reproduction number for the dynamics of the virus and the target cell of class i.

Lemma 1. Consider the system (4)-(6). If $R_0 > 1$, then there exists a positive steady state E_1.

Proof. To compute the steady states of model (4)-(6), we let the right-hand sides of Eqs. (4)-(6) equal zero,

$$\lambda_i - d_i x_i - \frac{\beta_i x_i v}{(1+a_i x_i)(1+b_i v)} = 0, \qquad i = 1,...,n, \tag{11}$$

$$\frac{e^{-m_i\tau_i}\beta_i x_i v}{(1+a_i x_i)(1+b_i v)} - \delta_i y_i = 0, \qquad i = 1,...,n, \tag{12}$$

$$\sum_{i=1}^{n} e^{-n_i\mu_i} k_i y_i - rv = 0. \tag{13}$$

Solving Eq. (11) with respect to x_i, we get x_i as a function of v as:

$$x_i^+ = \frac{1}{2a_i(1+b_i v)} \left(a_i x_i^0(1+b_i v) - (1+\phi_i v) + \sqrt{\left[(1+\phi_i v) - a_i x_i^0(1+b_i v)\right]^2 + 4a_i x_i^0(1+b_i v)^2}\right), \tag{14}$$

$$x_i^- = \frac{1}{2a_i(1+b_i v)} \left(a_i x_i^0(1+b_i v) - (1+\phi_i v) - \sqrt{\left[(1+\phi_i v) - a_i x_i^0(1+b_i v)\right]^2 + 4a_i x_i^0(1+b_i v)^2}\right), \tag{15}$$

where, $\phi_i = b_i + \frac{\beta_i}{d_i}$.

It is clear that if $v > 0$ then $x_i^+ > 0$ and $x_i^- < 0$. Let us choose $x_i = x_i^+$. From Eqs. (11)-(13) we have

$$\sum_{i=1}^{n} \frac{k_i e^{-(m_i\tau_i + n_i\mu_i)}}{\delta_i} (\lambda_i - d_i x_i) - rv = 0. \tag{16}$$

Since x_i is a function of v, then we can define a function $S_1(v)$ as:

$$S_1(v) = \sum_{i=1}^{n} \frac{k_i e^{-(m_i\tau_i + n_i\mu_i)}}{\delta_i} (\lambda_i - d_i x_i) - rv = 0.$$

It is clear that when $v = 0$, then $x_i = x_i^0$ and $S_1(0) = 0$ and when $v = \overline{v} = \sum_{i=1}^{n} \frac{e^{-(m_i\tau_i + n_i\mu_i)} k_i \lambda_i}{\delta_i r} > 0$, then substituting it in Eq. (14) we obtain $\overline{x}_i > 0$ and

$$S_1(\overline{v}) = -\sum_{i=1}^{n} \frac{k_i d_i e^{-(m_i\tau_i + n_i\mu_i)}}{\delta_i} \overline{x}_i < 0.$$

Since $S_1(v)$ is continuous for all $v \geq 0$, we have that

$$S_1'(0) = \sum_{i=1}^{n} \frac{k_i \beta_i x_i^0 e^{-(m_i\tau_i + n_i\mu_i)}}{\delta_i (1+a_i x_i^0)} - r = r(R_0 - 1).$$

Therefore, if $R_0 > 1$, then $S_1'(0) > 0$. It follows that there exists $v^* \in (0, \overline{v})$ such that $S_1(v^*) = 0$. From Eq. (14), we obtain $x_i^* > 0$, $i = 1,...,n$. Moreover, from Eq, (12) we get $y_i^* > 0$, $i = 1,...,n$. □

2.3 Global stability analysis

In this section, we study the global stability of the uninfected and infected steady states of system (4)-(6). The strategy of the proofs is to use suitable Lyapunov functionals which are similar in nature to those used in [21]. Next we shall use the following notation: $z = z(t)$, for any $z \in \{x_i, y_i, v,\ i = 1,...,n\}$. We also define a function $H : (0,\infty) \to [0,\infty)$ as

$$H(z) = z - 1 - \ln z.$$

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

Theorem 1. Consider the system (4)-(6), (i) if $R_0 \leq 1$, then E_0 is GAS,

(ii) if $R_0 > 1$, then E_1 is GAS.

Proof. (i) Define a Lyapunov functional W_1 as follows:

$$W_1(\mathbf{x},\mathbf{y},v) = \sum_{i=1}^{n} \frac{k_i}{\delta_i} e^{-n_i\mu_i} \left[\frac{e^{-m_i\tau_i} x_i^0}{1+a_i x_i^0} H\left(\frac{x_i}{x_i^0}\right) + y_i + e^{-m_i\tau_i}\beta_i \int_0^{\tau_i} \frac{x_i(t-\theta)v(t-\theta)}{(1+a_i x_i(t-\theta))(1+b_i v(t-\theta))} d\theta + \delta_i \int_0^{\mu_i} y_i(t-\theta) d\theta \right]$$

We note that W_1 is defined and continuous for all $(\mathbf{x},\mathbf{y},v) > 0$. Also, the global minimum $W_1 = 0$ occurs at the uninfected steady state E_0. The time derivative of W_1 along the solution of (4)-(6) is given by

$$\begin{aligned}
\frac{dW_1}{dt} &= \sum_{i=1}^{n} \frac{k_i}{\delta_i} e^{-n_i\mu_i} \left[\frac{e^{-m_i\tau_i}}{1+a_i x_i^0} \left(1 - \frac{x_i^0}{x_i}\right) \left(\lambda_i - d_i x_i - \frac{\beta_i x_i v}{(1+a_i x_i)(1+b_i v)}\right) \right. \\
&+ \frac{e^{-m_i\tau_i}\beta_i x_i(t-\tau_i)v(t-\tau_i)}{(1+a_i x_i(t-\tau_i))(1+b_i v(t-\tau_i))} - \delta_i y_i + \frac{e^{-m_i\tau_i}\beta_i x_i v}{(1+a_i x_i)(1+b_i v)} \\
&\left. - \frac{e^{-m_i\tau_i}\beta_i x_i(t-\tau_i)v(t-\tau_i)}{(1+a_i x_i(t-\tau_i))(1+b_i v(t-\tau_i))} + \delta_i y_i - \delta_i y_i(t-\mu_i) \right] + \sum_{i=1}^{n} e^{-n_i\mu_i} k_i y_i(t-\mu_i) - rv \\
&= \sum_{i=1}^{n} \frac{k_i}{\delta_i} e^{-n_i\mu_i} \left[\frac{-e^{-m_i\tau_i}\lambda_i}{x_i x_i^0 (1+a_i x_i^0)} (x_i - x_i^0)^2 - \frac{e^{-m_i\tau_i}\beta_i x_i v}{(1+a_i x_i^0)(1+a_i x_i)(1+b_i v)} \right. \\
&\left. + \frac{e^{-m_i\tau_i}\beta_i x_i^0 v}{(1+a_i x_i^0)(1+a_i x_i)(1+b_i v)} + \frac{e^{-m_i\tau_i}\beta_i x_i v}{(1+a_i x_i)(1+b_i v)} \right] - rv \\
&= \sum_{i=1}^{n} \frac{k_i}{\delta_i} e^{-n_i\mu_i} \left[\frac{-e^{-m_i\tau_i}\lambda_i}{x_i x_i^0 (1+a_i x_i^0)} (x_i - x_i^0)^2 + \frac{e^{-m_i\tau_i}\beta_i x_i^0 v}{(1+a_i x_i^0)(1+b_i v)} \right] - rv \\
&= \sum_{i=1}^{n} \frac{-k_i d_i e^{-(m_i\tau_i + n_i\mu_i)}}{\delta_i x_i (1+a_i x_i^0)} (x_i - x_i^0)^2 + r\sum_{i=1}^{n} \frac{R_i v}{1+b_i v} - rv \\
&= -\sum_{i=1}^{n} \left(\frac{k_i d_i e^{-(m_i\tau_i + n_i\mu_i)}}{\delta_i x_i (1+a_i x_i^0)} (x_i - x_i^0)^2 + \frac{r b_i R_i v^2}{1+b_i v} \right) + (R_0 - 1) rv. \qquad (17)
\end{aligned}$$

It can be seen that, if $R_0 \leq 1$ then $\frac{dW_1}{dt} \leq 0$ for all $x_i, v > 0$, $i = 1,\ldots,n$. By Theorem 5.3.1 in [20], the solutions of system (4)-(6) limit to M, the largest invariant subset of $\left\{ \frac{dW_1}{dt} = 0 \right\}$. Clearly, it follows from (17) that $\frac{dW_1}{dt} = 0$ if and only if $x_i = x^0$, $i = 1,\ldots,n$ and $v = 0$. Noting that M is invariant, for each element of M we have $v = 0$, then $\dot{v} = 0$. From Eq. (6) we drive that

$$0 = \dot{v} = \sum_{i=1}^{n} e^{-n_i\mu_i} k_i y_i(t-\mu_i).$$

Since $y_i(t-\theta) \geq 0$ for all $\theta \in [0,\ell]$, then $\sum_{i=1}^{n} e^{-n_i\mu_i} k_i y_i(t-\mu_i) = 0$ if and only if $y_i(t-\mu_i) = 0$, $i = 1,\ldots,n$. Hence $\frac{dW_1}{dt} = 0$ if and only if $x_i = x^0$, $y_i = 0$, $i = 1,\ldots,n$ and $v = 0$. From LaSalle's invariance principle, E_0 is GAS.

To prove (ii), we consider the Lyapunov functional

$$W_2(\mathbf{x},\mathbf{y},v) = \sum_{i=1}^{n} \frac{k_i e^{-n_i\mu_i}}{\delta_i} \left[e^{-m_i\tau_i} \left(x_i - x_i^* - \int_{x_i^*}^{x_i} \frac{x_i^*(1+a_i\eta)}{\eta(1+a_i x_i^*)} d\eta \right) + y_i^* H\left(\frac{y_i}{y_i^*}\right) \right.$$
$$+ e^{-m_i\tau_i} \frac{\beta_i x_i^* v^*}{(1+a_i x_i^*)(1+b_i v^*)} \int_0^{\tau_i} H\left(\frac{x_i(t-\theta)v(t-\theta)(1+a_i x_i^*)(1+b_i v^*)}{x_i^* v^* (1+a_i x_i(t-\theta))(1+b_i v(t-\theta))} \right) d\theta$$
$$\left. + \delta_i y_i^* \int_0^{\mu_i} H\left(\frac{y_i(t-\theta)}{y_i^*}\right) d\theta \right] + v^* H\left(\frac{v}{v^*}\right).$$

Calculating the time derivative of W_2 along the solutions of model (4)-(6), we get

$$\begin{aligned}
\frac{dW_2}{dt} &= \sum_{i=1}^{n} \frac{k_i e^{-n_i\mu_i}}{\delta_i} \left[e^{-m_i\tau_i} \left(1 - \frac{x_i^*(1+a_i x_i)}{x_i(1+a_i x_i^*)}\right) \left(\lambda_i - d_i x_i - \frac{\beta_i x_i v}{(1+a_i x_i)(1+b_i v)}\right) \right. \\
&+ \left(1 - \frac{y_i^*}{y_i}\right) \left(\frac{e^{-m_i\tau_i}\beta_i x_i(t-\tau_i)v(t-\tau_i)}{(1+a_i x_i(t-\tau_i))(1+b_i v(t-\tau_i))} - \delta_i y_i \right) \\
&+ \frac{e^{-m_i\tau_i}\beta_i x_i v}{(1+a_i x_i)(1+b_i v)} - \frac{e^{-m_i\tau_i}\beta_i x_i(t-\tau_i)v(t-\tau_i)}{(1+a_i x_i(t-\tau_i))(1+b_i v(t-\tau_i))} \\
&+ \frac{e^{-m_i\tau_i}\beta_i x_i^* v^*}{(1+a_i x_i^*)(1+b_i v^*)} \ln\left(\frac{x_i(t-\tau_i)v(t-\tau_i)(1+a_i x_i)(1+b_i v)}{x_i v(1+a_i x_i(t-\tau_i))(1+b_i v(t-\tau_i))} \right) \\
&\left. + \delta_i y_i - \delta_i y_i(t-\mu_i) + \delta_i y_i^* \ln\left(\frac{y_i(t-\mu_i)}{y_i}\right) \right] \\
&+ \left(1 - \frac{v^*}{v}\right) \left(\sum_{i=1}^{n} e^{-n_i\mu_i} k_i y_i(t-\mu_i) - rv \right) \\
&= \sum_{i=1}^{n} \frac{k_i e^{-n_i\mu_i}}{\delta_i} \left[e^{-m_i\tau_i} \left(1 - \frac{x_i^*(1+a_i x_i)}{x_i(1+a_i x_i^*)}\right) (\lambda_i - d_i x_i) \right. \\
&+ \frac{e^{-m_i\tau_i}\beta_i x_i^* v}{(1+a_i x_i^*)(1+b_i v)} - \frac{y_i^* e^{-m_i\tau_i}\beta_i x_i(t-\tau_i)v(t-\tau_i)}{y_i(1+a_i x_i(t-\tau_i))(1+b_i v(t-\tau_i))} + \delta_i y_i^* \\
&\left. + \frac{e^{-m_i\tau_i}\beta_i x_i^* v^*}{(1+a_i x_i^*)(1+b_i v^*)} \ln\left(\frac{x_i(t-\tau_i)v(t-\tau_i)(1+a_i x_i)(1+b_i v)}{x_i v(1+a_i x_i(t-\tau_i))(1+b_i v(t-\tau_i))} \right) + \delta_i y_i^* \ln\left(\frac{y_i(t-\mu_i)}{y_i}\right) \right] \\
&- rv - \sum_{i=1}^{n} e^{-n_i\mu_i} k_i y_i(t-\mu_i) \frac{v^*}{v} + rv^*.
\end{aligned}$$

Using the infected steady state conditions (8)-(10), we obtain

$$\begin{aligned}
\frac{dW_2}{dt} &= \sum_{i=1}^{n} \frac{k_i e^{-n_i\mu_i}}{\delta_i} \left[e^{-m_i\tau_i} \left(1 - \frac{x_i^*(1+a_i x_i)}{x_i(1+a_i x_i^*)}\right) (d_i x_i^* + e^{m_i\tau_i}\delta_i y_i^* - d_i x_i) \right. \\
&+ \delta_i y_i^* \frac{v(1+b_i v^*)}{v^*(1+b_i v)} - \delta_i y_i^* \frac{x_i(t-\tau_i)v(t-\tau_i)y_i^*(1+a_i x_i^*)(1+b_i v^*)}{x_i^* v^* y_i(1+a_i x_i(t-\tau_i))(1+b_i v(t-\tau_i))} + 2\delta_i y_i^* \\
&\left. + \delta_i y_i^* \ln\left(\frac{x_i(t-\tau_i)v(t-\tau_i)y_i(t-\mu_i)(1+a_i x_i)(1+b_i v)}{x_i v y_i(1+a_i x_i(t-\tau_i))(1+b_i v(t-\tau_i))} \right) - \delta_i y_i^* \frac{v^* y_i(t-\mu_i)}{v y_i^*} - \delta_i y_i^* \frac{v}{v^*} \right] \\
&= \sum_{i=1}^{n} \frac{k_i e^{-n_i\mu_i}}{\delta_i} \left[e^{-m_i\tau_i} \left(1 - \frac{x_i^*(1+a_i x_i)}{x_i(1+a_i x_i^*)}\right) (d_i x_i^* - d_i x_i) \right. \\
&+ \delta_i y_i^* \left(-1 - \frac{v}{v^*} + \frac{v}{v^*} \frac{1+b_i v^*}{1+b_i v} + \frac{1+b_i v}{1+b_i v^*} \right) \\
&+ \delta_i y_i^* \left\{ 4 - \frac{x_i^*}{x_i} \frac{1+a_i x_i}{1+a_i x_i^*} - \frac{x_i(t-\tau_i)v(t-\tau_i)y_i^*(1+a_i x_i^*)(1+b_i v^*)}{x_i^* v^* y_i(1+a_i x_i(t-\tau_i))(1+b_i v(t-\tau_i))} - \frac{v^* y_i(t-\mu_i)}{v y_i^*} \right. \\
&\left. \left. - \frac{1+b_i v}{1+b_i v^*} + \ln\left(\frac{x_i(t-\tau_i)v(t-\tau_i)y_i(t-\mu_i)(1+a_i x_i)(1+b_i v)}{x_i v y_i(1+a_i x_i(t-\tau_i))(1+b_i v(t-\tau_i))} \right) \right\} \right]. \qquad (18)
\end{aligned}$$

Then using the following equality

$$\begin{aligned}
\ln\left(\frac{x_i(t-\tau_i)v(t-\tau_i)y_i(t-\mu_i)(1+a_i x_i)(1+b_i v)}{x_i v y_i(1+a_i x_i(t-\tau_i))(1+b_i v(t-\tau_i))} \right) &= \ln\left(\frac{x_i^*}{x_i} \frac{1+a_i x_i}{1+a_i x_i^*} \right) \\
&+ \ln\left(\frac{v^* y_i(t-\mu_i)}{v y_i^*} \right) \\
&+ \ln\left(\frac{x_i(t-\tau_i)v(t-\tau_i)y_i^*(1+a_i x_i^*)(1+b_i v^*)}{x_i^* v^* y_i(1+a_i x_i(t-\tau_i))(1+b_i v(t-\tau_i))} \right) \\
&+ \ln\left(\frac{1+b_i v}{1+b_i v^*} \right),
\end{aligned}$$

Eq. (18) can be rewritten as:

$$\begin{aligned}
\frac{dW_2}{dt} &= -\sum_{i=1}^{n} \frac{k_i e^{-n_i\mu_i}}{\delta_i} \left[\frac{e^{-m_i\tau_i} d_i (x_i - x_i^*)^2}{x_i (1+a_i x_i^*)} + \frac{\delta_i y_i^* b_i (v - v^*)^2}{v^*(1+b_i v)(1+b_i v^*)} \right. \\
&\left. + \delta_i y_i^* \left\{ H\left(\frac{x_i^*}{x_i} \frac{1+a_i x_i}{1+a_i x_i^*} \right) + H\left(\frac{v^* y_i(t-\mu_i)}{v y_i^*} \right) + H\left(\frac{1+b_i v}{1+b_i v^*} \right) \right. \right. \\
&\left. \left. + H\left(\frac{x_i(t-\tau_i)v(t-\tau_i)y_i^*(1+a_i x_i^*)(1+b_i v^*)}{x_i^* v^* y_i(1+a_i x_i(t-\tau_i))(1+b_i v(t-\tau_i))} \right) \right\} \right]. \qquad (19)
\end{aligned}$$

It is obvious that if $x_i^*, y_i^* v^* > 0$ then $\frac{dW_2}{dt} \leq 0$ for all $(x_i, y_i, v) > 0$. By Theorem 5.3.1 in [20], the solutions of system (4)-(6) limit to M, the largest invariant subset of $\left\{\frac{dW_2}{dt} = 0\right\}$. It can be seen that $\frac{dW_2}{dt} = 0$ if and only if $x_i = x_i^*$, $v = v^*$, and $H = 0$ i.e.

$$\frac{v^* y_i(t-\mu_i)}{v y_i^*} = 1. \tag{20}$$

If $v = v^*$ then from (20) we have $y_i = y_i^*$, and hence $\frac{dW_2}{dt}$ equal to zero at E_1. LaSalle's invariance principle implies global stability of E_1. □

3 Conclusion

In this paper, we have investigated mathematical model of virus dynamics with discrete delay. We have assumed that the virus attack n classes of target cells. The infection rate is given by Crowley-Martin functional response. By defining the delay-dependent basic reproduction number R_0, we have discussed the existence of the steady states. The global stability of the uninfected and infected steady states of the model has been established using suitable Lyapunov functionals and LaSalle's invariant principle. We have proven that, if $R_0 < 1$, then the uninfected steady state is GAS and if $R_0 > 1$, then infected steady state is GAS.

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