Global analysis of a virus infection model with multitarget cells and distributed intracellular delays

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Abstract: In this paper, we investigate the global analysis of a virus infection model with multitarget cells and multiple distributed intracellular delays. The model is a $(2n+1)$-dimensional nonlinear delay differential equations that describes the dynamics of the virus, n classes of uninfected target cells and n classes of infected cells. The incidence rate of infection is given by saturation functional response. The model has two types of distributed time delays describing the time needed for infection of target cell and virus replication. This model can be seen as a generalization of several models given in the literature describing the interaction of the virus with one class of target cells. Lyapunov functionals are constructed to establish the global asymptotic stability of the uninfected and infected steady states of the model. We have proven that if the basic reproduction number is less than unity then the uninfected steady state is globally asymptotically stable, and if the infected steady state exists then it is globally asymptotically stable.

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1 Introduction

In the last decades, there has been much interest in developing mathematical models of virus infection dynamics of many diseases [1]. This is because their importance to explore possible mechanisms and dynamical behaviors of the viral infection process, to estimate key parameter values, and to guide development efficient anti-viral drug therapies. Some of these models are given by ODEs under an assumption that, the infection could occur and the viruses are produced from infected target cells instantaneously, once the uninfected target cells are contacted by the virus particles (see e.g. [2], [3], [4], [5], [6] and [7]). Other accurate models incorporate the delay between the time the viral entry into the target cell and the time the production of new virus particles, modeled with discrete time delay or distributed time delay using functional differential equations (see e.g. [9], [10], [11], [26] and [28]). The basic virus dynamics model with distributed intracellular time delay has been proposed in [28] and given by

$$\dot{x}(t) = \lambda - dx(t) - (1-u_{rt})\bar{\beta}x(t)v(t) \tag{1}$$

$$\dot{y}(t) = (1-u_{rt})\bar{\beta}\int_0^\infty f(\tau)e^{-m\tau}x(t-\tau)v(t-\tau)d\tau - ay(t), \tag{2}$$

$$\dot{v}(t) = (1-u_p)\bar{p}\int_0^\infty g(\tau)y(t-\tau)d - cv(t), \tag{3}$$

where $x(t), y(t)$ and $v(t)$ represent the populations of uninfected target cells, infected cells and free virus particles at time t, respectively. Here λ, represents the rate of which new target cells are generated from sources within the body, d is the death rate constant, and $\bar{\beta}$ is the constant rate at which a target cell becomes infected via contacting with virus. Equation (2) describes the population dynamics of the infected cells and shows that they die with rate constant a. The virus particles are produced by the infected cells with rate constant $\bar{p}$ and are removed from the system with rate constant c. The model includes two kinds of antiretroviral drugs, reverse transcriptase inhibitors (RTI) to prevent the virus from infecting cells and protease inhibitors (PI) to prevent already infected host cells from producing infectious virus particles. The parameters $u_{rt}\epsilon[0,1]$ and $u_p\epsilon[0,1]$ are the efficacies of RTI and PI, respectively. To account for the time lag between viral contacting a target cell and the production of new virus particles, two distributed intracellular delays are introduced. It is assumed that the target cells are contacted by the virus particles at time $t-\tau$ become infected cells at time t, where τ is a random variable with a probability distribution $f(\tau)$. The factor $e^{-m\tau}$ accounts for the loss of target cells during time period $[t-\tau,t]$. On the other hand, it is assumed that, a cell infected at time $t-\tau$ starts to yield new infectious virus at time t where τ is distributed according to a probability distribution $g(\tau)$.

Many authors have devoted their effort in developing various mathematical models of viral infections with discrete or distributed delays and studying their qualitative behaviors (see [9], [11], [26], [10], [28], [22], [23], [21], [27], [24], [31] and [33]). These works addressed the virus dynamics models under the assumption that the virus attack one class of target cells (e.g. $CD4^{+}T$ cells in case of HIV or hepatic cells in case of HCV and HBV). In case of HIV infection, the HIV has two classes of target cells, $CD4^{+}T$ cells and macrophages [29]. In ([8], [30], [12], [13], [14], [17], [15], [19]), a class of HIV infection models with two classes of target cells has been proposed. The global stability of these models has been investigated in ([12], [13], [14], [15] and [19]). Since the interactions of some types of viruses inside the human body are not very clear and complicated, therefore the virus may attack more than two classes of target cells. In very recent works, Elaiw [18] and [16], has proposed some virus dynamics models with multitarget cells and investigated the global asymptotic stability of its steady states. In [16], multiple discrete-time delays have been incorporated into the model.

The purpose of this paper is to propose a delayed virus dynamics model with multi-target cells and establish the global stability of its steady states. We incorporate two types of distributed delays into this model to account the time delay between the time the target cells are contacted by the virus particle and the time the emission of infectious (matures) virus articles. We assume that the infection rate is given by saturation functional response. The global stability of these models is established using Lyapunov functionals, which are similar in nature to those used in [25]. We prove that if the basic reproduction number is less than unity, then the uninfected steady state is globally asymptotically stable (GAS) and if the infected steady state exists, then it is GAS.

2 Virus infection model with multitarget cells and distributed delays

In this section we propose a virus dynamics model which describes the interaction of the virus with n classes of target cells taking into account the saturation infection rate and multiple distributed intracellular delays.

$$\dot{x}_i(t) = r_i(x_i) - \frac{\beta_i x_i(t) v(t)}{1+\alpha_i v(t)}, \qquad i = 1,\cdots,n \quad (4)$$

$$\dot{y}_i(t) = \beta_i \int_0^\infty f_i(\tau)\, e^{-m_i\tau} \frac{x_i(t-\tau)v(t-\tau)}{1+\alpha_i v(t-\tau)} d\tau - a_i y_i(t), \qquad i = 1,\cdots,n \quad (5)$$

$$\dot{v}(t) = \sum_{i=1}^{n} p_i \int_0^\infty g_i(\tau) e^{-\delta_i \tau} y_i(t-\tau) d\tau - cv(t), \quad (6)$$

where x_i and y_i represent the populations of the uninfected target cells and infected cells of class i, respectively, and v is the population of the virus particles. Here $\alpha_i, i=1,\cdots,n$ are positive constants, $\beta_i = (1-u_{rt})\bar{\beta}_i$ and $p_i = (1-u_p)\bar{p}_i, i=1,\cdots n$. The factors $e^{\delta_i \tau}, i=1,\cdots,n$ account for the cells loss during the delay period. All the other parameters of the model have the same meanings as given in (1)-(3). The growth rate of the uninfected target cells of class i is given by the function $\tilde{r}_i(x_i)$. The following particular forms of function $\tilde{r}_i(x_i)$ have widely been used in the literature of virus dynamics:

$$\bar{r}_i(x_i) = \lambda_i - dx_i,$$

$$\tilde{r}_i(x_i) = \lambda_i - dx_i + b_i x_i \left(1 - \frac{x_i}{x_{i,max}}\right),$$

where b_i is the maximum proliferation rate of the target cells of class, i and $x_{i,max}$ is the maximum level of target cells population in the body. We mention that, if $n=1, \alpha_1 = 0$ and $r_1 = \bar{r}_1$, then model (4)-(6) leads to the model presented in [33] and [31].

The probability distribution functions $f_i(\tau)$ and $g_i(\tau)$ are assumed to satisfy $f_i(\tau) > 0$ and $g_1(\tau) > 0$ and

$$\int_0^\infty f_i(\tau)d\tau = \int_0^\infty g_i(\tau)d\tau = 1, \int_0^\infty f_i(u)e^{su}du < \infty$$

$$\int_0^\infty g_i(u)e^{su}du < \infty \quad i = 1, \cdots, n,$$

where s is a positive number. Let $F_i = \int_0^\infty f_i(\tau)e^{-m_i\tau}d\tau$ and $G_i = \int_0^\infty g_i(\tau)e^{-\delta_i\tau}d\tau$,

$m_i \geq 0$, $\delta_i \geq 0$, then $0 < F_i \leq 1$ and $0 < G_i \leq 1$, $i = 1, \cdots, n$. The initial conditions for system

(4)-(6) take the form

$$x_j(\theta) = \varphi_j(\theta), \qquad y_j(\theta) = \varphi_{j+n}(\theta).\ j = 1, \cdots, n,$$

$$v(\theta) = \varphi_{2n+1}(\theta), \varphi_j(\theta) \geq 0, \qquad j = 1, \cdots, 2n+1,$$

$$\theta \in (-\infty, 0), \tag{7}$$

$$\varphi_j(0) > 0, j = 1, \cdots, 2n+1,$$

where, $(\varphi_1(\theta), \varphi_2(\theta), \cdots, \varphi_{2n+1}(\theta) \in UC\big((-\infty, 0], \mathbb{R}_+^{2n+1}\big)$, and UC is the Banach space of fading memory type defined as [32]:

$$UC\big((-\infty, 0), \mathbb{R}_+^{2n+1}\big) = \{\phi \in C((-\infty, 0], \mathbb{R}_+^{2n+1}) : \phi(u)e^{su} \text{ is uniformly continuous on } (-\infty, 0] \text{ and } \|\phi\| = \sup_{u\leq 0} \phi(u)e^{su} < \infty\}$$

where $C((-\infty, 0], \mathbb{R}_+^{2n+1})$ is the Banach space of continuous functions mapping the interval $(-\infty, 0]$ into $\mathbb{R}_+^{2n+1}$. By the fundamental theory of functional differential equations [20], system (4)-(6) has a unique solution satisfying the initial conditions (7).

Assumption A1 For $i = 1, \cdots, n$, function $\tau_i : [0, \infty) \to \mathbb{R}$ satisfies:

(i) $r_i(x_i)$ is continuous, differentiable and $r_i(0) > 0$,

(ii) there exits an $x_i^0 > 0$ such that

$$r_i(x_i^0) = 0, \quad r_i'(x_i^0) < 0$$

$$(x_i - x_i^0)r_i(x_i) \leq 0, \quad x_i \neq x_i^0$$

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 $\mathbf{x} = (x_1, x_2, \cdots, x_n)^T$ and $\mathbf{y} = (y_1, y_2, \cdots, y_n)^T$.

Proposition 1. Suppose that Assumptions A1 holds true and $(\mathbf{x}(t), \mathbf{y}(t), v(t))$ 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 $x_i(t) > 0$ for all $t \geq 0$. Assume that $x_i(t)$ lose its non-negativity on some local existence interval $[0, \sigma]$ for some constant σ and let t^* be such that $x_i(t^*) = 0$. From Eq. (4) we have $\dot{x}_i(t^*) = r_i(0) > 0$, $i = 1, \cdots, n$. Hence $x_i(t) < 0$

for some $t \in (t^* - \varepsilon, t^*)$, 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

$$y_i(t) = y_i(0)e^{-a_i t} + \beta_i \int_0^t e^{-a_i(t-\eta)} \int_0^\infty f_i(\tau)e^{-m_i\tau} \frac{x_i(\eta-\tau)v(\eta-\tau)}{1+\alpha_i v(\eta-\tau)} d\tau d\eta$$

$$i = 1, \cdots, n,$$

$$v(t) = v(0)e^{-ct} + \sum_{i=1}^n p_i \int_0^t e^{-c(t-\eta)} \int_0^\infty g_i(\tau)e^{-\delta_i\tau} y_i(\eta-\tau) d\tau d\eta.$$

Then similar arguments can easily be used to show that $y_i(t) \geq 0$ and $v(t) \geq 0$ for all $t \geq 0$.

Next we show the boundedness of the solutions. Assumption A1 and Eqs. (4) imply that $\lim\ sup_{t\to\infty} x_i(t) \leq x_i^0$.

If follows that $\int_0^\infty f_i(\tau)e^{-m_i\tau}x_i(t-\tau)d\tau \leq F_i x_i^0$.

Let $X_i(t) = \int_0^\infty f_i(\tau)e^{-m_i\tau}x_i(t-\tau)d\tau + y_i(t)$,

$i = 1, \cdots, n, S_i = sup_{x_i\in[0,x_i^0]} r_i(x_i)$ and $\bar{a}_i \leq \min\left\{a_i, \frac{S_i}{x_i^0}\right\}$, then

$$\dot{X}_i(t) = \int_0^\infty f_i(\tau)e^{-m_i\tau}(r_i(x_i(t-\tau)) - \frac{\beta_i x_i(t-\tau)v(t-\tau)}{1+\alpha_i v(t-\tau)}d\tau$$

$$+\int_0^\infty f_i(\tau)e^{-m_i\tau}\frac{\beta_i x_i(t-\tau)v(t-\tau)}{1+\alpha_i v(t-\tau)}d\tau - a_i y_i(t),$$

$$\leq F_i S_i - a_i y_i(t) \leq F_i S_i - a_i y_i(t) + F_i S_i - \bar{a}_i \int_0^\infty f_i(\tau)e^{-m_i\tau}x_i(t-\tau)d\tau$$

$$\leq 2F_i S_i - \bar{a}_i X_i(t).$$

Hence $\lim sup_{t\to\infty} X_i(t) \leq L_i$, where $L_i = 2F_i S_i/\bar{a}_i$. Since $\int_0^\infty f_i(\tau)e^{-m_i\tau}x_i(t-\tau)d\tau > 0$,

we get $\lim sup_{t\to\infty} y_i(t) \leq L_i$. On the other hand,

$$v(t) \leq \sum_{\iota=1}^n p_\iota L_\iota \int_0^\infty g_\iota(\tau)e^{-\delta_\iota\tau}d\tau - cv = \sum_{\iota=1}^n p_\iota L_\iota G_\iota - cv,$$

then $\lim sup_{t\to\infty} v(t) \leq L^*$, where $L^* = \sum_{i=1}^n \frac{p_i L_i G_i}{c}$. Therefore, $\boldsymbol{x}(t), \boldsymbol{y}(t)$ and $v(t)$ are ultimately bounded.

2.2 Steady states

Assumption A1 ensures that system (4)-(6) has an uninfected steady state $E_0 = (\boldsymbol{x}^0, \boldsymbol{y}^0, v^0)$, where x_i^0 is the solution of $r_i(x_i^0) = 0$, $y_i^0 = 0$ and $v^0 = 0$. In addition to E_0, the system can has a positive infected steady state $E_1(\boldsymbol{x}^*, \boldsymbol{y}^*, v^*)$. The coordinates of the infected steady state, if they exist, satisfy the equalities:

$$r_i(x_i^*) = \frac{\beta_i x_i^* v^*}{1+\alpha_i v^*}, \quad a_i y_i^* = F_i \frac{\beta_i x_i^* v^*}{1+\alpha_i v^*}, \quad i = 1, \cdots, n \quad (8)$$

$$cv^* = \sum_{i=1}^n G_i p_i y_i^*. \quad (9)$$

The basic reproduction number of system (4)-(6) is given by

$$R_0 = \sum_{i=1}^n R_i = \sum_{i=1}^n \frac{F_i G_i \beta_i p_i x_i^0}{\alpha_i c}, \quad (10)$$

where R_i is the basic reproduction number for the dynamics of the interaction of the virus only with the target cells of class i.

2.3 Global stability analysis

In this section, we prove the global stability of the uninfected and infected steady states of system (4)-(6) employing the method of Lyapunov functional which is used in [25] for SIR epidemic model with distributed delay. Next we shall use the following notation: $z = z(t)$, for any $z \in \{x_i, y_i, v, i = 1, \cdots, n\}$. 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. If $R_0 \leq 1$ and Assumption A1 holds true, then E_0 is GAS.

Proof. Define a Lyapunov functional W_1 as:

$$W_1 = \sum_{i=1}^n \gamma_i \left[x_i^0 H\left(\frac{x_i}{x_1^0}\right) + \frac{1}{F_i} y_i + \frac{\beta_i}{F_i}\int_0^\infty f_i(\tau)e^{-m_i\tau}\int_0^\tau \frac{x_i(t-\theta)v(t-\theta)}{1+\alpha_i v(t-\theta)}d\theta d\tau + \frac{a_i}{F_i G_i}\int_0^\infty g_i(\tau)e^{-\delta_i\tau}\int_0^\tau y_i(t-\theta)d\theta d\tau \right] + v,$$

where $\gamma_i = \frac{p_i F_i G_i}{\alpha_i}$

The time derivative of W_1 along the trajectories of (4)-(6) satisfies

$$\frac{dW_1}{dt} = \sum_{i=1}^{n} \gamma_i \left[\left(1 - \frac{x_i^0}{x_i}\right)\left((r_i(x_i) - \frac{\beta_i x_i v}{1+\alpha_i v} \right) + \frac{\beta_i}{F_i}\int_0^\infty f_i(\tau) e^{-m_i\tau} \frac{x_i(t-\tau)v(t-\tau)}{1+\alpha_i v(t-\tau)} d\tau - \frac{a_i}{F_i} y_i + \frac{\beta_i}{F_i}\int_0^\infty f_i(\tau) e^{-m_i\tau}\left(\frac{x_i v}{1+\alpha_i v} - \frac{x_i(t-\tau)v(t-\tau)}{1+\alpha_i v(t-\tau)}\right) d\tau + \frac{a_i}{F_i G_i}\int_0^\infty g_i(\tau) e^{-\delta_i \tau}\big(y_i - y_i(t-\tau)\big) d\tau \right] + \sum_{i=1}^{n} p_i \int_0^\infty g_i(\tau) e^{-\delta_i\tau} y_i(t-\tau) d\tau - cv.$$

Collecting terms we get

$$\frac{dW_1}{dt} = \sum_{i=1}^{n} \gamma_i \left(\left(1 - \frac{x_i^0}{x_i}\right) r_i(x_i) + \frac{\beta_i x_i^0 v}{1+\alpha_i v} \right) - cv$$

$$= \sum_{i=1}^{n} \gamma_i \left(1 - \frac{x_i^0}{x_i}\right) r_i(x_i) - cv + cv \sum_{i=1}^{n} \frac{F_i G_i p_i \beta_i x_i^0}{a_i c(1+\alpha_i v)}$$

$$= \sum_{i=1}^{n} \gamma_i \left(1 - \frac{x_i^0}{x_i}\right) r_i(x_i) - cv + cv \sum_{i=1}^{n} \frac{R_i}{1+\alpha_i v}$$

$$= \sum_{i=1}^{n} \frac{\gamma_i}{x_i}\left(x_i - x_i^0\right) r_i(x_i) - \sum_{i=1}^{n} \frac{R_i \alpha_i c v^2}{1+\alpha_i v} + (R_0 - 1) cv$$

If $R_0 \le 1$ and Assumption A1 is satisfied, then $\frac{dW_1}{dt} \le 0$ for all $x, y > 0$. By Theorem 5.3.1 in [20], the solutions of system (4)-(6) limit to M, the largest invariant subset of $\left\{ \frac{dW_1}{dt} = 0 \right\}$. Clearly, it follows from (11) that $\frac{dW_1}{dt} = 0$ if and only if $\boldsymbol{x} = \boldsymbol{x}^0$ $v = 0$. Noting that M is invariant, for each element of M we have $v = 0$, then $\dot{v} = 0$. From Eq. (6) we drive that

$$0 = \dot{v} = \sum_{i=1}^{n} \int_0^\infty g_i(\tau)\, e^{-\delta_i \tau}\, p_i y_i(t-\tau) d\tau$$

This yields $y_i = 0$. Hence $\frac{dW_1}{dt} = 0$ if and only if $x = x^0$ $y_i = 0$ and $v = 0$. From LaSalle.s invariance principle, E_0 is GAS.

Assumption A2. For $i = 1, \cdots, n$, function r_i satisfies:

$$\left(1 - \frac{x_i^*}{x_i}\right)(r_i(x_i) - r_i(x_i^*)) \le 0 \text{ for all } x_i > 0$$

Theorem 2. If E_1 exists and Assumptions A1-A2 hold true, then E_1 is GAS.

Proof. We construct the following Lyapunov functional

$$W_2 = \sum_{i=1}^{n} \gamma_i [\, x_i^* H\left(\frac{x_i}{x_i^*}\right) + \frac{1}{F_i} y_i^* H\left(\frac{y_i}{y_i^*}\right) + \frac{1}{F_i}\frac{\beta_i x_i^* v^*}{1+\alpha_i v^*}\int_0^\infty f_i(\tau) e^{-m_i\tau} \int_0^\tau H\left(\frac{x_i(t-\theta)v(t-\theta)(1+\alpha_i v^*)}{x_i^* v^*(1+\alpha_i v(t-\theta))}\right) d\theta d\tau + \frac{a_i y_i^*}{F_i G_i}\int_0^\infty g_i(\tau) e^{-\delta_i\tau}\int_0^\tau H\left(\frac{y_i(t-\theta)}{y_i^*}\right) d\theta d\tau\,] + v^* H\left(\frac{v}{v^*}\right).$$

Differentiating with respect to time yields

$$\frac{dW_2}{dt} = \sum_{i=1}^{n} \gamma_i \, [\left(1 - \frac{x_i^*}{x_i}\right)\left(r_i(x_i) - \frac{\beta_i x_i v}{1+\alpha_i v}\right) + \frac{1}{F_i}\left(1 - \frac{y_i^*}{y_i}\right)\left(\beta_i \int_0^\infty f_i(\tau) e^{-m_i\tau}\frac{x_i(t-\tau)v(t-\tau)}{11+\alpha_i v(t-\tau)} d\tau - a_i y_i\right)$$

$$+ \frac{\beta_i}{F_i}\int_0^\infty f_i(\tau) e^{-m_i\tau} (\frac{x_i v}{1+\alpha_i v} - \frac{x_i(t-\tau)v(t-\tau)}{1+\alpha_i v(t-\tau)} + \frac{x_i^* v^*}{1+\alpha_i v^*}\ln\left(\frac{x_i(t-\tau)v(t-\tau)(1+\alpha_i v)}{x_i v(1+\alpha_i v(t-\tau))}\right)) d\tau$$

$$+\frac{\alpha_i}{F_iG_i}\int_0^\infty g_i(\tau)e^{-\delta_i\tau}(y_i-y_i(t-\tau)$$

$$+y_i^*\ln\left(\frac{y_i(t-\tau)}{y_i}\right))d\tau]+\left(1-\frac{v^*}{v}\right)\times$$

$$\left(\sum_{i=1}^n p_i\int_0^\infty g_i(\tau)e^{-\delta_i\tau}y_i(t-\tau)d\tau-cv\right).$$

Collecting terms we obtain

$$\frac{dW_2}{dt}=\sum_{i=1}^n\gamma_i[\left(1-\frac{x_i^*}{x_i}\right)r_i(x_i)+\frac{\beta_i x_i^* v}{1+\alpha_i v}$$

$$-\frac{\beta_i}{F_i}\int_0^\infty f_i(\tau)e^{-m_i\tau}\ \frac{x_i(t-\tau)v(t-\tau)y_i^*}{1+\alpha_i v(t-\tau)y_i}d\tau+\frac{\alpha_i}{F_i}y_i^*$$

$$+\frac{1}{F_i}\frac{\beta_i x_i^* v^*}{1+\alpha_i v^*}\int_0^\infty f_i(\tau)e^{-m_i\tau}$$

$$\ln\left(\frac{x_i(t-\tau)v(t-\tau)(1+\alpha_i v)}{x_i v(1+\alpha_i v(t-\tau))}\right)d\tau$$

$$+\frac{a_i y_i^*}{F_iG_i}\int_0^\infty g_i(\tau)e^{-\delta_i\tau}\ln\left(\frac{y_i(t-\tau)}{y_i}\right)d\tau\ ]$$

$$-cv-\frac{v^*}{v}\sum_{i=1}^n p_i\int_0^\infty g_i(\tau)e^{-\delta_i\tau}\,y_i(t-\tau)d\tau+cv^*.$$

Using the infected steady state conditions (8)-(9), and the following equality

$$cv=cv^*\frac{v}{v^*}=\frac{v}{v^*}\sum_{i=1}^n G_ip_iy_i^*=\frac{v}{v^*}\sum_{i=1}^n\frac{\gamma_i a_i}{F_i}y_i^*$$

we obtain

$$\frac{dW_2}{dt}=\sum_{i=1}^n\gamma_i\left[\left(1-\frac{x_i^*}{x_i}\right)(r_i(x_i)-r_i(x_i^*))\right.$$

$$+\frac{a_i}{F_i}y_i^*\left(1-\frac{x_i^*}{x_i}\right)+\frac{a_i}{F_i}y_i^*\frac{v(1+\alpha_i v^*)}{v^*(1+\alpha_i v)}+\frac{a_i}{F_i}y_i^*$$

$$-\frac{a_i}{F_i^2}y_i^*\int_0^\infty f_i(\tau)e^{-m_i\tau}\frac{y_i^*x_i(t-\tau)v(t-\tau)(1+\alpha_i v^*)}{y_ix_i^*v^*(1+\alpha_i v(t-\tau))}\ d\tau$$

$$+\frac{a_i}{F_i^2}y_i^*\int_0^\infty f_i(\tau)e^{-m_i\tau}\ln\left(\frac{x_i(t-\tau)v(t-\tau)(1+\alpha_i v)}{x_i v(1+\alpha_i v(t-\tau))}\right)d\tau$$

$$+\frac{a_i}{F_iG_i}y_i^*\int_0^\infty g_i(\tau)e^{-\delta_i\tau}\ln\left(\frac{y_i(t-\tau)}{y_i}\right)d\tau-\frac{a_i}{F_i}y_i^*\frac{v}{v^*}$$

$$\left.-\frac{a_i}{F_iG_i}y_i^*\int_0^\infty g_i(\tau)e^{-\delta_i\tau}\frac{v^*y_i(t-\tau)}{vy_i^*}d\tau+\frac{a_i}{F_i}y_i^*\right].\qquad(12)$$

Then collecting terms of (12) and using the following equalities

$$\ln\left(\frac{x_i(t-\tau)v(t-\tau)(1+\alpha_i v)}{x_i v(1+\alpha_i v(t-\tau))}\right)=$$

$$\ln\left(\frac{y_i^*x_i(t-\tau)v(t-\tau)(1+\alpha_i v^*)}{y_ix_i^*v^*(1+\alpha_i v(t-\tau))}\right)+\ln\left(\frac{x_i^*}{x_i}\right)$$

$$+\ln\left(\frac{v^*y_i}{vy_i^*}\right)+\ln\left(\frac{1+\alpha_i v}{1+\alpha_i v^*}\right),$$

$$\ln\left(\frac{y_i(t-\tau)}{y_i}\right)=\ln\left(\frac{vy_i^*}{v^*y_i}\right)+\ln\left(\frac{v^*y_i(t-\tau)}{vy_i^*}\right),$$

$$\ln\left(\frac{v^*y_i}{vy_i^*}\right)+\ln\left(\frac{vy_i^*}{v^*y_i}\right)=\ln(1)=0.$$

We obtain

$$\frac{dW_2}{dt}=\sum_{i=1}^n\gamma_i\left[\left(1-\frac{x_i^*}{x_i}\right)(r_i(x_i)-r_i(x_i^*))\right.$$

$$+\frac{a_i}{F_i}y_i^*\left(1-\frac{x_i^*}{x_i}\right)+\frac{2a_i}{F_i}y_i^*$$

$$+\frac{a_i}{F_I}y_i^*\left(\frac{v(1+\alpha_i v^*)}{v^*(1+\alpha_i v)}-\frac{v}{v^*}\right)-\frac{a_i}{F_i^2}y_i^*$$

$$\int_0^\infty f_i(\tau)e^{-m_i\tau}\frac{y_i^*x_i(t-\tau)v(t-\tau)(1+\alpha_i v^*)}{y_ix_i^*v^*(1+\alpha_i v(t-\tau))}d\tau$$

$$+\frac{a_i}{F_i^2}y_i^*\int_0^\infty f_i(\tau)e^{-m_i\tau}\times$$

$$\left(\ln\left(\frac{y_i^* x_i(t-\tau)v(t-\tau)(1+\alpha_i v^*)}{y_i x_i^* v^*(1+\alpha_i v(t-\tau))}\right)+\ln\left(\frac{x_i^*}{x_i}\right)+\ln\left(\frac{v^* y_i}{v y_i^*}\right)+\ln\left(\frac{1+\alpha_i v}{1+\alpha_i v^*}\right)\right)d\tau+\frac{a_i}{F_i G_i}y_i^*\times \int_0^\infty g_i(\tau)e^{-\delta_i\tau}\left(\ln\left(\frac{v y_i^*}{v^* y_i}\right)+\ln\left(\frac{v^* y_i(t-\tau)}{v y_i^*}\right)\right)d\tau -\frac{a_i}{F_i G_i}y_i^*\int_0^\infty g_i(\tau)e^{-\delta_i\tau}\frac{v^* y_i}{v y_i^*}d\tau \Bigg] \qquad (13)$$

Eq.(13) can be rewritten as

$$\frac{dW_2}{dt}=\sum_{i=1}^n \gamma_i\Bigg[\left(1-\frac{x_i^*}{x_i}\right)(r_i(x_i)-r_i(x_i^*)) +\frac{a_i}{F_i}y_i^*\left(\frac{x_i^*}{x_i}-1-\ln\left(\frac{x_i^*}{x_i}\right)\right)+\frac{a_i}{F_i}y_i^*\times \left(-1+\frac{v(1+\alpha_i v^*)}{v^*(1+\alpha_i v)}-\frac{v}{v^*}+\frac{1+\alpha_i v}{1+\alpha_i v^*}\right) -\frac{a_i}{F_i}y_i^*\left(\frac{1+\alpha_i v}{1+\alpha_i v^*}-1-\ln\left(\frac{1+\alpha_i v}{1+\alpha_i v^*}\right)\right) -\frac{a_i}{F_i}y_i^*\int_0^\infty f_i(\tau)e^{-m_i\tau}\times \left(\frac{y_i^* x_i(t-\tau)v(t-\tau)(1+\alpha_i v^*)}{y_i x_i^* v^*(1+\alpha_i v(t-\tau))}-1 -\ln\left(\frac{y_i^* x_i(t-\tau)v(t-\tau)(1+\alpha_i v^*)}{y_i x_i^* v^*(1+\alpha_i v(t-\tau))}\right)\right)d\tau -\frac{a_i}{F_i G_i}y_i^*\int_0^\infty g_i(\tau)e^{-\delta_i\tau}\times \left(\frac{v^* y_i(t-\tau)}{v y_i^*}-1-\ln\left(\frac{v^* y_i(t-\tau)}{v y_i^*}\right)\right)d\tau\Bigg].$$

Using the following equality

$$-1+\frac{v(1+\alpha_i v^*)}{v^*(1+\alpha_i v)}-\frac{v}{v^*}+\frac{1+\alpha_i v}{1+\alpha_i v^*}=\frac{-\alpha_i(v-v^*)^2}{v^*(1+\alpha_i v^*)(1+\alpha_i v)},$$

we can rewrite $\frac{dW_2}{dt}$ as:

$$\frac{dW_2}{dt}=\sum_{i=1}^n \gamma_i\Bigg[\left(1-\frac{x_i^*}{x_i}\right)(r_i(x_i)-r_i(x_i^*)) +\frac{a_i}{F_i}y_i^*\frac{-\alpha_i(v-v^*)^2}{v^*(1+\alpha_i v^*)(1+\alpha_i v)} +\frac{a_i}{F_i}y_i^* H\left(\frac{x_i^*}{x_i}\right)+\frac{a_i}{F_i}y_i^* H\left(\frac{1+\alpha_i v}{1+\alpha_i v^*}\right) +\frac{a_i y_i^*}{F_i^2}\int_0^\infty f_i(\tau)e^{-m_i\tau}\times H\left(\frac{y_i^* x_i(t-\tau)v(t-\tau)(1+\alpha_i v^*)}{y_i x_i^* v^*(1+\alpha_i v(t-\tau))}\right)d\tau +\frac{a_i y_i^*}{F_i G_i}\int_0^\infty g_i(\tau)e^{-\delta_i\tau}H\left(\frac{v^* y_i(t-\tau)}{v y_i^*}\right)d\tau\Bigg].$$

It is easy to see that if Assumption A2 is satisfied and $x_i^*, y_i^*, v^* > 0,\ i=1,\cdots,n$, then $\frac{dW_2}{dt}\le 0$. 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.,

$$\frac{y_i^* x_i(t-\tau)v(t-\tau)(1+\alpha_i v^*)}{y_i x_i^* v^*(1+\alpha_i v(t-\tau))}=\frac{v^* y_i(t-\tau)}{v y_i^*}=1$$

For almost all $\tau\in[0,\infty)$. (14)

If $v=v^*$ then from (14) 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 proposed a virus dynamics model describing the interaction of the virus with n classes of target cells taking into account the saturation infection rate. Two types of distributed time delays describing time needed for infection of target cell and virus replication have been incorporated into the model. The global stability of the uninfected and infected steady states of the model have been established by using suitable Lyapunov functionals and LaSalle invariant principle. We have proven that, if the basic reproduction number is less than unity, then the uninfected steady state is GAS and if the infected steady state exists then it is GAS.

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