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Global properties for virus dynamics model with mitotic transmission and intracellular delay

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ABSTRACT

In this paper we study the basic model of viral infections with mitotic transmission and intracellular delay discrete. The delay corresponds to the time between infection of uninfected cells and the emission of virus on a cellular level. By means of Volterra-type Lyapunov functionals, we provide the global stability for this model. Let η be the number of virus produced per infected cell. If η_{crit}, the critical number, satisfies $\eta \leqslant \eta_{crit}$, then the virus-free steady state is globally asymptotically stable. On the contrary if $\eta > \eta_{crit}$, then the infected steady state is globally asymptotically stable if a sufficient condition is satisfied.

1. Introduction

In the mathematics of viral infections usually the mathematical models are written in the form of ordinary differential equations [4,23–26,30–32]. This class of models assumed that infection could occur instantaneously once a virus contacted a uninfected cell to infect a target cell.

Other class of virus dynamics models incorporate the delay between the time a cell is infected and the time it starts producing virus, modeled with discrete time delay [1–3,6,11,16,17,28,22,29,30,33] or distributed time delay [18,21] using functional differential equations.

The question of global stability in population models is a very interesting mathematical problem. Many authors have studied the global stability of virus dynamics models without delay using the second Lyapunov method. The Lyapunov function candidate for population biology models is the Volterra-type function. This function was applied by Korobeinikov [14] and other authors [3,10,12,13,27] to prove global stability of the steady states of viral infections models.

Recently, McCluskey and other authors study the global stability of the steady states of epidemic models with delay [9,19,20] and in [8,16,18,21,22] analyzed virus dynamics models with intracellular delay, using the method of Lyapunov functionals.

In this paper, we consider a viral infection model with mitotic transmission that was presented and studied in [1,7]. It is a refinement of earlier models (see [6,16,33], for example) that ignores density-dependent proliferation of infected cells and uninfected cells. The general viral model given in [1,7] without delay, this coincides with the models studied in [4,31] for which the global stability analysis was completed in [27,31].

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The goal of this paper is study the global stability of a delayed viral infection model with mitotic transmission, assuming that infection is transmitted directly from free virus to target cells and by divisions of infected cells. We present the construction of Lyapunov functionals for this model, using Volterra-type Lyapunov functionals.

The paper is organized as follows. The delayed model with mitotic transmission is described in Section 2. The global asymptotic stability of the virus-free steady state is established in Section 3. The global asymptotic stability of the infected steady state is established in Section 4. The paper ends with a discussion in Section 5.

2. Basic model with mitotic transmission and intracellular delay

In this section, we describe the basic model of viral infections with mitotic transmission and intracellular delay. We use the convention that $x = x(t)$, $y = y(t)$, $v = v(t)$, $x_\tau = x(t-\tau)$, and $v_\tau = v(t-\tau)$, in order to avoid excessive use of parentheses in some of the later calculations. The model given in [1,7] is formulated by the following system of delay differential equations:

$$\begin{aligned}
\frac{dx}{dt} &= \lambda + rx\left[1 - \frac{x+y}{K}\right] - \mu x - \beta x v,\\
\frac{dy}{dt} &= \beta x_\tau v_\tau + ry\left[1 - \frac{x+y}{K}\right] - \alpha y,\\
\frac{dv}{dt} &= \alpha\eta y - \gamma v,
\end{aligned} \tag{1}$$

where $x(t)$, $y(t)$ and $v(t)$ denote the concentration of uninfected cells, infected cells and free virus, respectively. Here, uninfected cells are generated at a constant rate λ and die at rate μ per uninfected cell. These cells are infected at rate β per uninfected cell per virion. τ denotes the lag between the time of the virus contacts the uninfected cell and the time of the cell becomes actively infected. The model considers that all infected cells survive the latent period, this assumption is common in delayed HIV pathogenesis models [11,28–30]. Actively infected cells die at rate α per cell by cytopathic effects. The basic model of viral infections with intracellular delays [6,16,33] assumes a source of uninfected cells but ignores proliferation of both actively infected cells and uninfected cells. The proliferation of actively infected cells and uninfected cells due to mitotic division obeys a logistic growth. The mitotic proliferation of uninfected cells described by $rx[1 - \frac{x+y}{K}]$ and mitotic transmission occurs at a rate $ry[1 - \frac{x+y}{K}]$, that is the mitotic division of actively infected cells. Uninfected cells and actively infected cells growth at a the same constant rate r and K is the maximal number that total cell population proliferate. Each actively infected cell is assumed to produce η virus particles during its life time, and γ is the clearance rate of virus particles. All parameters are positive constants with the exception of τ that is non-negative.

The model (1) without delay is developed by Wang and Ellermeyer [31] for describes the dynamics of the infection of human immunodeficiency virus type 1 (HIV-1) and considers the logistic growth of uninfected and infected lymphocyte T cells. Independently Dahari, Lo, Ribeiro and Perelson developed in [4] for hepatitis C viral (HCV) the same model without delay, extending the basic model [23] including density-dependent proliferation terms for both infected and uninfected hepatocytes.

Huang, Takeuchi and Ma, in [8] constructed Lyapunov functionals and analyzed a class of models in three dimensional with intracellular delay discrete, that incorporate generalized nonlinear incidence rate. The model (1) does not correspond to the structures of the equations of the study system in [8].

3. Known results

We begin by presenting some notations that will be used throughout this paper. Let $\mathcal{C}([-\tau, 0], \mathbb{R}^3_+)$ be the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into $\mathbb{R}^3_+$, where

$$\mathbb{R}^3_+ = \left\{(x, y, v) \in \mathbb{R}^3 \colon x \geqslant 0,\ y \geqslant 0,\ v \geqslant 0\right\}.$$

It is biologically reasonable to consider the following initial conditions for (1):

$$x(\theta) = \varphi_1(\theta), \qquad y(\theta) = \varphi_2(\theta), \qquad v(\theta) = \varphi_3(\theta) \quad (-\tau \leqslant \theta \leqslant 0), \tag{2}$$

where $\varphi = (\varphi_1(0), \varphi_2(0), \varphi_3(0)) \in \mathcal{C}$. From the fundamental theory of functional differential equations [5] and [15], it is easy to see that the solution $(x(t), y(t), v(t))$ of system (1) with the initial condition (2) exists for all $t \geqslant 0$ and is unique.

In [1,7] study the basic mathematical properties of the model (1). The results are presented in the following theorems:

Theorem 3.1. *(See [1,7].) For sufficiently large t, all solutions of system* (1) *with initial conditions* (2) *are positive and ultimately bounded.*

Theorem 3.2. *(See [1,7].) The critical number η_{crit} defined by*

$$\eta_{crit} = \frac{\gamma}{\alpha\beta x^{\circ}}\left(\frac{\lambda}{x^{\circ}} + \alpha - \mu\right) > 0. \tag{3}$$

If $\eta \leqslant \eta_{crit}$, then system (1) has only the virus-free steady state $E^{\circ}(x^{\circ}, 0, 0)$, where

$$x^{\circ} = \frac{K}{2r}\left[(r-\mu) + \sqrt{(r-\mu)^2 + \frac{4r\lambda}{K}}\right], \tag{4}$$

and it has no infected steady state. Whereas if $\eta > \eta_{crit}$, then system (1) has two steady states: the virus-free steady state E° and the unique infected steady state $E^*(x^*, y^*, v^*)$.

The infected steady state of (1) satisfies the following algebraic equations:

$$\begin{aligned} 0 &= \lambda + rx^*\left[1 - \frac{x^* + y^*}{K}\right] - \mu x^* - \beta x^* v^*, \\ 0 &= \beta x^* v^* + ry^*\left[1 - \frac{x^* + y^*}{K}\right] - \alpha y^*, \\ 0 &= \alpha\eta y^* - \gamma v^*. \end{aligned} \tag{5}$$

The global stability properties of (1) without delay are obtained by Vargas-De-León and Esteva [27] in the following results.

Theorem 3.3. *(See [27].) If $\eta \leqslant \eta_{crit}$, then the virus-free steady state E° of (1) is globally asymptotically stable when $\tau = 0$.*

Theorem 3.4. *(See [27].) If $\eta > \eta_{crit}$ and $r \leqslant \mu + \frac{r}{K}[x^* + y^*]$, then the unique infected steady state E^* of (1) is globally asymptotically stable when $\tau = 0$.*

The local stability of virus-free and infected steady states (1) with delay are studied in [1,7] and obtained the following result.

Theorem 3.5. *(See [1,7].) If $\eta < \eta_{crit}$ then E° is locally asymptotically stable for any time delay $\tau \geqslant 0$. If $\eta > \eta_{crit}$ then E° is unstable.*

Theorem 3.6. *(See [1,7].) Let*

$$\begin{aligned} p_1 &= \frac{\lambda}{x^*} + \frac{r}{K}\left[x^* + y^*\right] + \frac{\beta x^* v^*}{y^*} + \gamma, \\ p_2 &= \frac{\lambda}{x^*}\left(\frac{\beta x^* v^*}{y^*} + \frac{r}{K}y^* + \gamma\right) + \frac{\beta\gamma x^* v^*}{y^*} + \frac{r\beta(x^*)^2 v^*}{Ky^*} + \frac{r\gamma}{K}\left[x^* + y^*\right], \\ p_3 &= \frac{r\beta\gamma x^* v^*}{K} + \frac{\beta^2\gamma x^*(v^*)^2}{y^*} - \frac{\beta\gamma x^* v^*}{y^*}\left(\frac{\lambda}{x^*} + \frac{r}{K}x^*\right), \\ p_4 &= \frac{r\beta x^* v^*}{K} - \frac{\beta\gamma x^* v^*}{y^*}, \\ p_5 &= \frac{\beta\gamma x^* v^*}{y^*}\left(\frac{\lambda}{x^*} + \frac{r}{K}x^*\right) + \frac{r\gamma\lambda y^*}{Kx^*} - \frac{r\beta\gamma x^* v^*}{K}. \end{aligned}$$

Assume $\eta > \eta_{crit}$. If (i) $p_1(p_2 + p_4) > p_3 + p_5$, $\alpha - r[1 - \frac{x^*+y^*}{K}] > 0$, (ii) $p_1^2 > 2p_1p_5 + p_4^2$, $p_5^2 > p_3^2$, *then E^* is locally asymptotically stable for any time delay $\tau > 0$.*

4. Global stability of virus-free steady state

In this section, we shall consider the global stability of the virus-free steady state of system (1) by means of Lyapunov functionals.

Theorem 4.1. *If $\eta \leqslant \eta_{crit}$, then the virus-free steady state E° of (1) is globally asymptotically stable for any $\tau \geqslant 0$.*

Proof. Define a Lyapunov functional

$$U = \int_{x^\circ}^{x} \frac{(\sigma - x^\circ)}{\sigma}\,d\sigma + y + \frac{\beta x^\circ}{\gamma} v + \beta \int_0^\tau x(t-\omega)v(t-\omega)\,d\omega.$$

Then U is defined and continuous for all $x(t)$, $y(t)$, $v(t) > 0$, and $U = 0$ at $(x^\circ, 0, 0)$. The time derivative of U computed along solutions of (1), is given by the expression

$$\begin{aligned}\frac{dU}{dt} &= \frac{(x-x^\circ)}{x}\frac{dx}{dt} + \frac{dy}{dt} + \frac{\beta x^\circ}{\gamma}\frac{dv}{dt} - \beta \int_0^\tau \frac{d}{d\omega}x(t-\omega)v(t-\omega)\,d\omega \\ &= \big(x-x^\circ\big)\left(\frac{\lambda}{x} + r\left[1 - \frac{x+y}{K}\right] - \mu - \beta v\right) + \beta x_\tau v_\tau + ry\left[1 - \frac{x+y}{K}\right] - \alpha y \\ &\quad + \frac{\beta x^\circ}{\gamma}(\alpha\eta y - \gamma v) - \beta x_\tau v_\tau + \beta x v.\end{aligned}$$

Using $r - \mu = \frac{r}{K}x^\circ - \frac{\lambda}{x^\circ}$, we get

$$\begin{aligned}\frac{dU}{dt} &= \big(x-x^\circ\big)\left(-\lambda\frac{(x-x^\circ)}{xx^\circ} - \frac{r}{K}\big(x-x^\circ\big) - \frac{r}{K}y - \beta v\right) + \beta x_\tau v_\tau + ry\left(1 - \frac{x^\circ}{K}\right) \\ &\quad - \alpha y - \frac{r}{K}\big(x-x^\circ\big)y - \frac{r}{K}y^2 + \frac{\alpha\beta\eta x^\circ}{\gamma}y - \beta x^\circ v - \beta x_\tau v_\tau + \beta x v \\ &= -\lambda\frac{(x-x^\circ)^2}{xx^\circ} - \frac{r}{K}\big(x-x^\circ\big)^2 - 2\frac{r}{K}\big(x-x^\circ\big)y + \frac{\alpha\beta\eta x^\circ}{\gamma}y + ry\left(1 - \frac{x^\circ}{K}\right) - \alpha y - \frac{r}{K}y^2 \\ &= -\lambda\frac{(x-x^\circ)^2}{xx^\circ} - \frac{r}{K}\big[\big(x-x^\circ\big) + y\big]^2 + \left[\frac{\alpha\beta\eta x^\circ}{\gamma} + r\left(1 - \frac{x^\circ}{K}\right) - \alpha\right]y.\end{aligned}$$

Using $r(1 - \frac{x^\circ}{K}) = \mu - \frac{\lambda}{x^\circ}$, we have

$$\frac{dU}{dt} = -\lambda\frac{(x-x^\circ)^2}{xx^\circ} - \frac{r}{K}\big[\big(x-x^\circ\big) + y\big]^2 - \frac{\alpha\beta x^\circ}{\gamma}\left[\frac{\gamma}{\alpha\beta x^\circ}\left(\frac{\lambda}{x^\circ} + \alpha - \mu\right) - \eta\right]y.$$

Rewritten $\frac{dU}{dt}$ in terms of the critical number (3), we get

$$\frac{dU}{dt} = -\lambda\frac{(x-x^\circ)^2}{xx^\circ} - \frac{r}{K}\big[\big(x-x^\circ\big) + y\big]^2 - \frac{\alpha\beta x^\circ}{\gamma}(\eta_{crit} - \eta)y.$$

If $\eta \leqslant \eta_{crit}$, then $\frac{dU}{dt} \leqslant 0$ any solution is also bounded on $[0, +\infty)$. If $\eta < \eta_{crit}$, from Corollary 5.2 of [15], E° is globally asymptotically stable. Also, for $\eta = \eta_{crit}$, $\frac{dU}{dt} = 0$ implies that $x(t) = x^\circ$ and $y(t) = 0$. It is easy to show that $E^\circ(x^\circ, 0, 0)$ is the largest invariant set in $\{(x(t), y(t), v(t))\colon \frac{dU}{dt} = 0\}$. By the classical Lyapunov–LaSalle invariance principle (Theorem 5.3 of [15]), E° is globally asymptotically stable. □

5. Global stability of infected steady state

We motivated by the works of McCluskey [19,20], and other authors [8,16,18,21,22], we constructed Volterra-type functionals for established the conditions of the global stability of the infected steady state of (1).

Theorem 5.1. *If $\eta > \eta_{crit}$ and $r \leqslant \mu + \frac{r}{K}[x^* + y^*]$, then the unique infected steady state E^* of (1) is globally asymptotically stable for any $\tau \geqslant 0$.*

Proof. Define a Lyapunov functional for E^*,

$$L(t) = \widetilde{L}(t) + \beta x^* v^* L_+(t),$$

where

$$\widetilde{L} = \int_{x^*}^{x} \frac{(\sigma - x^*)}{\sigma}\,d\sigma + \int_{y^*}^{y} \frac{(\sigma - y^*)}{\sigma}\,d\sigma + \frac{\beta x^* v^*}{\alpha\eta y^*}\int_{v^*}^{v}\left(1 - \frac{v^*}{\sigma}\right)d\sigma,$$

and

$$L_+ = \int_0^\tau \left(\frac{x(t-\omega)v(t-\omega)}{x^*v^*} - 1 - \ln \frac{x(t-\omega)v(t-\omega)}{x^*v^*} \right) d\omega.$$

At infected steady state, we have

$$r - \mu = -\frac{\lambda}{x^*} + \beta v^* + \frac{r}{K}\left(x^* + y^*\right), \tag{6}$$

$$r - \alpha = -\beta \frac{x^*v^*}{y^*} + \frac{r}{K}\left(x^* + y^*\right), \tag{7}$$

$$\gamma = \alpha\eta \frac{y^*}{v^*}. \tag{8}$$

The derivative of $\widetilde{L}$ with respect to t along the solutions of (1), we get

$$\begin{aligned}\frac{d\widetilde{L}}{dt} &= \frac{(x-x^*)}{x}\frac{dx}{dt} + \frac{(y-y^*)}{y}\frac{dy}{dt} + \frac{\beta x^*v^*}{\alpha\eta y^*}\left(1 - \frac{v^*}{v}\right)\frac{dy}{dt} \\ &= \left(x-x^*\right)\left(\frac{\lambda}{x} - \frac{r}{K}(x+y) - \beta v + r - \mu\right) + \left(y-y^*\right)\left(\beta\frac{x_\tau v_\tau}{y} - \frac{r}{K}(x+y) + r - \alpha\right) \\ &\quad + \frac{\beta x^*v^*}{\alpha\eta y^*}\left(1 - \frac{v^*}{v}\right)(\alpha\eta y - \gamma v).\end{aligned}$$

Using (6)–(8), we get

$$\begin{aligned}\frac{d\widetilde{L}}{dt} &= \left(x-x^*\right)\left(-\lambda\frac{(x-x^*)}{xx^*} - \frac{r}{K}\left[\left(x-x^*\right) + \left(y-y^*\right)\right] - \beta\left(v-v^*\right)\right) \\ &\quad + \left(y-y^*\right)\left(\beta\left(\frac{x_\tau v_\tau}{y} - \frac{x^*v^*}{y^*}\right) - \frac{r}{K}\left[\left(x-x^*\right) + \left(y-y^*\right)\right]\right) + \frac{\beta x^*v^*}{\alpha\eta y^*}\left(1 - \frac{v^*}{v}\right)\left(\alpha\eta y - \alpha\eta y^*\frac{v}{v^*}\right).\end{aligned}$$

Canceling identical terms with opposite signs and collecting terms, yields

$$\frac{d\widetilde{L}}{dt} = -\lambda\frac{(x-x^*)^2}{xx^*} - \frac{r}{K}\left[\left(x-x^*\right) + \left(y-y^*\right)\right]^2 + \beta x^*v^*\left(1 + \frac{x}{x^*} - \frac{xv}{x^*v^*} + \frac{x_\tau v_\tau}{x^*v^*} - \frac{yv^*}{y^*v} - \frac{x_\tau y^*v_\tau}{x^*yv^*}\right).$$

We can rewrite $\frac{d\widetilde{L}}{dt}$ as

$$\begin{aligned}\frac{d\widetilde{L}}{dt} &= -\lambda\frac{(x-x^*)^2}{xx^*} - \frac{r}{K}\left[\left(x-x^*\right) + \left(y-y^*\right)\right]^2 + \beta x^*v^*\left(3 - \frac{x^*}{x} - \frac{xv}{x^*v^*} + \frac{x_\tau v_\tau}{x^*v^*} - \frac{yv^*}{y^*v} - \frac{x_\tau y^*v_\tau}{x^*yv^*}\right) \\ &\quad + \beta x^*v^*\left(\frac{x^*}{x} + \frac{x}{x^*} - 2\right),\end{aligned}$$

replacing the term $\frac{x}{x^*} + \frac{x^*}{x} - 2$ by $\frac{(x-x^*)^2}{xx^*}$,

$$\frac{d\widetilde{L}}{dt} = -\left(\lambda - \beta x^*v^*\right)\frac{(x-x^*)^2}{xx^*} - \frac{r}{K}\left[\left(x-x^*\right) + \left(y-y^*\right)\right]^2 + \beta x^*v^*\left(3 - \frac{x^*}{x} - \frac{xv}{x^*v^*} + \frac{x_\tau v_\tau}{x^*v^*} - \frac{yv^*}{y^*v} - \frac{x_\tau y^*v_\tau}{x^*yv^*}\right).$$

Using $\lambda - \beta x^*v^* = (\mu - r)x^* + \frac{rx^*}{K}[x^* + y^*]$, we get

$$\begin{aligned}\frac{d\widetilde{L}}{dt} &= -\left(\mu - r + \frac{r}{K}\left[x^* + y^*\right]\right)\frac{(x-x^*)^2}{x} - \frac{r}{K}\left[\left(x-x^*\right) + \left(y-y^*\right)\right]^2 \\ &\quad + \beta x^*v^*\left(3 - \frac{x^*}{x} - \frac{xv}{x^*v^*} + \frac{x_\tau v_\tau}{x^*v^*} - \frac{yv^*}{y^*v} - \frac{x_\tau y^*v_\tau}{x^*yv^*}\right).\end{aligned}$$

Let $x_\omega = x(t-\omega)$ and $v_\omega = v(t-\omega)$. It is easy to see that

$$\begin{aligned}\frac{dL_+}{dt} &= \frac{d}{dt}\int_0^\tau \left(\frac{x_\omega v_\omega}{x^*v^*} - 1 - \ln\frac{x_\omega v_\omega}{x^*v^*}\right)d\omega = \int_0^\tau \frac{d}{dt}\left(\frac{x_\omega v_\omega}{x^*v^*} - 1 - \ln\frac{x_\omega v_\omega}{x^*v^*}\right)d\omega \\ &= -\int_0^\tau \frac{d}{d\omega}\left(\frac{x_\omega v_\omega}{x^*v^*} - 1 - \ln\frac{x_\omega v_\omega}{x^*v^*}\right)d\omega = -\left[\frac{x_\omega v_\omega}{x^*v^*} - 1 - \ln\frac{x_\omega v_\omega}{x^*v^*}\right]_{\omega=0}^{\tau} \\ &= -\frac{x_\tau v_\tau}{x^*v^*} + \frac{xv}{x^*v^*} + \ln\frac{x_\tau v_\tau}{x^*v^*} + \ln\frac{x^*v^*}{xv} = -\frac{x_\tau v_\tau}{x^*v^*} + \frac{xv}{x^*v^*} + \ln\frac{x_\tau y^* v_\tau}{x^* y v^*} + \ln\frac{x^*}{x} + \ln\frac{yv^*}{y^*v}.\end{aligned}$$

Since

$$\frac{dL}{dt} = \frac{d\widetilde{L}}{dt} + \beta x^* v^* \frac{dL_+}{dt},$$

we obtain

$$\begin{aligned}\frac{dL}{dt} &= -\left(\mu - r + \frac{r}{K}\left[x^* + y^*\right]\right)\frac{(x-x^*)^2}{x} - \frac{r}{K}\left[\left(x-x^*\right) + \left(y-y^*\right)\right]^2 - \beta x^* v^*\left(\frac{x^*}{x} - 1 - \ln\frac{x^*}{x}\right) \\ &\quad - \beta x^* v^*\left(\frac{yv^*}{y^*v} - 1 - \ln\frac{yv^*}{y^*v}\right) - \beta x^* v^*\left(\frac{x_\tau y^* v_\tau}{x^* y v^*} - 1 - \ln\frac{x_\tau y^* v_\tau}{x^* y v^*}\right).\end{aligned}$$

Thus, $r \leqslant \mu + \frac{r}{K}[x^* + y^*]$ implies that $\frac{dL}{dt} \leqslant 0$. By Corollary 5.2 of [15], solutions limit to $\mathbb{M}$, the largest invariant subset of $\{\frac{dL}{dt} = 0\}$. Furthermore, $\frac{dL}{dt} = 0$ if and only if $x(t) = x(t-\tau) = x^*$, $v(t) = v(t-\tau) = v^*$ and $y(t) = y^*$. Therefore the largest compact invariant set in $\mathbb{M}$ is the singleton $\{E^*\}$, where E^* is the infected steady state. This shows that $\lim_{t\to\infty}(x(t), y(t), v(t)) = (x^*, y^*, v^*)$. By the classical Lyapunov–LaSalle invariance principle (Theorem 5.3 of [15]), if $r \leqslant \mu + \frac{r}{K}[x^* + y^*]$ then E^* is globally asymptotically stable. This proves Theorem 5.1. □

6. Discussion

In this paper, our goal is the construction of Lyapunov functionals is to prove the global stability of the steady states of a virus dynamics model with density-dependent proliferation of infected cells and intracellular delay.

We obtained that if $\eta \leqslant \eta_{crit}$, will only virus-free steady state, which is globally asymptotically stable; and the virus is cleared of the cells population irrespective to the initial conditions. In [1,7] proved that if $\eta > \eta_{crit}$ then virus-free steady state becomes unstable and a unique infected steady state exists. We proved the global stability of the infected steady state if the condition $r \leqslant \mu + \frac{r}{K}[x^* + y^*]$ is satisfied. In this case, the viral infection is present in the cells population and will become a persistent infection.

The results show that, for the viral infection model with mitotic transmission, the time delay has no effect on both global asymptotic properties of the virus-free steady state and global asymptotic properties of the infected steady state.

Our results of model (1) can be used to prove the global stability of the following system:

$$\begin{aligned}\frac{dx(t)}{dt} &= \lambda + rx(t)\left[1 - \frac{x(t)+y(t)}{K}\right] - \mu x(t) - (1-\varepsilon)\beta x(t) v_i(t), \\ \frac{dy(t)}{dt} &= (1-\varepsilon)\beta x(t-\tau) v_i(t-\tau) + ry(t)\left[1 - \frac{x(t)+y(t)}{K}\right] - \alpha y(t), \\ \frac{dv_i(t)}{dt} &= (1-\epsilon)\alpha\eta y(t) - \gamma_i v_i(t), \\ \frac{dv_{ni}(t)}{dt} &= \epsilon\alpha\eta y(t) - \gamma_{ni} v_{ni}(t),\end{aligned}$$

that incorporates the combination of two drug therapies [7]. Where v_i and v_{ni} denote infectious and non-infectious viral particles, respectively.

Parameters ε and ϵ are defined as follows: ε efficiency of drug therapy in preventing new infections, and ϵ efficiency of drug therapy in inhibiting viral production. With $0 \leqslant \varepsilon, \epsilon \leqslant 1$. An efficacy of 0 indicates that there is no inhibition, whereas an efficacy of 1 (100%) indicates complete inhibition. Values of the efficacy between 0 and 1 indicate partial inhibition.

Note that the first three equations are decoupled from the last one and that this subsystem is essentially similar to (1).

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