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Analysis of a viral infection model with immune impairment, intracellular delay and general non-linear incidence rate

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ABSTRACT

In this article we study the dynamical behaviour of a intracellular delayed viral infection with immune impairment model and general non-linear incidence rate. Several techniques, including a non-linear stability analysis by means of the Lyapunov theory and sensitivity analysis, have been used to reveal features of the model dynamics. The classical threshold for the basic reproductive number is obtained: if the basic reproductive number of the virus is less than one, the infection-free equilibrium is globally asymptotically stable and the infected equilibrium is globally asymptotically stable if the basic reproductive number is higher than one.

1. Introduction

The study of epidemic and viral dynamics via mathematical modelling has been an interesting topic to investigate in the last decades. Researchers have constructed mathematical models which could play a significant role in better understanding diseases and drug therapy strategies to fight against them.

During the process of viral infection, as soon a virus invades host cells, Cytotoxic T Lymphocytes (CTL's) play an important role in responding to the aggression. Lymphocytes are programmed to kill the infected cells through the lysine of the infected ones.

To model the immune response during a viral infection, taking into account the CTL response, researchers consider the following set of differential equations

$$\dot{x} = s - dx - \beta xy,$$
$$\dot{y} = \beta xy - ay - pyz,$$
$$\dot{z} = f(y,z) - bz,$$

where variable x, y and z represent the populations of uninfected cells, infected cells, and number of CTL's by ml of peripheral blood, respectively. The parameter s represents a constant source of susceptible cells, β is the infection rate constant, we assume that a susceptible cell become infected at rate proportional to the number of infected cells. Constants d and a represents the death rates of susceptible and infected respectively. Infected cells are killed at a rate p by the CTL immune response. The function $f(y,z)$ describes the rate of immune response due to virus activation. In this paper we consider $f(y,z) = cy - myz$, the term myz represents an immune impairment according to [1], the CTL cells proliferate at a rate c and decay at rate m. Linear and bilinear immune response have been considered in [2–5].

In [4,6,7] time delays have been incorporated for immune response, since antigenic stimulation generating CTLs may need a period of time, that is, the activation rate of CTL response at time t may depend on the population of antigen at a previous time. On the other hand, it has been realised recently [8,9,13] that there are also delays in the process of cell infection and virus production, and thus, delays should be incorporated into the infection equation and/or the virus production equation of a model. In this paper, we consider the following model,

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$$\begin{aligned}\dot{x} &= s - dx - F(x,y),\\ \dot{y} &= F(x(t-\tau),y(t-\tau)) - ay - pyz,\\ \dot{z} &= cy - bz - myz.\end{aligned} \tag{1}$$

We assume that the force of infection at any time t is given by the general function $F(x,y)$ [14], this general function includes the cases: bilinear incidence rate βxy, where β is the average number of contacts per infective; standard incidence rate $\beta xy/(x+y)$; the Holling type incidence rate of the form $\beta xy/(1+\alpha_1 x)$ where α_1 is a positive constant; the saturated incidence rate of the form $\beta xy/(1+\alpha_2 y)$, where α_2 is a positive constant; the saturated incidence of the form $\beta xy/(1+\alpha_1 x+\alpha_2 y)$, where α_1 and α_2 are constants.

In our work we present global stability results for system (1), several authors have studied the dynamics of systems with nonlinear incidence rate. Huang et. al. [10] studied a model with general incidence rate $F(s(t))G(i(t-\tau))$ which did not consider some of our functions, for instance $\frac{\beta xy}{x+y}, \frac{\beta xy}{1+\alpha_1 x+\alpha_2 y}$. Korobeinikov [11] and Enatsu et al. [12] considered epidemic SIR, SEIR models, and used Volterra-type Lyapunov functions to prove the global stability of the endemic equilibrium state. In our work we consider a Susceptible–Infected–Virus dynamics, we use a combination of quadratic and Volterra-type functionals to prove global stability, we also take into account immune response due to virus activation. This consideration renders a modification of Lyapunov functions used in previous works, in order to prove global stability of the infected equilibrium. In a related work, Muroya et. al. [13] used combinations of common quadratic and Volterra-type functionals to prove global stability for this immune response, their results are only for a bilinear incidence rate and delay on the rate of virus production and delay in the production of virus. They can prove the global stability for a model without delay and for the delayed model a Hopf bifurcation occurs. We proposed a general interaction $F(x,y)$ and a delay in the process of cell infection and virus production.

The paper is organised as follows in Section 2 we prove the existence of the positive equilibrium. In Section 3 we prove that solutions of (1) with positive initial conditions will remain positive for all time and their boundedness. The global stability analysis of infected-free and infected equilibria is analysed in Section 4. We perform a local sensitivity analysis in Section 5 and in Section 6 we present simulations to illustrate our findings. Finally we draw our conclusions in Section 7.

2. Existence of equilibria

To find the equilibria of system (1) we need to solve

$$0 = s - dx - F(x,y), \tag{2}$$
$$0 = F(x,y) - ay - pyz, \tag{3}$$
$$0 = cy - bz - myz. \tag{4}$$

With this end we propose the following conditions for $F(x,y)$

1. $F(x,y)$ is continuously differentiable in $[0,\infty)\times[0,\infty)$.
   (H1) $F(x,y) > 0$, $\frac{\partial F}{\partial x}(x,y) > 0$, $\frac{\partial F}{\partial y}(x,y) > 0$, for $x > 0$ and $y > 0$.
   (H2) $F(x,0) = F(0,y) = 0$, $\frac{\partial F}{\partial x}(x,0) = 0$, $\frac{\partial F}{\partial y}(x,0) > 0$ for $x > 0$ and $y > 0$.

When $x = \frac{s}{d}$, $y = 0$ and $z = 0$ the Eqs. (2)–(4) are satisfied, therefore $E_0(\frac{s}{d},0,0)$ is a steady state called the infection-free equilibrium.

To find a positive equilibrium we proceed as follows. From Eq. (4) we have

$$z = \frac{cy}{b+my}. \tag{5}$$

From Eqs. (2) and (3) we have

$$s - dx = ay + pyz \Rightarrow x = \frac{s}{d} - \frac{a}{d}y - \frac{p}{d}yz, \quad \text{substituting (5)}$$
$$\Rightarrow x = \frac{s}{d} - \frac{a}{d}y - \frac{pc}{d}\frac{y^2}{b+my}. \tag{6}$$

Substituting (5) and (6) in (3) we have the following function $H(y)$

$$H(y) = F\left(\frac{s}{d} - \frac{a}{d}y - \frac{pc}{d}\frac{y^2}{b+my}, y\right) - ay - pc\frac{y^2}{b+my}.$$

Let $x_0 = \frac{s}{d}$, note that $H(0) = 0$, because $F(x_0,0) = 0$. We can compute that there exists a positive root y_0 such that $s = ay + pc\frac{y^2}{b+my}$, hence

$$H(y_0) = F(0,y_0) - s = -s < 0.$$

And when $y \geqslant 0$, since $H(y)$ is continuously differentiable, we have

$$H'(0) = -\frac{a}{d}\frac{\partial F}{\partial x}(x_0,0) + \frac{\partial F}{\partial y}(x_0,0) - a = \frac{\partial F}{\partial y}(x_0,0) - a$$
$$= a\left(\frac{F_y(x_0,0)}{a} - 1\right).$$

Let $R_0 = \frac{F_y(x_0,0)}{a}$. Thus, $R_0 > 1$ ensures that $H'(0) > 0$. And $H(y)$ is continuous in $[0,y_0]$, then there exist some $y^* \in [0,y_0]$, such that $H(y^*) = 0$. Since $ay + pc\frac{y^2}{b+my}$ is increasing, we have $ay^* + pc\frac{(y^*)^2}{b+my^*} < ay_0 + pc\frac{y_0^2}{b+my_0}$. Therefore $x^* = \frac{s}{d} - \frac{a}{d}y^* - \frac{pc}{d}\frac{(y^*)^2}{b+my^*} > 0$, also $z^* = \frac{cy^*}{b+my^*} > 0$ and we have proved the existence of the endemic equilibrium $E^*(x^*,y^*,z^*)$ for system (1) under the condition $R_0 > 1$.

Hence we have proved the following theorem:

Theorem 1. *Assume that $F(x,y)$ satisfies (H1) and (H2), if $R_0 > 1$ then system (1) has a positive equilibrium state $E^*(x^*,y^*,z^*)$.*

3. Positivity and boundedness of solutions

We denote by $\mathcal{C} = C([-\tau,0],\mathbb{R}^3)$ the Banach space of continuous functions $\phi : [-\tau,0] \to \mathbb{R}^3$ with norm

$$||\phi|| = \sup_{-\tau\leqslant\theta\leqslant 0}\{|\phi_1(\theta)|, |\phi_2(\theta)|, |\phi_3(\theta)|\},$$

where $\phi = (\phi_1,\phi_2,\phi_3)$. The nonnegative cone of $\mathcal{C}$ is defined by $\mathcal{C}_+ = C([-\tau,0],\mathbb{R}^3_+)$.

The initial condition for system (1) is given as

$$x(\theta)=\phi_1(\theta)\geqslant 0,\quad y(\theta)=\phi_2(\theta)\geqslant 0,$$
$$z(\theta)=\phi_3(\theta)\geqslant 0,\quad -\tau\leqslant\theta\leqslant 0,\quad \phi(0)>0. \tag{7}$$

The following result establishes the positivity and boundedness of solution for system (1) with initial condition (7).

Theorem 2. *Under the initial condition (7), then $x(t), y(t)$ and $z(t)$ are positive and bounded for all $t\geqslant 0$ at which the solution exists.*

Proof. To see that $x_1(t)$ is positive, we proceed by contradiction. Let t_0 the first value of time such that $x_1(t)=0$, so $x(t)>0$ for all $t<t_0$. By the first equation of (1) we see that $\dot{x}(t_1)=s>0$ and $x(t_1)=0$, therefore there exist $\epsilon>0$ such that $x(t)<0$ for $t\in(t_0-\epsilon,t_0)$, this leads to a contradiction. It follows that $x(t)$ is always positive. With a similar argument we see that $y(t)$ and $z(t)$ are positive for $t>0$.

To prove the ultimate boundedness, we note that $\dot{x}(t)\leqslant s-dx(t)$ implies that $\limsup_{t\to\infty}x(t)\leqslant\frac{s}{d}$.

Consider $N(t)=x(t-\tau)+y(t)$, $y(t)$ and $z(t)$ are positive then we obtain,

$$\begin{aligned}\dot{N}(t)&=\dot{x}(t-\tau)+\dot{y}(t)=s-dx(t-\tau)-ay(t)-py(t)z(t)\\&<s-dx(t-\tau)-ay(t)<s-qN(t),\end{aligned}$$

where $q=\min\{a,d\}$, therefore $N<\frac{s}{q}+\epsilon$ for $\epsilon>0$ and t large enough which implies that there exists $M>0$ such that $y(t)<M$.

Now consider the third equation of system (1), $y(t)<M$ and $z(t)$ is positive, then we have $\dot{z}(x)<cM-bz$ which implies that $\limsup_{t\to\infty}z(t)\leqslant\frac{cM}{b}$.

Therefore there exists $K>0$ such that $x(t)<K, y(t)<K$ and $z(t)<K$. □

4. Stability analysis

In this section, we give conditions for the global stability of the infection-free steady state and the infected steady state of system (1). The technique of proofs is the second Lyapunov method.

For simplicity, we will use the following notation in the proof. $x=x(t)$, $y=y(t)$, $z=z(t)$, $x_\tau=x(t-\tau)$, $y_\tau=y(t-\tau)$, the following result establishes the global stability for the uninfected equilibrium $E_0(s/d,0,0)$ if $R_0\leqslant 1$.

For the global stability of the infection-free equilibrium $E_0(x_0,0,0)$ of system (1). We propose the following conditions:

(H3) $\frac{\partial F}{\partial y}(x,0)$ is increasing with respect to $x>0$.

(H4) $F(x,y)\leqslant y\frac{\partial F}{\partial y}(x,0)$ with respect $y>0$.

By (H3), the following inequalities hold true:

$$\begin{aligned}&\frac{F_y(x_0,0)}{F_y(x,0)}>1\quad\text{for } x\in(0,x_0),\\&\frac{F_y(x_0,0)}{F_y(x,0)}<1\quad\text{for } x>x_0.\end{aligned} \tag{8}$$

Under these conditions we have the following theorem

Theorem 3. *Suppose that conditions (H1)–(H4) are satisfied. Then the disease-free equilibrium $E_0(x_0,0,0)$ of system (1) is globally asymptotically stable for any $\tau>0$ if $R_0\leqslant 1$.*

Proof. We define the Lyapunov functional

$$L=x-x_0-\int_{x_0}^{x}\lim_{y\to0^+}\frac{F(x_0,y)}{F(\eta,y)}\,d\eta+y+\int_{-\tau}^{0}F(x(t+\theta),y(t+\theta))\,d\theta.$$

By (H1)–(H4), L is defined and continuously differentiable for all $x(t),\ y(t)>0,\ z(t)>0$, and $L=0$ at $E_0(x_0,0,0)$. The system (1) at $E_0(x_0,0,0)$ has $s=dx_0$. The time derivative of L along the solutions of system is given by

$$\begin{aligned}\dot{L}&=\dot{x}-\lim_{y\to0^+}\frac{F(x_0,y)}{F(x,y)}\dot{x}+\dot{y}+F(x,y)-F(x_\tau,y_\tau)\\&=\left(1-\lim_{y\to0^+}\frac{F(x_0,y)}{F(x,y)}\right)(s-dx-F(x,y))+F(x_\tau,y_\tau)-ay\\&\quad-pyz+F(x,y)-F(x_\tau,y_\tau)\\&=\left(1-\lim_{y\to0^+}\frac{F(x_0,y)}{F(x,y)}\right)(dx_0-dx)\\&\quad-\left(1-\lim_{y\to0^+}\frac{F(x_0,y)}{F(x,y)}\right)F(x,y)-ay-pyz+F(x,y)\\&=dx\left(1-\lim_{y\to0^+}\frac{F(x_0,y)}{F(x,y)}\right)\left(\frac{x_0}{x}-1\right)-F(x,y)\\&\quad+F(x,y)\lim_{y\to0^+}\frac{F(x_0,y)}{F(x,y)}-ay-pyz+F(x,y)\\&=dx\left(1-\lim_{y\to0^+}\frac{F(x_0,y)}{F(x,y)}\right)\left(\frac{x_0}{x}-1\right)+F(x,y)\lim_{y\to0^+}\frac{F(x_0,y)}{F(x,y)}\\&\quad-ay-pyz.\end{aligned}$$

For the first term, of the above expression, we have by (8)

$$\begin{aligned}\left(1-\lim_{y\to0^+}\frac{F(x_0,y)}{F(x,y)}\right)\left(\frac{x_0}{x}-1\right)&=\left(1-\frac{F_y(x_0,y)}{F_y(x,0)}\right)\left(\frac{x_0}{x}-1\right)\\&\leqslant 0.\end{aligned}$$

For the second and third term we have, using (H4),

$$\begin{aligned}F(x,y)\lim_{y\to0^+}\frac{F(x_0,y)}{F(x,y)}-ay&=F(x,y)\frac{F_y(x_0,0)}{F_y(x,0)}-ay\\&\leqslant yF_y(x,0)\frac{F_y(x_0,0)}{F_y(x,0)}-ay\\&=y(F_y(x_0,0)-a)=ay(R_0-1),\end{aligned}$$

therefore if $R_0\leqslant 1$

$$\dot{L}\leqslant\left(1-\frac{F_y(x_0,y)}{F_y(x,0)}\right)\left(\frac{x_0}{x}-1\right)-ay(1-R_0)-pyz\leqslant 0$$

for all $x(t)\geqslant 0,\ y(t)\geqslant 0,\ z(t)\geqslant 0$. It is easy to verify that the infection-free equilibrium $E_0(x_0,0,0)$ is the only fixed point of the system on the plane $x=x_0$ and hence it is easy to show that the largest invariant set in $\{(x,y,z)|\dot{L}=0\}$ is the set $E=\{(x_0,0,z)|0\leqslant z\leqslant M\}$, where M is given in the proof of Theorem 2. Given that in this set the system is reduced to $z'=-bz$, any point in this set evolves towards E_0. By the Lyapunov–LaSalle theorem [15], E_0 is globally asymptotically stable for any $\tau>0$. □

In the following, we consider the global asymptotic stability of a unique infected steady state E^*. Motivated by the works and ideas of [4,9,14], in this work, we construct a Lyapunov functional for infected steady state, using suitable combinations of quadratic, Volterra-type functions and the Volterra-type functionals.

For this section we propose the following hypotheses

(H5) $\frac{y}{y^*} \leqslant \frac{F(x,y)}{F(x,y^*)}$ for $y \in (0,y^*)$, $\frac{F(x,y)}{F(x,y^*)} \leqslant \frac{y}{y^*}$ for $y \geqslant y^*$.

We have the following theorem.

Theorem 4. *Suppose that conditions (H1)–(H2) and (H5) are satisfied. If $R_0 > 1$ then the unique endemic equilibrium $E^*(x^*,y^*,z^*)$ of system (1) is globally asymptotically stable for any $\tau > 0$.*

Proof. We consider the following Lyapunov functional

$$L = x - x^* - \int_{x^*}^{x} \frac{F(x^*,y^*)}{F(\phi,y^*)}\,d\phi + y^*\left(\frac{y}{y^*} - 1 - \ln\left(\frac{y}{y^*}\right)\right) + \frac{p}{2(c-mz^*)}(z-z^*)^2 + F(x^*,y^*) \times \int_{t-\tau}^{t}\left(\frac{F(x(\theta),y(\theta))}{F(x^*,y^*)} - 1 - \ln\left(\frac{F(x(\theta),y(\theta))}{F(x^*,y^*)}\right)\right)d\theta.$$

L is defined and continuously differentiable for all $x(t) > 0$, $y(t) > 0$, $z(t) > 0$. And $L(0) = 0$ at $E^*(x^*, y^*, z^*)$. At $E^*(x^*, y^*, z^*)$, system (1) has

$$s = dx^* + F(x^*,y^*), \tag{9}$$

$$F(x^*,y^*) = ay^* + py^*z^*, \tag{10}$$

$$0 = cy^* - bz^* - my^*z^*. \tag{11}$$

The time derivative of L along the solutions of (1) is given by

$$\frac{dL}{dt} = \dot{x} - \frac{F(x^*,y^*)}{F(x,y^*)}\dot{x} + \left(1 - \frac{y^*}{y}\right)\dot{y} + \frac{p}{c-mz^*}(z-z^*)\dot{z} + F(x,y) - F(x_\tau,y_\tau) + F(x^*,y^*)\ln\left(\frac{F(x_\tau,y_\tau)}{F(x,y)}\right)$$
$$= \left(1 - \frac{F(x^*,y^*)}{F(x,y^*)}\right)(s - dx - F(x,y)) + \left(1 - \frac{y^*}{y}\right)(F(x_\tau,y_\tau) - ay - pyz) + \frac{p}{c-mz^*}(z-z^*)(cy - bz - myz) + F(x,y) - F(x_\tau,y_\tau) + F(x^*,y^*)\ln\left(\frac{F(x_\tau,y_\tau)}{F(x,y)}\right)$$

Recall $x_\tau = x(t-\tau), y_\tau = y(t-\tau)$. Using (9) the first term can be written as

$$\left(1 - \frac{F(x^*,y^*)}{F(x,y^*)}\right)(dx^* + F(x^*,y^*) - dx - F(x,y))$$
$$= dx^*\left(1 - \frac{F(x^*,y^*)}{F(x,y^*)}\right)\left(1 - \frac{x}{x^*}\right) + \left(1 - \frac{F(x^*,y^*)}{F(x,y^*)}\right)(F(x^*,y^*) - F(x,y))$$
$$= dx^*\left(1 - \frac{F(x^*,y^*)}{F(x,y^*)}\right)\left(1 - \frac{x}{x^*}\right) + F(x^*,y^*) - F(x,y)) - \frac{[F(x^*,y^*)]^2}{F(x,y^*)} + \frac{F(x^*,y^*)}{F(x,y^*)}F(x,y). \tag{12}$$

The second term can be written as

$$F(x_\tau,y_\tau) - ay - pyz - \frac{y^*}{y}F(x_\tau,y_\tau) + ay^* + py^*z. \tag{13}$$

Using Eq. (11) and $myz^* - myz^* = 0$ the third term can be expressed as

$$\frac{p}{c-mz^*}(z-z^*)(cy - bz - myz) = \frac{p}{c-mz^*}(z-z^*) \times (cy - bz - myz - cy^* + bz^* + my^*z^* + myz^* - myz^*)$$
$$= \frac{p}{c-mz^*}(z-z^*)(c(y-y^*) - b(z-z^*) - my(z-z^*) - mz^*(y-y^*))$$
$$= \frac{p}{c-mz^*}(z-z^*)((y-y^*)(c-mz^*) - (z-z^*)(b+my))$$
$$= -\frac{p}{c-mz^*}(b+my)(z-z^*)^2 + p(z-z^*)(y-y^*). \tag{14}$$

Therefore substituting (12)–(14) the derivative of L can be written as

$$\dot{L} = dx^*\left(1 - \frac{F(x^*,y^*)}{F(x,y^*)}\right)\left(1 - \frac{x}{x^*}\right) + F(x^*,y^*) - F(x,y)) - \frac{[F(x^*,y^*)]^2}{F(x,y^*)} + \frac{F(x^*,y^*)}{F(x,y^*)}F(x,y) + F(x_\tau,y_\tau) - ay - pyz - \frac{y^*}{y}F(x_\tau,y_\tau) + ay^* + py^*z - \frac{p}{c-mz^*}(b+my)(z-z^*)^2 + p(z-z^*)(y-y^*) + F(x,y) - F(x_\tau,y_\tau) + F(x^*,y^*)\ln\left(\frac{F(x_\tau,y_\tau)}{F(x,y)}\right)$$
$$= dx^*\left(1 - \frac{F(x^*,y^*)}{F(x,y^*)}\right)\left(1 - \frac{x}{x^*}\right) + F(x^*,y^*) - \frac{[F(x^*,y^*)]^2}{F(x,y^*)} + \frac{F(x^*,y^*)}{F(x,y^*)}F(x,y) - ay - pyz - \frac{y^*}{y}F(x_\tau,y_\tau) + ay^* + py^*z - \frac{p}{c-mz^*}(b+my)(z-z^*)^2 + p(z-z^*)(y-y^*) + F(x^*,y^*) \times \ln\left(\frac{F(x_\tau,y_\tau)}{F(x,y)}\right)$$
$$= dx^*\left(1 - \frac{F(x^*,y^*)}{F(x,y^*)}\right)\left(1 - \frac{x}{x^*}\right) + F(x^*,y^*)\left(1 - \frac{F(x^*,y^*)}{F(x,y^*)} + \frac{F(x,y)}{F(x,y^*)}\right) + F(x^*,y^*)\left(-\frac{y^*}{y}\frac{F(x_\tau,y_\tau)}{F(x^*,y^*)} + \ln\left(\frac{F(x_\tau,y_\tau)}{F(x,y)}\right)\right) - \frac{p}{c-mz^*} \times (b+my)(z-z^*)^2 - a(y-y^*) - pz(y-y^*) + p(z-z^*)(y-y^*).$$

Using (10) we can rewrite $-a(y-y^*) - pz(y-y^*) + p(z-z^*)(y-y^*)$ as

$$-\left(\frac{F(x^*,y^*)}{y^*} - pz^*\right)(y-y^*) - pz(y-y^*) + p(z-z^*)(y-y^*)$$
$$= -\frac{F(x^*,y^*)}{y^*}(y-y^*) + pz^*(y-y^*) - pz(y-y^*) + p(z-z^*)(y-y^*)$$
$$= F(x^*,y^*)\left(1 - \frac{y}{y^*}\right) - p(z-z^*)(y-y^*) + p(z-z^*)(y-y^*)$$
$$= F(x^*,y^*)\left(1 - \frac{y}{y^*}\right).$$

Therefore $\dot{L}$ can be rewritten as

$$\dot{L} = dx^*\left(1 - \frac{F(x^*,y^*)}{F(x,y^*)}\right)\left(1 - \frac{x}{x^*}\right) + F(x^*,y^*)\left(1 - \frac{F(x^*,y^*)}{F(x,y^*)} + \frac{F(x,y)}{F(x,y^*)}\right) + F(x^*,y^*)\left(1 - \frac{y}{y^*} - \frac{y^*}{y}\frac{F(x_\tau,y_\tau)}{F(x^*,y^*)} + \ln\left(\frac{F(x_\tau,y_\tau)}{F(x,y)}\right)\right)$$

$$
\begin{aligned}
&-\frac{p}{c-mz^*}(b+my)(z-z^*)^2\\
&=dx^*\left(1-\frac{F(x^*,y^*)}{F(x,y^*)}\right)\left(1-\frac{x}{x^*}\right)\\
&+F(x^*,y^*)\left(1-\frac{F(x^*,y^*)}{F(x,y^*)}+\ln\left(\frac{F(x^*,y^*)}{F(x,y^*)}\right)\right)\\
&+F(x^*,y^*)\left(1-\frac{y^*}{y}\frac{F(x_\tau,y_\tau)}{F(x^*,y^*)}+\ln\left(\frac{y^*}{y}\frac{F(x_\tau,y_\tau)}{F(x^*,y^*)}\right)\right)\\
&+F(x^*,y^*)\left(1-\frac{y}{y^*}\frac{F(x,y^*)}{F(x,y)}+\ln\left(\frac{y}{y^*}\frac{F(x,y^*)}{F(x,y)}\right)\right)\\
&+F(x^*,y^*)\left(\frac{y}{y^*}-\frac{F(x,y)}{F(x,y^*)}\right)\left(\frac{F(x,y^*)}{F(x,y)}-1\right)\\
&-\frac{p}{c-mz^*}(b+my)(z-z^*)^2.
\end{aligned}
$$

The function $F(x,y)$ is monotonically increasing for any $x>0$, hence the following inequality holds,

$$\left(1-\frac{F(x^*,y^*)}{F(x,y^*)}\right)\left(1-\frac{x}{x^*}\right)\leqslant 0. \tag{15}$$

And by the properties of the function $g(x)=1-x+\ln x,(x>0)$, we note that $g(x)$ has its global maximum $g(1)=0$. Hence $g(x)\leqslant 0$ when $x>0$ and the following inequalities hold

$$1-\frac{F(x^*,y^*)}{F(x,y^*)}+\ln\frac{F(x^*,y^*)}{F(x,y^*)}\leqslant 0, \tag{16}$$

$$1-\frac{y^*}{y}\frac{F(x_\tau,y_\tau)}{F(x^*,y^*)}+\ln\left(\frac{y^*}{y}\frac{F(x_\tau,y_\tau)}{F(x^*,y^*)}\right)\leqslant 0, \tag{17}$$

$$1-\frac{y}{y^*}\frac{F(x,y^*)}{F(x,y)}+\ln\left(\frac{y}{y^*}\frac{F(x,y^*)}{F(x,y)}\right)\leqslant 0, \tag{18}$$

And by (H5) and the fact that $F(x,y)$ is monotonically increasing for any $y>0$, we have the following inequality

$$\left(\frac{y}{y^*}-\frac{F(x,y)}{F(x,y^*)}\right)\left(\frac{F(x,y^*)}{F(x,y)}-1\right)\leqslant 0. \tag{19}$$

By (15)–(19), we have $dL/dt<0$. It follows from the classical Lyapunov–LaSalle invariance principle [15] that solutions converge to the largest invariant set $\{dL/dt=0\}$. We note that $dL/dt=0$ holds if and only if $x(t)=x^*$ and $y(t)=y^*$ and $z(t)=z^*$ for all t, and so the largest invariant set consists of the single point (x^*,y^*,z^*). Thus (x^*,y^*,z^*) is globally asymptotically stable.

The uniqueness of the infected equilibrium state (x^*,y^*,z^*) follows from the fact that the equality $\frac{dL}{dt}(x,y,z)=0$ holds only when $x=x^*$, and the point (x^*,y^*,z^*) is the only equilibrium state of the system, when $x=x^*$ □

5. Sensitivity analysis

For the local sensitivity analysis we calculate the sensitivity indices of the basic reproduction number, in order to assess which parameter has the greatest influence on changes of R_0 (see [16]).

To this aim, denote by ψ the generic parameter of model (1). We calculate the normalised sensitivity index, defined as the ratio of the relative change in R_0 to the relative change in the parameter ψ

$$S_\psi=\frac{\psi}{R_0}\frac{\partial R_0}{\partial\psi}.$$

This index indicates how sensitive R_0 is to a change of parameter ψ. A positive (respective negative) index indicates that an increase in the parameter value results in an increase (respectively decrease) in the R_0 value.

In Table 1 we list the different expressions of $R_0, R_0=\frac{F_y(x_0,0)}{a}$, depending on the incidence rate $F(x,y)$. Note that the value of $R_0=\frac{\beta s}{ad}$ when we consider the incidence rates as βxy or $\frac{\beta xy}{1+\alpha_2 y}$, also when we consider the incidence rates $\frac{\beta xy}{1+\alpha_1 x}$ or $\frac{\beta xy}{1+\alpha_1 x+\alpha_2 y}$ the value of $R_0=\frac{\beta s}{a(d+\alpha_1 s)}$. On the other hand, when $F(x,y)=\frac{\beta xy}{x+y}$ the basic reproductive number is $R_0=\frac{\beta}{a}$.

In the case of $F(x,y)=\beta xy$ the basic reproductive $R_0=\frac{\beta s}{ad}$, as we see in Table 1, note that:

$$S_s=\frac{s}{R_0}\frac{\partial R_0}{\partial s}=\frac{sad}{s\beta}\frac{\beta}{ad}=1,$$

which means that S_s, the index of R_0 respect the parameter s, does not depend on any parameter values in Fig. 1 we show the values of $S_\beta=1, S_a=-1$ and $S_d=-1$. Also in Fig. 1 we show the sensitivity index for the cases when $R_0=\frac{\beta}{a}$ and $\frac{\beta s}{a(d+\alpha_1 s)}$.

In Fig. 2, we present our calculations for the sensitivity of R_0 with respect to its parameters. In Fig. 1(a), we present the sensitivity for $R_0=\frac{\beta s}{ad}$ obtained in the cases when $F(x,y)$ is βxy or $\frac{\beta xy}{1+\alpha_2 y}$. In these cases we can appreciate that an increase in parameters β or s will increase, in the same percentage, the actual value for R_0. In the other hand an increase in the parameter a or d will cause a decrease in the same percentage, over the value of R_0. Similar conclusions can be obtained from Fig. 1(b) for the case when $F(x,y)=\frac{\beta xy}{x+y}$. For example to decrease the value of R_0, say by 10%, we need to increase the value of a by 10%, while R_0 will increase, say by 10% if β increases by 10%. In the case of $R_0=\frac{\beta s}{a(d+\alpha_1 s)}$ obtained in the cases when $F(x,y)$ is $\frac{\beta xy}{1+\alpha_1 x}$ or $\frac{\beta xy}{1+\alpha_1 x+\alpha_2 y}$, we can conclude from our calculations that the impact over R_0 of β or a is the same as in the previous cases, and the parameters s and d have minimal effect on the value of R_0. For example an increment of 50% on the value of s only increase the value of R_0 by 0.01%, a similar effect is observed for d, in the other hand by increasing α_1 by 10% will decrease R_0 by almost 10%.

We conclude this section by providing the sensitivity indices for the endemic equilibrium considering $F(x,y)=\beta xy$. Based on data parameter of [4], we consider the parameters values of case 1 in Table 3. The results are showed in Fig. 2.

The positive number in the bar indicates an increase in the coordinate when the parameter increases and a negative indicates a decrease in the value when the parameter increases. From Fig. 2 we can observe the following facts: for the value of x^*, showed in (a), the parameter with more influence is the contact rate, β, which means that the number of susceptible cells will decrease when the contact rate with the infected cells increases. By increasing this parameter 10% the amount of susceptible cells will decrease

Table 1
Values for R_0 depending of the incidence rate.

$F(x,y)$	R_0
βxy	$\frac{\beta s}{ad}$
$\frac{\beta xy}{x+y}$	$\frac{\beta}{a}$
$\frac{\beta xy}{1+\alpha_1 x}$	$\frac{\beta s}{a(d+\alpha_1 s)}$
$\frac{\beta xy}{1+\alpha_2 y}$	$\frac{\beta s}{ad}$
$\frac{\beta xy}{1+\alpha_1 x+\alpha_2 y}$	$\frac{\beta s}{a(d+\alpha_1 s)}$

9.8%, note that increasing the death rate of infected cells, a, the number of susceptible cells also increases. From panel (b) we can note that the parameter with more influence is the source of susceptible cells and the number of infected cells will decrease if their death rate increases. A similar analysis can be made from panel (c). In Table 2 we compare the change on the number of cells when we increase or decrease the value of R_0. The way to read Table 2 is as follows, for example when we increase β the basic reproductive number will increase, the number of susceptible cells decrease and the other populations form system will increase.

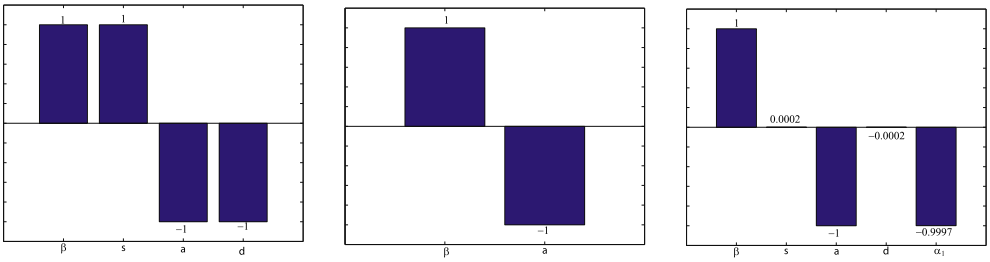
6. Numerical simulations

In the numerical simulations we illustrate the result obtained in Theorem 4 using the routine of MATLAB dde23 [17] and the values indicated in Table 3. We take the values as in [4,18].

In Fig. 3 we illustrate the dynamics of system (1) considering $F(x,y)=\beta xy$, this force of infection satisfies (H1)–(H5) in particular (H4) and (H5) satisfy the equality, we can appreciate that for a higher delay the stabilization take more time. In Fig. 4 we consider $F(x,y)=\frac{\beta xy}{x+y}$, in this case there are no significant variation on dynamics of system (1), this force of infection also satisfies (H1)–(H5) with strict inequality. In Figs. 5 and 6 we consider the force of infection $\frac{\beta xy}{1+\alpha_1 x}$ and $\frac{\beta xy}{1+\alpha_2 y}$ respectively. Note that this function also satisfies our hypothesis (H1)–(H5) with strict inequality, again we can appreciate the global stability for this simulations, but the dynamics is a different in these cases. The Fig. 7 presents the case when $F(x,y)=\frac{\beta xy}{1+\alpha_1 x+\alpha_2 y}$ the variation on dynamics is minimal in this scenario, also this force of infection satisfies our hypothesis (H1)–(H5).

Table 2
Relation between the parameters involving R_0 and their effect on the number of susceptible, infected cells and number of CTL's, considering the incidence rate $F(x,y)=\beta xy$.

Parameter to increase	R_0	x^*	y^*	z^*
s	Increase	Increase	Increase	Increase
β	Increase	Decrease	Increase	Increase
a	Decrease	Increase	Decrease	Decrease
d	Decrease	Decrease	Decrease	Decrease

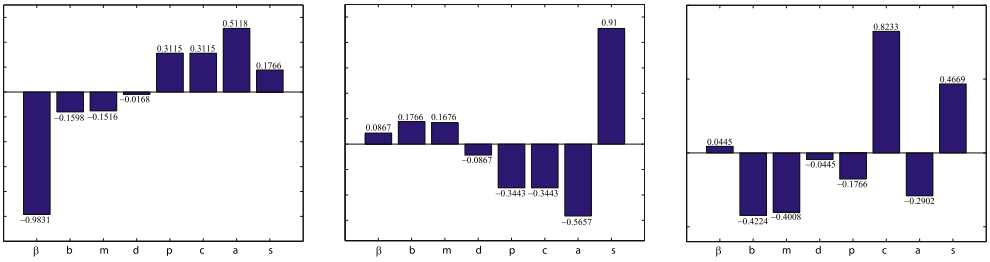


(a) Sensitivity index of R_0 when $F(x,y)=\beta xy$ and $F(x,y)=\frac{\beta xy}{1+\alpha_2 y}$

(b) Sensitivity index of R_0 when $F(x,y)=\frac{\beta xy}{x+y}$

(c) Sensitivity index of R_0 when $F(x,y)=\frac{\beta xy}{1+\alpha_1 x}$ and $F(x,y)=\frac{\beta xy}{1+\alpha_1 x+\alpha_2 y}$

Fig. 1. Sensitivity Index of basic reproduction number with respect to parameters of Table 3.



(a) Indices for x^*

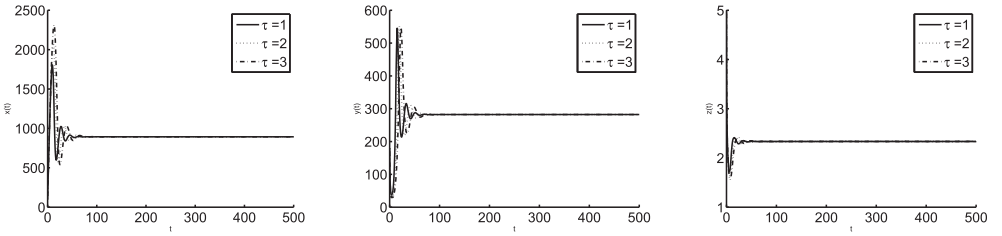
(b) Indices for y^*

(c) Indices for z^*

Fig. 2. Sensitivity Index of equilibria with respect to some chosen parameters and the incidence rate $F(x,y)=\beta xy$.

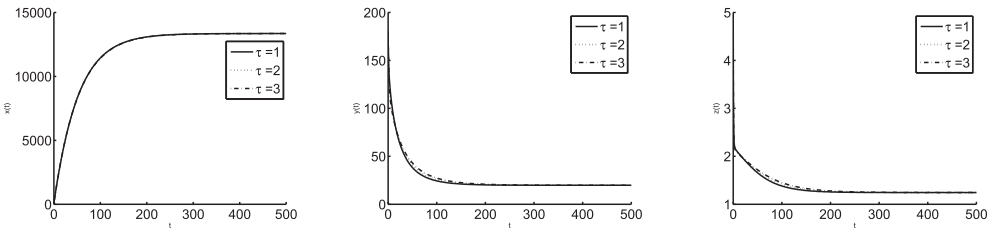
Table 3
Values for parameters in simulations.

Parameter	Description	Case 1	Case 2	Case 3	Case 4	Case 5
s	Proliferation rate of $CD4^+$ T cells (cells day^{-1} by ml^{-1} of peripheral blood)	270	270	270	270	270
d	Decay rate of $CD4^+$ T cells (day^{-1})	0.02	0.02	0.02	0.02	0.02
a	Decay rate of infected $CD4^+$ cells (day^{-1})	0.8	0.1	0.1	0.8	0.1
b	Decay rate of CTLs (day^{-1})	0.2	0.2	0.2	0.2	0.2
c	Proliferation rate of CTLs ($cell^{-2}$ day^{-1})	0.025	0.025	0.025	0.25	0.025
p	Killing rate of infected $CD4^+$ cells ($cells^{-1}$ day^{-1})	0.04	0.04	0.04	0.04	0.04
β	Infection rate of $CD4^+$ T cells ($cells^{-1}$ day^{-1})	0.001	0.15	0.05	0.001	0.05
m	Immune impairment rate of viral	0.01	0.01	0.01	0.01	0.01
α_1	Holling II parameter	–	–	0.3	–	0.3
α_2	Holling II parameter	–	–	–	0.3	0.3
R_0	Basic Reproductive number	16.88	1.5	1.6	16.88	1.6



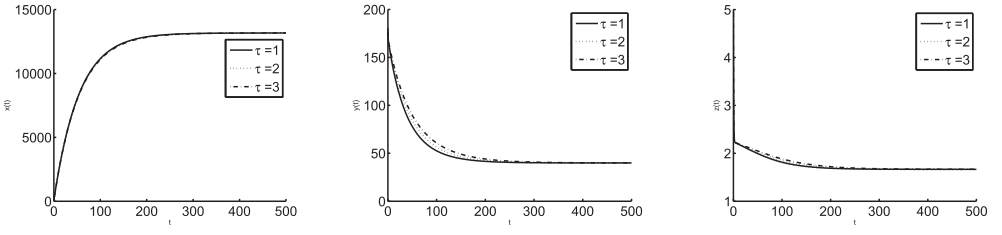
(a) Susceptible Cells (b) Infected Cells (c) CTL's

Fig. 3. Simulations with incidence rate $F(x,y) = \beta xy$, the value of parameters indicated in case 1, the infected equilibrium is $(893.4, 282.2, 2.33)$ and the values for the delay are $\tau = 1, \tau = 2$ and $\tau = 3$.



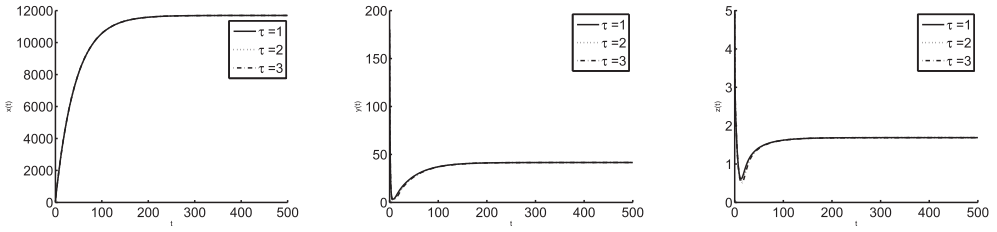
(a) Susceptible Cells (b) Infected Cells (c) CTL's

Fig. 4. Simulations with incidence rate $F(x,y) = \frac{\beta xy}{x+y}$, the value of parameters indicated in case 2, the infected equilibrium is $(13351.6, 19.8, 1.2)$ and the cases of $\tau = 1, \tau = 2$ and $\tau = 3$.



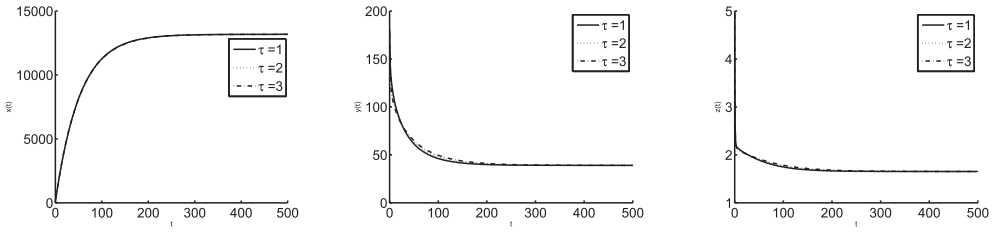
(a) Susceptible Cells (b) Infected Cells (c) CTL's

Fig. 5. Simulation with incidence rate $F(x,y) = \frac{\beta xy}{1+\alpha_1 x}$, the value of parameters indicated in case 3, the infected equilibrium is $(13167.4, 39.9, 1.7)$ and the values for the delay as $\tau = 1, \tau = 2$ and $\tau = 3$.



(a) Susceptible Cells (b) Infected Cells (c) CTL's

Fig. 6. Simulation with incidence rate $F(x,y)=\frac{\beta xy}{1+\alpha_2 y}$, value for the parameters indicated in case 4, the infected equilibrium is $(11695.4, 41.6, 1.68)$ and we take $\tau=1, \tau=2$ and $\tau=3$.



(a) Susceptible Cells (b) Infected Cells (c) CTL's

Fig. 7. Simulations with incidence rate $F(x,y)=\frac{\beta xy}{1+\alpha_1 x+\alpha_2 y}$, the value of parameters indicated in case 5, the infected equilibrium is $(13175.6, 39.05, 1.7)$ and the cases of $\tau=1, \tau=2$ and $\tau=3$.

7. Conclusions

In this work, we give a viral infection model with intracellular delay, immune impairment and a general non-linear incidence rate, global stability of the infection-free equilibrium and infected equilibrium have been given by the Lyapunov–LaSalle type theorem. We have built the Lyapunov function by combining linear, quadratic and Volterra-type functions, while the terms to construct the functional are similar to those presented by [10–12], we have considered within the dynamics, aside of susceptible and infected cells, the addition of population of CTL's, which requires the modification of functionals used in previous works. Therefore it is needed to consider a quadratic expression for the construction of functional to conclude satisfactorily the global stability. We have obtained sufficient conditions, which are entirely written in terms of the parameters of system, for the global asymptotic stability of both the virus-free ($R_0 \leqslant 1$) and the infected equilibrium ($R_0 > 1$). Such aspect is worth to be carefully investigated because it is biologically relevant. For example, the global stability of the infected equilibrium gives the conditions, written in terms of the parameters of the system, under which the virus cannot be eliminated.

The local sensitivity analysis shows that the basic reproductive number increases proportionally to parameters s and β and decreases proportionally to parameters a and d, which means that in order to eliminate the infection we must try to increase the value of a or d. From Table 2 a positive increment on the parameter a, will decrease the number of infected cells and CTL's and will increase the number of susceptible cells.

Our result establishes that no sustained oscillation regime exists which is similar to the conclusion of paper [9] but quite different from the conclusion of paper [4], where there are sustained oscillations. We think that if we introduce in model (1) a logistic proliferation term for the uninfected cells we could get sustained oscillations as in [7].

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