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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 $\mathcal{C}_+ = C([-\tau,0],\mathbb{R}^3_+)$.