Global analysis for delay virus dynamics model with Beddington–DeAngelis functional response☆

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A R T I C L E   I N F O

A B S T R A C T

A class of virus dynamics model with intracellular delay and nonlinear infection rate of Beddington–DeAngelis functional response is analysed in this paper. By constructing suitable Lyapunov functionals and using LaSalle-type theorem for delay differential equations, we show that the global stability of the infection-free equilibrium and the infected equilibrium depends on the basic reproductive ratio R_0, that is, the former is globally stable if $R_0 \leq 1$ and so is the latter if $R_0 > 1$. Our results extend the known results on delay virus dynamics considered in the other papers and suggest useful methods to control virus infection.

1. Introduction

A class of virus dynamics model was introduced by Anderson and May [1], and Nowak and Bangham [2]. Considering universal nonlinear infection rate in the process of virus infecting target cells, in [3] we proposed a class of virus dynamics model with Beddington–DeAngelis functional response as follows:

$$
\begin{aligned}
x'(t) &= \lambda - \mathrm{d}x(t) - \frac{\beta x(t)v(t)}{1 + ax(t) + bv(t)}, \\
y'(t) &= \frac{\beta x(t)v(t)}{1 + ax(t) + bv(t)} - py(t), \\
v'(t) &= ky(t) - uv(t).
\end{aligned}
\tag{1}
$$

In situation, there may be a lag between the time for target cells to be contacted by the virus particles and the time for the contacted cells to become actively affected, that is, the contacting virions need time to enter cells. Recently, it has been realized that time delay should be taken into consideration [4–6].

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In this paper we incorporate the intracellular delay in model (1), obtaining the following system of delay differential equations

$$
\begin{aligned}
x'(t) &= \lambda - \mathrm{d}x(t) - \frac{\beta x(t)v(t)}{1 + ax(t) + bv(t)}, \\
y'(t) &= \mathrm{e}^{-p\tau} \frac{\beta x(t-\tau)v(t-\tau)}{1 + ax(t-\tau) + bv(t-\tau)} - py(t), \\
v'(t) &= ky(t) - uv(t).
\end{aligned}
\tag{2}
$$

Here $x(t)$, $y(t)$, $v(t)$ represent the populations of uninfected cells, infected cells and free virus at time t, respectively. The constant $\lambda (\lambda > 0)$ is the rate at which new healthy cells are generated. The positive constant d and β are the death rate of uninfected cells and the rate constant characterizing infection of the cells, respectively. The function $\beta x(t)v(t)/(1 + ax(t) + bv(t))$, where $a, b > 0$ are constants, represents the Beddington–DeAngelis infection rate. The constant p $(p > 0)$ is the death rate of the infected cells due either to virus or the immune system. $\mathrm{e}^{-p\tau}$ denotes the surviving rate of infected cells before it becomes productively infected. Free virus is produced from the infected cells at the rate ky. The constant u $(u > 0)$ is the rate at which virus particles are removed from the system. We assume that the generation of virus producing cells at time t is due to the infection of target cells at time $t - \tau$, where τ is a constant.

Straightforward incorporating delay into a mathematical model generally leads to delay differential equations which are difficult to handle mathematically. We have studied the global properties of ordinary differential equation model (1) in [3] by Volterra-type Lyapunov functions. Recently, using Goh-type functionals McCluskey [7,8] has been solved elegantly global stability for delay SIR epidemic models. Utilizing the technology of constructing Lyapunov functionals in [3,7,8], we give a complete global stability analysis for delay differential equation model (2) and discuss the impact of time delay.

2. Non-negativity and boundedness of solutions

Let $C = C([-\tau, 0]; R^3)$ be the Banach space of continuous functions from $[-\tau, 0]$ to R^3 equipped with the sup-norm. The initial condition of (2) is given as

$$
x(\theta) = \varphi_1(\theta), \qquad y(\theta) = \varphi_2(\theta), \qquad v(\theta) = \varphi_3(\theta) \quad \theta \in [-\tau, 0],
\tag{3}
$$

where $\varphi = (\varphi_1, \varphi_2, \varphi_3)^T \in C$ such that $\varphi_i(\theta) \geq 0$ $(\tau \leq \theta \leq 0, i = 1, 2, 3)$.

The following theorem establishes the non-negativity and boundedness of solutions of (2).

Theorem 1. *Let* $(x(t), y(t), v(t))^T$ *be any solution of system* (2). *Then under the initial conditions* (3), *all solutions* $(x(t), y(t), v(t))^T$ *are non-negative on* $[0, +\infty)$ *and ultimately bounded.*

Proof. If $x(t)$ were to lose its non-negativity on some local existence interval $[0, T)$ for some constant $T > 0$, there would be a time at $t_1 > 0$ such that $x(t_1) = 0$. By the first equation of (2) we have $x'(t_1) = \lambda > 0$. That means $x(t) < 0$ for $t \in (t_1 - \varepsilon, t_1)$, where ε is an arbitrarily small positive constant. This leads to a contradiction. It follows that $x(t)$ is always positive. Further, form the second and the third equation in (2), we have, respectively

$$
\begin{aligned}
y(t) &= y(0)\mathrm{e}^{-pt} + \int_0^t \frac{\mathrm{e}^{-p\tau}\beta x(\theta-\tau)v(\theta-\tau)}{1 + ax(\theta-\tau) + bv(\theta-\tau)} \mathrm{e}^{-p(t-\theta)} \mathrm{d}\theta, \\
v(t) &= v(0)\mathrm{e}^{-ut} + \int_0^t ky(\theta)\mathrm{e}^{-u(t-\theta)} \mathrm{d}\theta.
\end{aligned}
$$

Then, it is easy to see that $y(t)$ and $v(t)$ are non-negative on $[0, T)$.

For $t \in [0, T)$, we have from (2) that $x'(t) \leq \lambda - \mathrm{d}x(t)$. Hence, the well-known comparison principle implies that $x(t)$ is bounded on $[0, T)$, i.e., $M_1 = \sup_{t \in [0,T)} x(t) < +\infty$. Therefore, we again have from (2) that on $[0, T)$,

(i) if $b = 0$, then $y'(t) \leq \frac{\beta M_1}{1 + M_1} v(t-\tau) - py(t)$, and $v'(t) = ky(t) - uv(t)$

(ii) if $b > 0$, then $y'(t) \leq \frac{\beta M_1}{b} - py(t)$, and $v'(t) = ky(t) - uv(t)$.

Hence, we also have from comparison principle that $y(t)$ and $v(t)$ are bounded on $[0, T)$. Boundedness of the solution $(x(t), y(t), v(t))^T$ implies that the local existence interval $[0, T)$ can be continued to $T = +\infty$. This proves that the solution $(x(t), y(t), v(t))^T$ is existent and non-negative on $[0, +\infty)$.

Define $F(t) = \mathrm{e}^{-p\tau}x(t) + y(t+\tau)$, and $\delta = \min\{d, p\}$. By non-negativity of the solution, it follows that

$$
F'(t) = \mathrm{e}^{-p\tau}\lambda - \mathrm{e}^{-p\tau}\mathrm{d}x(t) - py(t+\tau) < \mathrm{e}^{-p\tau}\lambda - \delta F(t).
$$

This implies that $F(t)$ is ultimately bounded, and so are $x(t), y(t)$. By the third equation, $v(t)$ is also ultimately bounded. This completes the proof. $\square$

The basic reproductive ratio of the virus for system (2) is

$$R_0 = \frac{\lambda \beta k e^{-p\tau}}{pu(d + a\lambda)}.$$

System (2) has always an infection-free equilibrium $E_0(x_0, 0, 0)$ where $x_0 = \lambda/d$, and an infected equilibrium $E^*(x^*, y^*, v^*)$ when $R_0 > 1$ where

$$x^* = \frac{\lambda bk + pue^{p\tau}}{k\beta + bdk - apue^{p\tau}}, \qquad y^* = \frac{\lambda \beta k e^{-p\tau}\left(1 - \frac{1}{R_0}\right)}{p(k\beta + bdk - apue^{p\tau})}, \qquad v^* = \frac{\lambda \beta k^2 e^{-p\tau}\left(1 - \frac{1}{R_0}\right)}{pu(k\beta + bdk - apue^{p\tau})}.$$

3. Global stability of the two equilibria

In this section, we would consider the global stability of the two equilibria. At first, we prove that E_0 is globally asymptotically stable for any time delay $\tau \geq 0$ under the condition $R_0 < 1$, by using stability theorems and the Lyapunov–LaSalle invariance principle.

Let $(x_t, y_t, v_t)^T = (x(t + \theta), y(t + \theta), v(t + \theta))^T (-\tau \leq \theta \leq 0)$ be any solution of (2) with the initial condition (3) for $t \geq 0$. Define a Lyapunov functional as follows:

$$V_1(x_t, y_t, z_t) = \frac{x_0}{1 + ax_0}\left(\frac{x(t)}{x_0} - 1 - \ln\frac{x(t)}{x_0}\right) + e^{p\tau}y(t) + \frac{e^{p\tau}p}{k}v(t) + U^-(t). \tag{4}$$

Here

$$U^-(t) = \int_0^\tau \frac{\beta x(t - \theta)v(t - \theta)}{1 + ax(t - \theta) + bv(t - \theta)}\,d\theta.$$

Calculating the derivative of $U^-(t)$,

$$\begin{aligned}
\frac{dU^-(t)}{dt} &= \frac{d}{dt}\int_0^\tau \frac{\beta x(t - \theta)v(t - \theta)}{1 + ax(t - \theta) + bv(t - \theta)}\,d\theta \\
&= \int_0^\tau \frac{d}{dt}\frac{\beta x(t - \theta)v(t - \theta)}{1 + ax(t - \theta) + bv(t - \theta)}\,d\theta \\
&= -\int_0^\tau \frac{d}{d\theta}\frac{\beta x(t - \theta)v(t - \theta)}{1 + ax(t - \theta) + bv(t - \theta)}\,d\theta \\
&= -\frac{\beta x(t - \theta)v(t - \theta)}{1 + ax(t - \theta) + bv(t - \theta)}\Big|_{\theta=0}^{\tau} \\
&= \frac{\beta x(t)v(t)}{1 + ax(t) + bv(t)} - \frac{\beta x(t - \tau)v(t - \tau)}{1 + ax(t - \tau) + bv(t - \tau)}.
\end{aligned}$$

Hence, we obtain

$$\begin{aligned}
\frac{dV_1}{dt} &= \frac{1}{1 + ax_0}\left(1 - \frac{x_0}{x(t)}\right)\left(dx_0 - dx(t) - \frac{\beta x(t)v(t)}{1 + ax(t) + bv(t)}\right) - \frac{e^{p\tau}pu}{k}v(t) + \frac{\beta x(t)v(t)}{1 + ax(t) + bv(t)} \\
&= -\frac{d(x(t) - x_0)^2}{x(t)(1 + ax_0)} + \frac{1 + ax(t)}{1 + ax_0}\frac{\beta x_0 v(t)}{1 + ax(t) + bv(t)} - \frac{e^{p\tau}pu}{k}v(t) \\
&= -\frac{d(x(t) - x_0)^2}{x(t)(1 + ax_0)} + \frac{e^{p\tau}puv(t)(1 + ax(t))}{k(1 + ax(t) + bv(t))}(R_0 - 1) - \frac{e^{p\tau}pub}{k(1 + ax(t) + bv(t))}v(t)^2.
\end{aligned}$$

Obviously, $R_0 \leq 1$ ensures that $dV_1/dt \leq 0$. It is clear that $V_1 \geq 0$, and $V_1 = 0$ iff $x(t) = x_0, y(t) = 0, v(t) = 0$. Hence, it follows from stability theorems [9] that the infection-free equilibrium E_0 is stable for any time delay $\tau \geq 0$ under the condition $R_0 \leq 1$. Furthermore, note that for each $t \geq 0, dV_1/dt = 0$ iff $x(t) = x_0, v(t) = 0$. For $(\varphi_1, \varphi_2, \varphi_3)^T \in C(\varphi_1 \geq 0, \varphi_2 \geq 0, \varphi_3 \geq 0)$, let M be the largest invariant set in the set

$$E = \{(\varphi_1, \varphi_2, \varphi_3)^T | V_1'(t) = 0\} = \{(\varphi_1, \varphi_2, \varphi_3)^T | \varphi_1(0) = x_0, \varphi_3(0) = 0\}.$$

We have from Eq. (2) and the invariance of M that $M = \{E_0\}$. Since any solution of (2) is bounded, it follows from the Lyapunov–LaSalle invariance principle for FED that E_0 is globally asymptotically stable when $R_0 \leq 1$.

Next, we consider the stability of $E^*(x^*, y^*, v^*)$ when it exists, that is, when $R_0 > 1$. Define a Lyapunov functional

$$V_2(x_t, y_t, v_t) = U(t) + py^* U^+(t), \tag{5}$$

where

$$U(t) = e^{-p\tau}\left(x(t) - x^* - \int_{x^*}^{x(t)} \frac{1 + a\theta + bv^*}{1 + ax^* + bv^*}\frac{x^*}{\theta}d\theta\right)$$

$$+ \left(y(t) - y^* - y^*\ln\frac{y(t)}{y^*}\right) + \frac{p}{k}\left(v(t) - v^* - v^*\ln\frac{v(t)}{v^*}\right),\tag{6}$$

and

$$U^+(t) = \int_0^\tau \left\{\frac{e^{-p\tau}\beta x(t-\theta)v(t-\theta)}{py^*(1 + ax(t-\theta) + bv(t-\theta))} - 1 - \ln\frac{e^{-p\tau}\beta x(t-\theta)v(t-\theta)}{py^*(1 + ax(t-\theta) + bv(t-\theta))}\right\}d\theta.\tag{7}$$

We note that function (6) is similar to the Lyapunov function for E^* in ordinary differential equation model (1) in [3] and only the first term of (6) has an additional term $e^{-p\tau}$. It is easy to find that

$$\frac{dU^+(t)}{dt} = \int_0^\tau \frac{d}{dt}\left\{\frac{e^{-p\tau}\beta x(t-\theta)v(t-\theta)}{py^*(1 + ax(t-\theta) + bv(t-\theta))} - 1 - \ln\frac{e^{-p\tau}\beta x(t-\theta)v(t-\theta)}{py^*(1 + ax(t-\theta) + bv(t-\theta))}\right\}d\theta$$

$$= -\int_0^\tau \frac{d}{d\theta}\left\{\frac{e^{-p\tau}\beta x(t-\theta)v(t-\theta)}{py^*(1 + ax(t-\theta) + bv(t-\theta))} - 1 - \ln\frac{e^{-p\tau}\beta x(t-\theta)v(t-\theta)}{py^*(1 + ax(t-\theta) + bv(t-\theta))}\right\}d\theta$$

$$= \frac{e^{-p\tau}\beta x(t)v(t)}{py^*(1 + ax(t) + bv(t))} - \frac{e^{-p\tau}\beta x(t-\tau)v(t-\tau)}{py^*(1 + ax(t-\tau) + bv(t-\tau))}$$

$$+ \ln\frac{x(t-\tau)v(t-\tau)}{1 + ax(t-\tau) + bv(t-\tau)}\frac{1 + ax(t) + bv(t)}{x(t)v(t)}.$$

Hence, we obtain

$$\frac{dV_2}{dt} = e^{-p\tau}\left(1 - \frac{x^*}{x(t)}\frac{1 + ax(t) + bv^*}{1 + ax^* + bv^*}\right)x'(t) + \left(1 - \frac{y^*}{y(t)}\right)y'(t) + \frac{p}{k}\left(1 - \frac{v^*}{v(t)}\right)v'(t) + py^*\frac{dU^+(t)}{dt}$$

$$= -\frac{de^{-p\tau}(1 + bv^*)(x(t) - x^*)^2}{x(t)(1 + ax^* + bv^*)} + py^*\ln\frac{x(t-\tau)v(t-\tau)}{1 + ax(t-\tau) + bv(t-\tau)}\frac{1 + ax(t) + bv(t)}{x(t)v(t)}$$

$$+ py^*\left(3 - \frac{x^*(1 + ax(t) + bv^*)}{x(t)(1 + ax^* + bv^*)} - \frac{y(t)v^*}{y^*v(t)} - \frac{y^*(1 + ax^* + bv^*)x(t-\tau)v(t-\tau)}{y(t)x^*v^*(1 + ax(t-\tau) + bv(t-\tau))}\right)$$

$$+ py^*\left(-\frac{v(t)}{v^*} + \frac{v(t)(1 + ax(t) + bv^*)}{v^*(1 + ax(t) + bv(t))}\right).$$

Using equality

$$\ln\frac{x(t-\tau)v(t-\tau)}{1 + ax(t-\tau) + bv(t-\tau)}\frac{1 + ax(t) + bv(t)}{x(t)v(t)} = \ln\frac{x^*(1 + ax(t) + bv^*)}{x(t)(1 + ax^* + bv^*)} + \ln\frac{y(t)v^*}{y^*v(t)}$$

$$+ \ln\frac{y^*(1 + ax^* + bv^*)x(t-\tau)v(t-\tau)}{y(t)x^*v^*(1 + ax(t-\tau) + bv(t-\tau))} + \ln\frac{1 + ax(t) + bv(t)}{1 + ax(t) + bv^*},$$

we obtain

$$\frac{dV_2}{dt} = -\frac{de^{-p\tau}(1 + bv^*)}{x(t)(1 + ax^* + bv^*)}\left(x(t) - x^*\right)^2 + py^*\left(1 - \frac{x^*(1 + ax(t) + bv^*)}{x(t)(1 + ax^* + bv^*)} + \ln\frac{x^*(1 + ax(t) + bv^*)}{x(t)(1 + ax^* + bv^*)}\right)\tag{8}$$

$$+ py^*\left(1 - \frac{y(t)v^*}{y^*v(t)} + \ln\frac{y(t)v^*}{y^*v(t)}\right)\tag{9}$$

$$+ py^*\left(1 - \frac{y^*(1 + ax^* + bv^*)x(t-\tau)v(t-\tau)}{y(t)x^*v^*(1 + ax(t-\tau) + bv(t-\tau))} + \ln\frac{y^*(1 + ax^* + bv^*)x(t-\tau)v(t-\tau)}{y(t)x^*v^*(1 + ax(t-\tau) + bv(t-\tau))}\right)\tag{10}$$

$$+ py^*\left(1 - \frac{1 + ax(t) + bv(t)}{1 + ax(t) + bv^*} + \ln\frac{1 + ax(t) + bv(t)}{1 + ax(t) + bv^*}\right)\tag{11}$$

$$+ py^*\left(-1 - \frac{v(t)}{v^*} + \frac{1 + ax(t) + bv(t)}{1 + ax(t) + bv^*} + \frac{v(t)(1 + ax(t) + bv^*)}{v^*(1 + ax(t) + bv(t))}\right).\tag{12}$$

By calculating the term (12), we have

$$py^*\left(-1 - \frac{v(t)}{v^*} + \frac{1 + ax(t) + bv(t)}{1 + ax(t) + bv^*} + \frac{v(t)(1 + ax(t) + bv^*)}{v^*(1 + ax(t) + bv(t))}\right)$$

$$= -\frac{py^*b(1 + ax(t))}{v^*(1 + ax(t) + bv(t))(1 + ax(t) + bv^*)}(v(t) - v^*)^2.$$

Since the function

$$H(t) = 1 - f(t) + \ln f(t)$$

is always non-positive for any function $f(t) > 0$, and $H(t) = 0$ iff $f(t) = 1$. Therefore, the terms (8)–(11) are always non-positive.

It is easy to see that $\frac{dV_2}{dt} \leq 0$. It is clear that $V_2 \geq 0$, and $V_2 = 0$ if and only if $x(t) = x^*$, $y(t) = y^*$, $v(t) = v^*$. Hence, it also follows from stability theorems [9] that the infected equilibrium E^* is stable for any time delay $\tau \geq 0$ under the condition $R_0 > 1$. Furthermore, note that for each $t \geq 0$, $\frac{dV_2}{dt} = 0$ iff $x(t) = x^*$, $y(t) = y^*$, $v(t) = v^*$. From the Lyapunov–LaSalle invariance principle, it shows that E^* is globally stable when $R_0 > 1$.

We have proved the following theorem.

Theorem 2. (i) *If $R_0 \leq 1$, then the infection-free equilibrium E_0 is globally asymptotically stable for any time delay $\tau \geq 0$.*
(ii) *If $R_0 > 1$, then the infected equilibrium E^* is globally asymptotically stable for any time delay $\tau \geq 0$.*

4. Conclusion

Usually, it is difficult to obtain global properties for a delay differential equation model with nonlinear functional response. The Lyapunov direct method and the LaSalle theorem provide effective approach to prove global dynamical properties for FDE. In this paper, by constructing two suitable and simple Lyapunov functionals, we found the sufficient and necessary conditions of the global stability for all equilibria. For a special case $a = 0$, $b = 0$, system (2) is similar to that considered by Nelson et al. [6], and Zhu et al. [10]. For the case $a = 0$, $b = 1$ our results provide an answer to the open question given in [11]. For $ax(t) \gg 1$, or $bv(t) \gg 1$, the Beddington–DeAngelis functional response is simplified to ratio dependent functional response. Gourley et al. [12] consider the HBV infection model with time delay for this case, and our results are also applicable to it.

Recently, Korobeinikov [13,14] considered more general epidemic and virus dynamic models with nonlinear transmission. It is expected that the type of Lyapunov functionals in this paper are also useful to study delay virus dynamics model with more general infection rate [15]. Compared with the results obtained in this paper with those for the ODE model (1), this paper shows that the global dynamical properties of the DDE model (2) also depend on the basic reproductive ratio. The reproductive ratio plays a crucial role for virus infection dynamics. Actually, in model (2), the basic reproductive ratio R_0 is a decreasing function on time delay τ. When all other parameters are fixed and delay τ is sufficiently large, R_0 becomes less than one, which makes the infection-free equilibrium globally asymptotically stable. By biological meanings, intracellular delay plays a positive role in virus infection process in order to eliminate virus. Sufficiently large intracellular delay makes the virus development slower and the virus has been controlled and disappeared. This gives us some suggestions on new drugs to prolong the time of infected cells producing virus.

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