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Stability and bifurcation analysis in a viral infection model with delays

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Abstract

In this paper, a class of virus infection models with CTLs response is considered. We incorporate an immune delay and two intracellular delays into the virus infection model. It is found that only incorporating two intracellular delays almost does not change the dynamics of the system, but incorporating an immune delay changes the dynamics of the system very greatly, namely, a Hopf bifurcation and oscillations can appear. Those results show immune delay dominates intracellular delays in some viral infection models, which indicates the human immune system has a special effect in virus infection models with CTLs response, and the human immune system itself is very complicated. In fact, people are aware of the complexity of the human immune system in medical science, which coincides with our investigating. We also investigate the global Hopf bifurcation of the system with the immune delay as a bifurcation parameter.

Keywords: virus infection model; CTLs response; time delay; Lyapunov functionals; global stability; Hopf bifurcation; global Hopf branch

1 Introduction

People utilize widely mathematical models to investigate viral infections currently, for example, HBV (hepatitis B virus), HCV (hepatitis C virus), HIV, and so on [1–7]. Perelson *et al.* proposed a standard and classic model (probably the first) for HIV dynamics in [8, 9] as follows:

$$\begin{cases} x'(t) = \lambda - d_1 x(t) - \beta x(t)v(t), \\ y'(t) = \beta x(t)v(t) - d_2 y(t), \\ v'(t) = ky(t) - d_3 v(t). \end{cases} \tag{1.1}$$

Here $x(t)$ represents the concentration of uninfected cells at time t, $y(t)$ represents the concentration of infected cells that can produce a virus at time t, $v(t)$ represents the concentration of viruses at time t. λ is the rate at which new healthy cells are generated. d_1, d_2, d_3 are the death rates of uninfected cells, infected cells, and virus cells, respectively. $\beta x(t)v(t)$ is the bilinear incidence between infected cells and uninfected cells. Free virus is produced from infected cells at the rate $ky(t)$.

Many researchers also consider system (1.1) as a basic virus infection model for various other viruses, such as HBV [10, 11]; HCV [12]. It is well known that an immune response exists universally and plays an important role in many viral infections [3, 13, 14]. So a typical extension model for those infections with a cytotoxic T lymphocytes (CTLs) response is considered in [14],

$$\begin{cases} x'(t) = \lambda - d_1x(t) - \beta x(t)v(t), \\ y'(t) = \beta x(t)v(t) - d_2y(t) - \mu y(t)z(t), \\ v'(t) = ky(t) - d_3v(t), \\ z'(t) = \gamma y(t)z(t) - d_4z(t). \end{cases} \tag{1.2}$$

Here $z(t)$ represents the concentration of the cells of the immune response. d_4 is the death rate of cells of the immune response. CTLs-driven elimination of infected cells is assumed to be of the form $\mu y(t)z(t)$, where μ is the rate of CTLs elimination. The CTLs response to the infection is modeled by $\gamma y(t)z(t)$.

In fact, we should note that there are delays in the infection process, including intracellular delay and CTLs immune response delay. We refer readers to [4, 5] and references therein. In [15], Zhu and Zou studied a HIV infection model with intracellular delay as follows:

$$\begin{cases} x'(t) = \lambda - d_1x(t) - \beta x(t)v(t), \\ y'(t) = \beta x(t-\tau)v(t-\tau) - d_2y(t) - \mu y(t)z(t), \\ v'(t) = ky(t) - d_3v(t), \\ z'(t) = \gamma y(t)z(t) - d_4z(t). \end{cases} \tag{1.3}$$

In this paper, we incorporate two intracellular delays and immune response delay in system (1.2). Namely, we incorporate a time delay τ_1 to describe the period between healthy cells' contacting with viruses and complete production of viral RNA and protein. We incorporate the time delay τ_2 to describe the period between complete production of viral RNA and protein and actually releasing new mature viruses. τ_3 represents the CTLs immune response delay. So we have the following system:

$$\begin{cases} x'(t) = \lambda - d_1x(t) - \beta x(t)v(t), \\ y'(t) = \beta x(t-\tau_1)v(t-\tau_1) - d_2y(t) - \mu y(t)z(t), \\ v'(t) = ky(t-\tau_2) - d_3v(t), \\ z'(t) = \gamma y(t-\tau_3)z(t-\tau_3) - d_4z(t). \end{cases} \tag{1.4}$$

A question is how the intracellular delays τ_1, τ_2 and the immune delay τ_3 affect the dynamics of the system (1.4). That is the main goal of this paper. We find that only incorporating two intracellular delays τ_1 and τ_2 almost does not change the dynamics of the system, but incorporating the immune delay τ_3 changes the dynamics of the system very greatly, namely, a Hopf bifurcation and oscillations can occur. Those results show that the immune delay dominates the intracellular delays in this class of viral infection models, which indicates the human immune system has a special effect in virus infection models with CTLs response, and the human immune system itself is very complicated. People are aware of the complexity of the human immune system in medical science, which coincides with our investigation.

The paper is organized as follows. In the next section, the attractive region and equilibria for system (1.4) are discussed and the two threshold parameters R_0 and R_1 are introduced.

In Section 3, by combining the linear stability theory and the LaSalle-Lyapunov theorem, the global stability of P_0 and P_1 when $R_0 < 1$ and $R_1 < 1 < R_0$ is discussed, respectively. By analyzing the distribution of the eigenvalues, the dynamics of the system when $R_1 > 1$ is investigated. In Section 4, we study the global Hopf branch of the system. Numerical simulations are presented in Section 5 to illustrate the analysis results. The paper ends with a brief conclusion.

2 Attractive region and equilibria

Let $\tau = \max\{\tau_1, \tau_2, \tau_3\}$; we denote by $\mathcal{C} = \mathcal{C}([-\tau, 0], \mathbb{R}^4)$ the Banach space of continuous real-valued functions on the interval $[-\tau, 0]$, with norm

$$\|\phi\| = \sup_{-\tau\leq\theta\leq 0} \bigl|\phi(\theta)\bigr| \quad \text{for } \phi \in \mathcal{C}.$$

The nonnegative cone of $\mathcal{C}$ is defined as

$$\mathcal{C}^+ = \mathcal{C}\bigl([-\tau, 0], \mathbb{R}^4_+\bigr).$$

The initial conditions for system (1.4) are chosen at $t = 0$ as

$$\varphi \in \mathcal{C}^+, \quad \varphi = \{\varphi_1, \varphi_2, \varphi_3, \varphi_4\}, \qquad \varphi_i(0) > 0, \quad i = 1, 2, 3, 4. \tag{2.1}$$

Proposition 2.1 *Under the initial condition* (2.1), *all solutions of system* (1.4) *are positive and ultimately bounded in* $\mathcal{C}$. *Furthermore, all solutions eventually enter and remain in the following bounded region*:

$$\begin{aligned} \Gamma^* = \biggl\{&(x, y, v, z) \in \mathcal{C}^+ : \|x\| \leq \frac{\lambda}{d_1} + \varepsilon, \|x + y\| \leq \frac{\lambda}{\tilde{d}} + \varepsilon, \\ &\biggl\|x + y + \frac{d_2}{2k} v\biggr\| \leq \frac{\lambda}{\hat{d}} + \varepsilon, \biggl\|x + y + \frac{d_2}{2k} v + \frac{\gamma}{\mu} z\biggr\| \leq \frac{\lambda}{d} + \varepsilon\biggr\}, \end{aligned}$$

where

$$\tilde{d} = \min\{d_1, d_2\}, \qquad \hat{d} = \min\biggl\{d_1, \frac{d_2}{2}, d_3\biggr\}, \qquad d = \min\biggl\{d_1, \frac{d_2}{2}, d_3, d_4\biggr\},$$

and ε *is an arbitrarily small positive number.*

Proof First, we prove that $x(t)$ is positive for $t \geq 0$. Assuming the contrary and letting $t_1 > 0$ be the first time such that $x(t_1) = 0$, by the first equation of system (1.4), we have $x'(t_1) = \lambda > 0$, and hence $x(t) < 0$ for $t \in (t_1 - \eta, t_1)$ and sufficiently small $\eta > 0$. This contradicts $x(t) > 0$ for $t \in [0, t_1)$. It follows that $x(t) > 0$ for $t > 0$. From the fourth equation of (1.4), we use the method of the steps to prove $z(t) > 0$ for $t > 0$. From the third equation of (1.4), we can prove $v(t) > 0$ for $t > 0$. From the second equation of (1.4), we can obtain $y(t) > 0$ for $t > 0$.

Next we show that positive solutions of (1.4) are ultimately uniformly bounded for $t \geq 0$. From the first equation of system (1.4), we obtain

$$x'(t) \leq \lambda - d_1 x(t),$$

and thus

$$\limsup_{t\to\infty} x(t) \le \frac{\lambda}{d_1}.$$

Adding the first two equations of (1.4) leads to

$$\big(x(t) + y(t+\tau_1)\big)' \le \lambda - \tilde{d}\big(x(t) + y(t+\tau_1)\big),$$

where $\tilde{d} = \min\{d_1, d_2\}$. Thus

$$\limsup_{t\to\infty}\big(x(t) + y(t+\tau_1)\big) \le \frac{\lambda}{\tilde{d}}.$$

Adding the first three equations of (1.4), we have

$$\begin{aligned}
&\left(x(t) + y(t+\tau_1) + \frac{d_2}{2k}v(t+\tau_1+\tau_2)\right)' \\
&\quad = \lambda - d_1 x(t) - \frac{d_2}{2}y(t+\tau_1) - \mu y(t+\tau_1)z(t+\tau_1) - \frac{d_2}{2k}d_3 v(t+\tau_1+\tau_2) \\
&\quad \le \lambda - \hat{d}\left(x(t) + y(t+\tau_1) + \frac{d_2}{2k}v(t+\tau_1+\tau_2)\right),
\end{aligned}$$

where $\hat{d} = \min\{d_1, \frac{d_2}{2}, d_3\}$. Thus

$$\limsup_{t\to\infty}\left(x(t) + y(t+\tau_1) + \frac{d_2}{2k}v(t+\tau_1+\tau_2)\right) \le \frac{\lambda}{\hat{d}}.$$

Adding all four equations of (1.4), we have

$$\begin{aligned}
&\left[x(t) + y(t+\tau_1) + \frac{d_2}{2k}v(t+\tau_1+\tau_2) + \frac{\mu}{\gamma}z(\tau_1+\tau_3)\right]' \\
&\quad = \lambda - d_1 x(t) - \frac{d_2}{2}y(t+\tau_1) - \frac{d_2}{2k}d_3 v(t+\tau_1+\tau_2) - d_4\frac{\mu}{\gamma}z(t+\tau_1+\tau_3) \\
&\quad \le \lambda - d\left[x(t) + y(t+\tau_1) + \frac{d_2}{2k}v(t+\tau_1+\tau_2) + \frac{\mu}{\gamma}z(t+\tau_1+\tau_3)\right],
\end{aligned}$$

where $d = \min\{d_1, \frac{d_2}{2}, d_3, d_4\}$. Thus

$$\limsup_{t\to\infty}\left(x(t) + y(t+\tau_1) + \frac{d_2}{2k}v(t+\tau_1+\tau_2) + \frac{\mu}{\gamma}z(t+\tau_1+\tau_3)\right) \le \frac{\lambda}{d}.$$

Therefore, $x(t)$, $y(t)$, $v(t)$, and $z(t)$ are ultimately uniformly bounded in $\mathcal{C}$. □

As a consequence of Proposition 2.1, we know that the dynamics of system (1.4) can be analyzed in the following bounded region:

$$\begin{aligned}
\Gamma = \Bigg\{&(x,y,v,z) \in \mathcal{C}^+ : \|x\| \le \frac{\lambda}{d_1}, \|x+y\| \le \frac{\lambda}{\tilde{d}}, \\
&\left\|x + y + \frac{d_2}{2k}v\right\| \le \frac{\lambda}{\hat{d}}, \left\|x + y + \frac{d_2}{2k}v + \frac{\gamma}{\mu}z\right\| \le \frac{\lambda}{d}\Bigg\}.
\end{aligned}$$

Furthermore, the region Γ is attractive with respect to system (1.4).

The system has two threshold parameters,

$$R_0 = \frac{\lambda\beta k}{d_1 d_2 d_3}, \qquad R_1 = \frac{\lambda\beta\gamma k}{d_1 d_2 d_3\gamma + \beta k d_2 d_4}. \tag{2.2}$$

They are called the basic reproduction numbers for viral infection and for CTL response [3, 16]. We note that $R_1 < R_0$ always holds.

System (1.4) always has an infection-free equilibrium $P_0 = (x_0, 0, 0, 0)$, $x_0 = \frac{\lambda}{d_1}$. In addition to P_0, the system can have two other equilibria $P_1 = (\overline{x}, \overline{y}, \overline{v}, 0)$ and $P_2 = (x^*, y^*, v^*, z^*)$, where $\overline{x}$, $\overline{y}$, $\overline{v}$, x^*, y^*, v^*, and z^* are all positive. The equilibrium $P_1 = (\overline{x}, \overline{y}, \overline{v}, 0)$ exists if and only if $R_0 > 1$ and

$$\overline{x} = \frac{d_2 d_3}{\beta k}, \qquad \overline{y} = \frac{\lambda\beta k - d_1 d_2 d_3}{\beta k d_2}, \qquad \overline{v} = \frac{\lambda\beta k - d_1 d_2 d_3}{\beta d_2 d_3}. \tag{2.3}$$

The equilibrium P_2 exists if and only if $R_1 > 1$. The equilibrium $P_2 = (x^*, y^*, v^*, z^*)$ is given by

$$\begin{aligned} &x^* = \frac{\lambda\gamma d_3}{\gamma d_1 d_3 + \beta k d_4}, \qquad y^* = \frac{d_4}{\gamma}, \\ &v^* = \frac{k d_4}{\gamma d_3}, \qquad z^* = \frac{\gamma\beta\lambda k - \gamma d_1 d_2 d_3 - \beta k d_2 d_4}{(d_1 d_3\gamma + \beta k d_4)\mu}. \end{aligned} \tag{2.4}$$

3 Global stability and Hopf bifurcation

We investigate stability of the equilibria and the Hopf bifurcation in this section. First, P_0 is considered in the following.

3.1 Global stability of P_0

In this subsection, we rigorously show that when $R_0 < 1$, the infection-free equilibrium P_0 is globally asymptotically stable in Γ.

Theorem 3.1 *If $R_0 < 1$, the infection-free equilibrium P_0 of system* (1.4) *is globally asymptotically stable in Γ. If $R_0 > 1$, P_0 is unstable.*

Proof First we prove P_0 is locally asymptotically stable. The characteristic equation associated with the linearization of system (1.4) at P_0 is given by

$$(\xi + d_1)(\xi + d_4)\left(\xi^2 + (d_2 + d_3)\xi + d_2 d_3 - \frac{\beta\lambda k}{d_1} e^{-\xi(\tau_1+\tau_2)}\right) = 0. \tag{3.1}$$

Obviously we have

$$\xi_1 = -d_1 < 0, \qquad \xi_2 = -d_4 < 0,$$

and we consider the equation

$$\xi^2 + (d_2 + d_3)\xi + d_2 d_3 - \frac{\beta\lambda k}{d_1} e^{-\xi(\tau_1+\tau_2)} = 0. \tag{3.2}$$

Notice 0 is not a root of (3.2) because of $R_0 < 1$. Following the method in [17], if $\xi = i\omega$ ($\omega > 0$) is a purely imaginary root of (3.2), we have

$$\begin{aligned} d_2 d_3 - \omega^2 &= \frac{\beta\lambda k}{d_1}\cos(\tau_1 + \tau_2)\omega, \\ -(d_2 + d_3)\omega &= \frac{\beta\lambda k}{d_1}\sin(\tau_1 + \tau_2)\omega. \end{aligned} \tag{3.3}$$

Squaring and adding both equations of (3.3), it follows that

$$\omega^4 + \left(d_2^2 + d_3^2\right)\omega^2 + d_2^2 d_3^2 - \left(\frac{\beta k\lambda}{d_1}\right)^2 = 0. \tag{3.4}$$

Let $u = \omega^2$. Then (3.4) becomes

$$u^2 + \left(d_2^2 + d_3^2\right)u + d_2^2 d_3^2 - \left(\frac{\beta k\lambda}{d_1}\right)^2 = 0. \tag{3.5}$$

From $R_0 < 1$, we easily see that (3.5) has no positive root. Therefore, all roots of (3.1) have negative real parts. So P_0 is locally asymptotically stable when $R_0 < 1$.

Next, we prove P_0 is globally attractive in Γ if $R_0 < 1$. To prove this, we consider a Lyapunov functional $L : \mathcal{C} \to \mathbb{R}$ given by

$$\begin{aligned} L(x_t, y_t, v_t, z_t) &= x_t(0) - x_0 \ln x_t(0) + y_t(0) + \frac{d_2}{k}v_t(0) + \frac{\mu}{\gamma}z_t(0) \\ &\quad + \beta\int_{-\tau_1}^{0} x_t(\theta)v_t(\theta)\,d\theta + d_2\int_{-\tau_2}^{0} y_t(\theta)\,d\theta + \mu\int_{-\tau_3}^{0} y_t(\theta)z_t(\theta)\,d\theta. \end{aligned} \tag{3.6}$$

Here $x_t(s) = x(t+s)$, for $s \in [-\tau, 0]$, and thus $x(t) = x_t(0)$ in this notation.

Calculating the time derivative of L along solution of system (1.4), it follows that

$$\begin{aligned} L'|_{(1.4)} &= x'(t) - x_0\frac{x'(t)}{x(t)} + y'(t) + \frac{d_2}{k}v'(t) + \frac{\mu}{\gamma}z'(t) + \beta\bigl(x(t)v(t) - x(t-\tau_1)v(t-\tau_1)\bigr) \\ &\quad + d_2\bigl(y(t) - y(t-\tau_2)\bigr) + \mu\bigl(y(t)z(t) - y(t-\tau_3)z(t-\tau_3)\bigr) \\ &= \lambda\left(2 - \frac{x}{x_0} - \frac{x_0}{x}\right) + \beta x_0 v - \frac{d_2 d_3}{k}v - \frac{\mu d_4}{\gamma}z \\ &= \lambda\left(2 - \frac{x}{x_0} - \frac{x_0}{x}\right) + \frac{d_2 d_3}{k}(R_0 - 1)v - \frac{\mu d_4}{\gamma}z. \end{aligned}$$

$R_0 < 1$ ensures that $L'|_{(1.4)} \le 0$, and $L' = 0$ if and only if

$$x(t) = x_0, \qquad y(t) = 0, \qquad v(t) = 0, \qquad z(t) = 0,$$

it can be verified that the maximal invariant set in $\{L'|_{(1.4)} = 0\}$ is the set

$$M = \bigl\{(x_0, 0, 0, 0)\bigr\}.$$

By the LaSalle-Lyapunov theorem, we conclude that M is globally attractive in Γ if $R_0 < 1$. So P_0 is globally attractive in Γ.

Therefore, P_0 is globally asymptotically stable in Γ.

We can easily see that (3.1) has a root with a positive real part when $R_0 > 1$. P_0 is unstable when $R_0 > 1$. □

Remark 3.2 Obviously P_0 is globally asymptotically stable without any delays when $R_0 < 1$, but after incorporating three delays (a immune delay and two intracellular delays), P_0 is still globally asymptotically stable. Delays do not destroy the globally asymptotical stability of P_0.

3.2 Global stability of P_1

Theorem 3.3 *If $R_1 < 1 < R_0$, then the equilibrium P_1 is globally asymptotically stable. If $R_1 > 1$, P_1 is unstable.*

Proof Let

$$g(u) = u - \ln u - 1, \quad u > 0.$$

Define a Lyapunov functional

$$V : \mathcal{C} \to \mathbb{R}$$

in the following form:

$$\begin{aligned} V(x_t, y_t, v_t, z_t) = {} & \overline{x} g\left(\frac{x_t(0)}{\overline{x}}\right) + \overline{y} g\left(\frac{(y_t(0))}{\overline{y}}\right) + \frac{d_2}{k}\overline{v} g\left(\frac{v_t(0)}{\overline{v}}\right) + \frac{\mu}{\gamma} z_t(0) \\ & + \beta\overline{x}\overline{v}\int_{-\tau_1}^{0} g\left(\frac{x_t(\theta)v_t(\theta)}{\overline{x}\overline{v}}\right) d\theta + \beta\overline{x}\overline{v}\int_{-\tau_2}^{0} g\left(\frac{y_t(\theta)}{\overline{y}}\right) d\theta \\ & + \mu\int_{-\tau_3}^{0} y_t(\theta) z_t(\theta)\, d\theta. \end{aligned} \tag{3.7}$$

Calculating the time derivative of V along the solution of system (1.4), we obtain

$$\begin{aligned} V'|_{(1.4)} = {} & \lambda - d_1 x(t) - \beta x(t)v(t) - \overline{x}\left(\frac{\lambda}{x(t)} - d_1 - \beta v(t)\right) + \beta x(t-\tau_1)v(t-\tau_1) \\ & - d_2 y(t) - \mu y(t)z(t) - \overline{y}\left(\frac{\beta x(t-\tau_1)v(t-\tau_1)}{y(t)} - d_2 - \mu z(t)\right) + d_2 y(t-\tau_2) \\ & - \frac{d_2 d_3}{k} v(t) - \frac{d_2\overline{v}}{k}\left(\frac{k y(t-\tau_2)}{v(t)} - d_3\right) + \mu y(t-\tau_3)z(t-\tau_3) - \frac{\mu}{\gamma} d_4 z(t) \\ & + \beta\overline{x}\overline{v}\left(\frac{x(t)v(t) - x(t-\tau_1)v(t-\tau_1)}{\overline{x}\overline{v}} - \ln\frac{x(t)v(t)}{\overline{x}\overline{v}} + \ln\frac{x(t-\tau_1)v(t-\tau_1)}{\overline{x}\overline{v}}\right) \\ & + \beta\overline{x}\overline{v}\left(\frac{y(t) - y(t-\tau_2)}{\overline{y}} - \ln\frac{y(t)}{\overline{y}} + \ln\frac{y(t-\tau_2)}{\overline{y}}\right) \\ & + \mu\bigl(y(t)z(t) - y(t-\tau_3)z(t-\tau_3)\bigr). \end{aligned}$$

Using

$$\beta\overline{x}\overline{v} = d_2\overline{y}, \qquad k\overline{y} = d_3\overline{v}, \qquad \lambda = d_1\overline{x} + d_2\overline{y},$$

we have

$$
\begin{aligned}
V'|_{(1.4)} = {} & d_1\overline{x}\left(2 - \frac{x(t)}{\overline{x}} - \frac{\overline{x}}{x(t)}\right) + \beta\overline{xv}\left(1 - \frac{\overline{x}}{x(t)} + \ln\frac{\overline{x}}{x(t)}\right) - \beta\overline{xv}\ln\frac{\overline{x}}{x(t)} \\
& + \beta\overline{xv}\left(1 - \frac{\overline{y}x(t-\tau_1)v(t-\tau_1)}{\overline{xv}y(t)} + \ln\frac{\overline{y}x(t-\tau_1)v(t-\tau_1)}{\overline{xv}y(t)}\right) \\
& - \beta\overline{xv}\ln\frac{\overline{y}x(t-\tau_1)v(t-\tau_1)}{\overline{xv}y(t)} + \beta\overline{xv}\left(1 - \frac{\overline{v}y(t-\tau_2)}{\overline{y}v(t)} + \ln\frac{\overline{v}y(t-\tau_2)}{\overline{y}v(t)}\right) \\
& - \beta\overline{xv}\ln\frac{\overline{v}y(t-\tau_2)}{\overline{y}v(t)} + \left(\mu\overline{y} - \frac{\mu}{\gamma}d_4\right)z(t) - \beta\overline{xv}\ln\frac{x(t)v(t)}{\overline{xv}} \\
& + \beta\overline{xv}\ln\frac{x(t-\tau_1)v(t-\tau_1)}{\overline{xv}} - \beta\overline{xv}\ln\frac{y(t)}{\overline{y}} + \beta\overline{xv}\ln\frac{y(t-\tau_2)}{\overline{y}} \\
= {} & d_1\overline{x}\left(2 - \frac{x(t)}{\overline{x}} - \frac{\overline{x}}{x(t)}\right) - \beta\overline{xv}g\left(\frac{\overline{x}}{x(t)}\right) - \beta\overline{xv}g\left(\frac{\overline{y}x(t-\tau_1)v(t-\tau_1)}{\overline{xv}y(t)}\right) \\
& - \beta\overline{xv}g\left(\frac{\overline{v}y(t-\tau_2)}{\overline{y}v(t)}\right) + \frac{d_2\mu(\gamma d_1 d_3 + \beta k d_4)}{\gamma\beta k d_2}(R_1 - 1) \le 0,
\end{aligned}
$$

when $R_1 < 1$. Furthermore,

$$V'|_{(1.4)} = 0 \quad \Leftrightarrow \quad x(t) = \overline{x}, \qquad y(t) = \overline{y}, \qquad v(t) = \overline{v}, \qquad z(t) = 0,$$

and thus the maximal invariant set in the set $\{V' = 0\}$ is the singleton $\{P_1\}$. Therefore, P_1 is globally attractive.

The characteristic equation associated with the linearization of system (1.4) at P_1 is given by

$$\left(\xi + d_4 - \gamma\overline{y}e^{-\xi\tau_3}\right)\left[(\xi + d_1 + \beta\overline{v})(\xi + d_2)(\xi + d_3) - d_2 d_3(\xi + d_1)e^{-\xi(\tau_1+\tau_2)}\right] = 0. \tag{3.8}$$

We first consider

$$\xi + d_4 - \gamma\overline{y}e^{-\xi\tau_3} = 0.$$

When $\tau_3 = 0$, we have

$$\xi = \gamma\overline{y} - d_4 = \frac{\gamma d_1 d_2 d_3 + \beta k d_2 d_4}{\beta k d_2}(R_1 - 1) < 0.$$

Assuming $\tau_3 > 0$ and $\xi = i\omega$ ($\omega > 0$) is the purely imaginary root of this equation, then we obtain

$$i\omega + d_4 - \gamma\overline{y}\cos\omega\tau_3 + i\gamma\overline{y}\sin\omega\tau_3 = 0.$$

So, $\omega^2 + d_4^2 = (\gamma\overline{y})^2$, namely, $\omega^2 = (\gamma\overline{y})^2 - d_4^2 < 0$. Obviously, this is a contradiction. Note that 0 is not the root of the equation. Therefore, all roots of this equation have a negative real part.

Next, we address the following equation:

$$(\xi + d_1 + \beta\overline{v})(\xi + d_2)(\xi + d_3) - d_2 d_3(\xi + d_1)e^{-\xi(\tau_1+\tau_2)} = 0. \tag{3.9}$$

We rewrite this equation in the following form:

$$\begin{aligned}&\xi^3 + (d_1 + d_2 + d_3 + \beta\overline{v})\xi^2 + \bigl[(d_1 + \beta\overline{v})(d_2 + d_3) + d_2d_3\bigr]\xi \\ &\quad + (d_1 + \beta\overline{v})d_2d_3 - d_2d_3(\xi + d_1)e^{-\xi(\tau_1+\tau_2)} = 0.\end{aligned}$$

When $\tau_1 + \tau_2 = 0$, the equation becomes

$$\xi^3 + a_1\xi^2 + a_2\xi + a_3 = 0,$$

where

$$a_1 = d_1 + d_2 + d_3 + \beta\overline{v} > 0, \qquad a_2 = (d_1 + \beta\overline{v})(d_2 + d_3) > 0, \qquad a_3 = \beta\overline{v}d_2d_3 > 0,$$

and $a_1a_2 - a_3 > 0$. By the Routh-Hurwitz criteria, all roots of (3.9) have negative real parts when $\tau_1 + \tau_2 = 0$.

Assume $\tau_1 + \tau_2 > 0$, and $\xi = i\omega$ ($\omega > 0$) is the purely imaginary root of (3.9). Substituting $\xi = i\omega$ ($\omega > 0$) into equation (3.9), we obtain

$$\begin{aligned}&-i\omega^3 - (d_1 + d_2 + d_3 + \beta\overline{v})\omega^2 + i\bigl[(d_1 + \beta\overline{v})(d_2 + d_3) + d_2d_3\bigr]\omega \\ &\quad - (d_1 + \beta\overline{v})d_2d_3 - d_2d_3(i\omega + d_1)\bigl(\cos\omega(\tau_1 + \tau_2) - i\sin\omega(\tau_1 + \tau_2)\bigr) = 0.\end{aligned}$$

Separating the real and imaginary parts, we have

$$\begin{aligned}&-\omega^3 + \bigl[(d_1 + \beta\overline{v})(d_2 + d_3) + d_2d_3\bigr]\omega \\ &\quad = d_2d_3\bigl(\omega\cos\omega(\tau_1 + \tau_2) - d_1\sin\omega(\tau_1 + \tau_2)\bigr), \\ &-(d_1 + d_2 + d_3 + \beta\overline{v})\omega^2 + (d_1 + \beta\overline{v})d_2d_3 \\ &\quad = d_2d_3\bigl(\omega\sin\omega(\tau_1 + \tau_2) + d_1\cos\omega(\tau_1 + \tau_2)\bigr).\end{aligned} \tag{3.10}$$

Squaring and adding both equations lead to

$$\omega^6 + b_1\omega^4 + b_2\omega^2 + b_3 = 0, \tag{3.11}$$

where

$$\begin{aligned}&b_1 = (d_1 + \beta\overline{v})^2 + d_2^2 + d_3^2 > 0, \qquad b_2 = (d_1 + \beta\overline{v})^2\bigl(d_2^2 + d_3^2\bigr) > 0, \\ &b_3 = \bigl((\beta\overline{v})^2 + 2d_1\beta\overline{v}\bigr)d_2^2d_3^2 > 0 \quad \text{and} \quad b_1b_2 - b_3 > 0.\end{aligned}$$

By the Routh-Hurwitz criteria,

$$u^3 + b_1u^2 + b_2u + b_3 = 0 \quad \bigl(u = \omega^2\bigr)$$

has no positive root. So (3.11) has no positive root. Equation (3.9) has no pure imaginary root. Also 0 is not root of equation (3.9), therefore, all roots of equation (3.9) have negative real parts for $\tau_1 + \tau_2 \geq 0$. Hence P_1 is locally asymptotically stable.

Further, P_1 is globally asymptotically stable.

For $R_1 > 1$, we can find the characteristic equation (3.9) has positive root. Thus P_1 is unstable when $R_1 > 1$. □

Remark 3.4 P_1 is globally asymptotically stable without any delays when $R_1 < 1 < R_0$. Although incorporating three delays (a immune delay and two intracellular delays), P_1 is still globally asymptotically stable. Delays do not destroy the globally asymptotical stability of P_1.

3.3 Dynamics when $R_1 > 1$

When $R_1 > 1$, there exists an interior equilibrium $P_2 = (x^*, y^*, v^*, z^*)$, where

$$\begin{aligned} x^* &= \frac{\lambda\gamma d_3}{\gamma d_1 d_3 + \beta k d_4}, \qquad y^* = \frac{d_4}{\gamma}, \\ v^* &= \frac{k d_4}{\gamma d_3}, \qquad z^* = \frac{\gamma\beta\lambda k - \gamma d_1 d_2 d_3 - \beta k d_2 d_4}{(d_1 d_3 \gamma + \beta k d_4)\mu}. \end{aligned}$$

The characteristic equation associated with the linearization of system (1.4) at P_2 is given by

$$\begin{aligned} &\xi^4 + a_3\xi^3 + a_2\xi^2 + a_1\xi - \left(b_3\xi^3 + b_2\xi^2 + b_1\xi + b_0\right)e^{-\xi\tau_3} \\ &\quad - \left(c_2\xi^2 + c_1\xi + c_0\right)e^{-\xi(\tau_1+\tau_2)} + (e_1\xi + e_0)e^{-\xi(\tau_1+\tau_2+\tau_3)} = 0, \end{aligned} \tag{3.12}$$

where

$$\begin{aligned} a_3 &= d_1 + d_2 + d_3 + d_4 + \beta v^* + \mu z^*, \\ a_2 &= \left(d_1 + \beta v^*\right)\left(d_2 + d_3 + d_4 + \mu z^*\right) + \left(d_2 + \mu z^*\right)(d_3 + d_4) + d_3 d_4, \\ a_1 &= \left(d_1 + \beta v^*\right)\left(d_2 + \mu z^*\right)(d_3 + d_4) + \left(d_1 + \beta v^*\right)d_3 d_4 + \left(d_2 + \mu z^*\right)d_3 d_4, \\ a_0 &= \left(d_1 + \beta v^*\right)\left(d_2 + \mu z^*\right)d_3 d_4, \\ b_3 &= d_4, \qquad b_2 = \left(d_1 + d_2 + d_3 + d_4 + \beta v^*\right)d_4, \\ b_1 &= \left(d_2 d_3 + \left(d_1 + \beta v^*\right)(d_2 + d_3)\right)d_4, \qquad b_0 = d_2 d_3 d_4\left(d_1 + \beta v^*\right), \\ c_2 &= \beta k x^*, \qquad c_1 = \beta k x^*(d_1 + d_4), \qquad c_0 = \beta k x^* d_1 d_4, \\ e_1 &= \beta k x^* d_4, \qquad e_0 = \beta k x^* d_1 d_4 = c_0. \end{aligned}$$

3.3.1 When $\tau_1 \geq 0$, $\tau_2 \geq 0$, $\tau_3 = 0$

Theorem 3.5 *If $R_1 > 1$, then the equilibrium P_2 is globally attractive when*

$$\tau_1 \geq 0, \qquad \tau_2 \geq 0 \quad \textit{and} \quad \tau_3 = 0.$$

Proof Let

$$g(u) = u - \ln u - 1, \quad u > 0.$$

Define a Lyapunov functional

$$U : \mathcal{C} \to \mathbb{R}$$

in the following form:

$$U(x_t, y_t, v_t, z_t) = x^* g\left(\frac{x_t(0)}{x^*}\right) + y^* g\left(\frac{y_t(0)}{y^*}\right) + \frac{\beta x^*(v^*)^2}{ky^*} g\left(\frac{v_t(0)}{v^*}\right) + \frac{\mu z^*}{\gamma} g\left(\frac{z_t(0)}{z^*}\right)$$
$$+ \beta x^* v^* \int_{-\tau_1}^{0} g\left(\frac{x_t(\theta)v_t(\theta)}{x^* v^*}\right) d\theta + \beta x^* v^* \int_{-\tau_2}^{0} g\left(\frac{y_t(\theta)}{y^*}\right) d\theta. \tag{3.13}$$

Calculating the time derivative of V along solution of system (1.4), we obtain

$$\begin{aligned} U'|_{(1.4)} &= x' - \frac{x^*}{x}x' + y' - \frac{y^*}{y}y' + \frac{\beta x^* v^*}{ky^*}v' - \frac{\beta x^* v^* v^*}{ky^* v}v' + \frac{\mu}{\gamma}z' - \frac{\mu z^*}{\gamma z}z' \\ &\quad + \beta x^* v^* \left(\frac{xv - x(t-\tau_1)v(t-\tau_1)}{x^* v^*} - \ln\frac{xv}{x^* v^*} + \ln\frac{x(t-\tau_1)v(t-\tau_1)}{x^* v^*}\right) \\ &\quad + \beta x^* v^* \left(\frac{y - y(t-\tau_2)}{y^*} - \ln\frac{y}{y^*} - \ln\frac{y(t-\tau_2)}{y^*}\right). \end{aligned}$$

Using

$$\lambda = d_1 x^* + \beta x^* v^*, \qquad (d_2 + \mu z^*) = \beta x^* v^*, \qquad y^* = \frac{d_4}{\gamma} \quad \text{and} \quad v^* = \frac{kd_4}{\gamma d_3},$$

it follows that

$$\begin{aligned} U'|_{(1.4)} &= d_1 x^* \left(2 - \frac{x}{x^*} - \frac{x^*}{x}\right) + \beta x^* v^* \left(1 - \frac{x^*}{x} + \ln\frac{x^*}{x}\right) - \beta x^* v^* \ln\frac{x^*}{x} \\ &\quad + \beta x^* v^* \left(1 - \frac{y^* x(t-\tau_1)v(t-\tau_1)}{x^* v^* y} + \ln\frac{y^* x(t-\tau_1)v(t-\tau_1)}{x^* v^* y}\right) \\ &\quad - \beta x^* v^* \frac{y^* x(t-\tau_1)v(t-\tau_1)}{x^* v^* y} + \beta x^* v^* \left(1 - \frac{v^* y(t-\tau_2)}{y^* v} + \ln\frac{v^* y(t-\tau_2)}{y^* v}\right) \\ &\quad - \beta x^* v^* \ln\frac{v^* y(t-\tau_2)}{y^* v} - \beta x^* v^* \ln\frac{xv}{x^* v^*} + \beta x^* v^* \ln\frac{x(t-\tau_1)v(t-\tau_1)}{x^* v^*} \\ &\quad - \beta x^* v^* \ln\frac{y}{y^*} + \beta x^* v^* \ln\frac{y(t-\tau_2)}{y^*} \\ &= d_1 x^* \left(2 - \frac{x}{x^*} - \frac{x^*}{x}\right) - \beta x^* v^* g\left(\frac{x^*}{x}\right) \\ &\quad - \beta x^* v^* g\left(\frac{y^* x(t-\tau_1)v(t-\tau_1)}{x^* v^* y}\right) - \beta x^* v^* g\left(\frac{v^* y(t-\tau_2)}{y^* v}\right) \le 0. \end{aligned}$$

This implies that

$$U'|_{(1.4)} = 0 \quad \Leftrightarrow \quad x(t) = x^*, \qquad y(t) = y^*, \qquad v(t) = v^*, \qquad z(t) = z^*,$$

and thus the maximal invariant set in the set $\{U' = 0\}$ is the singleton $\{P_2\}$. Therefore, P_2 is globally attractive. □

Remark 3.6 It is very difficult to analyze the characteristic roots of the characteristic equation (3.12). But we conjecture that all characteristic roots of the characteristic equation (3.12) have negative real parts when $\tau_1 > 0$, $\tau_2 > 0$, $\tau_3 = 0$. Namely, P_2 is locally asymptotically stable, and P_2 is also globally asymptotically stable when $\tau_1 \geq 0$, $\tau_2 \geq 0$, $\tau_3 = 0$. We find the intracellular delays τ_1 and τ_2 do not destroy global attractability of P_2.

3.3.2 When $\tau_1 = 0$, $\tau_2 = 0$, $\tau_3 > 0$

When $\tau_1 = 0$, $\tau_2 = 0$, $\tau_3 > 0$, system (1.4) becomes

$$\begin{cases} x'(t) = \lambda - d_1x(t) - \beta x(t)v(t), \\ y'(t) = \beta x(t)v(t) - d_2y(t) - \mu y(t)z(t), \\ v'(t) = ky(t) - d_3v(t), \\ z'(t) = \gamma y(t-\tau_3)z(t-\tau_3) - d_4z(t). \end{cases} \tag{3.14}$$

The characteristic equation of system (3.14) at P_2 is given by

$$\begin{aligned} &\xi^4 + a_3\xi^3 + (a_2 - c_2)\xi^2 + (a_1 - c_1)\xi + (a_0 - c_0) \\ &\quad + \left(-b_3\xi^3 - b_2\xi^2 + (e_1 - b_1)\xi + e_0 - b_0\right)e^{-\xi\tau_3} = 0. \end{aligned} \tag{3.15}$$

When $\tau_3 = 0$, (3.15) becomes

$$\xi^4 + m_3\xi^3 + m_2\xi^2 + m_1\xi + m_0 = 0,$$

where

$$\begin{aligned} &m_3 = a_3 - b_3 > 0, \qquad m_2 = a_2 - b_2 - c_2, \qquad m_1 = a_1 - b_1 - c_1 + e_1 > 0, \\ &m_0 = a_0 - b_0 - c_0 + e_0 > 0 \quad \text{and} \quad m_3m_2m_1 - m_1^2 - m_3^2m_0 > 0. \end{aligned}$$

By the Routh-Hurwitz criteria, all roots of this equation have negative real parts. Clearly, 0 is not the root of (3.15).

For $\tau_3 > 0$, assuming $\xi = i\omega$ ($\omega > 0$) is a purely imaginary root of (3.15). It satisfies

$$\begin{aligned} &\omega^4 - ia_3\omega^3 - (a_2 - c_2)\omega^2 + i(a_1 - c_1)\omega + a_0 - c_0 \\ &\quad + \left(ib_3\omega^3 + b_2\omega^2 + i(e_1 - b_1)\omega + e_0 - b_0\right)(\cos\omega\tau_3 - i\sin\omega\tau_3) = 0. \end{aligned} \tag{3.16}$$

Separating the real and imaginary parts, we get

$$\begin{aligned} &\omega^4 - (a_2 - c_2)\omega^2 + (a_0 - c_0) = -\left(b_2\omega^2 + e_0 - b_0\right)\cos\omega\tau_3 - \left(b_3\omega^3 + (e_1 - b_1)\omega\right)\sin\omega\tau_3, \\ &-a_3\omega^3 + (a_1 - c_1)\omega = \left(b_2\omega^2 + e_0 - b_0\right)\sin\omega\tau_3 - \left(b_3\omega^3 + (e_1 - b_1)\omega\right)\cos\omega\tau_3. \end{aligned}$$

Squaring and adding both above equations lead to

$$\omega^8 + p\omega^6 + q\omega^4 + u\omega^2 + v = 0, \tag{3.17}$$

where

$$\begin{aligned} &p = a_3^2 - 2(a_2 - c_2) - b_3^2, \\ &q = (a_2 - c_2)^2 + 2(a_0 - c_0) - 2a_3(a_1 - c_1) - b_2^2 - 2b_3(e_1 - b_1), \end{aligned}$$

$$u = (a_1 - c_1)^2 - 2(a_2 - c_2)(a_0 - c_0) - 2b_2(e_0 - b_0) - (e_1 - b_1)^2,$$
$$v = (a_0 - c_0)^2 - (e_0 - b_0)^2.$$

Let $\omega^2 = s$, we have

$$F(s) = s^4 + ps^3 + qs^2 + us + v = 0. \tag{3.18}$$

Then

$$F'(s) = 4s^3 + 3ps^2 + 2qs + u.$$

Set

$$4s^3 + 3ps^2 + 2qs + u = 0. \tag{3.19}$$

Let $r = s + \frac{p}{4}$, then (3.19) becomes

$$r^3 + p_1 r + q_1 = 0,$$

where $p_1 = \frac{q}{2} - \frac{3p^2}{16}$, $q_1 = \frac{p^3}{32} - \frac{pq}{8} + \frac{u}{4}$.

Define

$$\Delta = \left(\frac{q_1}{2}\right)^2 + \left(\frac{p_1}{3}\right)^3, \qquad \delta = \frac{-1 + i\sqrt{3}}{2},$$
$$r_1 = \sqrt[3]{-\frac{q_1}{2} + \sqrt{\Delta}} + \sqrt[3]{-\frac{q_1}{2} - \sqrt{\Delta}},$$
$$r_2 = \sqrt[3]{-\frac{q_1}{2} + \sqrt{\Delta}}\,\delta + \sqrt[3]{-\frac{q_1}{2} - \sqrt{\Delta}}\,\delta^2,$$
$$r_3 = \sqrt[3]{-\frac{q_1}{2} + \sqrt{\Delta}}\,\delta^2 + \sqrt[3]{-\frac{q_1}{2} - \sqrt{\Delta}}\,\delta,$$
$$s_i = r_i - \frac{p}{4}, \quad i = 1, 2, 3.$$

We cite the results in [18] about the existence of positive roots of the fourth-degree polynomial equation, namely, we have the following lemma.

Lemma 3.7

(i) *If* $v < 0$, *then* (3.18) *has at least one positive root.*
(ii) *If* $v \geq 0$ *and* $\Delta \geq 0$, *then* (3.18) *has positive roots if and only if* $s_1 > 0$ *and* $F(s_1) < 0$.
(iii) *If* $v \geq 0$ *and* $\Delta < 0$, *then* (3.18) *has positive roots if and only if there exists at least one* $s^* \in \{s_1, s_2, s_3\}$ *such that* $s^* > 0$ *and* $F(s^*) < 0$.

Supposing one of the above three cases in Lemma 3.7 is satisfied, (3.18) has finite positive roots $s_1, s_2, \ldots, s_k$, $k \leq 4$. Therefore (3.17) has finite positive roots

$$\omega_1 = \sqrt{s_1}, \qquad \omega_2 = \sqrt{s_2}, \qquad \ldots, \qquad \omega_k = \sqrt{s_k}, \quad k \leq 4.$$

For every fixed ω_i ($i = 1, 2, \dots, k$, $k \le 4$), there exists a sequence

$$\tau_{3_i}^j = \frac{1}{\omega_i}(\arccos U_i + 2j\pi), \quad i = 1, 2, \dots, k, k \le 4, j = 0, 1, 2, 3, \dots, \tag{3.20}$$

where

$$U_i = \frac{(\omega_i^4 - (a_2 - c_2)\omega_i^2 + a_0 - c_0)(-b_2\omega_i^2 + b_0 - e_0) + (-a_3\omega_i^3 + (a_1 - c_1)\omega_i)(-b_3\omega_i^3 + (b_1 - e_1)\omega_i)}{(b_3\omega_i^3 + (e_1 - b_1)\omega_i)^2 + (b_2\omega_i^2 + e_0 - b_0)^2},$$

such that (3.16) holds. Let

$$\tau_3^* = \min\{\tau_{3_i}^0 | i = 1, 2, \dots, k, k \le 4\} = \frac{1}{\omega^*}\arccos U^*, \quad \omega^* = \omega_i \text{ for some } 1 \le i \le 4.$$

Then (3.15) has a pair of purely imaginary roots $\pm i\omega^*$ when $\tau_3 = \tau_3^*$.

After a long and tedious computation, we get the following lemma.

Lemma 3.8

$$\left[\frac{d}{d\tau_3}(\operatorname{Re}\xi)\right]^{-1}_{\tau_3 = \tau_{3_i}^j} = \frac{F'(\omega_i^2)}{(b_3\omega^3 + (e_1 - b_1)\omega)^2 + (b_2\omega^2 + e_0 - b_0)^2}. \tag{3.21}$$

Especially, supposing $F'((\omega^*)^2) \neq 0$, *then*

$$\left[\frac{d}{d\tau_3}(\operatorname{Re}\xi)\right]^{-1}_{\tau_3 = \tau_3^*} = \frac{F'((\omega^*)^2)}{(b_3(\omega^*)^3 + (e_1 - b_1)\omega^*)^2 + (b_2(\omega^*)^2 + e_0 - b_0)^2} > 0. \tag{3.22}$$

Remark 3.9 For the nth degree exponential polynomial

$$\xi^n + a_{n-1}\xi^{n-1} + \cdots + a_1\xi + a_0 + (b_{n-1}\xi^{n-1} + b_{n-2}\xi^{n-2} + \cdots + b_1\xi + b_0)e^{-\xi\tau} = 0,$$

we conjecture there are similar equations to (3.21). To the best of our knowledge, it is correct for $n = 1, 2, 3, 4$.

From Lemma 3.8, we can get the following result.

Theorem 3.10 *For system* (3.14), *there exists*

$$\tau_3^* = \min\{\tau_{3_i}^0 | i = 1, 2, \dots, k, k \le 4\},$$

such that P_2 *is asymptotically stable when* $\tau_3 \in [0, \tau_3^*)$. *Furthermore, if* $F'((\omega^*)^2) \neq 0$ *holds, and system* (3.14) *undergoes a Hopf bifurcation at* P_2 *when* $\tau_3 = \tau_3^*$.

Remark 3.11 We find that incorporating an immune delay can destroy the global attractability of P_2 on proper conditions when $R_1 > 1$, and a Hopf bifurcation occurs. That is, a periodic oscillation appears. Stability switches can appear when $k \ge 2$. Those results show immune delay dominates intracellular delays in this class of viral infection models. Those indicate the human immune system has a special effect in virus infection models with a CTLs response, and the human immune system itself is very complicated.

4 Global Hopf bifurcation analysis

Many researchers studied global Hopf bifurcations in their research, for example [19, 20]. In this section, we will investigate the global existence of periodic solutions of system (3.14) by using the global Hopf bifurcation theorem given by Wu [21] when $R_1 > 1$. So we consider the following system:

$$\begin{cases} x'(t) = \lambda - d_1x(t) - \beta x(t)v(t), \\ y'(t) = \beta x(t)v(t) - d_2y(t) - \mu y(t)z(t), \\ v'(t) = ky(t) - d_3v(t), \\ z'(t) = \gamma y(t-\tau)z(t-\tau) - d_4z(t). \end{cases} \tag{4.1}$$

Note that we omit the subscript '3' of τ_3 for convenience.

Firstly, we suppose (3.18) has a unique positive root s^* in this section, therefore, $\omega^* = \sqrt{s^*}$, and

$$\tau^j = \frac{1}{\omega^*}\bigl(\arccos U^* + 2j\pi\bigr), \quad j = 0,1,2,3,\ldots, \tag{4.2}$$

where

$$\begin{aligned} U^* = {} & \frac{((\omega^*)^4 - (a_2 - c_2)(\omega^*)^2 + a_0 - c_0)(-b_2(\omega^*)^2 + b_0 - e_0)}{(b_3(\omega^*)^3 + (e_1 - b_1)\omega^*)^2 + (b_2(\omega^*)^2 + e_0 - b_0)^2} \\ & + \frac{(-a_3(\omega^*)^3 + (a_1 - c_1)\omega^*)(-b_3(\omega^*)^3 + (b_1 - e_1)\omega^*)}{(b_3(\omega^*)^3 + (e_1 - b_1)\omega^*)^2 + (b_2(\omega^*)^2 + e_0 - b_0)^2}. \end{aligned}$$

$\tau^0 = \min\{\tau^j, j = 0,1,2,\ldots\}$. It is reasonable that we suppose (3.18) has a unique positive root s^*. For example, we consider the following case:

$$\begin{aligned} &F(s) = s^4 + ps^3 + qs^2 + us + v = 0, \\ &F'(s) = 4s^3 + 3ps^2 + 2qs + u, \\ &F''(s) = 12s^2 + 6ps + 2q, \end{aligned}$$

when $(3p)^2 - 4 \times 6q < 0$ and $v < 0$, $F(s) = 0$ has only one positive root. Furthermore, in Section 5, we can choose proper parameters such that $F(s) = 0$ has unique positive root when we carry out numerical simulations.

From Lemma 3.8, we obtain the following lemma.

Lemma 4.1 *τ^j, ω^* are defined as above. The following holds*:

$$\left[\frac{d}{d\tau}(\operatorname{Re}\xi)\right]^{-1}_{\tau=\tau^j} = \frac{F'((\omega^*)^2)}{(b_3(\omega^*)^3 + (e_1 - b_1)\omega^*)^2 + (b_2(\omega^*)^2 + e_0 - b_0)^2} > 0.$$

Furthermore, if $\tau \in (0, \tau^0]$, then all roots of (3.15) *have negative real parts*; *if $\tau \in (\tau^j, \tau^{j+1}]$, $j = 0,1,2,\ldots$, then* (3.15) *has exactly* $2(j+1)$ *roots with positive real parts*.

Lemma 4.2 *System* (4.1) *has no nonconstant periodic solution when* $\tau = 0$.

Proof Theorem 3.5 shows P_2 is globally attractive when $\tau = 0$. This lemma follows from the fact that P_2 is globally attractive when $\tau = 0$. □

Lemma 4.3 *All the nontrivial periodic solutions of* (4.1) *are positive and uniformly bounded.*

Proof The proof of this lemma can be obtained from Proposition 2.1. □

Lemma 4.4 *When* $R_1 > 1$, *system* (4.1) *has no nonconstant periodic solution of period* τ. *Furthermore, system* (4.1) *has no nonconstant periodic solution of period* $\frac{\tau}{j}$, $j = 2, 3, 4, \ldots$.

Proof We prove by contradiction. Suppose system (4.1) has a periodic solution of periodic τ, $W(t) = (x(t), y(t), v(t), z(t))^T$, and $W(t+\tau) = (x(t+\tau), y(t+\tau), v(t+\tau), z(t+\tau))^T = W(t)$. So $W(t) = (x(t), y(t), v(t), z(t))^T$ is also τ-periodic solution of the following system:

$$\begin{cases} x'(t) = \lambda - d_1 x(t) - \beta x(t)v(t), \\ y'(t) = \beta x(t)v(t) - d_2 y(t) - \mu y(t)z(t), \\ v'(t) = ky(t) - d_3 v(t), \\ z'(t) = \gamma y(t)z(t) - d_4 z(t). \end{cases} \tag{4.3}$$

However, this system has no periodic solutions, which follows from Theorem 3.5. Therefore, system (4.1) has no periodic solution of period τ. □

Let $W(t) = (x(t), y(t), v(t), z(t))^T$, we rewrite system (4.1) as the following functional differential equation:

$$\frac{dW(t)}{dt} = F(W_t, \tau, T), \tag{4.4}$$

where $W_t(\theta) = (x(t+\theta), y(t+\theta), v(t+\theta), z(t+\theta)) \in C([-\tau, 0], \mathbb{R}^4_+)$, and

$$F(W_t, \tau, T) = \begin{pmatrix} \lambda - d_1 x(t) - \beta x(t)v(t) \\ \beta x(t)v(t) - d_2 y(t) - \mu y(t)z(t) \\ ky(t) - d_3 v(t) \\ \gamma y(t-\tau)z(t-\tau) - d_4 z(t) \end{pmatrix}.$$

Let

$$\widehat{F}(W, \tau, T) = \begin{pmatrix} \lambda - d_1 x - \beta xv \\ \beta xv - d_2 y - \mu yz \\ ky - d_3 v \\ \gamma yz - d_4 z \end{pmatrix},$$

$$\begin{aligned} \Delta_{(P_2,\tau,T)}(\xi) &= \xi^4 + a_3\xi^3 + (a_2 - c_2)\xi^2 + (a_1 - c_1)\xi + (a_0 - c_0) \\ &\quad + \left(-b_3\xi^3 - b_2\xi^2 + (e_1 - b_1)\xi + e_0 - b_0\right)e^{-\xi\tau_3}. \end{aligned}$$

It is easy to see the assumptions (A1), (A2), and (A3) in [21] are satisfied.

Note that the periodic solutions are all bounded away from zero, which follows from Lemma 4.2, thus we need not to consider the boundary equilibria P_0 and P_1.

It is convenient to introduce the following notations:

$$\begin{aligned}
&X = C\bigl([-\tau,0],\mathbb{R}^4\bigr),\\
&\Sigma = \mathrm{Cl}\bigl\{(W,\tau,T)\in X\times\mathbb{R}_+\times\mathbb{R}_+ : W \text{ is a } T\text{-periodic solution of (4.1)}\bigr\}\\
&\quad\subset X\times\mathbb{R}_+\times\mathbb{R}_+,\\
&N(F) = \bigl\{(\widehat{W},\tau,T) : F(\widehat{W},\tau,T) = 0\bigr\}.
\end{aligned}$$

Let $C(P_2,\tau^j,\frac{2\pi}{\omega^*})$ denote the connected component of $(P_2,\tau^j,\frac{2\pi}{\omega^*})$ in Σ, where τ^j, ω^* are defined in (4.2).

Now, we are in a position to state the following global Hopf bifurcation results.

Theorem 4.5 *When $R_1 > 1$, for each $\tau > \tau^j$, $j = 1,2,3,\ldots$, system* (4.1) *has at least $j + 1$ positive periodic solutions, where τ^j is defined in* (4.2).

Proof It is obvious that $(P_2,\tau^j,\frac{2\pi}{\omega^*})$ are isolated centers. By Lemma 4.1, there exist $\varepsilon > 0$, $\delta > 0$, and a smooth curve $l : (\tau^j-\delta,\tau^j+\delta)\to\mathbb{C}$, such that

$$\Delta\bigl(\xi(\tau)\bigr) = 0, \qquad \bigl|\xi(\tau) - i\omega^*\bigr| < \varepsilon$$

for all $\tau\in[\tau^j-\delta,\tau^j+\delta]$, where Δ is defined above, and

$$\xi\bigl(\tau^j\bigr) = i\omega^*, \qquad \left[\frac{d}{d\tau}(\mathrm{Re}\,\xi)\right]_{\tau=\tau^j} > 0.$$

Let

$$\Omega_\varepsilon = \left\{(u,T) : 0 < u < \varepsilon, \left|T - \frac{2\pi}{\omega^*}\right| < \varepsilon\right\}.$$

Clearly, if $|\tau-\tau^j|\le\delta$ and $(u,T)\in\partial\Omega_\varepsilon$ such that $\Delta_{(P_2,\tau,T)}(u+\frac{2\pi i}{T}) = 0$, then $\tau = \tau^j$, $u = 0$, and $T = \frac{2\pi}{\omega^*}$. So (A4) is satisfied in [21] for $m = 1$. Moreover, let

$$H^{\pm}\left(P_2,\tau^j,\frac{2\pi}{\omega^*}\right)(u,T) = \Delta_{(P_2,\tau^j\pm\delta,T)}\left(u+\frac{2\pi i}{T}\right),$$

then we see, from $\mathrm{Re}\,\xi'(\tau^j) > 0$, that the crossing number is

$$\gamma_1\left(P_2,\tau^j,\frac{2\pi}{\omega^*}\right) = \deg_B\left(H^-\left(P_2,\tau^j,\frac{2\pi}{\omega^*}\right),\Omega_\varepsilon\right) - \deg_B\left(H^+\left(P_2,\tau^j,\frac{2\pi}{\omega^*}\right),\Omega_\varepsilon\right) = -1.$$

Using the local Hopf bifurcation theorem in [21], we conclude that the connected component $C(P_2,\tau^j,\frac{2\pi}{\omega^*})$ through $(P_2,\tau^j,\frac{2\pi}{\omega^*})$ in Σ is nonempty. Meanwhile, we have

$$\sum_{(\widehat{W},\tau,T)\in C(P_2,\tau^j,\frac{2\pi}{\omega^*})}\gamma_1\bigl((\widehat{W},\tau,T)\bigr) < 0.$$

By Theorem 3.3 in [21], $C(P_2,\tau^j,\frac{2\pi}{\omega^*})$ is unbounded.

Lemma 4.3 shows the projection of $C(P_2, \tau^j, \frac{2\pi}{\omega^*})$ onto W-space is bounded. Lemma 4.2 implies the projection of $C(P_2, \tau^j, \frac{2\pi}{\omega^*})$ onto τ-space is bounded below.

From the definition of τ^j in (4.2), we have

$$2\pi < \omega^* \tau^j < 2(j+1)\pi < 2(j+2)\pi, \quad j \geq 1,$$

namely,

$$\frac{1}{j+1} < \frac{2\pi}{\omega^* \tau^j} < \frac{1}{j}, \quad j \geq 1.$$

From Lemma 4.4, we know if

$$(W, \tau, T) \in C\left(P_2, \tau^1, \frac{2\pi}{\omega^*}\right),$$

then

$$\frac{1}{2} < \frac{2\pi}{\omega^* \tau^2} < 1;$$

if

$$(W, \tau, T) \in C\left(P_2, \tau^2, \frac{2\pi}{\omega^*}\right),$$

then

$$\frac{1}{3} < \frac{2\pi}{\omega^* \tau^2} < \frac{1}{2};$$

and so on. This shows that the projection of $C(P_2, \tau^j, \frac{2\pi}{\omega^*})$ onto T-space is bounded. Therefore in order for $C(P_2, \tau^j, \frac{2\pi}{\omega^*})$ to be unbounded, its projection onto the τ-space must be unbounded. The projection of $C(P_2, \tau^j, \frac{2\pi}{\omega^*})$ onto the τ-space includes $[\tau^j, +\infty)$. Note $\frac{1}{j+1} < \frac{2\pi}{\omega^* \tau^j} < \frac{1}{j}$, $j \geq 1$, we can see that the connected components $C(P_2, \tau^j, \frac{2\pi}{\omega^*})$, $j \geq 1$ are disjoint. This shows system (4.1) has at least j positive periodic solutions for each $\tau > \tau^j$. The proof is completed. □

5 Numerical simulations

In this section, we shall carry out some numerical simulations for illustrating our theoretical analysis. As regards the selected parameters in this section, we refer to [15, 22].

First, we consider the following set of parameter values:

$$\begin{aligned}
&\lambda = 10, \quad \beta = 0.02, \quad d_1 = 0.2, \quad d_2 = 1.8, \\
&d_3 = 1.5, \quad d_4 = 0.5, \quad k = 2, \quad \mu = 0.2, \\
&\gamma = 0.2, \quad \tau_1 = 1, \quad \tau_2 = 2, \quad \tau_3 = 3.
\end{aligned}$$

For the above parameter set, $R_0 = 0.7407 < 1$, system (1.4) has a unique infection-free equilibrium $P_0 = (50, 0, 0, 0)$. Figure 1 shows P_0 is globally asymptotically stable when $R_0 < 1$.

Figure 1 P_0 **is globally asymptotically stable.** Here $\lambda = 10$, $\beta = 0.02$, $d_1 = 0.2$, $d_2 = 1.8$, $d_3 = 1.5$, $d_4 = 0.5$, $k = 2$, $\mu = 0.2$, $\gamma = 0.2$, $\tau_1 = 1$, $\tau_2 = 2$, $\tau_3 = 3$, and $R_0 = 0.7407 < 1$.

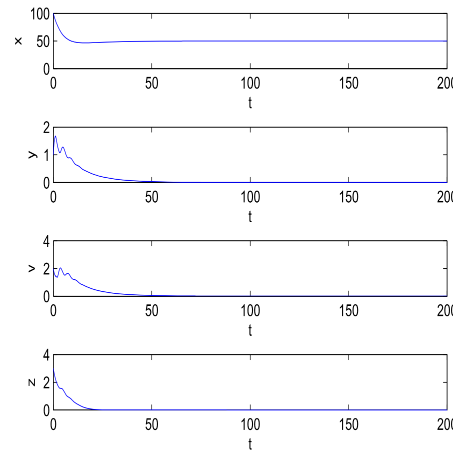
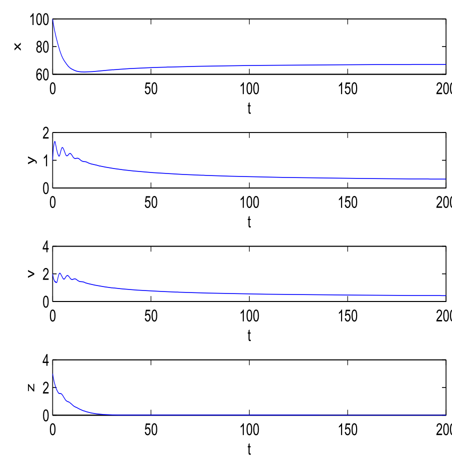


Figure 2 P_1 **is globally asymptotically stable.** Here $\lambda = 14$, $\beta = 0.02$, $d_1 = 0.2$, $d_2 = 1.8$, $d_3 = 1.5$, $d_4 = 0.5$, $k = 2$, $\mu = 0.2$, $\gamma = 0.2$, $\tau_1 = 1$, $\tau_2 = 2$, $\tau_3 = 3$, and $R_1 = 0.7778 < 1 < R_0 = 1.0370$.



Next, we use the following parameters: $\lambda = 14$, $\beta = 0.02$, $d_1 = 0.2$, $d_2 = 1.8$, $d_3 = 1.5$, $d_4 = 0.5$, $k = 2$, $\mu = 0.2$, $\gamma = 0.2$, $\tau_1 = 1$, $\tau_2 = 2$, $\tau_3 = 3$. For those parameters, $R_1 = 0.7778 < 1 < R_0 = 1.0370$, system (1.4) has a chronic-infection equilibrium $P_1 = (67.5, 0.2778, 0.3704, 0)$. Figure 2 demonstrates the equilibrium P_1 is globally asymptotically stable when $R_1 < 1 < R_0$.

In Figures 3 and 4, we adopt the following set of parameter values:

$$\lambda = 40, \quad \beta = 0.02, \quad d_1 = 0.2, \quad d_2 = 1.8, \quad d_3 = 1.5,$$
$$d_4 = 0.5, \quad k = 2, \quad \mu = 0.2, \quad \gamma = 0.2.$$

Thus $R_1 = 2.2222 > 1$, system (1.4) has the equilibrium $P_2 = (150, 2.5, 3.3333, 11)$ and $F(0) = -0.0176 < 0$, $F(s) = 0$ has only one positive root $s^* \approx 0.2927$. $\tau_3^* \approx 0.7392$, $\tau_3^1 \approx 12.3529$. Figure 3 demonstrates that P_2 is asymptotically stable when $R_1 > 1$ and $\tau_3 < \tau_3^*$, where $\tau_3 = 0.7 < \tau_3^*$. Figure 4 demonstrates that oscillations appear, where $\tau_3 = 0.8 > \tau_3^*$. Using those parameter values, global Hopf branches diagrams are shown in Figures 5 and 6.

Figure 3 **P_2 is asymptotically stable.** Here $\lambda = 40$, $\beta = 0.02$, $d_1 = 0.2$, $d_2 = 1.8$, $d_3 = 1.5$, $d_4 = 0.5$, $k = 2$, $\mu = 0.2$, $\gamma = 0.2$, $\tau_1 = 0$, $\tau_2 = 0$, $\tau_3 = 0.7 < \tau_3^* = 0.7392$, and $R_1 = 2.2222 > 1$.

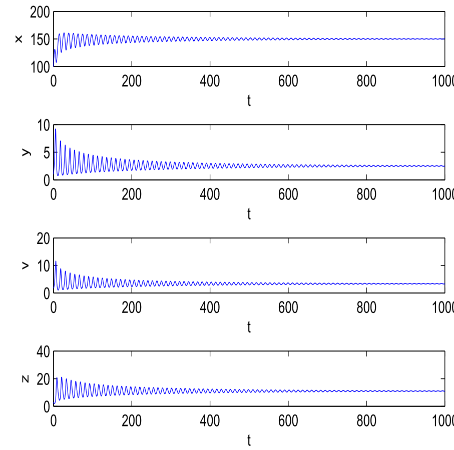


Figure 4 **P_2 is not asymptotically stable, and oscillations appear.** Here $\lambda = 40$, $\beta = 0.02$, $d_1 = 0.2$, $d_2 = 1.8$, $d_3 = 1.5$, $d_4 = 0.5$, $k = 2$, $\mu = 0.2$, $\gamma = 0.2$, $\tau_1 = 0$, $\tau_2 = 0$, $\tau_3 = 0.8 > \tau_3^* = 0.7392$, and $R_1 = 2.2222 > 1$.

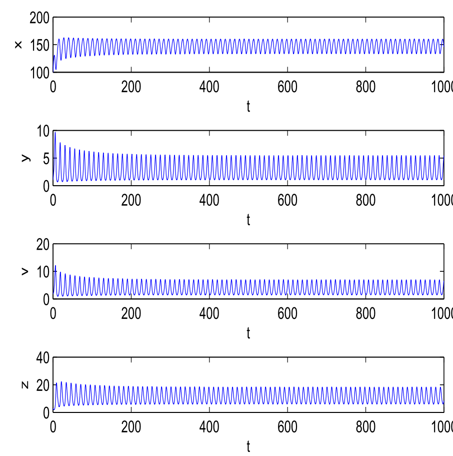
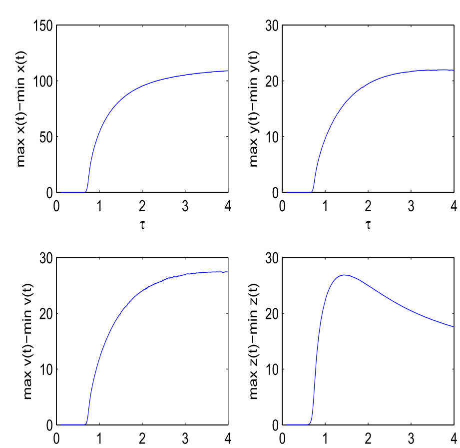


Figure 5 **Global Hopf branches diagrams.** Here $\lambda = 40$, $\beta = 0.02$, $d_1 = 0.2$, $d_2 = 1.8$, $d_3 = 1.5$, $d_4 = 0.5$, $k = 2$, $\mu = 0.2$, $\gamma = 0.2$, $\tau_1 = 0$, $\tau_2 = 0$, $\tau_3^* \approx 0.7392$, and $R_1 = 2.2222 > 1$.



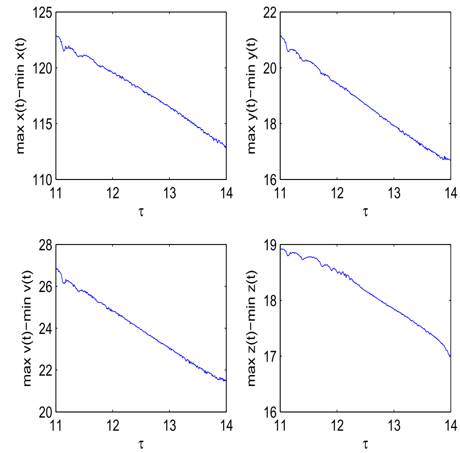


Figure 6 Global Hopf branches diagrams. Here $\lambda = 40$, $\beta = 0.02$, $d_1 = 0.2$, $d_2 = 1.8$, $d_3 = 1.5$, $d_4 = 0.5$, $k = 2$, $\mu = 0.2$, $\gamma = 0.2$, $\tau_1 = 0$, $\tau_2 = 0$, $\tau_3^1 \approx 12.3529$, and $R_1 = 2.2222 > 1$.

6 Conclusion

In this paper, we considered a class of virus infection models with three time lags, two intracellular delays and one immune delay. We have carried out a mathematical analysis of the dynamics of the model. We proved that P_0 is globally asymptotically stable when $R_0 < 1$, and the three delays do not destroy the globally asymptotical stability of P_0. P_1 is globally asymptotically stable when $R_1 < 1 < R_0$, and the three delays also do not destroy the globally asymptotical stability of P_1. When $R_1 > 1$, we found P_2 has still global attractability under only incorporating two intracellular delays τ_1 and τ_2. But on only incorporating the immune delay τ_3, P_2 can undergo a Hopf bifurcation on proper conditions, furthermore, oscillations and stability switches can appear. The immune delay can destroy the global attractability of P_2. Those results show immune delay dominates intracellular delays in some viral infection models, which indicates the human immune system has a special effect in virus infection models with CTLs response, and the human immune system itself is very complicated. People are aware of the complexity of human immune system in medical science, which coincides with our investigation. Finally, we studied the global Hopf bifurcation of the system, and we obtained the global existence of periodic solutions.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions
The authors had equal contributions to each part of this paper. All the authors read and approved the final manuscript.

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