Research Article

Analysis of a Viral Infection Model with Delayed Nonlytic Immune Response

Mengye Chen,¹ Liang You,¹ Jie Tang,¹ Shasha Su,² and Ruiming Zhang¹

¹College of Science, Northwest A&F University, Yangling, Shaanxi 712100, China

²School of Economics and Management, Xidian University, Xi'an, Shaanxi 710071, China

Correspondence should be addressed to Ruiming Zhang; ruimingzhang@yahoo.com

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We investigate the dynamical behavior of a virus infection model with delayed nonlytic immune response. By analyzing corresponding characteristic equations, the local stabilities of two boundary equilibria are established. By using suitable Lyapunov functional and LaSalle's invariance principle, we establish the global stability of the infection-free equilibrium. We find that the infection free equilibrium E_0 is globally asymptotically stable when $R_0 \leq 1$, and the infected equilibrium without immunity E_1 is local asymptotically stable when $1 < R_0 \leq 1 + b\beta/cd$. Under the condition $R_0 > 1 + b\beta/cd$ we obtain the sufficient conditions to the local stability of the infected equilibrium with immunity E_2 . We show that the time delay can change the stability of E_2 and lead to the existence of Hopf bifurcations. The stabilities of bifurcating periodic solutions are studied and numerical simulations to our theorems are provided.

1. Introduction

Mathematical models have been proven valuable in understanding the population dynamics of viral load in vivo. A proper model may play significant role in a better understanding of the disease and the various drug therapy strategies. Viral infection models have received great attention in recent years [1–7]. In most viral infections, cytotoxic T lymphocytes (CTLs) play a critical role in antiviral defense by providing a cell-mediated response to specific foreign antigens associated with cells. Therefore, the immune response after a viral infection is universal and necessary to eliminate or control the disease.

Recently, there have been a lot of papers on virus dynamics within host; some include the immune response directly [8–13]. During viral infections, the host immune system reacts with innate and antigen-specific immune response. Both types of response can be subdivided broadly into lytic and nonlytic components. Lytic components kill infected cells, whereas the nonlytic components inhibit viral replication through soluble mediators. As a part of the innate response, cytotoxic T lymphocytes (CTLs) kill infected

cells, while antibodies neutralize free virus particles and thus inhibit the infection of susceptible cells. In addition, CD4+ and CD8+ T cells can secrete cytokines that inhibit viral replication [12]. In order to investigate the role of direct lytic and nonlytic inhibition of viral replication by immune cells in viral infections, a mathematical model was constructed to describe the basic dynamics of the interaction among susceptible host cells, a virus population, and immune response, which is described by the following differential equations [14, 15]:

$$\begin{aligned}x'(t) &= s - dx - \frac{\beta xy}{1 + qz}, \\y'(t) &= \frac{\beta xy}{1 + qz} - ay - pyz, \\z'(t) &= cy - bz,\end{aligned}\tag{1}$$

where $x(t)$, $y(t)$, and $z(t)$ represent the densities of uninfected target cells, virus, and CTL cells at time t , respectively. Uninfected cells are produced at rate s , die at rate dx , and become infected by virus at rate βxy without the immune

response; to model nonlytic antiviral, viral replication is inhibited by the immune response at rate $1 + qz$; infected cells die at rate ay and are removed at rate pyz by the CTL immune response. The virus-specific CTL cells proliferate at rate cy by contact with infected cells and die at rate bz . The parameter p expresses the strength of the lytic component; the parameter q expresses the efficacy of the nonlytic component.

Time delays cannot be ignored in models for immune response. Antigenic stimulation generating CTLs may need a period of time τ [16–18]; the CTL response at time t may depend on the population of antigen at a previous time $t - \tau$. Under the assumption of retarded immune response, Wang et al. [18] studied the effects of the time delay for immune response and assumed the time evolution of the population of CTL cells z is governed by the delayed nonlinear differential equation $z'(t) = cy(t - \tau) - bz$. Li and Shu [19] and Xie et al. [20] investigated the effects of a time delay on a three-dimensional system with $z'(t) = cy(t - \tau)z(t - \tau)$. However, both studies do not consider the nonlytic component. In this paper we propose a more general model,

$$\begin{aligned} x'(t) &= s - dx - \frac{\beta xy}{1 + qz}, \\ y'(t) &= \frac{\beta xy}{1 + qz} - ay - pyz, \\ z'(t) &= cy(t - \tau)z(t - \tau) - bz, \end{aligned} \quad (2)$$

with the initial conditions

$$(x(0), y_0(\theta), z_0(\theta)) \in \mathbb{R}_+ \times \mathbb{C}^+ \times \mathbb{C}^+, \quad (3)$$

where $\mathbb{C}^+ = \mathbb{C}([-\tau, 0], \mathbb{R}_+)$ which is the Banach space of continuous functions mapping the interval $[-\tau, 0]$ into $\mathbb{R}_+$ with the topology of uniform convergence. Clearly, the models studied in [18–20] correspond to the case $q = 0$ in our general model (2). In this work we study (2) in the more general case $q \geq 0$.

This paper is organized as follows. In Section 2, we study the local asymptotic stability of the infection-free equilibrium and the immune-exhausted equilibrium of system (2), and the global asymptotic stability of the infection-free equilibrium also is investigated. In Section 3, we analyze the local stability of the positive equilibrium and the existence of Hopf bifurcations. In Section 4, the direction and stability of Hopf bifurcation are analyzed by the normal form theory and center manifold approach. In Section 5, we present numerical simulations to illustrate our results. Finally, in Section 6 we provide concluding remarks.

2. The Stability Analysis of Equilibrium

Considering the existence of the three equilibria, then we have the following conclusions.

Proposition 1. *Let $R_0 = s\beta/ad$. Then, consider the following.*

- (1) *If $R_0 < 1$, system (2) only has an infection-free equilibrium $E_0 = (x_0, 0, 0)$, where $x_0 = s/d$.*

- (2) *If $1 < R_0 \leq 1 + b\beta/cd$, in addition to the infection-free equilibrium E_0 , system (2) has another unique equilibrium $E_1(x_1, y_1, 0)$ where $x_1 = a/\beta$ and $y_1 = (s\beta - ad)/a\beta$.*

- (3) *If $R_0 > 1 + b\beta/cd$, in addition to the infection-free equilibrium E_0 , system (2) has another infected equilibrium $E_2 = (x_2, y_2, z_2)$ that corresponds to the survival of free virus and CTL, where*

$$\begin{aligned} x_2 &= \frac{-1}{dc} (bpz_2 + ab - sc), \\ y_2 &= \frac{b}{c}, \\ z_2 &= \left(\frac{\sqrt{(acdq + b\beta p + cdp)^2 - 4cdpq(ab\beta + acd - \beta cs)} - acdq - b\beta p - cdp}{(2cdpq)^{-1}} \right) \end{aligned} \quad (4)$$

By the similar method in [20], we have the following result.

Theorem 2. *Under the above initial conditions (3), all solutions of system (2) are positive for $t > 0$ and there exists $M > 0$, such that all the solutions satisfy $x(t) < M$, $y(t) < M$, and $z(t) < M$ for all large t .*

Theorem 3. *If $R_0 < 1$, then the infection-free equilibrium E_0 is locally asymptotically stable, and E_0 is unstable if $R_0 > 1$.*

Proof. The characteristic equation about E_0 is given by

$$\begin{vmatrix} d + \lambda & \frac{s\beta}{d} & 0 \\ 0 & a + \lambda - \frac{s\beta}{d} & 0 \\ 0 & 0 & b + \lambda \end{vmatrix} = 0; \quad (5)$$

that is,

$$(\lambda + b)(\lambda + d) \left(\lambda + a - \frac{\beta s}{d} \right) = 0. \quad (6)$$

It is clear that (6) has negative roots $\lambda_1 = -d$ and $\lambda_2 = -b$. If $R_0 < 1$, then $\lambda_3 = (s\beta - ad)/d < (ad - ad)/d = 0$. This shows that all roots of (6) have the negative real part; infection-free equilibrium E_0 is locally asymptotically stable. If $R_0 > 1$, then $\lambda_3 > 0$. Equation (6) has a positive root; infection-free equilibrium E_0 is unstable. $\square$

Theorem 4. *If $1 < R_0 \leq 1 + b\beta/cd$, then immune-exhausted equilibrium $E_1(x_1, y_1, 0)$ is locally asymptotically stable, and E_1 is unstable if $R_0 > 1 + b\beta/cd$.*

Proof. The characteristic equation about E_1 is given by

$$\begin{vmatrix} d + y_1\beta + \lambda & a & -aqy_1 \\ -y_1\beta & \lambda & py_1 + aqy_1 \\ 0 & 0 & b - ce^{-\lambda\tau}y_1 + \lambda \end{vmatrix} = 0; \quad (7)$$

that is,

$$(a\beta y_1 + d\lambda + \lambda^2 + \beta\lambda y_1)(b - cy_1e^{-\lambda\tau} + \lambda) = 0. \quad (8)$$

It is easy to see that

$$\begin{aligned} \lambda_1 + \lambda_2 &= -\frac{s\beta}{a} < 0, \\ \lambda_1\lambda_2 &= s\beta - ad > 0. \end{aligned} \quad (9)$$

If $R_0 > 1$, then λ_1 and λ_2 are both negative real roots, and λ_3 is determined by the following equation:

$$f(\lambda) \triangleq (b - cy_1e^{-\lambda\tau} + \lambda) = 0. \quad (10)$$

If $1 < R_0 \leq 1 + b\beta/cd$ and $\tau = 0$, then $\lambda_3 = cy_1 - b = (-ab\beta - acd + \beta cs)/a\beta < 0$. Therefore, if $\tau = 0$ and $1 < R_0 \leq 1 + b\beta/cd$, then E_1 is locally asymptotically stable. If $\tau > 0$, let $i\omega$ ($\omega > 0$) be a solution of (10). Substituting $\lambda = i\omega$ into (10) and separating the real and imaginary parts, we have

$$\begin{aligned} b &= cy_1 \cos(\tau\omega) \\ \omega &= -cy_1 \sin(\tau\omega). \end{aligned} \quad (11)$$

Squaring and adding the two equations of (11) together, we obtain $b^2 + \omega^2 = c^2 y_1^2$, which has solution

$$\omega^2 = \frac{(c(ad - s\beta) - ab\beta)(ab\beta + acd - \beta cs)}{a^2\beta^2}. \quad (12)$$

Since $1 < R_0 \leq 1 + b\beta/cd$, then we have $(ad - s\beta) < 0$ and $(ab\beta + acd - \beta cs) \geq 0$; thus we get $\omega^2 \leq 0$, which contradicts with our original assumption $\omega > 0$. Therefore, (10) must have no pure imaginary root. Hence, in the case of $1 < R_0 \leq 1 + b\beta/cd$, E_1 is locally asymptotically stable for all $\tau \geq 0$. If $R_0 > 1 + b\beta/cd$, then $f(0) = (ab\beta + acd - \beta cs)/a\beta < 0$, and $\lim_{\lambda \rightarrow +\infty} f(\lambda) = +\infty$. By the intermediate value theorem of continuous functions, we see that equation $f(\lambda) = 0$ has at least one positive real root; thus the immune-exhausted equilibrium E_1 is unstable. $\square$

Theorem 5. If $R_0 \leq 1$, the infection-free equilibrium $E_0(x_0, 0, 0)$ is globally asymptotically stable.

Proof. Define the Lyapunov functional

$$V_1(t) = x - x_0 - x_0 \ln \frac{x}{x_0} + y + \frac{p}{c}z + p \int_{t-\tau}^t y(\theta)z(\theta) d\theta; \quad (13)$$

we calculate the derivative of $V_1(t)$ along positive solutions of system (2) then substitute s for $s = dx_0$ to obtain

$$\begin{aligned} \frac{dV_1(t)}{dt} &= \left(1 - \frac{x_0}{x(t)}\right) \left[-d(x(t) - x_0) - \frac{\beta x(t)y(t)}{qz(t) + 1}\right] \\ &\quad + \frac{\beta x(t)y(t)}{qz(t) + 1} - ay(t) - \frac{pb}{c}z(t) \\ &= -d \frac{[x_0 - x(t)]^2}{x(t)} - \frac{bpz(t)}{c} \\ &\quad + \frac{y(t)[-adqz(t) + \beta s - ad]}{d(qz(t) + 1)} \\ &= -d \frac{[x_0 - x(t)]^2}{x(t)} - \frac{bpz(t)}{c} \\ &\quad + \frac{y(t)[-adqz(t) + ad(R_0 - 1)]}{d(qz(t) + 1)}. \end{aligned} \quad (14)$$

Clearly, in the case of $R_0 \leq 1$, we have $dV_1(t)/dx \leq 0$ since $x(t)$, $y(t)$, and $z(t)$ are positive, and $dV_1(t)/dx = 0$ if and only if $(x, y, z) = (x_0, 0, 0)$. Thus E_0 is globally asymptotically stable by Lyapunov-LaSalle invariance principle. $\square$

3. The Stability of Infected Equilibrium and Hopf Bifurcation

Let $y_2/(1 + qz_2) = A$, apply $\beta x_2/(1 + qz_2) = a + pz_2$ to the characteristic equation of system (2) at the positive equilibrium E_2 , and we have

$$\begin{vmatrix} \lambda + d + A\beta & a + pz_2 & -Aq(a + pz_2) \\ -A\beta & \lambda & A(aq + p + 2pqz_2) \\ 0 & -ce^{-\lambda\tau}z_2 & \lambda - e^{-\lambda\tau}b + b \end{vmatrix} = 0; \quad (15)$$

that is,

$$P(\lambda, \tau) + Q(\lambda, \tau)e^{-\lambda\tau} = 0, \quad (16)$$

where

$$\begin{aligned} P(\lambda, \tau) &= \lambda^3 + a_1\lambda^2 + a_2\lambda + a_3, \\ Q(\lambda, \tau) &= a_4\lambda^2 + a_5\lambda + a_6, \\ a_1 &= A\beta + b + d, \\ a_2 &= aA\beta + Ab\beta + A\beta pz_2 + bd, \\ a_3 &= aAb\beta + Ab\beta pz_2, \\ a_4 &= -b, \end{aligned} \quad (17)$$

$$\begin{aligned} a_5 &= aAcqz_2 - Ab\beta + 2Acpqz_2^2 + Acpz_2 - bd, \\ a_6 &= aAcqdqz_2 + A^2\beta cpqz_2^2 + A^2\beta cpz_2 \\ &\quad - Ab\beta pz_2 + 2Acdpqz_2^2 + Acdpz_2 - aAb\beta. \end{aligned}$$

If $\tau = 0$, (16) becomes

$$\lambda^3 + (a_1 + a_4)\lambda^2 + (a_2 + a_5)\lambda + a_3 + a_6 = 0, \quad (18)$$

where

$$\begin{aligned} a_1 + a_4 &= A\beta + d > 0, a_2 + a_5 \\ &= aA\beta + aAcqz_2 + 2Acpqz_2^2 \\ &\quad + Acpz_2 + A\beta pz_2 > 0, a_3 + a_6 \\ &= aAcdqz_2 + A^2\beta cpqz_2^2 + A^2\beta cpz_2 \\ &\quad + 2Acdpqz_2^2 + Acdpz_2 > 0. \end{aligned} \quad (19)$$

Then,

$$\begin{aligned} \Delta_1 &= a_1 + a_4 > 0, \\ \Delta_2 &= (a_1 + a_4)(a_2 + a_5) - (a_3 + a_6) \\ &= A\beta(a + pz_2)(A\beta + Acqz_2 + d) > 0. \end{aligned} \quad (20)$$

By the Routh-Hurwitz criterion, we know that all roots of (18) have negative real parts. From the above analysis, the following theorem holds.

Theorem 6. *If $R_0 > 1 + b\beta/cd$, the equilibrium E_2 is locally asymptotically stable for $\tau = 0$.*

From Theorem 6, when $\tau = 0$, all roots of (16) lie to the left of imaginary axis. But, as τ is increased from zero, some of the roots may cross the imaginary axis to the right. Then the equilibrium E_2 becomes unstable. Now we suppose (16) has a pure imaginary root $\lambda = i\omega$ ($\omega > 0$). Obviously, $\lambda = i\omega$ ($\omega > 0$) is a root of (16) if and only if ω satisfies

$$\begin{aligned} -i\omega^3 - a_1\omega^2 + ia_2\omega + a_3 + (-a_4\omega^2 + ia_5\omega + a_6) \\ \times (\cos(\tau\omega) - i\sin(\tau\omega)) = 0. \end{aligned} \quad (21)$$

Separating the real and imaginary parts, we have

$$\begin{aligned} a_3 - a_1\omega^2 &= (a_4\omega^2 - a_6)\cos(\tau\omega) - a_5\omega\sin(\tau\omega), \\ \omega^3 - a_2\omega &= (a_4\omega^2 - a_6)\sin(\tau\omega) + a_5\omega\cos(\tau\omega). \end{aligned} \quad (22)$$

From (21), we also obtain

$$|-i\omega^3 - a_1\omega^2 + ia_2\omega + a_3|^2 = |-a_4\omega^2 + ia_5\omega + a_6|^2 |e^{-i\omega\tau}|^2. \quad (23)$$

So we have

$$\omega^6 + b_1\omega^4 + b_2\omega^2 + b_3 = 0, \quad (24)$$

where

$$\begin{aligned} b_1 &= a_1^2 - a_4^2 - 2a_2, \\ b_2 &= a_2^2 - a_5^2 - 2a_1a_3 + 2a_4a_6, \\ b_3 &= a_3^2 - a_6^2. \end{aligned} \quad (25)$$

Denote

$$G(x) = x^3 + b_1x^2 + b_2x + b_3. \quad (26)$$

Therefore, if (16) has a pure imaginary root $i\omega$, then equation

$$G(x) = 0 \quad (27)$$

has a positive real root ω^2 .

Suppose that (27) has K , $1 \leq K \leq 3$, positive real roots, which are x_k , $1 \leq k \leq K$, respectively. From (22), we have

$$\begin{aligned} \cos(\tau\sqrt{x_k}) &= Q_k \\ &= -\frac{a_5\sqrt{x_k}(x_k^{3/2} - a_2\sqrt{x_k}) - (a_3 - a_1x_k)(a_6 - a_4x_k)}{-(a_6 - a_4x_k)^2 - a_5^2x_k}, \end{aligned} \quad (28)$$

$$\begin{aligned} \sin(\tau\sqrt{x_k}) &= P_k \\ &= \frac{\sqrt{x_k}(a_4x_k^2 - a_2a_4x_k + a_1a_5x_k - a_6x_k - a_3a_5 + a_2a_6)}{a_5^2x_k + a_4^2x_k^2 - 2a_4a_6x_k + a_6^2}. \end{aligned} \quad (29)$$

Let

$$\tau_k^{(j)} = \begin{cases} \frac{1}{\sqrt{x_k}} [\arccos(Q_k) + 2j\pi], & \text{if } P_n \geq 0, \\ \frac{1}{\sqrt{x_k}} [2\pi - \arccos(Q_k) + 2j\pi], & \text{if } P_n < 0, \end{cases} \quad (30)$$

where $1 \leq k \leq K$ and $j = 0, 1, 2, \dots$. Then $\pm i\sqrt{x_k}$ is a pair of pure imaginary roots of (16).

Theorem 7 (see [21]). *Suppose the characteristic equation is the form*

$$f_0(s) + f_1(s)e^{-s\tau} = 0, \quad (31)$$

where f_0 and f_1 are continuously differentiable with respect to s . One of the roots to (31) is $s(\tau) = \alpha(\tau) + i\omega(\tau)$, where $s(\tau)$ is continuously differentiable with respect to τ , satisfying $\alpha(\tau_0) = 0$ and $\omega(\tau_0)$ for a positive real number τ_0 . Denote $\Phi(\omega) = |f_0(i\omega)|^2 - |f_1(i\omega)|^2$; then we have $\text{sign}[d\text{Re}(s)/d\tau|_{\tau=\tau_0}] = \text{sign}[(1/2\omega) \cdot (d\Phi/d\omega)]|_{\omega=\omega_0}$.

Let $\lambda(\tau) = \xi(\tau) + i\omega(\tau)$ be the root of (16) near $\tau = \tau_k^{(j)}$ satisfying $\xi(\tau_k^{(j)}) = 0$, $\omega(\tau_k^{(j)}) = \sqrt{x_k}$. Then, by Theorem 7, we have the following theorem.

Theorem 8. $d\xi/d\tau|_{\tau=\tau_k^{(j)}}$ and $dG/dx|_{x=x_k}$ have the same sign.

We choose $\tau_0 = \min\{\tau_k^{(j)} \mid 1 \leq k \leq K, j = 0, 1, 2, \dots\}$, where $\tau_k^{(j)}$ is defined by (30). Summarizing the above analysis and combining [22], the following theorem holds.

Theorem 9. (1) *For system (2), its equilibrium E_2 is asymptotically stable for $\tau \in [0, \tau_0]$ if (27) has some positive real roots;*
(2) *if x_{k_0} is a simple positive real root of (27), then system (2) undergoes a Hopf bifurcation at the equilibrium E_2 when $\tau = \tau_0$.*

4. Direction and Stability of Hopf Bifurcation

In this section, we will study the direction of the Hopf bifurcations and stability of bifurcating periodic solutions by applying the normal theory and the center manifold theorem introduced in [22]. We always assume that system (2) undergoes Hopf bifurcation at the positive equilibrium E_2 for $\tau = \tau_0$, and then $\pm i\omega$ are pure imaginary roots of the characteristic equation at the positive equilibrium E_2 .

Let $u_1(t) = x(\tau t) - x^*$, $u_2(t) = y(\tau t) - y^*$, and $u_3(t) = z(\tau t) - z^*$, $\tau = \tau_0 + \nu$; then $\nu = 0$ is the Hopf bifurcation value. The Taylor expansion of (2) at the equilibrium point is given by

$$\begin{aligned} \frac{du_1(t)}{dt} &= (\tau_0 + \nu) \\ &\times \left\{ -\left(d + \frac{\beta y^*}{qz^* + 1}\right)u_1 - \frac{\beta x^*}{qz^* + 1}u_2 + \frac{\beta qx^* y^*}{(qz^* + 1)^2}u_3 \right. \\ &\quad \left. + \frac{\beta qu_1 u_3 y^*}{(qz^* + 1)^2} - \frac{\beta u_1 u_2}{qz^* + 1} + \frac{\beta qx^* u_2 u_3}{(1 + qz^*)^2} + \dots \right\}, \\ \frac{du_2(t)}{dt} &= (\tau_0 + \nu) \\ &\times \left\{ \frac{\beta y^*}{qz^* + 1}u_1 - \left(py^* + \frac{\beta qx^* y^*}{(qz^* + 1)^2}\right)u_3 \right. \\ &\quad \left. - \left(p + \frac{\beta qx^*}{(qz^* + 1)^2}\right)u_2 u_3 \right. \\ &\quad \left. - \frac{\beta qy^* u_1 u_3}{(qz^* + 1)^2} + \frac{\beta u_1 u_2}{qz^* + 1} + \dots \right\}, \\ \frac{du_3(t)}{dt} &= (\tau_0 + \nu) \{-bu_3 + cz^* u_2(t-1) + cy^* u_3(t-1) \\ &\quad + cu_3(t-1)u_2(t-1)\}. \end{aligned} \quad (32)$$

We denote the above system by

$$\dot{u}(t) = L_\nu(u_t) + f(\nu, u_t), \quad (33)$$

where $u(t) = (u_1(t), u_2(t), u_3(t))^T \in \mathbb{R}^3$, and the maps $L_\nu : \mathbb{C} \rightarrow \mathbb{R}^3$, $f : \mathbb{R} \times \mathbb{C} \rightarrow \mathbb{R}^3$ are given by

$$\begin{aligned} L_\nu(\phi) &= (\tau_0 + \nu) \\ &\times \begin{pmatrix} -\left(d + \frac{\beta y^*}{qz^* + 1}\right) - \frac{\beta x^*}{qz^* + 1} & \frac{\beta qx^* y^*}{(qz^* + 1)^2} \\ \frac{\beta y^*}{qz^* + 1} & 0 & -\left(py^* + \frac{\beta qx^* y^*}{(qz^* + 1)^2}\right) \\ 0 & 0 & -b \end{pmatrix} \end{aligned}$$

$$\begin{aligned} &\times \begin{pmatrix} \phi_1(0) \\ \phi_2(0) \\ \phi_3(0) \end{pmatrix} \\ &+ (\tau_0 + \nu) \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & cz^* & cy^* \end{pmatrix} \begin{pmatrix} \phi_1(-1) \\ \phi_2(-1) \\ \phi_3(-1) \end{pmatrix}, \\ f(\nu, \phi) &= (\tau_0 + \nu) \left\{ \begin{pmatrix} -\frac{\beta \phi_1(0) \phi_2(0)}{qz^* + 1} \\ \frac{\beta \phi_1(0) \phi_2(0)}{qz^* + 1} \\ 0 \end{pmatrix} \right. \\ &\quad \left. + \begin{pmatrix} \frac{\beta qy^* \phi_1(0) \phi_3(0)}{(qz^* + 1)^2} \\ -\frac{\beta qy^* \phi_1(0) \phi_3(0)}{(qz^* + 1)^2} \\ 0 \end{pmatrix} \right. \\ &\quad \left. + \begin{pmatrix} \frac{\beta qx^* \phi_2(0) \phi_3(0)}{(qz^* + 1)^2} \\ -\frac{(\beta qx^* + p) \phi_2(0) \phi_3(0)}{(qz^* + 1)^2} \\ c\phi_2(-1) \phi_3(-1) \end{pmatrix} + \dots \right\}. \end{aligned} \quad (34)$$

By the Riesz representation theorem, there exists a function $\eta(\theta, \nu)$ of bounded variation for $\theta \in [0, 1]$ such that

$$L_\nu(\phi) = \int_{-1}^0 \phi(\theta) d\eta(\theta, \nu), \quad \phi \in C. \quad (35)$$

In fact, we can choose

$$\begin{aligned} \eta(\theta, \nu) &= (\tau_0 + \nu) \\ &\times \begin{pmatrix} -\left(d + \frac{\beta y^*}{qz^* + 1}\right) - \frac{\beta x^*}{qz^* + 1} & \frac{\beta qx^* y^*}{(qz^* + 1)^2} \\ \frac{\beta y^*}{qz^* + 1} & 0 & -\left(py^* + \frac{\beta qx^* y^*}{(qz^* + 1)^2}\right) \\ 0 & 0 & -b \end{pmatrix} \\ &\times \delta(\theta) - (\tau_0 + \nu) \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & cz^* & cy^* \end{pmatrix} \delta(\theta + 1), \end{aligned} \quad (36)$$

where δ denote the Dirac delta function. For $\phi \in \mathbb{C}([-1, 0], \mathbb{R}^3)$, let

$$A(\nu)\phi(\theta) = \begin{cases} \frac{d\phi(\theta)}{d\theta}, & \text{if } \theta \in [-1, 0), \\ \int_{-1}^0 d\eta(\xi, \nu)\phi(\xi), & \text{if } \theta = 0; \end{cases} \quad (37)$$

$$R(\nu)\phi(\theta) = \begin{cases} 0, & \text{if } \theta \in [-1, 0), \\ f(\nu, \phi), & \text{if } \theta = 0, \end{cases}$$

then system (33) is equivalent to

$$\dot{u}(t) = A(\nu)u_t(\theta) + R(\nu)u_t(\theta), \quad (38)$$

where $u_t(\theta) = u(t + \theta)$ for $\theta \in [-1, 0]$.

For $\varphi \in \mathbb{C}([-1, 0], \mathbb{R}^3)$, the adjoint operator of $A(0)$ is defined by

$$A^*(0)\varphi(s) = \begin{cases} -\frac{d\varphi(s)}{ds}, & \text{if } s \in (0, 1], \\ \int_{-1}^0 d\eta^\top(\xi, 0)\varphi(-\xi), & \text{if } s = 0, \end{cases} \quad (39)$$

and define a bilinear inner product

$$\langle \varphi(s), \phi(\theta) \rangle = \bar{\varphi}^\top(0)\phi(0) - \int_{-1}^0 \int_{\xi=0}^\theta \bar{\varphi}^\top(\xi - \theta) d\eta(\theta)\phi(\xi) d\xi, \quad (40)$$

where $\eta(\theta) = \eta(\theta, 0)$. By the discussion in Section 3 we know that $\pm i\omega\tau_0$ are eigenvalues of $A(0)$. Hence, they are also eigenvalues of A^* . We define $q(\theta)$ and $q^*(s)$ to be the eigenvectors of A and A^* corresponding to the eigenvalues $i\omega\tau_0$ and $-i\omega\tau_0$, respectively.

Assume that $q(\theta) = (1, q_1, q_2)^\top e^{i\omega\tau_0\theta}$ is the eigenvector of $A(0)$ corresponding to $i\omega\tau_0$; then $A(0)q(\theta) = i\omega\tau_0 q(\theta)$. It follows from the definition of $A(0)$ that we have

$$\tau_0 \begin{pmatrix} i\omega + \left(d + \frac{\beta y^*}{qz^* + 1}\right) & \frac{\beta x^*}{qz^* + 1} & \frac{-\beta q x^* y^*}{(qz^* + 1)^2} \\ -\frac{\beta y^*}{qz^* + 1} & i\omega & \left(py^* + \frac{\beta q x^* y^*}{(qz^* + 1)^2}\right) \\ 0 & -cz^* e^{-i\omega\tau_0} & i\omega + b - cy^* e^{-i\omega\tau_0} \end{pmatrix} q(0) = \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}. \quad (41)$$

Then we obtain

$$\begin{aligned} q_1 &= -((qz^* + 1)(p(qz^* + 1)(\beta y^* + (d + i\omega)(qz^* + 1)) \\ &\quad + \beta q x^* (d + i\omega)) \\ &\quad \times (\beta x^* (\beta q x^* + (qz^* + 1)(pqz^* + p + iq\omega)))^{-1}, \end{aligned}$$

$$\begin{aligned} q_2 &= (i(qz^* + 1)(\omega(d + i\omega)(qz^* + 1)^2 \\ &\quad + \beta y^* (q\omega z^* - i\beta x^* + \omega))) \\ &\quad \times (\beta x^* y^* (\beta q x^* + (qz^* + 1)(pqz^* + p + iq\omega)))^{-1}. \end{aligned} \quad (42)$$

Similarly, let $q^*(s) = D(1, q_1^*, q_2^*)^\top e^{i\omega\tau_0 s}$ be the eigenvector of A^* corresponding to $-i\omega\tau_0$; by the definition of A^* we get

$$\begin{aligned} q_1^* &= \frac{\beta y^* + (d - i\omega)(qz^* + 1)}{\beta y^*}, \\ q_2^* &= -\left(ie^{-i\tau_0\omega}(\omega(d - i\omega)(qz^* + 1)^2 + \beta y^* \right. \\ &\quad \times (q\omega z^* + i\beta x^* + \omega)) \\ &\quad \times (\beta cy^* z^* (qz^* + 1))^{-1}). \end{aligned} \quad (43)$$

In order to assure $\langle q^*(s), q(\theta) \rangle = 1$, we need to determine the value of D . From (40) we have

$$\begin{aligned} \langle q^*(s), q(\theta) \rangle &= \bar{D}(1, \bar{q}_1^*, \bar{q}_2^*)(1, q_1, q_2)^\top \\ &\quad - \int_{-1}^0 \int_{\xi=0}^\theta \bar{D}(1, \bar{q}_1^*, \bar{q}_2^*) e^{-i\omega\tau_0(\xi-\theta)} d\eta(\theta) \\ &\quad \times (1, q_1, q_2)^\top e^{i\omega\tau_0\xi} d\xi \\ &= \bar{D} \left\{ 1 + q_1 \bar{q}_1^* + q_2 \bar{q}_2^* - \int_{-1}^0 (1, \bar{q}_1^*, \bar{q}_2^*) \theta e^{i\omega\tau_0\theta} \right. \\ &\quad \times [d\eta(\theta)] (1, q_1, q_2)^\top \Big\} \\ &= \bar{D} \left\{ (1 + q_1 \bar{q}_1^* + q_2 \bar{q}_2^*) + \tau_0 e^{-i\omega\tau_0} (1, \bar{q}_1^*, \bar{q}_2^*) \right. \\ &\quad \times \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & cz^* & cy^* \end{pmatrix} (1, q_1, q_2)^\top \Big\} \\ &= \bar{D} \left\{ (1 + q_1 \bar{q}_1^* + q_2 \bar{q}_2^*) + c\tau_0 e^{-i\omega\tau_0} \bar{q}_2^* \right. \\ &\quad \times (z^* q_1 + y^* q_2) \Big\} = 1. \end{aligned} \quad (44)$$

Hence

$$\bar{D} = \left[(1 + q_1 \bar{q}_1^* + q_2 \bar{q}_2^*) + c\tau_0 e^{-i\omega\tau_0} \bar{q}_2^* (z^* q_1 + y^* q_2) \right]^{-1}. \quad (45)$$

Using the method in [22] we obtain the following coefficients:

$$\begin{aligned} g_{20} &= 2\tau_0 \overline{D} (F_{21} \overline{q_1^*} + F_{31} \overline{q_2^*} + F_{11}), \\ g_{11} &= \tau_0 \overline{D} (F_{22} \overline{q_1^*} + F_{32} \overline{q_2^*} + F_{12}), \\ g_{02} &= 2\tau_0 \overline{D} (F_{23} \overline{q_1^*} + F_{33} \overline{q_2^*} + F_{13}), \\ g_{21} &= 2\tau_0 \overline{D} (F_{24} \overline{q_1^*} + F_{34} \overline{q_2^*} + F_{14}), \end{aligned} \quad (46)$$

where

$$\begin{aligned} F_{11} &= \beta (-q^2) q_2^2 Q^3 x^* y^* + Q^2 \\ &\quad \times (\beta q q_1 q_2 x^* + \beta q q_2 y^*) - \beta q_1 Q, \\ F_{12} &= -2\beta q^2 q_2 Q^3 x^* y^* \overline{q_2} + Q^2 \\ &\quad \times (\beta q q_1 x^* \overline{q_2} + \beta q q_2 x^* \overline{q_1} + \beta q y^* \overline{q_2} + \beta q q_2 y^*) \\ &\quad + Q (-\beta \overline{q_1} - \beta q_1), \\ F_{13} &= \beta (-q^2) Q^3 x^* y^* \overline{q_2}^2 + Q^2 \\ &\quad \times (\beta q x^* \overline{q_1} \overline{q_2} + \beta q y^* \overline{q_2}) - \beta Q \overline{q_1}, \\ F_{14} &= 3\beta q^3 q_2^2 Q^4 x^* y^* \overline{q_2} + Q^3 \\ &\quad \times (-\beta q_2^2 q^2 x^* \overline{q_1} - 2\beta q_1 q_2 q^2 x^* \overline{q_2} - 2\beta q_2 q^2 y^* \overline{q_2} \\ &\quad - \beta q_2^2 q^2 y^* - \beta q^2 W_{320}(0) x^* y^* \overline{q_2} \\ &\quad - 2\beta q_2 q^2 W_{311}(0) x^* y^*) \\ &\quad + Q^2 (\beta q q_1 \overline{q_2} + \beta q q_2 \overline{q_1} + \beta q q_2 q_1 \\ &\quad + \frac{1}{2} \beta q W_{120}(0) y^* \overline{q_2} \\ &\quad + \beta q q_2 W_{111}(0) y^* + \frac{1}{2} \beta q W_{220}(0) x^* \overline{q_2} \\ &\quad + \beta q q_2 W_{211}(0) x^* \\ &\quad + \beta q q_1 W_{311}(0) x^* + \frac{1}{2} \beta q W_{320}(0) x^* \overline{q_1} \\ &\quad + \beta q W_{311}(0) y^* + \frac{1}{2} \beta q W_{320}(0) y^*) \\ &\quad + Q (-\beta W_{211}(0) - \beta q_1 W_{111}(0) \\ &\quad - \frac{1}{2} \beta W_{220}(0) - \frac{1}{2} \beta W_{120}(0) \overline{q_1}), \\ F_{21} &= -p q_1 q_2 + \beta q^2 q_2^2 Q^3 x^* y^* + Q^2 \\ &\quad \times (\beta (-q) q_1 q_2 x^* - \beta q q_2 y^*) + \beta q_1 Q, \end{aligned}$$

$$\begin{aligned} F_{22} &= -p q_1 \overline{q_2} - p q_2 \overline{q_1} + 2\beta q^2 q_2 Q^3 x^* y^* \overline{q_2} \\ &\quad + Q (\beta \overline{q_1} + \beta q_1) \\ &\quad + Q^2 (\beta (-q) q_1 x^* \overline{q_2} - \beta q q_2 x^* \overline{q_1} \\ &\quad - \beta q y^* \overline{q_2} - \beta q q_2 y^*), \\ F_{23} &= -p \overline{q_1} \overline{q_2} + \beta q^2 Q^3 x^* y^* \overline{q_2}^2 + Q^2 \\ &\quad \times (\beta (-q) x^* \overline{q_1} \overline{q_2} - \beta q y^* \overline{q_2}) + \beta Q \overline{q_1}, \end{aligned}$$

$$\begin{aligned} F_{24} &= -\frac{1}{2} p W_{220}(0) \overline{q_2} - 3\beta q^3 q_2^2 Q^4 x^* y^* \overline{q_2} \\ &\quad - p q_2 W_{211}(0) - \frac{1}{2} p W_{320}(0) \overline{q_1} - p q_1 W_{311}(0) \\ &\quad + Q \left(\frac{1}{2} \beta W_{120}(0) \overline{q_1} + \beta q_1 W_{111}(0) \right. \\ &\quad \left. + \beta W_{211}(0) + \frac{1}{2} \beta W_{220}(0) \right) \\ &\quad + Q^2 \left(-\beta q q_2 q_1 - \beta q q_2 \overline{q_1} - \frac{1}{2} \beta q W_{120}(0) y^* \overline{q_2} \right. \\ &\quad \left. - \beta q q_2 W_{111}(0) y^* - \beta q q_2 W_{211}(0) x^* \right. \\ &\quad \left. - \frac{1}{2} \beta q W_{220}(0) x^* \overline{q_2} - \frac{1}{2} \beta q W_{320}(0) x^* \overline{q_1} \right. \\ &\quad \left. - \beta q q_1 \overline{q_2} + \beta (-q) q_1 W_{311}(0) x^* \right. \\ &\quad \left. - \beta q W_{311}(0) y^* - \frac{1}{2} \beta q W_{320}(0) y^* \right) \\ &\quad + Q^3 (\beta q_2^2 q^2 x^* \overline{q_1} + 2\beta q_1 q_2 q^2 x^* \overline{q_2} \\ &\quad + 2\beta q_2 q^2 y^* \overline{q_2} + \beta q_2^2 q^2 y^* \\ &\quad + 2\beta q^2 q_2 W_{311}(0) x^* y^* \\ &\quad + \beta q^2 W_{320}(0) x^* y^* \overline{q_2}), \\ F_{31} &= c q_1 q_2 e^{-2i\tau_0 \omega}, \\ F_{32} &= c q_1 \overline{q_2} + c q_2 \overline{q_1}, \\ F_{33} &= c \overline{q_1} \overline{q_2} e^{2i\tau_0 \omega}, \\ F_{34} &= \frac{1}{2} c W_{220}(-1) \overline{q_2} e^{i\tau_0 \omega} + \frac{1}{2} c W_{320}(-1) \overline{q_1} e^{i\tau_0 \omega} \\ &\quad + c q_2 W_{211}(-1) e^{-i\tau_0 \omega} + c q_1 W_{311}(-1) e^{-i\tau_0 \omega}, \\ Q &= \frac{1}{1 + q z^*}, \end{aligned}$$

$$\begin{aligned}
W_{120} &= W_{20}^{(1)}, & W_{220} &= W_{20}^{(2)}, \\
W_{320} &= W_{20}^{(3)}, & W_{111} &= W_{11}^{(1)}, \\
W_{211} &= W_{11}^{(2)}, & W_{311} &= W_{11}^{(3)}, \\
W_{20}(\theta) &= \frac{ig_{20}}{\omega\tau_0} q(0) e^{i\theta\omega\tau_0} \\
&\quad + \frac{\overline{ig_{02}}}{3\omega\tau_0} q(0) e^{-i\theta\omega\tau_0} + E_1 e^{2i\theta\omega\tau_0}, \\
W_{11}(\theta) &= -\frac{ig_{11}}{\omega\tau_0} q(0) e^{i\theta\omega\tau_0} \\
&\quad + \frac{\overline{ig_{11}}}{\omega\tau_0} q(0) e^{-i\theta\omega\tau_0} + E_2,
\end{aligned}$$

E_1

$$= \begin{pmatrix} d + 2i\omega + \frac{\beta y^*}{qz^* + 1} & \frac{\beta x^*}{qz^* + 1} & -\frac{q\beta x^* y^*}{(qz^* + 1)^2} \\ -\frac{\beta y^*}{qz^* + 1} & 2i\omega & py^* + \frac{q\beta x^* y^*}{(qz^* + 1)^2} \\ 0 & -ce^{-2i\omega\tau_0} z^* & b + 2i\omega - ce^{-2i\omega\tau_0} y^* \end{pmatrix}^{-1} \times \begin{pmatrix} F_{11} \\ F_{21} \\ F_{31} \end{pmatrix},$$

E_2

$$= \begin{pmatrix} d + \frac{\beta y^*}{qz^* + 1} & \frac{\beta x^*}{qz^* + 1} & -\frac{q\beta x^* y^*}{(qz^* + 1)^2} \\ -\frac{\beta y^*}{qz^* + 1} & 0 & py^* + \frac{q\beta x^* y^*}{(qz^* + 1)^2} \\ 0 & -cz^* & b - cy^* \end{pmatrix}^{-1} \begin{pmatrix} F_{12} \\ F_{22} \\ F_{32} \end{pmatrix}. \quad (47)$$

Then we get

$$\begin{aligned}
c_1(0) &= \frac{i}{2\omega\tau_0} \left(g_{20}g_{11} - 2|g_{11}|^2 - \frac{|g_{02}|}{3} \right) + \frac{g_{21}}{2}, \\
\gamma_2 &= -\frac{\operatorname{Re}\{c_1(0)\}}{\operatorname{Re}\{\lambda'(\tau_0)\}}, \\
\beta_2 &= 2\operatorname{Re}\{c_1(0)\}, \\
T_2 &= -\frac{\operatorname{Re}\{c_1(0)\} + \gamma_2 \operatorname{Re}\{\lambda'(\tau_0)\}}{\omega\tau_0},
\end{aligned} \quad (48)$$

which determine the quantities of bifurcating periodic solutions reduced on the central manifold at the critical value τ_0 . More precisely, γ_2 determines the direction of Hopf bifurcation and β_2 determines the stability of bifurcating periodic solution. Summarizing the above discussion, we have the following main result.

Theorem 10. *If $\gamma_2 > 0$ ($\gamma_2 < 0$), then the Hopf bifurcation is supercritical (subcritical) and the bifurcating periodic solutions*

FIGURE 1: The phase diagram of system (2) with different initial values and different τ .

FIGURE 2: Local asymptotic stability of the immune-exhausted equilibrium E_1 .

exist for $\tau > \tau_0$ ($\tau < \tau_0$). Moreover, β_2 determines the stability of the bifurcating periodic solutions. The bifurcating periodic solutions are stable (unstable) if $\beta_2 < 0$ ($\beta_2 > 0$).

5. Numerical Simulation

In order to demonstrate our results and find complex dynamic behavior of system (2), we provide numerical calculations for different birth rates of susceptible cells s and time delays τ . The parameter values are chosen from literatures [14, 15, 20]. If we choose the following data set: $s = 200$, $\beta = 0.002$, $q = 0.01$, $a = 5$, $b = 0.1$, $c = 0.2$, $d = 0.1$, and $p = 0.1$, then we get $R_0 = 0.8 < 1$, $E_0 = (2000, 0, 0)$. Hence, by Theorem 5, E_0 is globally asymptotically stable. Figure 1 illustrates this fact.

If we choose the following data set: $s = 251$, $\beta = 0.002$, $q = 0.01$, $a = 5$, $b = 0.1$, $c = 0.2$, $d = 0.1$, and $p = 0.1$, then we get $1 < R_0 \leq 1.01$, $E_1 = (2500, 0.3, 0)$. Hence, by Theorem 4, E_1 is local asymptotically stable. Figure 2 illustrates this fact.

In addition, we choose a set of parameters: $s = 257$, $\beta = 0.002$, $q = 0.01$, $a = 5$, $b = 0.1$, $c = 0.2$, $d = 0.1$, and $p = 0.1$, then we get $R_0 > 1.01$, $E_2 = (2544.7, 0.5, 0.5937)$, the positive real roots of (27), $x_1 = 0.00607941$ and $x_2 = 0.00194817$. It satisfies the conditions (2) of Theorem 9. We can calculate that

$$\begin{aligned}
c_1(0) &= -0.00241449 - 0.003121i, \\
\tau_1^{(0)} &= 8.78303, & \tau_2^{(0)} &= 37.8851, \\
\tau_1^{(1)} &= 89.3671, & \tau_1^{(2)} &= 169.951.
\end{aligned} \quad (49)$$

FIGURE 3: Stability of E_2 for $\tau = 5$. FIGURE 4: A stable bifurcating periodic solution for $\tau = 13$.

By Theorem 9, we have that E_2 is stable when $\tau < \tau_1^{(0)}$ (Figure 3). Let $\tau_0 = \tau_1^{(0)}$; we can compute $c_1(0) = -0.000199515 - 0.0139977i$, $G'(x_1) = 0.000059 > 0$. Since $\text{sign}[\text{Re} \lambda'(\tau_0)] = \text{sign}[G'(x_1)]$ and $\text{Re}\{c_1(0)\} < 0$, then $\nu_2 > 0$; according to Theorem 10, there exist stable periodic solutions (Figure 4) for $\tau > \tau_1^{(0)}$ in a $\tau_1^{(0)}$ neighborhood. When τ exceeds $\tau_2^{(0)}$, we can observe that another change of stability appears (Figure 5). Since $G'(x_2) = -0.00004 < 0$ and $\text{Re}\{c_1(0)\} < 0$ then $\nu_2 > 0$. Applying Theorem 10, there exist stable periodic solutions for $\tau < \tau_2^{(0)}$. By the same method, the stability of E_2 is changed when τ exceeds $\tau_1^{(1)}$, $\tau_1^{(2)}$. We can also obtain that there exist stable periodic solutions for $\tau > \tau_1^{(1)}$ (Figure 6). The bifurcation diagram (Figure 7) shows that the stability of E_2 is changed at $\tau_1^{(0)}$, $\tau_2^{(0)}$, and $\tau_1^{(1)}$ clearly.

As shown in Figures 3–7, for different delays in CTL response, the system is stable at a positive equilibrium when the delay is small or it is at a stable periodic oscillation when the delay is large. Our simulations demonstrated that delays

may affect cell-virus and virus-immune system dynamics. These results could provide insights into many important questions such as how to further improve our mathematical model, how to better implement clinical diagnosis, and how to design and administrate more efficient medical treatment.

6. Conclusion

In this paper, we have studied a virus infection model with delayed nonlytic immune response. We obtain the sufficient and necessary conditions for the existence of the equilibria. Global stability of the infection-free equilibrium has been given by the Lyapunov-LaSalle type theorem. We find that the infection-free equilibrium E_0 is globally asymptotically stable if $R_0 \leq 1$. In this case, the virus is finally cleared up. By analyzing corresponding characteristic equation, we obtain that the immune-exhausted equilibrium E_1 is locally asymptotically stable if $1 < R_0 \leq 1 + b\beta/cd$. In this case,

FIGURE 5: Stability of E_2 for $\tau = 40$. FIGURE 6: A stable bifurcating periodic solution for $\tau = 95$. FIGURE 7: A bifurcation diagram in which τ is bifurcating parameter.

the infection becomes chronic but without CTL immune response. By choosing time delay as a bifurcation parameter, we have shown that a limit cycle emerges via Hopf bifurcation when the delay passes through the critical value τ_0 . By applying normal form theory and center manifold theorem, the direction of Hopf bifurcation and stability of bifurcating

periodic solutions have been investigated. Some numerical simulations are performed to verify the correctness of theoretical analysis. Clearly, compared to the earlier studies, our analysis shows that the new time delay we introduce can change the stability of the equilibrium E_2 . We would like to mention that whether the equilibrium E_2 is globally asymptotically stable when $R_0 > 1 + b\beta/cd$. We leave this for our future work.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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