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Research Article

Spatiotemporal Dynamics of an HIV Infection Model with Delay in Immune Response Activation

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We propose and analyse an human immunodeficiency virus (HIV) infection model with spatial diffusion and delay in the immune response activation. In the proposed model, the immune response is presented by the cytotoxic T lymphocytes (CTL) cells. We first prove that the model is well-posed by showing the global existence, positivity, and boundedness of solutions. The model has three equilibria, namely, the free-infection equilibrium, the immune-free infection equilibrium, and the chronic infection equilibrium. The global stability of the first two equilibria is fully characterized by two threshold parameters that are the basic reproduction number R_0 and the CTL immune response reproduction number R_1. The stability of the last equilibrium depends on R_0 and R_1 as well as time delay τ in the CTL activation. We prove that the chronic infection equilibrium is locally asymptotically stable when the time delay is sufficiently small, while it loses its stability and a Hopf bifurcation occurs when τ passes through a certain critical value.

1. Introduction

HIV is a virus that attacks the $CD4^+$ T cells and reduces their number in the body. It is known that when the number of these cells is less than 200 cells per μl, the patient enters the phase of acquired immunodeficiency syndrome (AIDS). This phase is characterized by the appearance of opportunistic infections caused by bacteria, viruses, or fungi or by the appearance of certain types of cancer. From the world health organization (WHO) [1], HIV continues to be a major global public health issue, having claimed more than 35 million lives so far. In 2016, 1 million people died from HIV-related causes globally. Also, there were approximately 36.7 million people living with HIV at the end of 2016 with 1.8 million people becoming newly infected in 2016 globally. Therefore, many mathematical models have been developed to better understand the dynamics of HIV infection. One of the earliest of these models was presented by Nowak and Bangham [2] that considers three populations: uninfected target cells, productive infected cells, and free viral particles. Rong et al. [3] extended the model of [2] by including the infected cells in eclipse stage (unproductive infected cells) and considered that a portion of these cells returns to the uninfected state. In 2014, Hu et al. [4] replaced the bilinear incidence rate in [3] by a saturated infection rate and they studied the global stability of equilibria. In 2015, Maziane et al. [5] improved the model of [4] by considering the Hattaf's incidence rate [6] that includes the common types such as the bilinear incidence rate, the saturated incidence rate, the Beddington-DeAngelis functional response [7, 8] and the Crowley-Martin functional response [9].

Cytotoxic T lymphocytes (CTL) cells are responsible for cellular immunity and they play an important role in antiviral defense by killing the productive infected cells. For this, Lv et al. [10] proposed an HIV model with Beddington-DeAngelis functional response and CTL immune response. In 2016, Maziane et al. [11] generalized and extended the model of Lv et al. [10] by considering the mobility of cells and virus. They assumed that the motion of virus follows the Fickian diffusion and proposed the following model:

$$\begin{aligned}\frac{\partial T}{\partial t} &= \lambda - \mu_T T(x,t) - f(T(x,t), V(x,t)) V(x,t) \\ &\quad + \rho E(x,t), \\ \frac{\partial E}{\partial t} &= f(T(x,t), V(x,t)) V(x,t)\end{aligned}$$

$$
\begin{aligned}
&\quad - (\mu_E + \rho + \gamma) E(x,t), \\
\frac{\partial I}{\partial t} &= \gamma E(x,t) - \mu_I I(x,t) - pI(x,t) C(x,t), \\
\frac{\partial V}{\partial t} &= d\Delta V(x,t) + kI(x,t) - \mu_V V(x,t), \\
\frac{\partial C}{\partial t} &= aI(x,t) C(x,t) - \mu_C C(x,t),
\end{aligned} \tag{1}
$$

where $T(x,t)$, $E(x,t)$, $I(x,t)$, $V(x,t)$, and $C(x,t)$ represent the densities of uninfected CD4$^+$ T cells, unproductive infected cells, productive infected cells, and free virus particles and CTL cells at location x and time t, respectively. The positive parameters λ, γ, k, and a are the production rate of uninfected cells, the rate at which infected cells in the eclipse stage become productive infected cells, the production rate of virions by infected cells, and the proliferation rate of CTL cells, respectively. The positive constants μ_T, μ_E, μ_I, μ_V, and μ_C are, respectively, the death rates of uninfected CD4$^+$ T cells, unproductive infected cells, productive infected cells, free virus, and CTL cells. The unproductive infected cells return to the uninfected cells at rate ρ while the productive infected cells are killed by CTL at rate p. In model (1), the infection transmission process is modeled by Hattaf's incidence rate [6] of the form $f(T,V) = \beta T/(1 + \alpha_1 T + \alpha_2 V + \alpha_3 TV)$, where α_1, α_2, and $\alpha_3 \geq 0$ are the saturation factors measuring the psychological or inhibitory effect and $\beta > 0$ is the infection coefficient. Here $\Delta = \sum_{i=1}^{n} (\partial^2/\partial x_i^2)$ is the Laplacian operator and d is the diffusion coefficient of virus.

In the reality, the activation of the immune response is not instantaneous. When the virus invades the body, the immune system takes time to recognize and react to the virus. Therefore, system (1) becomes

$$
\begin{aligned}
\frac{\partial T}{\partial t} &= \lambda - \mu_T T(x,t) \\
&\quad - f(T(x,t), V(x,t)) V(x,t) + \rho E(x,t), \\
\frac{\partial E}{\partial t} &= f(T(x,t), V(x,t)) V(x,t) \\
&\quad - (\mu_E + \rho + \gamma) E(x,t), \\
\frac{\partial I}{\partial t} &= \gamma E(x,t) - \mu_I I(x,t) - pI(x,t) C(x,t), \\
\frac{\partial V}{\partial t} &= d\Delta V(x,t) + kI(x,t) - \mu_V V(x,t), \\
\frac{\partial C}{\partial t} &= aI(x,t-\tau) C(x,t-\tau) - \mu_C C(x,t),
\end{aligned} \tag{2}
$$

where τ denotes the time needed for the activation of the CTL immune response, namely, the immunological delay. The other parameters have the same biological meaning as system (1). In addition, we consider our model (2) with homogenous Neumann boundary condition

$$
\frac{\partial V}{\partial \nu} = 0 \quad \text{on } \partial\Omega \times (0, +\infty), \tag{3}
$$

and initial conditions

$$
\begin{aligned}
T(x,\theta) &= \phi_1(x,\theta) \geq 0, \\
E(x,\theta) &= \phi_2(x,\theta) \geq 0, \\
I(x,\theta) &= \phi_3(x,\theta) \geq 0, \\
V(x,\theta) &= \phi_4(x,\theta) \geq 0, \\
C(x,\theta) &= \phi_5(x,\theta) \geq 0, \\
&\qquad x \in \overline{\Omega},\ \theta \in [-\tau, 0],
\end{aligned} \tag{4}
$$

where Ω is a bounded domain in $\mathbb{R}^n$ with smooth boundary $\partial\Omega$, $\phi_i(x,\theta)$ $(i = 1,2,3,4,5)$ is Hölder continuous in $\overline{\Omega} \times [-\tau, 0]$, and $\partial V/\partial \nu$ is the outward normal derivative on $\partial\Omega$.

The rest of the paper is outlined as follows. In the next section we investigate the well-posedness and equilibria for system (2)–(4). The stability analysis and the existence of Hopf bifurcation are studied in Section 3. Finally, a brief conclusion is given in Section 4.

2. Well-Posedness and Equilibria

In this section, we establish the existence, positivity, and boundedness of solutions of problem (2)–(4) because this model describes the evolution of a cell population. Hence the densities of cells should remain nonnegative and bounded. In addition, we determine the basic reproduction number, the CTL immune response reproduction number, and equilibria of the model (2)–(4).

Before proceeding, we shall set some notations and terminology. X will denote a Banach space over a real or complex field. $C = C([-\tau, 0], X)$ will denote the Banach space of X-valued functions on $[-\tau, 0]$, with supremum norm, where $\tau > 0$. Here, $X = C(\overline{\Omega}, \mathbb{R}^5)$. If u is a continuous function from $[-\tau, b]$ to X and $t \in [0, b]$, then u_t denotes the element of C given by $u_t(\theta) = u(t + \theta)$, $-\tau \leq \theta \leq 0$.

Proposition 1. *For any initial conditions satisfying (4), there exists a unique solution of problem (2)–(4) defined on* $[0, +\infty)$ *and this solution remains nonnegative and bounded for all* $t \geq 0$.

Proof. Let $\phi = (\phi_1, \phi_2, \phi_3, \phi_4, \phi_5)^T \in C$ and $x \in \overline{\Omega}$. We define $F = (F_1, F_2, F_3, F_4, F_5)$ by

$$
\begin{aligned}
F_1(\phi)(x) &= \lambda - \mu_T \phi_1(x,0) \\
&\quad - f(\phi_1(x,0), \phi_4(x,0)) \phi_4(x,0) \\
&\quad + \rho \phi_2(x,0), \\
F_2(\phi)(x) &= f(\phi_1(x,0), \phi_4 x, 0) \phi_4(x,0) \\
&\quad - (\rho + \mu_E + \gamma) \phi_2(x,0), \\
F_3(\phi)(x) &= \gamma \phi_2(x,0) - \mu_I \phi_3(x,0) \\
&\quad - p\phi_3(x,0) \phi_5(x,0), \\
F_4(\phi)(x) &= k\phi_3(x,0) - \mu_V \phi_4(x,0), \\
F_5(\phi)(x) &= a\phi_3(x,-\tau) \phi_5(x,-\tau) - \mu_C \phi_5(x,0).
\end{aligned} \tag{5}
$$

Hence, system (2)–(4) can be written of the form

$$\begin{aligned} u'(t) &= Au(t) + F(u_t(t)), \quad t > 0 \\ u(0) &= \phi \in X, \end{aligned} \tag{6}$$

where $u = (T, E, I, V, C)^T$ and $Au(t) = (0, 0, 0, d\Delta V, 0)^T$. Obviously, F is locally Lipschitz in X. By [12–16], we deduce that system (2) admits a unique local solution on $[0, T_{\max})$, where $T_{\max}$ is the maximal existence time for solution of system (2). In addition, $(0, 0, 0, 0, 0)$ is a lower solution of each solution of system (2); then we deduce that $T(x,t) \geq 0$, $E(x,t) \geq 0$, $I(x,t) \geq 0$, $V(x,t) \geq 0$ and $C(x,t) \geq 0$.

Next, we prove the boundedness of solutions by considering the following function:

$$S(x,t) = T(x,t) + E(x,t) + I(x,t) + \frac{p}{a}C(x,t+\tau). \tag{7}$$

From system (2), we obtain

$$\begin{aligned} \frac{\partial S(x,t)}{\partial t} &= \lambda - \mu_T T(x,t) - \mu_E E(x,t) - \mu_I I(x,t) \\ &\quad - \mu_C \frac{p}{a} C(x,t+\tau) \leq \lambda - \mu S(x,t), \end{aligned} \tag{8}$$

where $\mu = \min\{\mu_T, \mu_E, \mu_I, \mu_C\}$. Thus,

$$\begin{aligned} S(x,t) \leq \max\Bigg\{ &\frac{\lambda}{\mu}, \max_{x\in\overline{\Omega}} \Bigg\{\phi_1(x,0) + \phi_2(x,0) + \phi_3(x,0) \\ &+ \frac{p}{a}\phi_5(x,-\tau)\Bigg\}\Bigg\}. \end{aligned} \tag{9}$$

Then, T, E, I, and C are bounded.

To prove the boundedness of V, from system (2), we get

$$\begin{aligned} \frac{\partial V(x,t)}{\partial t} - d_V \Delta V &\leq k\delta - \mu_V V, \\ \frac{\partial V(x,t)}{\partial \nu} &= 0, \\ V(x,0) &= \max_{x\in\overline{\Omega}} \phi_4(x,0), \end{aligned} \tag{10}$$

where $\delta = \max\{\lambda/\mu, \max_{x\in\overline{\Omega}}\{\phi_1(x,0) + \phi_2(x,0) + \phi_3(x,0) + (p/a)\phi_5(x,-\tau)\}\}$.

Using the comparison principle [17], we have $V(x,t) \leq \overline{V}(t)$, where $\overline{V}(t) = \phi_4(x)e^{-\mu_V t} + (k\delta/\mu_V)(1 - e^{-\mu_V t})$ is the solution of the problem

$$\begin{aligned} \frac{d\overline{V}}{dt} &= k\delta - \mu_V \overline{V} \\ \overline{V}(0) &= \max_{x\in\overline{\Omega}} \phi_4(x,0). \end{aligned} \tag{11}$$

Since $\overline{V}(t) \leq \max\{k\delta/\mu_V, \max_{x\in\overline{\Omega}}\phi_4(x,0)\}$, $\forall (x,t) \in \overline{\Omega} \times [0, T_{\max})$, we have that V is bounded.

Therefore, we have proved that $T(x,t)$, $E(x,t)$, $I(x,t)$, $V(x,t)$, and $C(x,t)$ are bounded on $\overline{\Omega} \times [0, T_{\max})$. Hence, it follows from the standard theory for semilinear parabolic systems [18] that $T_{\max} = +\infty$. □

As in [11], the basic reproduction number of virus in the absence of spatial dependence is given by

$$R_0 = \frac{\lambda\beta k\gamma}{\mu_I\mu_V(\lambda\alpha_1 + \mu_T)(\mu_E + \gamma)}. \tag{12}$$

In addition to R_0, we define the CTL immune response reproduction number R_1 of our model by

$$R_1 = \frac{aI_1}{\mu_C}, \tag{13}$$

which represents the threshold level to activate the CTL cells response.

Theorem 2.

(i) *If $R_0 \leq 1$, system (2) has always an infection-free equilibrium of the form $Q_0(\lambda/\mu_T, 0, 0, 0, 0)$.*

(ii) *If $R_0 > 1$, system (2) has an immune-free equilibrium of the form $Q_1(T_1, E_1, I_1, V_1, 0)$ with $T_1 \in (0, \lambda/\mu_T)$, $E_1 \geq 0$, $I_1 \geq 0$, and $V_1 \geq 0$.*

(iii) *If $R_1 > 1$, system (2) has a chronic infection equilibrium of the form $Q_2(T_2, E_2, I_2, V_2, C_2)$ with $T_2 \in (0, \lambda/\mu_T - \mu_I\mu_C(\mu_E + \gamma)/a\gamma\mu_T)$, $E_2 \geq 0$, $I_2 \geq 0$, $V_2 \geq 0$, and $C_2 \geq 0$.*

3. Stability Analysis and Hopf Bifurcation

First, we discuss the global stability of the infection-free equilibrium Q_0 and the immune-free equilibrium Q_1.

Theorem 3.

(i) *The infection-free equilibrium Q_0 is globally asymptotically stable if $R_0 \leq 1$.*

(ii) *The immune-free equilibrium Q_1 is globally asymptotically stable if $R_1 \leq 1 < R_0$ and*

$$\begin{aligned} R_0 &\leq 1 \\ &+ \frac{[\mu_T\mu_I\mu_V(\mu_E + \gamma) + \alpha_2\mu_T\lambda k\gamma](\mu_E + \rho + \gamma) + \rho\alpha_3 k\gamma\lambda^2}{\rho\mu_I\mu_V(\mu_E + \rho + \gamma)(\mu_T + \alpha_1\lambda)}. \end{aligned} \tag{14}$$

Proof. By using the method proposed by Hattaf and Yousfi [19], we propose the following Lyapunov functional for system (2)–(4) at Q_0:

$$\begin{aligned} W_0 = \int_\Omega \Bigg[&T(x,t) - T_0 - \int_{T_0}^{T(x,t)} \frac{f(T_0,0)}{f(S,0)} dS \\ &+ \frac{\rho(T(x,t) - T_0 + E(x,t))^2}{2(1+\alpha_1 T_0)(\mu_T + \mu_E + \gamma)T_0} + \frac{\rho + \mu_E + \gamma}{\gamma} \\ &\cdot I(x,t) + E(x,t) + \frac{\mu_I(\rho + \mu_E + \gamma)}{k\gamma} V(x,t) \\ &+ \frac{p(\rho + \mu_E + \gamma)}{a\gamma} C(x,t) + \frac{p(\rho + \mu_E + \gamma)}{\gamma} \\ &\cdot \int_{t-\tau}^{t} I(x,\theta) C(x,\theta) d\theta \Bigg] dx, \end{aligned} \tag{15}$$

where $T_0 = \lambda/\mu_T$. For convenience, we let $\psi(x,t) = \psi$ and $\psi(x,t-\tau) = \psi_\tau$, for any $\psi \in \{T,E,I,V,C\}$. By calculation, we have

$$\begin{aligned}\frac{dW_0}{dt} = \int_\Omega \Bigg[& \left(1 - \frac{f(T_0,0)}{f(T,0)}\right)\frac{\partial T}{\partial t} \\ & + \frac{\rho(T - T_0 + E)(\partial T/\partial t + \partial E/\partial t)}{(1+\alpha_1 T_0)(\mu_T + \mu_E + \gamma)T_0} \\ & + \frac{\rho + \mu_E + \gamma}{\gamma}\frac{\partial I}{\partial t} + \frac{\partial E}{\partial t} + \frac{\mu_I(\rho + \mu_E + \gamma)}{k\gamma}\frac{\partial V}{\partial t} \\ & + \frac{p(\rho + \mu_E + \gamma)}{a\gamma}\frac{\partial C}{\partial t} \\ & + \frac{p(\rho + \mu_E + \gamma)}{\gamma}\frac{\partial}{\partial t}\int_{t-\tau}^{t} I_\theta C_\theta \, d\theta \Bigg] dx.\end{aligned} \tag{16}$$

Noting that $\lambda = \mu_T T_0$, the time derivative of W_0 along the positive solutions of system (2) satisfies

$$\begin{aligned}\frac{dW_0}{dt} = \int_\Omega \Bigg[& \left(1 - \frac{f(T_0,0)}{f(T,0)}\right)\mu_T(T_0 - T) \\ & + \frac{f(T_0,0)f(T,V)}{f(T,0)}V + \rho\left(1 - \frac{f(T_0,0)}{f(T,0)}\right)E \\ & - \frac{\rho\mu_T(T - T_0)^2}{(1+\alpha_1 T_0)(\mu_T + \mu_E + \gamma)T_0} \\ & - \frac{\rho(\mu_E + \gamma)E^2}{(1+\alpha_1 T_0)(\mu_T + \mu_E + \gamma)T_0} \\ & + \frac{\rho E}{(1+\alpha_1 T_0)T_0}(T_0 - T) - \frac{p(\rho + \mu_E + \gamma)}{\gamma}IC \\ & - \frac{\mu_I\mu_V(\rho + \mu_E + \gamma)}{k\gamma}V + \frac{p(\rho + \mu_E + \gamma)}{\gamma}I_\tau C_\tau \\ & - \frac{\mu_C p(\rho + \mu_E + \gamma)}{a\gamma}C \\ & + \frac{p(\rho + \mu_E + \gamma)}{\gamma}[IC - I_\tau C_\tau] \\ & + \frac{d\mu_I(\rho + \mu_E + \gamma)}{k\gamma}\Delta V \Bigg] dx \\ = & -\int_\Omega \Bigg[\left(\frac{1}{T} + \frac{\rho}{(\mu_T + \mu_E + \gamma)T_0}\right)\frac{\mu_T(T - T_0)^2}{1+\alpha_1 T_0} \\ & + \frac{\rho(\mu_E + \gamma)E^2}{(1+\alpha_1 T_0)(\mu_T + \mu_E + \gamma)T_0} + \frac{\rho(T - T_0)^2 E}{(1+\alpha_1 T_0)TT_0} \\ & - \frac{\mu_I\mu_V(\rho + \mu_E + \gamma)}{k\gamma}(R_0 - 1)V \\ & + \frac{(\alpha_2 + \alpha_3 T)V^2}{1 + \alpha_1 T + \alpha_2 V + \alpha_3 TV} f(T_0,0) \\ & + \frac{\mu_C p(\rho + \mu_E + \gamma)}{a\gamma}C \Bigg] dx.\end{aligned} \tag{17}$$

Therefore, $dW_0/dt \le 0$ if $R_0 \le 1$. In addition, it is not hard to verify that the largest compact invariant set in $\{(T,E,I,V,C) \mid dW_0/dt = 0\}$ is just the singleton $\{Q_0\}$. From LaSalle invariance principle [20], we deduce that Q_0 is globally asymptotically stable.

Next, we construct the Lyapunov functional for system (2)–(4) at Q_1:

$$\begin{aligned}W_1 = \int_\Omega \Bigg[& T - T_1 - \int_{T_1}^{T}\frac{f(T_1,V_1)}{f(S,V_1)}dS \\ & + \frac{\rho(1+\alpha_2 V_1)(T - T_1 + E - E_1)^2}{2(1+\alpha_1 T_1 + \alpha_2 V_1 + \alpha_3 T_1 V_1)(\mu_T + \mu_E + \gamma)T_1} \\ & + \frac{f(T_1,V_1)V_1}{\gamma E_1}I_1\Phi\left(\frac{I}{I_1}\right) + E_1\Phi\left(\frac{E}{E_1}\right) \\ & + \frac{\mu_I f(T_1,V_1)V_1}{k\gamma E_1}V_1\Phi\left(\frac{V}{V_1}\right) + \frac{pf(T_1,V_1)V_1}{a\gamma E_1}C \\ & + \frac{pf(T_1,V_1)V_1}{\gamma E_1}\int_{t-\tau}^{t} I_\theta C_\theta \, d\theta \Bigg] dx,\end{aligned} \tag{18}$$

where $\Phi(x) = x - 1 - \ln(x)$. Obviously, the function Φ has a global minimum at 1 and satisfies $\Phi(1) = 0$. Calculating the time derivative of W_1 along the positive solutions of system (2) and applying $\lambda = \mu_T T_1 + f(T_1,V_1)V_1 - \rho E_1$, we obtain

$$\begin{aligned}\frac{dW_1}{dt} = \int_\Omega \Bigg[& \left(1 - \frac{f(T_1,V_1)}{f(T,V_1)}\right)\mu_T(T_1 - T) \\ & + \frac{f(T_1,V_1)f(T,V)}{f(T,V_1)}V + \rho\left(1 - \frac{f(T_1,V_1)}{f(T,V_1)}\right)E \\ & - \frac{\mu_T\rho(1+\alpha_2 V_1)}{(1+\alpha_1 T_1 + \alpha_2 V_1 + \alpha_3 T_1 V_1)(\mu_T + \mu_E + \gamma)T_1}(T - T_1)^2 \\ & - \frac{\rho(1+\alpha_2 V_1)(\mu_E + \gamma)}{(1+\alpha_1 T_1 + \alpha_2 V_1 + \alpha_3 T_1 V_1)(\mu_T + \mu_E + \gamma)T_1}(E - E_1)^2 \\ & - \frac{\rho(1+\alpha_2 V_1)(E - E_1)(T - T_1)^2}{(1+\alpha_1 T_1 + \alpha_2 V_1 + \alpha_3 T_1 V_1)T_1 T} - \frac{(f(T_1,V_1))^2}{f(T,V_1)}V_1 \\ & + 4f(T_1,V_1)V_1 - f(T_1,V_1)V - f(T_1,V_1)V_1\frac{I_1 E}{IE_1} \\ & - f(T,V)V\frac{E_1}{E} - f(T_1,V_1)V_1\frac{V_1 I}{I_1 V} + \frac{pf(T_1,V_1)V_1}{\gamma E_1}\Bigg(I_1 \\ & - \frac{\mu_C}{a}\Bigg)C \Bigg] dx + \frac{d\mu_I f(T_1,V_1)V_1}{k\gamma E_1}\int_\Omega\left(1 - \frac{V_1}{V}\right)\Delta V dx\end{aligned}$$

$$
\begin{aligned}
&= -\int_{\Omega}\left[\frac{(1+\alpha_2 V_1)(T-T_1)^2}{TT_1(1+\alpha_1 T_1+\alpha_2 V_1+\alpha_3 T_1 V_1)}\left((\mu_T T_1-\rho E_1)\right.\right.\\
&\quad\left.+\frac{\rho\mu_T T}{\mu_T+\mu_E+\gamma}+\rho E\right)\\
&\quad+\frac{\rho(E-E_1)^2(1+\alpha_2 V_1)(\mu_E+\gamma)}{T_1(1+\alpha_1 T_1+\alpha_2 V_1+\alpha_3 T_1 V_1)(\mu_T+\mu_E+\gamma)}-f(T_1,V_1)\\
&\quad\cdot V_1\left(5-\frac{f(T_1,V_1)}{f(T,V_1)}-\frac{I_1 E}{E_1 I}-\frac{f(T,V)}{f(T_1,V_1)}\frac{VE_1}{V_1 E}-\frac{V_1 I}{VI_1}\right.\\
&\quad\left.-\frac{f(T,V_1)}{f(T,V)}\right)\\
&\quad+\frac{f(T_1,V_1)(1+\alpha_1 T)(\alpha_2+\alpha_3 T)(V-V_1)^2}{(1+\alpha_1 T+\alpha_2 V_1+\alpha_3 T V_1)(1+\alpha_1 T+\alpha_2 V+\alpha_3 T V)}\\
&\quad\left.-\frac{p\mu_C f(T_1,V_1)V_1}{a\gamma E_1}(R_1-1)C\right]dx\\
&\quad-\frac{d\mu_I f(T_1,V_1)V_1^2}{k\gamma E_1}\int_{\Omega}\frac{\|\nabla V\|^2}{V^2}dx.
\end{aligned}
\tag{19}
$$

Using the arithmetic-geometric inequality, we get

$$
\begin{aligned}
&5-\frac{f(T_1,V_1)}{f(T,V_1)}-\frac{I_1 E}{E_1 I}-\frac{f(T,V)}{f(T_1,V_1)}\frac{VE_1}{V_1 E}-\frac{V_1 I}{VI_1}\\
&\quad-\frac{f(T,V_1)}{f(T,V)}\le 0.
\end{aligned}
\tag{20}
$$

Therefore, $dW_1/dt \le 0$ if $R_1 \le 1$ and $\rho E_1 \leqslant \mu_T T_1$.

Obviously, the condition $\rho E_1 \leqslant \mu_T T_1$ is equivalent to

$$
\begin{aligned}
&R_0 \le 1\\
&\quad+\frac{[\mu_T\mu_I\mu_V(\mu_E+\gamma)+\alpha_2\mu_T\lambda k\gamma](\mu_E+\rho+\gamma)+\rho\alpha_3 k\gamma\lambda^2}{\rho\mu_I\mu_V(\mu_E+\rho+\gamma)(\mu_T+\alpha_1\lambda)}.
\end{aligned}
\tag{21}
$$

In addition, $dW_1/dt = 0$ if and only if $T = T_1$, $E = E_1$, $I = I_1$, $V = V_1$, and $C = 0$. Hence, the largest compact invariant set in $\{(T,E,I,V,C) \mid dW_1/dt = 0\}$ is the singleton $\{Q_1\}$. This proves the global stability of Q_1 by using LaSalle's invariance principle [20]. □

From the above theorem, we deduce that the time delay in the activation of CTL immune response has no effect on the stability of Q_0 and Q_1. Next we investigate the stability and existence of Hopf bifurcation at the chronic infection equilibrium Q_2.

When $\tau = 0$, system (2) becomes system (1). By Theorem 3 (iii) [11], we deduce the following result.

Theorem 4. *When $\tau = 0$, the chronic infection equilibrium with immune response Q_2 is globally asymptotically stable if $R_1 > 1$ and*

$$
\begin{aligned}
k\beta\mu_C\rho \le{}& \alpha_1\lambda\rho a\mu_V+\mu_T(\rho+\mu_E+\gamma)(\alpha_2 k\mu_C+a\mu_V)\\
&+\alpha_3\rho\lambda k\mu_C.
\end{aligned}
\tag{22}
$$

Now, we study the existence of Hopf bifurcation by regarding time delay τ as the bifurcation parameter.

Let $0 = \mu_0 < \mu_1 < \cdots < \mu_n < \cdots$ be the eigenvalues of $-\Delta$ on Ω with homogeneous Neumann boundary conditions, and for $= 0, 1, 2, \ldots$, let $E(\mu_i)$ be the space of eigenfunctions corresponding to μ_i in $C^1(\Omega)$. Let $\{\phi_{ij} : j = 1, 2, \ldots, \dim E(\mu_i)\}$ be an orthonormal basis of $E(\mu_i)$, $X = [C^1(\Omega)]^5$ and $X_{ij} = \{c\phi_{ij} : c \in \mathbb{R}^5\}$. Then, $X = \bigoplus_{i=1}^{\infty} X_i$, $X_i = \bigoplus_{j=1}^{\dim[S(\mu_i)]} X_{ij}$.

The linearization of system (2) at the constant solution $Q_2(T_2, E_2, I_2, V_2, C_2)$ can be expressed by

$$
\frac{\partial Z}{\partial t} = D\Delta Z + JZ + J^* Z_\tau,
\tag{23}
$$

where $Z = (T, E, I, V, C)$, $Z_\tau = (T_\tau, E_\tau, I_\tau, V_\tau, C_\tau)$, and $D = (0, 0, 0, d, 0)$,

$$
J = \begin{pmatrix}
-\frac{\partial f(T_2,V_2)}{\partial T}V_2-\mu_T & \rho & -\frac{\partial f(T_2,V_2)}{\partial V}V_2-f(T_2,V_2) & 0 & 0\\
\frac{\partial f(T_2,V_2)}{\partial V}V_2 & -(\mu_E+\rho+\gamma) & 0 & \frac{\partial f(T_2,V_2)}{\partial V}V_2+f(T_2,V_2) & 0\\
0 & \gamma & \mu_I-pC_2 & 0 & -pI_2\\
0 & 0 & k & -\mu_V & 0\\
0 & 0 & 0 & 0 & -\mu_C
\end{pmatrix},
\tag{24}
$$

$$
J^* = \begin{pmatrix}
0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0\\
0 & 0 & 0 & 0 & 0\\
0 & 0 & aC_2 & 0 & aI_2
\end{pmatrix}.
$$

Let $\mathscr{L}Z = D\Delta Z + JZ(x,t) + J^{*}Z(x,t-\tau)$. For each $i = 0,1,2,\ldots$, X_i is invariant under the operator $\mathscr{L}$, and ξ is an eigenvalue of $\mathscr{L}$ if and only if it is satisfying the characteristic equation

$$\det\left(-\xi I - \mu_i D + J + e^{-\xi\tau}J^{*}\right) = 0. \tag{25}$$

Then, at Q_2, the associated characteristic equation of system (2) is given by

$$\begin{aligned}&\xi^5 + a_1\xi^4 + a_2\xi^3 + a_3\xi^2 + a_4\xi + a_5\\&\quad + e^{-\xi\tau}\left(b_1\xi^4 + b_2\xi^3 + b_3\xi^2 + b_4\xi + b_5\right) = 0,\end{aligned} \tag{26}$$

where

$$\begin{aligned}
a_1 &= \frac{\partial f(T_2,V_2)}{\partial T}V_2 + \mu_T + \mu_I + \mu_V + \mu_C + pC_2 + \mu_E\\
&\quad + \rho + \gamma + \mu_i d,\\
a_2 &= \left(\frac{\partial f(T_2,V_2)}{\partial T}V_2 + \mu_T\right)[(\mu_E + \rho + \gamma)\\
&\quad + (\mu_V + \mu_i d) + \mu_I + \mu_C + pC_2] + (\mu_E + \rho + \gamma)(\mu_V\\
&\quad + \mu_i d + \mu_I + \mu_C + pC_2) + (\mu_I + pC_2)(\mu_V + \mu_i d\\
&\quad + \mu_C) + (\mu_V + \mu_i d)\mu_C + \mu_T\rho,\\
a_3 &= \left(\frac{\partial f(T_2,V_2)}{\partial T}V_2 + \mu_T\right)[(\mu_V + \mu_i d + \mu_C)\\
&\quad \cdot (\mu_I + pC_2) + (\mu_V + \mu_i d)\mu_C] + \left(\frac{\partial f(T_2,V_2)}{\partial T}V_2\right.\\
&\quad \left. + \mu_T\right)(\mu_E + \gamma)(\mu_I + \mu_V + \mu_i d + \mu_C + pC_2)\\
&\quad + \mu_C(\mu_V + \mu_i d)(\mu_I + pC_2 + \mu_E + \rho + \gamma)\\
&\quad - k\gamma\frac{\partial f(T_2,V_2)}{\partial V}V_2 + \mu_T\rho(\mu_V + \mu_i d + \mu_I + \mu_C\\
&\quad + pC_2),\\
a_4 &= \left(\frac{\partial f(T_2,V_2)}{\partial T}V_2 + \mu_T\right)\left[(\mu_V + \mu_i d)\right.\\
&\quad \cdot \mu_C(\mu_I + pC_2) + (\mu_E + \gamma)(\mu_V + \mu_i d + \mu_I + pC_2)\\
&\quad \left.\cdot \mu_C - k\gamma\frac{\partial f(T_2,V_2)}{\partial V}V_2\right] - k\gamma\mu_C\frac{\partial f(T_2,V_2)}{\partial V}V_2\\
&\quad + \rho\mu_T((\mu_I + pC_2)(\mu_C + \mu_V + \mu_i d) + (\mu_V + \mu_i d)\\
&\quad \cdot \mu_C) + \frac{\partial f(T_2,V_2)}{\partial T}V_2\left[k\gamma\frac{\partial f(T_2,V_2)}{\partial V}V_2\right.\\
&\quad \left. + (\mu_V + \mu_i d)(\mu_E + \gamma)(\mu_I + pC_2)\right],\\
a_5 &= -\left(\frac{\partial f(T_2,V_2)}{\partial T}V_2 + \mu_T\right)k\gamma\frac{\partial f(T_2,V_2)}{\partial V}V_2\mu_C\\
&\quad - k\gamma\mu_T(\mu_V + \mu_i d)\frac{\partial f(T_2,V_2)}{\partial V}V_2\\
&\quad + \frac{\partial f(T_2,V_2)}{\partial T}V_2\mu_C\left(\frac{\partial f(T_2,V_2)}{\partial V}V_2 + f(T_2,V_2)\right),\\
b_1 &= -\mu_C,\\
b_2 &= -\mu_C\left[\frac{\partial f(T_2,V_2)}{\partial T}V_2 + \mu_T + \mu_I + \mu_V + \mu_i d + \mu_E\right.\\
&\quad \left. + \rho + \gamma\right],\\
b_3 &= -\mu_C\left[\left(\frac{\partial f(T_2,V_2)}{\partial T}V_2 + \mu_T\right)\right.\\
&\quad \cdot (\mu_I + \mu_V + \mu_i d + \mu_E + \gamma) + \mu_I(\mu_V + \mu_i d)\\
&\quad \left. + (\mu_I + \mu_V + \mu_i d)(\mu_E + \rho + \gamma) + \rho\mu_T\right],\\
b_4 &= -\mu_C\left[\left(\frac{\partial f(T_2,V_2)}{\partial T}V_2 + \mu_T\right)\right.\\
&\quad \cdot (\mu_I(\mu_V + \mu_i d) + (\mu_E + \gamma)(\mu_I + \mu_V + \mu_i d))\\
&\quad - k\gamma\left(\frac{\partial f(T_2,V_2)}{\partial V}V_2 + f(T_2,V_2)\right)\\
&\quad \left. + \mu_T\rho(\mu_I + \mu_V + \mu_i d)\right],\\
b_5 &= -\mu_C\left[\left(\frac{\partial f(T_2,V_2)}{\partial T}V_2 + \mu_T\right)\mu_I(\mu_V + \mu_i d)\right.\\
&\quad \cdot (\mu_E + \gamma) - k\gamma\mu_T\left(\frac{\partial f(T_2,V_2)}{\partial V}V_2 + f(T_2,V_2)\right)\\
&\quad \left. + \rho\mu_T\mu_I(\mu_V + \mu_i d)\right].
\end{aligned} \tag{27}$$

For $\tau \neq 0$, we suppose that (26) has a purely imaginary root $\xi = i\omega$ with $\omega > 0$. Substituting $\xi = i\omega$ in (26) and separating the real and the imaginary parts, we get

$$\begin{aligned}w^5 - a_2w^3 + a_4w &= \left(b_1w^4 - b_3w^2 + b_5\right)\sin\omega\tau\\&\quad + \left(b_2w^3 - b_4w\right)\cos\omega\tau,\end{aligned}$$

$$a_1w^4 - a_3w^2 + a_5 = -\left(b_1w^4 - b_3w^2 + b_5\right)\cos\omega\tau + \left(b_2w^3 - b_4w\right)\sin\omega\tau. \tag{28}$$

Squaring and adding the two equations of (28), we have

$$\omega^{10} + c_1\omega^8 + c_2\omega^6 + c_3\omega^4 + c_4\omega^2 + c_5 = 0, \tag{29}$$

where

$$\begin{aligned} c_1 &= a_1^2 - 2a_2 - b_1^2, \\ c_2 &= a_2^2 + 2a_4 - 2a_1a_3 + 2b_1b_3 - b_2^2, \\ c_3 &= a_3^2 - 2a_2a_4 - b_3^2 + 2b_2b_4 + 2a_1a_5 - 2b_1b_5, \\ c_4 &= a_4^2 - b_4^2 - 2a_3a_5 + 2b_3b_5, \\ c_5 &= a_5^2 - b_5^2. \end{aligned} \tag{30}$$

Letting $z = \omega^2$ we obtain

$$h(z) = z^5 + c_1z^4 + c_2z^3 + c_3z^2 + c_4z + c_5 = 0. \tag{31}$$

Denote

$$\begin{aligned} p_1 &= -\frac{6}{25}c_1^2 + \frac{3}{5}c_2, \\ q_1 &= \frac{8}{125}c_1^3 + \frac{6}{25}c_1c_2 + \frac{2}{5}c_3, \\ r_1 &= -\frac{3}{625}c_1^4 + \frac{3}{125}c_1^2c_2 - \frac{2}{25}c_1c_3 + \frac{1}{5}c_4, \\ p_2 &= -\frac{1}{3}p_1^2 - 4r_1, \\ q_2 &= -\frac{2}{27}p_1^3 + \frac{8}{3}p_1r_2 - q_1^2, \\ \Delta_1 &= \frac{1}{27}p_2^3 + \frac{1}{4}q_2^2, \\ s_* &= \sqrt[3]{-\frac{q_2}{2} + \sqrt{\Delta_1}} + \sqrt[3]{-\frac{q_2}{2} - \sqrt{\Delta_1}} + \frac{1}{3}p_1, \\ \Delta_2 &= -s_* - p_1 + \frac{2q_1}{\sqrt{s_* - p_1}}, \\ \Delta_3 &= -s_* - p_1 - \frac{2q_1}{\sqrt{s_* - p_1}}, \\ \overline{z} &= \frac{q_1}{2\left(p_1 - s_*\right)} - \frac{1}{5}p. \end{aligned} \tag{32}$$

Suppose that (31) has positive roots z_k, $k = 1, 2, 3, 4, 5$, where $w_k = \sqrt{z_k}$. From (28), we have

$$\cos\omega_k\tau = \frac{\left(w^5 - a_2w^3 + a_4w\right)\left(b_2w^3 - b_4w\right) - \left(a_1w^4 - a_3w^2 + a_5\right)\left(b_1w^4 - b_3w^2 + b_5\right)}{\left(b_2w^3 - b_4w\right)^2 + \left(b_1w^4 - b_3w^2 + b_5\right)^2} = L\left(\omega_k\right). \tag{33}$$

Therefore

$$\tau_j^k = \frac{1}{\omega_k}\left[\arccos L\left(\omega_k\right) + 2j\pi\right], \quad k = 1, 2, 3, 4, 5, \quad j = 0, 1, 2, \ldots. \tag{34}$$

Then $\pm i\omega_k$ are a pair of purely imaginary roots of (26) with $\tau = \tau_j^k$.

Define

$$\tau_0 = \tau_{j_0}^{k_0} = \min_{1\le k\le 5, j\ge 1}\left\{\tau_j^k\right\}, \quad w_0 = w_{k_0}. \tag{35}$$

From Theorem 4 and by a similar argument as that in [21, 22], we have the following results.

Lemma 5. *Suppose that $R_1 > 1$ and (22) hold.*

(i) *If one of the following holds: (a) $c_5 < 0$; (b) $c_5 \ge 0$, $q_1 = 0$, $\Delta_0 \ge 0$, and $p_1 < 0$ or $r_1 \le 0$ and there exist $z^* \in \{z_1, z_2, z_3, z_4\}$ such that $z^* > 0$ and $h(z^*) \le 0$; (c) $c_5 \ge 0$, $q_1 \ne 0$, $s_* > p_1$, $\Delta_2 \ge 0$, or $\Delta_3 \ge 0$ and there exist $z^* \in \{z_1, z_2, z_3, z_4\}$ such that $z^* > 0$ and $h(z^*) \le 0$; (d) $c_5 \ge 0$, $q_1 \ne 0$, $s_* < p_1$, $q_1^2/4(p_1 - s^*)^2 + (1/2)s_* = 0$, $\overline{z} > 0$, and $h(\overline{z}) \le 0$, then all the roots of (26) have negative real parts when $\tau \in [0, \tau_0)$.*

(ii) *If all the conditions (a)–(d) of (i) are not satisfied, then all roots of (26) have negative real parts for all $\tau \ge 0$.*

We consider $\xi(\tau) = \xi(\tau) + i\omega(\tau)$ to be a root of (26) satisfying $\xi(\tau) = 0$ and $\omega(\tau) = \omega_0$. Differentiating the two sides of (26) with respect to τ and noticing that ξ is a function of τ, then

$$\left(\frac{d\xi}{d\tau}\right)^{-1} = -\frac{5\xi^4 + 4a_1\xi^3 + 3a_2\xi^2 + 2a_3\xi + a_4}{\xi\left(\xi^5 + a_1\xi^4 + a_2\xi^3 + a_3\xi^2 + a_4\xi + a_5\right)} + \frac{4b_1\xi^3 + 3b_2\xi^2 + 2b_3\xi^1 + b_4}{\xi\left(b_1\xi^4 + b_2\xi^3 + b_3\xi^2 + b_4\xi + b_5\right)} - \frac{\tau}{\xi}. \tag{36}$$

From (28) we obtain

$$\begin{aligned}
&\left[\frac{d\,\mathrm{Re}\,(\xi(\tau))}{d\tau}\right]^{-1}_{\tau=\tau_k^j} \\
&= -\frac{\left(5\omega_k^4 - 3a_2\omega_k^2 + a_4\right)\left(-\omega_k^6 + a_2\omega_k^4 - a_4\omega_k^2\right)}{\left(-\omega_k^6 + a_2\omega_k^4 - a_4\omega_k^2\right)^2 + \left(a_1\omega_k^5 - a_3\omega_k^3 + a_5\omega_k\right)^2} \\
&\quad + \frac{\left(4a_1\omega_k^3 - 2a_3\omega_k\right)\left(a_1\omega_k^5 - a_3\omega_k^3 + a_5\omega_k\right)}{\left(-\omega_k^6 + a_2\omega_k^4 - a_4\omega_k^2\right)^2 + \left(a_1\omega_k^5 - a_3\omega_k^3 + a_5\omega_k\right)^2} \\
&\quad + \frac{\left(-3b_2\omega_k^2 + b_4\right)\left(b_2\omega_k^4 - b_4\omega_k^2\right)}{\left(b_2\omega_k^4 - b_4\omega_k^2\right)^2 + \left(b_1\omega_k^5 - b_3\omega_k^3 + b_5\omega_k\right)^2} \\
&\quad + \frac{\left(-4b_1\omega_k^3 + 2b_3\omega_k\right)\left(b_1\omega_k^5 - b_3\omega_k^3 + b_5\omega_k\right)}{\left(b_2\omega_k^4 - b_4\omega_k^2\right)^2 + \left(b_1\omega_k^5 - b_3\omega_k^3 + b_5\omega_k\right)^2}.
\end{aligned} \tag{37}$$

By (26) we get

$$\begin{aligned}
&\left(\omega^5 - a_2\omega^3 + a_4\omega\right)^2 + \left(a_1\omega^4 - a_3\omega^2 + a_5\right)^2 \\
&\quad = \left(b_2\omega^3 - b_4\omega\right)^2 + \left(b_1\omega^4 - b_3\omega^2 + b_5\right).
\end{aligned} \tag{38}$$

Then

$$\begin{aligned}
&\left[\frac{d\,\mathrm{Re}\,(\xi(\tau))}{d\tau}\right]^{-1}_{\tau=\tau_k^j} \\
&\quad = \frac{5z_k^4 + 4c_1z_k^3 + 3c_2z_k^2 + 2c_3z_k + a_4}{\left(b_1\omega_k^4 - b_3\omega_k^2 + b_5\right)^2 + \left(b_2\omega_k^2 - b_4\right)^2} \\
&\quad = \frac{h'(z_k)}{\left(b_1\omega_k^4 - b_3\omega_k^2 + b_5\right)^2 + \left(b_2\omega_k^2 - b_4\right)^2}.
\end{aligned} \tag{39}$$

Therefore, it follows that

$$\begin{aligned}
\mathrm{sign}\left[\frac{d\,\mathrm{Re}\,(\xi(\tau))}{d\tau}\right]_{\tau=\tau_k^j} &= \mathrm{sign}\left[\frac{d\,\mathrm{Re}\,(\xi(\tau))}{d\tau}\right]^{-1}_{\tau=\tau_k^j} \\
&= \mathrm{sign}\left[h'(z_k)\right].
\end{aligned} \tag{40}$$

Since $z_k > 0$, then $\mathrm{Re}[d\xi_k(\tau)/d\tau]_{\tau=\tau_k^j}$ and $h'(z_k)$ have the same sign.

From the above analysis and the Hopf bifurcation theorem for functional differential equation [20], we have the following result.

Theorem 6. *Suppose that $R_1 > 1$ and (22) hold.*

(i) *If the conditions (a)–(d) of Lemma 5 are all not satisfied, then the chronic infection equilibrium Q_2 is locally asymptotically stable for all time delay $\tau \geq 0$.*

(ii) *If one of the conditions (a)–(d) of Lemma 5 is satisfied, then the chronic infection equilibrium Q_2 is locally asymptotically stable for $\tau \in [0, \tau_0)$.*

(iii) *If the condition of (ii) is satisfied and $h'(z_k) \neq 0$, then system (2) undergoes a Hopf bifurcation at Q_2 when $\tau = \tau_0$.*

4. Conclusion

In this paper, we have studied an HIV infection model including infected cells in eclipse stage and delay in the activation of CTL immune response. The model is governed by reaction diffusion equations and the transmission process is modeled by a specific nonlinear incidence rate that includes many types of special incidence functions as special cases. First, we discussed the nonnegativity and boundedness of solutions and the existence of equilibria of system (2). The global stability of the infection-free equilibrium Q_0 has been given by the Lyapunov's direct method and LaSalle's invariance principal when the basic reproductive number $R_0 \leq 1$, which means that the infection is cleared and the virus dies out. We also obtained the global asymptotic stability of the immune-free infection equilibrium when $R_0 > 1$ and condition (14) is satisfied, which means that the infection will become chronic without persistent CTL immune response. If $R_0 > 1$ and $R_1 > 1$, there exists a chronic infection equilibrium with CTL immune response Q_2. We have shown that the chronic infection equilibrium Q_2 is locally asymptotically stable when the delay is sufficiently small, but with the increase of the time delay, the stability of Q_2 may destabilize and lead to Hopf bifurcation.

The results of this paper reflect the fact that the immunological delay in (2) do not affect the positivity and boundedness of solutions and the global stability of the infection-free equilibrium and immune-free equilibrium. For the chronic infection equilibrium, in the absence of delay, the globally stability is obtained, a small delay does not affect the local stability, and Hopf bifurcation may occur when the time delay is large enough.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

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