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Dynamical behaviors of an HTLV-I infection model with intracellular delay and immune activation delay

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Abstract

This paper investigates the dynamics of an HTLV-I infection model with intracellular delay and immune activation delay. The primary objective of the study is to consider the effect of the time delay on the stability of the infected equilibrium. Two sharp threshold parameters $\Re_0$ and $\Re_1$ are identified as the basic reproduction number for viral infection and for CTLs response, respectively, which determine the long time behaviors of the viral infection. In particular, our mathematical analysis reveals that a Hopf bifurcation occurs when immune activation delay passes through a critical value. Using the normal form theory and center manifold arguments, the explicit formulae which determine the stability, the direction, and the period of bifurcating periodic solutions are derived. Numerical simulations are given to support the theoretical results.

MSC: 34C05; 92D25

Keywords: HTLV-I; intracellular delay; immune activation delay; stability; Hopf bifurcation

1 Introduction

Human T-cell leukaemia/lymphoma virus type I (HTLV-I) is a retrovirus infecting primarily $CD4^+$ T cells, and the transmission occurs remarkably through direct cell-to-cell contact. It is reported that HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP) patients harbor higher proviral loads in peripheral blood lymphocytes than asymptomatic carriers [1]. Also, a remarkable amount of circulating HTLV-I specific $CD8^+$ cytotoxic T lymphocytes (CTLs) circulates in the peripheral blood of HAM/TSP patients present. It is convincing that the persistent cytotoxicity of the CTLs is the reason for the development of a progressive neurologic disease, *i.e.*, HAM/TSP [2, 3], and several HTLV-I-associated diseases.

Understanding the role played by the CTLs in controlling the HTLV-I infection is vital to identifying risk factors for the development of HAM/TSP. Several mathematical models have investigated the dynamics of the interaction in vivo among HTLV-I, the $CD4^+$ target cells, and the CTLs immune response in order to explain the pathogenesis of HTLV-I-associated diseases [4–10] and used as a tool to study the role of immune response in the viral dynamics. It is advocated that time delays cannot be ignored in models for im-

mune response [9]. Recently, HTLV-I infection models given by systems of delay differential equations (DDEs) have been studied by several authors, who analyzed the effect of delay in the local and global dynamics of the model, bifurcations, and several rich dynamical behaviors (see, *e.g.*, [1, 10–15] and the references cited therein).

Denote by $x(t)$, $y(t)$, $z(t)$ the concentrations of uninfected, infected, and HTLV-I-specific $CD8^+$ CTLs at time t, respectively. In [9], Wang *et al.* incorporated a time delay into the immune response, $z'(t) = cy(t-\omega) - bz(t)$, where the CTLs response is activated at a rate proportional to the number of infected cells at a previous time, $cy(t-\omega)$, and it also decays exponentially at a rate proportional to its current strength bz. Numerical results reveal that stability switches, periodic solutions, and chaotic solutions can be observed. Time delay is commonly incorporated to account for a series of immunological events leading to the CTLs response, and it may arise through a number of different processes. In [15, 16], the authors explored the effect of HTLV-I interaction through a system of delay differential equations (DDEs). The delayed CTLs immune response takes the following form: $z'(t) = cy(t-\omega)z(t-\omega) - bz(t)$, where the CTLs response activated at time t is proportional to the product of the amount of CTLs at $t-\omega$ and that of infected cells at $t-\omega$. It is shown through numerical simulations that delayed CTLs response can lead to sustained oscillations through a Hopf bifurcation.

Recently, HTLV-I model with time delays in the CTL response leading to the coexistence of multiple stable periodic solutions has been studied in [17]. These multiple stable periodic solutions differ in amplitude and period and have their own basins of attraction. In [18], by taking the immune delay as a bifurcation parameter, Xu and Wei theoretically proved the global existence of multiple periodic solutions in HTLV-I infection model with CTL immune response.

Because the principle of CTLs activation by infected cells is complex and is not known clearly, in the line of work of Huang *et al.* [19], we shall investigate the case where CTLs are stimulated at time t proportional to the product of the amount of CTLs at t and that of infected cells at $t-\omega$, which can be described in the following way:

$$z'(t) = cy(t-\omega)z(t) - bz(t). \tag{1.1}$$

Biologically, (1.1) represents that the immune system needs some time to develop a suitable response after the recognition of non-self cells.

In present paper, to further account for the latent period for the cell to cell infection, we assume that virus transmission occurs after the virus entry with a constant time lag $\tau > 0$. Here, the intracellular delay τ describes the latent period between the time when target cells are infected and the time when infected cells start producing virions to integration, *i.e.*, $CD4^+$ T cells infected at time t will be activated at time $t+\tau$. The number of actively infected target cells at time t is given by a delayed mass-action (bilinear incidence) term $\beta e^{-d\tau}x(t-\tau)y(t-\tau)$, where $e^{-d\tau}$ describes the probability of infected target cells surviving the period of intracellular delay from $t-\tau$ to t. Constant d denotes the death rate for infected cells (but not yet virus producing cells).

Denote by λ the recruitment rate of healthy $CD4^+$ T cells. CTL-driven elimination of infected $CD4^+$ T cells is assumed to be of the form γyz, where constant γ accounts for the strength of CTLs elimination. Denote by d_1, d_2, d_3 the turnover rates of uninfected, infected $CD4^+$ T, and $CD8^+$ CTLs, respectively. The preceding assumptions lead to the

following HTLV-I infection model with delayed cell to cell infection and CTLs response:

$$\begin{cases} x'(t) = \lambda - d_1 x(t) - \beta x(t) y(t), \\ y'(t) = \beta e^{-d\tau} x(t-\tau) y(t-\tau) - d_2 y(t) - \gamma y(t) z(t), \\ z'(t) = \mu y(t-\omega) z(t) - d_3 z(t). \end{cases} \tag{1.2}$$

All parameters in system (1.2) are assumed to be positive. The initial conditions of system (1.2) at $t = 0$ are given as

$$\varphi = (\varphi_1, \varphi_2, \varphi_3) \in \mathcal{C}^+, \qquad \varphi(0) > 0, \tag{1.3}$$

where $\mathcal{C}^+$ denotes the Banach space of continuous real-valued functions $\mathcal{C} = \mathcal{C}([-\sigma, 0], \mathbb{R}^3_+)$ with the sup-norm

$$\|\varphi\| = \max\left\{ \sup_{-\sigma \le \theta \le 0} |\varphi_1(\theta)|, \sup_{-\sigma \le \theta \le 0} |\varphi_2(\theta)|, \sup_{-\sigma \le \theta \le 0} |\varphi_3(\theta)| \right\} \tag{1.4}$$

for $\sigma = \max\{\tau, \omega\}$.

The aim of the present paper is to carry out a complete mathematical analysis of dynamic behaviors of system (1.2) and find out the different influences between intracellular delay and immune activation delay. The paper is organized as follows. In Section 2, we present preliminary results of system (1.2), including positivity and boundedness of solutions, the existence of equilibria, and the definition of the basic reproduction numbers for viral infection ($\Re_0$) and for CTLs response ($\Re_1$). Section 3 is devoted to the global dynamics of system (1.2) when $\Re_1 \le 1$. Using the two key threshold parameters $\Re_0$ and $\Re_1$, we establish the global dynamics of system (1.2) by the techniques of Lyapunov functionals. When $\Re_1 > 1$, Section 4 first gives the global dynamics of system (1.2) in the case where τ is present and ω is absent. The results indicate that the intracellular delay does not affect the stability of the system. Thus, we can neglect the intracellular delay τ in system (1.2). Therefore, we identify parameter regimes in which immune activation delay ω can destabilize the HAM/TSP equilibrium and lead to a Hopf bifurcation. Using the normal form theory and center manifold argument, the explicit formulae which determine the stability and direction of bifurcated periodic solutions are derived. Numerical simulations are carried out to explain the mathematical conclusions in Section 5. The last section ends with a summary and discussion.

2 Preliminaries

Proposition 2.1 *Under initial conditions in* (1.3), *all solutions of system* (1.2) *are positive and ultimately bounded in* $\mathcal{C}$.

Proof By the existence and uniqueness theorem (Theorem 2.1 of Kuang [20]) of DDEs, there exists $t_0 > 0$ such that there exists a solution $(x(t), y(t), z(t))$ of system (1.2) for $0 < t < t_0$. We assume that there exists a solution of system (1.2) for $0 < t < t_1$ for positive t_1, where the existence is assured by the theorem stated above.

First, we prove that $x(t)$ is positive for all $t \ge 0$. Assuming the contrary and letting $t_1 > 0$ be the first time such that $x(t_1) = 0$, we have $x'(t_1) = \lambda > 0$ by the first equation of system (1.2). Hence $x(t) < 0$ for $t \in (t_1 - \varepsilon, t_1)$, where $\varepsilon > 0$ is a sufficiently small constant. This contradicts $x(t) > 0$ for $t \in [0, t_1)$. It follows that $x(t) > 0$ for $t > 0$ as long as $x(t)$ exists.

By the second equation of system (1.2), we have

$$y(t) = y(0)e^{-d_2 t-\gamma \int_0^t z(\theta)\,d\theta} + \int_0^t \beta e^{-d\tau} x(\theta-\tau)y(\theta-\tau)e^{d_2(\theta-t)}e^{-\gamma \int_\theta^t z(\sigma)\,d\sigma}\,d\theta. \tag{2.1}$$

It follows that $y(t) > 0$ for $t > 0$.

From the third equation of system (1.2), we have

$$z(t) = z(0)e^{\int_0^t (\mu y(\theta-\omega)-d_3)\,d\theta}. \tag{2.2}$$

This shows that $z(t) \geq 0$ for $0 \leq t < t_1$ and that $z(t)$ is bounded as t tends to t_1, because $\theta - \omega \leq t_1 - \omega$. If $z(0) > 0$, then $z(t) > 0$ for $0 \leq t < t_1$ by (2.2).

Next we show that positive solutions of (1.2) are ultimately uniformly bounded for $t \geq 0$. Put

$$K(t) = e^{-d\tau}x(t) + y(t+\tau).$$

Adding all the equations of (1.2) we get

$$\begin{aligned} K'(t) &= \lambda e^{-d\tau} - d_1 e^{-d\tau}x(t) - d_2 y(t+\tau) - \gamma y(t+\tau)z(t+\tau) \\ &\leq \lambda e^{-d\tau} - \ell K(t), \end{aligned} \tag{2.3}$$

where $\ell = \min\{d_1, d_2\}$. There exist $M_2 > 0$ and $T_1 > 0$ such that $y(t) \leq M_2$ for each $t \geq T_1$. For example, we can take $M_2 = \frac{\lambda e^{-d\tau}}{\ell}$. If $t > T_1 + \tau + \omega$, we have

$$\begin{aligned} z(t) &= z(t-\omega)\exp\left(\mu \int_{t-\omega}^t y(\theta-\omega)\,d\theta - b\omega\right) \\ &\leq e^{\mu M_2 \omega} z(t-\omega). \end{aligned} \tag{2.4}$$

We put

$$G(t) = e^{-d\tau}x(t) + y(t+\tau) + \frac{\gamma}{\mu}e^{-\mu M_2 \omega}z(t+\tau+\omega).$$

Adding all the equations of (1.2) we get

$$\begin{aligned} G'(t) &= \lambda e^{-d\tau} - d_1 e^{-d\tau}x(t) - d_2 y(t+\tau) - \gamma y(t+\tau)z(t+\tau) \\ &\quad + \frac{\gamma}{\mu}e^{-\mu M_2\omega}\left[\mu y(t+\tau)z(t+\tau+\omega) - d_3 z(t+\tau+\omega)\right] \\ &\leq \lambda e^{-d\tau} - dG(t), \end{aligned} \tag{2.5}$$

where $d = \min\{d_1, d_2, d_3\}$. This shows that there exists T with $T > T_1 + \tau + \omega$ and $M_1 > 0$ such that $G(t) \leq M_1$ for each $t \geq T$. Each solution is contained in the bounded domain $\Gamma = \{(x, y, z) \in \mathbb{R}^3 \mid 0 \leq x \leq M_1, 0 \leq y \leq M_1, 0 \leq z \leq M_1\}$ for sufficiently large t, which does not depend on the initial conditions. □

System (1.2) always has an infection-free equilibrium $E_0 = (x_0, 0, 0)$, where $x_0 = \lambda/d_1$, which means that the infected cells are cleared. The basic reproductive number of the viruses for system (4.1) is given by

$$\Re_0 = \frac{\lambda\beta e^{-d\tau}}{d_1 d_2}. \tag{2.6}$$

This number describes the average number of newly generated infected cells from one infected cell at the beginning of the infection process. When $\Re_0 > 1$, in addition to E_0, the system can have two chronic-infection equilibria $E_1 = (x_1, y_1, 0)$ and $E_2 = (x_2, y_2, z_2)$ in Γ, where

$$x_1 = \frac{d_2 e^{d\tau}}{\beta}, \qquad y_1 = \frac{d_1}{\beta}(\Re_0 - 1).$$

At equilibrium E_1, the HTLV-I infection is persistent with a constant proviral load $y_1 > 0$, whereas the CTLs response is absent, which means that there is the risk for developing HAM/TSP. This corresponds to the situation of an asymptotic carrier.

$$x_2 = \frac{\lambda\mu}{\mu d_1 + \beta d_3} = \frac{d_2\Re_1 e^{d\tau}}{\beta}, \qquad y_2 = \frac{d_3}{\mu}, \qquad z_2 = \frac{d_1 d_2\mu + \beta d_2 d_3}{\gamma(\mu d_1 + \beta d_3)}(\Re_1 - 1),$$

where

$$\Re_1 = \frac{\lambda\beta\mu e^{-d\tau}}{d_1 d_2\mu + \beta d_2 d_3}. \tag{2.7}$$

Therefore, E_2 exists in the interior of Γ if and only if $\Re_1 > 1$. At equilibrium E_2, both the proviral load and CTLs response persist at a constant level. This corresponds to the situation of a HAM/TSP patient. By aforementioned analysis, we obtain that the existence of equilibria of (4.1) depends only on two threshold parameters ($\Re_0$ and $\Re_1$), which are called the basic reproduction numbers for viral infection and for CTLs response, respectively.

Note that

$$\Re_1 = \frac{\lambda\mu\beta e^{-d\tau}}{d_1 d_2\mu + \beta d_2 d_3} = \frac{\beta}{d_1\mu + \beta d_3}(\mu y_1 - d_3) + 1,$$

which implies that $\Re_1 < 1$ is equivalent to $y_1 < \frac{d_3}{\mu}$. On the other hand, the term $\mu y_1/d_3$ can be seen as the immune reproductive number, which expresses the average number of activated CTLs generated from one CTLs during its life time $1/d_3$ through the stimulation of the infected cells y_1. It is reasonable that immune is activated in the case where $\Re_1 > 1$.

We summarize the above analysis in the following result.

Proposition 2.2 *If $\Re_0 \le 1$, $E_0 = (\lambda/d_1, 0, 0)$ is the only equilibrium in Γ. If $\Re_1 \le 1 < \Re_0$, the carrier equilibrium $E_1 = (x_1, y_1, 0)$ appears and is the only chronic-infection equilibrium in Γ. If $\Re_1 > 1$, both the carrier equilibrium E_1 and the HAM/TSP equilibrium $E_2 = (x_2, y_2, z_2)$ appear.*

3 Dynamics of system (1.2) for $\Re_1 \leq 1$

In what follows, we investigate the dynamics of system (1.2) when $\Re_1 \leq 1$. We begin by using the inequality $g(x) = x - 1 - \ln x \geq g(1) = 0$ with equality holding if and only if $x = 1$, which can simplify many of the expressions in the following calculations. Note that $g : \mathbb{R}^+ \to \mathbb{R}^+$ has strict global minimum $g(1) = 0$.

We have the following theorem.

Theorem 3.1 *Let $\Re_0$ and $\Re_1$ be as defined in* (2.6) *and* (2.7). *Then, for $\tau > 0$ and $\omega > 0$, the following statements hold for system* (1.2).

(i) *If $\Re_0 \leq 1$, then E_0 is globally asymptotically stable.*

(ii) *If $\Re_1 \leq 1 < \Re_0$, then E_1 is globally asymptotically stable.*

Proof (i) Define a Lyapunov functional

$$W_1 = e^{-d\tau} x_0 g\left(\frac{x(t)}{x_0}\right) + y(t) + \frac{\gamma}{\mu} z(t) + \beta e^{-d\tau} \int_0^\tau x(t-\theta) y(t-\theta)\, d\theta + \gamma \int_0^\omega y(t-\xi) z(t)\, d\xi.$$

Using $\lambda = d_1 x_0$ and calculating the time derivative of W_1 along the solutions of (1.2), we obtain

$$\begin{aligned} W_1'\big|_{(1.2)} &= e^{-d\tau}\left(1 - \frac{x_0}{x(t)}\right) x'(t) + y'(t) + \frac{\gamma}{\mu} z'(t) + \beta e^{-d\tau}\big[x(t)y(t) - x(t-\tau)y(t-\tau)\big] \\ &\quad + \gamma\big(y(t)z(t) - y(t-\omega)z(t)\big) \\ &= -\frac{d}{x} e^{-d\tau}\big(x(t) - x_0\big)^2 + \left(\beta e^{-d\tau}\frac{\lambda}{d_1} - d_2\right) y(t) - \frac{\gamma d_3}{\mu} z(t) \\ &= -\frac{d}{x} e^{-d\tau}\big(x(t) - x_0\big)^2 + d_2(\Re_0 - 1) y(t) - \frac{\gamma d_3}{\mu} z(t). \end{aligned}$$

Therefore, $\Re_0 \leq 1$ ensures that $W_1'|_{(1.2)} \leq 0$ for all $x \geq 0$, $y \geq 0$, $z(t) \geq 0$, and $W_1'|_{(1.2)} = 0$ if and only if $x(t) = x_0$, $y(t) = 0$, $z(t) = 0$ for $\Re_0 < 1$ or $x(t) = x_0$, $z(t) = 0$ for $\Re_0 = 1$. For the both cases, it is easy to show that the largest invariant set in $\{(x, y, \nu) \mid W_1'|_{(1.2)} = 0\}$ is $\{E_0\}$. LaSalle's invariance principle (Theorem 2.5.3 of Kuang [20]) shows that E_0 is globally asymptotically stable when $\Re_0 \leq 1$.

(ii) Define a Lyapunov functional

$$\begin{aligned} W_2 &= e^{-d\tau} x_1 g\left(\frac{x(t)}{x_1}\right) + y_1 g\left(\frac{y(t)}{y_1}\right) + \frac{\gamma}{\mu} z(t) \\ &\quad + d_2 y_1 \int_0^\tau g\left(\frac{x(t-\theta)y(t-\theta)}{x_1 y_1}\right) d\theta + \gamma \int_0^\omega y(t-\xi) z(t)\, d\xi. \end{aligned}$$

Calculating the time derivative of W_2 along the solution of (1.2), we obtain

$$\begin{aligned} W_2'\big|_{(1.2)} &= e^{-d\tau}\left(1 - \frac{x_1}{x(t)}\right) x'(t) + \left(1 - \frac{y_1}{y(t)}\right) y'(t) \\ &\quad + \frac{\gamma}{\mu} z'(t) + \beta e^{-d\tau}\big[x(t)y(t) - x(t-\tau)y(t-\tau)\big] \\ &\quad + d_2 y_1 \ln\frac{x(t-\tau)y(t-\tau)}{x(t)y(t)} + \gamma\big(y(t)z(t) - y(t-\omega)z(t)\big) \end{aligned}$$

$$= -\frac{d}{x}e^{-d\tau}\big(x(t)-x_1\big)^2 + d_2y_1\left(1-\frac{x_1}{x(t)}+\ln\frac{x_1}{x(t)}\right)$$
$$+ d_2y_1\left(1-\frac{x(t-\tau)y(t-\tau)}{x_1y(t)}+\ln\frac{x(t-\tau)y(t-\tau)}{x_1y(t)}\right)+\gamma z(t)\left(y_1-\frac{d_3}{\mu}\right).$$

Here we used the facts that $\lambda = d_1x_1 + \beta x_1y_1$ and $d_2 = \beta e^{-d\tau}x_1$. Therefore, $\Re_1 \le 1$ ensures that $W_2'|_{(1.2)} \le 0$ for all $x \ge 0, y \ge 0, z(t) \ge 0$, and $W_2'|_{(1.2)} = 0$ if and only if $x(t) = x_1, y(t) = y_1$, $z(t) = 0$ for $\Re_1 < 1$ or $x(t) = x_1$, $y(t) = y_1$ for $\Re_1 = 1$. For the both cases, it is easy to show that the largest invariant set in $\{(x,y,z) \mid W_2'|_{(1.2)} = 0\}$ is $\{E_1\}$. LaSalle's invariance principle (Theorem 2.5.3 of Kuang [20]) shows that E_1 is globally asymptotically stable when $\Re_1 \le 1 < \Re_0$. □

Remark 3.1 Theorem 3.1 gives a complete picture of global dynamics of system (1.2) for the case where $\Re_1 \le 1$. It is shown that $\Re_0$ and $\Re_1$ as two sharp threshold parameters together determine the outcomes of the HTLV-I infection: when $\Re_0 \le 1$, then the HTLV-I viruses are cleared; when $\Re_1 \le 1 < \Re_0$, then HTLV-I infection becomes chronic with no persistent CTLs immune response. The patient remains as an asymptotic carrier.

4 Dynamics of system (1.2) when $\Re_1 > 1$

From Proposition 2.2, when $\Re_1 > 1$, the HAM/TSP equilibrium $E_2 = (x_2, y_2, z_2)$ appears and both HTLV-I infection and CTLs immune response will persist. The patient has a high risk to developing HAM/TSP. In this section, we will focus on the stability of the HAM/TSP equilibrium E_2.

We first consider the infection process without immune activation delay ω but with intracellular delay τ. In this case, system (1.2) will reduce to the following system of delay differential equations:

$$\begin{cases} x'(t) = \lambda - d_1x(t) - \beta x(t)y(t), \\ y'(t) = \beta e^{-d\tau}x(t-\tau)y(t-\tau) - d_2y(t) - \gamma y(t)z(t), \\ z'(t) = \mu y(t)z(t) - d_3z(t), \end{cases} \tag{4.1}$$

associated with initial conditions

$$\varphi = (\varphi_1, \varphi_2, \varphi_3) \in \mathcal{C}^+, \qquad \varphi(0) > 0. \tag{4.2}$$

Based on Theorem 3.1, it is easy to see that the infection-free equilibrium E_0 and immune-free equilibrium E_1 of (4.1) (remains the same as the ones in (1.2)) can be proved to be globally asymptotically stable by using the Lyapunov functionals W_1 and W_2 when $\omega = 0$. Furthermore, using similar arguments to Theorem 3.1, combining the equations $\lambda = d_1x_2 + \beta x_2y_2$, $\beta e^{-d\tau}x_2y_2 = d_2y_2 + \gamma y_2z_2$ and $\mu y_2 = d_3$, we can prove that HAM/TSP equilibrium E_2 of (4.1) is globally asymptotically stable by using a Lyapunov functional

$$W_3 = e^{-d\tau}x_2g\left(\frac{x(t)}{x_2}\right) + y_2g\left(\frac{y(t)}{y_2}\right) + \frac{\gamma}{\mu}z_2g\left(\frac{z(t)}{z_2}\right)$$
$$+ (d_2y_2 + \gamma y_2z_2)\int_0^\tau g\left(\frac{x(t-\theta)y(t-\theta)}{x_2y_2}\right)d\theta.$$

Hence we arrive at the following theorem on the global dynamics of (4.1) with (4.2).

Theorem 4.1 *Let* $\Re_0$ *and* $\Re_1$ *be as defined in* (2.6) *and* (2.7), *the following statements hold for system* (4.1).

(i) *If* $\Re_0 \leq 1$, *then the infection-free equilibrium* $E_0(x_0, 0, 0)$ *is globally asymptotically stable*;

(ii) *If* $\Re_1 \leq 1 < \Re_0$, *then the immune-free equilibrium* $E_1(x_1, y_1, 0)$ *is globally asymptotically stable*;

(iii) *If* $\Re_1 > 1$, *then the HAM/TSP equilibrium* $E_2(x_2, y_2, z_2)$ *is globally asymptotically stable*.

Remark 4.1 As to the main results in Song *et al.* [21], Theorem 4.1 gives a confirmative answer that there are no sustained oscillations to occur when the immune response is not incorporated with time delay.

From Theorem 4.1 we know that the intracellular delay τ does not affect the stability of the HAM/TSP equilibrium E_2 besides the numeric values of E_2 and the basic reproductive numbers. In order to discuss the effects of immune activation delay ω, for mathematical tractability, we next just consider the case $\tau = 0$ and $\omega > 0$ without losing the major biological feature. In this case, system (1.2) will reduce to the following system of delay differential equations:

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

Now the basic reproductive number and the immune reproductive number of (4.3) should be written by

$$\Re_0^* = \frac{\lambda\beta}{d_1 d_2}, \quad \text{and} \quad \Re_1^* = \frac{\lambda\beta\mu}{d_1 d_2 \mu + \beta d_2 d_3},$$

and E^* is denoted as the interior equilibrium for DDEs models (4.3). In the following, we shall show that the time delay ω can destabilize E^* and leads to Hopf bifurcations. Concretely, using the normal form theory and center manifold argument, we will give the explicit formulae which determine the stability and direction of bifurcated periodic solutions.

Translating E^* to the origin through a change of variables $x_2(t) = x(t) - x^*$, $y_2(t) = y(t) - y^*$, $z_2(t) = z(t) - z^*$, system (4.3) becomes

$$\begin{cases} x_2'(t) = -(\beta y^* + d_1) x_2(t) - \beta x^* y_2(t) - \beta x_2(t) y_2(t), \\ y_2'(t) = \beta x_2(t) y_2(t) + \beta y^* x_2(t) - \gamma y^* z_2(t) - \gamma y_2(t) z_2(t), \\ z_2'(t) = \mu y_2(t-\omega) z_2(t) + \mu z^* y_2(t-\omega). \end{cases} \tag{4.4}$$

The characteristic equation associated with the linearization of system (4.3) at $(0, 0, 0)$ is

$$\det \begin{pmatrix} \xi + \beta y^* + d_1 & \beta x^* & 0 \\ -\beta y^* & \xi & \gamma y^* \\ 0 & -\mu z^* e^{-\xi\omega} & \xi \end{pmatrix} = 0.$$

We obtain

$$\xi^3 + a_1\xi^2 + b_1\xi + (c_1\xi + c_0)e^{-\xi\omega} = 0, \tag{4.5}$$

where

$$a_1 = \beta y^* + d_1, \qquad b_1 = \beta^2 x^* y^*, \qquad c_0 = \left(\beta y^* + d_1\right)\gamma d_3 z^*, \qquad c_1 = \gamma d_3 z^*.$$

When $\omega = 0$, the characteristic equation is calculated as follows:

$$\xi^3 + a_1\xi^2 + (b_1 + c_1)\xi + c_0 = 0. \tag{4.6}$$

By the Routh-Hurwitz criterion we know that

$$\begin{aligned} &a_1 > 0, \qquad c_0 > 0, \\ &a_1(b_1 + c_1) - c_0 = \left(\beta y^* + d_1\right)\left(\beta^2 x^* y^* + \gamma d_3 z^*\right) - \left(\beta y^* + d_1\right)\gamma d_3 z^* \\ &\qquad\qquad = \beta^3 x^* \left(y^*\right)^2 + \beta^2 d_1 x^* y^* > 0, \end{aligned}$$

then all roots of (4.6) have negative real parts.

Next, we will use the delay $\omega > 0$ as a bifurcation parameter and investigate stability changes at the HAM/TSP equilibrium E^*. We will show that a Hopf bifurcation occurs for an open set of parameter values. This rigorously establishes that periodic oscillations exist in system (4.3).

Obviously, $\xi = 0$ is not a root of (4.5) and $\xi = ip$ is a root of (4.5) if and only if

$$-p^3 i - a_1 p^2 + b_1 p i + (i c_1 p + c_0)(\cos p\omega - i \sin p\omega) = 0.$$

Separating the real and imaginary parts gives

$$\begin{cases} -p^3 + b_1 p = c_0 \sin p\omega - c_1 p \cos p\omega, \\ a_1 p^2 = c_0 \cos p\omega + c_1 p \sin p\omega. \end{cases} \tag{4.7}$$

Squaring and adding both equations of (4.7) lead to

$$F(p) = p^6 + \left(a_1^2 - 2b_1\right)p^4 + \left(b_1^2 - c_1^2\right)p^2 - c_0^2 = 0. \tag{4.8}$$

Let $u = p^2$, then it follows that

$$G(u) = u^3 + \left(a_1^2 - 2b_1\right)u^2 + \left(b_1^2 - c_1^2\right)u - c_0^2 = 0 \tag{4.9}$$

has a positive root $u = p^2$ since ip is a purely imaginary root of (4.5). Note that

$$G'(u) = 3u^2 + 2\left(a_1^2 - 2b_1\right)u + \left(b_1^2 - c_1^2\right).$$

Let

$$\Delta = \left(a_1^2 - 2b_1\right)^2 - 3\left(b_1^2 - c_1^2\right). \tag{4.10}$$

Then

(1) If $\Delta \le 0$, then $G'(u) \ge 0$, and thus $G(u)$ is monotonically increasing. Therefore, by $-c_0^2 = G(0) < 0$ and $\lim_{u\to\infty} G(u) = \infty$, we know that (4.9) has at least one positive root, and characteristic roots can cross the imaginary axis.

(2) If $\Delta > 0$, then the graph of $G(u)$ has critical points

$$u^* = \frac{-(a_1^2 - 2b_1) + \sqrt{\Delta}}{3}, \qquad u^{**} = \frac{-(a_1^2 - 2b_1) - \sqrt{\Delta}}{3}.$$

Clearly, $G''(u^*) = 2\sqrt{\Delta} > 0$ and $G''(u^{**}) = -2\sqrt{\Delta} < 0$, it follows that u^* and u^{**} are the local minimum and the local maximum of $G(u)$, respectively.

If $u^* > 0$ and $G(u^*) < 0$, then $G(u) = 0$ has positive roots. Without loss of generality, let u_k, $1 \le k \le 3$, be the three positive roots of $G(u) = 0$, respectively. Then $F(p) = 0$ has three positive roots $p_k = \sqrt{u_k}$, $1 \le k \le 3$. Solving (4.7) for ω yields

$$\cos p_k\omega = \frac{c_0a_1p_k^2 + c_1p_k^4 - b_1c_1p_k^2}{c_0^2 + c_1^2p_k^2}. \tag{4.11}$$

Denote

$$\omega_k^{(j)} = \frac{1}{p_k}\left[\arccos\frac{c_0a_1p_k^2 + c_1p_k^4 - b_1c_1p_k^2}{c_0^2 + c_1^2p_k^2} + 2j\pi\right], \tag{4.12}$$

where $1 \le k \le 3$, $j = 0, 1, 2\ldots$. Then $\pm ip_k$ is a pair of purely imaginary roots of (4.5) with $\omega = \omega_k^{(j)}$.

Define

$$\begin{aligned} &\omega_0 = \omega_k = \min_{1\le i\le 3}\{\omega_i \mid u_i \text{ is a positive solution of } G(u) = 0\},\\ &p_0 = p_k. \end{aligned} \tag{4.13}$$

Then ω_0 is the first value of ω when a pair of characteristic roots cross the imaginary axis at $\pm ip_0$. We thus obtain the following result.

Theorem 4.2 *If $\Delta > 0$, $u^* = \frac{-(a_1^2-2b_1)+\sqrt{\Delta}}{3} > 0$ and $G(u^*) < 0$, then there exist $\omega_0 > 0$ and p_0 as in* (4.13) *such that the HAM/TSP equilibrium E^* is asymptotically stable for $\omega \in [0, \omega_0)$. Furthermore, if $G'(p_0^2) \ne 0$, then system* (4.3) *undergoes a Hopf bifurcation at the HAM/TSP equilibrium E^* when $\omega = \omega_0$.*

Proof It remains to show that the transversality condition for the Hopf bifurcation holds at $\omega = \omega_0$. Differentiating (4.6) with respect to ω gives

$$\left[\xi'(\omega)\right]^{-1} = \frac{[3\xi^2 + 2a_1\xi + b_1]e^{\xi\omega}}{\xi(c_1\xi + c_0)} + \frac{c_1}{\xi(c_1\xi + c_0)} - \frac{\omega}{\xi}. \tag{4.14}$$

Using (4.5) we obtain

$$\begin{aligned} \left[\left(\operatorname{Re}\xi(\omega)\right)'\right]^{-1}_{\omega=\omega_0} &= \operatorname{Re}\left[\frac{[3\xi^2 + 2a_1\xi + b_1]e^{\xi\omega}}{\xi(c_1\xi + c_0)}\right]_{\omega=\omega_0} + \operatorname{Re}\left[\frac{c_1}{\xi(c_1\xi + c_0)}\right]_{\omega=\omega_0}\\ &= \frac{1}{p_0^2(c_1^2p_0^2 + c_0^2)}\left[\left(b_1 - 3p_0^2\right)p_0(c_0\sin p_0\omega_0 - c_1p_0\cos p_0\omega_0)\right. \end{aligned}$$

$$
\begin{aligned}
&+ 2a_1p_0^2(c_0\cos p_0\omega_0 + c_1p_0\sin p_0\omega_0) - c_1^2p_0^2\big] \\
&= \frac{3p_0^6 + 2(a_1^2 - 2b_1)p_0^4 + (b_1^2 - c_1^2)p_0^2}{p_0^4c_1^2 + p_0^2c_0^2} \\
&= \frac{G'(p_0^2)}{c_1^2p_0^2 + c_0^2}. \qquad (4.15)
\end{aligned}
$$

Therefore, $\operatorname{sign}[(\operatorname{Re}\xi(\omega))']_{\omega=\omega_0} = \operatorname{sign} G'(p_0^2)$. Thus, if $G'(p_0^2) \neq 0$, the transversality condition holds and a Hopf bifurcation occurs at $\omega = \omega_0$. This completes the proof. □

We have identified parameter regimes in which delay ω can destabilize the HAM/TSP equilibrium and lead to a Hopf bifurcation. This shows that when $\omega > \omega_0$ and is close to ω_0, periodic solutions exist. As a consequence, when HAM/TSP develops, the $CD4^+$ count, proviral load, and the HTLV-I specific CTLs frequency can oscillate around the equilibrium level. Next, using techniques from normal form and center manifold theory (see, *e.g.*, Hassard *et al.* [22]), we study the direction of the Hopf bifurcation and the stability of the bifurcating periodic solutions when $\omega = \omega_0$.

Let $\omega = \omega_0 + \mu$, and we use μ as the bifurcation parameter with $\mu = 0$ the Hopf bifurcation value. We first scale the time $t \mapsto t/\omega$ in system (4.3) and set

$$
B_1 = \begin{pmatrix} -(\beta y^* + d_1) & -\beta x^* & 0 \\ \beta y^* & 0 & -\gamma y^* \\ 0 & 0 & 0 \end{pmatrix}, \qquad B_2 = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & \mu z^* & 0 \end{pmatrix}.
$$

Define an operator $L_\mu : C([-1,0],\mathbb{R}^3) \to \mathbb{R}$ as

$$
L_\mu(\phi) = (\omega_0 + \mu)B_1\phi(0) + (\omega_0 + \mu)B_2\phi(-1)
$$

with

$$
f(\mu,\phi) = (\omega_0 + \mu)\begin{pmatrix} -\beta\phi_1(0)\phi_2(0) \\ \beta\phi_1(0)\phi_2(0) - \gamma\phi_2(0)\phi_3(0) \\ \mu\phi_2(-1)\phi_3(0) \end{pmatrix}
$$

for $\phi = (\phi_1,\phi_2,\phi_3)^T \in C([-1,0],\mathbb{R}^3)$. We can rewrite system (4.3) as an abstract FDE in $C([-1,0],\mathbb{R}^3)$

$$
v'(t) = L_\mu(v_t) + f(\mu, v_t), \qquad (4.16)
$$

where $v_t = (x_2(t), y_2(t), z_2(t))^T \in \mathbb{R}^3$. Let

$$
\delta(\theta) = \begin{cases} 0, & \theta \neq 0; \\ 1, & \theta = 0 \end{cases}
$$

and define

$$
\eta(\theta,\mu) = (\omega_0 + \mu)B_1\delta(\theta) - (\omega_0 + \mu)B_2\delta(\theta + 1).
$$

Then operator L_μ in (4.16) can be represented in an integral form as

$$L_\mu\phi = \int_{-1}^{0} d\eta(\theta,0)\phi(\theta), \quad \text{for } \phi \in C\big([-1,0],\mathbb{R}^3\big).$$

Define operators

$$A(\mu)\phi(\theta) = \begin{cases} \frac{d\phi(\theta)}{d\theta}, & \theta \in [-1,0); \\ \int_{-1}^{0} d\eta(s,\mu)\phi(s), & \theta = 0 \end{cases}$$

and

$$R(\mu)\phi(\theta) = \begin{cases} 0, & \theta \in [-1,0); \\ f(\mu,\phi), & \theta = 0. \end{cases}$$

Then system (4.3) is written as an abstract ordinary differential equation in the Banach space $C([-1,0],\mathbb{R}^3)$

$$v_t' = A(\mu)v_t + R(\mu)v_t.$$

For $\psi \in C^1([0,1],(R^3)^*)$, define an operator

$$A^*\psi(s) = \begin{cases} -\frac{d\psi(s)}{ds}, & s \in (0,1]; \\ \int_{-1}^{0} d\eta^T(t,0)\phi(-t), & s = 0 \end{cases}$$

and a bilinear form

$$\big\langle \psi(s),\phi(\theta)\big\rangle = \bar{\psi}(0)\phi(0) - \int_{-1}^{0}\int_{\xi=0}^{\theta} \bar{\psi}(\xi-\theta)\,d\eta(\theta)\phi(\xi)\,d\xi, \tag{4.17}$$

where $\eta(\theta) = \eta(\theta,0)$. Then $A(0)$ and A^* are adjoint operators with respect to this bilinear form. From the previous section, we know that $\pm ip_0\omega_0$ are eigenvalues of $A(0)$ and therefore they are also eigenvalues of A^*. Suppose that $q(\theta) = q(0)e^{ip_0\omega_0\theta}$ is an eigenvector of $A(0)$ corresponding to the eigenvalue $ip_0\omega_0$. Then $A(0) = ip_0\omega_0 q(\theta)$. When $\theta = 0$, we obtain

$$\left[ip_0\omega_0 I - \int_{-1}^{0} d\eta(\theta)e^{ip_0\omega_0\theta}\right]q(0) = 0, \tag{4.18}$$

which yields $q(0) = (1,q_2,q_3)^T$, where

$$q_2 = -\frac{ip_0 + d_1 + \beta y^*}{\beta x^*}, \qquad q_3 = \frac{\beta}{\gamma} + \frac{ip_0(ip_0 + d_1 + \beta y^*)}{\beta\gamma x^* y^*}.$$

Similarly, it can be verified that $q^*(s) = D(1,q_2^*,q_3^*)e^{ip_0\omega_0 s}$ is the eigenvector of A^* corresponding to $-ip_0\omega_0$, where

$$q_2^* = 1 + \frac{d_1 - ip_0}{\beta y^*}, \qquad q_3^* = \frac{\beta^2 x^* y^* - ip_0(\beta y^* + d_1 - ip_0)}{\beta\mu y^* z^* e^{ip_0\omega_0}}.$$

By (4.17), we get

$$\begin{aligned}\big\langle q^*(s), q(\theta)\big\rangle &= \overline{D}\big(1, q_2^*, q_3^*\big)(1, q_2, q_3)^T \\ &\quad - \int_{-1}^{0}\int_{\xi=0}^{\theta} \big(1, q_2^*, q_3^*\big)e^{-ip_0\omega_0(\xi-\theta)}\,d\eta(\theta)(1, q_2, q_3)^T e^{ip_0\omega_0\xi}\,d\xi \\ &= 1 + \overline{q}_2 q_2^* + \overline{q}_3 q_3^* + \mu z^*\omega_0\overline{q}_2 q_3^* e^{ip_0\omega_0}.\end{aligned}$$

We can choose $\overline{D} = (1 + \overline{q}_2 q_2^* + \overline{q}_3 q_3^* + \mu z^*\omega_0\overline{q}_2 q_3^* e^{ip_0\omega_0})^{-1}$ such that $\langle q^*, q\rangle = 1$.

Following the algorithms in [22] and using the same notations as there to compute the coordinates describing the center manifold C_0 at $\mu = 0$, we obtain the coefficients:

$$\begin{aligned}
g_{20} &= 2\omega_0\overline{D}q_2\big[\big(q_2^* - 1\big)\beta - \overline{q}_2^*\gamma q_3 + \mu q_3\overline{q}_3^* e^{-ip_0\omega_0}\big], \\
g_{11} &= \omega_0\overline{D}\big[\big(q_2^* - 1\big)\beta(q_2 + \overline{q}_2) - \overline{q}_2^*\gamma(q_2\overline{q}_3 + \overline{q}_2 q_3) + \mu\overline{q}_3^*\big(q_2\overline{q}_3 e^{-ip_0\omega_0} + \overline{q}_2 q_3 e^{ip_0\omega_0}\big)\big], \\
g_{02} &= 2\omega_0\overline{D}\overline{q}_2\big[\big(q_2^* - 1\big)\beta - \overline{q}_2^*\gamma\overline{q}_3 + \mu\overline{q}_3\overline{q}_3^* e^{ip_0\omega_0}\big], \\
g_{21} &= 2\omega_0\overline{D}\Big[\big(q_2^* - 1\big)\beta\Big(W_{11}^{(2)}(0) + \frac{1}{2}W_{20}^{(2)}(0) + \frac{1}{2}\overline{q}_2 W_{20}^{(1)}(0) + q_2 W_{11}^{(1)}(0)\Big) \\
&\quad - \overline{q}_2^*\gamma\Big(q_2 W_{11}^{(3)}(0) + \frac{1}{2}\overline{q}_2 W_{20}^{(3)}(0) + \frac{1}{2}\overline{q}_3 W_{20}^{(2)}(0) + q_3 W_{11}^{(2)}(0)\Big) \\
&\quad + \mu\overline{q}_3^*\Big(q_2 W_{11}^{(3)}(0)e^{-ip_0\omega_0} + \frac{1}{2}\overline{q}_2 W_{20}^{(3)}(0)e^{ip_0\omega_0} + \frac{1}{2}\overline{q}_3 W_{20}^{(2)}(-1) + q_3 W_{11}^{(2)}(-1)\Big)\Big],
\end{aligned}$$

where $\theta \in [-1, 0]$. We still need to compute $W_{20}(\theta)$ and $W_{11}(\theta)$.

$$\begin{aligned}
W_{20}(\theta) &= \frac{ig_{20}}{p_0\omega_0}q(0)e^{ip_0\omega_0\theta} + \frac{i\overline{g}_{02}}{3p_0\omega_0}\overline{q}(0)e^{-ip_0\omega_0\theta} + E_1 e^{2ip_0\omega_0\theta}, \\
W_{11}(\theta) &= -\frac{ig_{11}}{p_0\omega_0}q(0)e^{ip_0\omega_0\theta} + \frac{i\overline{g}_{11}}{p_0\omega_0}\overline{q}(0)e^{-ip_0\omega_0\theta} + E_2,
\end{aligned}$$

where

$$\begin{aligned}
E_1 &= \begin{pmatrix} 2ip_0 + \beta y^* + d_1 & \beta x^* & 0 \\ -\beta y^* & 2ip_0 & \gamma y^* \\ 0 & -\mu z^* e^{-2ip_0\omega_0} & 2ip_0 - \mu y^* + d_3 \end{pmatrix}^{-1} \begin{pmatrix} -\beta q_2 \\ \beta q_2 - \gamma q_2 q_3 \\ \mu q_2 q_3 e^{-ip_0\omega_0} \end{pmatrix}, \\
E_2 &= \begin{pmatrix} -(\beta y^* + d_1) & -\beta x^* & 0 \\ \beta y^* & 0 & -\gamma y^* \\ 0 & \mu z^* & \mu y^* - d_3 \end{pmatrix}^{-1} \begin{pmatrix} -\beta(q_2 + \overline{q}_2) \\ \gamma(q_2\overline{q}_3 + \overline{q}_2 q_3) - \beta(q_2 + \overline{q}_2) \\ \mu(q_3\overline{q}_2 e^{ip_0\omega_0} + q_2\overline{q}_3 e^{-ip_0\omega_0}) \end{pmatrix}.
\end{aligned}$$

And consequently g_{21} can be expressed explicitly, and we can compute the following quantities:

$$\begin{aligned}
c_1(0) &= \frac{i}{2p_0\omega_0}\left[g_{21}g_{20} - 2|g_{11}|^2 - \frac{|g_{02}|^2}{3}\right] + \frac{g_{21}}{2}, \\
\mu_2 &= \frac{Re(c_1(0))}{Re(\xi'(p_0))}, \\
\beta_2 &= 2Re\big(c_1(0)\big).
\end{aligned}$$

Table 1 Parameter values of system (4.3) used in Section 5

Parameter	Value	Unit
λ	160	$\text{day}^{-1}\ \text{mm}^{-3}$
β	0.002	$\text{day}^{-1}\ \text{mm}^{-3}$
μ	0.2	day^{-1}
γ	0.2	day^{-1}
d_1	0.16	day^{-1}
d_2	1.85	day^{-1}
d_3	0.8	day^{-1}

By the result of Hassard *et al.* [22], we have the following theorem.

Theorem 4.3 *μ_2 determines the direction of the Hopf bifurcation*: *if $\mu_2 > 0$ ($\mu_2 < 0$), then the Hopf bifurcation is supercritical* (*subcritical*) *and the bifurcating periodic solutions exist for $\omega > \omega_0$ ($\omega < \omega_0$); $\beta_2 > 0$ ($\beta_2 < 0$) determines the stability of bifurcating periodic solutions*: *the bifurcating periodic solutions are orbitally asymptotically stable* (*unstable*) *if $\omega > \omega_0$ ($\omega < \omega_0$).*

5 Numerical simulation

In this section, we further investigate the dynamical behaviors of (4.3) through numerical simulations with the aid of MATHEMATICA. It is shown that the parameter values can be chosen simply to establish the possibility for oscillations in the viral load and T cell populations.

As in [23, 24], time is measured in days and x, y, z have units mm^{-3}. In the absence of infection, the rate of production of healthy $CD4^+$ T cells from the bone marrow falls in the range of 100-1,500 cells/mm^3/day [23, 24], and all three populations considered in our model display natural death rates between 0.001-5/day.

We set the same values of different parameters as in [15] and [21], which is referred in Table 1. After a simple algebraic calculation, it can be verified that the conditions of Theorem 4.2 are satisfied. We can compute that $\omega_0 = 0.6974$. The HAM/TSP equilibrium E^* is $E^*(952.381, 4, 3.0282)$, $\Re_0^* = 1.08108$ and $\Re_1^* = 1.0296$. From the analysis in Section 4 and Theorem 4.2, immune activation delay ω gives more complex behaviors to the dynamics of (4.3): the HAM/TSP equilibrium E^* is locally asymptotically stable when $\omega < \omega_0$, and a Hopf bifurcation occurs at $\omega = \omega_0$; a periodic solution exists when $\omega > \omega_0$. Furthermore, we compute $c_1(0) = 0.0286 - 7.5081i$. Therefore $\text{Re}(c_1(0)) > 0$ on the center manifold. By Theorem 4.3, we know that the Hopf bifurcation of system (4.3) at the HAM/TSP equilibrium E^* is supercritical and the bifurcating periodic solutions are orbitally asymptotically stable. We fix $\omega_i = 0.05; 0.3; 0.7; 0.9$ ($i = 1, 2, 3, 4$). Figure 1 illustrates that a Hopf bifurcation occurs from the HAM/TSP equilibrium for (4.3). Furthermore, from Figure 1(c) and (d), we can find that there is a growing amplitude along with the increase of immune activation delay.

6 Conclusion and discussion

In this paper, we have investigated the dynamics of an HTLV-I model which incorporates intracellular delay and immune activation delay based on the rigorous mathematical analysis. Using two threshold parameters $\Re_0$ and $\Re_1$, named as the basic reproduction number for viral persistence and for CTLs response, the global dynamics of the proposed system can be obtained by constructing suitable Lyapunov functionals under LaSalle's invariance

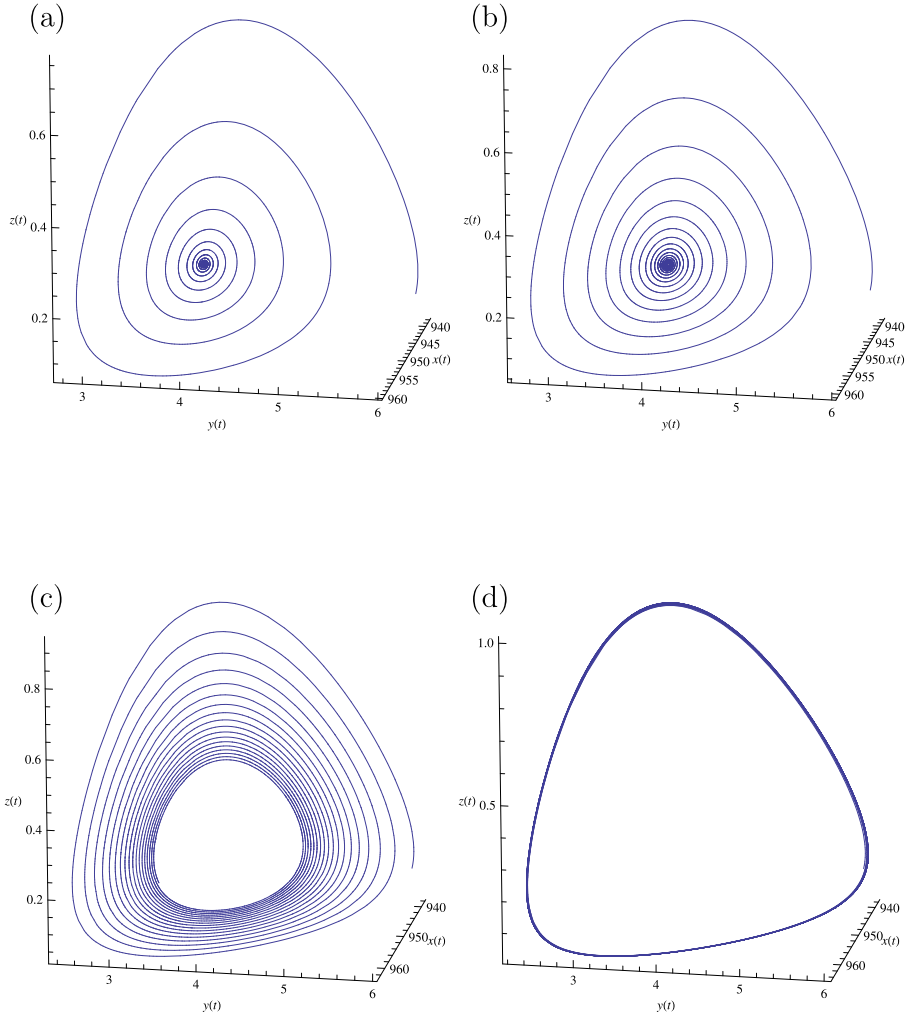

Figure 1 Behavior and phase portrait of system (4.3) with values as in Table 1. $\omega = 0.05$ in **(a)**; $\omega = 0.3$ in **(b)**; $\omega = 0.7$ in **(c)**; $\omega = 0.9$ in **(d)**. By Theorem 4.2, we know that a Hopf bifurcation occurs from the HAM/TSP equilibrium. The initial value is (942, 5.97, 0.15).

principle. Our results show that the intracellular delay τ does not affect the stability of the HAM/TSP equilibrium, but the immune activation delay can destabilize the equilibrium and lead to a Hopf bifurcation.

As to the previous studies, Wodarz *et al.* [5], Li and Shu [15, 25], Song *et al.* [21], Wang *et al.* [9], Canabarro *et al.* [16], our results are the first to establish the existence of a Hopf bifurcation in a HTLV-I model with delayed immune response ($z'(t) = cy(t - \omega)z(t) - bz$) using rigorous mathematical analysis. On the other hand, the results in the present paper (combined with the results in [25] and [15]) show that a mitosis component is not required for sustained oscillations to occur when the immune response is incorporated into the model. These results together have largely enriched our understanding of the effects of intracellular delays in dynamics of viral infection and its interaction with the CTLs immune response. Further, numerical simulation in Figure 1 reveals that the stability switch occurs at critical value of ω_0, and the periodic solutions exist with an increasing amplitude when ω continues to increase.

HTLV-I infection is rarely cleared from the body. The dynamical outcomes that are biologically relevant are the carrier state and HAM/TSP state. Furthermore, considering that the large number of HTLV-I infected patients are asymptomatic carriers, it is a realistic control and treatment strategy in preventing carriers from developing HAM/TSP by keeping the threshold parameter $\Re_1$ below 1, which may have potential implications for future studies.

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

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

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