MATHEMATICAL BIOSCIENCES
AND ENGINEERING
Volume **12**, Number **3**, June **2015**

doi:10.3934/mbe.2015.12.431

pp. **431–449**

A MATHEMATICAL MODEL OF HTLV-I INFECTION WITH TWO TIME DELAYS

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(Communicated by James Watmough)

Abstract. In this paper, we include two time delays in a mathematical model for the CD8$^+$ cytotoxic T lymphocytes (CTLs) response to the Human T-cell leukaemia virus type I (HTLV-I) infection, where one is the intracellular infection delay and the other is the immune delay to account for a series of immunological events leading to the CTL response. We show that the global dynamics of the model system are determined by two threshold values R_0, the corresponding reproductive number of a viral infection, and R_1, the corresponding reproductive number of a CTL response, respectively. If $R_0 < 1$, the infection-free equilibrium is globally asymptotically stable, and the HTLV-I viruses are cleared. If $R_1 < 1 < R_0$, the immune-free equilibrium is globally asymptotically stable, and the HTLV-I infection is chronic but with no persistent CTL response. If $1 < R_1$, a unique HAM/TSP equilibrium exists, and the HTLV-I infection becomes chronic with a persistent CTL response. Moreover, we show that the immune delay can destabilize the HAM/TSP equilibrium, leading to Hopf bifurcations. Our numerical simulations suggest that if $1 < R_1$, an increase of the intracellular delay may stabilize the HAM/TSP equilibrium while the immune delay can destabilize it. If both delays increase, the stability of the HAM/TSP equilibrium may generate rich dynamics combining the "stabilizing" effects from the intracellular delay with those "destabilizing" influences from immune delay.

1. **Introduction.** HTLV-I is a human retrovirus that can cause a slowly progressive neurologic disease, HTLV-I-associated myelopathy spastic paraparesis (HAM/TSP) [4, 18, 25]. The number of HTLV-I-infected people is estimated between 15 to 25 million worldwide. Unlike HIV viruses, which break free from host cells and infect other T cells, HTLV-I viruses are not very infectious and seldom found in plasma [17]. Direct cell-to-cell contact is required to transmit the viruses among

2010 *Mathematics Subject Classification.* Primary: 34K20, 34K60; Secondary: 34K18.
Key words and phrases. Epidemic threshold, HTLV-I infection, Lyapunov functional, time delay, Hopf bifurcation.
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CD4$^+$ T cells, while HTLV-I preferentially infects in vivo [2, 23, 22]. After an individual is infected by HTLV-I viruses, the incubation period is from 15 to 30 years. Most HTLV-I infected individuals are lifelong carriers, and about 0.25 percent to 3 percent of those develop into HAM/TSP patients [8, 28], in which at least 85 percent of the patients will die in four years. On the other hand, CTL has a protective part to the host by lowering the proviral load, and HAM/TSP patients' peripheral blood cells show very high CTL [1, 6]. The evidence implies that cytotoxicity of the CTL is ultimately responsible for the demyelination of the central nervous system resulting in HAM/TSP [5].

Mathematical models have been formulated to describe the in-vivo infection process with the humoral immune response to HTLV-I infections [2, 6, 9, 11, 12, 16, 26, 25, 14] as well as to the human immunodeficiency virus (HIV) [13, 15, 19, 21, 24, 27]. In [6], Gómez-Acevedo et al consider the following mathematical model for the HTLV-I infection of CD4$^+$ T cells that incorporates the CD8$^+$ cytotoxic T-cell response:

$$\begin{aligned}
\frac{dx}{dt} &= \lambda - \mu_1 x(t) - \beta x(t) y(t), \\
\frac{dy}{dt} &= \sigma\beta x(t) y(t) - \mu_2 y(t) - \gamma y(t) z(t), \\
\frac{dz}{dt} &= v\frac{y(t) z(t)}{z(t) + K} - \mu_3 z(t),
\end{aligned} \tag{1}$$

where $x(t)$, $y(t)$ are the population sizes of the uninfected and infected CD4$^+$ T-cells, and $z(t)$ the number of HTLV-I-specific CD8$^+$ T cells at time t, respectively. Parameter λ is a constant input rate of CD4$^+$ T-cells, μ_1, μ_2, and μ_3 the removal rates of uninfected and infected CD4$^+$ T cells, and HTLV-I-specific CD8$^+$ T cells, respectively, β the transmission coefficient, $\sigma \in [0, 1]$ a fraction of cells newly infected by contacts that survive the antibody immune response, γ the rate of CTL mediated lysis. The anti-HTLV-I CTLs reduce the proviral load, but this reduction implies less stimulation for the CTL proliferation. Thus it is assumed in [6] that the CD8$^+$ T-cell stimulation has a density-dependent form $vy(t)z(t)/(z(t) + K)$. Two threshold parameters R_0 and R_1, the basic reproduction numbers for viral persistence and for CTL response, respectively are obtained to determine the global dynamics of system (1) [6, Theorem 3.1]. If $R_0 < 1$, the so-called infection-clearance equilibrium is globally asymptotically stable, if $R_1 < 1 < R_0$, the the so-called carrier equilibrium with no persistent CTL response is globally asymptotically stable, and if $1 < R_1$, the HAM/TSP equilibrium is globally asymptotically stable.

Time delays have also been introduced into HTLV-I mathematical models to study the transmission dynamics [11, 12, 25, 14]. In [11, 12], Li and Shu formulate HTLV-I virus infection models for the CD4$^+$ T cells with delayed CTL response, where the time delay is to account for the lag incurred by a sequence of events such as antigenic activation, selection, and proliferation of the CTLs. It is shown that the immune delay can destabilize the HAM/TSP equilibrium, leading to Hopf bifurcations, stable periodic oscillations [12], or the coexistence of multiple stable periodic solutions [11]. To characterize the time between the initial infected CD4$^+$ T target cells entering a target cell and the subsequent infection, Sun and Wei [25], and Muroya et al [14] incorporate the intracellular infection delay into the HTLV-I infection models. It is concluded in [25, 14] that, different from the results in [11, 12], the infection delay does not change the stability of the system.

A time delay representing either the immune response delay or the intracellular delay has been included in HTLV-I models, but to the best of our knowledge, there is no model that has included both of the two delays together, which are biologically reasonable during the HTLV-I infection. In this paper, using system (1) as our baseline model, we incorporate the intracellular delay τ_1 and the immune delay τ_2 both into it and consider the following system:

$$\begin{aligned}\frac{dx}{dt} &= \lambda - \mu_1 x(t) - \beta x(t)y(t),\\ \frac{dy}{dt} &= \sigma\beta x(t-\tau_1)y(t-\tau_1) - \mu_2 y(t) - \gamma y(t)z(t),\\ \frac{dz}{dt} &= v\frac{y(t-\tau_2)z(t-\tau_2)}{z(t-\tau_2)+K} - \mu_3 z(t).\end{aligned} \tag{2}$$

This study seems to be the first with the model system including the both delays.

The main purpose of this study is to explore the global dynamics of system (2) and investigate the impact of the intracellular delay τ_1 and the immune delay τ_2 on the dynamical behavior of the system. In general, including more than one time delay increases the model complexity and bring challenges in mathematical analysis. By developing different Lyapunov functionals, we establish conditions ensuring global stability of the infection-free equilibrium, the immune-free equilibrium with the chronic HTLV-I infection, and the HAM/TSP equilibrium. Using the uniform persistence theory, we obtain criteria that determine if the HTLV-I infection becomes chronic with a persistent CTL response. We also investigate the impact of the combined effects from the two delays together on the global dynamics of model system (2) analytically as well as numerically.

The paper is organized as follows. In Section 2, the threshold parameters R_0 and R_1 are derived and the existence conditions for all equilibria are established in terms of the values of R_0 and R_1. In Section 3, main analytical results on the stability of the equilibria, uniform persistence of the system, and the Hopf bifurcations due to immune delay are obtained. Numerical simulations are presented in Section 4, and brief discussions finally complete the paper in Section 5.

2. **Preliminaries.**

To investigate the dynamics of system (2), we need to consider a suitable phase space and a feasible region.

For $\tau_1, \tau_2 \geq 0$, define the following Banach space $C = C([-\tau, 0], R)$, $\tau = max\{\tau_1, \tau_2\}$, and we assume

$$x(t) = \phi_1(\theta),\ y(t) = \phi_2(\theta),\ z(t) = \phi_3(\theta),\ \text{for } -\tau \leq \theta \leq 0.$$

In addition, throughout this paper, we set $\phi = (\phi_1, \phi_2, \phi_3)$ and $\phi_i \in C (i = 1, 2, 3)$ for $-\tau \leq \theta \leq 0$, with norm $||\phi|| = sup_{-\tau\leq\theta\leq 0}\{|\phi_1(\theta)|, |\phi_2(\theta)|, |\phi_3(\theta)|\}$ for $\phi_i \in C$, $i = 1, 2, 3$. The nonnegative cone of C is defined as $C^+ = C([-\tau, 0], R^3_+)$. Initial conditions for system (2) are chosen at $t = 0$ as

$$\phi = (\phi_1,\ \phi_2,\ \phi_3) \in C^+,\ \phi_i(0) > 0,\ i = 1, 2, 3. \tag{3}$$

Lemma 2.1. *Under initial conditions in (3), all solutions of system (2) are positive and ultimately bounded in $R \times C \times C$.*

Proof. First, we prove $x(t)$ is positive for $t \geq 0$.

Assume the contrary and let $t_1 > 0$ be the first time reached by x such that $x(t) > 0$, $0 \leq t < t_1$ and $x(t_1) = 0$. It then follows from the first equation in (2) that $x'(t_1) = \lambda > 0$, and hence $x(t) < 0$ for $t \in (t_1 - \varepsilon, t_1)$ where $\varepsilon > 0$ is sufficiently

small. This contradicts $x(t) > 0$ for $t \in [0, t_1)$, and thus it follows that $x(t) > 0$ for $t > 0$ so long as $x(t)$ exists.

Second, it follows from the second equation in system (2), for $\tau_1, \tau_2 > 0$, that

$$y(t) = y(0)e^{-\int_0^t \mu_2+\gamma z(\tau)d\tau} + \int_0^t \sigma\beta x(s-\tau_1)y(s-\tau_1)e^{\int_t^s \mu_2+\gamma z(\tau)d\tau}ds.$$

Suppose there exists $t_0 > 0$, such that $y(t_0) = 0$, and $y(t) > 0$ for $0 < t < t_0$. Then

$$y(t_0) = y(0)e^{-\int_0^{t_0} \mu_2+\gamma z(\tau)d\tau} + \int_0^{t_0} \sigma\beta x(s-\tau_1)y(s-\tau_1)e^{\int_{t_0}^s \mu_2+\gamma z(\tau)d\tau}ds > 0,$$

a contraction. Thus $y(t)$ is positive.

Similarly, if there exists $t_0 > 0$, such that $z(t_0) = 0$, and $z(t) > 0$ for $0 < t < t_0$, it follows from the third equation in (2) that

$$z(t) = z(0)e^{-\mu_3 t} + v\int_0^t e^{\mu_3(s-t)}\frac{y(s-\tau_2)z(s-\tau_2)}{z(s-\tau_2)+K}ds,$$

and then it leads to a contradiction as before. Hence we have $z(t) > 0$, for all $t > 0$.

Next we prove that positive solutions of (2) are ultimately uniformly bounded for $t > 0$. From the first equation in (2), it follows that $x'(t) \le \lambda - \mu_1 x(t)$, and thus $\limsup_{t\to\infty} x(t) \le \lambda/\mu_1$. Adding the first two equations in (2) together, we have

$$\begin{aligned}(x(t) + y(t+\tau_1))' &= \lambda - \mu_1 x(t) - \beta(1-\sigma)x(t)y(t) - \mu_2 y(t+\tau_1)\\ &\quad - \gamma y(t+\tau_1)z(t+\tau_1)\\ &\le \lambda - \bar{\mu}(x(t) + y(t+\tau_1))\end{aligned}$$

where $\bar{\mu} = \min\{\mu_1, \mu_2\}$. Thus $\limsup_{t\to\infty}(x(t) + y(t+\tau_1)) \le \lambda/\bar{\mu}$. It then follows, in addition from (2), that, for any $\varepsilon > 0$ and for a solution $y(t)$ of system (2) with $y(t) < \frac{\lambda}{\bar{\mu}} + \varepsilon$, there exists $T = T(\varepsilon) > 0$ such that for $t > T$, the following differential inequality holds:

$$z(t+\tau_2)' \le vy(t) - \mu_3 z(t+\tau_2) \le v\left(\frac{\lambda}{\bar{\mu}} + \varepsilon\right) - \mu_3 z(t+\tau_2).$$

Let $\varepsilon \to 0$. Then $\limsup_{t\to\infty} z(t) \le \frac{v\lambda}{\mu_3\bar{\mu}}$. Hence, $x(t)$, $y(t)$ and $z(t)$ are all ultimately uniformly bounded in $R \times C \times C$. □

As a consequence of the proof of Lemma 2.1, we know that the dynamics of system (2) can be analyzed in the following feasible region:

$$\mathcal{F} = \left\{(x, y, z) \in R_+ \times C^+ \times C^+, |x| \le \frac{\lambda}{\mu_1}, \|x + y\| \le \frac{\lambda}{\bar{\mu}}, |z| \le \frac{v\lambda}{\mu_3\bar{\mu}}\right\}.$$

Moreover, the region $\mathcal{F}$ is positively invariant and hence the model system is well posed.

Lemma 2.2. *Given system (2) with $\phi_i(0) \ge 0$, $i = 1, 2, 3$, we have all solutions $x(t) > 0$, $y(t) \ge 0$, $z(t) \ge 0$, $\forall t > 0$.*

Proof. By similar arguments as in the proof of Lemma 2.1, the positivity of $x(t)$ for all $t > 0$ follows directly.

Next, we show that $y(t)$ and $z(t)$ must be non-negative for all $t > 0$. Otherwise, there must exist $t_0 > 0$ such that $\min\{y(t_0), z(t_0)\} < 0$.

Let

$$\check{t}_0 = \inf_{t_0}\{t_0 > 0 | \min\{y(t_0), z(t_0)\} < 0\}.$$

Then we have $\check{t}_0 > 0$ and there exists a sufficiently small constant $\varepsilon > 0$, $\varepsilon < \frac{1}{2}\min\{\tau_1, \tau_2\}$, such that $\min\{y(\check{t}_0 + \varepsilon), z(\check{t}_0 + \varepsilon)\} < 0$. Hence we have the following three cases:

(i) $y(\check{t}_0 + \varepsilon) < 0$.
(ii) $z(\check{t}_0 + \varepsilon) < 0$.
(iii) $y(\check{t}_0 + \varepsilon) < 0$ and $z(\check{t}_0 + \varepsilon) < 0$.

We first assume (i), and put $\check{t}_0 + \varepsilon$ into (5). Then we have

$$y(\check{t}_0 + \varepsilon) = y(0)e^{-\int_0^{\check{t}_0+\varepsilon} \mu_2 + \gamma z(\tau) d\tau} + \int_0^{\check{t}_0+\varepsilon} \sigma\beta x(s-\tau_1)y(s-\tau_1)e^{\int_{\check{t}_0+\varepsilon}^{s} \mu_2+\gamma z(\tau)d\tau} ds. \tag{4}$$

This contradicts $y(\check{t}_0 + \varepsilon) \geq 0$ for $t > 0$. Similarly, we can prove (ii) and (iii). □

System (1) has the infection-free equilibrium $P_1 = \left(\frac{\lambda}{\mu_1}, 0, 0\right)$. Using the next generation matrix method [3], we have the transmission and transition matrices as

$$F = \begin{pmatrix} 0 & \sigma\beta\frac{\lambda}{\mu_1} \\ 0 & 0 \end{pmatrix}, \quad V = \begin{pmatrix} 0 & \mu_2 \\ \mu_1 & \beta\frac{\lambda}{\mu_1}. \end{pmatrix}$$

Then it follows that

$$FV^{-1} = \frac{1}{\mu_1\mu_2}\begin{pmatrix} -\sigma\beta\lambda & 0 \\ 0 & 0 \end{pmatrix}.$$

Then the reproductive number of a viral infection is defined as $R_0 := \rho(FV^{-1}) = \frac{\sigma\beta\lambda}{\mu_1\mu_2}$.

There exists an equilibrium $P_2 = \left(\frac{\mu_2}{\sigma\beta}, \frac{\sigma\beta\lambda - \mu_1\mu_2}{\mu_2\beta}, 0\right)$ with no CTL response, as $R_0 > 1$, that we call the immune-free equilibrium. The corresponding transmission and transition matrices are

$$F = \begin{pmatrix} 0 & 0 & \frac{v\sigma\beta\lambda - v\mu_1\mu_2}{K\mu_2\beta} \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}, V = \begin{pmatrix} 0 & 0 & \mu_3 \\ -\frac{\sigma^2\beta^2\lambda - \sigma\beta\mu_1\mu_2}{\mu_2\beta} & 0 & \frac{\gamma\sigma\beta\lambda - \gamma\mu_1\mu_2}{\mu_2\beta} \\ \mu_1 + \frac{\sigma\beta^2\lambda - \beta\mu_1\mu_2}{\mu_2\beta} & \frac{\mu_2}{\sigma} & 0, \end{pmatrix}$$

Hence it follows from

$$FV^{-1} = \frac{1}{\mu_1\mu_2}\begin{pmatrix} \frac{v\sigma\beta\lambda - v\mu_1\mu_2}{K\mu_3\mu_2\beta} & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix}$$

that if we define $R_1 := \dfrac{\sigma\beta\lambda v}{\mu_2(\mu_1 v + \beta\mu_3 K)}$, then P_2 is locally asymptotically stable if $R_1 < 1$, and unstable if $R_1 > 1$. We call R_1 the basic reproductive number of a CTL response.

A chronic infection equilibrium $P_3 = (x^*, y^*, z^*)$ with CLT response ($z^* > 0$) is called a HAM/TSP equilibrium. The coordinates x^*, y^*, z^* satisfy

$$\begin{aligned} \lambda - \mu_1 x^* - \beta x^* y^* &= 0, \\ \sigma\beta x^* y^* - \mu_2 y^* - \gamma y^* z^* &= 0, \\ v\frac{y^* z^*}{z^* + K} - \mu_3 z^* &= 0, \end{aligned} \tag{5}$$

and P_3 exists as $R_1 > 1$.

3. **Main results.** In this section, we investigate the stability of the equilibria P_1, P_2, P_3, respectively. In order to avoid an excessive use of parentheses in some of later calculations, we write $x = x(t)$, $y = y(t)$, $z = z(t)$, and let $g(x) := x - \ln x - 1$, such that $g(x) \geq 0$ for $x > 0$, and $g(x) = 0$ if and only if $x = 1$.

3.1. Global stability of the infection-free equilibrium P_1 as $R_0 < 1$.

Theorem 3.1. *For system (2), if $R_0 < 1$, the infection-free equilibrium P_1 is globally asymptotically stable in $\mathcal{F}$.*

Proof. For $\tau_1, \tau_2 > 0$, the characteristic equation of system (2) in $P_1 = (x^*, 0, 0)$, $x^* = \dfrac{\lambda}{\mu_1}$ is

$$G(s) = det\left(sE - A - A_1 e^{-\lambda\tau_1}\right) = (s+\mu_1)(s+\mu_3)\left(s + \mu_2 - \frac{\sigma\beta\lambda}{\mu_1}e^{-\lambda\tau_1}\right), \tag{6}$$

where

$$A := \begin{pmatrix} -\mu_1 & -\dfrac{\beta\lambda}{\mu_1} & 0 \\ 0 & -\mu_2 & 0 \\ 0 & 0 & -\mu_3 \end{pmatrix}, \quad A_1 := \begin{pmatrix} 0 & 0 & 0 \\ 0 & \dfrac{\sigma\beta\lambda}{\mu_1} & 0 \\ 0 & 0 & 0 \end{pmatrix}.$$

Set $G(s) = 0$ in (6). We have

$$s_1 = -\mu_1, \quad s_2 = -\mu_3,$$

and

$$s + \mu_2 - \frac{\sigma\beta\lambda}{\mu_1}e^{-\lambda\tau_1} = 0. \tag{7}$$

As in [21], if $\dfrac{\sigma\beta\lambda}{\mu_1} < \mu_2$, all roots of equation (7) have negative real parts. Thus the infection-free equilibrium P_1 is locally asymptotically stable.

We define the following Lyapunov functional

$$V(\phi) = U_1(\phi) + U_2(\phi) + U_3(\phi),$$

where

$$U_1(\phi) := x^* g\left(\frac{\phi_1(0)}{x^*}\right), \tag{8}$$

$$U_2(\phi) := \frac{1}{\sigma}\left(\phi_2(0) + \sigma\beta\int_{-\tau_1}^{0}\phi_1(s)\phi_2(s)ds\right), \tag{9}$$

and

$$U_3(\phi) := \frac{K\gamma}{v\sigma}\left(\phi_3(0) + v\int_{-\tau_2}^{0}\frac{\phi_2(s)\phi_3(s)}{\phi_3(s)+K}ds\right). \tag{10}$$

Calculating the time derivatives of (8), (9), and (10) along solutions of system (2), we have

$$\begin{aligned}\frac{dU_1(\phi)}{dt} &= x^*\left(\frac{1}{x^*}-\frac{1}{x}\right)(\lambda-\mu_1 x-\beta xy)\\ &= -\frac{\mu_1(x-x^*)^2}{x}-\frac{x-x^*}{x}\beta xy,\end{aligned} \tag{11}$$

$$\frac{dU_2(\phi)}{dt} = \frac{1}{\sigma}(\sigma\beta xy-\mu_2 y-\gamma yz), \tag{12}$$

and

$$\frac{dU_3(\phi)}{dt} = \frac{K\gamma}{v\sigma}\left(v\frac{yz}{z+K}-\mu_3 z\right). \tag{13}$$

Combining (11), (12), and (13), we have

$$\begin{aligned}\left.\frac{dV}{dt}\right|_{(2)} &= -\frac{\mu_1(x-x^*)^2}{x}+\beta x^* y-\frac{\mu_2}{\sigma}y-\frac{\gamma}{\sigma}yz\left(1-\frac{K}{z+K}\right)-\frac{K\gamma\mu_3}{v\sigma}z\\ &= -\frac{\mu_1(x-x^*)^2}{x}+\beta x^* y-\frac{\mu_2}{\sigma}y-\frac{\gamma yz^2}{\sigma(z+K)}-\frac{K\gamma\mu_3}{v\sigma}z\\ &= -\frac{\mu_1(x-x^*)^2}{x}+\frac{\mu_2}{\sigma}y(R_0-1)-\frac{\gamma yz^2}{\sigma(z+K)}-\frac{K\gamma\mu_3}{v\sigma}z.\end{aligned}$$

Therefore, it follows from $R_0<1$ that $\frac{dV}{dt}|_{(2)}\le 0$ for all $x(t),y(t),z(t)>0$.

Set

$$\mathcal{A}_0=\{(x,y,z)\in\mathcal{F}|V'=0\}.$$

Then $V^{'}=0$ if and only if

$$x=x^*,\quad z=0. \tag{14}$$

Substituting (14) into the first equation in system (2) then yields $y=0$. By the LaSalle-Lyapunov theorem ([10], Theorem 3.4.7), the largest compact invariant set of $\mathcal{A}_0$ is the singleton point P_1. Thus we conclude that P_1 is globally attractive in $\mathcal{F}$. Since it has been shown above that P_1 is locally asymptotically stable, P_1 is globally asymptotically stable in $\mathcal{F}$ as $R_0<1$. □

3.2. Global stability of the immune-free equilibrium P_2 as $R_0>1>R_1$.

Theorem 3.2. *For system (2), if $R_0>1>R_1$, the immune-free equilibrium P_2 is globally asymptotically stable in $\mathcal{F}\backslash\{x\text{-axis}\}$.*

Proof. For $\tau_1,\tau_2>0$, the characteristic equation of system (2) in P_2 is

$$G(s)=\det\left(sE-A(P_1)-A_1(P_1)e^{-s\tau_1}-A_2(P_1)e^{-s\tau_2}\right), \tag{15}$$

where

$$A(P_1):=\begin{pmatrix}-\mu_1-\dfrac{\sigma\beta\lambda-\mu_1\mu_2}{\mu_2} & -\dfrac{\mu_2}{\sigma} & 0\\ 0 & -\mu_2 & -\gamma\dfrac{\sigma\beta\lambda-\mu_1\mu_2}{\mu_2}\\ 0 & 0 & -\mu_3\end{pmatrix},$$

$$A_1(P_1):=\begin{pmatrix}0 & 0 & 0\\ \dfrac{(\sigma\beta\lambda-\mu_1\mu_2)\sigma}{\mu_2} & \mu_2 & 0\\ 0 & 0 & 0\end{pmatrix},\ A_2(P_1):=\begin{pmatrix}0 & 0 & 0\\ 0 & 0 & 0\\ 0 & 0 & \dfrac{(\sigma\beta\lambda-\mu_1\mu_2)v}{\beta\mu_2 K}\end{pmatrix}$$

Setting $G(s)=0$ in (15), we have

$$\left(s+\mu_3-v\frac{\sigma\beta\lambda-\mu_1\mu_2}{\mu_2\beta K}e^{-s\tau_2}\right)$$
$$\times\left(s^2+\left(\frac{\sigma\beta\lambda}{\mu_2}-\mu_2e^{-s\tau_1}+\mu_2\right)s+\sigma\beta\lambda-\mu_1\mu_2e^{-s\tau_1}\right)=0.$$

It then follows that

$$s+\mu_3-v\frac{\sigma\beta\lambda-\mu_1\mu_2}{\mu_2\beta K}e^{-s\tau_2}=0. \tag{16}$$

Hence, if $R_1<1$, namely, $v\dfrac{\sigma\beta\lambda-\mu_1\mu_2}{\mu_2\beta K}<\mu_3$, all the roots of equation (16) have negative real parts.

We next set

$$F(s)=s^2+\left(\frac{\sigma\beta\lambda}{\mu_2}-\mu_2e^{-s\tau_1}+\mu_2\right)s+\sigma\beta\lambda-\mu_1\mu_2e^{-s\tau_1}, \tag{17}$$

and we consider the following two cases:

(i) Suppose $\tau_1=0$. Then $F(s)=0$ is equivalent to

$$s^2+\frac{\sigma\beta\lambda}{\mu_2}s+\sigma\beta\lambda-\mu_1\mu_2=0. \tag{18}$$

If $R_0>1$, namely, $\sigma\beta\lambda-\mu_1\mu_2>0$, then each root of (18) has only a negative real part.

(ii) Suppose $\tau_1\neq0$. It is obvious that $s=0$ is not a root of (17) when $R_0>1$. Now, let $s=i\omega$, $\omega\geq0$. Then (17) is equivalent to

$$F(s)=F(i\omega)=-\omega^2+\left(\frac{\sigma\beta\lambda}{\mu_2}-\mu_2e^{-i\omega\tau_1}+\mu_2\right)i\omega+\sigma\beta\lambda-\mu_1\mu_2e^{-i\omega\tau_1}=0,$$

and it follows that

$$\omega^4+\frac{\sigma^2\beta^2\lambda^2}{\mu_2^2}\omega^2+\sigma^2\beta^2\lambda^2-\mu_1^2\mu_2^2=0. \tag{19}$$

If $R_0>1$, then $\sigma^2\beta^2\lambda^2-\mu_1^2\mu_2^2>0$, and each root of (19) has only a negative real part. Combined (i) with (ii), the roots of zeros of $F(s)$ on $\tau_1\geq0$ have negative real parts. Thus, all the roots of $G(s)=0$ have negative real parts, and P_2 is locally asymptotically stable as $R_1<1<R_0$.

Write $P_2=(\bar{x},\bar{y},0)$, with $\bar{x}=\dfrac{\mu_2}{\sigma\beta},\bar{y}=\dfrac{\sigma\beta\lambda-\mu_1\mu_2}{\mu_2\beta}$ and consider the following Lyapunov functional:

$$V(\phi)=V_1(\phi)+V_2(\phi)+V_3(\phi),$$

where

$$V_1(\phi):=\bar{x}g\left(\frac{\phi_1(0)}{\bar{x}}\right), \tag{20}$$

$$V_2(\phi):=\frac{1}{\sigma}\left(\bar{y}g\left(\frac{\phi_2(0)}{\bar{y}}\right)+\bar{x}\bar{y}\sigma\beta\int_{-\tau_1}^{0}g\left(\frac{\phi_1(s)\phi_2(s)}{\bar{x}\bar{y}}\right)ds\right), \tag{21}$$

and

$$V_3(\phi):=\frac{K\gamma}{v\sigma}\left(\phi_3(0)+v\int_{-\tau_2}^{0}\frac{\phi_2(s)\phi_3(s)}{\phi_3(s)+K}\right)ds. \tag{22}$$

Then calculating the time derivatives of (20), (21), and (22) along solutions of system (2) yields

$$\frac{dV_1(\phi)}{dt} = \frac{x-\bar{x}}{x}\big(\mu_1(\bar{x}-x) + \beta\bar{x}\bar{y} - \beta xy\big), \tag{23}$$

$$\begin{aligned}\frac{dV_2(\phi)}{dt} = {} & \frac{1}{\sigma}\frac{y-\bar{y}}{y}\big(\sigma\beta x(t-\tau_1)y(t-\tau_1) - \mu_2 y - \gamma yz\big) \\ & +\bar{x}\bar{y}\beta\left(\frac{xy - x(t-\tau_1)y(t-\tau_1)}{\bar{x}\bar{y}} + \ln\frac{x(t-\tau_1)y(t-\tau_1)}{xy}\right),\end{aligned} \tag{24}$$

and

$$\frac{dV_3(\phi)}{dt} = \frac{K\gamma}{v\sigma}\left(-\mu_3 z + v\frac{yz}{z+K}\right). \tag{25}$$

Combining (23), (24), (25), we have

$$\begin{aligned}\left.\frac{dV}{dt}\right|_{(2)} = {} & \frac{dV_1(\phi)}{dt} + \frac{dV_2(\phi)}{dt} + \frac{dV_3(\phi)}{dt} \\ = {} & -\mu_1\frac{(x-\bar{x})^2}{x} - \frac{\gamma yz^2}{\sigma(z+K)} + \frac{\gamma}{\sigma}z\left(\frac{\sigma\beta\lambda - \mu_1\mu_2}{\mu_2\beta} - \frac{K\mu_3}{v}\right) \\ & +\beta\bar{x}\bar{y}\left(2 - \frac{\bar{x}}{x} - \frac{x(t-\tau_1)y(t-\tau_1)}{\bar{x}y} + \ln\frac{x(t-\tau_1)y(t-\tau_1)}{xy}\right) \\ = {} & -\mu_1\frac{(x-\bar{x})^2}{x} - \beta\bar{x}\bar{y}\left(\frac{\bar{x}}{x} - \ln\frac{\bar{x}}{x} - 1\right) \\ & -\beta\bar{x}\bar{y}\left(\frac{x(t-\tau_1)y(t-\tau_1)}{\bar{x}y} - \ln\frac{x(t-\tau_1)y(t-\tau_1)}{\bar{x}y} - 1\right) \\ & -\frac{\gamma yz^2}{\sigma(z+K)} + \frac{\gamma}{\sigma}z\left(\frac{\sigma\beta\lambda - \mu_1\mu_2}{\mu_2\beta} - \frac{K\mu_3}{v}\right) \\ = {} & -\mu_1\frac{(x-\bar{x})^2}{x} - \beta\bar{x}\bar{y}g\left(\frac{\bar{x}}{x}\right) - \beta\bar{x}\bar{y}g\left(\frac{x(t-\tau_1)y(t-\tau_1)}{\bar{x}y}\right) \\ & -\frac{\gamma yz^2}{\sigma(z+K)} + \frac{\gamma z}{\sigma}\frac{v\sigma\beta\lambda - \mu_2(\mu_1 v + \mu_3\beta K)}{v\mu_2\beta}.\end{aligned}$$

Then, $V' = 0$ if and only if

$$x = \bar{x}, \quad z = 0. \tag{26}$$

Substitute (26) into the first equation in system (2), we have $y = \bar{y}$. By the LaSalle-Lyapunov theorem ([10],Theorem 3.4.7), the largest compact invariant set of $\mathcal{A}_0$ is the singleton point P_2. Thus, we conclude that P_2 is globally attractive in $\mathcal{F}\backslash\{\text{x-axis}\}$. Since we have shown above that P_2 is locally asymptotically stable in $\mathcal{F}\backslash\{\text{x-axis}\}$ as $R_1 < 1 < R_0$, the proof is complete. □

3.3. **Uniform persistence when $R_1 > 1$.** As $R_1 > 1$, system (2) has a unique endemic HAM/TSP equilibrium $P_3 = (x^*, y^*, z^*)$. We further have the following uniform persistence result.

Theorem 3.3. *System (2) with $\tau_1 \geq 0$, $\tau_2 \geq 0$, and initial conditions given in (3) is uniformly persistent if $R_1 > 1$; that is, there exists a positive constant $\varepsilon_0 > 0$ such that all solutions of (2) satisfy*

$$\liminf_{t\to\infty}\big(x(t,\phi), y(t,\phi), z(t,\phi)\big) \geq \varepsilon_0.$$

Proof. It follows from Lemma 2.1 and the similar arguments in [19, Proposition 1] that $x(t)$ has positive ultimate lower boundary. Thus it suffices to prove both of $y(t)$ and $z(t)$ have positive eventual lower boundaries.

Define

$$X := \{(\phi_1, \phi_2, \phi_3) \in R_+ \times C^+ \times C^+\},$$

and

$$X_0 := \{(\phi_1, \phi_2, \phi_3) \in X : \phi_2(0) > 0, \phi_3(0) > 0\}, \quad \partial X_0 = X \backslash X_0.$$

Let $\Psi(t) : X \to X$ be the solution semiflow of system (2), that is, $\Psi(\phi) = (x_t(\phi), y_t(\phi), z_t(\phi))$. We proved earlier that the solution semiflow $\Psi(\phi)$ of (2) has a global attractor $\mathcal{F}$ on X. Clearly, X_0 is relatively closed in X. Moreover, by Lemma 2.2, system (2) is positively invariant and point dissipative in R_3^+. Thus X_0 is positively invariant for Ψ.

Define

$$\Omega_\partial := \{\phi \in X : \Psi(\phi) \in \partial X_0, \ \forall t \geq 0\}.$$

We now claim that

$$\Omega_\partial = \{\phi \in \partial X_0 : y(t, \phi) = 0 \text{ for } \forall t \geq 0, \text{ or } z(t, \phi) = 0 \text{ for } \forall t \geq 0\}. \tag{27}$$

Assume $\phi \in \Omega_\partial$. We only need to show that either $y(t, \phi) = 0$ for $\forall t \geq 0$ or $z(t, \phi) = 0$ for all $t \geq 0$. For the sake of contradiction, assume that there exist two nonnegative constants $t_0 \geq t_1$ such that $y(t_0, \phi) > 0, z(t_1, \phi) > 0$. Following the definition of Ω_∂, one must have $y(t_1, \phi) = z(t_0, \phi) = 0$.

By the last two equations in (2) and Lemma 2.2, we have

$$\frac{dy(t, \phi)}{dt} \geq -(\mu_2 + \gamma z(t, \phi))y(t, \phi), \ \forall t \geq t_0,$$

and

$$\frac{dz(t, \phi)}{dt} \geq -\mu_3 z(t, \phi), \forall t \geq t_1.$$

Thus using the comparison principle, we have $y(t, \phi) > 0$, for all $t \geq t_0$, and $z(t, \phi) > 0$, for all $t \geq t_1$, which contradicts $y(t_1, \phi) = z(t_0, \phi) = 0$. This proves (27).

We now let

$$\Theta_0 := \bigcap_{\phi \in Z_0} w(\phi).$$

Here Z_0 is the global attractor of $\Psi(t)$ restricted to ∂X_0. We claim that $\Theta_0 = \{P_1\} \bigcup \{P_2\}$. In fact, $\Theta_0 \subseteq \Omega_\partial = \{(x(t, \phi), y(t, \phi), 0), (x(t, \phi), 0, z(t, \phi))\}$. If $y(t, \phi) = z(t, \phi) = 0$, for all $t \geq 0$, by (2), we obtain $\lim_{t \to \infty} x(t) = \lambda/\mu_1$. Thus $P_1 \in \Theta_0$. For other cases, using Theorem 3.2, we have $\lim_{t \to \infty}(x(t, \phi), y(t, \phi), 0) = P_2$ if $y(t, \phi) > 0$ for some $t \geq 0$; and we get $\lim_{t \to \infty}(x(t, \phi), 0, z(t, \phi)) = P_1$ given that $z(t, \phi) > 0$ for some $t \geq 0$, proving $\Theta_0 = \{P_1\} \bigcup \{P_2\}$.

Since $\{P_1\}, \{P_2\}$ are two isolated invariant sets of $\Psi(t)$ in Ω_∂, using the similar arguments for Theorem 3.2 and noting $R_0 > R_1 > 1$, we can prove that P_2 is asymptotically stable in Ω_∂ as defined in (27). Hence Θ_0 has an acyclic covering.

Next, we prove that $W^s(P_i) \cap X_0 = \emptyset$, $i = 1, 2$. For $i = 1$, suppose it is not true; that is, there exists a solution $(x(t, \phi), y(t, \phi), z(t, \phi)) \in X_0$, such that $\lim_{t \to \infty}(x(t, \phi), y(t, \phi), z(t, \phi)) = P_1$. Then for any sufficiently small $\varepsilon > 0$, there is $T_1 = T_1(\varepsilon)$ large enough, such that $x(t) > \frac{\lambda}{\mu_1} - \varepsilon, \max\{y(t), z(t)\} < \varepsilon$ for all $t \geq T_1$, and $y, z \to 0$, as $t \to \infty$.

Let

$$U(t) := \int_{t - \tau_1}^{t} \sigma \beta x(\xi) y(\xi) d\xi + y.$$

Then we have $U(t) > 0$ and $\lim_{t \to \infty} U(t) = 0$.

However, by the assumption $R_0 > R_1 > 1$, we have the time derivative of $U(t)$ satisfy

$$\frac{dU}{dt}\Big|_{(2)} \geq \left(\sigma\beta(\frac{\lambda}{\mu_1} - \varepsilon) - \mu_2 - \gamma\varepsilon\right) y > 0, \ \forall\ t \geq T_1,$$

which is a contradictions to $\lim_{t\to\infty} U(t) = 0$. This proves the case $i = 1$. Similarly we can prove the case $i = 2$. By [29, Theorem 1.3.2], we conclude that there exists $\varepsilon_0 > 0$ such that $\liminf_{t\to\infty}(y(t,\phi), z(t,\phi)) \geq \varepsilon_0$ for any $\phi \in X_0$. This shows the uniform persistence of solutions of system (2). The proof is completed. □

3.4. **Special case with $R_1 > 1$, $\tau_1 > 0$, and $\tau_2 = 0$.**

Theorem 3.4. *For system (2), if $R_1 > 1$, the HAM/TSP equilibrium P_3 is globally attractive.*

Proof. Consider the following Lyapunov functional

$$V(\phi) = W_1(\phi) + W_2(\phi) + W_3(\phi),$$

where

$$W_1(\phi) := x^* g\left(\frac{\phi_1(0)}{x^*}\right), \tag{28}$$

$$W_2(\phi) := \frac{1}{\sigma} y^* g\left(\frac{\phi_2(0)}{y^*}\right) + \beta x^* y^* \int_{-\tau_1}^{0} g\left(\frac{\phi_1(s)\phi_2(s)}{x^* y^*}\right) ds, \tag{29}$$

and

$$W_3(\phi) := \frac{\gamma(z^* + K)}{v\sigma} z^* g\left(\frac{\phi_3(0)}{z^*}\right), \tag{30}$$

respectively.

The derivatives of (28), (29), and (30) along the solutions of system (2) are

$$\frac{dW_1(\phi)}{dt} = \left(1 - \frac{x}{x^*}\right)(\mu_1 x^* - \mu_1 x + \beta x^* y^* - \beta x y), \tag{31}$$

$$\begin{aligned}\frac{dW_2(\phi)}{dt} = \ & \frac{1}{\sigma}\left(1 - \frac{y}{y^*}\right)\left(\sigma\beta x(t-\tau_1)y(t-\tau_1) - \mu_2 y - \gamma y z\right) \\ & + \beta x^* y^* \left(\frac{xy - x(t-\tau_1)y(t-\tau_1)}{x^* y^*}\right) + \ln\frac{x(t-\tau_1)y(t-\tau_1)}{xy},\end{aligned} \tag{32}$$

and

$$\frac{dW_3(\phi)}{dt} = \frac{\gamma(z^* + K)}{v\sigma} z^* \left(1 - \frac{z}{z^*}\right)\left(v\frac{yz}{z + K} - \mu_3 z\right), \tag{33}$$

respectively.

Combining (31), (32), (33), we have

$$\begin{aligned}\frac{dV}{dt}\Big|_{(2)} = & -\frac{\mu_1(x - x^*)^2}{x}\beta x^* y^* \left(g\left(\frac{x^*}{x}\right) + g\left(\frac{x(t-\tau_1)y(t-\tau_1)}{x^* y}\right)\right) \\ & - \frac{\gamma y}{\sigma(z + K)}(z - z^*)^2.\end{aligned}$$

It then follows that $\frac{dV}{dt} \leq 0$, and $\frac{dV}{dt} = 0$ if and only if

$$z = z^*, \quad y = y^*, \quad z = z^*.$$

Similarly as in the proof of Theorem 3.1, by LaSalle-Lyapunov theorem ([10],Theorem 3.4.7), P_3 is globally attractive in $\mathcal{F}$ if $R_1 > 1$. □

3.5. **Special case with $R_1 > 1$, $\tau_1 = 0$, and $\tau_2 > 0$.** For $\tau_1 = 0, \tau_2 > 0$, the characteristic equation of system (2) in $P_3 = (x^*, y^*, z^*)$ is

$$G(s) = \det\left(sE - A_0 - A_1 e^{-s\tau_2}\right), \tag{34}$$

where

$$A_0 := \begin{pmatrix} -\mu_1 - \beta y^* & -\beta x^* & 0 \\ \sigma\beta y^* & 0 & -\gamma y^* \\ 0 & 0 & -\mu_3 \end{pmatrix}, \; A_1 := \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & \dfrac{vz^*}{z^*+K} & \dfrac{vKy^*}{(z^*+K)^2} \end{pmatrix}.$$

It follows from $G(s) = 0$ that we have the following characteristic equation

$$s^3 + a_1 s^2 + a_3 s + a_6 + (a_2 s^2 + a_4 s + a_5) e^{-s\tau_2} = 0, \tag{35}$$

where

$$a_1 := \mu_1 + \mu_3 + \beta y^*, \quad a_2 := -\frac{Kvy^*}{(z^*+K)^2},$$

$$a_3 := \sigma\beta^2 x^* y^* + \mu_3(\mu_1 + \beta y^*), \quad a_4 := \frac{v\gamma y^* z^*}{z^*+K} - \frac{vKy^*(\mu_1 + \beta y^*)}{(z^*+K)^2},$$

$$a_5 := (\mu_1 + \beta y^*)\frac{v\gamma y^* z^*}{z^*+K} - \frac{vKy^*}{(z^*+K)^2}\sigma\beta^2 x^* y^*, \quad a_6 := \mu_3\sigma\beta^2 x^* y^*.$$

Since $a_5 + a_6 > 0$, $\lambda = 0$ is not a root of (35). If $i\omega$, $\omega > 0$, is a purely imaginary root of (35), separating the real and imaginary parts leads to

$$\begin{cases} \omega^3 - a_3\omega = & (a_2\omega^2 - a_5)\sin\omega\tau_2 + a_4\omega\cos\omega\tau_2, \\ a_1\omega^2 - a_6 = & a_4\omega\sin\omega\tau_2 - (a_2\omega^2 - a_5)\cos\omega\tau_2. \end{cases} \tag{36}$$

Squaring the both sides of the two equations in (36) and adding them up gives

$$\omega^6 + (a_1^2 - 2a_3 - a_2^2)\omega^4 + (a_3^2 - 2a_1a_6 + 2a_2a_5 - a_4^2)\omega^2 + a_6^2 - a_5^2 = 0. \tag{37}$$

Write $z := \omega^2$, $a := a_1^2 - 2a_3 - a_2^2$, $b := a_3^2 - 2a_1a_6 + 2a_2a_5 - a_4^2$, and $c := a_6^2 - a_5^2$. Then equation (37) becomes

$$h(z) := z^3 + az^2 + bz + c. \tag{38}$$

By the Routh-Hurwitz criterion, we know that if

$$a_1 + a_2 > 0, (a_1 + a_2)(a_3 + a_4) - (a_5 + a_6) > 0, a_5 + a_6 > 0, \tag{39}$$

equation (35) has no positive real roots. Accordingly, we have the following result.

Theorem 3.5. *Suppose conditions in (39) hold and $a > 0$, $b > 0$, $c \geq 0$. Then the HAM/TSP equilibrium P_3 of system (2) is asymptotically stable.*

Proof. For h defined in (38), we have

$$\frac{dh(z)}{dz} = 3z^2 + 2az + b, \tag{40}$$

and the zeros of (40) are

$$z_{1,2} = \frac{-a \pm \sqrt{a^2 - 3b}}{3}. \tag{41}$$

If $b > 0$, then $a^2 - 3b < a^2$, that is $\sqrt{a^2 - 3b} < a$ for $a > 0$. Hence, neither z_1 nor z_2 is positive. Thus $\dfrac{dh(z)}{dz} = 0$ has no positive root. Since $h(0) = c \geq 0$, it follows that $h(z) = 0$ has no positive roots. So, the HAM/TSP equilibrium P_3 is asymptotically stable. □

Theorem 3.6. *Suppose that conditions in (39) are satisfied and that*

(i) *either* $c < 0$,
(ii) *or* $c \geq 0$, $b < 0$, *and* $H'(\omega_0^2) \neq 0$,

where ω_0 *satisfies* $G(i\omega_0) = 0$ *with* G *given in (34). Then the HAM/TSP equilibrium* P_3 *of model system (2) is asymptotically stable is* $\tau_2 < \tau_{20}$, *and is unstable if* $\tau_2 > \tau_{20}$, *where*

$$\tau_{20} = \frac{1}{\omega_0} \cos^{-1} \frac{a_4\omega_0(\omega_0^3 - a_3\omega_0) - (a_1\omega_0^2 - a_6)(a_2\omega_0^2 - a_5)}{(a_4\omega_0)^2 + (a_2\omega_0^2 - a_5)^2}.$$

As $\tau_2 = \tau_{20}$, *a Hopf bifurcation occurs; that is, a family of periodic solutions are bifurcated from* P_3 *as* τ_2 *passes through the critical value* τ_{20}.

Proof. If $c < 0$, then it follows from (38) that $h(0) < 0$ and $\lim_{z\to\infty} h(z) = \infty$. Thus, equation (37) has at least one positive root. If $b < 0$, then $\sqrt{a^2 - 3b} > a$, and function $h(z)$ in (38) has a unique positive zero $z_1 = \dfrac{-a + \sqrt{a^2 - 3b}}{3} > 0$ as in (41). As a consequence, equation (37) has a unique positive root ω_0. This implies that the characteristic equation (35) has a pair of purely imaginary roots.

Let $s(\tau_2) = \eta(\tau_2) + i\omega(\tau_2)$ be the eigenvalue of equation (35) such that $\eta(\tau_{20}) = 0$ and $\omega(\tau_{20}) = \omega_0$. From Theorem 3.5 it follows that if $b < 0$, there exists $\omega_0 > 0$, such that $G(i\omega) = 0$. Then by the first equation of (36), we have

$$\cos(\omega_0\tau_{2j}) = \frac{a_4\omega_0(\omega_0^3 - a_3\omega_0) - (a_1\omega_0^2 - a_6)(a_2\omega_0^2 - a_5)}{(a_4\omega_0)^2 + (a_2\omega_0^2 - a_5)^2},$$

and then

$$\tau_{2j} = \frac{1}{\omega_0} \cos^{-1} \frac{a_4\omega_0(\omega_0^3 - a_3\omega_0) - (a_1\omega_0^2 - a_6)(a_2\omega_0^2 - a_5)}{(a_4\omega_0)^2 + (a_2\omega_0^2 - a_5)^2} + \frac{2\pi j}{\omega_0}, j = 0, 1, \cdots.$$

We can also verify the following transversality condition ([12])

$$\begin{aligned}\left(\frac{d(Res(\tau_2))}{d\tau_2}\bigg|_{\tau_2=\tau_{20}}\right)^{-1} =& Re\left(\frac{(3s^2 + 2a_1s + a_3)e^{s\tau_2}}{s(a_2s^2 + a_4s + a_5)}\right)\bigg|_{\tau_2=\tau_{20}} \\ &+ Re\left(\frac{2a_2s + a_4}{s(a_2s^2 + a_4s + a_5)}\right)\bigg|_{\tau_2=\tau_{20}} \\ =& \frac{H'(\omega_0^2)}{a_4^2\omega_0^2 + (a_5 - a_2\omega_0^2)^2} \neq 0,\end{aligned}$$

such that if $\tau_2 = \tau_{20}$, a Hopf bifurcation occurs; that is, a family of periodic solutions appear as τ_2 passes through the critical value τ_{20}. □

4. **Numerical simulations.** To verify our analytic results, we provide numerical examples in this section.

We choose a set of parameters from Tables 1-3 corresponding to the conditions in Theorem 3.1, Theorem 3.2, and Theorem 3.4, respectively. The corresponding numerical simulations are shown in Figures 1-3.

The time scale is based on days, a production rate of $CD4^+$ T cells is within the range of $(20 - 120)$ cells/mm/day^3 [6, 12, 15], the removal rates for uninfected and infected $CD4^+$ T cells are selected in the range of $(0.01 - 0.05)$ day^{-1} [15], the death rate for HTLV-I-specific $CD8^+$ cells is selected in the range of $(0.01 - 0.4)$ day^{-1} [6, 12], and β is chosen in the range of 10^{-3}mm^3/cell/day [20]. The range

for σ is chosen as $(0.01-0.05)$ [6], for v as $(0.001-0.03)$ [6], for γ as $(0.002-0.02)$ [6], respectively. We let K be in the range of $(1-20)$ [6, 12].

Figure 4 describes the phenomenon stated in Theorem 3.6, where the set of parameters are selected from Table 4 so that we have $1 < R_1 = 8 < R_0 \approx 10.667$, $\omega_0 \approx 0.086$, and $\tau_{20} \approx 9.577$. Correspondingly, by Theorem 3.6, the HAM/TSP equilibrium P_3 is locally asymptotically stable as $\tau_2 < \tau_{20}$, and a Hopf bifurcation occurs as $\tau_2 = \tau_{20}$ such that periodic solutions exist for $\tau_2 > \tau_{20}$.

Figure 5 shows the solutions of model system (2) corresponding to the increase of τ_1 from 0 to 20, while $\tau_2 = 15$. For $\tau_1 < 8$ approximately, the solutions are all oscillatory. As τ_1 increases from 0 to 8, the vertical amplitudes of $x(t)$, $y(t)$, and $z(t)$ become smaller and smaller, and the HAM/TSP equilibrium P_3 changes from unstable for $\tau_1 < 8$ to stable for $\tau_1 > 8$.

On the other hand, it shows, in Figure 6, the stability change for the HAM/TSP equilibrium P_3 as τ_2 increases from 0 to 20 while $\tau_1 = 1$. For $\tau_2 < 7.5$ approximately, P_3 is asymptotically stable. As τ_2 increases in the interval $(7.5, 20)$, the HAM/TSP equilibrium P_3 is unstable, and the vertical amplitudes of $x(t)$, $y(t)$, $z(t)$ become larger and larger.

We then show, in Figure 7, the stability change of the HAM/TSP equilibrium P_3 as τ_1 and τ_2 simultaneously increase from 0 to 15. It seems clear that P_3 is stable as $(\tau_1, \tau_2) \in (10, 15) \times (1, 7)$. For $(\tau_1, \tau_2) \in (0, 10) \times (7, 15)$ and $\tau_1 > \frac{5}{4}\tau_2 - \frac{35}{4}$, the vertical amplitude of each component for the differences between the solutions and P_3 is sufficiently small, suggesting that P_3 is asymptotically stable. For $\tau_1 \in (0, 10), \tau_2 \in (7, 15)$ and $\tau_1 < \frac{5}{4}\tau_2 - \frac{35}{4}$ approximately, on the other hand, those vertical amplitudes become larger than zero, suggesting that P_3 is unstable. Furthermore, those vertical amplitudes become larger and larger as τ_2 increases from 7 to 15 while τ_1 gradually decreases from 10 to 0, suggesting that the HAM/TSP equilibrium P_3 becomes increasingly unstable with those parameter values.

TABLE 1.

parameter	λ	μ_1	σ	β	μ_2	γ	v	K	μ_3	τ_1	τ_2
value	20	0.05	0.01	0.001	0.05	0.02	0.03	1	0.01	5	5

TABLE 2.

parameter	λ	μ_1	σ	β	μ_2	γ	v	K	μ_3	τ_1	τ_2
value	20	0.015	0.05	0.001	0.01	0.02	0.001	1	0.4	5	5

TABLE 3.

parameter	λ	μ_1	σ	β	μ_2	γ	v	K	μ_3	τ_1	τ_2
value	20	0.01	0.02	0.001	0.005	0.02	0.03	1	0.01	10	0

TABLE 4.

parameter	λ	μ_1	σ	β	μ_2	γ	v	K	μ_3	τ_1
value	160	0.01	0.02	0.001	0.03	0.02	0.03	1	0.1	0

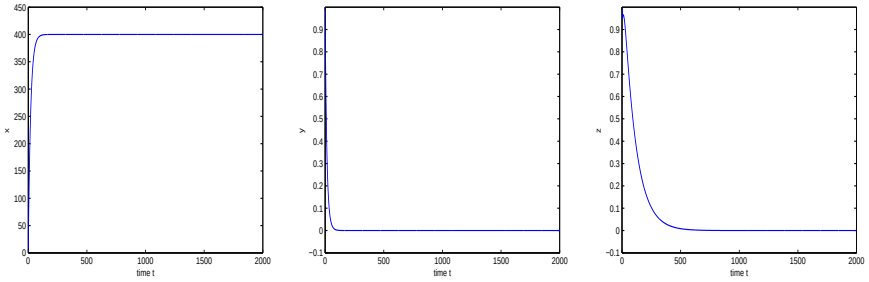

FIGURE 1. The above three graphs are about x, y, z when $R_0 = 0.08 \leq 1$.

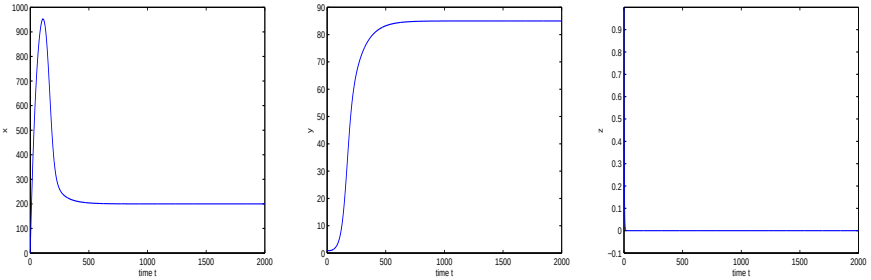

FIGURE 2. The above three graphs are about x, y, z when $R_1 \approx 0.24 < 1 < R_0 \approx 6.67$.

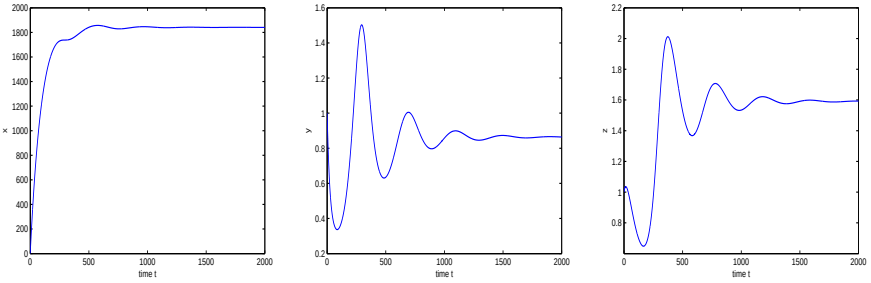

FIGURE 3. The above three graphs are about x, y, z when $R_1 \approx 7.74 > 1$.

5. **Discussion.** In this paper, we include the intracellular delay and the immune delay in an HTLV-I infection model and investigate their impact on the transmission dynamics. We derive formulas for the basic reproductive numbers of a viral

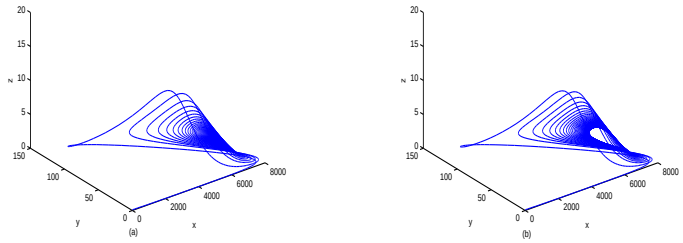

FIGURE 4. In(a), $\tau_2 = 9.4 < \tau_{20} = 9.5767$; In(b), $\tau_2 = 9.8 > \tau_{20} = 9.5767$.

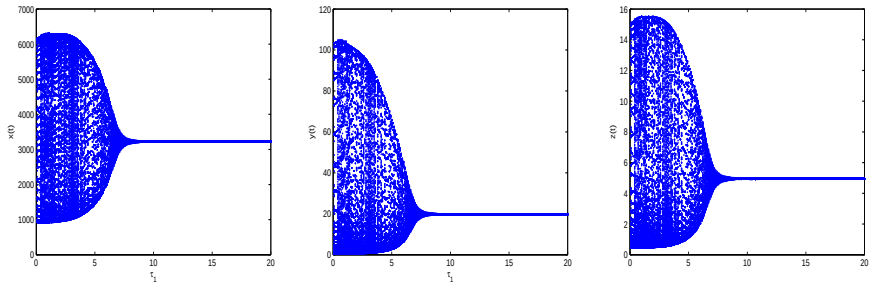

FIGURE 5. The ultimate oscillation interval of the solution to system (2) when τ_1 increases from 0 to 20, here $\tau_2 = 15, t \in [500, 5000]$.

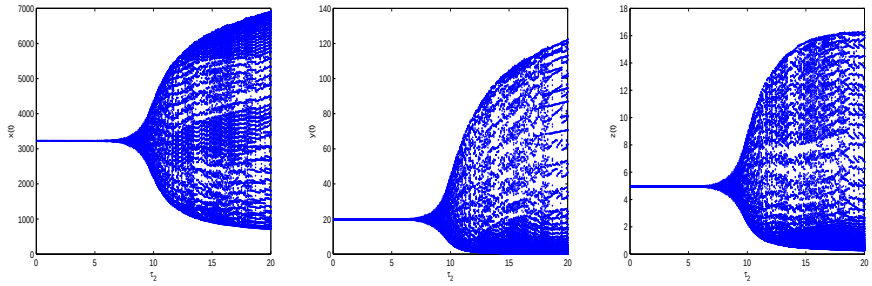

FIGURE 6. The ultimate oscillation interval of the solution to system (2) as τ_2 increases from 0 to 20, here $\tau_1 = 1, t \in [500, 5000]$.

infection, R_0, and of a CTL response, R_1, and show that the infection-free equilibrium P_1 is globally asymptotically stable if $R_0 < 1$ (Theorem 3.1 and Figure 1), the immune-free equilibrium P_2 is globally asymptotically stable if $R_1 < 1 < R_0$ (Theorem 3.2 and Fig. 2), and the HAM/TSP equilibrium P_3 is globally attractive if $\tau_1 > 0, \tau_2 = 0$ (Theorem 3.4 and Figure 3). Moreover, if $1 < R_1$, system (2) is uniformly persistent with chronic infection and CTL response (Theorem 3.3). We also show that if $\tau_1 = 0$ and $\tau_2 > 0$, P_3 is asymptotically stable for small τ_2 (Theorem 3.5 and Figure 4 (a)) and that an increase of τ_2 can destabilize P_3 and lead to a Hopf bifurcation (Theorem 3.6 and Figure 4 (b)). Theorems 3.1, 3.2 and 3.4 in

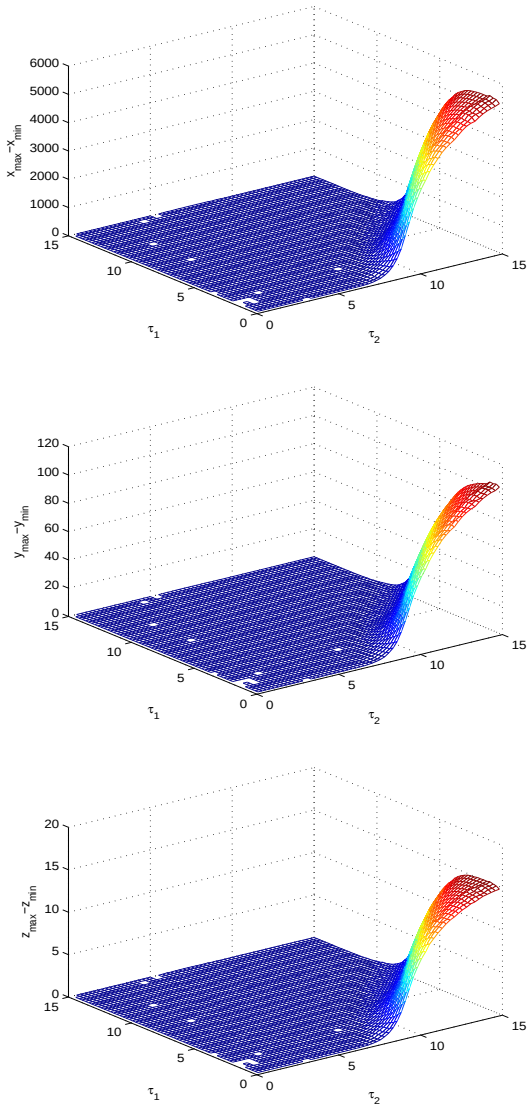

FIGURE 7. The ultimate vertical amplitude of the solution to system (2) according to increase of τ_1, τ_2, here $t \in [500, 5000]$.

this paper improve and extend the results of [6, Theorem 3.1]. Comparing (1) with [6, Theorem 3.1], our results also suggest that introducing the intracellular delay τ_1 does not necessarily alter the stability of equilibria.

The more interesting results from this paper are the effects by delays τ_1, τ_2. First, τ_1 may stabilize P_3 such that the increase of τ_1 from zero can reduce the oscillation amplitudes of solutions, and a sufficiently large τ_1 may drive P_3 into asymptotically stable (Figures 5 and 7), suggesting that ignoring τ_1 may miss some stability region of P_3. Second, we show that as τ_2 increases from zero, P_3 may lose its stability and a Hopf bifurcation may appear. With further increases of τ_2 P_3 becomes increasingly

unstable by enlarging the amplitude of the oscillation interval (Figures 6 and 7), implying that time delays in the CTL activation process may be responsible for the oscillations of the proviral load and the CTL frequency. Moreover, if both delays τ_1 and τ_2 increase, the stability of P_3 may generate rich dynamics in mixing the "stabilizing" effects from τ_1 with those "destabilizing" influences from τ_2, suggesting that introducing the two delays does not necessarily lead to increasingly unstable behaviors (Figure 7).

For the case where both delays τ_1 and τ_2 exist, we remark that the stability switching regions of the HTLV-I model and the stability of the bifurcated periodic solutions are still analytically unclear. As is shown in [7], the stability crossing set can be expressed by a few inequality constraints and the crossing curves may be closed curves, open ended curves, or spiral-like curves oriented horizontally, vertically, or diagonally. Identifying the local stability regions if both the intracellular delay and the immune delay vary within their biologically reasonable ranges remains a potential topic for future investigations.

Acknowledgments. The authors are grateful to the editor, Professor Yang Kuang, the handling editor, Professor James Watmough, and the two anonymous referees for their valuable comments and suggestions, which greatly improved the presentation of this work. XL is supported by Heilongjiang Provincial Education research grant (No. 12531763). This work is partially completed during XL's visit to Harbin Institute of Technology, she would like to acknowledge the hospitality received there and the support of Visiting Scholar Program by the Department of Education, Heilongjiang Province. SL is supported by the NNSF of China (No. 11471089, 11301453) and the Fundamental Research Funds for the Central Universities (Grant No. HIT. IBRSEM. A. 201401). JL is supported partially by U.S. National Science Foundation grant DMS-1118150.

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Received December 30, 2013; Accepted December 15, 2014.

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