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

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Abstract. In this paper, the main purpose is to promote the global dynamics of system (2) in [1]. By using method of constructing Lyapunov functionals, we establish global asymptotic stability of the infection-free equilibrium, the immune-free equilibrium and the existence of a unique HAM/TSP equilibrium. 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.

Keywords: HTLV-I infection; Epidemic threshold; Time delay; Lyapunov functional; Global dynamics.

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1. Introduction

In [1], Lu , Hui and Liu consider the following system:

$$\frac{dx}{dt} = \lambda - \mu_1 x(t) - \beta x(t)y(t),$$
$$\frac{dy}{dt} = \sigma\beta x(t-\tau_1)y(t-\tau_1) - \mu_2 y(t) - \gamma y(t)z(t),$$

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$$\frac{dz}{dt} = v\frac{y(t-\tau_2)z(t-\tau_2)}{z(t-\tau_2)+K} - \mu_3 z(t). \quad (1)$$

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 main purpose of [1] is to explore the global dynamics of system (1) and investigate the impact of the intracellular delay τ_1 and the immune delay τ_2 on the dynamical behavior of the system. Lu et al 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, Lu et al [1] show that the immune delay can destabilize the HAM/TSP equilibrium, leading to Hopf bifurcations. 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. In this paper, we shall investigate HTLV-I Infection Model which includes a nonlinear incidence rate $h(x,y)$. We consider the following system:

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

where all the other parameters of model (1) except τ_1, τ_2 are the same as model (2). The nonlinear incidence function $h(x,y)$ is assumed to satisfy the following conditions: In this paper, we assume that the function $h(x,y)$ is always positive, differentiable, and monotonically increasing for all $x>0, y>0$, and that $h(x,y)$ is concave with respect to y; that is, it satisfies the following :

(H1) $h(x,y), h_x(x,y), h_y(x,y)$, and $-h_{yy}(x,y)$ are positive for any $x>0$ and $y>0$. Furthermore $h(x,0)=h(0,y)=0$, $h_y(x,y)>0$ for $x>0$ and $y>0$.

(H2)$h'_y(x,0)$ is increasing with respect to $x>0$.

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. Numerical simulations are presented in Section 4, and brief conclusions 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 (**??**) 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

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

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

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

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

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

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:

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

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

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

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

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

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 $P_1 = \left(\frac{\lambda}{\mu_1}, 0, 0\right)$. The reproductive number of a viral infection is defined as $R_0 := \left(\frac{\sigma}{\mu_2} \frac{\partial h(x_0, 0)}{\partial y}\right)$. There exists an equilibrium $P_2 = (\bar{x}, \bar{y}, 0)$ with no CTL response, as $R_0 > 1$, that we call the immune-free equilibrium, which satisfies

$$\lambda - \mu_1 \bar{x} - h(\bar{x}, \bar{y}) = 0,$$

$$\sigma h(\bar{x}, \bar{y}) - \mu_2 \bar{y} = 0,$$

We define $R_1 := \left(\frac{v\bar{y}}{\mu_3 k}\right)$. We call R_1 the basic reproductive number of a CTL response.

In the following, we give a lemma gives the existence condition of the immune-free equilibrium.

Lemma 2.3. *If $R_0 > 1$, then there exists a immune-free equilibrium $P_2 = (\bar{x}, \bar{y}, 0)$.*

Proof. Let the right-hand sides of the three equations in system (2) equal zero, and we have that

$$\lambda - \mu_1 x = h(x,y) = \frac{\mu_2}{\sigma} y.$$

After substituting the expression of x by y, we obtain the following equation for y:

$$H(y) = h(\frac{\lambda\sigma - \mu_2 y}{\sigma\mu_1}, y) - \frac{\mu_2}{\sigma} = 0.$$

It is obvious that $H(0) = 0$, and when $y = y_0 = \frac{\lambda\sigma}{\mu_2}$,

$$H(y_0) = h(0, y_0) - \lambda = -\lambda < 0.$$

Since $H(y)$ is continuous for $y \geq 0$, we have that

$$H'(0) = \lim_{y\to 0^+} \frac{H(y) - H(0)}{y} = \frac{\partial h(x_0,0)}{\partial y} - \frac{\mu_2}{\sigma} - \frac{\mu_2}{\sigma\mu_1}\partial h'_x(x_0,0) = \frac{\mu_2}{\sigma}(R_0 - 1).$$

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

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

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 $x = 1$.

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

Proof. From (**H2**), it is easy to see that the following inequalities hold:

$$\frac{h'_y(x_0,0)}{h'_y(x,0)} > 1 \ \ for \ \ x \in (0,x_0) \ \ and \ \ \frac{h'_y(x_0,0)}{h'_y(x,0)} < 1 \ \ for \ \ x > x_0. \tag{6}$$

We define the following Lyapunov functional

$$U = U_1(x_t, y_t, z_t) + U_2 + U_3,$$

where

$$U_1(x_t, y_t, z_t) := x(t) - x_0 - \int_{x_0}^{x(t)} \lim_{y \to 0^+} \frac{h(x_0,y)}{h(\theta,y)} d\theta + \frac{1}{\sigma} y + \frac{k\gamma}{v\sigma} z, \tag{7}$$

$$U_2 := \int_0^{\tau_1} h(x(t-\theta), y(t-\theta)) d\theta, \tag{8}$$

and

$$U_3 := \frac{k\gamma}{v\sigma} \int_0^{\tau_2} \frac{vy(t-\theta)z(t-\theta)}{z(t-\theta)+k} d\theta. \tag{9}$$

Calculating the time derivatives of (7), (8) and (9) along solutions of system (2), we have

$$\begin{aligned} \frac{dU_1}{dt} = &\left(1 - \lim_{y \to 0^+} \frac{h(x_0,y)}{h(x,y)}\right)(\lambda - \mu_1 x - h(x,y)) + h(x(t-\tau_1), y(t-\tau_1)) \\ &- \frac{\mu_2}{\sigma} y - \frac{\gamma}{\sigma} yz + \frac{k\gamma}{v\sigma}\left(v\frac{y(t-\tau_2)z(t-\tau_2)}{z(t-\tau_2)+K} - \mu_3 z(t)\right), \end{aligned} \tag{10}$$

$$\frac{dU_2}{dt} = h(x,y) - h(x(t-\tau_1), y(t-\tau_1)), \tag{11}$$

and

$$\frac{dU_3}{dt} = \frac{K\gamma}{v\sigma}\left(v\frac{yz}{z+K} - v\frac{y(t-\tau_2)z(t-\tau_2)}{z(t-\tau_2)+K}\right). \tag{12}$$

Combining(10), (11), and (12), we have

$$\begin{aligned}\frac{dU}{dt}\bigg|_{(2)} &= -\mu_1 x\left(\frac{x_0}{x}-1\right)\left(1-\lim_{y\to 0^+}\frac{h(x_0,y)}{h(x,y)}\right)\\ &\quad + h(x,y)\lim_{y\to 0^+}\frac{h(x_0,y)}{h(x,y)} - \frac{\mu_2}{\sigma}y - \frac{\gamma}{\sigma}yz + \frac{K\gamma}{\sigma}\frac{yz}{z+K} - \frac{K\gamma\mu+3}{v\sigma}z\\ &= -\mu_1 x\left(\frac{x_0}{x})-1\right)\left(1-\lim_{y\to 0^+}\frac{h(x_0,y)}{h(x,y)}\right)\\ &\quad + \frac{\mu_2}{\sigma}\left(\frac{\sigma}{\mu_2}\frac{h(x,y)}{y})\lim_{y\to 0^+}\frac{h(x_0,y)}{h(x,y)}-1\right) - \frac{\gamma y z^2}{\sigma(z+k)}.\end{aligned}$$

From **(H2)**, it is easy to see that the following inequalities hold:

$$\frac{h'_y(x_0,0)}{h'_y(x,0)} > 1 \quad for \quad x\in(0,x_0),$$

$$\frac{h'_y(x_0,0)}{h'_y(x,0)} < 1 \quad for \quad x > x_0.$$

We have

$$\left(\frac{x_0}{x}-1\right)\left(1-\lim_{y\to 0^+}\frac{h(x_0,y)}{h(x,y)}\right) = \left(\frac{x_0}{x}-1\right)\left(1-\frac{h'_y(x_0,0)}{h'_y(x,0)}\right) \le 0.$$

Furthermore, the concavity of $h(x,y)$, with respect to y implies that

$$\begin{aligned}\frac{\sigma}{\mu_2}\frac{h(x,y)}{y}\lim_{y\to 0^+}\frac{h(x_0,y)}{h(x,y)} &= \frac{\sigma}{\mu_2}\frac{h(x,y)}{y}\frac{\frac{\partial h(x_0,0)}{\partial y}}{\frac{\partial h(x,0)}{\partial y}}\\ &\le \frac{\sigma}{\mu_2}\frac{\partial h(x_0,0)}{\partial y}\\ &= R_0.\end{aligned}$$

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

Set

$$\mathscr{A}_0 = \left\{(x,y,z)\in\mathscr{F} | U' = 0\right\}.$$

Then $\frac{\mathrm{d}U}{\mathrm{d}t} = 0$ if and only if

$$x = x^*, \;\; z = 0. \tag{13}$$

Substituting (13) into the first equation in system (2) then yields $y = 0$. By the LaSalle-Lyapunov theorem ([2], Theorem 3.4.7), the largest compact invariant set of $\mathscr{A}_0$ is the singleton point P_1. Thus we conclude that P_1 is globally asymptotically stable in $\mathscr{F}$.

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

Proof. From (2), there exists a immune-free equilibrium P_2, when $R_0 > 1$. Define a Lyapunov functional for P_2:

$$V = V_1 + V_2 + V_3,$$

where

$$V_1 := x - \bar{x} - \int_{\bar{x}}^{x} \frac{h(\bar{x},\bar{y})}{h(s,\bar{y})} ds, \tag{14}$$

$$V_2 := \frac{1}{\sigma}\left(\bar{y} g\left(\frac{y}{\bar{y}}\right) + \sigma h(\bar{x},\bar{y}) \int_0^{\tau_1} g\left(\frac{h(x,y)}{h(\bar{x},\bar{y}}\right) ds\right), \tag{15}$$

and

$$V_3 := \frac{K\gamma}{v\sigma}\left(z + v\int_0^{\tau_2} \frac{yz}{z+K} ds\right). \tag{16}$$

Then calculating the time derivatives of (14), (15), and (16) along solutions of system (2) yields

$$\frac{dV_1}{dt} = \left(1 - \frac{h(\bar{x},\bar{y})}{h(x,\bar{y})}\right)(\lambda - \mu_1 - h(x,y)), \tag{17}$$

$$\begin{aligned} \frac{dV_2}{dt} =& \frac{1}{\sigma}\frac{y-\bar{y}}{y}\left(\sigma h(x(t-\tau_1),y(t-\tau_1)) - \mu_2 y - \gamma yz\right) \\ &+ h(x,y) - h(x(t-\tau_1),y(t-\tau_1)) + h(\bar{x},\bar{y}) \ln \frac{h(x(t-\tau_1),y(t-\tau_1))}{h(x,y)}, \end{aligned} \tag{18}$$

and

$$\frac{dV_3}{dt} = \frac{K\gamma}{v\sigma}\left(-\mu_3 z + v\frac{yz}{z+K}\right). \tag{19}$$

Combining (17), (18), (19), we have

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

From the monotonicity of the function $h(x,y)$ on x, the following inequality holds:

$$\left(1-\frac{x}{\bar{x}}\right)\left(1-\frac{h(\bar{x},\bar{y})}{h(x,\bar{y})}\right)\le 0.$$

Furthermore, from the concavity and monotonicity of the function $h(x,y)$ on y, the inequalities

$$1\ge\frac{h(x,y)}{h(x,\bar{y})}\ge\frac{y}{\bar{y}}\ \ for\ \ 0<y\le y^*,\quad and\quad 1\le\frac{h(x,y)}{h(x,\bar{y})}\le\frac{y}{\bar{y}}\ \ for\ \ y\ge y^*. \tag{20}$$

hold, which implies that

$$\left(\frac{y}{\bar{y}}-\frac{h(x,y)}{h(x,\bar{y})}\right)\left(\frac{h(x,\bar{y})}{h(x,y)}-1\right)\le 0.$$

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

$$x = \bar{x}, \;\; z = 0. \tag{21}$$

Substitute (21) into the first equation in system (2), we have $y = \bar{y}$. By the LaSalle-Lyapunov theorem ([2], Theorem 3.4.7), the largest compact invariant set of $\mathscr{A}_0$ is the singleton point P_2. Thus, we conclude that P_2 is globally asymptotically stable in $\mathscr{F}\backslash\{\text{x-axis}\}$. This completes the proof.

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 [8, Proposition 1]8 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

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

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 $\mathscr{F}$ 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

$$\Omega_\partial = \{\phi \in \partial X_0 : y(t,\phi) = 0 \text{ for } \forall t \geq 0, \text{ or } z(t,\phi) = 0 \text{ for } \forall t \geq 0\}. \tag{22}$$

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 (22).

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 (9). 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

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

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

$$\frac{dU}{dt}\bigg|_{(2)} \geq \left(\sigma h'_y(\frac{\lambda}{\mu_1} - \varepsilon, 0) - \mu_2 - \gamma\varepsilon\right) y > 0, \ \forall\, t \geq T_1,$$

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 ([7] 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).This completes the proof.

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

$$W = W_1 + W_2 + W_3,$$

where

$$W_1 := x - x^* - \int_{x^*}^{x} \frac{h(x^*, y^*)}{h(s, y^*)} ds, \tag{23}$$

$$W_2 := \frac{1}{\sigma} y^* g\left(\frac{y}{y^*}\right) + h(x^*, y^*) \int_0^{\tau_1} g\left(\frac{h(x(t-\tau_1), y(t-\tau_1))}{h(x^*, y^*)}\right) ds, \tag{24}$$

and

$$W_3 := \frac{\gamma(z^* + K)}{v\sigma} g\left(\frac{z}{z^*}\right), \tag{25}$$

respectively.

The derivatives of (23), (24), and (25) along the solutions of system (2) are

$$\frac{dW_1}{dt} = \left(1 - \frac{h(x^*, y^*)}{h(x, y^*)}\right)\left(\mu_1 x^* - \mu_1 x + h(x^*, y^*) - h(x, y)\right), \tag{26}$$

$$\begin{aligned}\frac{dW_2}{dt} =& \frac{1}{\sigma}\left(1 - \frac{y}{y^*}\right)\left(\sigma h(x(t-\tau_1), y(t-\tau_1)) - \mu_2 y - \gamma y z\right) \\ &+ h(x^*, y^*)\left(\frac{h(x, y) - h(x(t-\tau_1), y(t-\tau_1))}{h(x^*, y^*)}\right) + \ln\frac{h(x(t-\tau_1), y(t-\tau_1))}{h(x, y)},\end{aligned} \tag{27}$$

and

$$\frac{dW_3}{dt} = \frac{\gamma(z^* + K)}{v\sigma}\left(1 - \frac{z^*}{z}\right)\left(v\frac{yz}{z + K} - \mu_3 z\right), \tag{28}$$

respectively.

Combining (26), (27), (28), we have

$$
\begin{aligned}
\left.\frac{dW}{dt}\right|_{(2)} =&\mu_1 x^* \left(\frac{x}{x^*}\right)\left(\frac{h(x^*,y^*)}{h(x,y^*)}\right) - h(x^*,y^*) g\left(\frac{h(x^*,y^*)}{h(x,y^*)}\right) \\
&- h(x^*,y^*) g\left(\frac{y^* h(x(t-\tau_1), y(t-\tau_1))}{y h(x^*,y^*)}\right) - h(x^*,y^*) g\left(\frac{y h(x,y^*)}{y^* h(x,y)}\right) \\
&+ h(x^*,y^*)\left(\frac{y}{y^*} - \frac{h(x,y)}{h(x,y^*)}\right)\left(\frac{h(x,y^*)}{h(x,y)} - 1\right) \\
&- \frac{\gamma y}{\sigma(z+K)}(z-z^*)^2.
\end{aligned}
\tag{29}
$$

It then follows that $\frac{dW}{dt} \leq 0$, and $\frac{dW}{dt} = 0$ 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 ([2], Theorem 3.4.7), P_3 is globally attractive in $\mathscr{F}$ if $R_1 > 1$. This completes the proof.

4. Numerical simulations

In this section, we present computer simulation of some results of the system (2) with $h(x,y) = \frac{\beta xy}{1+cy}, c = 0.01$ using MATLAB, and most of these values are taken from the data of [1], that is: 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 [3][4][5], the removal rates for uninfected and infected $CD4^+$ T cells are selected in the range of $(0.01-0.05)$ day^{-1} [5], the death rate for HTLV-I-specific $CD8^+$ cells is selected in the range of $(0.01-0.4)$ day^{-1} [3][4], and β is chosen in the range of 10^{-3}mm^3/cell/day [6]. The range for σ is chosen as $(0.01-0.05)$ [3], for ν as $(0.001-0.03)$ [3], for γ as $(0.002-0.02)$ [3], respectively. We let K be in the range of $(1-20)$ [3][4].

Figure 4 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

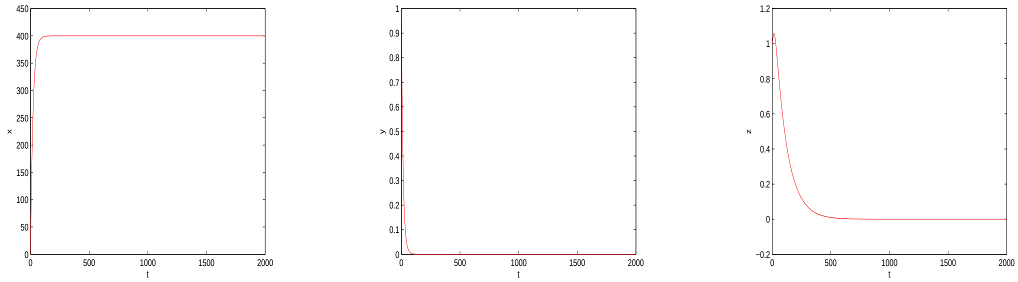

FIGURE 1. The above three graphs are about x, y, z when $R_0 = 0.08 \leq 1$.

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 5, 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.

Parameter table

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

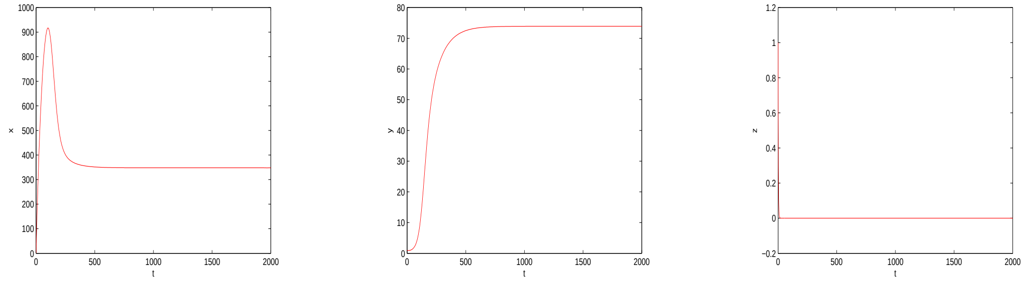

FIGURE 2. The above three graphs are about x, y, z when $R_1 \approx 0.24 < 1 < R_0 \approx 6.67$.

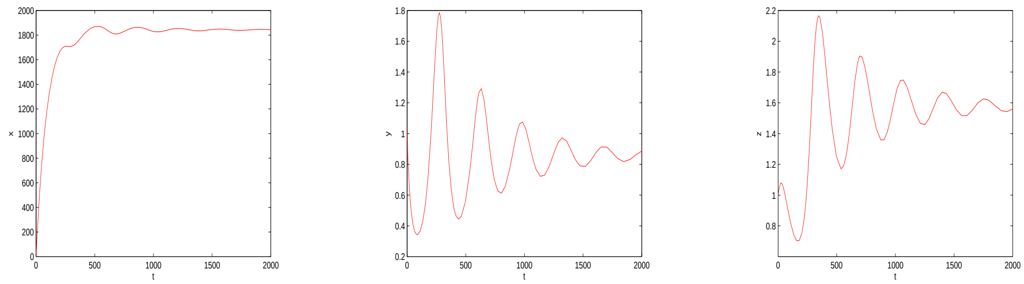

FIGURE 3. The above three graphs are about x, y, z when $R_1 \approx 7.74 > 1$.

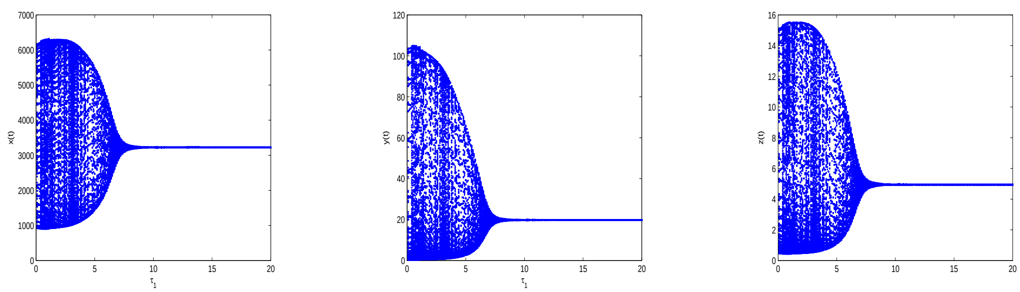

FIGURE 4. The ultimate oscillation interval of the solution to system (2) when τ_1 increases from 0 to 20, here $\tau_2 = 15, t \in [500, 5000]$.

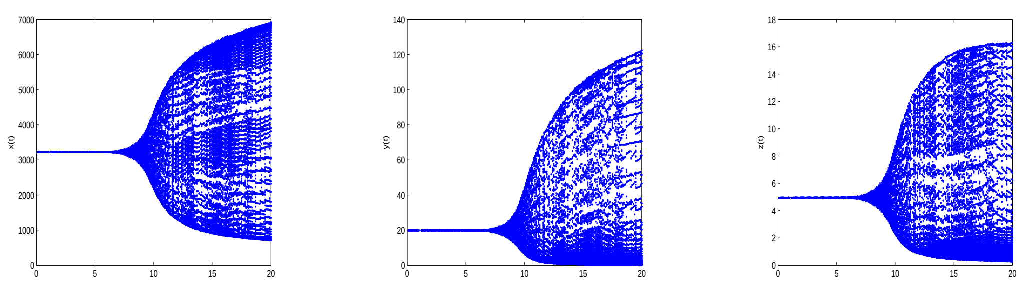

FIGURE 5. The ultimate oscillation interval of the solution to system (2) as τ_2 increases from 0 to 20, here $\tau_1 = 1, t \in [500, 5000]$.

5. Conclusion

In this paper, we consider the generalized system (2) that incorporates non-liner incidence rates. We derive formulas for the basic reproductive numbers of a viral 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).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.

The bilinear incidence rate βxy and saturated incidence rate $\frac{\beta xy}{1+cy}$ are two special cases of $h(x,y)$. Our result also generalizes the global stability results in [1].

Conflict of Interests

The authors declare that there is no conflict of interests.

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