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Global dynamics of a HTLV-I infection model with CTL response *

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Abstract

In this paper, a HTLV-I infection model with CTL response is considered. To account for a series of events in infection process, we incorporate a intracellular time delay in the model. We prove that the global dynamics are determined by two threshold parameters R_0 and R_1, basic reproduction numbers for viral infection and for CTL response, respectively. If $R_0 < 1$, the infection-free equilibrium P_0 is globally asymptotically stable. If $R_1 < 1 < R_0$, the asymptomatic-carrier equilibrium P_1 is globally asymptotically stable. If $R_1 > 1$, there exists a unique HAM/TSP equilibrium P_2, and the equilibrium P_2 is asymptotically stable under certain conditions.

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1 Introduction

HTLV-I is an abbreviation for the human T-cell lymphotropic virus type 1, also called the Adult T-cell lymphoma virus type 1, a virus that has been seriously implicated in several kinds of diseases. The Human T-lymphotropic virus Type I (HTLV-I)

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is a human RNA retrovirus that is known to cause a type of cancer, referred to as adult T-cell leukemia and lymphoma, and a demyelinating disease called HTLV-I associated myelopathy/Tropical spastic paraparesis (HAM/TSP). HTLV-I is one of a group of closely related primate T lymphotropic viruses (PTLVs). Approximately 20 to 40 million people are infected by HTLV-I worldwide. The majority of HTLV-I infected individuals remain lifelong asymptomatic carriers. Approximately 0.25%-3.8% of individuals develop HAM/TSP, and another 2%-3% develop ATL [1]. HTLV-I infection is achieved through cell-to-cell contact [2]. The immune system reacts to HTLV-I infection with a strong cytotoxic T-lymphocyte (CTL) response. HTLV-I infection models have been studied by many researchers [1,4,5]and mathematical models have been developed to describe the interaction in vivo HTLV-I, the $CD4^+$ target cells, and the CTL immune response.

In order to establish the model, we partition the $CD4^+$ T-cell population into uninfected and infected compartments, whose numbers at time t are denoted by $x(t), y(t)$, respectively. Let $z(t)$ denote the number of HTLV-I-specific $CD8^+$ CTLs at time t. The production of health $CD4^+$ T cells is assumed to at a constant rate λ. Since HTLV-I infection occurs by cell-to-cell contact between infected cells and uninfected cells, a bilinear incidence βxy is assumed. CTL-driven elimination of infected $CD4^+$ cells is assumed to be of the form γyz, where γ is the rate of CTL elimination. The CTL response to the HTLV-I infection is modeled by a general function $f(y, z)$, dependent of the number of CTLs and infected $CD4^+$ T cells. The turnover rates of uninfected and infected $CD4^+$ are d_1 and d_2, respectively, and the turnover rate of CTLs is d_3. All parameters are assumed to be positive. Based on the preceding assumptions, we can obtain the following basic HTLV-I infection model with CTL response

$$\begin{cases} x'(t) = \lambda - d_1 x(t) - \beta x(t) y(t), \\ y'(t) = \beta x(t) y(t) - d_2 y(t) - \gamma y(t) z(t), \\ z'(t) = f(y, z) - d_3 z(t). \end{cases} \tag{1.1}$$

This model with several forms of CTL response function $f(y, z)$ have been considered and analyzed by Nowak [13] and Wodarz, Nowak and Bangham [14], respectively.

However, there exist obvious delays in the infection process. We briefly summarize the main stages following Li and Shu [6]. The first stage of infection is the period between the viral entry of a target cell and integration of viral DNA into the host genome. The second stage is the period from the integration of viral DNA to the transcriptase of viral RNA and translation of viral proteins. The third stage is the period between the transcription of viral RNA and the release and maturation of virus. To account for these events in the infection process, we incorporate a time delay in the model. Therefore, in the present paper, we consider the model in the

following form:

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

Here we use $f(y,z) = \mu y(t) z(t)$.

The organization of this paper is as follows. In the next section, we discuss the feasible region for system (1.2) and derive two threshold parameters R_0 and R_1, and show existence of equilibria in relation to values of R_0 and R_1. In Section 3 and 4, global stability of P_0 when $R_0 < 1$ and global stability of P_1 when $R_1 < 1 < R_0$ are discussed. The stability of equilibrium P_2 is investigated in Section 5. Numerical simulations are presented in Section 6, to illustrate and support our analyzed results. The paper ends with brief remarks.

2 Preliminaries

To investigate the dynamics of system (1.2), we need to consider a suitable phase space and a feasible region. For $\tau > 0$, we denote by $\mathcal{C} = \mathcal{C}([-\tau, 0], \mathbb{R})$ the Banach space of continuous real-valued function on the interval $[-\tau, 0]$, with norm $\|\phi\| = \sup_{-\tau \le \theta \le 0} |\phi(\theta)|$ for $\phi \in \mathcal{C}$. The nonnegative cone of $\mathcal{C}$ is defined as $\mathcal{C}^+ = \mathcal{C}([-\tau, 0], \mathbb{R}_+)$. Initial conditions for system (1.2) are chosen as

$$\varphi \in \mathcal{C}^+ \times \mathcal{C}^+ \times \mathbb{R}_+, \varphi = (\varphi_1, \varphi_2, \varphi_3) \text{ with } \varphi_i(0) > 0,\ i = 1, 2 \text{ and } \varphi_3 > 0. \tag{2.1}$$

Proposition 2.1. *Under initial condition* (2.1)*, all solutions of system* (1.2) *are positive and ultimately bounded in* $\mathcal{C} \times \mathcal{C} \times \mathbb{R}$*. Furthermore, all solutions eventually enter and remain in the following bounded and positively invariant region:*

$$\Gamma = \{(x, y, z) \in \mathcal{C}^+ \times \mathcal{C}^+ \times \mathbb{R}_+ : \| x \| \le \tfrac{\lambda}{d_1} + \varepsilon, \| x + y \| \le \tfrac{\lambda}{\widetilde{d}} + \varepsilon, \| x + y + \tfrac{\gamma}{\mu} z \| \le \tfrac{\lambda}{d} + \varepsilon\},$$

where $d = \min\{d_1, d_2, d_3\} > 0, \widetilde{d} = \min\{d_1, d_2\} > 0$*,* ε *is arbitrarily small positive number.*

Proof. First, we prove that $x(t)$ is positive for $t \ge 0$. Assuming the contrary and letting $t_1 > 0$ be the first time such that $x(t_1) = 0$, by the first equation of system (1.2), we have $x'(t_1) = \lambda > 0$, and hence $x(t) < 0$ for $t \in (t_1 - \eta, t_1)$ and sufficiently small η. 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. Similarly, we can show that $y(t) > 0$ for $t > 0$. From the third equation of (1.2), we have

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

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

Next we show that positive solutions of (1.2) are ultimately bounded for $t \geq 0$. From the first equation of system (1.2), we obtain

$$x'(t) \leq \lambda - d_1 x(t), \qquad t \geq 0,$$

and thus

$$\limsup_{t\to\infty} x(t) \leq \frac{\lambda}{d_1}.$$

Adding the first two equations of (1.2), we get

$$(x(t) + y(t+\tau))' \leq \lambda - \tilde{d}(x(t) + y(t+\tau)), \qquad t \geq 0,$$

where $\tilde{d} = \min\{d_1, d_2\}$. Thus

$$\limsup_{t\to\infty}(x(t) + y(t+\tau)) \leq \frac{\lambda}{\tilde{d}}.$$

Adding all the equations of (1.2), we get

$$\begin{aligned}(x(t) + y(t+\tau) + \frac{\gamma}{\mu}z(t+\tau))' &= \lambda - d_1 x(t) - d_2 y(t+\tau) - \frac{\gamma}{\mu}d_3 z(t+\tau) \\ &\leq \lambda - d(x(t) + y(t+\tau) + \frac{\gamma}{\mu}z(t+\tau)),\end{aligned}$$

where $d = \min\{d_1, d_2.d_3\}$. Thus

$$\limsup_{t\to\infty}(x(t) + y(t+\tau) + \frac{\gamma}{\mu}z(t+\tau)) \leq \frac{\lambda}{d}.$$

Based on the discussion above, we have obtained that all solutions of system (1.2) with initial condition (2.1) eventually enter and remain in the region Γ. Therefore, the solutions of system (1.2) with initial condition (2.1) are ultimately uniformly bounded in $\mathcal{C} \times \mathcal{C} \times \mathbb{R}$ by $(\lambda/d) + \varepsilon$. It is not difficult to verify that the region Γ is positive invariant for system (1.2). □

As a consequence of proposition 2.1, we know that the dynamics of system (1.2) can be analyzed in the following bounded feasible region

$$\Gamma = \{(x, y, z) \in \mathcal{C}^+ \times \mathcal{C}^+ \times \mathbb{R}_+ : \| x \| \leq \tfrac{\lambda}{d_1} + \varepsilon, \| x+y \| \leq \tfrac{\lambda}{\tilde{d}} + \varepsilon, \| x+y+\tfrac{\gamma}{\mu}z \| \leq \tfrac{\lambda}{d} + \varepsilon\}.$$

Furthermore, the region Γ is positively invariant with respect to system (1.2) and the model is well posed.

System (1.2) always has an infection-free equilibrium $P_0 = (x_0, 0, 0), x_0 = \frac{\lambda}{d_1}$. In addition to P_0, the system can have two chronic-infection equilibria $P_1 = (\overline{x}, \overline{y}, 0)$ and $P_2 = (x^*, y^*, z^*)$ in Γ, where $\overline{x}, \overline{y}, x^*, y^*$ and z^* are all positive. At equilibrium

P_1, the HTLV-I infection is persistent with a constant proviral load $\overline{y} > 0$, whereas CTL response is absent, so is the risk for developing HAM/TSP. This corresponds to the situation of an asymptotic carrier. At equilibrium P_2, both the proviral load and CTL response persist at a constant level. This corresponds to the situation of a HAM/TSP patient. Which of the three steady-states is the final outcome of the system will be determined by a combination of two threshold parameters.

$$R_0 = \frac{\lambda\beta}{d_1 d_2}, \quad R_1 = \frac{\lambda\beta\mu}{d_1 d_2 \mu + \beta d_2 d_3}. \tag{2.2}$$

They are called the basic reproduction numbers for viral infection and for CTL response, respectively (Gomez-Acevedo et al. [4]). We note that $R_1 < R_0$ always holds.

It can be verified that the carrier equilibrium $P_1 = (\overline{x}, \overline{y}, 0)$ exists if and only if $R_0 > 1$ and that

$$\overline{x} = \frac{d_2}{\beta} = \frac{\lambda}{d_1 R_0}, \quad \overline{y} = \frac{\lambda\beta - d_1 d_2}{\beta d_2} = \frac{d_1(R_0 - 1)}{\beta} \tag{2.3}$$

The coordinates of the HAM/TSP equilibrium $P_2 = (x^*, y^*, z^*)$ are given by

$$x^* = \frac{\lambda\mu}{d_1\mu + \beta d_3} = \frac{d_2 R_1}{\beta}, y^* = \frac{d_3}{\mu}, z^* = \frac{\beta\lambda\mu - d_1 d_2 \mu - \beta d_2 d_3}{(d_1\mu + \beta d_3)\gamma} = \frac{d_1 d_2 \mu + \beta d_2 d_3}{(d_1\mu + \beta d_3)\gamma}(R_1 - 1). \tag{2.4}$$

Therefore, P_2 exists in the interior of Γ if and only if $R_1 > 1$. We thus have the following result.

Proposition 2.2. *If $R_0 < 1, P_0 = (\frac{\lambda}{d_1}, 0, 0)$ is the only equilibrium in Γ. If $R_1 < 1 < R_0$, the carrier equilibrium $P_1 = (\overline{x}, \overline{y}, 0)$ exists and is the only chronic-infection equilibrium in Γ. If $R_1 > 1$, both the carrier equilibrium P_1 and the HAM/TSP equilibrium $P_2 = (x^*, y^*, z^*)$ exist.*

3 Global stability of P_0 when $R_0 < 1$

In this section, we rigorously show that when $R_0 < 1$, the infection-free equilibrium P_0 is globally asymptotically stable in Γ.

Theorem 3.1. *If $R_0 < 1$, then the infection-free equilibrium P_0 of system (1.2) is globally asymptotically stable in Γ. If $R_0 > 1$, then P_0 is unstable.*

Proof. Firstly we prove P_0 is globally attractive in Γ if $R_0 < 1$. To prove this, we consider a Lyapunov functional $L : \mathcal{C} \times \mathcal{C} \times \mathbb{R} \to \mathbb{R}$ given by

$$L(x_t, y_t, z(t)) = x_0 g(\frac{x_t(0)}{x_0}) + y_t(0) + \beta \int_{-\tau}^{0} x_t(\theta) y_t(\theta) d\theta, \tag{3.1}$$

where x_0 is the first coordinate of P_0, $g(u) = u - \ln u - 1, u > 0$. Here $x_t(s) = x(t+s), y_t(s) = y(t+s)$ for $s \in [-\tau, 0]$, and thus $x(t) = x_t(0), y(t) = y_t(0)$ in this notation. Calculating the time derivative of L along the solution in Γ of system (1.2), we obtain

$$\begin{aligned} L'|_{(1.2)} &= \lambda - d_1 x(t) - \frac{x_0\lambda}{x(t)} + d_1 x_0 + x_0\beta y(t) - d_2 y(t) - \gamma y(t) z(t) \qquad \left(x_0 = \frac{\lambda}{d_1}\right) \\ &= d_1 x_0 \left(2 - \frac{x(t)}{x_0} - \frac{x_0}{x(t)}\right) + d_2 y(t)(R_0 - 1) - \gamma y(t) z(t). \end{aligned}$$

Therefore, $R_0 < 1$ ensures that $L'|_{(1.2)} \leq 0$ is satisfied in Γ. Clearly, for $(x_t, y_t, z(t)) \in \Gamma$ satisfying $L' = 0$ if and only if $x(t) = x_0, y(t) = 0$ and $z(t) \in \mathbb{R}_+$. Clearly, $(x_0, 0, z(t))$ is a solution of (1.2) if and only if $z(t) \equiv 0$. This implies that the maximal invariant set of system (1.2) in $\{L'|_{(2.1)} = 0\}$ is the set $M = \{(x_0, 0, 0)\}$. By the LaSalle-Lyapunov theorem (LaSalle and Lefschetz [15] theorem 3.4.7), we conclude that M is globally attractive in Γ if $R_0 < 1$. So P_0 is globally attractive in Γ.

Secondly we prove that P_0 is locally asymptotically stable. The characteristic equation associated with the linearization of system (1.2) at P_0 is given by

$$(\xi + d_1)(\xi + d_3)\left(\xi + d_2 - \frac{\beta\lambda}{d_1} e^{-\xi\tau}\right) = 0. \tag{3.2}$$

Obviously we have $\xi_1 = -d_1 < 0, \xi_2 = -d_3 < 0$, and we can easily prove that all roots of the equation $\xi + d_2 - \frac{\beta\lambda}{d_1} e^{-\xi\tau} = 0$ have negative real parts when $R_0 < 1$ with $\tau \geq 0$. So when $R_0 < 1$, P_0 is locally asymptotically stable.

From global attraction and locally asymptotical stability of P_0 , we obtain that P_0 is globally asymptotically stable in Γ when $R_0 < 1$.

Next, we show that P_0 is unstable when $R_0 > 1$. The characteristic equation associated with the linearization of system (1.2) at P_0 is

$$(\xi + d_1)(\xi + d_3)\left(\xi + d_2 - \frac{\beta\lambda}{d_1} e^{-\xi\tau}\right) = 0.$$

Now we consider equation $\xi + d_2 - \frac{\beta\lambda}{d_1} e^{-\xi\tau} = 0, \tau \geq 0$. The curve $w = \xi + d_2$ and the curve $w = \frac{\beta\lambda}{d_1} e^{-\xi\tau}$ must have intersection point in the first quadrant when $R_0 > 1$. So the equation

$$(\xi + d_1)(\xi + d_3)\left(\xi + d_2 - \frac{\beta\lambda}{d_1} e^{-\xi\tau}\right) = 0$$

has at least one positive root. Hence P_0 is unstable when $R_0 > 1$. □

4 Global stability of P_1 when $R_1 < 1 < R_0$

In this section, we shall study the global stability of the fixed point P_1 when $R_1 < 1 < R_0$. The main result is the followings.

Theorem 4.1. *If $R_1 < 1 < R_0$, then the equilibrium P_1 is globally asymptotically stable in $\Gamma\backslash\{x-axis\}$. If $R_1 > 1$, then P_1 is unstable.*

Proof. Let $g(u) = u - \ln u - 1, u > 0$. $P_1 = (\overline{x}, \overline{y}, 0)$ is the carrier equilibrium.

Define a Lyapunov functional $V : \mathcal{C} \times \mathcal{C} \times \mathbb{R} \to \mathbb{R}$

(4.1)
$$V(x_t, y_t, z(t)) = \overline{x} g\left(\frac{x_t(0)}{\overline{x}}\right) + \overline{y} g\left(\frac{(y_t(0))}{\overline{y}}\right) + \frac{\gamma}{\mu} z(t) + \beta\overline{xy} \int_{-\tau}^{0} g\left(\frac{x_t(\theta) y_t(\theta)}{\overline{xy}}\right) d\theta.$$

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

$$\begin{aligned} V'|_{(1.2)} =& \lambda - d_1 x(t) - \beta x(t) y(t) - \overline{x}\left(\frac{\lambda}{x(t)} - d_1 - \beta y(t)\right) + \beta x(t-\tau) y(t-\tau) - d_2 y(t) \\ & - \gamma y(t) z(t) - \overline{y}\left(\frac{\beta x(t-\tau) y(t-\tau)}{y(t)} - d_2 - \gamma z(t)\right) + \gamma y(t) z(t) - \frac{\gamma}{\mu} d_3 z(t) \\ & + \beta\overline{xy}\left(\frac{x(t)y(t) - x(t-\tau)y(t-\tau)}{\overline{xy}} - \ln\frac{x(t)y(t)}{\overline{xy}} + \ln\frac{x(t-\tau)y(t-\tau)}{\overline{xy}}\right). \end{aligned}$$

Using $\lambda = d_1\overline{x} + \beta\overline{xy}$ and $d_2 = \beta\overline{x}$, it follows that

$$\begin{aligned} V'|_{(1.2)} =& d_1\overline{x}\left(2 - \frac{x(t)}{\overline{x}} - \frac{\overline{x}}{x(t)}\right) - \beta\overline{xy}\left(\frac{\overline{x}}{x(t)} - 1 - \ln\frac{\overline{x}}{x(t)}\right) - \beta\overline{xy}\ln\frac{\overline{x}}{x(t)} \\ & - \beta\overline{xy}\left(\frac{x(t-\tau)y(t-\tau)}{\overline{x}y(t)} - 1 - \ln\frac{x(t-\tau)y(t-\tau)}{\overline{x}y(t)}\right) \\ & - \beta\overline{xy}\ln\frac{x(t-\tau)y(t-\tau)}{\overline{x}y(t)} + \gamma\overline{y}z(t) - \frac{\gamma}{\mu}d_3 z(t) \\ & - \beta\overline{xy}\ln\frac{x(t)y(t)}{\overline{xy}} + \beta\overline{xy}\ln\frac{x(t-\tau)y(t-\tau)}{\overline{xy}} \\ =& d_1\overline{x}\left(2 - \frac{x(t)}{\overline{x}} - \frac{\overline{x}}{x(t)}\right) - \beta\overline{xy}g\left(\frac{\overline{x}}{x(t)}\right) - \beta\overline{xy}g\left(\frac{x(t-\tau)y(t-\tau)}{\overline{x}y(t)}\right) \\ & + \gamma\left(\overline{y} - \frac{d_3}{\mu}\right)z(t) \\ =& d_1\overline{x}\left(2 - \frac{x(t)}{\overline{x}} - \frac{\overline{x}}{x(t)}\right) - \beta\overline{xy}\left[g\left(\frac{\overline{x}}{x(t)}\right) + g\left(\frac{x(t-\tau)y(t-\tau)}{\overline{x}y(t)}\right)\right] \\ & + \frac{\gamma(d_1\mu + \beta d_3)}{\beta\mu}(R_1 - 1)z(t) \le 0, \end{aligned}$$

when $R_1 < 1$. Furthermore, $V' = 0 \Leftrightarrow x(t) = \overline{x}, y(t) = \overline{y}, z(t) = 0$, and thus the maximal invariant set in the set $\{V' = 0\}$ is the singleton $\{P_1\}$. Therefore, P_1 is globally attractive in $\Gamma \setminus \{\text{x-axis}\}$ when $R_1 < 1$. Along the invariant x-axis, solutions converge to the infection-free equilibrium P_0.

We investigate local stability of P_1 in following. The characteristic equation associated with the linearization of system (1.2) at P_1 is

$$(\xi + d_3 - \mu\overline{y})(\xi^2 + (d_1 + d_2 + \beta\overline{y})\xi + d_1d_2 + d_2\beta\overline{y} - (\xi + d_1)\beta\overline{x}e^{-\xi\tau}) = 0. \tag{4.2}$$

We easily get $\xi_1 = \mu\overline{y} - d_3 < 0$ when $R_1 < 1$. Next we consider the following equation

$$\xi^2 + (d_1 + d_2 + \beta\overline{y})\xi + d_1d_2 + d_2\beta\overline{y} - (\xi + d_1)\beta\overline{x}e^{-\xi\tau} = 0. \tag{4.3}$$

Using $\overline{y} = \frac{\lambda\beta - d_1d_2}{\beta d_2}, \overline{x} = \frac{d_2}{\beta}$, we obtain

$$\xi^2 + \frac{d_2^2 + \lambda\beta}{d_2}\xi + \lambda\beta - d_2(\xi + d_1)e^{-\xi\tau} = 0. \tag{4.4}$$

The Eq. (4.4) with $\tau = 0$ is $\xi^2 + \frac{\lambda\beta}{d_2}\xi + \lambda\beta - d_1d_2 = 0$, whose roots have negative real parts if $R_1 < 1 < R_0$. Now we consider the roots of the equation (4.4) with $\tau > 0$. Denotes $a_1 = \frac{d_2^2 + \lambda\beta}{d_2}, a_2 = \lambda\beta, b_1 = d_2$ and $b_2 = d_1d_2$. Then Eq. (4.4) becomes

$$\xi^2 + a_1\xi + a_2 - (b_1\xi + b_2)e^{-\xi\tau} = 0. \tag{4.5}$$

Assuming $\xi = i\omega(\omega > 0)$ is a purely imaginary root of the equation (4.5) for $\tau > 0$. Substituting $\xi = i\omega$ into the equation and separating the real and imaginary parts, we obtain

$$\begin{aligned} a_2^2 - \omega^2 &= b_1\omega\sin\omega\tau + b_2\cos\omega\tau, \\ a_1\omega &= b_1\omega\cos\omega\tau - b_2\sin\omega\tau. \end{aligned} \tag{4.6}$$

Squaring and adding both equations of (4.6) leads to

$$F(\omega) = \omega^4 + (a_1^2 - 2a_2 - b_1^2)\omega^2 + a_2^2 - b_2^2 = 0.$$

Let

$$G(u) = u^2 + (a_1^2 - 2a_2 - b_1^2)u + a_2^2 - b_2^2 = 0.$$

We easily find that $a_1^2 - 2a_2 - b_1^2 = \frac{\lambda^2\beta^2}{d_2} > 0$, and $a_2^2 - b_2^2 = \lambda^2\beta^2 - d_1^2d_2^2 > 0$ for $R_1 < 1 < R_0$. Therefore, the equation $G(u) = 0$ has no positive roots. Namely, the equation $F(\omega) = 0$ has no positive roots. Thus the equation (4.5) has no purely imaginary roots. Notice that 0 is not the root of the equation (4.5). We obtain that all roots of the characteristic equation (4.2) have negative real parts. So P_1 is locally asymptotically stable for $R_1 < 1 < R_0$.

From global attraction and locally asymptotical stability of P_1, the equilibrium P_1 is globally asymptotically stable in $\Gamma\backslash\{x-axis\}$.

For $R_1 > 1$, the characteristic equation has a positive root given by

$$\xi_1 = \mu\overline{y} - d_3 > 0.$$

Thus P_1 is unstable when $R_1 > 1$.

□

5 Dynamics when $R_1 > 1$

We have shown in above sections that, if $R_1 > 1$ both the equilibrium P_0 and the carrier equilibrium P_1 are unstable. And the HAM/TSP equilibrium P_2 exists in the interior of Γ. We will investigate the stability of P_2 in this section.

The characteristic equation associated with the linearization of system (1.2) at P_2 is

$$\begin{aligned}(5.1)\quad &\xi^3 + (d_1+d_2+\beta y^*+\gamma z^*)\xi^2 + (d_1d_2+\mu\gamma y^*z^*+\gamma d_1 z^*+\beta d_2 y^*+\beta\gamma y^*z^*)\xi\\ &+ d_1d_3\gamma z^* + \beta\gamma d_3 y^*z^* + e^{-\xi\tau}(-\beta x^*\xi^2 - \beta d_1 x^*\xi) = 0.\end{aligned}$$

Using $\gamma z^* = \beta x^* - d_2$ and the expression of x^*, y^*, z^*, we get

$$\begin{aligned}(5.2)\quad &\xi^3 + (d_1+\beta x^*+\beta y^*)\xi^2 + (\beta d_1 x^* + \beta^2 x^* y^* + \beta d_3 x^* - d_2 d_3)\xi\\ &+ d_1d_3\beta x^* - d_1d_2d_3 + \beta^2 d_3 x^* y^* - \beta d_2 d_3 y^* + e^{-\xi\tau}(-\beta x^*\xi^2 - \beta d_1 x^*\xi) = 0.\end{aligned}$$

Let

$a_2 = d_1 + \beta x^* + \beta y^* (> 0), a_1 = \beta d_1 x^* + \beta^2 x^* y^* + \beta d_3 x^* - d_2 d_3,$
$a_0 = d_1 d_3 \beta x^* - d_1 d_2 d_3 + \beta^2 d_3 x^* y^* - \beta d_2 d_3 y^* (> 0),$
$b_2 = -\beta x^* (< 0), b_1 = -\beta d_1 x^* (< 0).$
Then the equation (5.2) changes into

$$(5.3)\qquad \xi^3 + a_2\xi^2 + a_1\xi + a_0 + e^{-\xi\tau}(b_2\xi^2 + b_1\xi) = 0.$$

When $\tau = 0$, the equation (5.3) becomes

$$(5.4)\qquad \xi^3 + (a_2+b_2)\xi^2 + (a_1+b_1)\xi + a_0 = 0.$$

Noticing that
$a_2 + b_2 = d_1 + \beta y^* > 0, a_0 = d_1 d_3 \gamma z^* + \beta d_3 \gamma y^* z^* > 0,$
$(a_2+b_2)(a_1+b_1) - a_0 = d_1\beta^2 x^* y^* + \beta^3 x^* (y^*)^2 > 0,$
and by the Routh-Hurwitz criterion, we know that all roots of equation (5.4) have negative real parts. Thus we obtain the following result.

Proposition 5.1. *Suppose $R_1 > 1$. Then the HAM/TSP equilibrium P_2 is locally asymptotically stable when $\tau = 0$.*

Remark 5.2. Using a Lyapunov function

$U(x,y,z) = (x - x^* \ln x) + (y - y^* \ln y) + \frac{\gamma}{\mu}(z - z^* \ln z)$,

we can show that, if $R_1 > 1$, then the equilibrium P_2 is globally asymptotically stable in the interior of Γ when $\tau = 0$.

Since when $\tau = 0$, all roots of the characteristic equation (5.3) lie to the left of the imaginary axis, a stability change at P_2 can only happen when characteristic roots cross the imaginary axis to the right. We thus consider the possibility of purely imaginary roots $\xi = i\omega(\omega > 0)$ for $\tau > 0$. Substituting $\xi = i\omega$ into equation (5.3) and separating the real and imaginary parts, we obtain

$$\begin{aligned} \omega^3 - a_1\omega &= b_1\omega\cos\omega\tau + b_2\omega^2\sin\omega\tau, \\ a_2\omega^2 - a_0 &= b_1\omega\sin\omega\tau - b_2\omega^2\cos\omega\tau. \end{aligned} \tag{5.5}$$

Squaring and adding both equations of (5.5) lead to

$$F(\omega) = \omega^6 + (a_2^2 - 2a_1 - b_2^2)\omega^4 + (a_1^2 - 2a_0a_2 - b_1^2)\omega^2 + a_0^2 = 0. \tag{5.6}$$

Let

$$G(u) = u^3 + (a_2^2 - 2a_1 - b_2^2)u^2 + (a_1^2 - 2a_0a_2 - b_1^2)u + a_0^2 = 0. \tag{5.7}$$

Therefore, if $\xi = i\omega(\omega > 0)$ is a purely imaginary root of equation (5.6), then the equation (5.7)

$G(u) = 0$

must has at least a positive root $u = \omega^2$. Notice that

$G'(u) = 3u^2 + 2(a_2^2 - 2a_1 - b_2^2)u^2 + (a_1^2 - 2a_0a_2 - b_1^2)$.

Let

$\Delta = (a_2^2 - 2a_1 - b_2^2)^2 - 3(a_1^2 - 2a_0a_2 - b_1^2)$.

Note that $G(0) = a_0^2 > 0$. Then

(1) If $\Delta \le 0$, noticing $G(0) = a_0^2 > 0$, and thus $G(u)$ is monotonically increasing. Therefore, equation $G(u) = 0$ has no positive roots, and all characteristic roots will remain to the left of the imaginary axis for all $\tau > 0$.

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

$$u^* = \frac{-(a_2^2 - 2a_1 - b_2^2) + \sqrt{\Delta}}{3}, u^{**} = \frac{-(a_2^2 - 2a_1 - b_2^2) - \sqrt{\Delta}}{3}. \tag{5.8}$$

Obviously $u^* > u^{**}$,and if $u^* < 0$, then $G(u) = 0$ has no positive roots.

(3)If $\Delta > 0$,$u^* > 0$ and $G(u^*) > 0$, then $G(u) = 0$ has no positive roots.

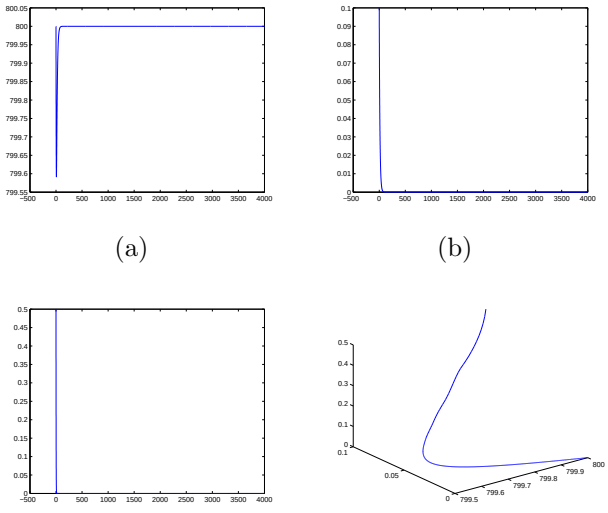
From (1), (2) and (3),We have the following theorem.

Theorem 5.3. *If (1*)$\Delta \le 0$, or (2*) $\Delta > 0$, $u^* < 0$, or (3*) $\Delta > 0$, $u^* > 0$, $G(u^*) > 0$. Then the HAM/TSP equilibrium P_2 remains asymptotically stable for all $\tau \ge 0$.*

6 Numerical simulations

In this section, we shall carry out some numerical simulations for supporting our theoretical analysis. In the following, the data chosen are borrowed from Li and Shu [5].

Firstly, we consider the following set of parameter values: $\lambda = 160$ cells/mm^3/day, $\beta = 0.002$ mm^3/cells/day, $d_1 = 0.2$ day^{-1}, $d_2 = 1.8$ day^{-1}, $d_3 = 0.5$ day^{-1}, $\mu = 0.2$ mm^3/cells/day, $\gamma = 0.2$ mm^3/cells/day, $\tau = 1$ day. For the above parameter set, $R_0 = 0.8889 < 1$, the system (1.2) has an unique infection-free equilibrium P_0=(800,0,0). Figure 1 shows P_0 is globally asymptotically stable when $R_0 < 1$.



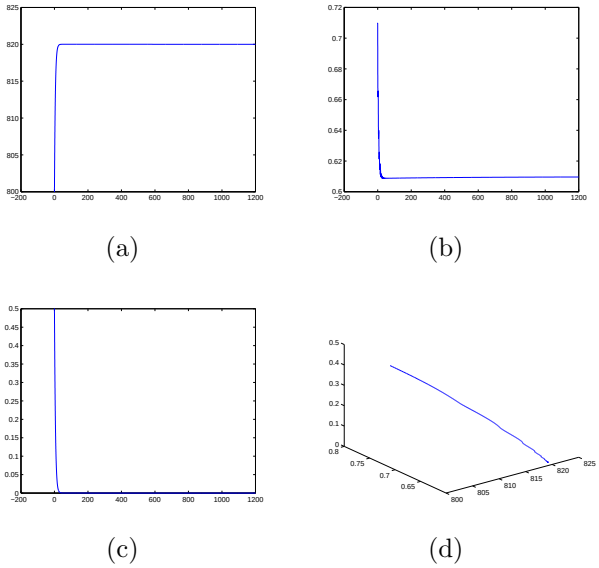
(a) (b)

(c) (d)

Figure 1: P_0 is globally asymptotically stable. Here $\lambda = 160, \beta = 0.002, d_1 = 0, 2, d_2 = 1.8, d_3 = 0.5, \mu = 0.2, \gamma = 0.2, \tau = 1$ and $R_0 = 0.8889 < 1$.

Next, we use the following parameters: $\lambda = 165$ cells/mm^3/day, $\beta = 0.002$ mm^3/cells/day, $d_1 = 0.2$ day^{-1}, $d_2 = 1.64$ day^{-1}, $d_3 = 0.3$ day^{-1}, $\mu = 0.2$ mm^3/cells/day, $\gamma = 0.2$ mm^3/cells/day, $\tau = 3$ days. For those parameters, $R_1 = 0.9912 < 1 < R_0 = 1.0061.$, the system (1.2) has a chronic-infection equilibrium P_1=(820,0.6098,0). Figure 2 demonstrates this chronic-infection equilibrium P_1 is globally asymptotically stable when $R_1 < 1 < R_0$.

In figure 3, we adopt the following set of parameter values: $\lambda = 160$ cells/mm^3/day, $\beta = 0.002$ mm^3/cells/day, $d_1 = 0.16$ day^{-1}, $d_2 = 1.9$ day^{-1}, $d_3 = 0.5$ day^{-1}, $\mu = 0.2$ mm^3/cells/day, $\gamma = 0.2$ mm^3/cells/day, $\tau = 3$ days. Thus $R_1 = 1.0207 > 1$, the system (1.2) has a chronic-infection equilibrium $P_2 = (969.6970, 2.5, 0.1970)$ and $\Delta = -0.0161 < 0$. Figure 3 demonstrates P_2 is asymptotically stable when $R_1 > 1$ and $\Delta < 0$.



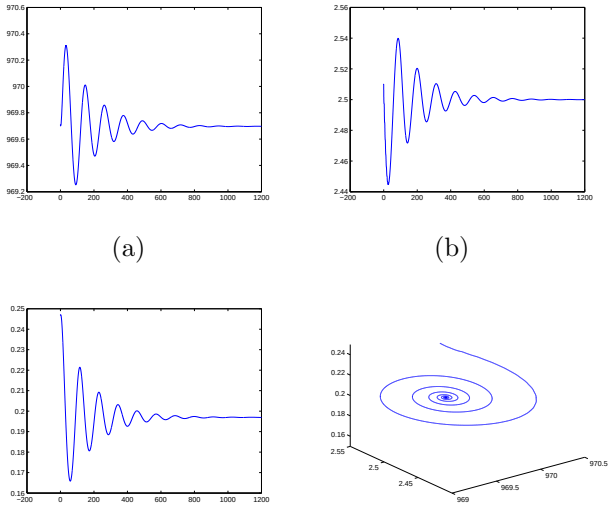
(a) (b)

(c) (d)

Figure 2: P_1 is globally asymptotically stable. Here $\lambda = 165, \beta = 0.002, d_1 = 0.2day^{-1}, d_2 = 1.64, d_3 = 0.3, \mu = 0.2, \gamma = 0.2, \tau = 3$ and $R_1 = 0.9912 < 1 < R_0 = 1.0061$.

In figure 4, we use the following parameters: $\lambda = 160$ cells/mm^3/day, $\beta = 0.002$ mm^3/cells/day, $d_1 = 0.16$ day^{-1}, $d_2 = 1.85$ day^{-1}, $d_3 = 0.02$ day^{-1}, $\mu = 0.2$ mm^3/cells/day, $\gamma = 0.2$ mm^3/cells/day, $\tau = 3$ days. Thus $R_1 = 1.0797 > 1$, the system (1.2) has a chronic-infection equilibrium $P_2 = (998.7516, 0.1, 0.7375)$ and $\Delta = 0.0001 > 0, u^* = -0.0042 < 0$. Figure 4 demonstrates P_2 is asymptotically stable when $R_1 > 1$ and $\Delta > 0, u^* < 0$.

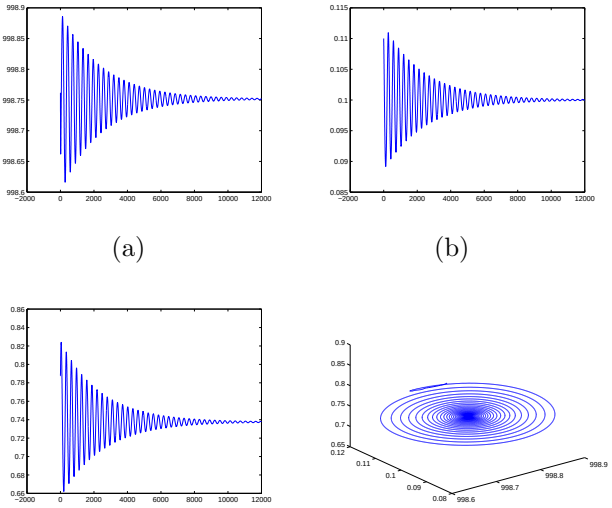
In figure 5, the following parameter values are employed: $\lambda = 160$ cells/mm^3/day, $\beta = 0.002$ mm^3/cells/day, $d_1 = 0.16$ day^{-1}, $d_2 = 1.7$ day^{-1}, $d_3 = 0.5$ day^{-1}, $\mu = 0.2$ mm^3/cells/day, $\gamma = 0.2$ mm^3/cells/day, $\tau = 3$ days. Thereby we obtain $R_1 = 1.1408 > 1$ and the system (1.2) has a chronic-infection equilibrium $P_2 = (969.6970, 2.5000, 1.1970)$. Furthermore, $\Delta = 0.0032 > 0, u^* = 0.0897 > 0, G(u^*) = 0.007 > 0$. Figure 4 shows P_2 is asymptotically stable when $R_1 > 1$ and $\Delta > 0, u^* > 0, G(u^*) > 0$.



(a) (b)

(c) (d)

Figure 3: P_2 is asymptotically stable. Here $\lambda = 165, \beta = 0.002, d_1 = 0.16, d_2 = 1.9, d_3 = 0.5, \mu = 0.2, \gamma = 0.2, \tau = 3$ and $R_1 = 1.0207 > 1, \Delta = -0.0161 < 0$.



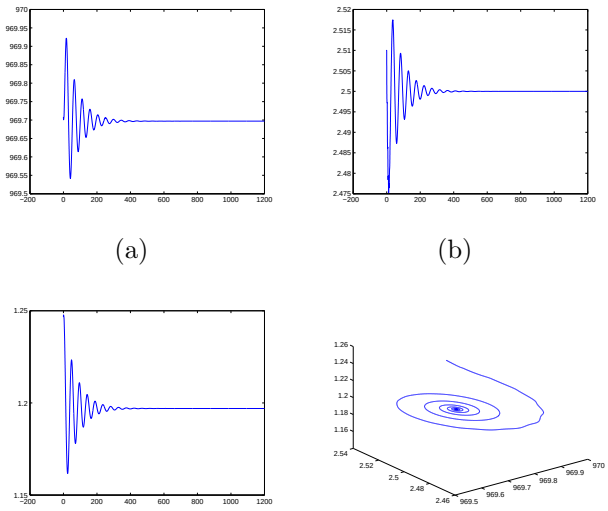
(a) (b)

(c) (d)

Figure 4: P_2 is asymptotically stable. Here $\lambda = 160, \beta = 0.002, d_1 = 0.16, d_2 = 1.85, d_3 = 0.02, \mu = 0.2, \gamma = 0.2, \tau = 3$ and $R_1 = 1.0797 > 1, \Delta = 0.0001 > 0, u^* = -0.0042 < 0$.

7 Conclusion

Based on the system (1.1), we propose the system (1.2) with delay, and investigate its dynamics. We roughly prove that P_0 is globally asymptotically stable when $R_0 < 1$



(a) (b)

(c) (d)

Figure 5: P_2 is asymptotically stable. Here $\lambda = 160, \beta = 0.002, d_1 = 0.16, d_2 = 1.7, d_3 = 0.5, \mu = 0.2, \gamma = 0.2, \tau = 3$ and $R_1 = 1.0797 > 1, \Delta = 0.0032 > 0, u^* = 0.0897 > 0, G(u^*) = 0.007 > 0$.

and P_1 is globally asymptotically stable when $R_1 < 1 < R_0$ by Lyapunov functionals. When $R_1 > 1$, we obtain P_2 is asymptotically stable under certain conditions. At last, we carry out some numerical simulations to support the analysis results.

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